

SCIENTIFIC PAPER COMPETITION – NEPAL

BURDEN OF COPD IN BUTWAL, NEPAL

AN EPIDEMIOLOGICAL STUDY IN LUMBINI ZONAL HOSPITAL, BUTWAL, NEPAL -AMSA-NEPAL

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. COPD includes *emphysema*, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; *chronic bronchitis*, a clinically defined condition with chronic cough and phlegm; and *small airways disease*, a condition in which small bronchioles are narrowed. This study was aimed to find the inconsistencies in prevalence and management and to understand how medical students could play a role in addressing the issue.

Methods: This retrospective epidemiological study was conducted by medical students and Intern doctors from Nepal using hospital data of LZH and questionnaire based in-depth interviews with participants including stakeholders, policy makers, medical professionals, COPD patients and family members of patients in Nepal. The data has been collected from 2010 to 2013 and Data analysis has been conducted in the month of August.

Results: COPD is one of the leading causes of hospital admission in Lumbini Zonal Hospital (LZH). The number of admissions due to COPD is relatively stable, around 500 cases per year. The majority of patients are elderly females (60-69 age group), 19% of patients admitted to the medical ward of LZH are admitted for COPD. Though that is a significant proportion, the actual prevalence of COPD is probably far higher as COPD is an "iceberg disease". We noticed that the lack of accurate data, shortage of good quality medicines, illiteracy, social stigma, social customs, political instability, lack of specialized health care facilities and lack of skilled human resources were seen to have a significant role in hindrance to management.

Conclusion: We concluded that accurate data collection is pivotal in understanding the disease pattern. There is need to conduct awareness programmes using School Programmes, Street Plays, audiovisual aids, in rural areas to improve disease awareness and tackle these problems in the prevalent areas. Specialized health care facilities are needed for prompt management of COPD and also for training health workers specializing in COPD management.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is defined by WHO as a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. COPD includes *emphysema*, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; *chronic bronchitis*, a clinically defined condition with chronic cough and phlegm; and *small airways disease*, a condition in which small bronchioles are narrowed. The main risk factors for COPD are active and/or passive cigarette smoking, airway hyper responsiveness, respiratory infections, occupational exposures & ambient air pollution, and genetic factors like α_1 antitrypsin deficiency. The patients with COPD present primarily with cough, sputum production and exertional dyspnoea.

Pathophysiology

COPD is characterized by chronic inflammation of the airways, lung tissue and pulmonary blood vessels as a result of exposure to inhaled irritants such as tobacco smoke.

The inhaled irritants cause inflammatory cells such as neutrophils, CD8⁺ T-lymphocytes, B cells and macrophages to accumulate. When activated, these cells initiate an inflammatory cascade that triggers the release of inflammatory mediators such as tumour necrosis factor alpha (TNF- α), interferon gamma (IFN- γ), matrix-metalloproteinases (MMP-6, MMP-9), C-reactive protein (CRP), interleukins (IL-1, IL-6, IL-8) and fibrinogen. These inflammatory mediators sustain the inflammatory process and lead to tissue damage as well as a range of systemic effects. The chronic inflammation is present from the outset of the disease and leads to various structural changes in the lung which further perpetuate airflow limitation.

Structural changes

Airway remodeling in COPD is a direct result of the inflammatory response associated with COPD and leads to narrowing of the airways. Three main factors contribute to this: peribronchial fibrosis, build-up of scar tissue from damage to the airways and over-multiplication of the epithelial cells lining the airways.

Parenchymal destruction is associated with loss of lung tissue elasticity, which occurs as a result of destruction of the structures supporting and feeding the alveoli (emphysema). This means that the small airways collapse during exhalation, impeding airflow, trapping air in the lungs and reducing lung capacity.

Mucociliary dysfunction

Smoking and inflammation enlarge the mucous glands that line airway walls in the lungs, causing goblet cell metaplasia and leading to healthy cells being replaced by more mucus-secreting cells.⁵ Additionally, inflammation associated with COPD causes damage to the mucociliary transport which is responsible for clearing mucus from the airways. Both these factors contribute to excess mucus in the airways which eventually accumulates, blocking them and worsening airflow.

