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The Journal of Asian Medical Students’ Association (JAMSA) (ISSN: 2226-3403) is an international peer-reviewed, online open-access student-led biomedical journal of the Asian Medical Students’ Association-International (AMSA International). It is published biannually and listed in ICMJE, member of the CrossRef, and indexed in Ulrichsweb, Google Scholar, ROAD (Directory of Open Access Scholarly Resources) Indexing, Gale Cengage, BASE (Bielefeld Academic Search Engine), and Genamics Journal Seek. Its vision is to foster student-led research in regions of Asia, Asia-Pacific, and beyond.

Research and Scientific writing by medical students is being increasingly acknowledged all over the world. AMSA International with its vision of Knowledge, Action and Friendship, wants to encourage all forms of research and creative work from medical students. JAMSA is a platform for young and budding researchers from Asia-Pacific and beyond who are just beginning their careers in the medical and scientific fields.

SCOPE
The main objective of JAMSA is to serve as a portal by documenting the research activities. We encourage all forms of scientific writing including Original Research articles, Review Articles, Case Reports, feature articles, letters to the editor etc. If you are interested in submitting your research article please go through the Author Guidelines and Submission Guidelines under the Submission section of our website.

The journal accepts scientific articles authored by medical students including but not limited to the member countries of AMSA International. Scientific articles related to all the disciplines of medicine, public health or health care management and those articles having impact on health in any form will be accepted. However, the editorial board reserves the right to deny publication of any article if it deems so. One of our priorities is to keep the article processing time to a minimum. Our online submission and article processing system has been tailored to fulfill this objective.

If you have any questions feel free to contact us at j-amsa@amsa-international.org or refer to our website (here).
Dear Readers,

It is my great pleasure to introduce and welcome you all to 10th Volume of The Journal of Asian Medical Students’ Association (JAMSA) journal, which showcases the latest research and insights on a wide range of topics in biomedical fields. The contributors to this journal have devoted countless hours to advancing knowledge in their respective fields, and their work represents a significant contribution to the ongoing conversation within academia.

The articles featured in this journal cover a broad range of subjects, from the preclinical laboratory studies to clinical sciences and offer a variety of perspectives on the scientific discoveries in the world around us. Whether you are interested in cutting-edge research on neurobiology, insights into psychological health, or new approaches to understanding human diseases, this journal has something for you.

As a reader, you will have the opportunity to explore the latest findings in fields. The research presented here is sure to challenge your assumptions, broaden your horizons, and inspire new ideas.

I would like to extend my thanks to the contributors, whose hard work and dedication have made this journal possible. I would also like to thank my editorial and management boards, reviewers, and international research board members from chapters who have worked and contributed tirelessly to ensure that the content is of the highest quality.

I hope that you find this journal to be a valuable resource, and I encourage you to engage with the content, share your thoughts and ideas, and continue the conversation in your own work.

Sincerely,

Unleash the scientists within you and become the physician-scientists of tomorrow!

With warm regards

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Journal of Asian Medical Students’ Association
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Original Research
Awareness about Abortion among the Students in Malaysia

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Abstract:

Objectives Malaysia’s law and regulation on abortion ties in closer to the Islamic beliefs which vary from western countries such as the United States. However, misinformation and anti-abortion myths are heavily propagated through channels such as family and friends. This research aims to investigate the students' knowledge of abortion laws and to discern between the facts and myths concerning abortion.

Study design This was a cross-sectional study of English-speaking students aged 18 and above in Malaysia. Data was collected and interpreted through online resources such as Google Forms, Google Sheet & Google Feedback. This investigative study focuses on primary questions catered towards abortion.

Results Based on the results of 195 students, majority (113/195; 57.9%) felt that it would be illegal for her to get an abortion if mother is healthy, while (112/195; 57.4%) felt that if her life, or was the result of rape, or was the result of incest, it would be legal for her to get an abortion. For three out of the assessed myths, students are unable to discern and remain uncertain. Most students (92/195; 47.2%) are personally against abortion and feels that the government should not prevent a woman from making the decision herself. While (85/195; 43.6%) believe that having an abortion is morally acceptable and should be made legal. The remaining (18/195; 9.2%) believes that abortion is morally wrong and should be made illegal.
Conclusions  Malaysian students have a very minimal level of comprehension regarding the country’s abortion laws, all the while remaining unclear of the misconception and facts of abortion.

Implications: Present abortion policies and guidelines will remain redundant unless they are actively endorsed to HCPs and incorporated into legal medical facilities as well as incorporating sexual education into curricular activities, making it vital.

Keywords: Abortion Awareness, Malaysia, Students, Abortion, Awareness
Introduction

Pregnancy can be a time of joy, hope, and excitement for a mother, but it can also be a period of tremendous fear and stress since it can be dangerous for both the mother and her child, as it is a life-changing experience for the majority of women. This is true regardless of whether the pregnancy is intended or unplanned.

Abortion may be a course of action to an unwanted pregnancy. The consensus is that society would allow abortion in "hard" conditions, such as sexual assault, incest, or danger to the pregnant woman's health and welfare, in which case abortion may be performed. But not in milder circumstances such as economic difficulties, resentment towards the unborn child, potential birth deformities, or contraception malfunction. Although abortion can be done for a variety of causes, one of the most common is when a woman's health is in jeopardy.

The topic chosen is an unplanned pregnancy. An unwanted pregnancy is defined as a pregnancy that was not planned for or not desired by either of the couple at the time of conception. On some occasions, it is due to an abnormality of the fetus or of an illness in the mother (1). There will be 3 outcomes from an unwanted pregnancy, which would be the continuation of pregnancy, abortion, or unsafe abortion.

Abortion is described as the removal of an embryo or fetus that is in the stage where it is incapable of independent survival (500 gms or 22 weeks’ gestation) (1). Natural cases without the intent to terminate the pregnancy, it would be called a spontaneous miscarriage. However, if there is intent of terminating a pregnancy due to medical reasons, such as an infection, an ectopic pregnancy, or postpartum psychosis, where the gynecologist deems that the pregnancy threatens the wellbeing of the mother, abortion can be allowed in a case-by-case basis (2).

In Malaysia, abortion law states that the termination of pregnancy is permitted to save a woman's life and preserve her physical and mental health. It is stated in the Penal Code 574 Section 213, which was amended in 1989 (2). However, that is the only exception for abortion in Malaysia. Therefore, abortion in Malaysia is mostly illegal and the issues arise when there are no facilities to provide care and consultation to couples or mothers that have unwanted pregnancies with invalid complications like social stigma and economic difficulties.
Unfortunately, the abortion mortality rate accounts for 13% of global maternal mortalities (1). This is due to the combination of restrictive laws and unsafe abortion procedures done by untrained practitioners that may chronically disable or cause death to the mother (1).

Federation of Reproductive Health Associations, Malaysia (FRHAM) reported that (5,512/90,032; 6.1%) of abortion done in Malaysia were by the younger population aged less than 24 years old (3). There are possibilities that there are some areas in which the younger population of Malaysia lacks in the understanding of the laws: the interpretation of the law about abortion and whether the law allows abortion; if so, what kind of circumstances? (4). Will knowledge and understanding lower the incidence of mortality induced by unsafe abortion? Thus, this next section of the research would lead to the aims and objectives of the research to assess the level of understanding of abortion of students and their personal attitudes towards the matter.

Methodology
Survey Background
To assess the level of understanding regarding abortion among students in Malaysia, a survey is conducted online via Google Forms.

Survey Goals
The purpose of the research is to assess the level of knowledge among students regarding the terms, medical facts, abortion laws in Malaysia, myths regarding abortions and personal attitudes about abortion.

Survey Target Population
The required data was collected from 195 students in Malaysia over the age of 18 years old.

Survey Content
The relevant data were gathered using an existing five-part survey template that was sampled and changed accordingly (5). The first part of the survey included demographic information (sex and age group). The second, third and fourth parts were respectively related to assessing the knowledge regarding abortion laws in Malaysia, abortion myths and finally the search terms used on Google. The fifth part of the survey summarizes the personal attitudes to abortion and experiences on the matter. The survey consisted of 19 questions. The first 9 questions (yes/no/don’t know) were related to the level of awareness of the abortion law in Malaysia followed by 2 questions about medical insurance coverage for
abortion. The next 5 questions were statements that were closer to the truth about abortion where 2 opinions were to be chosen and 1 (don’t know/not sure) was given. Next, 1 open-ended question was asked on the term used for searching abortion clinics on the internet. Lastly, 2 questions about personal attitudes and experiences on abortions were asked.

**Survey Timing**
The survey was conducted for a period of 1 week from the 13th of April 2022 to the 20th of April 2022.

**Survey Method**
The survey was conveyed online via social media platforms such as WhatsApp, Telegram & Instagram which directs responders to the Google Form link containing the survey.

**Survey Data Collection**
Google Forms Feedback & Google Sheets.

**Survey Language**
English

**Results:**
The total number of respondents is 195 from the survey. Out of 195, 124 are female and 71 males.

The majority of the respondents are aged between 18-30 years old (n=178), with the highest number of respondents from the individual age group of 22 years old. Minority groups are aged between 31-65 years old (n=17).
The majority (113/195; 57.9%) felt that it would be illegal for her to get an abortion if mother is healthy, while (112/195; 57.4%) felt that if her life, or was the result of rape, or was the result of incest, it would be legal for her to get an abortion. Next, the majority (100/195; 51.2%) believes that there is a law that requires a doctor to review a script or specific information with women prior to an abortion. Majority (103/195; 52.8%) believes that there is a law that requires minors to get parental consent and/or notify their parent(s) before an abortion.

However, respondents (113/195; 57.9%) are uncertain whether there is a law requiring women to have an ultrasound before an abortion and (89/195; 45.6%) are also unclear whether there is a law that requires a married woman to have their husband’s consent before an abortion. Majority (144/195; 73.8%) does not believe that it is legal to have an abortion based on whether the woman wants a boy or a girl and (93/195; 47.7%) thinks it is illegal to have an abortion because the fetus has Down syndrome. Lastly, majority (110/195; 56.4%) were not sure if there is a law that requires a woman seeking an abortion to wait a specified period between receiving counseling and when the procedure is performed.

Results showed (58/195; 29.7%) answered correctly ‘No’ to [Does medical insurance cover abortion]. Majority of the answers were (81/195; 41.5%) ‘I don’t know’.

Results showed (58/195; 29.7%) answered correctly ‘No’ to [Does medical insurance cover abortion]. Majority of the answers were (81/195; 41.5%) ‘I don’t know’.
A follow-up question [If answer to question 1. was ‘Yes, medical insurance covers abortion, but only for some reasons’, under what circumstances does it cover abortion?] and the majority (26/53; 49.1%) answered ‘All of the above’.

Figure 5 Follow-up result

Results showed the majority of students answered ‘Not sure’ for the following 3 questions about (safety, breast cancer and regret) with 36.4%, 53.8% & 43.6% respectively. Majority answered inaccurately (66.7%) to the question relating to depression and lastly the majority answered accurately for infertility questions (35.4%).

Google Term Results: Most average terms used: were “Abortion clinic” (17), followed by “Abortion clinic near me” (11). The word ‘Abortion’ and ‘Clinic’ was used (126/195; 64.2%) in the response registered.

Most students (92/195; 47.2%) are ‘personally against abortion and the government should not prevent a woman from making the decision herself’. While (85/195; 43.6%) believe that ‘having an abortion is morally acceptable and should be made legal’. The remaining (18/195; 9.2%) believes that abortion is morally wrong and should be made illegal.

Figure 7 Personal Attitude towards abortion

Results showed that the majority (178/195; 91.3%) have not accompanied someone else to obtain an abortion.
Discussion

Only several students were precise in their facts pertaining to the security and legal implications of the matter at hand in this evaluation of students over the age of 18 based on their understanding of Malaysian abortion laws. Major national research in the United States yielded identical findings (5).

Nearly identical to other investigations, our results of the research demonstrate that students have a minimal level of understanding of abortion laws. The bulk of students are uninformed that abortion is prohibited in Malaysia, and they are also oblivious that medical coverage does not support abortion. The lack of information about abortion services and abortion opinions continues to be a taboo topic in Malaysia, therefore students are incapable of discerning appropriately.

Not only that, but doctors also working in the government healthcare industry were accused of being condescending and seeing abortion as a heinous crime (6). Women were instructed and warned to keep the pregnancy going and then offer the kid up for adoption shortly afterwards. Sexual education, which includes birth control procedures, was not taught in Malaysia until recently (6,7). In biology, ethics, and religion classes, only a few parts of sexual education were explored (6).

Other comparable survey investigations that were done based on peer research had revealed that acquaintances were the key resource of knowledge, regarding women's reproductive health, for 64.4 percent of high school seniors in a study of 1,034 secondary students (6). Since the majority of the women in this study seemed to obtain their information through friends and family, it's possible that inaccurate sexual and reproductive health information was disseminated through these channels (6).

There have been previous investigations on the myths and misconceptions and actual truth surrounding abortion (5). In line with other findings, the statistics reveal that irrespective of gender, students'
perceptions of abortion's impact on women's safety, psychological well being, and sexual wellness are mingled with incorrect anti-abortion beliefs and clouded with ambiguity. A significant proportion of students in the survey believed that abortion causes detrimental psychological effects like depression, although this has been debunked in both the short and long haul (5).

This research, although produced hard facts and collected information, still has several drawbacks. Firstly, attributable to the fact that it is still during Covid-19 travel mobility and interpersonal limitations, the quantity of the intended demographic was quite small. This rendered it challenging to acquire satisfactory conclusions. Furthermore, because respondents' responses revealed poor standards of healthcare awareness and education, the research findings were perhaps skewed toward 'Not sure' because survey participants didn't comprehend some of the phrases employed in the questionnaire.

Conclusions
Despite the fact that we live in an era where knowledge is freely attainable at our disposal, the bulk of Malaysians are still unsure about the country's abortion policies and guidelines. There appears to be a lack of understanding and a conventional societal prejudice that has not been alleviated, and when younger generations assume leadership roles, the ancient mentality persists.

Amid efforts to promote knowledge and understanding and set rules on abortion, women's accessibility to legal abortion facilities in Malaysia still needs to be improved. It also shows Malaysia's pledge to advance women's privileges to universal sexual and reproductive health treatments. Current protocols will be ineffective unless they have been aggressively publicized to HCPs and integrated into real medical treatments, as well as embedded into sexual education essentials. Hospitals and medical practitioners must also be qualified and endowed with the necessary information, capabilities, and funds to provide secure abortion procedures.

Malaysians must also be enlightened and notified of their constitutional privileges to protected, ethical abortions, as well as where to locate these facilities. In addition to the Ministry of Health, continuous intergovernmental endeavors to overcome these hurdles and increase women's accessibility to legal abortion services in Malaysia must engage the law enforcement
agencies, social ministries, nursing and medical institutions, and women/health NGOs.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Availability of data and material**

Not applicable.

**Conflict of interests**

Not applicable.

**Funding**

Not applicable.

**Authors' contributions**

A Ambi was the sole contributor of the manuscript

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Abstract:

Objectives To observe an association between playing mobile games and reaction time among students aged 18-25 years. Variation in reaction time with types of games, time spent on gaming, age of starting to play, and time of day was studied.

Methods This is a case-control study in which 94 participants studying MBBS at the University College of Medical Sciences were included after they consented to participate. Their gaming status was recorded and their reaction time was tested using the tap reaction time test and Reaction time ruler test. Unpaired t-test was applied to compare the reaction time of gamers and non-gamers.

Results The average reaction time was 488 milliseconds (+12 milliseconds) for gamers and 535 milliseconds (+20 milliseconds) for non-gamers with the tap reaction time test. With the reaction time ruler test, the average reaction time of gamers was 182 milliseconds (+30 milliseconds) and 196 milliseconds (+30 milliseconds) for non-gamers. The first reading was found to be higher than the subsequent readings. The age of commencement of playing did not significantly affect the reaction time. The increase in the variety of games and the number of days a person plays per week yielded better reaction times. The time of the day significantly affected the tap reaction time test but not the reaction time ruler test.

Conclusions People qualifying as gamers record lower response times than non-gamers. This may enable designers to create games fit for individuals with slower response time. Gaming can also benefit medical professionals by enabling them to react much faster in life-and-death situations and
increasing their proficiency in the daily management of patients.

Keywords: Gamers, Response time, Smartphone, Students, Technology.

**Introduction**

In recent times, technology has influenced different circles of our lives like never before in our history. Technology has had an impact on many things and the gaming sector is no exception. Regular gamers are likely to play a more extensive scope of game classes than non-daily gamers. (1) With technological advances occurring every day in the gaming industry, it is sheltered to state that gaming is setting down deep roots. Reaction time is defined as the period of time between the detection of a stimulus at a sensory receptor and the performance of the appropriate response by the effector organ. (2) The agility and the ability to deal with different stimuli and situations like driving are better in people who have a good reaction time. Good response time enables us to be agile and proficient with regards to reacting to improvements and circumstances like playing sports, having a discussion, etc. (3–5) In a study conducted on 711 individuals, it was found that people involved in Virtual reality gaming had a 20 percent decrease in reaction time as well as an increase in accuracy. (6) Dye et al. also proved that involvement in video gaming leads to a reduction in reaction time without compromising on accuracy and the increase in speed was observed in various tasks of daily life besides gaming. (7) Different studies have shown that people who play more video games tend to have a better reaction time. (8) A faster response time while playing virtual reality games definitely translates into a better reaction time in daily life. Certain studies have found that playing computer games helped improved a wide assortment of general aptitudes that can help with regular exercises like performing various tasks, perusing little print, monitoring companions in a group, and exploring around town because of the expanded affectability of surroundings in gamers. (9) In the field of medicine, quick response is almost always essential in making life-and-death decisions, especially in an emergency setting. Since reaction time can be enhanced using gaming, it can be used by medical students as well as doctors to help them react and make critical decisions faster. A study of the relationship between reaction time and different games
may help developers make suitable games for people and will also help in understanding the positive effects of gaming. The primary objective of this study was to observe an association between playing mobile games and reaction time among students aged 18-25 years. The variation in reaction time with the types of games played, time spent on playing games, the age at which the person started playing as well as the time of the day at which the games were being played were also studied.

**Material and Methods**
This is a case-control study in which students of the University College of Medical Sciences, Delhi aged between 18-24 years were included after they consented to participate. No exclusion criteria were defined. A sample size of 94 was taken in this case-control study. To calculate the sample size, we used a case-control design and after reviewing previous studies, (10) we found that the mean reaction time in gamers is 301.836 milliseconds and the mean reaction time in non-gamers is 346.326 milliseconds with standard deviations of 10.207 and 5.595 respectively. Using these values in Stata 13 software, we calculated the sample size of 34 gamers to 34 controls to correctly identify this sample size with a power of 80% and with an acceptable error limit of 0.05. In addition, we also evaluated and assessed the data in the statistical analysis plan by doing a regression analysis using the amount of time spent on gaming as a linear variable and using the co-variates and the risk factors envisaged in the study as independent variables. We invited students to complete an online screening form using the Google platform. Based on the responses to this form, we included all the responders who qualified as per our definition of “gamers”. Then we included age, gender, and semester-matched students in a 1:1 ratio as "non-gamers".

While there were no previous studies available to determine what percentage of students in medical schools would qualify the definition of gamers, our best estimate based on informal conversations with students was that almost one in three students indulges in playing games enough to fulfill our definition. In addition, we assumed that only about 50% of students would respond to our initial screening request, and estimated that to identify 34 gamers, we were required to reach out to 204 students. Hence, we planned to reach out to students across two student batches (from years 2017-18, a total strength of 300) to enable us...
to identify 34 responders who are “gamers”.

A questionnaire was made to assess the use of mobile games by the students. All the data that was required for the study was included in the questionnaire. Their reaction time was calculated using two different approaches to reduce bias. The first method, i.e., tap reaction time was calculated using an online app “Human Benchmark” (11). The participant was asked to tap the screen as soon as the color on the screen changed. Five attempts were recorded and the average was calculated. In the second test (reaction time ruler test), the time taken by the participant to react by measuring the distance the ruler drops before the participant caught it was tested. Five attempts were recorded and the average was taken. From this information, the reaction time was formulated.

Unpaired t-test was applied to compare the reaction time of gamers and non-gamers. A gamer was defined as a person who engaged in gameplay for more than four hours a week irrespective of the type of game. On the other hand, a non-gamer was defined as a person who didn’t engage in gameplay or played for less than four hours a week. Effect of various parameters on the reaction time was also observed:

- Age of commencement of game playing
- Time spent per day
- Time spent playing in a week
- Time of the day at which the games are mostly being played
- Type of games played (Single-player, Two players, Multiplayer)

The study was approved by the Institutional Ethics Committee with reference number IEC-HR/2019/38/5R. All the personal data collected was kept completely confidential.

Results
Out of the 300 students to which the screening questionnaire was administered, 160 responded. Of these 160 responders, 47 gamers were identified based on the above-mentioned criteria. Non-gamers were matched with gamers based on age, gender, and semester.
In our study sample, 88 of the 94 participants were males and six were females. The mean age was 19.6 (+1.0). All the respondents had their own smartphones and 79.8% played games on them. The median age for starting to play was 11-15 years. Non-gamers play for less than 2 days a week whereas Gamers played almost daily. It was seen that Gamers preferred playing at night whereas the afternoon was preferable for non-gamers. The evening was a common time in which both gamers and non-gamers enjoyed playing. Action was the most preferred genre. Single-player and multiplayer games were preferred over two-player games. The basic demographic details have been summarized in Table 1.

**Tap Reaction Time**
The average reaction time of gamers was found to be 488 milliseconds (+12 milliseconds), whereas for non-gamers the mean reaction time was 535 milliseconds (+20 milliseconds). The first of the five readings taken was found to be higher than the rest of the readings. *(Figure 1)*
The effect of various parameters on reaction time was also studied. There was no significant relationship (p>0.05) between tap reaction time and the age of starting to play or the number of days spent gaming per week. There was a significant impact (p=0.002) of the time at which game playing is preferred on tap reaction time. The variety of games played had no influence on the tap reaction time of individuals.

![Figure 1 Pattern in readings of Tap Reaction Time in gamers and non-gamers.](image)

Legend: x-axis indicates the reaction time noted using tap reaction time in seconds; y-axis indicates the order of readings, 1 referring to the first reading, 2 to the second, and so on.

The reaction time was non-gamers (red) was lower than that of gamers (blue). Also, the first reading of both gamers and non-gamers in tap reaction time test was higher than the consecutive 4 readings.

**Reaction Time Ruler Test**
The average reaction time of gamers was found to be 182 milliseconds (+30 milliseconds), whereas for non-gamers the mean reaction time was 196 milliseconds (+30 milliseconds).
milliseconds). The first of the five readings taken was found to be higher than the rest of the readings. (Figure 2)

\[ \text{Figure 2 Pattern in readings of Reaction Time Ruler Test in gamers and non-gamers.} \]

Legend: x-axis indicates the reaction time noted using the reaction time ruler test in seconds; y-axis indicates the order of readings, 1 referring to the first reading, 2 to the second, and so on.

The reaction time was non-gamers (red) was lower than that of gamers (blue). Also, the first reading of both gamers and non-gamers in the reaction time ruler test was higher than the consecutive 4 readings.

There was no significant relationship (p>0.05) between tap reaction time and the age of starting to play. The number of days spent gaming per week negatively correlated with the reaction time ruler test (r = -0.270; p=0.008). There was no significant association of the time at which game playing is preferred on the reaction time ruler test. The variety of games played influenced the reaction time of individuals (r = -0.245; p=0.017). There was a significant difference in the means of reaction times of players who played two-player games (p=0.002) and multiplayer games (p=0.011) versus those who did not. Playing single-player games did not affect reaction time. The reaction time ruler test also negatively correlated (r = -0.221; p=0.032) with the age of the participants. Reaction times of gamers and non-gamers were compared using unpaired t-test. There was no significant difference in the means of reaction times when compared using the tap reaction time test. On the other hand, Reaction time ruler test results significantly (p=0.013) differed between the two groups. The results of the regression model are given in Table 2.
Table 1. Basic demographic details of the participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total participants</td>
<td>94</td>
</tr>
<tr>
<td>Number of gamers</td>
<td>47 (50%)</td>
</tr>
<tr>
<td>Number of non-gamers</td>
<td>47 (50%)</td>
</tr>
<tr>
<td>Gender of the participants</td>
<td></td>
</tr>
<tr>
<td>Number of males</td>
<td>88 (93.6%)</td>
</tr>
<tr>
<td>Number of females</td>
<td>06 (6.4%)</td>
</tr>
<tr>
<td>Semester</td>
<td></td>
</tr>
<tr>
<td>2nd semester</td>
<td>56 (59.57%)</td>
</tr>
<tr>
<td>4th semester</td>
<td>38 (40.43%)</td>
</tr>
<tr>
<td>Mean age of participants (in years)</td>
<td>19.6 ± 1.0</td>
</tr>
<tr>
<td>Number of participants with a smartphone</td>
<td>94 (100%)</td>
</tr>
</tbody>
</table>

Table 2. Linear Regression analysis for average Reaction time ruler test readings

<table>
<thead>
<tr>
<th>Exposure of interest</th>
<th>Confounders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaming status</td>
<td>Age</td>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td><strong>Crude</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-13.7</td>
<td></td>
<td></td>
<td>(-25.8, -1.6)</td>
</tr>
<tr>
<td><strong>Adjusted</strong></td>
<td>-6.5</td>
<td>-12.5</td>
<td>6.8(-1.7, 31.2)</td>
</tr>
<tr>
<td>(-25.5, -1.7)</td>
<td>(-0.5)</td>
<td>(-7.6, 31.2)</td>
<td></td>
</tr>
</tbody>
</table>

Legend: Data is presented as the coefficient of the individual independent variable in the multivariable linear regression with the respective dependent variable.

*p-value of <0.05, considered significant*
Discussion

In this case-control study of ninety-four young adults studying at the University College of Medical Sciences, Delhi, the mean reaction time of Gamers was found to be higher than the mean reaction time of non-gamers in both the tap reaction time test and the reaction time ruler test. Against the assumption, it was seen that the age of commencement of playing did not significantly affect the reaction time. The increase in the number of days a person plays per week yielded better reaction times. Also, people playing a wide variety of games had better reaction times than those who just play the same type of game every day. Time of the day at which the games are mostly being played significantly affected the tap reaction time test but had no effect on the reaction time ruler test.

Richardson et al. studied the differences in Reaction times in video game and non-video game players in 87 healthy adults aged 18-40 years in Washington using the visual oddball detection task as the stimulus and mouse-click as the reaction. They observed that the average reaction time of Gamers (people who played more than 4 hours a week) was significantly more than the non-gamers and the difference in reaction time due to gender was not significant. Another study by Rosenbaum RA found that the response time was significantly different (p=0.007) between gamers and non-gamers. (10) The findings of these studies are consistent with the findings of our study.

Bakar et al studied the effects of 12 weeks of exergaming using Xbox Kinect on the reaction time of adults (aged 18-40) in Turkey in 2018. Auditory and visual reaction times were measured using auditory and visual reaction time machines (Newtest 1000). They found that there was a significant difference in the visual reaction times at both baseline and post-intervention assessments (p=0.032). (12) This study had a wider age group than our study, which includes young adults (aged 18-25 years) only. Our study only tested the visual reaction time and was mainly focused on mobile gaming which does not include much physical activity.

Another study that analyzed the data from seven studies found that in gamers there is no speed-accuracy trade-off (the accuracy decreases with a decrease in reaction time) and also the speed-of-processing increases in not just gaming but also in other spectrums of life. (7) Gaming is also known to have a positive impact on visual cognition,
with gamers usually having better hand-eye coordination, increased visual processing in the periphery, and enhanced visuospatial memory. (13) All of our study findings can be explained by the above-mentioned studies.

**Strengths and Limitations**
This is the first study observing the impact that gaming has on the reaction time of medical sciences students thereby opening up new horizons for future improvements in medicine by incorporating gaming in training. While there have been previous studies to observe the impact that the number of hours spent on gaming has on the reaction time of individuals, the present work examines this relationship in more detail by studying the impact of several other parameters like the age of commencement of playing, time of the day at which gaming is preferred, variety of games played and types of games played. Also, most studies have used computer-based tests that could have shown bias towards gamers as they would be familiar with the interface, ours is the first study using the reaction time ruler test that tests the reaction time in a more realistic environment.

**Conclusions**
Gaming is frequently seen in a negative light, particularly by guardians and educators of kids. This investigation builds up the reality that gaming has some constructive outcomes as well, especially response time which is the main parameter being studied. The statistical distinction seen between gamers and non-gamers affirms the first theory that people qualifying as gamers would essentially record lower response times than non-gamers.

**Declarations**

**Ethics approval and consent to participate**
Not applicable.

**Conflict of interests**
There was no conflict of interest.

**Acknowledgement**
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**Authors' contributions**
YX Lee was the sole contributor of the manuscript
References


Anemia in early life (up to the age of 6 months) – Is it really a disease burden? A cross sectional study from Sub Himalayan region

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Abstract:

Background The study aims to settle the question of giving prophylactic iron to all breastfed infants (up to age of 6 months). It will determine the disease burden & clinicopathological profile of anemia in infants up to 6 months and its correlation with maternal Hb levels.

Material and Methods A hospital based cross-sectional study was undertaken for four months in all infants up to 6 months of age and their mothers getting admitted in the pediatrics ward of a tertiary health care centre in Sub-Himalayan region.

Results 42 % of infants and 64 % of mothers were found to be anemic. It was found that mothers of 74% of total anemic infants were also anemic. Also in 79% cases mothers with good ferritin stores (≥12ng/ml) also have infants with good ferritin stores (≥10 ng/ml). It was found that mothers who have not consumed adequate amount of iron in their pregnancy, 44% of them have anemic infants. Though the relationship between infant and maternal parameters is not statistically significant, the figures are large enough, indicating the need for a further comprehensive study to determine the relationship between the two.

Conclusions High rates of anemia in early life points to the need of multicentric as well as population based study so that we can collect evidence to start iron prophylaxis in this highly vulnerable developing age group of 0 to 6 months. Further higher rates of anemia in mothers warrants the strengthening in the implementation plan of IFAS to all females of reproductive age group.

Keywords: Anemia, Development, Infant, Iron deficiency
Introduction
In early years of life, iron deficiency anemia is associated with psychomotor & cognitive development problems which may be irreversible even after appropriate treatment. Hence nutrition interventions are important at many points in life course and attention to practices in the early period will bring benefits throughout [1]. Infants in early life (up to the age of 6 months) are exclusively breastfed, making the concentration of iron and lactoferrin in breast milk essential to maintain body iron levels in them. Maternal anemia could affect these concentrations in breast milk. There is evidence that even children with normal birth weight, but born of anemic mothers will have low iron reserves at birth and are more likely to develop anemia [2]. Based on recent estimates from the WHO, the prevalence of anemia is 24.8% globally and the highest rates are found in pre-school age children (67.6%) and pregnant women (57.1%) in sub-Saharan Africa.[3] Therefore knowledge of risk factors, which may be already present in early life, is essential to support control and prevention strategies. WHO committee has expressed concern that some exclusively breast fed infants may become iron deficient.[4]

Glader and Calvo et al in their work have recommended that infants who are exclusively breastfed should receive iron supplementations from 4 months of age.[5,6] Dewey et al has also recommended iron drops for breastfed infants with birth weight between 2500 g & 3000 g.[7] On the contrary Mc Millan et al and Owen et al have reported that term breastfed infants did not need supplemental iron until 12 months of age[8] and 6 months of age[9] respectively. Zavaleta et al has reported that maternal anemia did not affect breast milk iron or lactoferrin concentration at birth or during lactation.[10]

Hence there is controversy about adequacy of breast milk in maintaining optimum iron status of exclusively breastfed infants. Although iron deficiency has been reported as the most common nutritional deficiency in the world, the available literature of disease burden due to anemia in early life (up to 6 months) is limited. Thus the question of giving prophylactic iron to all breastfed infants remains far from settled. We have planned to do this study to find the status of disease burden due to anemia in infants up to the age of 6 months so that appropriate measures can be taken for early identification and treatment of anemia in these infants.
Subsequently we can plan strategies to strengthen maternal health services for improvement of maternal iron status.

**Material and Methods**

This was a hospital based cross sectional study, conducted in the Department of Pediatrics of our tertiary care institute for 4 months after taking approval from the institutional ethic committee. All the infants up to 6 months of age admitted in pediatric wards and mother-baby pairs were taken into the study group after taking informed consent. Exclusion criteria for infants were: Infants getting discharged after stay in NICU/SNCU during neonatal period, the infants with recurrent admissions and/or suffering from chronic illness eg hemolytic diseases, parvovirus infection, chronic kidney disease etc, infants on iron therapy in last one month, infants who received blood transfusion in last 2 months or infants who have undergone double volume exchange/partial exchange in last 2 months, infants with any bleeding disorder or coagulation defect and infants with any acute blood loss eg. Trauma. Exclusion criteria for enrollment of mothers were: Any chronic illness in the mother, mother who had suffered from any excessive bleeding during antenatal and postpartum period in last 2 months, mother suffering from any bleeding disorder, mothers who have received blood transfusion in last 2 months and mothers who are on therapeutic doses of iron therapy. After history taking and detailed examination, following investigations were sent for infant-mother pairs - haemogram, peripheral blood film, reticulocyte count, iron studies, vitamin B12 levels, folate levels, electrophoresis if there is evidence of haemolysis.(Fig. 1 Study design) Blood sample was taken by peripheral venipuncture method, 5 ml of blood from the mother and 3 ml blood from the infant was withdrawn under all aseptic conditions and was collected in EDTA vials and plain vials for further processing. A predesigned Performa was used for collection of data which included: Socio-demographic and socio-economic information of the households and the care giver for example; name, age, sex, marital status, Infant information included type of feeding, feeding practices, complementary feeding practices, health information and anthropometric measurements and morbidity experience of the infant. Maternal information included maternal nutrition status, iron supplementation status during pregnancy, incidences of anemia etc. Definitions utilized for the present study were - Anemia in infants: Hb
levels < 10 g/dl for infants up to 5 months (Brault-Dubuc et al.) and < 11 g/dl for infants of 6 months of age. (WHO). Iron deficiency in infants: plasma ferritin concentration <10ng/ml. Anemia in mothers: Hb <12g/dl. (WHO). Iron deficiency in mothers: plasma ferritin <12 ng/ml. (WHO). Data collected was then transferred to MS Excel sheet for further analysis. It was analyzed as mean, percentage, frequency; other statistical tests were applied as per requirement. Chi-square test was used for categorical variables. The value of P <0.05 was considered statistically significant.

Results
During our study period of four months, 1750 patients were admitted in the pediatric ward. Out of these 547 patients were infants. In the infants 398 were of ages≤6 months. Out of these 398 patients, 298 patients were excluded on the basis of exclusion criteria given in the methodology section. Our study group hence comprised of 100 infants. Majority of infants in our study group belong to age group of 0 to 2 months (38%) followed by 31% of infants each in 2.1 -4 and 4.1 -6 months. 68% of total study group were males, making ratio of male to female of about 2:1. (Fig.2) Majority of infants presented with chief complaints of cough (54%) followed by fever (51%). About 16 % of infants have history of previous hospitalization due to variable complaints. Exclusive breastfeeding was found to be the most common mode of feeding (72%). A declining trend was observed with increasing age in practice of exclusive breastfeeding as only 51% of total infants of age 4.1-6 months were exclusively breastfed compared to 79% of infants of 0-2 months. Majority of infants (63%) weighed ≥2.5 kg at birth. Majority of infant mothers: (64%) belong to upper middle class according to Modified Kuppuswamy scale. 21% of infants were found to have abnormal OFC. 54 % of infants were found to have length < -2 SD. 64% of infants were having weight below -2 SD with maximum cases above 2 months of age (44%).42% of infants were found to be anemic with maximum cases at 2.1 to 4 months of age. (Fig. 3) 97% of mothers in our study group were found to be literate. 61% of them have completed their high school and 24% are graduated. 84% of mothers have taken IFAS for adequate period. However 16% have consumed incompletely, out of which 2 % have never consumed the prophylaxis. 64% of mothers were found to be anemic.24% of them have mild anemia (11-11.9 g/dl) and 35% moderate anemia (8-10.9g/dl) and 5% severe anemia (hb<8gm/dl). (Fig. 3)
31% of mothers were found to have serum iron < 41 µg/dl. 12% of mothers were found to have poor ferritin stores (<10 ng/ml). It was found that mothers of 74% of total anemic infants were also anemic. (Table 1) Also in 79% cases mothers with good ferritin stores (≥12ng/ml) also have infants with good ferritin stores (≥10 ng/ml). (Table 1) It was found that mothers who have not consumed adequate amount of iron in their pregnancy, 44% of them have anemic infants. (Table 1)

**Discussion**

We have conducted this study at our tertiary care health centre to find out the burden of anemia in early life (up to the age of 6 months). During our study period of four months, the infants up to the age of 6 months were 22.7% of total admissions and 72.7% of total infants. Our study group comprised a total of 100 infants which were further divided into 3 age groups. Maximum number of infants were from 0-2 months (38%) followed by 31% each of 2.1-4 and 4.1-6 months. 68% of the total study group were males, making the ratio of male to female of about 2:1. These finding on age distribution are comparable to those reported by Etti Sudaryati in which 50% of study group was from 0-2 months, 31% from 2.1-4 and 19% from 4.1-6 months.[11]

Majority of infants in our study group were admitted with chief complaints of cough (54%) and fever (51%). Other illnesses reported were lethargy, diarrhea, convulsion, failure to thrive and excessive crying. An almost similar trend was witnessed by Nyamasege who found common cold to be the commonest illness in his study group[12]. In our study group 16% infants also have a history of previous hospitalization due to variable symptoms, with maximum infants admitted due to respiratory illness (38%). This could be due to the fact that infants' immunity is not well developed which makes them more prone to infections like common cold, pneumonia, etc.

In feeding practices, exclusive breastfeeding was found to be the most common mode of feeding (72%). A declining trend was observed with increasing age in practice of exclusive breastfeeding as only 51% of total infants of age 4.1-6 months were exclusively breastfed compared to 79% of infants of 0-2 months. Overall the rate of exclusive breastfeeding is higher when compared to study at Nairobi which reported 57% of exclusive breastfeeding.[12] This could be attributed to better awareness programs regarding exclusive breastfeeding being implemented in
India. However this rate is lower when compared to the recommendation of 90% given by WHO (2009) for exclusive breastfeeding among infants up to age of 6 months. Majority of infants (63%) weighed ≥2.5 kg at birth. Majority of our study population belong to the upper middle class according to the Modified Kuppuswamy Scale. Anthropometric measurements of infants were done at the time of admission and it was found that 21% of infants were of abnormal head circumference (11% microcephaly and 10% macrocephaly). The mean weight in the study sample was 4.5±1.3 kg with the lightest child weighing 2 kg and heaviest child 11 kg. 64% of infants have weight for age <-2SD, with a drastic increase in number as the age group shifts from 0-2 months (53%) to 2.1-4 months (71%). The mean length was found to be 57.4 ±6 cm with the shortest child of length 37 cm and longest child of 71 cm. 54% of the population have length for age <-2 SD with maximum number in 0-2 months of age (23%). The rates were found to be higher when compared to findings at Nairobi where only 9.2% of infants were found to be suffering from failure to thrive and only 11.2% were stunted.[12] The rates depict the poor nutritional status of infant –mother pairs in India. Reasons could range from poverty (making mothers unable to buy required amount of food) to consumption of highly adulterated foods.