Treatment

A diagnosis of COPD is not the end of the world. For all stages of disease, effective therapy is available which can control symptoms, reduce your risk of complications and exacerbations, and improve your ability to lead an active life.

Smoking cessation

The most essential step in any treatment plan for COPD is to stop all smoking. It's the only way to keep COPD from getting worse — which can eventually reduce your ability to breathe. But quitting smoking isn't easy. And this task may seem particularly daunting if you've tried to quit and have been unsuccessful. Talk to your doctor about nicotine replacement products and medications that might help, as well as how to handle relapses. It's also a good idea to avoid secondhand smoke exposure whenever possible.

Medications

Doctors use several kinds of medications to treat the symptoms and complications of COPD. You may take some medications on a regular basis and others as needed:

Bronchodilators. These medications — which usually come in an inhaler — relax the muscles around your airways. This can help relieve coughing and shortness of breath and make breathing easier. Depending on the severity of your disease, you may need a short-acting bronchodilator before activities, a long-acting bronchodilator that you use every day, or both.

Inhaled steroids. Inhaled corticosteroid medications can reduce airway inflammation and help prevent exacerbations. Side effects may include bruising, oral infections and hoarseness. These medications are useful for people with frequent exacerbations of COPD.

Combination inhalers. Some medications combine bronchodilators and inhaled steroids.

Oral steroids. For people who have a moderate or severe acute exacerbation, oral steroids prevent further worsening of COPD. However, these medications can have serious side effects, such as weight gain, diabetes, osteoporosis, cataracts and an increased risk of infection.

Phosphodiesterase-4 inhibitors. A new type of medication approved for people with severe COPD. This drug decreases airway inflammation and relaxes the airways. Common side effects include diarrhea and weight loss.

Theophylline. This very inexpensive medication helps improve breathing and prevents exacerbations. Side effects may include nausea, fast heartbeat and tremor.

Antibiotics. Respiratory infections, such as acute bronchitis, pneumonia and influenza, can aggravate COPD symptoms. Antibiotics help fight acute exacerbations. The antibiotic azithromycin prevents exacerbations, but it isn't clear whether this is due to its antibiotic effect or its anti-inflammatory properties.

Lung therapies

Doctors often use these additional therapies for people with moderate or severe COPD:

Oxygen therapy. If there isn't enough oxygen in your blood, you may need supplemental oxygen. There are several devices to deliver oxygen to your lungs, including lightweight, portable units that you can take with you to run errands and get around town. Some people with COPD use oxygen only during activities or while sleeping. Others use oxygen all the time. Oxygen therapy can improve quality of life and is the only COPD therapy proven to extend life. Talk to your doctor about your needs and options.

Pulmonary rehabilitation program. These programs typically combine education, exercise training, nutrition advice and counseling. You'll work with a variety of specialists, who can tailor your rehabilitation program to meet your needs. Pulmonary rehabilitation may shorten hospitalizations, increase your ability to participate in everyday activities and improve your quality of life. Talk to your doctor about referral to a program.

Managing exacerbations

Even with ongoing treatment, you may experience times when symptoms become worse for days or weeks. This is called an acute exacerbation, and it may lead to lung failure if you don't receive prompt treatment. Exacerbations may be caused by a respiratory infection, air pollution, or other triggers of inflammation. Whatever the cause, it's important to seek prompt medical help if you notice a sustained increase in coughing, a change in your mucus or if you have a harder time breathing.

When exacerbations occur, you may need additional medications (such as antibiotics or steroids), supplemental oxygen or treatment in the hospital. Once symptoms improve, you'll want to take measures to prevent future exacerbations, such as taking inhaled steroids or long-acting bronchodilators, getting your annual flu vaccine and avoiding air pollution whenever possible.

Surgery

Surgery is an option for some people with some forms of severe emphysema who aren't helped sufficiently by medications alone:

Lung volume reduction surgery. In this surgery, your surgeon removes small wedges of damaged lung tissue. This creates extra space in your chest cavity so that the remaining lung tissue and the diaphragm work more efficiently. In some people, this surgery can improve quality of life and prolong survival.