Hematological profile of infants was analyzed and it was observed 42% of the study group were anemic with maximum cases in age group 2.1-4 months (38%). The mean hemoglobin level was found to be 9.9±2.7 g/dl. Results are comparable to findings of RK Chandyo et al. in Nepal where 49% infants were found to be anemic.[13] These findings were in contrast to the assumption that breast fed infants do not develop anemia as they get whatever they need from their mother’s milk. Also 8% of infants in our study groups were found to have low ferritin stores.

Majority of women in our study group are literate (97%). 61% of them have completed their high school and 24% have graduated. The values are high when compared to the national women literacy rate of 65.46% as per census 2011. Higher education rates is probably the reason for higher exclusive breastfeeding rates in our region.

Most mothers (84%) in our study group have consumed iron and folic acid supplementation for the required period of 180 days.16% mothers have consumed it for lesser duration, out of which 2% have never
consumed the prophylaxis. The results are comparable to findings at Nairobi where 73% mothers have consumed IFAS tablets for the required period of time.[12] The number are very high when compared to findings of national family health survey (2015-16) where an average of only 30.3% of mothers consumed IFAS for 100 or more days, this ranged from the lowest in Nagaland (4.4%) to the highest in Lakshadweep (82.1%).The better rates in our region could be attributed to better implementation of government schemes and better educational status of women.

Hematological profile of the mother was analyzed. 64% of mothers were found to be anemic.24% of them have mild anemia (11-11.9 g/dl) and 35% moderate anemia (8-10.9g/dl) and 5% severe anemia (Hb<8gm/dl). The figures were less when compared to results of Rita Panyang's cross sectional study in Assam which found 100 % population to be anemic with 91.6% suffering from moderate anemia and 8.4% from severe anemia.[14] The high rates of mild, moderate and severe anemia demands a due emphasis on implementation of INIPI program and health education regarding consumption of iron rich foods to bring down the prevalence of anemia among the women of reproductive age group in India.

31% of mothers were found to have low serum iron <41µg/dl.12% of total mothers had low ferritin stores (<10ng/ml).

It was found that mothers of 74% of total anemic infants were also anemic. Also in 79% cases mothers with good ferritin stores (≥12ng/ml) also have infants with good ferritin stores (≥10 ng/ml). It was found that mothers who have not consumed an adequate amount of iron in their pregnancy, 44% of them have anemic infants.

**Conclusions**

42 % of infants and 64 % of mothers were found to be anemic. Mothers of 74% of total anemic infants were also anemic. 79% cases mothers with good ferritin stores (≥12ng/ml) also have infants with good ferritin stores (≥10 ng/ml). Also mothers who have not consumed adequate amount of iron in their pregnancy, 44% of them have anemic infants. Though the relationship between the two is not statistically significant but the figures indicating anemia burden in early life, hence we suggest a multicentric as well as population based study so that we can collect evidence to start iron prophylaxis in this highly
vulnerable developing age group of 0 to 6 months. Further we suggest strengthening the implementation plan of IFAS to all females of reproductive age group.

Declarations

Ethics approval and consent to participate
Not applicable.

Availability of data and material
Not applicable.

Conflict of interests
Not applicable.

Funding
Not applicable.

Authors' contributions

References


Gap between Knowledge and Practice Regarding Surgical Attire Among Medical Students in Pakistan: A Cross-Sectional Study

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Abstract:

Background Surgical attire is an important component of maintaining a sterile operating room environment, however lack of adherence to their appropriate usage can lead to increased hospital acquired infections.

Purpose of the Study This study aims to describe the current knowledge and practice of medical students regarding surgical attire.

Methods A total number of 216 medical students with exposure to clinical rotations were administered a questionnaire based on knowledge from the medical school student handbook and American Association of Surgical Technologists Standards of Practice for Surgical Attire, Surgical Scrub, Hand Hygiene, and Handwashing. The data was analyzed using SPSS v23.0. Categorical variables were reported as a frequency and percentages and were assessed by the chi-square/ Fisher exact test.

Results Most students correctly identified the components of surgical scrubs including scrub suit (95.5%), shoe covers (95.4%), headcover (94.9%), and masks (93.9%). 82.7% of students were aware of the policy of wearing surgical scrubs off-campus, 78.7% knew the correct method of using the protective over gowns, only 52.8% knew permissible areas for wearing surgical scrubs. Students’ adequate knowledge did not translate into their practices. 57.1% of the students reported not having received any formal education on scrub use. Inconvenience (66.9%), was cited as the most common cause of scrub re-use and unsafe practices.
Conclusions  Medical students have sufficient knowledge regarding surgical scrubs which does not translate into their practices. The majority of the students report as not having received any formal training regarding surgical scrub usage.

Keywords: Medical students, Surgical Scrubs, Practice, Knowledge

Introduction  Healthcare-Associated Infections (HAIs) are a major cause of morbidity, mortality, and economic burden(1,2), increased length of hospital stay(3,4), and the emergence of multidrug-resistant bacteria(5). The risk of developing these HAIs is substantial in both the patients as well as health care workers (HCWs), including the medical students(6,7). A major contributor of HAIs are surgical site infections (SSI) especially in the developing world(8).

Surgical scrubs are an important component of the healthcare provider’s attire and were primarily introduced to maintain the sterility of a surgical setting. Various measures have been enacted to decrease the occurrence of SSIs involving the regulation of the attire worn by the operating room (OR) staff. The Association of Perioperative Registered Nurses (AORN) made several recommendations in 2015 regarding appropriate surgical attire(9). Literature suggests that if surgical scrubs were to be worn in the appropriate way such as tucked, majority of the students report as not having received any formal training regarding surgical scrub usage.

The surgical attire that should be worn in the semi-restricted and restricted areas of the surgery department includes the head cover, mask, scrubs, warm-up jacket, and shoes(11). A publication by the Indian Society of Critical Care Medicine outlined how to prevent hospital acquired infections, by highlighting where and when to wear scrubs. For example, changing into normal attire
before leaving a designated sterile area. This has been shown to decrease the incidence of SSI (surgical site infection), or to decrease the bacterial counts of the OR floor(12). Studies have concluded increased bacterial colonization on surgical attire that wasn’t used properly(13).

As an essential component of medical training, medical students are often involved in direct patient care. They can be a potential source of harboring bacteria(14) and are considered to be super-spreaders(15). Medical students are the youngest members of a surgical team and are often less knowledgeable than other members of the operating room staff(16,17). A study from Pakistan showed that medical students have limited knowledge regarding infection control(18). A Lack of knowledge regarding standard protocols may lead to unsafe practices which further adds to the burden of healthcare associated infections.

Understanding the current level of medical student knowledge and practices can help us explore a potential area where targeted interventions can improve compliance with standard protocols. Globally, data regarding medical student knowledge of surgical scrubs and its correct usage remains scarce, especially in lower- and middle-income countries. There is already a higher burden of HAIs in developing countries, therefore identification of deficiencies can help in improving current practices. In this study, we aim to describe medical students’ knowledge and practice regarding surgical attire, specifically the surgical scrubs.

**Objective**
To describe medical students’ knowledge and practice regarding surgical attire.

**Methods**
A descriptive cross-sectional study which was conducted among medical students enrolled in a Bachelor of Medicine, Bachelor of Surgery program (MBBS) at a private medical school in Pakistan. Ethical approval was obtained from the ethical review committee of the institution and the study was performed in accordance with the ethical standards as laid down by the Declaration of Helsinki ethical standards. Students who were currently rotating in clinical years (3rd, 4th and 5th year) and had completed at least one surgical rotation were included in the study. Students were approached by the
data collectors for a period of 1 month from 8th June 2018 to 8th July 2018, to fill out an anonymous, newly formulated, self-administered questionnaire. Questionnaire did not contain any personal identification except year of study, gender and residence. Questionnaires were marked by serial numbers and responses were collected anonymously, filled in private, away from the data collector, to reduce knowledge bias. Participation in this study was completely voluntary. An informed consent form was signed by the participant, which clearly stated the purpose and objectives of the study. Information was only available to the research investigators. The Questionnaire had two sections, namely a “Knowledge” and “practice” section, and the questions were based on international guidelines such as the American Association of Surgical Technologists (AST) Standards of Practice for Surgical Attire, Surgical Scrub, Hand Hygiene, and Handwashing(21). Surgical attire was defined as a protective garment designed to be worn by the doctor, nurse, and others in the operating room including, but limited to, the shirt and pants worn by those who scrub in for surgery. Correct knowledge and practice was recorded for individual items of the surgical attire (for e.g. correct usage of gowns, head covers etc) and was based on an outline described in the Student Handbook, dress code policy of the institution and (AST) Standards of Practice for Surgical Attire. The questionnaire was contextualized, and the cultural sensitivity and quality of the content were validated by surgeons at the institute. The sample size was calculated via calculator.net. As this is a previously untested population in our subject of research, the prevalence was estimated at 50% to get the maximum sample size, which was found to be 169. Data from the questionnaire were entered and analyzed using SPSS 23. Categorical variables such as correct usage of individual items of the surgical attire (e.g. head covers, shoes, surgical scrubs, protective overgown etc.) were reported as a frequency and percentages and were assessed by the chi-square/ Fisher exact test. Correct knowledge and practice patterns were also compared among participants who received formal education regarding scrub etiquette vs those who did not. A p-value of <0.05 was considered significant.

Results
A total of 216 students were administered the questionnaire, from which 196 provided complete information. Of the 196 students, 96 (48.7%) were males and 101 (51.3%)

were females. Of these, 80 (40.8%) were students living off-campus, and 116 (59.2%) were living on-campus, at the hospital’s hostel buildings.

**Knowledge**

Our results showed that almost all the participants had good knowledge regarding the major components of surgical scrubs including surgical scrub suit (95.9%), shoe covers (95.4%), head covers (94.9%), and masks (93.9%). In terms of surgical scrub usage, a proportion of respondents were knowledgeable as shown below:

Surgical scrubs: 52.8% were able to correctly identify the areas where surgical scrubs were permissible; 82.7% knew that surgical scrubs were not permissible to be worn off-campus.

Protective gowns: 81.3% of the students knew that protective gowns need to be worn over surgical scrubs before leaving the operating room; and 78.7% of the students were aware of the correct method of using a protective gown (i.e tied at 3 ends).

Laundering: 78.2% of the students knew that surgical scrubs should be laundered through hospital designated laundry services.

Shoe Covers: 80.2% of students knew the appropriate colors of outside shoe covers while 92.3% of students knew to change the shoe covers immediately after surgery if contaminated.

Masks: Most students (92.4%) knew that masks must be discarded and not dangle in the neck.

**Practices:**

The percentage of students reporting correct practices regarding important components of surgical scrubs are shown in table 1 (see Table 1). The percentage of students reporting correct practices was lower than the percentage of students reporting correct knowledge. Gaps between knowledge and practice of medical students regarding surgical scrubs are depicted in **figure 1** (see figure 1).

![Figure 1: Gaps between Knowledge and Practices of Medical Students regarding Surgical Scrubs](image-url)

Practices were most deficient in the cover gown and shoe cover usage. Among the 80% of students who do
wear the cover gown when leaving the OR (vs those who do not), only 13.2% of them wear it in the proper way (tied at back and waist). While 80% of the students reported being able to correctly differentiate between white outside shoe covers and blue inside shoe covers, only 39% were appropriately switching between the two and utilizing the outside shoe covers. Out of 35.5% of students who used the surgical scrubs as nightwear, 9.6% did not change into a new pair of scrubs before entering the Operating Room.

Table 1. Students with Correct Practices regarding Surgical Scrubs

<table>
<thead>
<tr>
<th>Practice components</th>
<th>Correct Practice Responses Percentages (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriately wearing a scrub protective overcoat while leaving the OR</td>
<td>80.6 (158)</td>
</tr>
<tr>
<td>Using a fresh mask while returning to the OR (from outside)</td>
<td>76.5 (150)</td>
</tr>
<tr>
<td>Surgical scrub use off campus*</td>
<td>75.1 (148)</td>
</tr>
<tr>
<td>Surgical scrub use as nightwear*</td>
<td>64.5 (127)</td>
</tr>
<tr>
<td>Re-entering the OR with a fresh pair of surgical scrubs</td>
<td>19.3 (38)</td>
</tr>
</tbody>
</table>

The results depicted that 57.1% of students reported not having received formal training regarding surgical scrub use. Only 12.7% of students read up on proper guidelines regarding surgical scrub detailed in the student handbook or institution’s Dress code policy regarding operating room attire. 52% of the participants reported that they have neither received formal training nor have read up on the rules and procedures in the handbook. Students who said that they received formal education had higher responses for the correct use of protective over-gown (P-value=0.038) and shoe covers (P-value of 0.016).

Area of residence and the “Receipt of Formal Education regarding scrub etiquette” was significant for unsafe practices using Chi-Square analysis. On-campus students were 14.2% more likely to use scrubs as nightwear compared to students living off-campus (P-value=0.04). Off-campus students were 17.7% more likely to use surgical scrubs off-campus when compared to those who reside in the hostel (P-value=0.005).

With regards to the reasons for gaps in knowledge and practice, the major reasons reported were inconvenience (66.9%), lack of appropriate scrub sizes (63.3%), and the risk of theft from changing rooms (83.7%) contributed to unsafe practices by the students. ext for this Chapter(2,3).
Discussion

Medical student’s knowledge regarding components of surgical scrubs is sufficient however their knowledge regarding surgical scrub usage is deficient. Practice of surgical scrub usage is majorly incorrect and in areas where the knowledge is sufficient practice remains insufficient. More than half the students believe that they have never received any formal education/training regarding surgical scrub use.

Our study showed that most students were aware of the general components of the surgical scrubs, however, they lacked knowledge in the details of its usage. Furthermore, medical students’ knowledge did not appear to translate into their practices. Even in areas where knowledge was sufficient, practices remained sub-par. The most striking was the majority of the students reporting as not having received formal education training despite having received mandatory orientation at the beginning of the clinical years. Studies from regional neighbors including India and China showed similar results. Students had sufficient knowledge regarding provider attire, however, when probing for details, the level of knowledge decreased significantly(19–21). This provides insight into medical student’s lack of importance given to details of protocols. One way of addressing this problem is to teach medical students the implications of unsafe practices. For example, while teaching students about the correct method of wearing a protective gown while leaving the operating room, it would be beneficial to emphasize the rate or risk of HAIs associated with incorrect practices. Furthermore, a special emphasis on the details of the protocols may curb the deficiencies in the knowledge. These “how-to” instructions can be displayed in key areas such as changing rooms, entrances, and exits of the ORs, etc, in the form of posters or distributed as flyers or manuals. These instructions must be included as part of the undergraduate curriculum and may be tested in objective structured clinical examinations (OSCEs) to increase their knowledge(22).

Our study highlighted that medical student’s knowledge did not translate into their practice. This is consistent with a study conducted in India that showed that a significant proportion of medical students were not laundring their lab coats routinely, despite being aware that their white coats harbored pathogen bacteria (23). This shows that merely
Educating medical students is not enough, as sufficient knowledge does not translate into good practices. Institutions should make efforts to explore the reason behind these negligent practices. As in our study, medical students reported “inconvenience” as the most common reason for having unsafe practices. Reasons can differ based on individual institutions’ circumstances. Therefore, it is important to explore how to minimize inconvenience for medical students so that their practices can be improved.

Interestingly, more than half of the students believed that they have never received any formal education/training regarding surgical scrub. This is of concern as all the students receive training at the beginning of the clinical years as well as before starting their first surgical rotation. Furthermore, since the knowledge regarding most components of surgical scrubs in medical students is adequate, a lack of formal training would have not produced such results. Students may have forgotten the initial training they received (as it was on time only) or may have not attended it voluntarily. Similarly, a study conducted in Brazil showed that medical students were generally dissatisfied with the previously received instructions on exposure prevention(24). Furthermore, a study from the United Kingdom found that half the students thought that there was not enough emphasis on infection control in their curriculum(27). These findings highlight the disadvantage of one-time training which does not increase(24) or improve medical student knowledge in the long term(25,26). Once missed, it cannot be rescheduled and students resort to learning from their peers. A recommended method to bridge this gap is through more frequent refresher courses or arranging infection control workshops.

This study has major implications in the field of medical education. Our results emphasized the need to integrate standard guidelines regarding surgical scrubs into the current medical undergraduate curriculum. Medical institutes shall ensure that content targeting correct surgical scrub use guidelines becomes a mandatory part of surgical clerkship examinations or OSCEs. Furthermore, state licensing exams and international accreditation bodies should monitor the institutional undergraduate curriculum. Quality control regulation bodies can penalize hospitals that fail to display surgical scrub guidelines in ORs and related
areas such as changing rooms, recovering rooms, entrances, and exits. Further research is needed to study the medical students’ practice across the region and identify similarities and differences in their knowledge and practices. Furthermore, medical student’s attitudes need to be explored to learn the reasons behind such behaviors. It is worth exploring a direct link between the misuse of scrubs leading to growth and the possible transmission of pathogens.

Our study is the first study within the region to assess the knowledge and practice of medical students regarding surgical scrubs. The study also attempts to explore why practices or knowledge may be lacking, as opposed to simply reporting the deficit. Our biggest limitation was using a self-created questionnaire, however, researchers created the content based on standard guidelines and ensured content validation by the surgeons and medical students of the university. Data were collected from a single institute and may not represent the entire medical student population of the country. Therefore, multi-institution, large sample studies should be conducted to evaluate the knowledge and practice patterns of medical students regarding the surgical attire.

**Conclusions**

Medical students had good knowledge regarding surgical scrub components but lacked details regarding permissible areas where scrubs can be used. This adequate knowledge however did not translate into their practices. The findings of our study suggest that the knowledge and practices of medical students regarding surgical scrubs need improvement. A one-time training at the beginning of the clinical years does not suffice. Training should be integrated into the curriculum and more repeated and structured training is required to improve medical student practices regarding the appropriate use of surgical scrubs. These results can potentially contribute to shaping the curriculum regarding infection control measures in medical colleges of -lower and -middle-income countries that could be mandated to medical schools and as continuing education for doctors in practice. Thus, infection control is not just an issue of individual practice, it is also relevant to the policy at national levels. A coherent policy to mandate infection control training by the medical students can evoke a trickle-down effect on other professions, health care agencies, as well as national and international
health care outcomes which may reduce the burden of HAIs in developing countries in the future.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Availability of data and material**

Not applicable.

**Conflict of interests**

All authors declare that they have no conflicting interests.

**Funding**

This study did not receive any internal or external funding.

**Authors’ contributions**

H Shahzad was the sole contributor of the manuscript.

**References**

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The Relation Between Family-Centered Approach toward Medication Adherence of Antihypertensive Drug Consumption in Indonesia
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Abstract:

This study focuses on examining the relation between family-centered approach and medication adherence in antihypertensive drug consumption in Indonesia. 87 participants aged more than 25 years, having a family and undergoing treatment with an antihypertensive drug for more than 1 month were asked to fill out questionnaires or were interviewed to obtain information about gender, level of education, family history of hypertension, family-centered approach, history of visit from community health center health worker in relation with Indonesian Health Program by Family-Centered Approach, physical activity, and medical adherence without any lost data. Obtained data was then categorized in several groups. Chi-square test showed that family-centered approach is significantly improved antihypertensive drug medical adherence (p=0.006). Participants with a higher family-centered approach showed a four times higher adherence to antihypertensive drug therapy (OR 4.34; 95% CI: 1.45–12.99). However, this study cannot explain the optimal family-centered approach to improve antihypertensive drug therapy medical adherence.

Keywords: Family-centered approach, Medication adherence, Antihypertensive drug, Hypertension
Introduction

In 2016, The Ministry of Health of Republic of Indonesia published “Pedoman Umum Program Indonesia Sehat dengan Pendekatan Keluarga (PIS-PK)” or General Guideline of Indonesian Health Program by Family-Centered Approach. This program was established based on the 5th Agenda of Nawa Cita (President of Republic of Indonesia Agenda): to increase the quality of life in Indonesia. There are 12 prime indicators that indicate family health. One of the indicators that attracted the researcher’s attention was the patients with hypertension (high blood pressure) who took regular medicine.\(^1\)

Based on Riset Kesehatan Dasar or Basic Health Research by The Ministry of Health of Republic of Indonesia in 2013, the prevalence of hypertension in Indonesia decreased from 31.7% in 2007 to 25.8% in 2013.\(^2\)

This could be the result of increased medication adherence in the patients or due to different blood pressure measurement tools. In 2014, the hypertension prevalence in West Java reached 13,612,359 people or 29.4% of the total population.\(^3\)

Nevertheless, based on interviews with hypertensive patients who have been taking medicine, there is an increase in the prevalence of hypertension from 7.6% in 2007 to 9.5% in 2013.\(^2\) Furthermore, Center of Data and Information in Indonesia stated that hypertension control is not adequate although many effective drugs are available.\(^3\) Hence, researchers are interested to know how a family-centered approach was related to blood pressure control in hypertensive patients.

Xu et al. in 2018 conducted research about the intervention that improves medication adherence of hypertensive patients in China. The study found that interventions such as blood pressure self-monitoring, alarm control, and intervention duration could raise the medication adherence and lower the blood pressure of hypertensive patients.\(^4\)

The prevalence of hypertensive patients who are undergoing treatment goes on increasing because hypertension treatment is not controlled. This could be aggravated by the problem of medication adherence. At the same time, the government is currently promoting the “PIS-PK”. This program attempts to lower hypertension prevalence in patients who are taking medicine. Therefore, we need to study the relationship between family-centered approach and adherence to take antihypertensive drugs.
Methods

Research Design
This research was conducted in several “Pusat Kesehatan Masyarakat (Puskesmas)” or public health centers in Indonesia from November 2018 to May 2019. This was an observational study with a cross-sectional analytic design. The independent variable in this research was family-centered approach and the dependent variable was medication adherence towards antihypertensive drugs. The confounding variables included age, gender, physical activity, level of education, and family medical history of hypertension in participants.

Sample Size
Hypertensive patients over 25 years old who were advised to take antihypertensive drugs in Indonesia, with exclusion criteria of not having a family, living alone, or having taken the drug for a time period less than or equal to 1 month. The sampling technique in this research was stratified random sampling which was conducted multicenter at several public health centers in Indonesia. The minimum sample size refers to the data from Sankar et al in 2015, which is that 74% of patients do not adhere to treatment.\(^5\) Thus, the minimum sample size for this study was 77 people using the following formula.

\[
n = \frac{4pq}{d^2}
\]

\[
n = \frac{4 \times 0.74 \times 0.26}{(0.1)^2}
\]

\[
n = 76.96 \approx 77
\]

\(n\) = number of minimum sample size

\(Z\alpha\) = confidence level 95% = 1.96

\((Z\alpha)^2\) = \((1.96)^2 \approx 4\)

\(p\) = proportion of who adhere to take medicine

\(q\) = 1 - \(p\) = proportion of who do not adhere to take medicine

\(d\) = fixed margin of error = 10%

Data Collection
The data collection was carried out either through interviews with participants followed by filling in the answers on a questionnaire, or the participants directly filling in the questionnaire assisted by the researchers which took about 10 minutes. There was no risk of inconvenience toward sampling methods. The participants had the right to refuse to fill in the questionnaire if they were not willing to. The data was analyzed using the chi-square statistical test through the IBM SPSS Statistics Base 20.0.

Results

Demographic characteristics
There were 87 hypertensive patients who met the inclusion criteria in this study. All patients agreed to be interviewed and no data was lost during the data analysis process. Thus, the level of validity for data analysis was 100%. The figure below shows the distribution of the study participants' regional origins from across Indonesia.

![Figure 1 Distributions of the participants](image)

Sociodemographic characteristics of the participants in this study are listed in Table 1. The majority of study participants came from the adult age group (56%); women (59.8%); more than half of the research participants took tertiary education, namely in the range of junior high schools to tertiary institutions (58.7%); there was a family history of hypertension in the majority of study participants (56%); physical activity was generally low (54%). Physical activity was assessed through a physical activity questionnaire. Physical activity assessment was in accordance with the guidelines on the International Physical Activity Questionnaire; for analysis purposes, the category of moderate physical activity was combined with high physical activity.

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Frequency, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Adult (26 - 59 th)</td>
<td>49 (56)</td>
</tr>
<tr>
<td>Elderly (&gt;59 th)</td>
<td>38 (44)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35 (40.2)</td>
</tr>
<tr>
<td>Female</td>
<td>52 (59.8)</td>
</tr>
<tr>
<td><strong>Education Level</strong></td>
<td></td>
</tr>
<tr>
<td>Low (not in school yet - elementary school)</td>
<td>36 (41.3)</td>
</tr>
<tr>
<td>High (junior high school - college)</td>
<td>51 (58.7)</td>
</tr>
<tr>
<td><strong>Family history of hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49 (56)</td>
</tr>
<tr>
<td>No</td>
<td>38 (44)</td>
</tr>
<tr>
<td><strong>Physical Activity</strong></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>47 (54)</td>
</tr>
<tr>
<td>High</td>
<td>40 (46)</td>
</tr>
</tbody>
</table>
Family-centered approach assessment
The independent variable in this study was a family-centered approach to patients with hypertension. The family-centered approach was assessed using a questionnaire on the subject’s perception of the family approach (Perceived Social Support Scale-Family) which was coined by Procidano et al in 2014. There are 20 questions that refer to feelings and experiences at one time or another regarding relationships with families. For each question, there are three answer options: Yes, No, and Do not Know. The family-centered approach assessment is divided into high and low family approaches. Research participants were also asked to answer the questionnaire on Monitoring and Evaluation of the Implementation of Family Visits and Early Intervention at the Community Health Center, which is one of the government programs, namely the Program Indonesia Sehat dengan Pendekatan Keluarga (PIS-PK). However, more than half (62.1%) of study participants felt that they had never been visited by a Puskesmas related to PIS-PK.

Medication adherence assessment
The participants were then asked to answer a medication adherence questionnaire (Medication Adherence Questionnaire) by Culig et al in 2014. For analysis purposes, the adherence category was combined with high adherence. Chi-square test was performed on variables to determine the relationship between each variable and adherence to antihypertensive treatment. The results of the chi-square test are listed in Table 2. Of all variables, only the family-centered approach showed a relationship with medication adherence ($p = 0.006$). The odds ratio (OR) was then calculated with a confidence interval (CI) of 95%. Participants with a high family approach were four times more likely to have high medication adherence (OR 4.34, 95% CI: 1.45–12.99).

Discussion Association between the family-centered approach and medication adherence
This study aims to determine the relationship between family-centered approach and adherence to consumption of antihypertensive drugs. Based on data analysis, there is a directly proportional relationship between family-centered approach and adherence to the consumption of antihypertensive drugs. Patients treated with a family-centered approach were four times more likely
to have high adherence to antihypertensive drug consumption.

**Table 1. Chi-square test**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Medication Adherence</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low, n (%)</td>
<td>High, n (%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>18 (51.5)</td>
<td>17 (48.5)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>33 (63.5)</td>
<td>19 (36.5)</td>
</tr>
<tr>
<td>Age</td>
<td>Adult</td>
<td>31 (63.3)</td>
<td>18 (36.7)</td>
</tr>
<tr>
<td></td>
<td>Elderly</td>
<td>20 (52.6)</td>
<td>18 (47.4)</td>
</tr>
<tr>
<td>Education Level</td>
<td>Low</td>
<td>22 (61.1)</td>
<td>14 (38.9)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>29 (56.9)</td>
<td>22 (43.1)</td>
</tr>
<tr>
<td>Family History of Hypertension</td>
<td>Yes</td>
<td>30 (61.2)</td>
<td>19 (38.8)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>21 (55.3)</td>
<td>17 (44.7)</td>
</tr>
<tr>
<td>PIS-PK</td>
<td>Yes</td>
<td>22 (66.7)</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>29 (53.7)</td>
<td>25 (46.3)</td>
</tr>
<tr>
<td>Family-centered Approach</td>
<td>Low</td>
<td>21 (80.7)</td>
<td>5 (19.3)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>30 (49.1)</td>
<td>31 (50.9)</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>Low</td>
<td>27 (57.4)</td>
<td>20 (42.6)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>24 (60)</td>
<td>16 (40)</td>
</tr>
</tbody>
</table>

Implementing the family-centered approach requires instruments, communication forums, and community involvement. At the family level, instruments such as Family Health Profile (Prokesga) and a Family Information Package (Pinkesga) are needed. With regard to contact with families, communication forums are needed, such as family home visits, focus group discussions, counseling opportunities, and community forums. Community involvement can be pursued through health cadres and community organization administrators.\textsuperscript{1} In a study conducted by Mengendai, et al. It was found that one of the factors that influence adherence to medication was family support. Family support was defined as the form of attitudes, actions and
treatment by the family towards sufferers of the disease. Another study by Shen et al. showed similar results, in which a positive effect was found between family-centered approach and treatment adherence in hypertensive patients in China (OR: 1.74, 95% CI: 0.91-3.32). Similar results were also found in studies with different disease variables, for example the study conducted by Nayeri et al., which was done on stroke patients. Study by Nayeri et al compared groups given a family-centered approach program with a control group. showed that the level of adherence to the drug regimen was higher in the treated group than in the control group (p <0.001). Another study by Lyon et al. also showed an increase in adherence to therapy in 91% of HIV-infected adolescents who were treated with family-centered approach. Based on the results of the mentioned studies, a family-centered approach can improve adherence towards taking medication in not just hypertensive patients, but in multiple other conditions as well. The use of the family-centered approach in medicine is also one of the programs being promoted by the government in Indonesia, namely PIS-PK. However, this study could not determine the effect of PIS-PK on increasing medication adherence because only a few participants had ever been visited by Puskesmas related to PIS-PK.

Limitations of the study
There are several limitations to this study. First, the data obtained in this study was not evenly distributed from all regions of Indonesia. Thus, the results of this study may not be relevant to all regions of Indonesia. Second, there is no further assessment of the family-centered approach questionnaire used. Different results may be obtained in studies using other family approach questionnaires. In addition, there is no standardization from different studies to anticipate differences in perceptions of the questionnaire by each research participant. This study has also not been able to determine the optimal family-centered approach for improving medication adherence. Furthermore, future studies are needed to find the optimal family-centered approach which can be applied on a daily basis in order to increase adherence to consumption of antihypertensive drugs.

Conclusions
This study shows the relationship between family-centered approach and adherence to consumption of antihypertensive drugs. This study found that hypertensive patients
with higher levels of family-centered approach were four times more likely to be adherent to taking medication than hypertensive patients with low or no family-centered approach. Further research is needed to determine the optimal type of family approach to be carried out daily for increasing adherence to consumption of antihypertensive drugs.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Availability of data and material**

Not applicable.

**Conflict of interests**

All authors declare that they have no conflicting interests.

**Funding**

This study did not receive any internal or external funding.

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A Cross-Sectional Study of Behaviors Towards Sun Protection among Filipino using Filipino-Translated Version of Readiness to Alter Sun-Protective Behavior Questionnaire (RASP-B)

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Abstract:

Background From 2011 to 2014, there were 866 cases of non-melanoma skin cancer and 107 cases of melanoma skin cancer that had been documented by the Philippines Dermatological Society. Despite its low incidence, the disease is fatal yet addressable by applying sun-protective behaviors.

Objective To determine the behaviors towards Sun Protection among patients using Readiness to Alter Sun-Protective Behaviour Questionnaire (RASP-B) in the Department of Dermatology in Ospital ng Maynila Medical Center.

Methods A cross sectional study, was conducted among Filipino adult patients consulting at the Department of Dermatology of Ospital ng Maynila Medical Center Outpatient Department. Readiness to alter sun-protective behavior (RASP-B), a 12-item questionnaire originally developed by Borschmann, was translated into Filipino language (Tagalog) and validated with Cronbach’s Alpha for use in the study.

Results A total of 278 respondents participated in the study. Majority of the patients were already in the action state with a total of 221 patients (79.50%). There were more males in the precontemplation
(9.52%) and action state (80%), there were more females in the contemplation state (15.61%). Sex, civil status, and body mass index were found to be not associated with the state of change of the participants.

**Conclusions** The feasibility and validity of using a translated version of the RASP-B questionnaire in Filipino language to determine the readiness to change sun-protective behaviors among Filipino adult patients was assessed in this study. Findings revealed that a majority of the respondents were already in the action stage and only a few were still on the precontemplation stage, which are findings that are far from what is expected.

**Keywords:** Sun Protection Behaviors, Readiness to alter sun-protective behavior
Introduction
Skin cancer is an abnormal growth of skin cells. It most often develops on areas of the skin exposed to the sun light. Skin cancer affects people of all colors and races, although those with light skin who sunburn easily have a higher risk.¹

The escalation in the incidence of skin cancer over the past decades is strongly related to outdoor activities and recreational exposure. Overexposure to Ultraviolet light plays a major role as the underlying cause. As ozone levels are depleted, the atmosphere loses more and more of its protective filter function and more solar UV radiation reaches the Earth’s surface. It is estimated that a 10 percent decrease in ozone levels will result in an additional 300,000 non-melanoma and 4,500 melanoma skin cancer cases.²

According to WHO, the incidence of skin cancer, both melanoma and non-melanoma are rising worldwide. Current estimates are that one in five people will develop skin cancer in their lifetime. It is estimated that approximately 9,500 people are diagnosed with skin cancer every day. Research estimates that nonmelanoma skin cancer, including basal cell carcinoma and squamous cell carcinoma, affects more than 3 million annually. In the Philippines, the annual mortality rate per 100,000 have been affected by malignant skin melanoma since 1990, an average of 4.2% a year. In 2013, the peak mortality rate for women was higher than that of men which was 5.6 per 100,000 men.² There were 866 cases of non-melanoma skin cancer and 107 cases of melanoma skin cancer recorded from 2011-2014 in the Philippines Dermatological Society Health Information System.³

Host factors that confer an increased risk include skin type (Fitzpatrick skin types I and II at increased risk), number of melanocytic nevi, presence of dysplastic nevi, and skin cancer in a first-degree relative. Although most of the population of the Philippines have Fitzpatrick skin types III or IV, they may also have risks of both sunburn and skin cancer.

It has been suggested that around 80% of skin cancer cases are preventable with the implementation of Sun protection measures and appropriate behaviors. Sun-protection behavior and attitude begin at a young age; therefore, it is important to heighten the awareness in adolescents. Since children and adolescents are an important target group for skin cancer prevention, developing comprehensive programs including physical, social, and
organizational environments that promote UVR protection. Educating young people about Sun safety is strongly recommended. Sun protection, including wearing protective clothing, staying in the shade, avoiding the sun in the middle of the day, and regularly applying sunscreen when outdoors are therefore important public health messages for skin cancer prevention. Sunscreen is a well-documented method of preventing skin cancer. It has been reported to reduce the carcinogenic effects of sunlight on human skin by reducing the amount of UV radiation that can penetrate the skin by reflecting, absorbing, or dispersing sunlight. As a result, applying sunscreen can protect against sunlight-associated damages. The public health care providers should be educated about the effects of long-time sunlight exposure and the advantages of sun protection.

Education is important to reflect advances in knowledge regarding protection against the potentially harmful effects of the sun so that changes in behavior patterns are produced. Education is the key in raising awareness. Studies have been carried out in many countries to determine awareness levels of the effects of the sun, of skin cancer and of behavior regarding sun protection, usually with the intention of creating effective health campaigns to prevent skin cancer. However, there is no study using RASP-B reported in the Philippines. Hence, this study aims to determine the behaviors towards Sun Protection among patients seen in the Department of Dermatology Ospital ng Maynila Medical Center.

Material and Methods

Study Design
A cross sectional study was employed for this study.

Study Population
This study was done among Filipino adults who consulted at Ospital ng Maynila Medical Center Outpatient Department. The age range was at least 18 to 35 years old. This was a group of individuals likely to engage in risky sun exposure behaviors and therefore a particularly relevant group to examine. The exclusion criteria include subjects who were unable to understand either Filipino and/or English and unwilling to participate in the study.

Sample size Estimation
Based on the census of Ospital ng Maynila Medical Center, Metro Manila in 2018, there were a total of 13200 patients who consulted in the Department of Dermatology. Epi Info 7 software, the minimum sample size
was computed using 50% expected frequency and 95% confidence level. A minimum sample size of 373 patients will be included in the study.

**Research Instrument**

RASP-B contains 12 items and is designed to assess which stage of change respondents are regarding sun protective behavior. Four items refer to each of the precontemplation, contemplation and active stages of the transtheoretical model of behavior. Respondents will be asked to endorse one of 5 options ranging from "strongly agree" to "strongly disagree". To calculate these stage scores, responses to each stage of change item were scored as follows: 

-2 = Strongly disagree, 
-1 = Disagree, 
0 = Neither agree nor disagree, 
+1 = Agree, and 
+2 = Strongly agree. 

There were four statements corresponding to each stage and therefore the total score for each stage ranged from -8 to +8. One participant obtained a score of zero for each of the three stages (by endorsing "0 = Neither agree nor disagree" for all 12 of the stages of change items in the questionnaire) and was consequently not assigned to any of the three stages. (See Table 1)

<table>
<thead>
<tr>
<th>RASP-B Items</th>
<th>Table 1 RASP-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I do not think I spend too much time exposed to the sun.</td>
</tr>
<tr>
<td>2</td>
<td>I am trying to spend less time in the sun that I used to.</td>
</tr>
<tr>
<td>3</td>
<td>I enjoy spending time in the sun, but sometimes I spend too much time in the sun.</td>
</tr>
<tr>
<td>4</td>
<td>Sometimes I think I should spend less time in the sun.</td>
</tr>
<tr>
<td>5</td>
<td>It’s a waste of time thinking about how much time I spend in the sun.</td>
</tr>
<tr>
<td>6</td>
<td>I have just recently changed my sun exposure habits.</td>
</tr>
<tr>
<td>7</td>
<td>Anyone can talk about wanting to do something about reducing their sun exposure, but I am actually doing something about it.</td>
</tr>
<tr>
<td>8</td>
<td>I am at the stage where I should think about spending less time in the sun.</td>
</tr>
<tr>
<td>9</td>
<td>The amount of time I spend in the sun is a problem sometimes.</td>
</tr>
<tr>
<td>10</td>
<td>There is no need for me to think about changing my sun exposure habits.</td>
</tr>
<tr>
<td>11</td>
<td>I am actually changing my sun exposure habits right now.</td>
</tr>
<tr>
<td>12</td>
<td>Spending less time in the sun would be pointless for me.</td>
</tr>
</tbody>
</table>

Notes:
P, precontemplation; C, contemplation; A, action.
Permission to translate and to use RASP-B, a 12-item questionnaire, was sought and obtained from Borschmann et. al. The questionnaire was translated into Filipino by a native Filipino translator from the Sentro ng Wikang Filipino. The translated version, which was the first intermediary version of the questionnaire, was pre-tested and evaluated for internal consistency. The questionnaire has Cronbach’s alpha of 0.6283.

**Statistical Analysis**

Descriptive statistics of the demographic profile and behavior will be determined. For categorical variables, frequency and percentage will be used while for continuous variables, mean, standard deviation, median and mode will be determined. All analyses will be conducted using SPSS 20 for Windows.

**Ethical Consideration**

Informed consent will be given prior to administration of the questionnaire. RASP-B can be self-administered in approximately 10-15 minutes.

**Results**

There were 278 adult Filipinos included in the study. The age of the patients ranged from 18 to 35 years old. The mean age was 25.29 (±4.79) years old, while the median and the mode were 25 and 20 years old. Majority of the patients were female (62.2%) and were single (87.1%) (Table 2).

### Table 2 Demographic Profile of Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years old</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age (±SD)</td>
<td>25.29 (±4.79)</td>
<td></td>
</tr>
<tr>
<td>Median Age</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>173</td>
<td>62.2</td>
</tr>
<tr>
<td>Male</td>
<td>105</td>
<td>37.8</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>36</td>
<td>13.0</td>
</tr>
<tr>
<td>Single</td>
<td>242</td>
<td>87.0</td>
</tr>
</tbody>
</table>

The mean height of the patients was 162.09 (±6.82), while the mean weight was 58.52 (±10.36). More than half of the patients had normal BMI. A little less than one-fourth were overweight. Only a few were obese.
Table 3 Anthropometric measurements of the patients (N=278)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height in centimeter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>162.08 (±6.82)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>162.00</td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>160.00</td>
<td></td>
</tr>
<tr>
<td>Weight in kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>58.53 (±10.37)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>57.00</td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>55.00</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Underweight (&lt;18.55)</td>
<td>18</td>
<td>6.47</td>
</tr>
<tr>
<td>Normal (18.5-22.9)</td>
<td>168</td>
<td>60.43</td>
</tr>
<tr>
<td>Overweight (23.0-24.9)</td>
<td>63</td>
<td>22.66</td>
</tr>
<tr>
<td>Pre-obese (25-29.9)</td>
<td>22</td>
<td>7.91</td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>7</td>
<td>2.52</td>
</tr>
</tbody>
</table>

Table 4 Distribution of patients based on their reason for consultation (N=278)

<table>
<thead>
<tr>
<th>Reason for consultation</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne Scar</td>
<td>73</td>
<td>26.3</td>
</tr>
<tr>
<td>Acne Vulgaris</td>
<td>90</td>
<td>32.4</td>
</tr>
<tr>
<td>Alopecia Areata</td>
<td>1</td>
<td>.4</td>
</tr>
<tr>
<td>Arthropod Bite</td>
<td>9</td>
<td>3.2</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopic Dermatitis</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>compound Nevus</td>
<td>1</td>
<td>.4</td>
</tr>
<tr>
<td>Compound Nevus</td>
<td>6</td>
<td>2.2</td>
</tr>
<tr>
<td>Contact Dermatitis</td>
<td>4</td>
<td>1.4</td>
</tr>
<tr>
<td>Dyshidrotic eczema</td>
<td>4</td>
<td>1.4</td>
</tr>
<tr>
<td>Ephelides</td>
<td>11</td>
<td>4.0</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Keratosis Pilaris</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Melasma</td>
<td>1</td>
<td>.4</td>
</tr>
<tr>
<td>Milia</td>
<td>4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Fourteen percent had a family history of hypertension. There were 5 (1.8%) patients with asthma.

Table 5 Clinical history of patients n=278

<table>
<thead>
<tr>
<th>Clinical History</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
<td>.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12</td>
<td>4.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>39</td>
<td>14.0</td>
</tr>
<tr>
<td>Hypertension, Atopic Dermatitis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension, Diabetes</td>
<td>18</td>
<td>6.5</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>Atopic Dermatitis</td>
<td>4</td>
<td>1.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Diabetes, Hypertension</td>
<td>1</td>
<td>.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>1.1</td>
</tr>
</tbody>
</table>
The overall total score was 2.02 (±5.63) (Table 5). Males have a slightly higher total score than females. However, there were no significant difference observed between the mean scores of each sex (Table 6).

The Chi-Square Test of Independence was performed to determine association between each state. Majority of the patients were already in the action state. There were more males in the precontemplation and action state. However, sex was not associated with the state of change of patients (p=0.218) (Table 8). In the previous study, gender was significantly associated with reported sunscreen use, staying in the shade, or using an umbrella while in the sun, and wearing sunglasses. Females reported more frequent use for all items and tended to use sunscreen in a more appropriate way than males, but they tended to be more likely to be seeking a tan and increase their ultraviolet exposure. Additionally, gender was significantly associated with wearing shirts with sleeves that cover the shoulders and wearing hats while in the sun, with males reporting more frequent usage for both. The frequency of wearing clothing made with SPF capabilities was found to be similar and infrequent between males and females, with most respondents of both genders reporting wearing SPF clothing <50% of the time.

Among singles, there were more patients who were already in the action state. Among married, there were more patients who were also in the action state. However, marital status was found to be not associated with the state of change (p=1.000) (Table 9). The result however like the previous study, which was not satisfactory, the slight majority of female and married respondents with a higher level of education and economically stable use a higher level of sun protection.

Among those with normal BMI, majority were already in the action state. Among those who do not have normal BMI, majority were also in the action state. There was not significant association found between BMI classification and state of change (p=0.544). Several published studies suggest that obesity is a risk factor for the most common types of skin cancer, particularly in people with a history of skin cancer. It appears to be inversely associated with the development of non-melanoma skin cancers therefore it is most likely a surrogate marker for lack of chronic sun exposure.
Table 6 Sun-protective behavior of the patients (N=278)

<table>
<thead>
<tr>
<th>Scores</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td>2.02 ± 5.63</td>
<td>2.00</td>
<td>6.00</td>
</tr>
<tr>
<td>Precontemplation</td>
<td>-1.08 ± 2.80</td>
<td>-1.00</td>
<td>-2.00</td>
</tr>
<tr>
<td>Contemplation</td>
<td>0.64 ± 2.62</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Action</td>
<td>2.45 ± 2.61</td>
<td>3.00</td>
<td>4.00</td>
</tr>
</tbody>
</table>

Table 7 Mean RASP-B Scores classified according to sex

<table>
<thead>
<tr>
<th>RASP scores</th>
<th>Female (n=173)</th>
<th>Male (n=105)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Total Score</td>
<td>1.99</td>
<td>5.92</td>
<td>2.06</td>
</tr>
<tr>
<td>Precontemplation</td>
<td>-1.13</td>
<td>2.79</td>
<td>-1.01</td>
</tr>
<tr>
<td>Contemplation</td>
<td>0.61</td>
<td>2.86</td>
<td>0.69</td>
</tr>
<tr>
<td>Action</td>
<td>2.50</td>
<td>2.52</td>
<td>2.36</td>
</tr>
</tbody>
</table>

Table 8 State of change of patients according to sex (N=278)

<table>
<thead>
<tr>
<th>State</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Precontemplation</td>
<td>9</td>
<td>5.20</td>
<td>10</td>
</tr>
<tr>
<td>Contemplation</td>
<td>27</td>
<td>15.61</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 9 State of change of patients according to marital status (N=278)

<table>
<thead>
<tr>
<th>State</th>
<th>Single</th>
<th>Married</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Precontemplation and Contemplation</td>
<td>50</td>
<td>20.6</td>
<td>7</td>
</tr>
<tr>
<td>Action</td>
<td>192</td>
<td>79.3</td>
<td>29</td>
</tr>
<tr>
<td>TOTAL</td>
<td>242</td>
<td>100.00</td>
<td>105</td>
</tr>
</tbody>
</table>

Table 10 State of change of patients according to BMI classification (N=278)

<table>
<thead>
<tr>
<th>State</th>
<th>Single</th>
<th>Married</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Precontemplation and Contemplation</td>
<td>50</td>
<td>20.6</td>
<td>7</td>
</tr>
<tr>
<td>Action</td>
<td>192</td>
<td>79.3</td>
<td>29</td>
</tr>
<tr>
<td>TOTAL</td>
<td>242</td>
<td>100.00</td>
<td>105</td>
</tr>
</tbody>
</table>

Discussion

This study aimed at assessing the feasibility of using a translated version of the RASP-B questionnaire in Filipino language to determine the readiness to change sun-protective behaviors among adult patients who were consulting at the Outpatient Department of the Ospital ng Maynila Medical Center. A previous study had revealed that RASP-B has a three-factor structure that corresponds comparably and psychometrically with the three stages of the transtheoretical model (TTM) of behavior change. TTM is an integrative, biopsychosocial model that conceptualizes the process of intentional behavior change by
integrating key constructs from other theories into a comprehensive theory of change that can be applied across a variety of behaviors, population, and settings. In health psychology, TTM has already been used to explain the changes of behavioral state from acquisition to cessation of smoking behavior and alcohol consumption. The focus of the current study is on sun-protective behavior.

The study that developed and validated the RASP-B questionnaire to assess readiness of behavior was done in Queensland, Australia. Findings of that study highlighted the strength of the questionnaire for its use in the primary health care setting due to its brevity that facilitates expedited completion and its satisfactory psychometric properties. The internal consistency of the RASP-B in assessing each construct of the TTM were 0.67 for the precontemplation stage, 0.72 for the contemplation stage, and 0.76 for the action stage. The Filipino version of the instrument was comparable for having a Cronbach’s alpha of 0.63. The pattern of sunscreen use among the respondents aged 18 – 24 years old was also assessed in the previous study. Their findings showed that only one-fourth of the participants usually or always applied sunscreen when spending time outdoors and half never applied sunscreen when outdoors. Unfortunately, this objective was out of the scope of the current study. Considering that the age of the conveniently sampled population for the current study ranges from 18 to 35 years old, they are apparently likely to spend more time under the sun. Hence, assessing the relationship among time of sun exposure, use of sunscreen, and the readiness to change towards sun-protective behavior may be considered for future research.

Following the procedure of Rollnick et al. in allocating the respondents in each stage of change, findings of the current study showed more favorable results than what is expected. Prochaska made a prediction that for any health-related behavior in any population, approximately 40% will be in the precontemplation stage, 40% in the contemplation stage, and 20% in the action stage. For the previous study that was done in the Philippines, majority respondents were in the precontemplation stage, followed by the action stage. Apparently, this was not the case for the sampled population in the current study. Almost 80% of the respondents in the current study were already in the action stage and about 13% were on the contemplation stage. People at the action stage have made specific
overt modifications in their lifestyles within the past 6 months\textsuperscript{5}. People in the contemplation stage, on the other hand, are those who are intending to change in the next 6 months and are aware of the pros and cons of altering their behavior\textsuperscript{5}. Only 7\% of the respondents were on the precontemplation stage. People at this stage are not intending to take action in the next 6 months maybe due to resistance, misinformation, or lack of awareness about the consequences of altering the behavior\textsuperscript{5}. The progression of individuals across the stages of the model during the process of altering health behaviors appears to be sequential from precontemplation to action stage\textsuperscript{5}. The implication of this therefore is to implement reinforcing programs that will strengthen fidelity of the participants to the action stage. The challenge for the dermatology clinic is to incorporate in their counseling procedures techniques that will reinforce the healthy behavior.

In the previous study of Borschmann, there were significantly more females than males in the precontemplation stage and significantly fewer females in the action stage\textsuperscript{7}. In contrast, findings of this study showed no significant association between sex and the state of change of the respondents. The association of civil status and BMI classification with the state of change as assessed via RASP-B were the novelty of the current study, which had not been done in the previous study. Findings revealed that the two factors were not associated with the outcome interest. Hence, any counseling program aimed at reinforcing the action stage can be implemented in the institution without restriction based on sex, civil status, or BMI classification.

The recruitment of patients consulting at Ospital ng Maynila Medical Center (OMMC) for the purposes of this study serves as a limitation thereby affecting the generalizability of the findings. However, the careful implementation of the study in strict adherence to the approved protocol ensures the internal validity of the findings. Hence, for future research, conducting a population-based cross-sectional study may be implemented to address such limitations.

**Conclusions**
The feasibility of using a translated version of the RASP-B questionnaire in Filipino language to determine the readiness to change sun-protective behaviors among Filipino adult patients was assessed in this study.
The study was done among patients consulting at the Outpatient Department of the Ospital ng Maynila Medical Center. Findings revealed that a majority of the respondents were already in the action stage and only a few were still on the precontemplation stage, which are findings that are far from what is expected.

Declarations

Ethics approval and consent to participate
Not applicable.

Availability of data and material
Not applicable.

Conflict of interests
Not applicable.

Funding
Not applicable.

Authors' contributions
V Budiman was the sole contributor of the manuscript

References
A scoping review on the factors influencing the general acceptance of Southeast Asians towards HPV vaccination
DOI: 10.52629/jamsa.v10i1.190
Leonard Thomas Sy Lim, Pamela Bianca Manuel Pasco, Juancho Del Rosario Raymundo
Corresponding author:
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Abstract:

Background Southeast Asia is known to have one of the highest Human Papillomavirus (HPV) prevalence rates globally. HPV vaccination has been shown to be successful in the prevention of infection.

Objective This study aims to perform a scoping review of the factors influencing HPV acceptance in Southeast Asia, extract dominant themes, identify factors, describe subgroup representation, and suggest considerations in the creation of interventional and delivery strategies to increase vaccine uptake.

Methods PubMed was used to identify papers discussing vaccine acceptance, published from January 2009 to March 2020. After review, 41 studies were included in qualitative synthesis.

Findings The following outcomes were measured in the included studies: knowledge of HPV, attitudes towards vaccination, factors influencing attitudes towards vaccination, and the effectiveness of interventions and strategies in increasing vaccine uptake. There was an overall level of low to moderate knowledge, with generally high vaccine acceptance. Literacy was found to have a direct relationship with uptake, although limited by one’s resources and capability to get vaccinated. Price was noted to be the most crucial factor behind accessibility. Among delivery strategies, school-based and national immunization programs were found to be the most effective.

Conclusions Factors influencing attitudes towards vaccination include economic, personal, social, and cultural factors. Culturally-specific research and interventions that would better grasp the contexts of target communities are recommended.
Keywords: vaccine acceptance, vaccine hesitancy, vaccine uptake, health literacy, HPV
**Introduction**

**Health Literacy & Vaccine Hesitancy**

Health literacy is defined by the World Health Organization (WHO) as “the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain good health.”[1] It goes beyond the dissemination and communication of health information and involves health education that calls for individual and collective action that would modify the determinants of health, in order to promote both personal and social benefit[1].

Achieving health literacy implies the need for “interaction, participation, and critical analysis,”[1] leading to effective community action. One area of health care that is heavily influenced by this collective involvement is immunization. This can be observed in the context of Cuba, wherein the public's strong trust in the vaccine system is owed to the education provided for all, which results in high levels of health literacy[2].

On the other hand, poor health literacy can reduce the willingness to engage in protective behaviors, such as immunization[3]. This is termed as vaccine hesitancy, which is defined as the “delay in acceptance or refusal of vaccination despite availability of vaccination services.”[4] The context-specific and complex nature of vaccine hesitancy is influenced by various factors such as complacency, convenience, and confidence[4].

Vaccination complacency results from low awareness of the risks brought by vaccine-preventable diseases; this means that underestimating the consequences of the spread of infectious diseases can contribute to vaccine hesitancy. Convenience refers to the availability, affordability, and accessibility of the vaccine, as well as the appeal of deciding to get vaccinated. Lastly, vaccination confidence relies on trust towards the vaccine itself, its delivery system, and the motivations of the policies deciding which vaccines are needed.[4]

Considering these factors and the complexity of possible reasons for vaccine hesitancy, the study directs its focus to a specific vaccine and specific region, which are human papillomavirus (HPV) and Southeast Asia, respectively.

**Human Papillomavirus (HPV)**

According to the WHO, human papillomavirus (HPV) is the most common viral infection affecting the reproductive tract and is contracted...
through contact with genital skin, mucous membranes, or bodily fluids that are infected. It can be transmitted through sexual intercourse, including oral sex. Although most HPV infections are asymptomatic and resolve spontaneously, persistent infections of specific high-risk HPV types, such as HPV-16 and HPV-18, may result in precancerous lesions, progressing to invasive carcinoma if left undetected and untreated. Persistent infection with HPV is a necessary cause of cervical cancer and comprises 84% of all HPV-related cancers, accounting for 8% of all female cancer deaths in 2012. Oropharyngeal and anogenital cancers are also associated with HPV infection in both sexes.\(^{[5]}\)

This possibility of HPV infections progressing to cancer thus demands prevention and protection against re-infections. When it comes to prevention, the WHO recommends that HPV vaccines should be included in national immunization programs, with cervical cancer prevention as priority for HPV immunization. Vaccination of girls prior to their sexual debut would be the optimal prevention. All three licensed HPV vaccines, namely bivalent, quadrivalent and nonavalent, are safe, with similarly excellent efficacy and effectiveness profiles. These all work against HPV-16 and HPV-18, which are associated with 71% of cervical cancers globally. Bivalent and quadrivalent vaccines provide cross-protection to other HPV types which are associated with 13% of cases, while nonavalent vaccines provide protection against those associated with 18% of cases.\(^{[5]}\)

Based on a meta-analysis, the global HPV prevalence is estimated to be 11.7% among women with normal cytological findings, with Southeast Asia having a prevalence of 14%. This is among the highest globally, coming after sub-Saharan Africa with 24%, Latin America and the Caribbean with 16.1%, and Eastern Europe with 14.2%.\(^{[5]}\)

HPV prevalence was high in all regions for men but showed varied rates from low-risk men with 1% to 84%, and from 2% to 93% among those considered as high-risk, such as sexually-transmitted infection clinic attendees, HIV-positive men (especially those who have sex with men, which have the highest prevalence), and male partners of women with abnormal cytology or HPV infection.\(^{[5]}\)

More than 85% of cervical cancer cases are from less developed regions, accounting for 12% of all cancers in women.\(^{[5]}\) Despite the
efforts of countries to implement HPV immunization programs from 2006 to 2014, a study states that only 1% of the estimated targeted 118 million women were from low-income or lower-middle-income countries. This disparity is even more pronounced with an estimated only 2.7% of women aged 10-20 years in less developed regions receiving the full course of vaccine, compared to the 33.6% from more developed regions[6].

Rationale
Given the varying prevalence of HPV infection and cervical cancer across different demographics and the influential role of vaccine hesitancy, there is a need to identify the factors that affect vaccine acceptance to aid in developing guidelines for improved administration. These guidelines would address the social determinants of health, which by the definition of the WHO, are conditions that cause health inequities or “the unfair and avoidable differences in health status within and between countries[9].” Health is multifactorial, and it requires that its different aspects (including various beliefs, circumstances, and resources) be accounted for in order to improve health outcomes and reduce health inequities.

Due to the limited number of studies in the Philippines concerning this matter, this study takes the opportunity to look at its neighboring countries from Southeast Asia that have similar contexts, beliefs, and circumstances.

Objective
This study aims to determine the factors that influence the general acceptance of Southeast Asians towards HPV vaccination and as a secondary objective, to suggest considerations in the creation of interventional and delivery strategies to increase HPV vaccine uptake.

Methods
A structured literature review was used to synthesize research evidence on factors influencing HPV vaccination in Southeast Asia. This review type was selected due to heterogeneity of literature with relevance to context and the lack of available comprehensive literature. The reviewers followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMS-ScR)[8].

Online databases including PubMed were used for the literature search. Search terms included: (1) vaccine confidence; (2) vaccine acceptance; (3) vaccine hesitancy; (4) HPV; and (5)
Southeast Asia. The search was limited to full-text, peer-reviewed articles published in English, involving human participants, between January 2009 and March 2020. Quantitative, qualitative and mixed-method studies were included. Papers were excluded if they were not about vaccines, not localized to Southeast Asia (e.g. Cambodian-American parents, Vietnamese-American women), clinical trials (e.g. immunogenicity), and focused on the prevalence, incidence, and clinical progression of HPV. A four phase flow diagram was used to assist and represent the selection, inclusion, and exclusion of research papers. All three authors examined the titles and results of the publications independently to exclude studies that did not fit the inclusion criteria. The authors then conducted data extraction and independently evaluated all eligible publications. A narrative summary was used to present the results of the review.

Finding and Discussion

Search Results and Sources of Evidence

The database search returned 58 publications (see Figure 1). After exclusion and identification of additional records, 41 original research publications were included for qualitative analysis and extraction of dominant themes relating to HPV vaccine acceptance.

![Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram](image)

Summary of Included Studies

The 41 studies covered seven Southeast Asian countries, distributed as follows: Malaysia (n=12), Vietnam (n=12), Thailand (n=8), Indonesia (n=3), Singapore (n=3), Cambodia (n=2), and the Philippines (n=1).

Collectively, these studies delved into a variety of topics, all related to the objective of the scoping review. The following outcomes were measured: knowledge of HPV, acceptance or attitudes towards HPV vaccination, factors influencing one's attitude towards HPV vaccination, and the effectiveness of interventions and
delivery strategies in increasing vaccine uptake. The majority of the studies measured at least two of the aforementioned outcomes; a few were specific to each outcome. In spite of the variety of outcomes being measured, the strong interplay among them could still be observed, along with general trends amid different demographics.

**Health Literacy Assessment**

As a way to gauge the context of the participants, most of the studies began by assessing their knowledge of HPV, particularly the vaccine and the relationship of the virus to cervical cancer. Generally, the participants were given a “low to moderate” rating in terms of knowledge on HPV as evidenced by the twelve studies with participants of “low knowledge,” eight studies with participants of “moderate knowledge,” and just one study with participants of “high knowledge.” It is important to note, however, that the level descriptors used were not standardized; the researchers came up with their own criteria assessing their participants. Most of the studies measuring knowledge included asking participants if they have heard of HPV (and related terms) before.

The discussion can be further enriched by unveiling the respective contexts of some of the studies. In terms of demographics, almost all of the studies were conducted on women: mothers, adults, and young adolescents. Some studies delved into confounding factors by considering specific contexts, such as students taking medical/health science tracks and women living in rural areas. A few studies conducted research on other stakeholders of immunization programs, including educators, healthcare providers, and community and religious leaders.

Marginalized and rural communities were found to be less knowledgeable about HPV—all studies of which are classified under the “low knowledge” category. One study that focused on a marginalized community involved sex workers in Cambodia, reporting that only 23.6% of participants had heard of HPV upon initial assessment. After administering an educational intervention, 90% of the participants were capable of answering HPV-related questions correctly, thus demonstrating the quintessential role of such strategies in addressing lack of knowledge on HPV. Meanwhile, a cross-sectional survey that was conducted among Malaysian women found that those from universities, signifying urban
communities, had greater knowledge on HPV compared to those living in rural areas\textsuperscript{[30]}. This is worth noting because of the comparative nature of its findings, relative to the three other studies conducted in rural areas, measuring knowledge as an outcome.

Among the participants with higher knowledge of HPV, there were two notable factors observed: sex and background in medicine/healthcare. Two studies, both conducted on Malaysian university students, found that while students were moderately knowledgeable about HPV, females had a significantly higher mean knowledge score in comparison to males, possibly due to the HPV disease profiles that are more common to women\textsuperscript{[23, 31]}. It was also found that students from health-related colleges outperformed all other colleges\textsuperscript{[23]}. This is further supported by one study in which medical students were assessed to have “high knowledge” on HPV\textsuperscript{[29]}.

Aside from the aforementioned implications of particular contexts to knowledge on HPV, it is also worth noting the type of information or the levels of understanding among certain demographics. One extensive qualitative study, conducted among several stakeholders, including children, parents, teachers, administrators, health workers, and community and religious leaders, found that although knowledge on HPV itself was limited, the gravity of cervical cancer and other HPV-related symptoms was acknowledged\textsuperscript{[25]}. Another study on daughters and mothers in Vietnam found that mothers were more knowledgeable about cervical cancer and HPV, while the daughters were more knowledgeable about the HPV vaccine\textsuperscript{[24]}.

**Health Literacy**

Across most of the studies, the assessment of literacy was followed by determining its link to acceptance, the primary factor that this review aims to elucidate. In addition to knowledge, acceptance measures were typically found to be high. These findings were noted across different populations, particularly among parents\textsuperscript{[32, 21, 22, 10, 11, 12, 33, 14, 18, 34, 19]}, young women and students\textsuperscript{[22, 23, 31, 12, 29]}, adult women\textsuperscript{[22, 35, 13, 36, 27, 20, 37]}, health care professionals\textsuperscript{[38, 31, 28]}, teachers\textsuperscript{[39]}, sex workers\textsuperscript{[9]}, and different stakeholders (e.g., community and religious leaders)\textsuperscript{[25]}.

Although there is high acceptability regardless of demographic, the characteristics of the studied subgroups depict the association of knowledge, individual beliefs, and
health behaviors with vaccine acceptance.

Acceptance by parents, the most frequent demographic measured across studies, has been associated with their primary role in the decision-making process of vaccinating their children\(^{25}\). In the context of preventing cervical dysplasia, vaccination is most effective when given before sexual debut and HPV exposure. The Centers for Disease Control and Prevention (CDC) recommends administration of the vaccine to both boys and girls between the ages of 11 and 12 years, and as early as 9 years\(^{40}\). As a result, this window for vaccination often places the responsibility on the parents or guardians of the child. Additionally, acceptance of childhood vaccinations has been associated with parental HPV vaccine acceptance\(^{32}\).

All studies that measured vaccine acceptance found a direct relationship with vaccine literacy. The operational definition of vaccine literacy overarches perceived susceptibility, knowledge of benefits, perceived seriousness of illnesses\(^{27, 36}\), exposure to vaccine information in the form of intervention\(^{10, 33, 37}\), knowledge that multiple partners increased risk\(^{10, 41}\), and simply having heard of the virus and its associated disorders. The aforementioned study conducted on sex workers in Cambodia is an example of mass acceptance consequent to an educational intervention aiming to increase vaccine literacy\(^{9}\). This demonstrates the expected link between the two outcomes; however, several studies also found that low levels of literacy do not necessarily translate to lower acceptance\(^{11, 13, 18}\).

One cross-sectional study done in Thailand found that despite being judged to have little knowledge on HPV vaccination, participants still exhibited high willingness to copay if the vaccine was not free\(^{10}\). Another study, set in rural Indonesia, found that parents were supportive of vaccinating their children, even if the majority had no knowledge of HPV\(^{11}\). Despite being autonomous agents, this phenomenon can be attributed to the passive acceptance that was found to be the norm in households and communities of low-resource settings, unless acted upon by external factors (e.g., sociocultural, economic, or environmental)\(^{25, 33}\). In contrast, another study found that there was no significant difference between the general attitude of women from urban and rural areas\(^{30}\), which poses the possibility of overt bias among participants that claimed to be open to vaccination.
In discussing the relationship between literacy and acceptance, it is important to consider the reasons for vaccine hesitancy that stem from misconceptions, limited knowledge, and stigma on HPV. The reasons for refusal that have more to do with resources will be expounded on in the following sections. Several studies elicited the following reasons for vaccine hesitancy and decline of participation: possible side effects\cite{21, 17, 18, 25}, possible impact on fertility\cite{33, 25}, the possibility that it will not work\cite{19}, the embarrassment of getting screened by a male doctor\cite{11}, and the embarrassment of getting vaccinated per se\cite{27, 30}. Most of the studies necessitated appropriate educational interventions to fill in gaps of knowledge on HPV vaccination, thus it is more sound to conclude that increasing literacy can address reasons behind vaccine hesitancy rather than entirely confirming a non-dynamic relationship between literacy and acceptance, which, as evidenced by the earlier studies, is subject to confounding variables.

**Vaccine-Related Factors**

The economic aspect of demand is inextricable from vaccination, just as with any product. It is to no surprise then, that several studies deemed price the most pertinent factor in HPV uptake\cite{38, 18}, at the minimum highlighting its inverse relationship with acceptance\cite{22, 23, 38, 11, 42, 13, 15, 16, 18, 41, 26, 34, 19, 37}. The desire to avail of a vaccine is limited by the ability to do so, which is dictated by the consumer’s purchasing power, hence also household income\cite{21}. Similar studies in two different countries, Vietnam and Malaysia, measured the willingness of parents to pay for the full course of HPV vaccinations. The participants of the study conducted in North Vietnam were willing to pay from a range of under $23 to $46\cite{42}, while the participants of the Malaysian study were willing to pay an average of $27.7\cite{16}. The same study revealed that the market price was $342.85\cite{16}. It is also important to note that both studies were conducted in rural areas, which may suggest relatively lower income households. Two more Malaysian studies, when juxtaposed, can point out the role of price in HPV uptake. The first study measured the prevalence of HPV vaccination among secondary school girls after a newly employed government intervention of providing free vaccines and actively promoting HPV vaccination in the media; the study concluded that free vaccination significantly increased uptake\cite{43}. On the other hand, despite high awareness of HPV among adult women, low uptake persisted because there were no government
subsides for adults, only school girls\textsuperscript{[15]}. This brings forth the relationship between knowledge and uptake, in contrast to acceptance. Knowledge has a direct relationship with uptake but only to the extent that one has the resources and financial capabilities to get vaccinated. Apart from price, although not as pervasive across the studies, other vaccine-related factors include vaccine type, effectiveness, and duration of effectiveness. One study found that the quadrivalent HPV vaccine contributed to the most favorable scenario\textsuperscript{[38]}, while another found no significant difference between bivalent and quadrivalent in terms of acceptance\textsuperscript{[10]}. Regarding effectiveness, one study found that effectiveness was deemed more important than duration of effectiveness\textsuperscript{[34]}. Unfortunately, such factors were only discussed in the three mentioned studies, thus posing limitations on its generalizability.

**Personal Factors**

Upon reviewing the studies, several miscellaneous factors emerged; they can be categorized into personal and social factors. Compared to price and knowledge, these were not as pervasive across the studies, although many of them are related to the latter in terms of influencing acceptance. It has already been elucidated in the earlier sections that living in a rural area is associated with lower knowledge of HPV and lower purchasing power, but these do not translate to a negative attitude towards HPV vaccination\textsuperscript{[11]}. Aside from location, the following factors were also touched upon: age, sex, religion, and ethnicity. For age, younger women were more willing to get vaccinated than older women\textsuperscript{[13, 41]}. One study found that there was higher acceptance among women younger than 45 years old and that age was the strongest associated factor for acceptance\textsuperscript{[12]}. This was hypothesized to have been associated with participants’ sexual behavior, interest in health information, and beliefs prior to the release of the vaccine. According to the CDC, catchup vaccinations should be offered to all previously unvaccinated females aged 13 to 26 years, and are not recommended for adults aged 27 to 45 years due to minimal public health benefit\textsuperscript{[44]}. The existence of age group specific recommendations is congruent with the need for greater acceptance among younger women and mothers. Consequently, this underscores the need for adequate, accessible, and appropriate health information. For sex, it was found that women were more willing to get vaccinated than men\textsuperscript{[31]} and that mothers were more inclined to
vaccinate their daughters over their sons\textsuperscript{[19]}, again possibly due to the HPV-related disease profiles more common to women. In terms of religion, no association with acceptance has been established in any of the studies\textsuperscript{[39, 19]}. With ethnicity, on the other hand, only one study, conducted in rural Malaysia, found that there was higher perceived embarrassment for HPV vaccination among the Malay and the Indians as compared to the Chinese, hence the need for interventions that are culturally specific\textsuperscript{[29]}.

Social Factors

Compared to the personal factors that include a plethora of relatively unrelated elements, the social factors can be summarized through a qualitative study conducted among Chinese Singaporean women, that reported the role of passive and active acquisition in the decision-making process for HPV vaccination. Passive acquisition involves information from personal networks such as family and friends, while active acquisition involves information from credible sources such as medical pamphlets and health professionals\textsuperscript{[35]}. Both rely on the peripheral route to persuasion (acceptance due to credibility over reason), which trades literacy for conformity in terms of HPV acceptance. These concepts are supported by studies that highlight the role of recommendations from healthcare providers\textsuperscript{[23, 36, 20]} and partners\textsuperscript{[27, 13]} in HPV acceptance, accounting for passive and active acquisitions, respectively. For active acquisition, gynecologists and general practitioners were found to be the most credible sources\textsuperscript{[20]}. In line with active acquisition, a descriptive qualitative study in Vietnam also attributed an increase in support of HPV vaccination to the credibility that the government demonstrated in its implementation of the National Expanded Program of Immunization\textsuperscript{[33]}. The same study also contextualized the concepts of passive and active acquisition by claiming that active decision-making is more common in urban areas\textsuperscript{[33]}. For passive acquisition, the studies found that marital status had mixed findings, hence the conclusion that marital status is simply an avenue for decision-making in general, a factor that can increase or decrease vaccine acceptance\textsuperscript{[27, 13, 37]}, depending on other circumstances.

Interventions

Among the 41 studies, only a few specifically measured perception of outcomes after intervention\textsuperscript{[83, 43, 45, 46, 47]}, but the call for such strategies persisted as an overarching recommendation. School-based and national immunization programs
were found to be effective in significantly increasing HPV immunization\(^4\) with refusals mainly attributed to programmatic considerations such as absenteeism\(^5\). Nonetheless, it is our recommendation that such programs will only work with system preparedness\(^6\) in the form of human resources and proper delivery of vaccines via cold chain\(^7\). In addition, access to transportation\(^8\) and vaccine locations\(^9\) were found to be barriers to immunization and thus need to be incorporated in the creation of delivery strategies.

**Limitations of the Study**

Measures of vaccine hesitancy, acceptability, and confidence have remained unstandardized, as a result of a lack of clear operational definitions. This may result in discrepancies between interpretations of similar variables. Vaccine acceptability must be sufficiently defined and described using standard tools to allow for analysis of the same unit. The failure to do so may lead to limited comparability of studies. Studies focusing on different demographics (age-groups, sexes, occupations, cultural groups, urban populations, rural populations), resource settings (e.g. developing countries), and sociocultural landscapes demand context-specific interpretations. In addition to extracting overarching themes, it is recognized that deeper analysis by subgroups must also be conducted to identify the reasons behind heterogeneity. Lastly, it must be noted that the significant number of cross-sectional study designs employed by the included studies only allow for descriptions of association and not causation. A number of studies also make use of self-administered questionnaires, which are subject to end aversion and positive skewing of results. Potential confounders affecting exposure and outcome must also be taken into account to include the many factors affecting decision-making.

**Conclusions**

After reviewing 41 studies on acceptance and attitudes of Southeast Asians towards HPV vaccination, it can be concluded that in spite of varying contexts, general trends can be established. In terms of HPV literacy, an overall level descriptor of “low to moderate” persisted throughout all the studies, with those from the rural and marginalized communities scoring the lowest and those with a background in healthcare scoring the highest. It is also worth measuring the type of information that specific demographics are unaware of so that educational
Interventions can identify the gaps that need to be filled and address different levels of literacy in a community. Vaccine acceptance was generally high. It can be said that interventions that aim to increase literacy can address misconceptions that lead to vaccine hesitancy. It is wrong to claim, however, that there is a non-dynamic relationship between literacy and acceptance as there are other confounding variables at play, as evidenced by studies with high acceptance despite low literacy. A more sound conclusion would be that literacy has a direct relationship with uptake but is limited by one’s resources to get vaccinated. This brings forth the role of price as the most crucial factor behind accessibility, as supported by interventions facilitating free vaccination found to be the most effective in vaccination uptake. Aside from literacy and price, personal factors such as location, age, and sex were found to be moderately linked to acceptance, while religion and ethnicity were found to have no association. The limited knowledge on such factors calls for the need of more culturally-specific research and interventions that would better grasp the contexts of their target communities. Social influence also played a large role in decision-making and was often dictated by the credibility of the source—physicians and the government for active acquisition, partners, friends, and family for passive acquisition. The majority of studies called for the need of intervention. The most effective strategies are school-based and national immunization programs. In addition to price, other factors that reduce accessibility such as lack of transportation and inconvenient vaccine locations must be addressed when creating interventional and delivery strategies that aim to increase HPV vaccine uptake.

Declarations

Ethics approval and consent to participate
Not applicable.

Availability of data and material
Not applicable.

Conflict of interests
All authors declare that they have no conflicting interests.

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Authors’ contributions

References


51. Wong LP. HPV information needs, educational messages and channel of delivery preferences: views from developing country with multiethnic populations. Vaccine. 2009 Feb 25;27(9):1410-5.
A Comprehensive Assessment of Full-face Helmet Utilization in Preventing Head and Neck Injury in Motorcycle Accidents: A Systematic Review

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Abstract:

Introduction: Morbidity and mortality due to motorcycle accidents are still becoming a major problem that cannot be solved. A common cause of deaths in motorcycle road accidents is due to head, facial and neck injuries. One of the simple ways to overcome this problem is using a helmet, but the types of helmet that confers the best protection is not specified. This review aimed to evaluate the best type of helmet in reducing mortality and morbidity rate due to head-facial and cervical trauma. Material and Methods: A Systematic review evaluating the most prominent helm in conferring protection was carried out using PRISMA statement guidelines. Studies search were was conducted using search engine ScienceDirect, ProQuest, and PUBMED database with criterion papers published in English between 2009 to 2019 and comparing full face, partial face, and open face helmet effectivity in conferring protection. Appraisal tools of selected studies using Centre for Evidence-Based Medicine (CEBM) appraisal tools. Result and Discussion: From the search, 1477 studies were identified and finally obtained 8 studies that fulfill the criterion. Studies are organized according to comparison of a full-face helmet with partial face helmet and full-face helmet with partial face helmet. Studies show that a full-face helmet gives significant protection against head-facial and cervical injury. However, because many of the study criteria are not uniformed, the need for further study with better quality is a must. Conclusion: Full-face helmets reduce head-facial and neck injuries better than other helmets in motorcycle accidents thus reducing the morbidity and mortality rate.

Keywords: head-facial injuries, helmet, motorcycle accidents
Introduction:

The World Health Organization stated that every minute, three people die worldwide due to road traffic accidents.\(^1\) A road traffic accident has still become unsolved problems and it is predicated as the most common cause of death in children and young productive adults (age 5-29 years) on a trauma basis thus causing a high burden in many aspects, especially in economic basis.\(^1\) Moreover, the rate of events, and also the morbidity and mortality rates, keep increasing every year and it is known that it is three times higher in low-middle income countries than in high-income countries, especially in Thailand, Malaysia, and Indonesia.\(^1,2\) In Indonesia, the mortality rate due to road traffic accidents from 2010 until 2014 is increasing with motorcycles being the most commonly used vehicle in the accidents (627,116 units or 70% from all of the vehicles used).\(^2\) These data are supported by empirical facts that motorcycles are the most commonly used vehicles in many low-middle income countries.

From 1990 until 2018, the most common cause of deaths due to motorcycle road accidents has not changed.\(^3\) Head and neck injuries were the cause of death of more than 53% motorcycle accidents in the world and recent reports from Cochrane review also stating that craniocerebral, facial, and neck injuries were common too.\(^3-4\) In Indonesia, Indonesian Health Department (DepKes) stated that head-cervical traumas related to motorcycle accidents were the most common cause of death (74%) followed by hip and lower limb traumas (10%).\(^2\) Based on these problems, factors which caused the high rate, morbidity, and mortality rate due to road traffic accidents, especially motorcycle-related, must be evaluated.

Referring to the epidemiological triangle which is modified from Haddon’s matrix, three main factors are related to each other in determining the incidence of road accidents, namely agent (the human), host (vehicle factor), and environment (the road).\(^5\) In low-middle income countries, and also supported by data on Indonesia, undisciplined behavior is the leading cause of the incidence, morbidity, and mortality rate increase in road accidents and the commonest undisciplined behavior that is still being neglected in Indonesia is the usage of helmets.\(^2-5\) One of the effective preventive strategies of motorcycle accident severity is to use a helmet while riding a motorcycle due to its protective effect on death.
and head injuries based on Cochrane review with OR 0.58 and 0.31, respectively.4

Three common types of the helmet that are currently approved by SNI (Standart Nasional Indonesia), namely full-face, open face, and partial face helmet. But the law in many countries, including Indonesia, is not specifying the types of helmet.5 Whereas a case-control based review conducted by Lam, et al in Taiwan shows that the types of helmet that are used by the motorcyclist does influence the outcome of the motorcycle accidents patients including the rate of head-facial fracture and cervical spine injury compared to non-helmet user (OR = 0.19, 95% CI and OR = 0.35%, 95% CI respectively).7 Based on these problems, we have an initiative to find which helmet is the best to overcome the high morbidity and mortality rate due to motorcycle accidents with an idea stated on a systematic review. This study aimed to review what is the best helmet type to prevent head and cervical injuries in motorcycle accidents thus could support and determine the best helmet type that may be documented and implemented in the helmet law, especially in low middle-income countries such as Indonesia.

**Material and Methods:**

A systematic review of large observational studies comparing the protective effect of full-face, open face, and partial face helmet against head-facial and cervical traumas in motorcycle road accidents was carried out using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement rules. We searched works of literature published in Pubmed, ScienceDirect, and ProQuest databases with keywords “motorcycle accident (s), helmet, head injury (s), cervical injury (s) and only papers published in English from 2009 until 2019 which are included. The eligible studies were 1) those which are comparing the full-face helmet with other types of helmet (open face, and partial face) on motorcyclists who had traffic accidents 2) the outcomes of studies involved head-facial and cervical injuries (including spinal cord injuries). We appraised eight Selected studies by using the Centre for Evidence-Based Medicine (CEBM) appraisal tools. The literature selections were summarized in Figure 1.
Results:

From 1477 published papers from Pubmed, ScienceDirect, and ProQuest databases, we include 1154 studies because the other studies are not published in English and published below 2009. Of those, we finally include eight eligible and valid studies because of the other studies discussing other topics besides the comparison of full-face, open face, and partial face helmet in preventing head-facial and cervical injuries, unsuitable study design, studies not found, and study duplication. The final eligible and valid studies (n=8) then were reviewed here and the results were summarized in Table 1.

Full-face Helmet Versus Partial Face Helmet

This systematic review is comparing the effectiveness of the full-face helmet and many types of helmet, one of them is a partial type helmet.7,8,11,13 There were four studies from Malaysia, Taiwan, and the United States comparing the full-face helmet against partial-type helmet. The output evaluated were head and neck injuries (Table 1). Overall, wearing a full-face helmet compared to a partial helmet could reduce the incidences of cervical and head injuries by 17% compared to four prior studies that evaluated here (95% CI p-value <0.001). And also, all of the participants that are included
**Table 1.** Summary of Studies Comparing Between Full-face Helmet, Partial Face, and Open Helmet on Head-facial and Cervical Outcomes in Motorcyclists Who Had Road Accidents.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year</th>
<th>Study Design</th>
<th>Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramli et al</td>
<td>Malaysia</td>
<td>2014</td>
<td>Observation Case-control</td>
<td>All motorcyclists (Pillion or single rider). All age groups (&lt;16 – 25). All types and severity of injuries. Were involved in a motorcycle.</td>
</tr>
<tr>
<td>Cini et al</td>
<td>Brazil</td>
<td>2014</td>
<td>Observation Case-control</td>
<td>Patients injured in the face in a motorcycle accident.</td>
</tr>
<tr>
<td>Brewer et al</td>
<td>United States</td>
<td>2013</td>
<td>Observation Cohort Retrospective study</td>
<td>All helmeted adults patients older than 18 years old. Crashes on an all-terrain vehicle.</td>
</tr>
<tr>
<td>Erhardt et al</td>
<td>United States</td>
<td>2015</td>
<td>Observation Cohort Retrospective study</td>
<td>Riders who are using either full-face, half, and open-face helmet. Aged &gt; 15 years old.</td>
</tr>
<tr>
<td>Albuquerque et al</td>
<td>Brazil</td>
<td>2014</td>
<td>Observation Matched case-control</td>
<td>Motorcycle accident victims had to be referred to the outpatient clinic at the hospital.</td>
</tr>
<tr>
<td>Yu et al</td>
<td>Taiwan</td>
<td>2011</td>
<td>Observation Cohort Retrospective study</td>
<td>Age ≥15 y Lived in Taichung.</td>
</tr>
<tr>
<td>Sung et al</td>
<td>Korea</td>
<td>2016</td>
<td>Observation Cohort Retrospective study</td>
<td>All drivers and passengers over 15 years old who were riding a motorcycle. Visited the emergency room at China Medical University Hospital due to.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Taiwan Head injury registry</td>
<td>crash within the catchment Data from 2010 until 2011 in South Klang Malaysia</td>
<td>open-desert motorcycle injuries</td>
<td>motorcycle injuries</td>
</tr>
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<td>--------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Exclusion</td>
<td>Any cases with missing data on helmet use, types of helmet used, or cervical spine injury</td>
<td>Motorcyclists who did not sustain any injury, or discharged themselves from hospital care without a definitive diagnosis, Involved in a road crash outside South Klang</td>
<td>Those with injuries to any other part of the body or whose injuries resulted in the death</td>
<td>Unhelmeted Riders who fall on the open-desert environment</td>
</tr>
<tr>
<td>Number of Participants</td>
<td>Valley, Malaysia</td>
<td>city of Taichung</td>
<td></td>
<td></td>
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<tr>
<td>------------------------</td>
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<td>-----------------</td>
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</tr>
<tr>
<td>5,225 participants</td>
<td>755 participants</td>
<td>6460 participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,628 participants</td>
<td>151</td>
<td>253</td>
<td></td>
<td></td>
</tr>
<tr>
<td>458 participants</td>
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<tr>
<th>Primary Outcome</th>
<th>Cervical spine injuries</th>
<th>Facial injuries</th>
<th>Facial injuries</th>
<th>Skull-facial fractures, traumatic brain injury, cervical spine fractures</th>
<th>Neck and head injury</th>
<th>Facial Injury Severity Scale, traumatic brain injury, facial fractures</th>
<th>Head Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-face helmet with head injury, n</td>
<td>28 (2.1%)</td>
<td>2 (14%)</td>
<td>12 (16%)</td>
<td>16 (19%)</td>
<td>542 (12.7%)</td>
<td>24 (52%)</td>
<td>50 (40%)</td>
</tr>
<tr>
<td>Full-face helmet without head injury, n</td>
<td>1,259 (97.9%)</td>
<td>12 (86%)</td>
<td>63 (84%)</td>
<td>68 (81%)</td>
<td>3698 (87.3%)</td>
<td>22 (48%)</td>
<td>73 (60%)</td>
</tr>
<tr>
<td>Partial helmet with head injury, n</td>
<td>104 (3%)</td>
<td>304 (51%)</td>
<td>-</td>
<td>-</td>
<td>256 (24.7%)</td>
<td>-</td>
<td>274 (57%)</td>
</tr>
<tr>
<td>Partial helmet</td>
<td>3,385 (97%)</td>
<td>293 (49%)</td>
<td>-</td>
<td>-</td>
<td>780 (75.3%)</td>
<td>-</td>
<td>208 (43%)</td>
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<tr>
<td>without head injury, n</td>
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<td></td>
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</tr>
<tr>
<td>Open Helmet with head or cervical injury, n</td>
<td>-</td>
<td>-</td>
<td>9 (26%)</td>
<td>49 (73%)</td>
<td>125 (21%)</td>
<td>39 (76%)</td>
<td>-</td>
</tr>
<tr>
<td>Open Helmet without head or cervical injury, n</td>
<td>-</td>
<td>-</td>
<td>25 (74%)</td>
<td>18 (27%)</td>
<td>468 (89%)</td>
<td>12 (34%)</td>
<td>-</td>
</tr>
</tbody>
</table>
were all of the studies taken as a cohort-based study with the five latest year publications that were included.9,10,11,12,14 The setting of the studies also varies from countries with many sets of the event thus the validity of helm use in preventing motorcycle accidents has better external validity. The weakness of the studies was conducted with few subjects and some studies that included in the cohort are only patients who have been admitted to the hospital that cooperate with the researcher. The summary can be evaluated in Table 3.

Table 2. Summary of comparison of Full-face Helmet Versus Partial Face Helmet on Head-facial and Cervical Trauma on Motorcyclists Who Had Accidents based on This Review.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-face helmet</td>
<td>626</td>
<td>5042</td>
<td>5668</td>
</tr>
<tr>
<td>Partial helmet</td>
<td>938</td>
<td>4666</td>
<td>5,604</td>
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<tr>
<td>Total</td>
<td>1564</td>
<td>9708</td>
<td>5,996</td>
</tr>
</tbody>
</table>

Table 3. Summary of comparison of Full-face Helmet Versus Open Face Helmet on Head-facial and Cervical Trauma on Motorcyclists Who Had Accidents based on This Review.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-face helmet</td>
<td>759</td>
<td>4060</td>
<td>4819</td>
</tr>
<tr>
<td>Open face helmet</td>
<td>285</td>
<td>595</td>
<td>880</td>
</tr>
<tr>
<td>Total</td>
<td>1044</td>
<td>4655</td>
<td>5,996</td>
</tr>
</tbody>
</table>

Discussion

Road traffic accidents until now still become unsolved problems, and most of the incidents are caused by motorcycle accidents, especially in low-middle income countries worldwide.1,2 Many actions can be done to overcome the burden of these problems and based on the current review, using a helmet is one of the best ways to reduce the morbidity and mortality rate of motorcycle accidents.4 Here, we reviewed the best helm that can be used to reduce the burden of motorcycle accidents.

This review of large observational studies found that the overall full-face helmet is the most prominent to prevent head and cervical injuries in motorcycle accidents.7-14 The Full-face helmet
could ameliorate the outcomes of the victim compared to other helmet types of helmet either in preventing fracture or brain-spinal cord injuries. But, it does not mean that the full-face helmet did not have disadvantages. Lam, et al stated that a full-face helmet is heavier thus causing discomfort.\(^7\) The Full-face helmet also reduces the eye view of the rider compared to the other helmet. The main finding of this systematic review is that a full-face helmet was better than either partial or open face helmet in preventing head-facial and cervical injuries of motorcycle riders in an accident. The risks of head-facial and cervical injuries (including neurological deficit) were lower by 17% when compared with a partial-helmet and 24.26% when compared with an open face helmet.\(^7,14\)

The reason why a full-face helmet could confer better protection, especially in head injuries, is that three causative factors determining the prognosis of motorcycle-related accidents are helmet wearing, helmet fixation status and visor damage.\(^8\) It is highlighted that helmet fixation is a stronger predictor in determining the head injury than helmet types. Usage of the full-face helmet could prevent dislodgement due to its effect in fixating the head of the user. The problems arising from these cases are that the removal of the full-face helmet may be harder and causes discomfort due to more heat and moisture in tropical countries, such as Indonesia.\(^8\) Moreover, it needs support from the government in promoting and cutting the cost of the full-face helmet, especially in low-middle income countries to prevent more burden caused by disability or death due to motorcycle accidents.

There were some limitations to this review. First, the outcome criterion was not uniformed in the comparison between all helmets due to different specific types of head-facial and neck injuries. Second, the eligible participants vary among studies based on inclusion and exclusion criteria and there was still no study conducted in Indonesia, which is one of the main aims in this review implementation.

Our findings are in agreement and consistent with previous literature comparing the protective effect between full-face, partial, and open face helmets conducted by Liu, et al in 2008 published on Cochrane review.\(^4\) This systematic review suggests that using a full-face helmet offers the best solutions to overcome high morbidity and mortality rate due to head-facial and cervical trauma due to its protective
advantages. By implementing the law of using full-face helmet, namely in Indonesia, we are one step closer to achieve sustainable development goals for road safety (SDGs), namely good health and well-being by halving the number of global deaths and injuries from road traffic crashes and sustainable cities and communities by providing access to safe, affordable, accessible, and sustainable and safe transport system for all.

**Conclusion:**

In General, this review concludes that a full-face helmet reduces head-facial and neck injuries better than other helmets in motorcycle accidents thus reducing the morbidity and mortality rate. Policymakers may need to specify the full-face helmet as the recommended helmet especially in low-middle income countries.

**Declarations**

*Ethics approval and consent to participate*

Not applicable.

*Availability of data and material*

Not applicable.

*Conflict of interests*

The authors report no relationships that could be construed as a conflict of interest.

**Funding**

Not applicable.

**Authors’ contributions**

-
References


Risk and Protective Factors Associated with Nuclear Sclerotic Cataract among Adults: Systematic Review

DOI: 10.52629/jams.v10i1.189

Jeremy Rafael TANDAJU(1), Jessica Audrey (1)
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Abstract:
Visual impairment is currently suffered by 253 million people and leads to blindness in 15% of cases. Among them, cataract is the main cause in the world and Indonesia (52%), which could be prevented. Although actions have been taken in-order to manage cataract, the number is increasing 0.1% yearly, thus we conducted a systematic review of 11,377 subjects in 11 case-control studies from PubMed and EBSCOhost in-order to know the risk factors of nuclear sclerotic cataract (NSC), the most common cataract in the world, hence reduce incidence and prevalence of it and blindness. Full article study texts were assessed with STROBE’s criteria for further review. Within study, we concluded

Introduction:

three preventable risk factors of NSC. Sunlight exposure which is gained by being outside for leisure (OR=1.45) or work (OR=1.75), could even elevate the risk up to 4.19 folds due to the glycation process which occurs with the help of UV light. Diabetes is also linked, both acute (OR=1.66) and more dangerous chronic (OR=3.71) because of the retinopathy mechanism. Furthermore, alcohol (OR=1.18) and smoking (OR=5.44) are also responsible for elevating the risk. However, a healthy diet with complete vitamins and low triglycerides, uric acid, and creatinine are proven to be able to cut the risk of NSC by half. Thus, we would like to increase awareness of primary health-care workers and the community itself to educate the community about the risk factors of NSC in-order to reduce its incidence and prevalence rate as a step to achieve WHO’s “VISION 2020: The Right to Sight.”

Keywords: cataract, lifestyle, nuclear sclerotic, protective factors, risk factors
Visual impairment, especially blindness is a prolonged-major problem worldwide among adults. According to the World Health Organization (WHO) and International Agency for the Prevention of Blindness (IAPB), 253 million world population are visually impaired, dominated by adults – 36 million are blind including 3 million Indonesians, highest in South-East Asia.\(^1\)\(^2\) This could be caused by the fact that Indonesia is both a developing and tropical country, which speed up the occurrence of cataract by approximately 15 years. Among 1.5% blind Indonesians, 52% are caused by cataract which is acquired by 1.8% of the population and contribute to blindness more than any other diseases combined such as glaucoma and refractory impairment.\(^2\)

However, 80% of blindness causes could be prevented and cured beforehand, including cataract. WHO has taken efforts to eliminate avoidable blindness through “VISION 2020: The Right to Sight” – a long-time aimed program by the end of the year. Indonesia’s government has also done several steps in-order to support those programs, including donating US$ 72,762,237 yearly to fund a quarter of total 80,744 cataract operations performed yearly. Although actions have been taken, the number of blindness incidence in Indonesia is still climbing up to now with 210,000 (0.1%) additional population getting blind each year – which can be interpreted as one person going blind as a minute passes by.\(^2\) Thus, we conducted a scientific review to identify risk and protective factors of cataract which could be prevented and applied to reduce incidence and prevalence of cataract which could lead to blindness. Moreover, we choose to study nuclear sclerotic cataract (NSC) further because it is three times more likely to occur than other types of cataracts, which makes it the most common cataract in the world and Indonesia.\(^3\)

Since the early 1970s, interest in improving the end-of-life, palliative, and hospice care of patients has progressed from being the concern of a limited group of healthcare professionals to being the concern of the entire international healthcare community. While these three types of care are defined differently, they essentially comprise the idea of providing holistic care to patients who are about to succumb to death, as well as to their family members (I). The provision of this care is classified based on age (adult, geriatric, or pediatric patients) and occurs in settings such as hospitals, nursing homes, and patient homes. However,
the implementation of this care has been severely challenged during the COVID-19 pandemic due to the associated surge in patients needing palliative and hospice care.

Methods:

In order to determine factors contributing to development of nuclear sclerotic cataract among adults, we conducted a systematic review of large case-control studies based on PRISMA statement from PubMed and EBSCOhost using the keywords “nuclear OR sclerotic”, “cataract”, “risk factor OR risk OR cause”, “case-control OR case control”.4,5 Searching was done in November 2018. Afterward, inclusion criteria were set to filter the results including: case-control study, studying NSC, adult subject, study identifying preventable risk factors or applicable protective factors among adults population. In addition, exclusion criteria were also set: immunocompromised patients, unauthentic articles, not accessible articles, and written in languages other than English and Bahasa. We did not set a time range for selected studies to ensure sensitivity of our search. Subsequently, we set necessary data to be extracted from articles including: author and year of publication, study design, location of study, sample size and ratio, subject mean or range of age, method of analysis, and outcome which is picturized by odds ratio for each factor. Finally, the articles will be assessed through “Strengthening the Reporting of Observational Studies in Epidemiology” / STROBE's criteria of case-control study which includes 22 criteria in which 1 point is given for every criterion met. In this study, we did not find any potential confounding factor, thus matching was not necessary. The quality assessment was conducted by two reviewers collaboratively and concluded after consensus was reached.

Results:

The search was conducted via PubMed and EBSCOhost. Titles were screened for relevancy and duplication. Contents were screened for inclusion and exclusion criteria. Articles that went over criteria were fully assessed for eligibility and study design. Last, 11 suitable case-control articles were reviewed and included in this systematic review. Articles were assessed with STROBE's criteria to ensure it was in good quality. Due to limitation of page count, STROBE results of all articles could be seen in Table 1. The holistic process can be seen in Figure 1, while the included study design and characteristics are further shown in Table 2.
DISCUSSION

Analysis of the study

There are plenty of risk factors which are preventable and associated with NSC. However, considering the feasibility, page limitation, and importance based on the quality of previously assessed studies, we list three preventable risk factors and one feasible protective factor contributing largest towards NSC.

Sunlight exposure

Various studies showed that sunlight elevates the risk of NSC dramatically. Studies by Neale, Pastor-Valero, Rafnsson, Williams stated that exposure to sunlight enhances the risk by 2.80, 3.68, 4.19, 1.45 folds respectively. In addition, the risk also applies to occupational purposes which require daily outdoor activities – could be seen in studies held by Williams that job location in sunlight increases the risk by 1.75 times. More detailed occupations, such as pilot studies by Rafnsson and non-professional studies by Leske multiply the risk by 3.02 and 1.96 folds respectively. In addition, wearing no sunglasses outdoors elevates the risk by 1.30 folds according to Neale. However, according to Mohan, being in cloud cover could reduce the risk by 0.78 folds.

Those findings are proven to be true as chronic sunlight exposure could initiate and increase oxidative stress in the eye. Oxidative stress is a harmful chemical reaction which occurs as cells take oxygen to make energy. Eye lens consist mainly of water and proteins, lacking of organelles and oxygen, which minimize the risk of stress to happen. However, UV light contained in sunlight could replace oxygen role in oxidative reactions by damaging lens protein via glycation process, which could scramble and clump protein together to form a cloudy structure of cataract. In addition, people who
<table>
<thead>
<tr>
<th>Item No</th>
<th>Title and abstract</th>
<th>Recommendation</th>
<th>Ghanavati et al., 2015</th>
<th>Giuffre et al., 2005</th>
<th>Leske MC et al., 1990</th>
<th>Miglior S et al., 1994</th>
<th>Mohan M et al., 1989</th>
<th>Neale RE et al., 2003</th>
<th>Pastor-Valero M et al., 2007</th>
<th>Phillips CI et al., 1996</th>
<th>Rafnsson V et al., 2005</th>
<th>Shao M et al., 2017</th>
<th>Williams SL et al., 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td></td>
<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Objective(s)</td>
<td>3</td>
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<td>Methods</td>
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<td>State specific objectives, including any prespecified hypotheses</td>
<td>Yes</td>
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<td>Study design</td>
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<td>Present key elements of study design early in the paper</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Setting</td>
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<td>Participants</td>
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<td>(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</td>
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<td>(b) For matched studies, give matching criteria and the number of controls per case</td>
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5. potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.

For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.

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<td><strong>(b)</strong> Describe any methods used to examine subgroup interactions</td>
<td>Yes</td>
<td>Yes</td>
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<td><strong>(c)</strong> Explain how missing data were addressed</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<td><strong>(d)</strong> If applicable, explain how matching of cases and controls was addressed</td>
<td>Yes</td>
<td>No</td>
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**Results**

115
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<td>diagram</td>
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</table>
study participants (e.g., demographic, clinical, social) and information on exposure and potential confounders

(b) Indicate number of participants with missing data for each variable of interest

<table>
<thead>
<tr>
<th>Variable</th>
<th>No</th>
<th>No</th>
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Outcome data 15* Report numbers in each exposure category, or summary measures of exposure

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<tr>
<th>Subcategory</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
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<tbody>
<tr>
<td>Main results</td>
<td>16</td>
<td>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
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<td></td>
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<td>(b) Report category boundaries when continuous variables were categorized</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>Other analyses</td>
<td>17</td>
<td>Report other analyses done—eg analyses of subgroup s and interactio ns, and sensitivity analyses</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Key results</td>
<td>18</td>
<td>Summarise key results with reference to study objectives</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Limitations</td>
<td>19</td>
<td>Discuss limitations of the study</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</table>
taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.

Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.
<table>
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<tr>
<th>Generalisability</th>
<th>21</th>
<th>Discuss the generalisability (external validity) of the study results</th>
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<th>No</th>
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<tr>
<td>Funding</td>
<td>22</td>
<td>Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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</table>
Table 2. Included study designs and characteristics

<table>
<thead>
<tr>
<th>Author Year (STROBE’s score)</th>
<th>Study Design</th>
<th>Location</th>
<th>Sample Size</th>
<th>Case: control ratio</th>
<th>Range/mean of sample age</th>
<th>Method of analysis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghanavati M et al, 2015.[6] (18.17/22.00)</td>
<td>Matched case-control study</td>
<td>Tehran</td>
<td>295</td>
<td>1:0.49</td>
<td>57.29 years</td>
<td>Kolmogorov-Smirnov test, Chi-square test, Wilcoxon-McNemar tests, Kruskal-Wallis test, logistic regression</td>
<td>Healthy eating index (OR=0.19)</td>
</tr>
<tr>
<td>Giuffre G et al., 2005.[7] (16.43/22.00)</td>
<td>Population-based case-control study</td>
<td>Sicily</td>
<td>1068</td>
<td>1:3.90</td>
<td>70.08 years</td>
<td>Univariate analysis</td>
<td>Diabetes &gt;10 years (OR=1.66), Refractive defects &gt; -1.5D (OR=7.81)</td>
</tr>
<tr>
<td>Leske MC et al, 1990.[8] (19.17/22.00)</td>
<td>Case-control study</td>
<td>Massachusetts</td>
<td>1380</td>
<td>2.17:1</td>
<td>64.43 years</td>
<td>Mantel-Haenszel test, Polychotomous logistic regression</td>
<td>Low education (OR=1.46), Use of multivitamin supplements (OR=0.63), Smoking (OR=1.68), Nonprofessional occupation (OR=1.96), Nutritional intake: vitamin A (OR=0.45), vitamin C (OR=0.48),</td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Location</td>
<td>Year</td>
<td>Ratio (OR)</td>
<td>Age Range</td>
<td>Odds Ratio (OR)</td>
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<tr>
<td>Miglior S et al., 1994 [9] (20.17/22.00)</td>
<td>Case-control</td>
<td>Milan</td>
<td>375</td>
<td>1.34</td>
<td>40-86 years</td>
<td>Vitamin E (OR=0.66), riboflavin (OR=0.72), niacin (OR=0.57), thiamine (OR=0.60), iron (OR=0.59)</td>
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<td>Mohan M et al., 1989 [10]</td>
<td>Case-control</td>
<td>New Delhi</td>
<td>1990</td>
<td>2.62:1</td>
<td>52.95 years</td>
<td>Polychotomous logistic regression</td>
<td>Gas as cooking fuel (OR=0.62), Higher level of education (OR=0.62), Increased dietary protein (OR=0.84), Increase exposure to cloud cover (OR=0.78)</td>
</tr>
<tr>
<td>Study</td>
<td>Methodology</td>
<td>Location</td>
<td>Cases</td>
<td>Controls</td>
<td>Matched</td>
<td>Age</td>
<td>Risk Factors</td>
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<tr>
<td>Neale RE et al., 2003</td>
<td>Conjunct case-control study</td>
<td>Nambour</td>
<td>354</td>
<td>1:0.82</td>
<td>58 years</td>
<td>Not tertiary educated (OR=6.67), Diabetes (OR=1.66), Smoking (OR=1.28), Medium sun exposure (OR=2.80), No sunglasses (OR=1.30)</td>
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<tr>
<td>Pastor-Valero M et al., 2007</td>
<td>Frequency-matched case-control study</td>
<td>Valencia</td>
<td>677</td>
<td>1:0.97</td>
<td>66.35 years</td>
<td>No secondary education (OR=3.85), Sun exposure (OR=3.68)</td>
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<tr>
<td>Phillips CI et al., 1996</td>
<td>Stringent case-control study</td>
<td>Edinburgh</td>
<td>1848</td>
<td>1:0.87</td>
<td>&gt;17 years</td>
<td>Heavy alcohol (OR=1.18), Smoking (OR=1.11)</td>
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<tr>
<td>Rafnsson V et al., 2005</td>
<td>Population-based case control study</td>
<td>Reykjavik</td>
<td>445</td>
<td>1:0.19</td>
<td>67.46 years</td>
<td>Pilot (OR=3.02), Smoking (OR=1.92), Sun-radiation (OR=4.19)</td>
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<tr>
<td>Shao M et al., 2017</td>
<td>Case-control study</td>
<td>Shanghai</td>
<td>958</td>
<td>1:1.06</td>
<td>68.10 years</td>
<td>BMI (OR=1.22), Hypertension (OR=1.88), C3 levels (OR=0.92)</td>
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<tr>
<td>Study</td>
<td>Location</td>
<td>Year</td>
<td>Age Range</td>
<td>Methodology</td>
<td>Risk Factors</td>
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<tr>
<td>Williams SL et al., 2002^1^</td>
<td>Italian-American case-control study in Parma</td>
<td>1987</td>
<td>45-79 years</td>
<td>Cox proportional hazard models, logistic regression</td>
<td>Smoking (OR=1.74), No vitamin (OR=1.72), Diabetes (OR=1.25), Uneducated (OR=1.30), Job location in sunlight (OR=1.75), Leisure time in sunlight (OR=1.45)</td>
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</table>

Note: OR, odds ratio; SAS, statistical analysis software; SPIDA, spatial intensity distribution analysis; ANOVA, analysis of variance; ROC, receiver operating characteristic
has either or both of light colored eyes, photosensitization drugs (eg: fluoroquinolones, tetracycline, birth control pills, anti-malarial, psoralens), previous cataract surgery should be extra careful as those traits enhance eye proneness towards UV light in sunlight. Furthermore, outdoor occupations and living in tropical countries greatly enhances the amount of UV light received, thus could increase the risk of NSC.

**Diabetes**

Diabetes is linked with the elevation of NSC risk. Studies by Giuffre, Neale, Williams concluded that diabetes could increase the risk slightly by 1.66, 1.66, and 1.25 folds respectively. However, prolonged diabetes increases the risk dramatically by 3.71 folds according to Miglior.

Diabetes can cause NSC through retinopathy, which is damage and proliferation of blood vessels which affect the backside of the eye called macula in the retina as a complication of blood sugar disease. Retinopathy could cause retinal detachment, permanent vision loss, and diabetic macular edema. However, retinopathy is suspected to affect the front side of the eye by secreting growth factors which supposedly are used to grow new vessels. These growth factors are used by lens protein to proliferate, cramped, and forming a cloudy layer. In addition, 75% retinopathy occur after the fifth year of diabetes, thus acute diabetes cause much less impact on cataract compared to chronic diabetes.

**Alcohol and smoking**

Consumption of alcohol and cigarette smoking are found to be associated with an increased risk of cataract. In studies conducted by Miglior, Phillips, Neale, Rafnsson, Williams, and Leske, smoking was found to be associated with an increased risk of cataract by 5.44, 1.11, 1.28, 1.92, 1.74, and 1.68 folds respectively. In addition, the studies by Miglior and Phillips also revealed an increased risk of cataract by 1.06 and 1.18 times respectively with the consumption of alcohol.

Alcohol is found to facilitate the production of reactive oxygen species (ROS), as it stimulates the activity of enzyme cytochrome P450s which is believed to be involved in ROS production. Furthermore, the product of its metabolism may eventually lead to ROS generation in the cell. As a result, such conditions contribute to the development of oxidative stress in the body. Similarly, cigarette smoking is also linked to such an increase in oxidative stress. Cigarette smoke components, especially cigarette tar, are found to
contain high levels of both stable and unstable free radicals and ROS. Moreover, smokers are found to have an increased level of cadmium in their blood, and cadmium could subsequently replace metals associated with the enzyme superoxide dismutase (SOD), such as copper, zinc, and manganese, thereby inactivating the enzyme. SOD is an enzymatic antioxidant the function of which is to remove free radicals by converting them to harmless products. Reduction in SOD enzymatic activity therefore significantly weakens the antioxidant defense mechanism, increasing ocular lens susceptibility to ROS. The double effect of both increased oxidative burden and decreased protection by antioxidants in smokers therefore significantly contributes to early onset of cataractogenesis.

Nutrition

Research and various studies have also indicated the relationship between nutrition and cataract, in which diet and nutrition are shown to have an important role in helping to reduce the risk of cataract. A study conducted by Leske discovered that adequate nutritional intake of vitamin A, C, E, as well as riboflavin, niacin, thiamine, and iron is linked with the reduction of NSC risk by 0.45, 0.48, 0.66, 0.72, 0.57, 0.60, and 0.59 folds respectively. This shows consistency with the study by Ghanavati which concluded that a healthy diet has the chance of reducing the risk of cataract by 0.19 folds, considering fruits and vegetables are actually main sources of these vitamins. Tomatoes, papaya, and oranges, for examples, are proven to have a high content of vitamin C. On the other hand, Miglior found in his study that consumption of high levels of uric acid, creatinine, and triglycerides in the diet multiply the risk of cataract by 1.72, 2.16, and 2.32 folds respectively.

The findings above are consistent with the fact that several vitamins, such as vitamin C and E, can act as antioxidants. Moreover, several green leafy vegetables are also found to contain lutein and zeaxanthin, which also have important antioxidant properties. Damage to the ocular lens can be caused by the photochemical generation of reactive oxygen species, commonly known as oxygen radicals, eventually leading to oxidative stress and consequently, cataract. Antioxidants, however, are able to react with these free radicals, stopping the free radicals chain reaction, thereby preventing further damage done. A healthy diet which includes adequate amounts of...
vitamins and antioxidants, especially those consisting of fruits and vegetables, is therefore an important protective factor to fight against the risk of cataract.

Strengths and limitations of the study

This study is a primary review to give readers a broad image about nuclear sclerotic cataract conditions worldwide and factors which may precipitate or easen it. This study is expected to give information on prevention of nuclear sclerotic cataract occurrence. However, the exclusion of inaccessible and unpublished papers limited our review. In addition, heterogeneity of the subjects included in studies and places studies were held could lead to limitation on generalizability of data.

Conclusion:

This systematic review of large case-control studies is conducted to analyze preventable risk and applicable protective factors related to cataract, focusing primarily on NSC as the most common cataract in Indonesia. Based on the above review, we conclude that excessive sunlight exposure, diabetes, alcohol and smoking are important preventable risk factors contributing to incidence of NSC. A healthy diet and good nutrition, on the other hand, may help to reduce the risk of cataract with its protective traits. Those factors are expected to help primary health-care workers and others in educating the community in-order to reduce the incidence and prevalence of NSC in the world, especially Indonesia, thus eradicating preventable blindness, hence, make possible WHO’s aim: “VISION 2020: The Right to Sight.”

Declarations

Ethics approval and consent to participate

Not applicable.

Availability of data and material

Not applicable.

Conflict of interests

Writers declared that this research has no conflict of interest.

Funding

Not applicable.

Authors’ contributions

Jeremy Rafael Tandaju (Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing, visualization,
supervision, project administration), and Jessica Audrey (Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing, visualization, supervision, project administration).

References


25. Nimse SB, Pal D. Free radicals, natural antioxidants, and their...

Efficacy of Internet-Based Cognitive Behavioral Therapy for Adults with Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

DOI: 10.52629/jamsa.v10i1.409

Nathaniel Gilbert DYSON (1) Josh Nathaniel JOWONO (1) Cokorda Istri Agung Dewinta ADNYANI (1)
1- Medical Student, Faculty of Medicine, Universitas Indonesia
nathanielgilbert88@gmail.com

Abstract:
Introduction: The COVID-19 pandemic has brought tremendous impact to mental health management in patients with obsessive compulsive disorder (OCD). Internet-based cognitive behavior therapy (I-CBT) has been demonstrated to be efficacious on alleviating symptoms among adult patients with OCD. Purpose of study: This systematic review and meta-analysis aims to evaluate the efficacy of Internet-Based Cognitive Behavioral Therapy for adult OCD patient.

Methods: This review selects randomized controlled trials found in multiple databases searching for studies implementing I-CBT for OCD up to September 7th, 2021, using determined inclusion criteria, such as OCD patient with study population only adults age population, assess obsessive compulsive score and assess depression, and exclusion criteria such as unsuitable study design, studies with incomplete outcome data, and studies in languages other than English. This review was arranged based on PRISMA guideline. Results and Discussion: Our review includes 6 RCTs with a total of 590 participants. Quantitative analysis of mean differences was performed using Review Manager 5.4 in continuous, random-effects model. I-CBT demonstrates promising efficacy in reducing adverse psychosocial conditions in OCD patients including obsessive compulsive symptoms (pooled MD: -4.49 [95%CI: -6.78 – (-2.19)]; p=0.0001) and depression (pooled MD: -1.97 [95%CI: -3.61-(-0.34)]; p=0.02). Conclusion: I-CBT presents a promising solution for alleviating symptoms in OCD patients. We also recommend further studies to be done especially in developing countries to evaluate the cost effectiveness and feasibility of I-CBT.
Keywords: Obsessive compulsive disorder, Internet-based, Cognitive behavioral therapy, Adults, Efficacy

Introduction:

With the prevalence of 2-3% worldwide and its early development in life, obsessive compulsive disorder or OCD is a mental health condition that has tremendous effect on public health.\(^1\) Obsessive compulsive disorder (OCD) is a condition where intrusive thoughts and compulsive action are present when trigger(s), such as behavior or specific conditions, are met. The obsession can arise from common fears, such as contamination, unacceptability, aggression, hoarding, or symmetry concerns. Obsessive thoughts that are present can bring out many implications to action and mostly on their mental distress, anxiety, and excessive worries which occurs more frequently than we thought it would be.\(^2\)

The COVID-19 pandemic has also badly affected this condition. With the condition, people with OCD are constantly intruded with distress from virus related thoughts and hand washing behavior.\(^3\) With frequent triggers and inconsistent flow of information, people with OCD, especially contamination fear, has shown to have more severe and frequent symptoms. This condition has also pushed people with OCD to have personal coping mechanisms as physical therapy is restricted.\(^4,5\) Other than that, the high distress caused by the pandemic has also badly impacted people with no signs of OCD to have symptoms too.\(^3\)

Current study shows that cognitive behavioral therapy (CBT), especially exposure and response prevention (ERP) which is done by face-to-face meeting, is more favorable to be alleviate OCD symptoms than pharmacological treatment.\(^6,7\) However, with the present condition, I-CBT or internet-based cognitive behavioral therapy has gained more popularity with the ease of use and effective implementation. With the advancement in technology, this adaptation of CBT in the internet has found its place to be one of the alternative strategies to alleviate the condition. Many other symptoms such as anxiety, stress, and depression, have been proven to be decreased and controlled by I-CBT proven by the growing amount of research right now.\(^4,8\)

However, to our knowledge, there has not been any review or
meta-analysis done to conclude the findings. Therefore, we conducted a systematic review and meta-analysis to further promote the use of I-CBT in Indonesia, especially for OCD patients.

Material and Methods:

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which can be accessed through [http://www.prisma-statement.org/](http://www.prisma-statement.org/).

Search strategy

A comprehensive literature search was performed in multiple databases including PubMed, Scopus, Cochrane, ProQuest, Science Direct, and EBSCOhost, searching for studies implementing internet-based cognitive behavioral therapy for obsessive compulsive disorder from inception up to September 7th, 2021 with the following keywords: ("internet" [MeSH Terms] OR internet[Text Word] OR online) AND ("cognitive behavioral therapy"[MeSH Terms] OR cognitive behavioral therapy [Text Word]) AND (obsessive[All Fields] AND compulsive[All Fields]) AND efficacy.

The detailed keywords for each database are attached in Appendix 1.

Study eligibility criteria

Along with study screening, the authors predetermined the following inclusion criteria: (1) type of study, clinical randomized controlled trials; (2) study population, only adults age population; (3) intervention, internet-based cognitive behavioral therapy; (4) outcomes, which include obsessive compulsive score, depression, quality of life, and other secondary parameters reported. Meanwhile, the exclusion criteria are set to: (1) unsuitable study design, including cohort studies, preclinical studies, commentaries, conference abstracts, and letters to the editor; (2) studies with incomplete outcome data; (3) studies which are not completed yet at the time of retrieval; (4) studies with irretrievable full-text articles; (5) studies without a control group; and (6) studies in languages other than English. Furthermore, duplicate removal was performed using EndNote X9 software. Screening of titles and abstracts of studies was carried out according to criteria of accessibility by three independent reviewers. Any disagreements were discussed into consensus. The detailed planned procedure is illustrated in Figure 1.
Data extraction

We predetermined the outcome sheet in tabular form to include the following data to be extracted: (1) author and year of publication; (2) study characteristics, including study design and location of study; (3) study population, including sample size, mean age, and other related characteristics; (4) intervention, type of internet-based cognitive behavioral therapy used and duration of follow-up; and (5) study outcomes, including comparative indicators, values pre- and post-intervention, as well as effect size in Cohen’s d and significance (p) values. Qualitative characteristics were extracted by two reviewers, and an independent third author rechecked accuracy of extracted data while performing statistical analysis. Moreover, we present the extracted data in detail in Table 1.

Quality assessment

Quality of each study was accessed using the Cochrane Risk of Bias 2.0, which evaluates 5 domains including randomisation bias, bias due to deviations from intended interventions, missing outcome data, outcome measurement, and bias in reporting results. The overall quality of study is then converted based on the Agency for Healthcare Research and Quality (AHRQ) standards. This assessment was performed by three independent reviewers and if there is any disagreement, resolution would be made based on consensus by the three reviewers.

Statistical analysis

We performed statistical analysis using Review Manager ver. 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen). The mean differences and standard deviations (SDs) were extracted from studies, and we interpreted the pooled effects. We utilized continuous, DerSimonian-Laird random effects
model as proposed by Riley et al, since we considered that indecipherable heterogeneity could be discovered from studies. Heterogeneity was further evaluated using $I^2$ statistics, with cut-off limits of 0%, 25%, 50%, and 75% as insignificant, low, moderate, and high heterogeneity, respectively. Additionally, we performed sensitivity analysis following the Duval and Tweedie’s trim-and-fill method to identify any outlier study.

**Results and Discussion:**

**Search results and study selection**

Initial search is conducted using previously mentioned strategies from PubMed, Scopus, Cochrane, ProQuest, EBSCOhost, and ScienceDirect resulted in a total of 3,155 studies (Figure 1). Before the screening process, we exclude 110 studies which are either deduplicated, 1,955 studies which are marked as ineligible by automation tools and other reasons, such as ineligible language. Furthermore, 1,045 studies and 20 studies were excluded after title screening and abstract screening, respectively. Studies which are not related to our main topics are excluded in this phase. In addition, 19 studies were further excluded since 7 studies have unsuitable study design, 6 studies use inappropriate intervention type, and 9 studies were not available in full text version. The final search yielded in a final nine studies, consisting of mostly randomized controlled trials to be included in further analysis.

**Publication bias**

Critical appraisal was conducted using Cochrane Risk of Bias 2.0 for randomized controlled trials criteria which is then categorized into low-risk bias, some concerns, or high-risk bias. Detailed descriptions of each domain are available on Appendix 2. We found no study with high risk of bias. We only found one study by Schroder et al which considers the need of some concerns. However, the reported need of concerns is only due to no information about the randomization process or bias in deviations from intended interventions because the participants are aware of their assigned interventions which is relatively unavoidable as in this study, unguided I-CBT were given. Nevertheless, the other studies are evaluated as having low risk of bias, thus, may be concluded that our study included overall good quality of studies.

**Mechanisms of I-CBT for OCD patients**
Current available gold standard treatment for OCD is cognitive behavioral therapy which is given face-to-face with the patient at the healthcare facilities.\textsuperscript{6} Ironically, a lot of patients are late or cannot get CBT because of the barrier of the cost, time, and stigmatization.\textsuperscript{12–15} Yet, the COVID-19 pandemic also adds even
<table>
<thead>
<tr>
<th>Studies, year</th>
<th>Location</th>
<th>Study Design</th>
<th>Sample size; mean age</th>
<th>Sample characteristics</th>
<th>Intervention duration</th>
<th>Follow-up duration</th>
<th>Measured Parameters</th>
<th>Intervention Group (Mean; S.D)</th>
<th>Control Group (Mean; S.D)</th>
<th>Effect Size (Cohen's d)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersson et al, 2012</td>
<td>Sweden</td>
<td>RCT</td>
<td>101 patients; ICBT: 33 y (19-62 y); Control: 35 y (18-67 y)</td>
<td>Patients with primary diagnosis of OCD, without co-morbidity as primary condition, use of psychotropic was allowed (stable for 2 months), without having CBT for past 2 years, other psychological treatment, alcohol abuse, or drug abuse, minimal or extreme OCD, hoarding association, suicidal ideation, axis 2 diagnosis, or any OCD patients given either 10 weeks of ICBT (n=50) or attention control condition (n=51)</td>
<td>4 months</td>
<td>YBOCS 12.94 (6.26)</td>
<td>18.88 (4.18)</td>
<td>1.12 (0.69-1.53)</td>
<td>&lt;0.001</td>
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<td></td>
<td></td>
<td>OCI-R 12.50 (10.15)</td>
<td>19.22 (11.52)</td>
<td>0.62 (0.21-1.02)</td>
<td>&lt;0.001</td>
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<td></td>
<td>MADRS-S 8.90 (6.67)</td>
<td>10.16 (6.94)</td>
<td>0.89 (0.47-1.29)</td>
<td>&lt;0.05</td>
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<td></td>
<td></td>
<td></td>
<td>GAF 65.78 (8.65)</td>
<td>60.18 (10.94)</td>
<td>1.20 (0.76-1.61)</td>
<td>&lt;0.01</td>
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</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Type</td>
<td>Participants</td>
<td>Age (years)</td>
<td>Diagnosis and Treatment Details</td>
<td>Baseline Measures</td>
<td>Endpoint Measures</td>
<td>p-Value</td>
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<tr>
<td>Andersson et al, 2014</td>
<td>Sweden</td>
<td>RCT</td>
<td>101 patients</td>
<td>36.39 y;</td>
<td>Patients with principal diagnosis of OCD, with use of psychotropic medication was allowed</td>
<td>YBOCS</td>
<td>11.37 (6.61)</td>
<td>&lt;0.05</td>
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<td></td>
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<td></td>
<td></td>
<td>37.32 y</td>
<td>(stable for 2 months), without minimal or extreme OCD, hoarding symptoms, and No. co-morbidity</td>
<td>GAF 73.15 (12.46)</td>
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<td>Patients were randomized to a booster program (n=47) or no booster program (n=46)</td>
<td>MADRS-S 8.35 (6.75)</td>
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<tr>
<td>Mahoney et al, 2014</td>
<td>Australia</td>
<td>RCT</td>
<td>86 patients</td>
<td>37.69 y;</td>
<td>Patient with clinically significant symptoms of OCD without psychosis, significant alcohol</td>
<td>DOCS 19.83 (12.71)</td>
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<td>&lt;0.001</td>
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<td></td>
<td>40.46 y</td>
<td>dependence, suicidal ideation, or significant cognitive deficits</td>
<td>OBQ-20 70.71 (25.53)</td>
<td></td>
<td>&lt;0.001</td>
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<td></td>
<td>Patients were randomized to immediate I-CBT group (n=44) or treatment as usual group (n=42)</td>
<td>K10 19.75 (5.87)</td>
<td></td>
<td>&lt;0.001</td>
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<td>PHQ-9 7.21 (4.24)</td>
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<td>&lt;0.001</td>
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Notes:
- RCT: Randomized Controlled Trial
- YBOCS: Yale-Brown Obsessive-Compulsive Scale
- GAF: Global Assessment of Functioning
- MADRS-S: Montgomery-Asberg Depression Rating Scale
- DOCS: Diagnostic Observation Schedule
- OBQ-20: Obsessive-Compulsive Inventory
- K10: K10 Depression Scale
- PHQ-9: Patient Health Questionnaire

Sources:
- Andersson et al, 2014 Sweden RCT
- Mahoney et al, 2014 Australia RCT
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Sample Size</th>
<th>Age Range</th>
<th>Inclusion Criteria</th>
<th>Treatment Assignment</th>
<th>Baseline Measures</th>
<th>Treatment Duration</th>
<th>Follow-Up Measures</th>
<th>Effect Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbst et al, 2014</td>
<td>Germany</td>
<td>RCT</td>
<td>34 patients</td>
<td>28-59 y</td>
<td>Patients with OCD as their primary disorder according to DSM-IV and doesn't have another relevant current or past mental disorder.</td>
<td>14 sessions of ICBT (n=16) or waiting-list control group (n=18)</td>
<td>ISG: 38.19±8.80 y (28-59 y)</td>
<td>8 weeks and 6 months</td>
<td>Y-BOCS SR, Obsession, Compulsions</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Schroder et al, 2020</td>
<td>Germany</td>
<td>RCT</td>
<td>128 patients</td>
<td>18-59 y</td>
<td>Patients with OCD are randomly allocated to unguided I-CBT (n=64) or care-as-usual (n=64) for 8 weeks</td>
<td>8 Weeks</td>
<td>Intervention = 41.45 (SD 12.15)</td>
<td>WHO-QoL, PHQ-9, I-8, RSES, IQ-24</td>
<td>(&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Wootton et al, 2019</td>
<td>Australia</td>
<td>RCT</td>
<td>140 patients</td>
<td>18-64</td>
<td>Patients with OCD scored at least 7 on DOCS, scored 14 on YBOCS and did not have suicidal plans or history of self-harm, etc.</td>
<td>ICBT</td>
<td>ICBT = 34.03 (18-64)</td>
<td>8 Weeks and 3 Months</td>
<td>YBOCS-SR, PHQ-9, DOCS (Total), DOCS (Main)</td>
<td>(&lt;0.001)</td>
</tr>
</tbody>
</table>
severe symptoms, no reported psychotic illness, and no regular use of drinking alcohol.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Note</th>
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<tbody>
<tr>
<td>WLC group</td>
<td>75</td>
<td></td>
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<tr>
<td>Group (n=65)</td>
<td></td>
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</table>

**Note:** NR = Not reported; YBOCS : Yale–Brown Obsessive Compulsive Scale; OCI-R : Obsessive Compulsive Inventory - Revised; GAF : Global Assessment of Functioning; MADRS-S: self-rated Montgomery–Åsberg Depression Rating Scale; DOCS : Dimensional Obsessive-Compulsive Scale; OBQ-20 : Obsessional Beliefs Questionnaire-20 items; PHQ-9 : The Patient Health Questionnaire-9; K-10 : Kessler 10-item Psychological Distress Scale; OCI-R : Obsessive-Compulsive Inventory-Revised; BDI-II: The Beck Depression Inventory-II; Y-BOCS SR: Yale-Brown Obsessive Compulsive Scale Sel Reported; WHO-QoL: World Health Organization Quality-of-Life Scale; I-8: Impulsivity-8; RSES: Rosenberg’s Self-Esteem Scale; IQ-24: Insecure-Questionnaire-24; SD : standard deviation.
more urgency to make haste and find a solution that breaks the barrier.

I-CBT is a program that is delivered online and structured from treatment rationale, psychoeducation, cognitive treatment, and in vivo exposure and response prevention (ERP). The therapist is present to give support, assess the intervention, and giving feedback for the mental exercises. homework exercises.\textsuperscript{12\textendash 16} By using I-CBT, it will save therapist's time and also gives the chance of getting feedback within 24 hours. According to study by Andersson et al, conventional face-to-face CBT spent an average of 540-900 minutes over a 10 week10-week period. Much lower than face-face CBT, patients only spent an average of 129 minutes over a 10 week period.\textsuperscript{15,16} This treatment also removes the barriers from face-to-face CBT such as inconvenience, stigma, and personal embarrassment because I-CBT gives patients more privacy and anonymity. I-CBT is also cost-effective because I-CBT reduces travel cost because it is delivered online.\textsuperscript{12,15}

**Efficacy of I-CBT for obsessive compulsive symptoms**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean SD</th>
<th>Total Mean SD</th>
<th>Total Mean SD</th>
<th>Mean Difference IV, Random, 95% CI Year</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersson 2012</td>
<td>12.94</td>
<td>0.28</td>
<td>50 19.88 4.18</td>
<td>51 19.4% -5.94 [-0.02,-3.80] 2012</td>
<td></td>
</tr>
<tr>
<td>Andersson 2014</td>
<td>11.37</td>
<td>0.61</td>
<td>47 12.05 6.63</td>
<td>46 17.5% -0.68 [-3.37, 2.01] 2014</td>
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<tr>
<td>Harbd 2014</td>
<td>14.44</td>
<td>0.59</td>
<td>16 10.33 6.46</td>
<td>18 13.1% -4.86 [-0.04, 0.74] 2014</td>
<td></td>
</tr>
<tr>
<td>Voskoien 2019</td>
<td>15.42</td>
<td>5.269</td>
<td>65 21.61 3.93</td>
<td>75 20.8% -4.19 [-7.75, -0.63] 2019</td>
<td></td>
</tr>
<tr>
<td>Schuler 2020</td>
<td>17.39</td>
<td>7.35</td>
<td>94 18.98 0.17</td>
<td>84 19.5% -1.60 [-5.66, 2.47] 2020</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>286</td>
<td>300 100.0%</td>
<td></td>
<td>-4.49 [-6.78, -2.19]</td>
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</tr>
</tbody>
</table>

**Figure 2A. Forest Plot of I-CBT Effectiveness for Obsessive Compulsive Symptoms**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean SD</th>
<th>Total Mean SD</th>
<th>Total Mean SD</th>
<th>Mean Difference IV, Random, 95% CI Year</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersson 2012</td>
<td>12.94</td>
<td>0.28</td>
<td>50 18.88 4.18</td>
<td>51 31.3% -5.04 [-8.02, -2.06] 2012</td>
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<tr>
<td>Andersson 2014</td>
<td>11.37</td>
<td>0.61</td>
<td>47 12.05 6.63</td>
<td>48 0.0% -0.68 [-3.37, 2.01] 2014</td>
<td></td>
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<tr>
<td>Hymel 2014</td>
<td>14.44</td>
<td>5.80</td>
<td>16 16.33 5.46</td>
<td>18 7.0% -4.69 [-8.04, -1.34] 2014</td>
<td></td>
</tr>
<tr>
<td>Voskoien 2019</td>
<td>15.42</td>
<td>5.269</td>
<td>65 21.61 3.93</td>
<td>75 55.6% -4.19 [-7.75, -0.63] 2019</td>
<td></td>
</tr>
<tr>
<td>Schuler 2020</td>
<td>17.38</td>
<td>7.35</td>
<td>94 18.98 0.17</td>
<td>84 0.0% -1.60 [-5.66, 2.47] 2020</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>286</td>
<td>300 100.0%</td>
<td></td>
<td>-6.17 [-7.33, -5.00]</td>
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**Figure 2B. Sensitivity Analysis of Studies Evaluating I-CBT for Obsessive Compulsive Symptoms**
Patients with OCD are characterized by obsession and compulsion. Obsession is an unwanted intrusive thoughts, image, or impulses that are recurrent, persistent and lead to distress. In OCD, obsession is followed by compulsion which is a ritualized, repetitive, and intentional behaviour that aims to reduce and neutralize the distress from the obsessive content. Without any intervention OCD symptoms will worsen and affect the patient’s social and work life.\textsuperscript{12-18}

Six studies are included in our quantitative synthesis which demonstrated I-CBT as an effective treatment method for reducing obsessive and compulsive symptoms in adults with OCD, yielding a pooled mean difference (MD) value of -4.49 [p=0.0001; 95\%CI: -6.78 – (-2.19)] (\textbf{Figure 2A and 2B}). Although relatively high heterogeneity has been found, with an $I^2$ value of 78\%, our sensitivity analysis identified Andersson et al (2014) and Schroder et al's study as an outlier, and with its removal the heterogeneity has decreased to much lower value of 0\%. When these studies are removed, the pooled MD is -6.17 [p=<0.0001, 95\%CI: -7.33 – (-5.00)].\textsuperscript{16,18} Andersson et al's study (2014) has shown inferior results compared to the other studies, which might be due to the type of the intervention, which compare between booster and no booster group, in opposition to other studies which compare I-CBT and treatment as usual (TAU) group.\textsuperscript{16} On the other hand, Schroder et al's study has also shown inferior results which might be due to the use of unguided type of I-CBT. In this study, participants are given I-CBT without any guidance from the healthcare providers which might resulted in significantly less effective result compared to the other studies. Therefore, the guided type of I-CBT areis found to be more effective than the unguided type. The limited period of the intervention in the study was also concerned to affect the result.\textsuperscript{18} However, we do not perform further subgroup analysis which aims to explore further the heterogeneity as there is lack of similarities between the two outlier studies in term of obsessive and compulsive symptoms.

\textit{Efficacy of I-CBT for depressive symptoms}

Depression is a mood disorder that causes depressive episodes which make the person feel depressed, lose interest, and don't have energy to do activities. To be diagnosed with depression, at least five of nine depressive symptoms listed in the DSM-5 must be present. Which are sleep disturbance; interest/pleasure
reduction; guilt feelings or thoughts of worthlessness; energy changes/fatigue; concentration/attention impairment; appetite/weight changes; psychomotor disturbances; suicidal thoughts; and depressed mood.19,20

**Figure 3A** shows the forest plot of I-CBT in reducing the occurrence of depression in adult patients with OCD. The pooled MD yields a value of -1.97 [p=0.02, 95%CI: -3.61-(-0.34)], with moderate heterogeneity ($I^2=64\%$). Different type of assessment were used (i.e., MADRS-S, PHQ-9, BDI-II) but all of them are validated and have already been established.12–16,18

Furthermore, as we performed sensitivity analysis in **Figure 3B**, we found that Andersson et al’s (2014) and Schroder et al’s study are again identified as an outlier studies with inferior results as explained in the outcomes of obsessive compulsive symptoms before. The most logical explanation would be due to different type of interventions given in those studies.16,18 Recent meta-analyses by Karyotaki et al., also concluded that guided I-CBT is more effective than unguided I-CBT to reduce depression score for the patient which align with Schroder et al’s study that show less effective result in reducing depressive symptoms.18,21 Once removed, the heterogeneity is negligible ($I^2=3\%$) with pooled MD yielding a value of -3.19 [p=<0.00001, 95%CI: -4.34-(-2.03)]. Nevertheless, subgroup analysis is not performed due to lack of similarities between the outlier studies in terms of depressive symptoms.

**Other outcomes**

Besides the efficacy of I-CBT to reduce obsessive compulsive and depressive symptoms, Schroder et al’s study has also proven its positive impact to patient’s quality of life, although not statistically significant.18 Study by Wootton, et al., also shows that I-CBT has a high acceptability with 82% participants were either very satisfied or satisfied with the program and 96% participants would recommend it to their friends.14 It also aligned with other study that prove acceptability of I-CBT is high (Herbst, et al., 2014; Schroder, et al., 2021).13,18

**Applicability in Indonesia**
All in all, there are at least three main reasons why this innovation might be suitable to tackle current problems in Indonesia. Firstly, the internet users in Indonesia have reached 73.7% of the total population that has increased around 8.9% last year due to the pandemic and the advancement of Palapa Ring. Therefore, the internet base is suitable and viable to be used to help OCD patients in Indonesia.22

Secondly, inadequate knowledge and misperception due to several cultural beliefs have worsened the situation. People with mental disorders are likely to be outcasted or locked in another place by their own family rather than being brought to healthcare facilities. Moreover, the lack of transportation facilities in rural areas might also make it more difficult for patients to reach healthcare facilities.23

Lastly, the number of mental health professionals in Indonesia is still limited. According to the WHO Mental Atlas (2017), Indonesia has only 3 mental health professionals for every 100,000 people which is much lower than the global median, 9 per 100,000 people. It makes the accessibility to reach mental health treatment more exclusive. By using I-CBT the treatment for mental health, especially OCD will be more effective and inclusive for everyone, including people in rural areas and low socio-economic backgrounds.24,25

Strengths and limitations

There are strengths and limitations of this meta-analysis. From our knowledge, this is the first meta-analysis of I-CBT efficacy on adult OCD patients. The result of the meta-analysis shows a promising and significant pooled MD results for I-CBT efficacy on adult OCD patients. The risk of bias assessment results for the studies are also low.

Some limitations should be considered even though our findings are promising. The heterogeneity is high because the I-CBT intervention and period for each study is different. The limited access to full text studies should be considered. The language barrier should also be considered as we only include English studies.

Conclusion

The COVID-19 pandemic has increased OCD symptoms occurrence and burden the therapy management of patients. Therefore, this increased the urgency of a solution for alleviating the symptoms and decreased its depression level. Our study has proven that I-CBT as a novel treatment for OCD has significantly reduce obsessive
compulsive symptoms and depression levels with high acceptability rate. Yet, it also increases a patient's quality of life and general health. The internet base in Indonesia can also boost I-CBT applicability in Indonesia, relieve the high burden of mental health workers, and reduce misperception and the lack of knowledge of mental health disorder in Indonesia. As a recommendation, we suggest further clinical studies assessing I-CBT use in Indonesian OCD patients as well as the advancement of internet quality and widen its scope especially in rural areas.

Declarations

Ethics approval and consent to participate

Not applicable.

Availability of data and material

Not applicable.

Conflict of interests

Authors declare no competing intention for completing this review.

Funding

Not applicable.

Authors' contributions

Nathaniel Gilbert Dyson, Josh Nathaniel Jowono, Cokorda Istri Agung Dewinta Adnyani: All authors have contributed equally

References


20. Depression [Internet]. [cited 2021 Sep 12]. Available from: https://www.who.int/news-room/factsheets/detail/depression
### Appendix 1. Search keywords and databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopus</td>
<td>TITLE-ABS-KEY ( (internet OR online ) AND ( &quot;cognitive behavioral therapy&quot; OR CBT ) AND ( obsessive OR compulsive OR OCD OR &quot;obsessive compulsive disorder&quot; ) ) AND efficacy)</td>
</tr>
<tr>
<td>Cochrane</td>
<td>(Internet AND Cognitive Behavior Therapy AND Obsessive Compulsive Disorder AND efficacy)</td>
</tr>
<tr>
<td>ProQuest</td>
<td>(Internet AND Cognitive Behavior Therapy AND Obsessive Compulsive Disorder AND efficacy)</td>
</tr>
<tr>
<td>ScienceDirect</td>
<td>(Internet or online) AND (Cognitive Behavior Therapy or CBT) AND (Obsessive OR Compulsive OR OCD OR Obsessive Compulsive Disorder) AND Efficacy</td>
</tr>
<tr>
<td>EBSCOhost</td>
<td>(Internet OR online) AND (&quot;cognitive behavioral therapy&quot; OR CBT) AND (obsessive OR compulsive OR OCD OR &quot;obsessive compulsive disorder&quot;) AND efficacy</td>
</tr>
</tbody>
</table>
### Appendix 2. Risk of Bias Assessment

<table>
<thead>
<tr>
<th>Bias domain</th>
<th>Signalling questions</th>
<th>Response options</th>
<th>Authors: year of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias arising from the randomization process</td>
<td>1. Was the allocation sequence random?</td>
<td>Y</td>
<td>Andersson et al; 2012</td>
</tr>
<tr>
<td></td>
<td>1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Risk of bias judgement</td>
<td>-1/+1/?</td>
<td>Herbst et al; 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (low risk)</td>
<td>Schroeder et al; 2020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (low risk)</td>
<td>Wootton et al; 2019</td>
</tr>
<tr>
<td>Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)</td>
<td>2.1. Were participants aware of their assigned intervention during the trial?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>2.2. Were caregivers and people delivering the interventions aware of participants' assigned intervention during the trial?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>2.3. If Y/P/Y/N to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>2.4. If Y/P/Y to 2.3: Were these deviations from intended intervention balanced between groups?</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>2.5. If N/P/N to 2.4: Were these deviations likely to have affected the outcome?</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>2.7. If N/P/N to 2.6: Was there potential for a substantial impact (on the result) of the failure to randomise participants in the group to which they were randomized?</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Risk of bias judgement</td>
<td>-1/+1/?</td>
<td>- (low risk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (low risk)</td>
<td>- (low risk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- (low risk)</td>
<td>- (low risk)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>? (some concerns)</td>
<td>- (low risk)</td>
</tr>
<tr>
<td>Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)</td>
<td>2.1. Were participants aware of their assigned intervention during the trial?</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td></td>
<td></td>
<td>N</td>
<td>N</td>
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<td>N</td>
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</tbody>
</table>
The Potential of Folate-Positive Circulating Tumor Cells (FR+-CTC) as a Novel Diagnostic Biomarker for Non-Small Cell Lung Cancer: A Systematic Review of Clinical Trials

DOI: 10.52629/jamsa.v10i1.405

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Abstract:
Background: Non-small-cell lung cancer (NSCLC) is malignancy that remains the leading cause for cancer mortalities. Diagnosis is often made in advanced stages, hence, the unmet need for novel diagnostic methods. FR+-CTC is acknowledged as a potential diagnostic biomarker that detects NSCLC presence, distinguishing it from benign lung diseases and healthy individuals.

Purpose of Study: This study aims to investigate the potential of FR+-CTC to be utilized as an accurate, sensitive, and specific diagnostic biomarker for NSCLC.

Methods: This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Studies were obtained from databases namely Wiley Online Library, MEDLINE, Science Direct, CENTRAL, and ProQuest. The outcome assessed includes summary receiver operating characteristics (sROC) evaluating diagnostic accuracy taking form of area under the curve (AUC) analysis. Risk of bias assessment is carried out using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2).

Results: 5 studies confirm a higher amount of FR+-CTC in peripheral blood can be utilized as a diagnostic marker in NSCLC patients. Detection of FR+CTC in NSCLC diagnosis is superior to existing biomarkers with a sensitivity and specificity of 81.94% and 73.08%. FR+CTC presents the highest AUC (0.823; 95% CI, 0.773-0.874) compared to other biomarkers. FR + CTC levels can differentiate the types of lung adenocarcinoma with acceptable sensitivity.

Conclusion: FR+-CTC detection is a reliable diagnostic method with the
highest degree of accuracy for diagnosing NSCLC compared to other biomarkers. FR+-CTC can also be utilized to predict possible malignancies, even in its early stages.

**Keywords:** Biomarkers, circulating tumor cells, diagnosis, folate receptor, lung cancer, NSCLC
Introduction:
Globally, lung malignancies remain a significant healthcare challenge within the field of respiratory medicine, as acknowledged that lung cancer remains the leading cause for cancer-related deaths.\textsuperscript{1,2} Advancements in the understanding of non-small cell lung cancer (NSCLC) demonstrated that often, NSCLC is only diagnosed during the advanced stages, which results in a generally poor prognosis for patients.\textsuperscript{3} Hence, there is an unmet need for novel diagnostic and screening methods. An accumulating body of evidence had displayed the potential of folate receptor-positive circulating tumour cells (FR\textsuperscript{+}-CTC) as an accurate diagnostic biomarker that detects the presence of NSCLC and is also able to accurately distinguish it from other benign lung diseases that similarly manifests in non-specific symptoms of NSCLC such as coughing, chest pain, hemoptysis, and dyspnea. It is detected in significantly greater amounts in NSCLC patients, which underpins its utilization as a diagnostic marker. In the long run, the ability to carry out an accurate, sensitive sensitive, and specific diagnostic test for NSCLC would concurrently contribute to the realization of SDG number 3, indicator 3.4.1, which aims to reduce mortality rate from cancer among other diseases. Hence, the focus of this review would be to systematically review the potential of FR\textsuperscript{+}-CTC as a diagnostic biomarker for NSCLC.

Methods
This section contains the data sources, search terms and strategies, selection criteria, number of studies found and included.

Search Strategy
For this review, literature search was conducted based off the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). In obtaining the relevant studies, the following keywords was used: “folate receptor-positive" AND “non-small-cell lung cancer” OR “NSCLC” AND “Biomarker” altogether with appropriate Mesh terms and synonyms. The search strategy was carried out in PubMed/MEDLINE, Wiley Online Library, ProQuest, CENTRAL/Cochrane and Science Direct to disseminate articles that were published up until 6 April 2021.

Inclusion & Exclusion Criteria
Upon the creation of this review, the included studies possessed several inclusion criteria as follows: (1) Clinical trials (2) Studies that evaluate FR+-CTC altered expression to
distinguish between those who are, (3) either healthy, has a benign lung disease, or NSCLC. There is no limitation for age/gender/race. (4) Outcomes of: Area under the curve (AUC) value of ROC analysis; sensitivity & specificity; median FR’-CTC value; as well as any defined threshold or FR’-CTC cutoff levels. Meanwhile, the exclusion criteria applied includes: (1) literatures with irretrievable full text; (2) reviews, letters, commentaries & conference abstracts, (3) studies written in languages other than Bahasa Indonesia or English, (4) incomplete clinical trials.

**Data Extraction & Study Outcomes**

3 independent reviewers extracted data, with any discrepancies adjudicated through consensus. The details extracted from the reviewed studies includes (1) authors and year of publication; (2) disease characteristic of the population; (3) study characteristics: location, design, and sample size; (4) details regarding sampling method and method to analyze FR’-CTC levels. The main outcomes assessed is a summary of the receiver operating characteristics (ROC) curve that demonstrates the diagnostic accuracy of a diagnostic procedure, defined from the area under the curve (AUC). whereas an AUC <0.5 = not useful, 0.5-0.6 = bad, 0.6-0.7 = sufficient, 0.7-0.8 = good, 0.8-0.9 = very good, and 0.9-1.0 = excellent.

**Risk of Bias Assessment**

Risk of bias assessment was conducted using QUADAS-2. Among all the reviewed studies, 2 showed unclear risk of bias for patient selection, 2 showed unclear risk of bias for index test, and two studies showed unclear risk of bias for reference standard. These are due to the lack of clear explanation regarding certain parts of the methodology of the study. Regarding applicability concerns, all studies showed to have low risks. The full methodological quality assessment is displayed in Table 1.

**Table 1. Summary of Quality Assessment of Included Studies using QUADAS-2**

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of Bias</th>
<th>Applicability Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Selection</td>
<td>Index Test</td>
</tr>
<tr>
<td>Xu, 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ding, 2016</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Zeng, 2015</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Zeng, 2016</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

**Results:**

In this section, the authors should include data found from sources and organized systematically i.e., chronologically, thematically, methodologically, etc. Moreover, they should also include an analysis of primary study results based on current medical principles. Include
summary of results from included studies as well as your own analysis and evaluation of the articles. Avoid using personal opinions; be objective in the analysis.

Search Results

Search results from the 5 international databases yielded 172 studies. These were then initially screened through their title & abstract relevancy, and study type relevancy, which resulted in 11 studies and 8 studies after exclusion of duplicates. Full-text screening was then conducted resulting in further exclusion of 3 studies due to their incompatible study design. Complete visualization of the comprehensive selection process is attached as Figure 1.

Characteristics of Included Studies

5 included studies assessed the diagnostic accuracy of FR$^+$-CTC as a diagnostic biomarker for patients with NSCLC. All of the studies were conducted in various regions of China.$^{4-8}$ Of the 5 studies, 3 were single-blinded, prospective trial,$^{5,6,7}$ 1 was a double-blinded, prospective, single center trial,$^{4}$ and 1 study was a single-blinded, prospective, multi-centered trial.$^8$ All 5 studies defined “malignant” lesions as patients with NSCLC subtypes such as adenocarcinoma or squamous cell carcinoma. The results were compared to a control group consisting of a mixture of healthy patients and patients with benign lung diseases. All 5 studies used 3 mL of peripheral blood for samples and are FR$^+$-CTC profiling was conducted using Ligand-targeted polymerase chain reaction (LT-PCR). Data was gathered from 1702 volunteers, (1158 were NSCLC patients, 437 were benign lung disease patients, 107 were healthy patients). A comprehensive summary of characteristics of each study are presented in Table 2.

---

**Figure 1.** PRISMA Flow Chart of Search Strategies

**Characteristics of Included Studies**

5 included studies assessed the diagnostic accuracy of FR$^+$-CTC as a diagnostic biomarker for patients with NSCLC. All of the studies were conducted in various regions of China.$^{4-8}$ Of the 5 studies, 3 were single-blinded, prospective trial,$^{5,6,7}$ 1 was a double-blinded, prospective, single center trial,$^{4}$ and 1 study was a single-blinded, prospective, multi-centered trial.$^8$ All 5 studies defined “malignant” lesions as patients with NSCLC subtypes such as adenocarcinoma or squamous cell carcinoma. The results were compared to a control group consisting of a mixture of healthy patients and patients with benign lung diseases. All 5 studies used 3 mL of peripheral blood for samples and are FR$^+$-CTC profiling was conducted using Ligand-targeted polymerase chain reaction (LT-PCR). Data was gathered from 1702 volunteers, (1158 were NSCLC patients, 437 were benign lung disease patients, 107 were healthy patients). A comprehensive summary of characteristics of each study are presented in Table 2.
Discussion:

Current State of Lung Cancer Diagnostics

The clinical diagnosis and management of NSCLC is currently largely based on pathological findings and clinical symptoms, which would then further categorize NSCLC into different clinical stages, from stages.9,10 Due to a rapidly growing body of evidence, guidelines regarding lung cancer were established, and the most recent being the 8th American Joint Committee on Cancer stage classification for lung cancer. This guideline utilized the TNM criteria to assess the clinical stages of lung cancer, in which the T criteria assessed the size of the primary tumor, N assesses invasion to neighboring lymph node, and M assesses the presence of metastasis. The subsequent treatment plan and survival is then based largely on this clinical staging.11 Interestingly, how pathological, clinical, and sometimes radiological findings are staged into different groups still varies from one established guideline to another, and it is acknowledged, that the accuracy of these clinical staging, are generally low (50-60%).9

The Diagnostic Properties of FR+-CTC

FR+-CTC is a diagnostic marker where it assesses whether folate receptors (FR) are present in circulating tumor cells (CTC) cancer patients.12 CTCs are tumor cells that shed off from primary tumors and into the vasculature, indicating an intermediate stage tumor. The ultimate goal of CTCs is to eventually assert dominance over healthy cells within the body through metastasis, and metastasis and inflict extensive cell deaths and mutations.13 FR are membrane glycoproteins usually found on the CTC surface, hence making them a possible biomarker for the presence of CTCs in the circulation.12,14 Minimally invasive, liquid biopsies are usually taken to assess the quantification of FR+-CTCs in patients with suspected cancer, usually through qPCR methodologies. With little amounts of cells producing FRs on their surface, FR+-CTC detection is substantially more reliable for diagnosis of cancer.12

The Potential of FR+-CTC as a Biomarker to Diagnose Malignant Lung Cancer, and as a Screening Indicator

CTCs have the considerable potential to be acknowledged as a standard screening test and be used for molecular characterization of a tumor. Results of studies have confirmed that a higher amount of
FR'-CTC in peripheral blood is associated with adverse prognosis in NSCLC patients. Detection of CTCs in NSCLC has been challenging due to the rarity in circulation; hence, it is therefore critical that sensitive and specific CTC detection methods are generated to be used as a potential molecular marker not only for early detection of NSCLCs but also for assessing aspects of prognosis such as the possibility for metastasis. Currently, fields focusing on medical technology have been showing their ability to monitor CTC in patients with advanced lung cancer. For example, a study by Krebs et al. discovered that CTCs that were acknowledged by CellSearch System can perform as a novel prognostic factor in patients with NSCLC. The previous statement can be supported by Chen et al. which stated that a doubled number of patients with NSCLC presented with high CTC levels compared to patients with benign lung disease and healthy donors. Furthermore, FR expression was upregulated in about 75.7% of patients with NSCLC, indicating that FR may be a precise potential target for detecting CTCs in lung cancer patients. Xue et al. found that the performance of FR’CTC in the diagnosis of lung cancer is proven to have a sensitivity and specificity of 81.94% and 73.08% for the entire study cohort. Further analysis of FR-positive CTC detection in patients with distinct pathological varieties of lung adenocarcinoma shows a sensitivity of 60%, 73.2%, 73.9%, and 75% in patients with adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), invasive glands, and IA variants, respectively. Conjointly, its efficacy for detection also has a satisfactory diagnostic validity of P < 0.05.

Consistent with previously stated, CTC levels distinguishes lung cancer from nonmalignant lung disease with a consistently high AUC of 0.813 in the validation set, which was higher than the plasma tumor markers. To extensively investigate how FAR’CTC detection compares with currently used tumor biomarkers in patients with NSCLC, Yu et al. compared its diagnostic efficiency with the current clinical biomarkers, including NSE, CEA, CA125, cyfra 21-1, and SCC Ag. Providentially, FR’CTC detection method displays superior AUC (0.823; 95% CI, 0.773-0.874) compared with the other biomarkers. Moreover, a larger study by Chen et al. also confirmed a supporting result of the comparison, where FR’CTC displayed the highest AUC (0.815) and significant sensitivity (75%) and specificity (85%). Accordingly, these results indicate that CTCs could satisfactorily identify NSCLC patients.
with a greater degree of accuracy compared to current biomarkers, even in its early stages.\(^4\)

The potential of FR\(^{-}\)-CTCs to assess tumor metastasis is also an issue of notable importance which makes up for the deficiencies of other detection methods. The use of CTCs as a liquid biopsy is favorable for serial assessment of metastasis during the disease in a real-time manner via an uncomplicated form of blood draw. CTCs levels in patients with stage III-IV lung adenocarcinoma turned out to be higher than in stage I-II patients.\(^3\) Concerning previous reports, the FR\(^{-}\)-CTC count in lung cancer patients with a $>3$ cm nodule size was notably higher than those with a $\leq 3$ cm nodule size.\(^7\) Hence, these results proved the clinical significance of FR\(^{-}\)-CTC as a sensitive and reliable diagnostic assay for lung cancer metastasis screening that could drive further work-up decisions.

**Strength and Limitations**

Strengths of this systematic review includes the implementation of blinding, with 4 studies from Xue et al, Ding et al, Yu et al, and Zhou et al using the single-blinded method, while 1 study, by Chen et al uses double-blinded method.\(^4\)-\(^8\) Another strength also included in this review is the uniform use of LT-PCR for FR\(^{-}\)-CTC quantification across all studies.\(^4\)-\(^8\) Study results also investigates the diagnostic accuracy of FR\(^{-}\)-CTC to distinguish NSCLC patients from healthy and benign lung disease populations, in addition to comparing AUCs with several established reference standard. Finally, all the reviewed studies show generally low risk of bias in terms of flow and timing and applicability concerns. To our knowledge, this is the first systematic review that investigates the diagnostic accuracy of FR\(^{-}\)-CTC to distinguish NSCLC patients from a healthy/benign lung disease population.

The current study has certain limitations. Generalizability of the results is low as all studies are conducted in China. A larger one might be needed for the results to be globally representative. Furthermore, there is a relatively small unclear risk of bias in terms of patient selection, index test & reference standard, as the said studies did not specifically address the full extent of research methodology.

**Conclusion:**

Advancements in a wide variety of biomarkers have been investigated to predict diagnosis and prognosis; unfortunately, NSCLC, one of the causes of cancer-related death worldwide, is only often discovered at
an advanced stage when treatments have only narrowed efficacy.

In the five gathered studies we reviewed, we identified the potential of folate receptor-positive circulating tumor cells (FR+-CTC) as an absolute diagnostic biomarker with high sensitivity, specificity, and AUC for diagnosing NSCLC and is also able to differentiate it from other benign lung diseases in a precise manner. The folate receptor (FR), a cell-surface receptor glycoprotein, although also exhibited in multiple cancers—no cells expressing FR have been recognised in the circulatory system except for CTCs and activated monocytes. Hence, as FR expression was found to be upregulated in roughly 75.7% of patients with NSCLC, FR may be a specific potential target for detecting CTCs in a patient with NSCLC. Moreover, CTC detection in NSCLC also revealed significant correspondence between disease stages and CTC numbers, as CTC levels in patients with stage IV lung cancer were significantly higher than those with earlier stages. Taking everything into account, it is apparent that our results claim FR+-CTC as a reliable biomarker that would be clinically valuable for early diagnosis of NSCLC and treatment response assessment. Further investigation with a more extensive sample size is obligated to evaluate the diagnostic effectiveness of FR+CTC in subjects with large nodule sizes.

Declarations

Ethics approval and consent to participate

Not applicable.

Availability of data and material

Not applicable.

Conflict of interests

The authors report no relationships that could be construed as a conflict of interest.

Funding

Not applicable.

Authors' contributions

Garry Soloan (Conceptualization, Methodology, Writing - Original Draft, Visualization, Project administration), Kieran Pasha Ivan Sini (Writing-Original Draft, Investigation, Visualization) and Raisa Zalfa Meutia Abubakar (Writing - Original Draft, Investigation, Resources)
References


### Appendix

Table 2. Summary of Study Characteristics

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<thead>
<tr>
<th>Author; Year</th>
<th>Study Location</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Age</th>
<th>Characteristics of study population</th>
<th>Characteristics of Control Group</th>
<th>Sample source</th>
<th>Platform</th>
<th>Study Outcomes</th>
<th>Study Outcomes</th>
<th>FR+ CT Cutoff Levels</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen, 2015</td>
<td>Shanghai</td>
<td>Prospective, double-blinded, single center clinical trial</td>
<td>756</td>
<td>N/A</td>
<td>Training Set Healthy (n= 28)</td>
<td>Patients who are healthy or with benign lung disease (n=113)</td>
<td>LT-PCR</td>
<td>5,72</td>
<td>N/A</td>
<td>0.815 (0.772-0.853)</td>
<td>72.46% 88.65%</td>
<td>8,93</td>
<td>74.40% 86.60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NSCLC (n=236)</td>
<td></td>
<td>6.6</td>
<td>In comparison to healthy controls: 0.314</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>11.64</td>
<td>In comparison to healthy controls &amp; benign lung disease: &lt;0.001</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Validation Set Healthy (n =28)</td>
<td></td>
<td>5.95</td>
<td>N/A</td>
<td>0.813 (0.770 - 0.851)</td>
<td>76.37% 82.39%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
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<td>Controls</td>
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<td>Method</td>
<td>p-value</td>
<td>Odds Ratio (95% CI)</td>
<td>N/A/percentage</td>
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</tr>
<tr>
<td>Ding; Suzhou</td>
<td>2018</td>
<td>Single-blinded Prospective clinical trial</td>
<td>200</td>
<td>N/A</td>
<td>Benign SPN (n=30)</td>
<td>LT-PCR</td>
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<td>8,35</td>
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<td>79,30%</td>
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<td></td>
<td>Malignant SPN (n=50)</td>
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<td>Design</td>
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<td>Tumor Type</td>
<td>Control Group</td>
<td>LT-PCR</td>
<td>p-Value</td>
<td>AUC</td>
<td>Sensitivity</td>
<td>Specificity</td>
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<tr>
<td>Xue; 2018</td>
<td>Sichuan</td>
<td>Single-blinded Prospective clinical trial</td>
<td>98</td>
<td>NSCLC (n=72)</td>
<td>Twenty-four patients with benign lung diseases and two healthy volunteers</td>
<td>Three milliliters of peripheral blood sample</td>
<td>10.71</td>
<td>In comparison with control: &lt;0.001</td>
<td>0.8221 (0.7208-0.9235)</td>
<td>74.19%</td>
<td>73.08%</td>
<td></td>
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<tr>
<td>Yu; 2013</td>
<td>Beijing</td>
<td>Blinded Prospective Clinical Trial</td>
<td>266</td>
<td>Healthy (n=49)</td>
<td>Patients who are healthy or with benign lung disease</td>
<td>3 mL blood samples</td>
<td>5.71</td>
<td>N/A</td>
<td>0.823 (0.773 - 0.874)</td>
<td>73.20%</td>
<td>84.10%</td>
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<tr>
<td>Zhou; 2019</td>
<td>Wuhan, Shanghai</td>
<td>Blinded Prospective multi-center trial</td>
<td>382</td>
<td>Training Set</td>
<td>NSCLC (n=181)</td>
<td>Patients with benign lung disease</td>
<td>9.9</td>
<td>Comparison of malignant vs benign lung diseases: &lt;0.001</td>
<td>0.781 (0.698-0.864)</td>
<td>78.60%</td>
<td>78.40%</td>
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<tr>
<td>57</td>
<td>Other types of malignant tumour (n=16)</td>
<td>6,8</td>
<td></td>
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<tr>
<td>57</td>
<td>Validiation Set NSCLC (n=88)</td>
<td>9,9</td>
<td>0.792 (0.668–0.917)</td>
<td>82.70%</td>
<td>68.80%</td>
<td>82.70%</td>
<td>68.80%</td>
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<td>54</td>
<td>Other types of malignant tumour (n=5)</td>
<td>6,8</td>
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</table>

**Notes:** Legend: Non-small-cell lung cancer (NSCLC), Area under the curve (AUC), Ligand-targeted polymerase chain reaction (LT-PCR), Solitary pulmonary nodules (SPN)
A Comprehensive Look on Conjugated Targeted Therapies as A Novel Candidate for Personalized Thyroid Carcinoma Treatment

DOI: 10.52629/jamsa.v10i1.422

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Abstract:
Thyroid cancer is a substantial threat worldwide due to its prevalence and complication it follows. Current therapy is widely available, although failed to address the burdens associated with the disease, thus requiring a newer approach. Recently, the novel discovery of conjugated targeted therapy and its potential implementation enables a more specific, cancer-targeting mechanism, with potentially higher efficacy and minimum adverse effect than conventional treatments. This review was made to assess its potential, via comprehensive screening on several databases, such as Cochrane, PubMed, Scopus, ScienceDirect, and Wiley with set criterions. The search yielded 6 viable studies analyzing different forms of targeted therapies. Based on the included studies, conjugated targeted therapy displayed high selectivity and cytotoxicity toward cancer cells, while remained tolerable toward normal cells and the host. Not only as a therapeutic agent, this therapy also possessed imaging enhancement and metastasis detection, indicating high diagnostic value. Although, applicability and cost-efficiency of the treatment should be considered, due to extra costs in biosynthesizing therapeutic agents and phenotyping of targeted cells. Nonetheless, the high selectivity and potentially better safety profile of conjugated targeted therapy should be assessed further, and weighed with its limitations. All in all, conjugated targeted therapy has been proven to be selective towards cancer cell and a potent candidate as personalized treatment. Biosafety analysis of its implementation is recommended, followed by further clinical trials on human samples.

Keywords: antibody drug conjugate, carcinoma, targeted therapy, thyroid neoplasms
Introduction:
Thyroid cancer has been an increasing cause of concern worldwide, ranked as the 9th most common cancer with the greatest trend of increase in men and regions with middle socio-demographic index (SDI).\(^1\) In 2016, the number of thyroid cases worldwide is 238,000, and within only 2 years, the incidence has increased by 1.28 to 567,000 cases in 2018. Aside from causing significant morbidity and mortality, thyroid cancer also disrupts the balance of hormones, since thyroid is involved in many bodily functions. Currently, the standard treatment for thyroid cancer involves surgery and later radioactive iodine therapy or thyroid stimulating hormone (TSH) suppression. However, medullary and anaplastic thyroid cancer are more difficult to treat and thus as of now proposed treatments have only reached the phase of clinical trials, without significant established benefits when used singularly. While resection has insufficient benefits in treating metastatic thyroid cancer, iodine therapy carries the risk of second cancer, suppression of TSH the risk for hormonal disbalances, and drug combinations the risk of severe adverse effects without any clinically significant advantages.\(^1\) In the face of COVID-19, diagnosis, monitoring, and management of thyroid cancer has become even more challenging since availability of intensive care units, nuclear medicine services, and operating theaters have been limited, monitoring has been restricted, and there has to be consideration against risk of COVID-19 exposure in medical settings.\(^2\) Moreover, recent data has shown that malignancy significantly causes elevated risk of ICU admission and mortality (HR:3.50[95%CI:1.60-7.64]).\(^3\) Thus, it is of paramount importance that a more effective and efficient targeted treatment modality is developed, which allows better management and therefore reduced mortality due to thyroid cancer without causing extensive side effects.

There are various recent advancements that have pointed out potential drug targets, including the discovery of folate receptor expression in thyroid cancer cells, allowing the innovation of folate-mediated drug delivery,\(^4\) the production of carcinoembryonic antigen (CEA) by medullary carcinoma,\(^5\) which serves as potential targets for antibodies when conjugated with radiotherapy, and nanoparticles that enable better delivery of chemotherapeutic drugs such as methotrexate and fingolimod as well as the use in combination with cetuximab for theragnostic.\(^6\) Drug conjugation has
the potential to improve targeted delivery hence reducing side effects, hence better effectiveness in treating thyroid cancer. Thus, this literature aims to discuss potential efficacy and the clinical implications of conjugated targeted drug therapies for thyroid carcinoma.

Methods:
This literature review is conducted by the three reviewers screening databases including Cochrane, PubMed, Scopus, ScienceDirect, and Wiley, searching for primary studies and reviews with the inclusion criteria (1) searches for studies implementing drug conjugates as targeted therapy, (2) conducted for any types of thyroid cancer, and (3) study design either preclinical or clinical. Exclusion criteria include (1) studies with irretrievable full-text and (2) studies in languages other than English or Indonesian. Studies screened are within 10 years of publication and we used combination of keywords such as: (drug conjugate OR antibody-drug conjugate OR ADC OR radio-immunotherapy OR Immunotoxins) AND ((("Thyroid Neoplasms"[Mesh]) OR "Thyroid Carcinoma, Anaplastic"[Mesh]) OR "Thyroid Cancer, Papillary"[Mesh]). Further adjustments are made based on each database.

Results and Discussion:

Thyroid Carcinoma and The Endocrine System

Thyroid cancer can come in various clinical presentations ranging from low-risk nodules to high-risk metastatic malignancies. Thyroid nodules, although 90% of which are non-palpable, benign, and clinically insignificant, can in some cases become malignant and cause significant morbidity. Meanwhile, follicular thyroid carcinoma can be differentiated, which is the most common type and comprises 95% of all cases, or anaplastic, which is rare but very aggressive and can coexist with the differentiated type. Neuroendocrine thyroid cancer, which is derived from parafollicular c-cells, is also called medullary thyroid cancer. Commonly presenting as a solitary nodule accompanied by neck lymphadenopathy, this cancer also metastasizes quickly in 70% of patients.$^{1-5}$

Although in early stages minimal symptoms can be identified, as it progresses, thyroid cancer can cause voice hoarseness, dysphagia, and swollen lymph nodes. More importantly, thyroid cancer can cause imbalance of hormones, in the form of hypothyroidism or
hyperthyroidism, which are particularly harmful since thyroid is involved in gene expressions as well as the normal development and functions of the body. Hypothyroidism can cause fatigue, weight gain, emotional and sleep disturbances, peripheral neuropathy, infertility, as well as the risk of congenital defects for children from mothers with thyroid disturbances. Meanwhile, hyperthyroidism can result in weight loss, disruptions to the digestive system, arrhythmias and heart problems, osteoporosis, and thyroid toxicity. This further prompts the urgency of effective treatment for thyroid cancer.

Current Treatments for Thyroid Carcinoma and Their Pitfalls

The treatment approaches for thyroid cancer are diverse since there has to be a balance between not over-treating benign nodules and the need for aggressive approach in high-risk or advanced diseases. For small, unifocal tumors less than 4 cm without any evidence of spread, lobectomy is the treatment of choice. However, if nodal disease is discovered, total thyroidectomy is required, and in such cases the patient has to undergo lifelong hormone replacement therapy. These procedures should be followed by assessment whether the patient needs radioiodine ablation, in order to eliminate potential residues of neoplastic foci, or suppression of thyroid stimulating hormone (TSH), in order to reduce recurrence since TSH causes proliferation of both thyrocytes and malignant cells. However, radioiodine therapy carries with it the risk of short-term adverse effects as well as higher chances of relapses or second cancers, and studies have found many patients are unresponsive to this therapy. Moreover, TSH suppression has not yet any clear guidelines for concentrations, and hyperthyroidism that is induced can affect the heart, causing risk of atrial fibrillation for instance, and bones, resulting in osteoporosis.

In recent years, systemic medications have been developed for advanced differentiated and medullary thyroid cancer, including kinase inhibitors such as sorafenib, lenvatinib, vandetanib, and cabozantinib, but these cannot fully cure the disease and some subsets of patients also develop resistance. COVID-19 antiviral drugs also might have potential interactions with systemic thyroid cancer treatments, especially lenvatinib which might increase chances of arrhythmia and cabozantinib which can potentiate drug concentration. For anaplastic thyroid cancer however, current
interest of exploratory studies have been focused unto BRAF inhibitors, MEK inhibitor, mTOR inhibitors, microtubule inhibitors, PPAR-gamma agonists, and immunotherapy, but considering the rapid progression of the disease, use of one drug alone has not shown any promising results, and drug combinations especially during chemotherapy often result in extensive adverse effects harmful to normal cell functions. Thus, there are various loopholes in current treatment guidelines that can hopefully be solved through the use of drug conjugates, which might provide better drug delivery and improve efficacy while minimizing the occurrence of side effects.

Introduction of Targeted Therapies

Following the limitations brought by current treatments (of cancers in general), targeted agents accompanied by personalized cancer therapy has taken the spotlight for individual treatment of various carcinomas. Referring back to the advancements made under cancer at a molecular level, specific proteins and cell’s DNA pertaining to their involvement in how cancer was able to evade the immune system has been identified. Nicknamed the ‘forefront’ of cancer treatment, targeted cancer therapies implement specific pharmacological agents which in turn, inhibits metastases along with promoting apoptosis of individual cancer cells. Compared to household treatments such as radio- or chemotherapy, targeted therapies zero in on specific proteins involved in tumorigenesis and molecular changes unique to that particular cancer. Hence by doing so, targeted therapies were able to avoid affecting non-neoplastic cells undergoing mitosis (such as bone marrow, hair, and epithelium) and only block specific pathways important for the progression and growth of the particular tumor such as shown in Figure 1.

![Figure 1](image-url). Shows one of the schematic pathways of cell proliferation and tumor progression, potentially blocked by targeted therapy.
The specific nature of targeted therapy is considered the biggest selling point in providing more therapeutically beneficial treatment for cancer. Currently there are several acknowledged targeted agents, which include: monoclonal antibodies (mAbs), small molecule inhibitors (SMIs), interfering RNA (iRNA) molecules, and immunotoxins. Furthermore, the discovery of antibody-drug-conjugates (ADC) has opened a promising future in conjugated targeted therapies. By utilizing mABs and linking them with cytotoxic drugs, ADCs were able to push personalized therapies even further by specifically recognizing antigens expressed by the tumor cells, and deliver their cytotoxic payload without damaging non-neoplastic cells. Moreover, different from normal chemotherapy, ADCs also extend the therapeutic window of drugs via the decrease of minimum effective dose (MTD) and increase of maximum tolerated dose (MTD) (Figure 2). This type of targeted therapy offers advantages compared to the others. Conjugated targeted therapy utilizes targeting molecules, creating a more selective system compared to small molecule inhibitor targeted therapy, which can permeate and possibly interfere with normal cells. The selectivity might widen the therapeutic window of this therapy and creating less severe adverse effects. This therapy also offer versatility, which can be exploited for various uses, for example as a diagnostic and therapeutic agent. It can also be used for enhancing the efficacy of conventional therapies or as a single regimen drug. Compared to commonly used targeted therapy (SMIs such as tyrosine-kinase inhibitor or TKI), conjugated targeted therapy does not depend on signaling pathway, but rather having the sole purpose of delivering cytotoxic substances, thus making resistance harder to develop. All of these combined advantages make conjugated targeted therapy a prominent candidate for a novel, more effective cancer treatment.

Figure 2. A visual representation on how ADCs were able to increase the therapeutic window of drugs.9

Therapeutic Value of Conjugated Targeted Therapy
Based on the qualitative representation of the included studies as shown in Table 1, together with the quantitative measurement provided in the study's respective papers, targeted therapy using conjugated targeting molecules displayed a better safety profile and increased cytotoxicity performance than conventional therapy. These discoveries remain consistent across all the included studies, which are ranged from in vitro to clinical trial, further consolidating the therapy projected superiority compared to current regiments and the urgency for further investigation. As a therapeutic agent, conjugated targeted therapy agents differ from each other. The differences lay on the components, which consist of therapeutic agent (drug) and targeting agent (antibody or other targeting components) that can be freely manipulated, enabling tailor-made therapy based on the molecular characteristics of the cancer. The practical example was demonstrated by Jang et al., which agent showed high cytotoxicity toward cancer cells that highly express dysadherin while leaving normal and low-to-moderate-dysadherin-expressing cancer cells unharmed. The selectivity toward a specific type of cell is the main advantage of this technology, which enables minimum collateral damage that can cause adverse effects and maximum anticancer activity. The aforementioned statement was observed in human by Juweid et al. study which used the older version of targeted therapy. Regardless, it showcased tolerable adverse effect, high selectivity (as it was able to detect up to 13 sites of unconfirmed tumor metastases in one patient), and although could not be directly observed, efficacious, indicated by progressive betterment of thyroid biomarkers. Other than selectivity, increased cytotoxicity is also observed, which might be attributable to increased cellular uptake due to its conjugate interactions with tumor cell. Moreover, an in vivo study using chick chorioallantoic membrane also showed anti-metastatic activity of conjugated targeted therapy, though yet to be proven in human or animal model, would be tremendously beneficial for patient with highly metastatic cancer, such as thyroid cancer.

**Figure 3.** Radioimaging results obtained after 9 days of administration. (Left) Anterior plane and (Right) Lateral Plane of neck and
chest showed lymph node metastasis near the mediastinum (lower arrow)

Conjugated agents also possess high diagnostic value due to their selectivity. Selectivity enables the agent to accumulate in the tumor microenvironment. The accumulation of said agent can be detected using various modalities, such as USG, CT, and MRI scan, thus creating a contrast and easier visualization. As mentioned before, Juweid et al. reported detection of unconfirmed positives of metastatic thyroid cancer, which further solidify the high diagnostic value of conjugated agents. An exemplary radioimaging result can be seen in Fig. 3, showing intense accumulations of agent in tumor sites, which happened to also detects a metastasis in a nearby lymph node.16-17

There is also a trend of incorporating nanotechnology which enables further control of the treatment. Nanotechnology enables physical intervention, such as local hyperthermia induction. This intratumoral physical intervention is aimed to increase the potency of agent/co-treatment, direct necrosis induction (usually via ablation/direct heat exposure), or for diagnostic purposes. Study by Wang Qimeihui et al. reported complete removal of engrafted thyroid cancer. They achieved this result using encapsulated infrared dye inside the conjugated nanoparticles, which then irradiated. These procedures induced heat in intratumoral environment which peaked at 57°C, resulting necrosis after 2 days of treatment.17 Similar approach was adopted by Wang Yang et al. which aimed to release the loaded drug in controlled manner using Low Intensity Frequency Ultrasound (LIFU), yielding increased efficacy and better organ biomarkers profile, indicating good biocompatibility.14-17 Nanoparticles also function as contrast for various neuroimaging modalities. Both aforementioned studies enhanced USG visualization of the tumor using a phenomenon called microbubble-enhancement, which is created in vivo using perfluoro pentane (PFP), which sublime at body temperature (±25°C). The resulting PFP vapor then creates mini air pockets called microbubbles. The created microbubbles then resonate in USG field, which is detectable by conventional USG tools.17-21

Applicability and Future Prospects

The applicability of conjugated targeted therapies depends on several factors, with some to be
considered being: efficacy, safety profile, cost-effectiveness, and administration process. Based on this review, conjugated targeted therapy presented results as expected by its theoretical hypothesis. Although, realistically, the whole treatment process of using mAbs and other molecular agents are projected to be less cost-efficient than current therapies. A review by Crisci et al. included the outcomes and challenges of implementing wide-scale administration of targeted therapies, with some notable points being: biotechnical costs of producing therapeutics agents, genotyping and phenotyping of tumor tissues, and objectively new competencies needed to be introduced to oncologists worldwide. Nonetheless, the limitations brought by this treatment should be reconsidered rather than avoided. Looking forward, researchers and clinicians are responsible to evaluate the strengths and limitations conjugated targeted therapy has, and integrate those results in formulating a more cost-effective analysis on it. Furthermore, with pharmacogenetic tests being commonly introduced in the development of conjugated targeted therapy, this pioneers the growth of other biomedical technologies such as nano- or immune-diagnostic modalities.

**Strength and Limitations**

The strength of this review lies in the strength of the treatment itself. In theory, targeted therapy has been considered to be objectively and therapeutically better for cancer treatment due to its specific mechanism of action in targeting tumor cells. Moreover, some studies also analyzed the Theranostic potential of these treatments, via intra-tumoral accumulation which enhances current imaging modalities for diagnosis. Although, its relative novelty has limited the scope of this review, due to the small numbers of papers present implementing targeted therapy on thyroid carcinoma. Furthermore, only in vivo and in vitro studies were found testing different types of conjugated targeted therapies on thyroid cancer. Despite different targeting and therapeutic agents used for each study, all the studies reported positive selectivity on thyroid cancer cells, hence providing a number of different potential agents for further exploratory research.

**Conclusion:**

In conclusion, thyroid cancer has been an increasing problem worldwide with an incidence increase of about two times in the
past 5 years. Following those concerns, current treatments and medications are put to the test, with the constant dilemma of choosing between non-aggressive and aggressive approaches towards the current state of the carcinoma. Nonetheless, such treatment procedures were proven futile, with minimal results being shown as promising. However, with the recent breakthrough of personalized medicine, especially in targeted therapies, some studies have shown its potential alongside its theoretical approach in targeting specific tumor cells without diffusely damaging other cells. From this review, the included studies showed promising results with their high selectivity towards thyroid tumor cells. Furthermore, some studies also discovered and tested the conjugate's potential as a diagnostic tool, making this theranostic property superior to conventional therapies. However, due to the lack of recent clinical data on the efficacy of conjugated targeted therapies on human subjects, the authors recommend a full-fledge biosafety study to determine the conjugate's safety profile on human subjects. Afterwards, the author suggests the robust initiation of controlled clinical trials (in comparison to non-conjugated targeted therapies) to provide more baseline information on the effectiveness of this treatment. Nevertheless, with the ongoing stalemate of thyroid cancer treatment (and other cancer in general), the authors feel that conjugated targeted therapies are truly the ‘frontier’ and ‘future’ of cancer treatment.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Availability of data and material**

Not applicable.

**Conflict of interests**

The authors declare no competing interest.

**Funding**

Not applicable.

**Authors' contributions**
References


### Appendix 1. Author Commentaries

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<td>This study showcased the ability of targeted therapy as both a diagnostic and a therapeutic tool. It displayed the ability to detect unconfirmed positives metastatic thyroid cancer with relatively high sensitivity and specificity. Although due to its one-time dose, its efficacy could not be directly observed and only predicted by subject biomarkers, which displayed gradual betterment.</td>
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<td>2</td>
<td>Lin, 2021</td>
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<td>Both caerin 1.1 and 131-I possess targeting and cytotoxic activity. Caerin 1.1 directly enters the cells and inhibit p-Akt activity, Targeting is apparently enhanced by 131-I which is naturally transported into thyroid cells using Sodium-Iodide symporter</td>
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<td>3</td>
<td>Qim, 2019</td>
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<td>Complete nanoparticles complex paired with irradiation yielded a complete cancer removal in Balb/c mice subjects. No pathological enzymes increase observed, proving biocompatibility. System also enabled diagnostic imaging enhancement by providing microbubbles created from perfluoropentane core (PFP)</td>
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<td>Yan</td>
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<td>Complete complex was able to completely retard the tumor growth compared to incomplete complex and free drug (10-HCPT) of the same concentration. Moreover, local drug release could be</td>
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achieved by using LIFU, minimizing systemic effect. System also enabled diagnostic imaging enhancement by providing microbubbles created from perfluoropentane core (PFP).

The study compared nanoparticles loaded with FTY720 with FTY720 & MTX cocktail. Although it showcased a similar cytotoxicity toward cancer cell, it significantly lowered the therapeutic agent cytotoxicity toward normal thyroid cell.

Agent was highly efficient in inducing necrosis in all cancer groups, except the FTC133 and HTh7. This is due to the lack of dysadherin expression, suggesting high selectivity towards moderate-to-high dysadherin density malignancies. However, further study regarding biosafety is needed as CEN-106 is necrosis-inducing drugs and might triggers tumor lysis syndrome in human subject.
Mortality of Patients with Chronic Kidney Disease Post Percutaneous Coronary Intervention Compared with Coronary Artery Bypass Graft: An Evidence Based Case Report

DOI: 10.52629/jamsa.v10i1.275

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Abstract:

Background: Chronic kidney disease (CKD) is a disease that causes permanent kidney damage requiring dialysis or transplantation as a follow-up treatment. CKD is a common condition that has a high risk of coronary artery disease (CAD). In CKD patients with CAD, percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) is able to reduce mortality compared with conservative management. However, which method has the most influence on CKD patient mortality is unclear. Objective: To find out the prognosis of mortality in post-PCI CKD patients versus CABG. Methods: Literature search was done by using three electronic databases (Pubmed, Cochrane, and SCOPUS) using specific keywords. Keywords used were based on the authors' clinical questions. Inclusion and exclusion criteria were applied to the selected studies. Results: A total of seven literatures were selected for critical appraisal. These literatures consist of systematic review, meta-analysis, and cohort study. All of these literature demonstrated that mortality in CKD patients underwent PCI is significantly higher than CKD patients underwent CABG. Conclusion: PCI performed in patients with CKD causes a significantly higher mortality rate than patients who underwent CABG.

Keywords: chronic kidney disease, coronary artery bypass graft, mortality, percutaneous coronary intervention
**Introduction:**

Chronic kidney disease (CKD) is a condition characterized by decreased glomerular filtration function that has occurred for years. CKD can cause permanent kidney damage requiring dialysis or a transplant as follow-up treatment. Based on the Kidney Disease Improving Global Outcomes (KDIGO), CKD is defined as kidney damage or decreased glomerular filtration rate (GFR) <60 mL/minute/1.73 m² over three months. CKD is a common condition that can have a high risk of cardiovascular mortality and morbidity. Kidney disease also has an association with systemic inflammation that accelerates the incidence of cardiovascular atherosclerosis and thrombosis. Furthermore, coronary artery disease (CAD) is the most common cause of death in CKD patients.

CAD is initiated by calcification of the blood vessels or atherosclerosis. Atherosclerosis can cause three effects, namely arterial stiffness, endothelial dysfunction, and unstable plaque. Endothelial dysfunction and arterial stiffness can cause coronary circulation disorders that can lead to myocardial infarcts. However, in patients with CKD, most myocardial damage is caused by unstable plaque. These processes can increase mortality in patients with CAD.

Percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) are the most common intervention to treat CAD. PCI is a procedure for placing a stent on blocked blood vessels. CABG is a procedure for inserting a new pathway so that blood is able to flow other than through the obstructed vessel, this procedure is a surgical procedure, so it is more invasive than PCI. These two procedures are capable of providing revascularization of the heart. In CKD patients with CAD, these two approaches are able to reduce the mortality rate compared to conservative management. The CABG procedure is performed only once on indications of triple or more severe vessel occlusion, ventricular dysfunction, or comorbidity such as diabetes mellitus. PCI is indicated for patients who have had a sudden cardiac arrest. PCI needs to be done several times to reach complete revascularization. However, which method has the most significant impact to increase CKD patients mortality is still unclear.

**Case Illustration:**

A 63 year old male patient came for routine control because of the depleted medication. Twenty one
year ago the patient was diagnosed with hypertension. Before being diagnosed, patients often experienced dizziness.

Three years before being admitted to the hospital, the patient experienced continuous shortness of breath so he was taken to the emergency room. Initially, the patient complained of shortness of breath and fatigue when doing activities, such as walking and climbing dates. Shortness of breath gets worse when the patient sleeps so that the patient has to use two pillows.

In Cipto Mangunkusumo Hospital, electrocardiography (ECG) was performed and it was found that the patient had a heart attack accompanied by a heart rhythm disturbance. Therefore, the patient was catheterized and found vessel blockage. Two rings were placed inside the occluded vessels in August 2018 and other two rings were placed in November 2018.

Ten years before being admitted to the hospital, the patient had epistaxis. The bleeding did not stop for eight hours, so he was rushed to the emergency room. At the hospital, the patient was diagnosed with diabetes mellitus. Before being diagnosed, there were complaints of frequent hunger, frequent drinking, frequent urination. The patient was prescribed oral antidiabetic drugs. However, the patient admitted that he did not regularly take the medication.

Six years before being admitted to the hospital, the patient experienced foamy urine, intermittent urinary flow, and a feeling of incomplete urine. The patient admitted that he urinated frequently with a large volume. Patients often wake up from sleep to urinate with a frequency of urinating four times at night. There was no bloody urine, pain while urinating, bed-wetting, and abdominal pain. The patient was checked for a laboratory test at Depok Hospital. The result is high blood creatinine, which is 2.1 mg / dL. The patient was diagnosed with chronic kidney disease (CKD).

**Clinical Question**

Patient in this case had CABG indication such as CAD with involvement of four blood vessels and comorbid diabetes mellitus, but the patient also had an indication of PCI, a heart attack that brought him to the emergency room. The patient underwent a PCI method that was not as invasive as CABG. Therefore, the authors formulated a clinical question "is there a significant difference
between the prognosis of mortality in patients with CKD who received PCI procedure compared with CKD patients who received CABG?" The description of the authors' clinical question is presented in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical aspects</td>
<td>Prognosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>meta-analysis, systematic review, randomized controlled trial (RCT), cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Methods

#### Literature Search

The literature search was conducted on January 6, 2021 to June 6, 2021 with keywords that match the author's clinical questions. Literature search used the ‘OR’ and ‘AND’ booleans. Literature search was performed on three electronic databases, namely PubMed, Cochrane, and SCOPUS. The search strategy and keywords used can be seen in Table 2.

<table>
<thead>
<tr>
<th>Database</th>
<th>Keywords</th>
<th>Obtained</th>
<th>Be chosen</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>(&quot;chronic kidney disease&quot; [All Fields]) AND (&quot;PCI&quot; [All Fields]) AND (&quot;CABG&quot; [All Fields]) AND (&quot;mortality&quot; [All Fields])</td>
<td>65</td>
<td>7</td>
</tr>
<tr>
<td>Cochrane</td>
<td>&quot;chronic kidney disease&quot; in Title Abstract Keyword AND &quot;percutaneous coronary intervention&quot; in Title Abstract Keyword AND &quot;coronary artery bypass graft&quot; in Title Abstract Keyword AND &quot;mortality&quot; in Title Abstract Keyword</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>SCOPUS</td>
<td>TITLE-ABS-KEY (chronic AND kidney AND disease) AND TITLE-ABS KEY (pci) AND TITLE-ABS KEY (cagb) AND TITLE-ABS-KEY (mortality))</td>
<td>140</td>
<td>1</td>
</tr>
</tbody>
</table>
Selection of Articles

A total of 228 articles were obtained from search results in the PubMed, Cochrane, and SCOPUS databases. The title screening was carried out based on the study design that matched the authors' clinical questions. File selection was carried out based on exclusion criteria. Articles not written in English and not PICO-compliant were excluded. Double screening was performed to exclude duplicate articles. Full text selection is done based on the availability of full text articles. After going through the process of searching and selecting articles, there were three systematic review articles involved in the critical review process. The search and selection process is presented in the PRISMA diagram in Figure 1.

Results

Based on the results of search and selection of articles, there are seven articles that are suitable and can be continued for critical analysis. These articles are systematic review, meta-analysis, and cohort study.

**Figure 1. PRISMA Flowchart**

The author selected seven articles according to the author's PICO. A summary of the study can be seen in Table 3.

The critical analysis is carried out using the critical analysis instrument from the University of Oxford's Center of Evidence Based Medicine. The results of the critical review of the study of each article are presented in Table 4.

The observed parameter in this study was the mortality of post-PCI CKD patients compared with post-CABG CKD patients. The mortality rate is presented in the form of odds ratios and hazard ratios. The results of the study of each article can be seen in Table 5.
## Table 3. Study Summary

<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Total Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doulami et al</td>
<td>Percutaneous Coronary Intervention with Drug Eluting Stents Versus Coronary Artery Bypass Graft Surgery in Patients with Advanced Chronic Kidney Disease: A Systematic Review and Meta-Analysis</td>
<td>A total of 16 articles for a total of 15,313 patients (7,157 patients underwent CABG and 8,156 patients underwent PCI)</td>
</tr>
<tr>
<td>Barbara et al</td>
<td>Comparison of Coronary Artery Bypass Grafting and Drug-eluting Stents in Patients with Left Main Coronary Disease: A Systematic Review and Meta-Analysis</td>
<td>Total of 5 articles for a total of 1,212 patients (557 patients underwent PCI and 655 patients underwent CABG)</td>
</tr>
<tr>
<td>Bundhun et al</td>
<td>Impact of Coronary Artery Bypass Surgery and Percutaneous Coronary Intervention on Mortality in Patients with Chronic Kidney Disease and on Dialysis. A Systematic Review and Meta-Analysis</td>
<td>A total of 18 articles for a total of 69,456 patients (29,239 patients underwent CABG and 40,217 patients underwent PCI)</td>
</tr>
<tr>
<td>Yang et al</td>
<td>Survival outcomes and adverse events in patients with chronic kidney disease after coronary artery bypass grafting and percutaneous coronary intervention: a meta-analysis of propensity score-matching studies</td>
<td>A total of 13 articles for a total of 18,005 patients</td>
</tr>
<tr>
<td>Chang et al</td>
<td>Comparative effectiveness of coronary artery bypass grafting and percutaneous coronary intervention for multivessel coronary disease in a community-based population with chronic kidney disease</td>
<td>Total of 8,172 patients (4,086 patients underwent CABG and 4,086 patients underwent PCI)</td>
</tr>
<tr>
<td>Kilic et al</td>
<td>Surgical versus percutaneous multivessel coronary revascularization in patients with chronic kidney disease</td>
<td>Total of 1,853 patients (1,269 patients underwent CABG and 584 patients underwent PCI)</td>
</tr>
</tbody>
</table>
**Lautamaki et al**  
*Outcome after coronary artery bypass grafting and percutaneous coronary intervention in patients with stage 3b–5 chronic kidney disease*

Total of 258 patients (148 patients underwent CABG and 110 patients underwent PCI)

<table>
<thead>
<tr>
<th>Critical analysis</th>
<th>Doulamis et al</th>
<th>Barbara wi et al</th>
<th>Bundhun et al</th>
<th>Yang et al</th>
<th>Chang et al</th>
<th>Kilic et al</th>
<th>Lautamaki et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear PICO and PICO-compliant inclusion criteria</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Evidence found according to the search</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, but PRISMA is not suitable</td>
<td>Yes</td>
<td>No (cohort design)</td>
<td>No (cohort design)</td>
<td>No (cohort design)</td>
</tr>
<tr>
<td>The studies listed have been critically examined</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No (cohort design)</td>
<td>No (cohort design)</td>
<td>No (cohort design)</td>
</tr>
<tr>
<td>The studies used were of high quality</td>
<td>Yes</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Yes</td>
<td>No (cohort design)</td>
<td>No (cohort design)</td>
<td>No (cohort design)</td>
</tr>
<tr>
<td>Study results are presented in tables and appropriate forest plots</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes for tables, no forest plot</td>
</tr>
<tr>
<td>The heterogeneity between studies is clearly stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No (cohort design)</td>
<td>No (cohort design)</td>
<td>No (cohort design)</td>
</tr>
</tbody>
</table>
Table 5. Study Results

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doulamis et al</td>
<td>The overall mortality of PCI was higher than that of CABG (HR: 1.28, 95% CI: 1.13 - 1.46; P = 0.00; I² = 35.77%).</td>
</tr>
<tr>
<td>Barbarawi et al</td>
<td>There was no significant difference in overall mortality in patients undergoing PCI compared to CABG (OR: 0.9, 95% CI: 0.55 - 1.49; P = 0.68; I² = 54%)</td>
</tr>
<tr>
<td>Bundhun et al</td>
<td>Long-term follow-up mortality of more than one year was higher in PCI patients compared with CABG (OR: 0.81, 95% CI: 0.70–0.94; P = 0.007; I² = 75%). Mortality after more than three years was also higher for PCI compared with CABG (OR: 0.82, 95% CI: 0.70–0.95; P = 0.007; I² = 48.4%)</td>
</tr>
<tr>
<td>Yang et al</td>
<td>Long-term follow-up mortality was significantly lower in the CABG group than in the PCI group (HR: 0.76, 95% CI: 0.70 – 0.83; P &lt; 0.001; I² = 21%)</td>
</tr>
<tr>
<td>Chang et al</td>
<td>CABG was associated with a significantly lower mortality than PCI across all groups of estimated glomerular filtration rate (in mL/min/1.73 m²); the adjusted HR was 0.81; 95% CI: 0.68 – 1.00 for patients with eGFR ≥60; HR 0.73; 95% CI: 0.56 – 0.95 for eGFR of 45 – 59; and HR 0.87; 95% CI: 0.67 – 1.14 for eGFR&lt;45.</td>
</tr>
<tr>
<td>Kilic et al</td>
<td>CKD patients survival with one year follow up was higher in CABG groups than in PCI groups (88.92% vs 82.67%, P&lt;0.0001). In five years follow up, CKD patients survival was also higher in CABG groups than in PCI groups (73.93% vs 52.28%, P&lt;0.0001).</td>
</tr>
<tr>
<td>Lautamaki et al</td>
<td>PCI was associated with a significantly higher risk of mortality than CABG in three years follow up (50.4 vs 32.9, HR: 1.77; 95% CI: 1.13-2.77).</td>
</tr>
</tbody>
</table>

Discussion

Various studies have been conducted to determine the mortality of CKD patients undergoing PCI compared to CABG. Mortality in these studies is also described based on the duration of follow-up, so as to indicate the short-term and long-term mortality. Results presented in those studies are not only useful to identify patients prognosis but also to choose the best suited intervention to patient characteristics.

Doulamis et al's study entitled Percutaneous Coronary Intervention with Drug Eluting Stents Versus Coronary Artery Bypass Graft Surgery in Patients
with Advanced Chronic Kidney Disease: A Systematic Review and Meta-Analysis examined 16 articles with a patient population of 15,313 patients consisting of 7,157 CKD patients who underwent PCI and 8,156 patients who underwent CABG. The mortality in this study was divided into two, namely mortality with a follow-up duration of 30 days or while the patient was in hospital and mortality with a follow-up duration of one year. Mortality with a follow-up of 30 days was higher in CABG patients (2.4%) than in PCI (1.7%), with a value of $P = 0.39$. However, in mortality within one year of follow-up, PCI had a higher mortality rate (8.9%) than CABG (7.4%), with a value of $P = 0.83$. This study conducted a pooled analysis showing that PCI increased the risk of mortality in CKD patients compared to CABG (HR: 1.28, 95% CI: 1.13 - 1.46; $P <0.01$; $I^2 = 35.77\%$). In addition, this study also compares the incidence of MACCE (major adverse cardiac and cerebrovascular events) occurring in patients with PCI with CABG. In this study, the incidence of MACCE after PCI was more frequent than in CABG patients (HR: 1.44, 95% CI: 1.17 - 1.79; $P <0.01$; $I^2 = 82.6\%$). 

It was also stated that end stage renal disease (ESRD) can accelerate the formation of atherosclerosis due to increased inflammatory mediators and oxidative stress. In addition, the morphology of atherosclerotic plaque in CKD patients is different from that of patients without CKD. In patients with CKD, the plaque that forms has unstable medial and intimal microcalcifications. This process may lead to a high incidence of restenosis in the PCI stent. In CKD patients undergoing PCI, the use of antiplatelet and anticoagulants has also been associated with a high risk of bleeding and cardiovascular mortality.

The study of Doulamis et al. has limitations that need to be considered in a critical study. Because this study is a meta-analysis study, this study does not have access to detailed patient data, so the data used is data that has not been adjusted. It is this difference that causes the difference in the short-term and long-term mortality rates in CABG patients compared to PCI patients. This study also did not explain the adherence to medical therapy. The severity of CAD and the degree of
revascularization also differed among the included studies.\textsuperscript{12}

Barbarawi et al's study entitled \textit{Comparison of Coronary Bypass Grafting and Drug-Eluting Stents in Patients with Left Main Coronary Artery Disease and Chronic Kidney Disease: A Systematic Review and Meta-Analysis} examined five articles with a total of 1,212 patients consisting of 557 patients who underwent PCI and 655 patients underwent CABG. All the follow-ups for these five articles were more than one year long. This study showed that there was no significant difference between mortality in patients with PCI and CABG (OR 0.90; 95\% CI 0.55-1.49; \textit{P} = 0.68; \textsuperscript{I}^{2} = 54\%). A value of \textsuperscript{I}^{2} = 54\% indicates high heterogeneity, so that there is excessive variation between the study population.\textsuperscript{9}

Apart from being stated in this study that there is no significant difference between mortality in PCI patients with CABG, this study also does not show an excess of survival in patients who received CABG treatment. However, one of the articles used in this study, namely the study by Giustino et al, showed that PCI had a significantly higher mortality rate than CABG (OR 0.49; 95\% CI 0.25 - 0.93). It was also explained that the most common cause of death was sepsis, which occurred one month after the procedure.\textsuperscript{1}

The study of Barbarawi et al. has several limitations that need to be considered when conducting a critical analysis. The primary outcome in this study was MACCE (major adverse cardiac and cerebrovascular events), whereas mortality was the secondary outcome. The primary outcome in this study was considered to have greater analytical power. Meanwhile, secondary outcomes (including mortality) were considered to have low analytical power. In addition, due to the lack of RCT studies most of the studies included in this analysis were observational, thus increasing the risk of high selection bias and intervention bias.\textsuperscript{15} It was also stated in this study that the clinical data of patients were considered inadequate, so that the clinical outcome of each procedure could not be explained in detail.\textsuperscript{9}

Bundhun et al's study entitled \textit{Impact of Coronary Artery Bypass Surgery and Percutaneous Coronary Intervention on Mortality in Patients with Chronic Kidney Disease and on Dialysis. A
Systematic Review and Meta-Analysis examined 18 articles with a total of 69,456 patients consisting of 29,239 CKD patients who had undergone CABG and 40,127 CKD patients who had undergone PCI. The mortality in this study was grouped into three periods of follow-up duration, namely mortality with follow-up while the patient was hospitalized, mortality with a short-term follow-up duration of one month, mortality with one-year follow-up duration, mortality with long-term follow-up duration more than one year, and mortality with long-term follow-up duration greater than three years.\(^{11}\)

In mortality with inpatient follow-up, CABG showed a higher rate (7.16%) compared to PCI (3.87%), with an OR value of 1.55, 95% CI 0.82-292; \( P = 0.17, I^2 = 51\%\). Short-term mortality with the follow-up period also showed a higher rate of CKD patients undergoing CABG (2.45%) compared to PCI (1.72%), with an OR value of 1.24, 95% CI 0.93 - 1.65; \( P = 0.15, I^2 = 40\%\). In addition, in mortality with a follow-up duration of one year, CABG and PCI did not show significantly different rates (18.8% and 19.4%) with OR 0.99, 95% CI 0.91 - 1.08; \( P = 0.86, I^2 = 38\%\). However, it should be noted that these three results were not statistically significant. In addition, this study also compares the incidence of MAE (major adverse events) occurring in patients with PCI with CABG. MAE consists of MACE (major adverse cardiac events) and MACCE (major adverse cardiovascular and cerebrovascular events). In this study, the incidence of MAE after CABG (18.2%) was less frequent than in PCI patients (29.2%), with OR: 0.51, 95% CI: 0.28 - 0.92; \( P = 0.03\).\(^{11}\)

The mortality rate that was statistically significant was found in mortality with a longer follow-up duration. However, it was not stated in the study whether there was repeated PCI procedure and the progress of the patient’s CKD. When followed up with a duration of more than one year, it was shown that the mortality rate for CABG was lower (18.4%) compared to PCI (23.8%), with an OR of 0.81, 98% CI 0.70 - 0.94; \( P = 0.007, I^2 = 75\%\). At a follow-up duration of more than three years, it was also seen that the mortality rate for CABG was lower (18.8%) compared to PCI (24.7%), with an OR value of 0.82, 95% CI 0.70 - 0.95; \( P = 0.01, I^2 = 79\%\).
However, it should also be noted that the $I^2$ value is high, thus indicating high heterogeneity.\textsuperscript{11}

On these results, Bundhun et al. explained that the higher long-term mortality in PCI might be due to restenosis and incomplete revascularization of PCI. In addition, another possibility is contrast-induced acute nephropathy which may lead to other complications following PCI. The use of the internal mammary artery for CABG may be the reason why CABG produces a better outcome than PCI.\textsuperscript{11} One of the studies included in this study, Chen et al, who studied 38,740 patients showed that PCI had a higher long-term mortality rate compared with CABG (OR 1.29, 95% CI: 1.23 - 1.35; $P < 0.01$) so this study supports the results of the analysis in the study of Bundhun et al.\textsuperscript{16}

The study of Bundhun et al. has several limitations that need to be considered when conducting a critical analysis. The limited number of patients in this study may not show strong results. All studies involved in this study were observational studies, so the data obtained were not as good as the data in the RCT study. The high heterogeneity is a major limitation in this study. In addition, the studies that were involved were those taken after 2012 so there may be selection bias and publication bias. This study also only involved studies written in English, so the results of this study were also influenced by language bias.\textsuperscript{11}

Yang et al’s study entitled Survival outcomes and adverse events in patients with chronic kidney disease after coronary artery bypass grafting and percutaneous coronary intervention: a meta-analysis of propensity score-matching studies examined 13 articles with a total of 18,005 patients. All the follow-ups for these 13 articles were more than one year long. Long-term follow-up mortality was significantly lower in the CABG group than in the PCI group (HR: 0.76, 95% CI: 0.70 – 0.83; $P < 0.001$; $I^2 = 21\%$). A value of $I^2 = 21\%$ indicates low heterogeneity.\textsuperscript{17}

The study of Yang et al. has several limitations that need to be considered when conducting a critical analysis. There was still a limited number of total participants in this study. Medical treatments were also not evaluated in many included studies, this could influence the long-term outcomes.\textsuperscript{17}
Besides systematic review and meta-analysis articles, cohort studies were also included in this study. Chang et al cohort study demonstrated that CABG was associated with a significantly lower mortality than PCI across all groups of estimated glomerular filtration rate (eGFR) (in mL/min/1.73 m²): They divided the subjects into three groups of patients based on eGFR. The adjusted HR was 0.81; 95% CI: 0.68 – 1.00 for patients with eGFR ≥60; HR 0.73; 95% CI: 0.56 – 0.95 for eGFR of 45 – 59; and HR 0.87; 95% CI: 0.67 – 1.14) for eGFR<45. Kilic et al also demonstrated that CKD patients survival with one year follow up was higher in CABG groups than in PCI groups (88.92% vs 82.67%, P<0.0001). In five years follow up, CKD patients survival was also higher in CABG groups than in PCI groups (73.93% vs 52.28%, P<0.0001). Another cohort study was conducted by Lautamaki et al which demonstrated that PCI was associated with a significantly higher risk of mortality than CABG in three years follow up (50.4 vs 32.9, HR: 1.77; 95% CI: 1.13–2.77).

**Conclusion**

Based on these seven studies, six studies concluded that post-PCI CKD patients had a significantly higher mortality rate than those with CABG. One other study concluded that there was no significant difference in mortality rates between post-PCI and CABG patients. However, when viewed from the critical review and the limitations of each study, the authors conclude that PCI performed in patients with CKD resulted in a significantly higher mortality rate compared to patients who underwent CABG.

**Recommendation**

It is recommended to conduct a further review of existing studies without limiting publication time. Further investigation is also needed regarding the number of PCI procedures performed during the follow-up period, severity of blood vessels, and progression of CKD. It also needs to be confirmed regarding patients undergoing hemodialysis and non-hemodialysis. and the characteristics of CKD used in selected studies. Further studies regarding morbidity such as MACE or cardiac symptoms that occur during the study observation period also need to be done. Therefore, based on the results of the study in this report, CKD patients who meet the indications
for CABG and PCI are recommended to undergo CABG treatment because of the lower mortality and morbidity compared to PCI.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Availability of data and material**

Not applicable.

**Conflict of interests**

Not applicable.

**Funding**

Not applicable.

**References**

   https://doi.org/10.1016/j.jacc.2018.05.057

   https://doi.org/10.4244/EIJ-D-17-00620

   https://doi.org/10.1056/NEJMoa04031.


   https://doi.org/10.1016/j.jacc.2019.08.1017


Case Reports
False Negative Tests in Breast Cancer: A Case Report

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Abstract:

Background: Breast cancer is the most common cancer worldwide. An early and accurate diagnosis is essential in optimizing the disease outcome. Triple assessment, which includes clinical assessment, imaging and pathological examination, is recommended for diagnosing breast cancer.

Case: A 43-year-old lady with a strong family history of cancer presented with a right breast lump for 2 months. Physical examination revealed a 2x3 cm mass in the right breast with no malignancy features. Mammogram and ultrasound revealed BI-RADS 1 (negative) and BI-RADS 2 (benign) respectively. A lumpectomy was done, and the sample was sent for pathological examination. The result came back as a grade 2 invasive breast carcinoma, no special type, stage pT1b. ER was negative while PR and HER2 were not tested. The patient then underwent a right total mastectomy with level II axillary clearance. CT thorax, abdomen & pelvis was scheduled a month later to complete the cancer staging. PR and HER2 status were tested for further management.

Conclusions: All 3 components of triple assessment are indispensable for diagnosing breast cancer. Despite the high sensitivity of imaging modalities, the minimally invasive biopsy technique (MIBT) is still the gold standard. False-negative tests can happen due to multiple factors; they should not become the absolute guidance for further management of patients. A doctor’s clinical judgment, based on thorough history taking and physical examination, is more important in guiding the next step of patient care.

Keywords: Breast Neoplasms, Mammography, Ultrasonography, Biopsy
Introduction
Cancer is a leading cause of death worldwide, with nearly 10 million or 1 in 6 deaths in 2020 (1). Among all cancer types, breast cancer stands at the top, with 2.3 million (11.7% of all cancer cases) and 685,000 deaths in 2020. Women have more disability-adjusted life years (DALYs) lost from breast cancer than any other cancer (2). Incidence rates in transitioned countries are 88% higher than in transitioning countries, but mortality rates are 17% lower. This could be due to a higher detection rate through mammographic screening, higher prevalence of modifiable risk factors (Table 1), (2-4) and distribution of Ashkenazi Jewish women in Israel and Europe, who have an exceptionally high risk of BRCA1/2 gene mutation which leads to breast cancer (4). Unfortunately, half of breast cancer incidents occur in women without identifiable risk factors except being female and age over 40 years old. Furthermore, even with all modifiable risk factors controlled, there is only a maximum 30% decrease in the risk of developing breast cancer (2). Therefore, early diagnosis of breast cancer is imperative in optimizing the disease outcome, when less complex interventions with lower costs are required (3).

Mammography is an X-ray imaging modality commonly used in breast cancer screening and diagnosis (5). It has sensitivity at 63-95% and is the only test proven to reduce mortality in screening asymptomatic populations (6). In symptomatic patients, diagnosis is based on triple assessment, i.e., a combination of clinical examination, imaging and pathological assessment (7). Clinical examination includes a thorough history taking for risk assessment and clinical breast examination. General symptoms of breast cancer include palpable mass, breast pain and nipple discharge. Hard and fixed mass, asymmetric thickening or nodularity, overlying skin changes (peau d'orange, erythema, nipple excoriation, scaling or eczema, skin ulcer, satellite skin nodule), blood-stained nipple discharge and axillary mass are features suggestive of malignancy. For women >35 years, combined reporting of mammography and ultrasound (CRMU) is recommended (3). For women <35 years, ultrasound is preferred as the sensitivity of mammography reduces significantly in dense breasts (8). MRI and newer techniques like digital breast tomosynthesis (DBT), 3D ultrasound, shear wave elastography and contrast-enhanced mammography are not routinely performed (7). A standardized report system, known
as Breast Imaging Reporting and Data System (BI-RADS) is then used to report the findings and evaluate its benignity or malignancy (5). The last component of the assessment is a pathological examination of the primary tumor, as well as suspicious axillary nodes (7). Minimally invasive biopsy techniques (MIBT) such as core needle biopsy and fine-needle aspiration cytology (FNAC) are preferably done with ultrasound guidance to increase sampling accuracy and optimize patient comfort. Core needle biopsy provides better characterization of tumor type, marker analysis and immunohistochemistry (3). An excisional biopsy is not recommended unless repeated negative core biopsies (7). Final diagnosis should be made based on the 2019 World Health Organization (WHO) classification of breast tumors and the 8th edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system (3,7).
Table 1. Modifiable and non-modifiable risk factors of breast cancer

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong> Risk increases with age, peaking at 60-64 years.</td>
<td><strong>Reproductive factors:</strong> Nulliparity, lack of breastfeeding, older age at first live childbirth</td>
</tr>
<tr>
<td><strong>Gender:</strong> Risk of female&gt;male</td>
<td><strong>Hormonal factors:</strong> Oral contraceptives (OC) use (current use, use ≥10 years, &lt;10 years since last use), progestogen OC use ≥5 years, combination hormone replacement therapy, long term unopposed estrogen use (&gt;15 years)</td>
</tr>
<tr>
<td><strong>Family history:</strong> Family history of breast cancer at a young age, carrier of pathogenic variants (BRCA1/2, PALB2, ATM, CHEK2)</td>
<td><strong>Hormonal factors:</strong> Oral contraceptives (OC) use (current use, use ≥10 years, &lt;10 years since last use), progestogen OC use ≥5 years, combination hormone replacement therapy, long term unopposed estrogen use (&gt;15 years)</td>
</tr>
<tr>
<td><strong>Reproductive factors:</strong> Early menarche (≤12 years old) and late menopause (≥50 years old)</td>
<td><strong>Lifestyle:</strong> Overweight/ obese, lack of physical activity, alcohol &gt;10g/day, exposure to tobacco smoke</td>
</tr>
<tr>
<td><strong>History of neoplastic disease of the breast</strong></td>
<td><strong>Radiation exposure:</strong> Irradiation to the chest</td>
</tr>
<tr>
<td><strong>Breast density:</strong> 2x risk in scattered fibro glandular density (BI-RADS-B), 4x risk in extremely dense breast (BI-RADS-D)</td>
<td></td>
</tr>
</tbody>
</table>
The Case
A 43-year-old lady with no known medical illness presented with a right breast lump for 2 months. It is occasionally painful on touching, described as prickling pain with a pain score of 1-2. Otherwise, it does not increase in size, no overlying skin changes, and no nipple discharge or retraction. She had a weight loss of 18kg (83kg to 65kg) within 2 years, claimed due to strict diet control and regular exercise. She had no loss of appetite, no lethargy and no metastatic symptoms such as dyspnea, bone pain, jaundice or neurological symptoms. She had early menarche at 12 years old and her first childbirth at 31 years old. She breastfed her 2 children for 6 months, and never used oral contraceptives or received any hormone replacement therapy. However, she had a strong family history of cancer. Her maternal aunt was diagnosed with breast cancer at 50 years of age, surgery and chemotherapy were done but there was recurrence 10 years later, and she subsequently passed away within a month. Her late maternal grandfather and grandmother were diagnosed with colon and liver cancer respectively at 60+ years, and were on palliative care with no surgery done. She did not smoke, and she drank alcohol occasionally.

On physical examination, bilateral breasts are symmetrical, and overlying skin and nipples appear normal. There was a 2x3cm mass in the right breast at 9 o’clock direction, 2cm away from the nipple. The mass is soft and non-tender, and the surface is smooth with a well-defined edge. It is not warm, non-mobile, non-fluctuant, not tethered to the skin and not fixated to the pectoralis muscle. There was no palpable axillary, supraclavicular or cervical lymph node. Systemic examinations were normal. The patient then underwent both a mammogram and ultrasound, which showed different findings. The mammogram revealed normal fibro glandular tissues with no mass or lesion seen, no suspicious-looking calcification, and no axillary nodes seen, hence concluded as BI-RADS 1 (negative/normal study). Ultrasound showed the presence of a 17x12mm thin-wall, well-defined, homogeneously anechoic cyst at the 9 o’clock position in the right breast. Otherwise, no other lesions and no axillary nodes were seen. Ultrasound gave an impression of BI-RADS 2 (benign). A lumpectomy was done and the breast tissue was sent for histopathology and immunohistochemistry examinations. Surprisingly, the result came back as a grade 2 invasive breast carcinoma, no special type,
staged at pT1b and malignant cells was seen at the excised margins. Estrogen Receptor (ER) was negative, Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) were not examined. The patient then underwent a right total mastectomy (Figure 1) with level II axillary clearance (Figure 2). The operation was uneventful and there were no complications such as seroma formation, lymphoedema, wound infection, hematoma and skin flap necrosis. The first drain was off on day 3 post-op and the second drain off on day 8 just before discharge. CT thorax, abdomen & pelvis was scheduled 1 month later to complete the staging. On day 10 post-op, the clinic’s follow-up revealed good wound healing and the suture was off. Further management would be planned after confirming the staging by CT as well as PR and HER2 status.

**Long suture (red arrow) indicates lateral pole, short suture (green arrow) indicates superior pole. There is a 2 cm vertical flat lumpectomy scar in 9 o’clock direction, 3cm away from the nipple (yellow arrow).**

**Figure 1 Total right mastectomy.**

**Figure 2 Level II Axillary Clearance.**

**Discussion**

Combined reporting of mammography and ultrasound (CRMU) is recommended for patients with palpable breast masses (3). Mammogram and ultrasound have a sensitivity of 87.8% and 80.1% respectively (10). The addition of ultrasound to mammography reduces the false-negative rate from 15% to 2.4%, according to Chan and colleagues. They also predicted that the cancer rate and negative predictive value of a palpable breast mass of BI-RADS 1–2 to be 0.3% and 99.7% respectively (9). Nevertheless, a diagnosis of breast cancer could still be missed which leads to a delay in treatment, a higher risk of systemic
dissemination and hence a worse prognosis. Febles classified the possible causes into 6 main groups which are breast radiological anatomy, lesion radiological characteristics, radiologist performance, equipment quality, radiographer performance and imaging environment. Measures such as imaging quality control, professional training, repeated image reading and computer-aided detection could be done to diminish false-negative occurrences (8).

In this case, the patient is at high risk of breast cancer due to her age, strong family history of cancer and early menarche (longer duration of estrogen exposure). However, clinical breast examination gave an impression of a benign cyst, then further augmented by mammography and ultrasound findings: BI-RADS 1 and BI-RADS 2 respectively, which are suggestive of a 0% chance of malignancy. However, the histopathological result came back as a Grade 2 invasive breast carcinoma, no special type at pT1b stage. Initially, a lumpectomy, instead of a core needle biopsy or FNAC was done due to the diagnosis of a benign cyst. Fortunately, the excised tissue was sent for pathological examinations which overturned the previous impression and confirmed a final diagnosis of breast cancer.

The immunohistochemistry testing is incomplete; ER was negative, and PR and HER2 were not tested, thus unable to continue further workup on the treatment plan. Both hormone receptors (ER & PR) and HER2/ c-erb B2 status should be assessed for all samples of suspected breast cancer (3).

Conclusions
Triple assessment, which includes clinical assessment, imaging and pathological examination, is necessary for diagnosing breast cancer. Despite the high sensitivity of imaging modalities, minimally invasive biopsy technique (MIBT) such as core biopsy and fine-needle aspiration cytology (FNAC) is still the gold standard. False-negative tests can happen due to multiple factors; they should not become the absolute guidance for further management of patients. A doctor’s clinical judgment, based on thorough history taking and physical examination, is more important in guiding the next step of patient care.

Declarations
Ethics approval and consent to participate
Informed consent of publication was obtained from the patient.
Availability of data and material

Not applicable.

Conflict of interests

The author has no conflicts of interest to disclose.

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Authors' contributions

YX Lee was the sole contributor of the manuscript.

References


8. Febles G. False negatives in mammography. Revista De Imagenologia. 2013 Jun 10;16(2)


Perspective Articles
AMSEP Internal Audit - A Behind The Scenes Into Medical Students' Exchanges during the COVID-19 Pandemic.

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Keywords:
COVID-19; Medical Students; Management Audit; Cultural Diversity; Organizations;

Introduction:

Exchange programs have been practiced globally, especially among medical students. It is an arrangement where students from different countries interchange to explore the academic, socio-cultural and community service realms of their counterparts. Prior research has revealed the benefits of exchange programs among medical students and has recommended the globalization of the same [1]. These exchanges are highly desired by medical students as the majority claim that it helps them expand their horizons by inculcating differing views of medical practice. This can be done by incorporating a better understanding of social and public health awareness, the importance of cultural sensitivity and the differences in opportunities in the medical field of different countries [2].

The Asian Medical Students’ Association (AMSA) International is one such peak representative medical organization which has grown through the years since its establishment in 1985, carrying the aim to foster unity and promote everlasting bonds amongst its members. The Asian Medical Students’ Exchange Program
AMSEP, conceptualized in 2003, acted as a conduit for the same with its first pilot exchange program in 2006. AMSEP not only restricted itself to the Asian continent but also expanded itself by including students from the UK, Egypt, Australia, etc. with the number of exchanges steadily increasing each year without compromising on the quality of exchanges.

Through this program, AMSA members are given the opportunity to partake in a 5 to 10-day exchange. The activities held during the AMSEP exchange makes it unique from its equivalents as it follows the pillars: Academic, Sociocultural and Community Service. All of the exchanges conducted are derived from the foundation of AMSA’s philosophy of Knowledge, Action, and Friendship.

Due to the pandemic, medical student organizations have seen high numbers of cancellations and postponements in exchanges which have deprived students of the opportunity to experience these fine opportunities for training, exchange and sharing [3]. Despite this, AMSEP weathered the storm and grew to higher levels proving to be the standard for exchanges globally. Since this growth has never been documented, this study aimed to measure and compare the growth of AMSEP through the tenures of 2018/2019, 2019/2020, 2020/2021 and the ongoing tenure of 2021/2022.

Results:

AMSEP steadily progressed from 13 member countries or ‘chapters’ (20%) in the tenure of 2018/2019 & 2019/2020 to 17 chapters (26.15%) during the tenure of 2020/2021. Exponential growth was found in the tenure 2021/2022 amidst the second wave of the pandemic to 22 chapters (33.85%) as depicted in Figure 1.

Figure 2 graphically represents the Tenure-wise summarization of AMSEP Contracts. 2018/2019 documented a total of 22 physical AMSEP contracts and all of them were carried out. Followed by which in the tenure of 2019/2020, out of the 28 contracts which were assigned to all the chapters, 21 (75%) were carried out while 7 (25%) were terminated due to the COVID-19 pandemic. During the epicenter of the pandemic, AMSEP shifted to a virtual basis in the tenure 2020/2021 with a total of 26 contracts carried out with 10 (38.46%) from the past tenure and 16 (61.54%) from that tenure. With the feasibility of virtual exchange, 2021/2022 drew an unprecedented 53 contracts out of which 49 were fresh
while 4 were carried out from the past tenure. Thereby almost doubling from the previous tenure.

In retrospect, a tenure-wise summarization to understand the different backgrounds of delegates in AMSEP was done and depicted in Figure 3 and tabulated in Table 2. These were derived from the Official AMSEP Delegate Application Form through informed consent. In the tenure of 2018/2019, out of the 165 delegates, the major contributors were Taiwan - 64 (38.79%), China - 39 (23.64%) and Malaysia - 30 (18.18%). Whereas in 2019/2020, out of the 320 delegates who took part in either physical or virtual exchanges, Indonesia predominated with 89 delegates (27.81%), followed by Malaysia with 58 delegates (18.13%) and Taiwan with 46 delegates (14.38%). During 2020/2021 exchanges were only conducted on a virtual basis. Out of 916 delegates Indonesia had the maximum of 243 (26.53%) followed by 177 Taiwanese delegates (19.32%) and 117 Malaysian delegates (12.77%).

The educational status of the delegates was gauged through the aforementioned form to understand the sector from which students partake in exchanges. It can be seen clearly depicted through the bar graph in Figure 4 and tabulation in Table 3.

Through our partner organization the European Medical Students’ Association (EMSA), AMSEP chapters increased their opportunities to conduct exchanges with their European counterparts via the European-Asian Medical Students' Exchange program (EAMSEP). A tenure-wise summarization of EAMSEP contracts carried out from the past tenure is shown in Figure 5. The contracts double in the current tenure showing the fondness for the EAMSEP exchange. The Official EAMSEP Delegate Application Form gave valuable insight into the number of delegates and their backgrounds which is entailed in Figure 6 and Table 2. The tenure-wise summarization of the nationality of delegates from previous tenures was not available due to beta testing of EAMSEP Exchanges in the early stages. The form helped measure the educational status of the delegates partaking in these exchanges. Out of a total of 80 delegates in the tenure of 2020/2021, 69 (86.25%) delegates were in their preclinical year, 8 (10.00%) in the clinical year and 3 (3.75%) had graduated as shown in Figure 7 and tabulated through Table 3. The educational status and nationality of the delegates from
previous tenures were not available due to the beta testing of EAMSEP Exchanges in the early stages.

As a recent partner, FAMSEP has had a peculiar appeal to most chapters in AMSEP. With beta testing in 2020/2021, only 2 contracts were assigned to judge the feasibility of the program after which the number of exchanges quadrupled to 8 in the tenure of 2021/2022 (Figure 8).

Through the Official FAMSEP delegate application form, it was found that out of the 34 delegates that took part in the exchanges held via FAMSEP in 2020/2021 the nationality was maximum from Malaysia with 19 delegates (55.88%) followed by India with 14 delegates (41.18%) and the United States of America with 1 delegate (Figure 9 and Table 2).

The official FAMSEP delegate application form also brought to notice that out of the 34 delegates who took part in the exchanges occurring in the year 2020/2021 where the maximum number of delegates (i.e. 21 - 61.76%) were in their preclinical year followed by 13 (38.24%) in the clinical year (Figure 10 and Table 3).

**Discussion:**

The COVID-19 pandemic did take its toll on physical exchanges conducted by AMSEP; with the travel restriction and force majeure. This brought a huge transition from Physical to Virtual exchanges. These significant changes had a transitional effect, but once stabilized, the number of contracts and the number of chapters participating escalated steeply. This steady growth is attributed to the lack of opportunities presented by other medical organizations [3] and the applicability and efficiency of a Virtual AMSEP, which is more accessible than its Physical compeer. Chapters are more likely to do a visual tour as it proves to be less demanding and is easier to balance with their medical curriculum. On top of that, Clinical and Graduate Medical students are more likely to participate in Virtual AMSEP due to the flexible schedule.

Hosting Virtual AMSEP is quicker with lesser arrangements required; hence it contributes to the steady growth of contracts per year. The total number of delegates partaking in AMSEP as shown by Taiwan and Indonesia has created more opportunities for them to opt for and carry out more contracts per year.

Other chapters have shown increments as well. Chapters such as
Bangladesh and Hong Kong, which previously did not partake in exchanges, have successfully partaken in AMSEP by sending in an appreciable number of delegates.

Not to mention our collaboration with EMSA and FAMSA. The number of contracts for EAMSEP and FAMSEP has strenuously grown. It has proven to be a fruitful collaboration with EAMSEP and FAMSEP owing to the vastness of cultures and academics across continents.

However, despite various increments, several chapters show a reduction in their number of contracts, such as China, Japan and Singapore. It might be due to human resources issues and virtual fatigue (also known as “zoom fatigue” colloquially)[4] which have proven to be a significant problem in virtual exchanges.

Through the framework set in AMSEP, we see that it is a sustainable and ever-growing platform for medical students worldwide to experience knowledge, action, and friendship through academics, socio-cultural and community service. We hope that in the coming years more medical students explore the opportunities it has to offer and avidly take part in both virtual and physical exchanges alike.

**Tables:**

Table 1: Tabulated summarisation of the Tenure-Wise Distribution of AMSEP Contracts depicted graphically in Figure 2.

<table>
<thead>
<tr>
<th>Tenure</th>
<th>Contracts Carried Out</th>
<th>Contracts Terminated</th>
<th>Contracts Carried out from Past Tenure</th>
<th>Total Number of Contracts</th>
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Table 2: Tabulated summarisation of Delegates participating in AMSEP, EAMSEP & FAMSEP throughout the years on the basis of Nationality.

<table>
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<th></th>
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<th></th>
<th>FAMSEP</th>
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Table 3: Tabulated tenure-wise summarisation of the Educational Status of Delegates participating in AMSEP, EAMSEP & FAMSEP.

<table>
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<th>Nationality</th>
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<th>EAMSEP</th>
<th>FAMSEP</th>
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<td>Clinical</td>
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<td>42</td>
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<td>Graduated</td>
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<td>5</td>
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<tr>
<td>Total Number of Delegates</td>
<td>165</td>
<td>320</td>
<td>916</td>
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Figure 1: Total Number of Chapters taking part in AMSEP throughout the years.

Figure 2: Tenure-Wise Summarisation of AMSEP Contracts

Figure 3: Tenure-Wise Summarisation of the Number of Delegates partaking in AMSEP based on Nationality.

Figure 4: Tenure-Wise Summarisation of the Educational Status of the Delegates partaking in AMSEP.
Figure 5: Tenure-Wise Summarisation of EAMSEP Contracts

Figure 6: Tenure-Wise Summarisation of the Number of Delegates partaking in EAMSEP based on Nationality.

Figure 7: Tenure-Wise Summarisation of the Educational Status of the Delegates partaking in EAMSEP.

Figure 8: Tenure-Wise Summarisation of FAMSEP Contracts
Acknowledgement:

We would like to recognize the efforts of the previous flag bearers Ms. Marjorie Jia Yi Ong and Ms. Dayna Alysha, the current flag bearers - the authors of this study, all the National and Local Directors of AMSEP, the Liaison Officers for Medical Students’ Organizations of AMSA International and our valuable counterparts in EMSA and FAMSA, due to whom this progress was achievable.

Reference:


A call for standardized undergraduate end-of-life care education in the post-COVID era

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Abstract:
End-of-life care can effectively reduce the psychological stress of near-death patients and smoothen the bereavement of patients' relatives. However, the delivery of end-of-life care has been severely challenged by the pandemic due to an associated surge in patients. The major challenges include its adaptability to the pandemic and the enduring low level of competency in healthcare professionals. This prompts the question of whether the current end-of-life care education is sufficient for preparing future healthcare professionals in providing such services. This commentary highlights the importance of teaching end-of-life care at the undergraduate level and suggests 11 learning points across five themes for consideration.

Introduction:
Since the early 1970s, interest in improving the end-of-life, palliative, and hospice care of patients has progressed from being the concern of a limited group of healthcare professionals to being the concern of the entire international healthcare community. While these three types of care are defined differently, they essentially comprise the idea of providing holistic care to patients who are about to succumb to death, as well as to their family members (1). The provision of this care is classified based on age (adult, geriatric, or pediatric patients) and occurs in settings such as hospitals, nursing homes, and patient homes. However, the implementation of this care has been severely challenged during the COVID-19 pandemic due to the associated surge in patients needing palliative and hospice care.

End-of-life care in the pandemic:
The past two years have been a difficult time for many people, especially for COVID-19 patients, their families and friends, healthcare professionals, particularly in the early and middle phases of the pandemic when vaccines were not readily available. The last rites of patients...
were not allowed to be done at home due to concerns about the spread of infection. Strict rules regarding quarantine and isolation meant that patients' family members were unable to see their loved ones during their ending moments. While digital platforms did make it feasible for people to stay in touch, the security and emotional support provided by one's physical presence were lost. Without any doubt, this was not the traditional way to deliver end-of-life, palliative, or hospice care. Family and friends couldn't attend services or meet for funerals, making it harder to cope with one's grief. The lack of meaningful communication and bereavement hindered the peace of patients and their family members, violating the standard definition of a good death and smooth bereavement.

Healthcare professionals were also forced to drastically adapt as a result of the disruptions of the pandemic. Doctors and nurses were not able to act as mediators and provide simultaneous psychological support to both patients and patients' families (2). Healthcare professionals who had not previously provided end-of-life care were suddenly required to offer such services due to the high number of near-death patients. Hence, end-of-life care itself and the related skills of healthcare professionals were put to the test during the COVID-19 pandemic.

Importance of end-of-life care education:
The low level of competency of healthcare professionals in delivering end-of-life, palliative, and hospice care was completely exposed due to the pandemic. For instance, one report suggested there was a lack of healthcare professionals with the necessary skills in conversational techniques to identify patients who preferred comfort-focused management (3). Meanwhile, it found, especially during the COVID-19 pandemic, that some nurses do not identify themselves as part of the initiative to reduce overtreatment(4).

These results collected during the pandemic were similar to those from the pre-COVID era, particularly among healthcare professionals from specialties other than oncology and palliative care. Prior research showed that they often felt uneasy and found it difficult to offer compassionate care to terminally ill patients (5). Some doctors were reported to be learning palliative care via trial and error (6).

Therefore, the current tragic pandemic reminds all healthcare students and educators around the world that end-of-life care is no longer a service meant solely for patients with oncological conditions but is also for patients with many types of illnesses, including infectious diseases. Education about end-of-life, palliative, and hospice care is
obviously of utmost importance in healthcare education because (a) witnessing the death of patients is inevitable during a career in healthcare, (b) a good death must be provided for patients, regardless of a provider’s specialty, with the exceptions of laboratory- and radiology-intense roles, and (c) learning about end-of-life care provides healthcare students with a multitude of skills, such as communication, compassion, and the ability to share bad news, all of which help them enhance their prospects in the healthcare sector.

Provision of end-of-life care education

To understand the importance of learning end-of-life care, we must investigate the measures used to improve competency in this area. Research has suggested that the enduring hurdles healthcare professionals face in providing end-of-life care can be attributed to limited exposure during basic training (7). In other words, the inclusion of end-of-life, palliative, or hospice care education in the undergraduate curriculum is the key to solving the current problem of competency. In turn, this conclusion prompts the question regarding whether the current undergraduate education for these three types of care is sufficient for teaching the concepts and basic framework of palliation and instilling the correct attitudes in future healthcare professionals.

While evaluation of the many healthcare education programs is ongoing around the globe, there is a lack of consensus in terms of the ideal time to start a palliative care education program, the depth of the content, and the percentage of clinical teaching involved (8, 9). For example, evidence is contradictory regarding whether end-of-life care education should begin during the preclinical years, involve palliation for adult, geriatric, and pediatric patients, and should include hospice visits (2, 8). Furthermore, the evidence remains unclear regarding whether end-of-life care curricula should involve just oncological patients or even patients with infectious diseases who require more advanced technology, such as telemedicine, during forced isolation (10).

Based on these studies (2, 5, 8, 9) and the pandemic experience, 11 learning points across five themes have been identified for consideration when designing or improving a curriculum about end-of-life, palliative, and hospice care. These learning themes propose that such curricula should focus on (Figure 1):
1. both adult, geriatric, and pediatric streams;
2. fundamental concepts of end-of-life care, palliative care, and hospice care, as well as the incorporation of new technology such as telemedicine;
3. physical management, such as pain assessment and symptom management, as well as emotional management in an end-of-life care setting;
4. simulation and clinical practice at communication skills, bad-news delivery, ethical decision making, and interprofessional collaboration on end-of-life scenarios; and
5. stimulating healthcare students’ reflections on patients’ experiences and strengthening their concepts of patient- and family-centered care.

Figure 1. A total of 11 learning points across five themes proposed for end-of-life care education in undergraduate curricula.

Conclusion
In summary, the extraordinary circumstances of the pandemic compel us to reflect on the needs of patients, our level of competence, our perspective on end-of-life care, and the current methods of learning end-of-life care. We should begin by changing our own attitudes toward palliative care, continually reviewing the issue of end-of-life care in the post-COVID era, and recognizing the importance of learning end-of-life care. Moreover, we should also advise our faculties to incorporate all of the ideal approaches to end-of-life care, inclusive of new techniques, such as telemedicine, into our curricula for the benefit of future patients.

Declarations

**Ethics approval and consent to participate** - Not applicable.

**Availability of data and material**

Not applicable.

**Conflict of interests**

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Matrix-associated chondrocyte implantation versus autologous chondrocyte implantation for chondral knee defects: A protocol for a systematic review and updated meta-analysis

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Abstract:

Background:

Chondrocytes are essential for the smooth functioning of the knee joint. However, derangements of various metabolic processes leads to a high prevalence of insidious chondral defects which may predispose patients to osteoarthritis. This may lead to deterioration of the quality of life in physical, psychological and social domains. Though, autologous chondrocyte implantation (ACI) yields superior results in chondral defects as compared to microfractures, there has been no meta-analysis till date to quantify the clinical efficacy of various chondrocyte implantation techniques as compared to each other. Our review will synthesize current evidence on matrix-associated chondrocyte implantation versus autologous chondrocyte implantation to establish the superior technique for chondral knee defects in terms of clinical outcomes and post-operative quality of life.

Methods:

An exhaustive search will be undertaken on PubMed, Cochrane, Embase, International Clinical Trials Registry Platform (ICTRP), Trip Medical Database and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases to identify relevant studies. Primary human studies comparing matrix-associated chondrocyte implantation and autologous chondrocyte implantation in the context of knee chondral defects would be included. The primary outcome will be postoperative improvement in knee functions assessed clinically or via activity scores like International Knee
Documentation Committee (IKDC) subjective score, Lysholm-Gillquist score and Tegner Activity Score. The secondary outcomes will be radiological scores for monitoring structural improvement like Magnetic Resonance Observation of Cartilage Repair Tissue score and health-related quality of life scores.

**Discussion:**

This will be the first systematic review and meta-analysis in available literature comparing the clinical outcomes and post-operative quality of life in matrix-associated chondrocyte implantation versus autologous chondrocyte implantation for chondral knee defects. This review can be expected to guide clinical practice as well as research in the treatment of chondral defects of the knee.

**Keywords:**

Autologous chondrocyte implantation; Chondral defects, MACI, clinical efficacy, postoperative improvement, treatment outcome
Introduction

The knee joint has a very important role in the maintenance of postural stability and is subjected to severe stress frequently. [1] The range of movement coupled with the unique screw-home mechanism makes knee anatomy very complex. [2] The synovial fluid, the joint capsule, ligaments, tendons, muscles and cartilage play key roles in ensuring the maintenance of the knee joint.

Chondrocytes synthesize several cytokines and growth factors which regulate metabolic processes. [3] Derangement of these processes can lead to functional loss and structural damage, manifesting as a myriad of symptoms in patients. Patients may present with pain, joint oedema, impaired range of motion and are at a higher risk of developing osteoarthritis. [4] Self-repair is also restricted due to low cellularity and lack of vascular supply. [5]

Data from knee arthroscopies suggests that there may be a 34-62% prevalence of chondral defects with full thickness lesions being seen in 4.2-6.2% cases below the age of 40. [6, 7] This high prevalence is concerning since untreated chondral defects may lead to the development of osteoarthritis which adversely affects a patient’s quality of life, economically burdening patients to the tune of thousands of dollars. [8] Advanced imaging techniques have resulted in enhanced detection of these chondral defects. [7]

However, this increased detection has not necessarily translated to rapidly improved patient outcomes as joint replacement with an artificial prosthesis has remained the go-to option to restore the patient’s quality of life in osteoarthritis. Though there are established non-pharmacological, clinical and surgical guidelines, there is no conclusive mention yet on the utility of advanced bioengineering procedures like autologous chondrocyte implantation in the therapy. [9] These modern procedures may offer patients a viable long-term treatment option but more research is needed in this field.

Therapy by microfracture of the chondral defect was very common initially but the incidence of long-term complications leaves a lot to be desired. [10] Microfracture is based on the principle of migration of mesenchymal stem cells to stimulate growth of hyaline-like fibrocartilage. [11] It has been argued that supplementing
Microfracture with intra-articular injections may enhance efficacy of the procedure. [12-14] However, randomized clinical trials have shown that autologous chondrocyte implantation (ACI) yields superior results in the treatment of chondral defects as compared to microfracture. [15-16]

Autologous chondrocyte implantation was a novel procedure that was developed in 1994 by Brittberg et al. [17] A periosteal tibial flap was used to cover the defect using a fibrin glue. However, this commonly caused hypertrophy. Subsequently, porcine collagen was used which eliminated the need for a procedure at tibia and reduced the incidence of post-op complications. [17, 18] With the advent of latest bio-technological advancements, matrix-associated chondrocyte implantation (mACI) has been developed. [19] Autologous osteochondral transplantation, autologous matrix-induced chondrogenesis and osteochondral allograft transplantation are some other procedures which have been implemented in the treatment of chondral defects. [5]

Interestingly, though many reviews have advocated the suitability of chondrocyte implantation over microfracture, there has been no meta-analysis till date to statistically quantify the clinical efficacy of these various chondrocyte implantation techniques as compared to each other. [20] An extensive search will be undertaken in PubMed, Cochrane, Embase, International Clinical Trials Registry Platform (ICTRP), Trip Medical Database and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases to identify studies on mACI and ACI. Our review will overcome this lacuna and shall provide robust evidence on the relative superiority of these various chondrocyte implantation techniques and will guide clinical practice as well as research in the treatment of chondral knee defects.

**Methodology:**

This protocol adheres to Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines for new systematic reviews which included searches of databases, registries and other sources. [1] The PRISMA checklist has been supplemented in the appendix.
The studies identified in this review will be subject to inclusion based on the following criterias:

**Type of Study**

Only Randomized controlled trials (RCTs) or controlled clinical trials comparing the two techniques of matrix-induced autologous chondrocyte implantation (MACI) versus the original periosteum cover technique of autologous chondrocyte implantation (ACI) for treatment of symptomatic chondral or osteochondral defects of knee shall qualify to be included in the review. These eligible studies will yield us clinical (functional), radiological and health-related quality of life scores recorded on postoperative follow ups. We shall be excluding any trial which is non-randomised and possesses a threat to the quality of evidence. Literature from conference abstracts, unpublished RCTs or clinical registries shall be included if the required data needed for analysis is either available open-access or can be obtained from authors with due permission.

**Type of Population**

Eligible participants shall be broad to consider the relevancy of surgical procedures in various clinical settings. Patients aged equal or more than 16 years, without gender or ethnic distinction with symptomatic isolated full-thickness chondral or osteochondral defects of knee irrespective of center of study & concomitant etiology. Exclusion criteria will be extended cartilage erosion, restricted mobility, extended meniscal defect, untreated cruciate or collateral ligament laxity, untreated varus or valgus alignment, inflammation, any history of interventional procedures in the respective knee less than 1 year ago, hyaluronan injection less than 6 months ago. In case of a heterogenous group, we will try to obtain separate data but will not categorically exclude the study if otherwise eligible. An orthopedician shall approve the final inclusion decision at these instances.

**Type of Intervention**

Patients who underwent a Matrix-associated autologous chondrocyte implantation (MACI) where a bioscaffold "matrix" is implanted with fibrin glue and embedded with autologous chondrocytes. It is based on ACI's good long-term track record, but a clear cut clinical superiority is yet to be demonstrated. MACI therefore is based on a membrane that acts as a cell transporter to more equally
distribute the cells with a density of 500,000 to 1,000,000 cells per cm². Patients on concomitant non-surgical treatment modalities shall only be included if provided to both the groups or the contrast between the arms allow to delineate the net effect.

Type of Comparator

Patients who underwent an Autologous Chondrocyte Implantation With Periosteal Flap (ACI-P): ACI of the First Generation. Here a periosteal flap is excised from the tibia covering the cartilage defect (ACI-P). Fibrin glue is used to seal the bioactive chamber after it has been filled. Eligible controls in multi-arm studies will be included as well.

Type of Outcome

The primary outcome will be postoperative improvement in clinical or knee function or activity scores like subjective International Knee Documentation Committee (IKDC) score, Lysholm and Gillquist score or Tegner Activity Scores. Secondary outcomes will be radiological scores for monitoring structural improvement like Magnetic Resonance Observation of Cartilage Repair Tissue score or health-related quality of life scores. The frequency of common follow-ups will outlay the possibility of making multiple forest plots to analyze short term and long term improvement of these surgical procedures or doing a multivariate analysis if found feasible.

Search Strategy

Electronic search shall be run on PubMed, Cochrane, Embase, ICTRP, Trip Medical Database, CINHAL, Scopus with the broad spectrum keywords (to increase the possibility of least exclusion) of [(matrix-induced autologous chondrocyte implantation) OR matrix-associated autologous chondrocyte implantation) OR MACI OR mACI OR m-ACI OR (matrix AND chondrocyte implantation)] to identify studies from inception till 31st January, 2022 without any publication or language restriction. Manual searches on references of included articles and previous reviews as well as clinical trial registries shall be thoroughly searched. For Grey literature: MedRxiv, BioRxiv, AiXiv and other preprint servers will be searched.

Study Selection

Articles identified from the search results will be imported to Endnote X9 and duplicates will be removed. Eligibility screening will be done by
title and abstract of the articles by two independent reviewers. Any disagreement between the two reviewers shall be solved either by consensus or involving the third reviewer (faculty expert). All potential articles selected by screening will be sent for full-text review by both the independent reviewers and the same strategy will be followed upon disagreement. Finally, a third review will also be done by faculty experts of all included studies in consensus with the independent reviewers.

Data Extraction

Data shall be extracted to an excel sheet by a reviewer whereas the other reviewer will cross-check the entry from the original manuscript. Any disagreement between the two reviewers shall be solved either by consensus or involving the third reviewer (faculty expert). Corresponding authors shall be contacted upon lack of adequate data or in need of additional information.

We shall be extracting the following data:

1. Study Information: first author, year of publication, study location and corresponding author with details.


3. Intervention and Comparator: m-ACI and ACI with any significant surgical notes if present


Data will be obtained as Mean and standard deviation at each time point. If not available, we will try to reliably calculate the data if sufficient information is available or otherwise contact the corresponding author. The following data will be extracted via an objective data extraction form customized from Cochrane Development, Psychosocial and Learning Problems Review Group and therefore complies with Methodological Expectations of Cochrane Intervention Reviews. [20]

Risk of Bias Assessment

The revised Cochrane Risk of Bias instrument (RoB 2) will be used to assess the risk of bias in individual RCTs. For each of the domains of RoB 2, a low, high, or some concerns risk of bias will be determined by two independent
reviewers and a third faculty expert will be involved in disagreement.

Data synthesis

RevMan 5.4 will be used where the heterogeneity assessed by \( I^2 \) statistics will lead the way for a random or fixed effect analysis model. Inverse variance analysis will be done for each outcome using Mean and Standard Deviation with 95% confidence interval. Based on the possibility of sufficient power of heterogeneity, additional meta regression models might be implied.

Confidence in evidence

The strength of the evidence is assessed and qualitatively summarized based on the individual risk of bias assessment.

Discussion

Due to the immense epidemiological burden of the condition, it is important for orthopedics to be fully aware of the utility of various therapeutic procedures. The gap in literature necessitates the need for our review which will provide an insight into the efficacy of various ACI procedures. [21] This will in turn serve to improve patient prognosis as well.

We expect the sensitivity of our search to be limited by the lack of MeSH terms. To overcome this, we have used a wide range of word combinations. Also, medical databases in languages other than English would not be covered, so a language bias may exist in our findings. Nevertheless, to our knowledge, this systematic review and meta-analysis would be the first to assess the efficacy of mACI as compared to ACI. The study would also help to identify areas for future research, thus guiding clinical researchers.

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Implantation Using the Original Periosteum-Cover Technique Versus Matrix-Associated Autologous Chondrocyte Implantation: A Randomized Clinical Trial. 38(5), 924–933. https://doi.org/10.1177/0363546509351499


How a Small City in India, Chandigarh, Controlled the COVID-19 Pandemic: Strategies Used and Lessons to be Learned

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Abstract:

With the current COVID-19 pandemic sweeping across the globe, thousands have succumbed to the virus. Countries across the globe are desperately trying to take appropriate measures to prevent the spread of the coronavirus and to keep their population safe and healthy. While the predilection remains for older individuals, in countries where access to medical care is shorthanded, containing the virus is the best strategy. As many states and cities across the world grapple to combat the pandemic, this commentary focuses on the effective strategies implemented by one such city in India, Chandigarh, in an effort to control the COVID-19 pandemic. By implementing strict curfews, social distancing and preventative measures, Chandigarh has effectively contained the COVID-19 pandemic. As a result of all these measures, the current COVID-19 confirmed case rate in Chandigarh is 4155, 16 weeks after the first reported case. This article seeks to outline the strategies and methods implemented by Chandigarh in controlling the COVID-19 infection rate.

Key Words: COVID-19, Chandigarh, India, control, lockdown
Introduction:

The COVID-19 pandemic, stemming from the SARS-CoV-2 virus and otherwise known as coronavirus, began in Wuhan, China in December 2019. It has involved a significant portion of the world within the span of a few months. SARS-CoV-2 has affected the lives of millions, infecting over 25 million worldwide with a fatality of over 843,586. As of August 30th, 2020, the number of coronavirus cases has reached over 3.6 million in India. Despite a population of over 1.3 billion people, the number of confirmed cases across India is not what would have been expected.

This article seeks to highlight a small city called Chandigarh and how the administration implemented measures that curbed coronavirus infection rates. The methods employed by Chandigarh could also be similarly used for other cities around the globe. Chandigarh is a city in the northern part of India spanning 44 square miles that serves as the capital of two neighboring states, Punjab and Haryana. Despite being the capital of two separate states within India, it is directly governed by the Government of India itself. It has a population of 1,055,000 and a literacy rate of 89.99% and 81.19% among males and females respectively. The first COVID-19 case in Chandigarh was reported on March 19, 2020. At the time of this writing on August 30th, 2020, only 4155 cases have been confirmed, and 2296 patients have recovered with 52 mortalities. The number of people quarantined totals 23,671. The relatively low amount of confirmed cases and fatality rates could only happen because of the immense support from the Indian Ministry of Health, the Government of India, and the Chandigarh administration.

Janata Curfew

On March 22, 2020, the nation of India witnessed a "Janata Curfew" which was a lockdown requested by the Prime Minister of India, Narendra Modi, without any law being imposed and by the will of the whole nation. The Prime Minister addressed the entire country by requesting citizens to stay at home from 7 AM - 9 PM to test the effectiveness of a lockdown in stopping the spread of the coronavirus. He urged state government organizations such as the National Cadet Corps and National Service Scheme to encourage citizens to follow the Janata curfew actively. Most of the population complied and stayed inside. As a show of appreciation to those who had to remain working,
such as health care workers, police, and sanitization workers and to commend everyone who stayed home, there was a countrywide movement that spread virally. Across India, people clapped and banged utensils simultaneously on their balconies in the evening to show appreciation for the Prime Minister and their fellow citizens.\(^5\) This created a sense of unity during the time of the COVID-19 pandemic and the entire country was placed under strict lockdown starting the very next day.

**Lockdown**

The lockdown in Chandigarh, has been very successful. The Government under the Epidemic Disease Act, 1897, imposed Section 144 of the Code of Criminal Procedure (CrPC) and initiated a lockdown curfew on the city on March 23, 2020, which was extended to May 03, 2020. According to Section 144, no more than 5 people were allowed to gather at any place and individuals were not allowed to leave their homes, stand outside, or move on foot or vehicle on any road or public places (except for emergency medical aid). If a person was found doing so, they were subject to legal action.\(^6,7\) One person per household was allowed to leave their home between 10 AM and 6 PM to visit essential shops and supermarkets for groceries.\(^8\) This strict curfew was enforced with the help of drones to monitor individuals who broke the curfew.

The lockdown brought the entire city of Chandigarh to a halt. All social gatherings ceased, and means of domestic transportation, schools, and non-essential businesses were shut down. If any vehicle was found on the road without a valid reason, it was taken into custody. Daily official meetings were conducted to address new problems on a day-to-day basis. The city also created a COVID-19 website for citizens to access all information about the efforts to combat the pandemic, including daily press releases from the governing body. Additionally, the Government of India also developed a mobile application (App) called AAROGYA SETU to rally its citizens in the fight against COVID-19. The App was available for download on Android and iPhone and allowed people to assess their risk of getting coronavirus by tracking their movement through the use of cellular GPS and Bluetooth.\(^9,10\)

**Screening and quarantine**

Per the Government of India, all asymptomatic individuals with a
travel history to a foreign country, contact with a COVID-19 positive case or any COVID-19 symptoms were to be quarantined at home for 14 days. All individuals who met the criteria for coronavirus testing were offered tests at zero cost. Additionally, Chandigarh began door-to-door screening for coronavirus symptoms and travel history, becoming the first city in India to do so. All healthcare workers, hospital staff, police personnel, vendors, and government officials who were at high risk underwent thermal screening every day and were also monitored for exposure. If they were found to have exposure to a COVID-19 positive patient, they were subsequently quarantined and followed up for 14 days. If a person developed any symptoms, they were isolated and tested for COVID-19.

In Chandigarh, teams were made to enquire about suspected coronavirus cases, positive cases, track patients' contact history, and ensure quarantine of all the contacts for 14 days to prevent transmission. The suspected cases were monitored by these teams via telephone interviews and were tested if individuals developed any symptoms. The government offices, private hotels, and community centers were converted into quarantine facilities to maintain effective quarantine of all positive or suspected individuals.

**Delivery of essential goods**

The Chandigarh administration, by involving all government public departments such as the Municipal Corporation of Chandigarh, police authorities, and district magistrate authorities, chalked out all the essential goods needed to fulfill the basic needs of the residents so that effective lockdown was maintained. Some community centers and religious institutions were transformed into community kitchens where cooked food was provided to needy individuals. Since 10-15% of the Chandigarh population are daily wage earners, the lockdown created a temporary loss of employment and income for many. Hence, the community kitchens and shelter homes were made for individuals who might otherwise suffer economically due to the lockdown. As per the Chandigarh administration, cooked meals were distributed to approximately 15,000 needy persons daily. Rations and vegetables were also supplied to rehabilitation colonies, slum areas, and villages via buses. On April 9, 2020, the Chandigarh Administration authorized the distribution of 3 months' worth of
food grains to lower-income families at no cost. On April 17, 2020, the Department of Social Welfare of Chandigarh, distributed take-home rations including weaning foods, eggs, and milk. Included in this were sanitary pads for 530 women and girls to encourage good menstrual hygiene. Additionally, to provide accessibility to essential commodities, all shops with essential commodities like food grain, groceries, fruits, vegetables, milk, meat and fish were allowed to remain open from 10 am to 6.00 pm daily.

Those that were able to go grocery shopping in person had to follow strict guidelines as mandated by the city administration. In grocery stores, patrons were allowed to enter shops if they wore a mask and only after thermal screening using infrared thermometers and hand sanitization. Store workers were also given masks, hand wash, and sanitizers in an effort to prevent the spread of coronavirus. Markings were made for customers to stand in grocery stores at a distance of 6 feet to each to ensure social distancing. Home delivery and electronic payments were heavily encouraged to prevent in-person contact. In additional efforts to ensure social distancing and maintain lockdown, the city of Chandigarh also began implementing door-to-door delivery of daily essentials like meat, vegetables, and dry products with the help of local vendors who were screened, given masks, gloves, and sanitizers. To prevent price gouging and food scarcity, the costs of goods were regulated by the government and fixed-priced lists were displayed on buses delivering food to neighborhoods.

Sanitization of the City

The Office of the Medical Officer of Health maintains responsibility for the sanitation of the city of Chandigarh. The Municipal Corporation of Chandigarh has sanitized and fogged areas around the city, with trucks and drones, to prevent the spread of COVID-19. The entire city of Chandigarh was also sanitized by antibacterial sprays set up in vehicles provided by the Ministry of Health.

Healthcare Setup

In hospitals across the city, elective surgeries were halted and all doctors, nurses, and healthcare personnel were mobilized and trained on infection control and prevention. Hospitals were mandated to ensure appropriate staffing to handle overflow situations and to maintain a sufficient number of ventilators and
high-flow oxygen masks. If any healthcare personnel was infected with coronavirus, treatment was provided free of cost. All non-essential workers and medical students were given leave and telemedicine was implemented.

Three of twenty-two hospitals were designated as COVID-19 hospitals in Chandigarh and six fever clinics were set up as the first level of screening to identify and authorize suspected coronavirus cases for testing. Additionally, three sampling centers were designated for suspected COVID-19 sampling collection. Healthcare facilities were divided into three types of facilities: COVID-19 care centers for mild cases, dedicated health centers for moderate cases, and COVID-19 hospitals for severe cases. In each hospital, separate areas were made to designate a COVID-19 screening area and a COVID-19 ward. Medical supplies such as gloves, surgical and N95 masks, sanitizers, PPE as per requirement, gumboots and disinfectants were provided to the staff deployed at these facilities by the government. The healthcare workers were regularly monitored for any symptoms or any unprotected contact with a COVID-19 positive patient and immediate quarantine was advised. Accommodation and food for healthcare workers were arranged near the hospitals to prevent exposure to their families.

Methods

Much of the information for this article was gathered from the official website employed by the city of Chandigarh to inform residents of updates and maintain transparency while battling the COVID-19 pandemic. Many of the announcements by the Chandigarh administration are available on the website in PDF format for people to access. The uploading of official documents and press releases by the administration aids in keeping citizens informed by allowing information to be accessible at any time.

Conclusion:

Despite the alarming rate of coronavirus cases around the world, the city of Chandigarh has shown us how to effectively combat the spread of a deadly pandemic. By acting fast and implementing a strict lockdown, the government was able to control the number of positive coronavirus cases, and in turn, prevent many deaths. Strict curfew and social distancing, proper sanitization, and preventative spread techniques were implemented to curtail the spread of COVID-19. Food and shelter were provided to those who
needed and essential groceries were delivered in an effort to curb population movement and the spread of coronavirus. However, without the participation and help of the citizens, an effective lockdown could not have been maintained. The city of Chandigarh implemented many avenues such as websites, apps, and telephone numbers in an effort to keep its citizens calm and informed. This resulted in a population who willingly took the necessary steps to prevent a deadly pandemic in the city. Chandigarh and its citizens are an example of how to effectively curb the growing pandemic of COVID-19.

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References:


Letter to Editor and Editorial Reports
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Dear editor,

Academic participation in medical students has been correlated with future commitment and long-term achievement in research. Munzer et al suggested a growing trend of scholar engagement by physicians in training, and student-led journals (SLJ) were among the contributors which facilitate early exposure to the submission and peer-review process. However, the caliber of such a platform must adapt in the next decade to better nurture the development of research work. As a leading senior reviewer for the Journal, I herein address several personal perspectives regarding the future role of this SLJ.

First, an edition of a featured section on a regular basis is a feasible approach to collect quality research. In conjunction with the current academic competition in the annual assembly of the association and the bimonthly-published eNewsletter, a special issue focusing on topics with an ongoing debate or of contemporary significance, increments the value and visibility of the Journal. Artificial intelligence, telehealth, stem cell, and precision medicine exemplify those subjects with peculiar recent attention. Medical students could be trained to operate synergistically with senior editors and experience the procedure of establishing a topic, calling for papers, and article selection.

 Besides, modifying the review process to a more interactive fashion will encourage the participation of medical students as well as maximize educational benefit. As several SLJs adopt, I propose the incorporation of a two-stage workflow, in which students will evaluate the submission first and the comments on the manuscript before the article is advanced to be assessed by external senior reviewers. The advantage is to invigorate critical analysis of medical students at
first-hand, whereas discordant, if not contrary, opinions responded to the authors in the respective two stages has been a conundrum according to previous experience. Feedback by subsequent senior reviewer or even an author toward the primary student is therefore necessitated to improve future quality of assessments.

Finally, a multilateral and mutually interactive forum that allows conversation among students, reviewers, and Journal editors will enhance the capabilities of research articulation. Students will also be oriented with the characteristics of SLJ and appropriate submissions would therein be promoted. Meanwhile, junior reviewers could participate in the collaborative reviewing platform to sharpen the skills of critical appraisal. A rudimentary web-based methodology was established by Podder et al to evaluate randomized controlled trials before publication\(^3\). It is worthwhile to consider the implementation of such a modality in a SLJ as well.

As the next decade approaches, the role of SLJ in medical education will transform from a passive recipient of submission toward an active taskforce that expedite academic engrossment. Engagements from both ends of submitters and reviewers are prerequisite to facilitate such revolution.

Yours sincerely.

Dr. Ting Wei Kao, MD

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**References:**


AMSA International Report of Seventy-fifth Session of the WHO Regional Committee Meeting for South-East Asia

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Regional Committee Meeting Agenda and its Documents

The Regional Committee raised crucial topics in relation to healthcare. Topics which were debated during the Regional Committee Meeting include primary health care (PHC), noncommunicable diseases (NCDs), sustainable financing, health emergency preparedness, tuberculosis, cervical cancer, mental health, progress reports on WHO technical programmes and much more. Click here to access the meeting agenda and its documents.

AMSA delegation to 75th WHO RC SEARO

Asian Medical Students' Association (AMSA) International attended the 75th WHO Regional Committee for South-East Asia with a delegation of 8 youths across different chapters (included as authors of the report).

Preparation prior to the 75th WHO RC SEARO

AMSA International delegates hosted preparatory meetings prior to the 75th WHO RC SEARO. Key duties (such as social media advocacy, report writings to be executed during and after the RCM) were divided up among all delegates. These preparatory meetings were useful in explaining the mechanism of WHO regional committee meetings and the roles
Social Media Presence

Virtual meetings require consistent, contextual, and audience focused social media presence to have thoughtful engagement with relevant stakeholders in the South-East Asia Region (SEAR). Delegation transparency and engagement with AMSA Members are extremely important, this is done through providing daily updates on our core social media platforms as shown below (such as the AMSA International Instagram stories).

Parallel Event

As recommended by previous WHO Regional Committee Meeting evaluations, i.e. the 72nd Session of the WHO RC for WPRO and the 74th Session of the WHO RC for SEARO, a parallel event was organised by the delegates to further bring the WHO closer to medical students.

The delegates organised an online social media campaign entitled RISE UP! (Raising Awareness for Self-Harming and Suicide Prevention) which was held on Instagram from 13–16 October 2022. To kick start the campaign, the volunteers had the opportunity to be acquainted with fellow global volunteers as they introduced and got to know each other via the WhatsApp group. On the first day of the campaign, the volunteers shared infographics via their Instagram Story to quiz and educate their viewers about the myths or facts regarding self-harming and suicide. Following the first day, the volunteers had the chance to explore and express their thoughts as they are “put” in the shoes of responders and health workers working with people with suicide ideation through “What Would You Do?” case studies. Afterwards, an information ion where and how to offer help when meeting people with self-harming and suicidal tendencies is shared.

This campaign received 183 respondents from more than 29 different nations participating in this campaign effectively; 64.5% of respondents were from Indonesia, followed by more than 10% from Indi., while the remainder were from Bangladesh, China, Egypt, England, Hong Kong, Japan, Kazakhstan, Kyrgyzstan, Macau, Malaysia, Mongolia, Myanmar, and Nepal, among others. Up to one third of the participants were non-AMSA medical students, while more than half were AMSA members.
Future Recommendations

The Hybrid setting of the 75th WHO RC SEARO limits the delegation in engaging with other relevant stakeholders, WHO Member States. Due to these constraints, no new connections were formed throughout the RCM.

Since the format of the RCM is determined by the WHO Regional Office, our involvement in this RCM largely depends on the circumstances. Several recommendations were concluded during the post-mortem session of the RCM.

(i) Delegate Responsibilities
- The future Delegation Chair has to delegate responsibilities to all delegates and follow up on its execution periodically.
- AMSA Members who assume as a delegate of any WHO RCMs must be assigned with tasks within the delegation, regardless of his/her position within AMSA, and not limited to supervisory roles.
- Follow up meeting during the execution of WHO RCM would be highly encouraged to brief the delegates regarding their work as well to connect between both offline and online delegates regarding the conference situation.

(ii) Proper Delegation Seat Allocation
- Any delegates to WHO RCMs must only allow once per individual AMSA Member to attend one WHO RCM throughout one tenure, this is to increase transparency in seat allocation to WHO meetings.
- A maximum of two (2) AMSA International members are allowed to be involved in any WHO RCMs at one time, where one must assume as the Delegation Chair, and the other in providing direct assistance to the Delegation Chair.

(iii) Parallel Events
- To further bring the WHO closer to medical students, delegates to WHO RCMs are tasked to host a parallel or side event relevant to medical students, youths, adolescents, or children during any WHO RCMs.
- The theme set forth for any parallel events hosted during any WHO RCMs must be in accordance with (a) the
current Regional Committee thematic agenda or document(s), (b) the latest WHO General Programme of Work, (c) the main aim of the delegation - which is to bring the WHO closer to medical students and youths, (d) the WHO framework of engagement with Non-State Actors (FENSA), and (e) the WHO Constitution.

- To further increase the credibility and impact of AMSA International and the delegation parallel event, partnership with both IGOs and INGOs would be highly encouraged with fields detailed below
  - Broaden the publicity and promotions through collaborations with IGOs and/or INGOs
  - Collaborate with professionals affiliated with WHO and other IGOs/INGOs

(iv) Data Spotlight

- We recommend the future delegation to WHO RCMs to be on the lookout for keywords involving the younger generation mentioned during each day of the RCM (such as children, schoolchildren, students, adolescents, and youths). This can be termed as “Spot Youth”. A daily pie-chart and a graphical representation over time for the entire RCM detailing the amount of times the term(s) being mentioned may be generated for this matter and distributed through social media handles.

- Involvement of women in our society is crucial to break the perceived glass ceiling in the younger generation. “Spot Woman” aims for a balanced gender distribution in our workforce through increasing the representation of women. This is done through screening oratory and written (whenever possible) statements delivered by any representative of Member States, the WHO Regional Committee, Inter-Governmental Organisations, Non-State Actors, Private Entities, Non-Governmental Organisations, Philanthropic Entities, and Educational Institutions. Similarly, a daily pie-chart and a graphical representation over time for the entire RCM detailing the differences in representation may be generated for this.
purpose and distributed through social media platforms.

Reflections from the 75th WHO RC SEARO

The 75th WHO RC SEARO is an exceedingly insightful 5-day event (5 to 9 September 2022) for AMSA International delegates, especially because it is the first opportunity for AMSA International to send an onsite delegate to witness the event firsthand. Onsite or online, the agendas of health issues being discussed as national-level advances were reported reminded us of a duality: we have made a lot of progress, but a lot of work still has to be done. Mental health accessibility through primary health care (PHC) strengthening is particularly of interest as it was held in the Ministerial Roundtable. Whether it is mental health, cervical cancer, PHC, noncommunicable diseases (NCDs), sustainable financing, health emergency preparedness, or tuberculosis (TB), states can learn from each other through effective and evidence-based best practices in neighboring countries.

More compelling than the statements from health ministers and/or their proxies are the comments from non-state actors (NSAs), such as the Global Health Taskforce and Médecins Sans Frontières (MSF). While state actors’ comments tend to be similar, reiterating numbers, prevalences, and renowned recommendations, the impartiality of non-state actors and their experience in working on these health issues directly allowed meaningful insights to be heard on the floor. For instance, as countries share hopeful numbers of tuberculosis cases, MSF highlighted the need for shorter yet less toxic treatments for TB and the alarmingly worse forecasts in the following years. It is a shame that some NSAs’ speaking durations were cut due to time constraints. In various plenaries, NSAs reminded us that vulnerable populations are a priority; that despite grassroots efforts, health policy improvements are still needed for better outcomes; that holistic quality services are what we aim for.

Smiling was irresistible as the Flagship Song was played during short breaks between plenaries. In this song, children sang and danced along to lyrics about the eight flagship priority programs of SEARO. They represent a stronger presence of youths in advocacy of health issues, including but not limited to the international
stage. Perhaps they are invited to remind health leaders that younger generations are at stake. As this is reflected upon us, as medical students, we become more aware that health issues are of significance, as they will be part of our future. This delegation believes that our involvement, as youths, cannot be more crucial or timely.

**Report Conclusion:**

Throughout this RCM, engagement was limited due to the hybrid setting set forth by the organiser of the RCM this year, we hope that future delegates are able to join the delegation in-person at WHO RCMs for a better experience.

This report may be used for future delegates to prepare themselves for upcoming WHO Regional Committee Meetings (both virtually and physically), particularly to improve data utilisation, advocacy (via social media or in-person interaction), organising parallel events, engagement with relevant stakeholders, and most importantly aligning AMSA International’s work with the work of the WHO. We hope that this report provided you some insight into the works of AMSA in WHO Regional Committee Meetings. Thank you very much!

Viva AMSA!

**Disclosures:**

Ms. Charlotte Lintang Kinasih, Mr. Pratyush Kumar and Mr. Gunteshwar Singh was the leads of the project. Ms. Charlotte Lintang Kinasih the Liaison Officer to Governmental Organisations and Non-Governmental Organisations 2022/2023, Mr. Pratyush Kumar was the Chief Editor of JAMSA 2022/2023 and Mr. Guntesswar Singh was the Delegation Chair and General Secretary of AMSA Intl 2022/2023.

All other authors were AMSA Intl Delegates and had equal contribution and have been positioned alphabetically.
Figures:

**Figure 1:** Live Reports on Delegates’ Instagram were reposted on AMSA International’s Instagram account and put on a dedicated highlight for the 75th WHO RC SEARO.

**Figure 2:** Event Recaps were posted on Instagram Story within three consecutive days two weeks after the WHO RC meeting ended (25 September – 27 September 2022)
The Role of Student-led Journals in Capacity Building

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Medical students have been making substantial contributions to the practice of medicine since the 1600s by performing high-quality research and publishing papers. [1] The benefits and significance of early exposure to academic study have lately been examined. Undergraduate medical research is linked to short- and long-term academic successes, such as enhanced research knowledge and skills, greater interest in future research, peer-reviewed journal articles, funding, and recruitment to academic positions.[2] Medical student journals (MSJs) are a group of student-run journals that publish papers written by students. [3] Their main goal is to encourage medical students to publish scientific findings. Multiple factors contribute to long-term academic success, including early positive exposures to the publishing and peer-review process, development of key academic skills while still a medical student. Students can acquire a scholarly voice as not only authors but also as reviewers and editors in medical student research journals. As the corresponding author of their own work, student authors learn to communicate professionally to address reviewer concerns. As peer-reviewers in training, students learn to analyze manuscripts for quality and document their concerns in a cohesive manner under the supervision of a faculty advisor. [4] As part of the editorial board, with senior editors and reviewers offering help and support, students learn the process of manuscript handling and coordination. Most of the MSJs have faculty reviewers who actually give inputs on acceptance or rejection
which serves as a guide for student editors. It is also significant to note that here is a paucity of such journals in Low- and Middle-Income Countries (LMICs) while in the High-Income Countries (HICs) even universities have such journals. This training right from the medical student life capacitates them to bag more opportunities as journal editors in future which can be seen through the global Representation of specialty journals.

MSJs are of paramount importance in developing scientific and academic skills amongst medical students and cultivating future clinical academics. There are a number of MSJs available currently which provide avenues for students to publish their scientific work. (Table 1)

In conclusion, preconceptions about who can engage in knowledge sharing are challenged by putting students at the heart of the publishing process. All stakeholders, including students, should be able to expand their ability to consume, share, and produce information, while journals should include measures to encourage diversity and equal participation among academics and citizen researchers.
<table>
<thead>
<tr>
<th>Name of the Journal</th>
<th>Publisher</th>
<th>Year of Establishment</th>
<th>Global Representation in Editorial Board</th>
<th>Indexing</th>
<th>Peer-Review</th>
<th>Involvement of Residents/Faculty</th>
<th>Access Policy</th>
<th>Publication Fee/APCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal of Asian Medical Students' Association (JAMSA)</td>
<td>Asian Medical Students' Association (AMSA) International</td>
<td>2012</td>
<td>Australia, Bangladesh, China, England, Hong Kong, India, Indonesia, Japan, Nepal, Macau, Malaysia, Mongolia, Pakistan, Philippines, Scotland, Singapore, Taiwan, Thailand, Vietnam</td>
<td>ICMJE, CrossRef, Ulrichsweb, Google Scholar, ROAD, Gale Cengage, BASE, and Genamics Journal Seek, IndexCopernicus, Publons</td>
<td>Double Blind</td>
<td>3 Advisor(s) and Senior Reviewers</td>
<td>Online Open Access</td>
<td>None</td>
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<table>
<thead>
<tr>
<th>Internatio\nal Journal of Medical Students (IJMS)</th>
<th>University Library System, University of Pittsburgh</th>
<th>-</th>
<th>Australia, Austria, Belize, Bosnia and Herzegovina, Canada, Columbia, China, Czech Republic, Egypt, Ethiopia, Ghana, India, Iran, Ireland, Israel, Italy, Mexico, Nigeria, Palestine, Pakistan, Romania, USA, UK, Vietnam</th>
<th>BASE, DOAJ, EZB, Google Scholar, HINARI, Journal Seek, ICMJE, IMBIOMED, OCLC, WorldCat, Bibliotheca Alexandrina, Informatio for Africa, JournalGuide, J Gate, Publons</th>
<th>Double Blind</th>
<th>Recent Graduates as Associate Editors and Executive Committee, Experienced Researchers as Senior Editors as well as Reviewers</th>
<th>Online Open Access</th>
<th>None</th>
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<tbody>
<tr>
<td>Student British Medical Journal (sBMJ)</td>
<td>The BMJ</td>
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**Table 1 (a) - International MSJs**
<table>
<thead>
<tr>
<th>Name of the Journal</th>
<th>Publisher</th>
<th>Year of Establishment</th>
<th>Indexing</th>
<th>Involvement Residents/Faculty</th>
<th>Peer-Review</th>
<th>Access Policy</th>
<th>Publication Fee/APC</th>
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<tbody>
<tr>
<td>New Zealand Medical Student Journal (NZMSJ)</td>
<td>The New Zealand Medical Student Journal Society</td>
<td>2002-2003</td>
<td>Google Scholar</td>
<td>Reviewers</td>
<td>Double Blind</td>
<td>Online, Print Open Access</td>
<td>-</td>
</tr>
<tr>
<td>American Medical Student Research Journal (AMSRJ)</td>
<td>Independent</td>
<td>2013</td>
<td>AMSRJ uses the LOCKSS system to create a distributed archiving system among participating libraries and create permanent archives.</td>
<td>Final decision on Desk Rejection Reviewers</td>
<td>Is conducted</td>
<td>Online Open Access</td>
<td>-</td>
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<tr>
<td>Australian Medical Student's Journal (AMSJ)</td>
<td>Independent</td>
<td>2010</td>
<td>-</td>
<td>Reviewers</td>
<td>Double Blind</td>
<td>Online Open Access</td>
<td>-</td>
</tr>
<tr>
<td>Cooper Rowan Medical Journal (CRMJ)</td>
<td>Cooper Medical School of Rowan University</td>
<td>2018</td>
<td>CrossRef, SPARC, PORTICO, DOAJ, Google Scholar</td>
<td>Editorial Board (partially student-run journal), Reviewers.</td>
<td>Double Blind</td>
<td>Online, Print Open Access</td>
<td>None</td>
</tr>
<tr>
<td>Harvard Medical Student Review (HMSR)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Advisors and Reviewers</td>
<td>-</td>
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**Table 1 (b) - National MSJ**
References


Potential of Medical Students for Ukrainian Refugees in COVID-19 Pandemic

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In response to the situation in Russia and Ukraine, the United Kingdom (UK) and many other European countries are accepting Ukrainian refugees.¹ As of May, 2022, more than 4 million people have managed to leave Ukraine,¹ but their grief and suffering is immeasurable, and even after evacuation, people are reported to be at high risk of suffering from conflict-related stress disorders, depression, and anxiety disorders.² Refugees are also prone to social isolation, a risk factor for mental health problems due to differences in language, environment, and culture,³ and require proper support.

However, in the UK, restrictions against COVID-19 were lifted on February 24, and the number of infected and hospitalized patients has shown an increasing trend, beginning to put a strain on the medical environment, and healthcare professionals are being forced to deal with COVID-19 patients.⁴ Consequently, the refugees may not be able to get the timely care and support both mentally and physically. Moreover, this problem could happen anywhere in the world, as long as there is no telling when the re-expansion of COVID-19 may occur.

Medical students may be able to assist refugees and make up for the lack of medical resources. In the UK, medical students actually assisted medical professionals and patients during the COVID-19 outbreak, and their effectiveness has been reported.⁵ Similar to this experience, we believe that medical students could be incorporated as part of the medical team for refugees by, for example, providing
video communication to refugees and their families, measuring routine clinical outcomes, listing and delivering daily medications, and training in self-compassion through communication among the refugees. However, we also need to be careful because medical students may misjudge what they can do in the chaos of the field and make the wrong interventions. Since medical students vary in ability from lower to higher grades, it is necessary to clarify in advance the support that each student can take according to their abilities and to share the details that must be discussed with doctors and nurses to prevent mistakes. In addition, refugees may feel insecure about whether they can receive adequate support from medical students, and it is important to explain the situation to them in advance and establish mutual consent. It is essential for all countries accepting refugees to put in place a system for cooperation and collaboration between medical students and medical institutions to minimize the impact of secondary damage to the refugees in advance.

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