Lung transplant. Lung transplantation may be an option for certain people who meet specific criteria. Transplantation can improve your ability to breathe and to be active, but it's a major operation that has significant risks, such as organ rejection and the need for lifelong immune-suppressing medications.

Methods

Data collection was performed in Lumbini Zonal Hospital, Butwal, Nepal. In-depth interviews were performed with key stakeholders, policy makers, medical professionals, COPD patients and their family members to explore the current scenario of the disease, the policies being implemented by government and other organization and the role of medical students in addressing the disease.

All interviews were performed in Nepali and English by Medical Students and intern Doctors from Nepal. Tapes of the interviews were also taken by the interviewer. In the first stage of the interview, interviewees determined themes rather than being guided by the interviewer. In the second stage, interviewees were prompted on any of the themes that had not already been covered. Themes were identified based on the lack of accurate data, shortage of good quality medicines, illiteracy, social stigma, political instability, lack of specialized health care facilities and lack of skilled human resources. Where necessary, interviewees were interviewed on more than one occasion, to build trust and rapport, and to probe specific issues. Interviews took on average about 45 minutes. No-one identified as a potential interviewee refused to be interviewed, although several interviewees asked that the interview take place in a discrete location to avoid being seen by anyone known to the interviewee.

Informed consent was obtained from all interviewees.

Study duration: 4 weeks

Study design: Retrospective, Descriptive

Study population: COPD cases treated at LZH from 15th April 2010 to 14th April 2013.

Study method: Quantitative

Literature review

Data collection: secondary data review from hospital discharge register

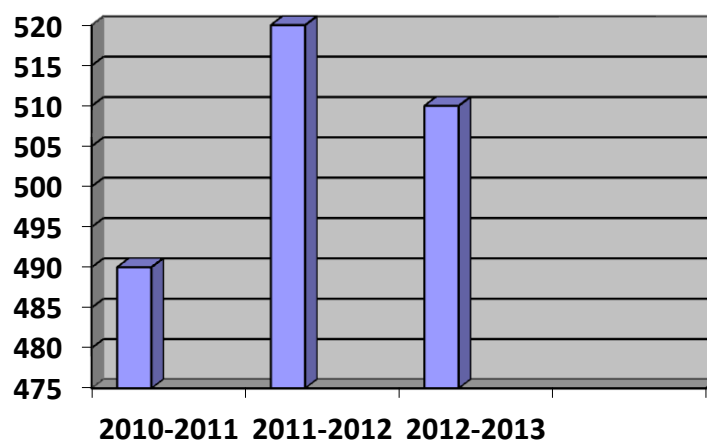
Data analysis and interpretation

Results

1) Time Distribution

A. Yearly Trend

The yearly trend of COPD cases in LZH is fairly static over the past 3 fiscal year

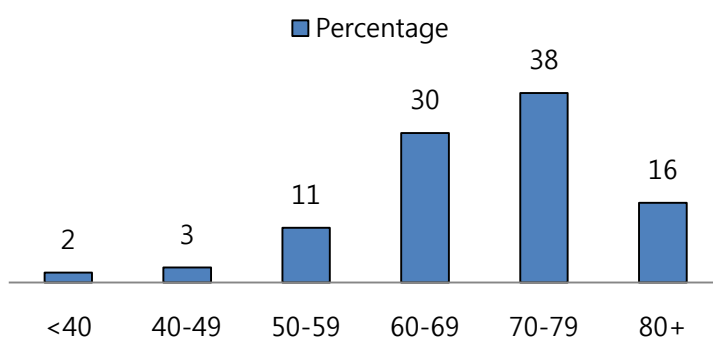


2) Person Distribution

A. Age Wise Distribution of COPD Cases

The figure shows that the incidence of COPD in <40 years age group is uncommon as they constitute only 2% of the total patients with COPD. On the other hand, 84% of the total patients are above 60 years of age which shows that COPD is more common in elderly age groups.

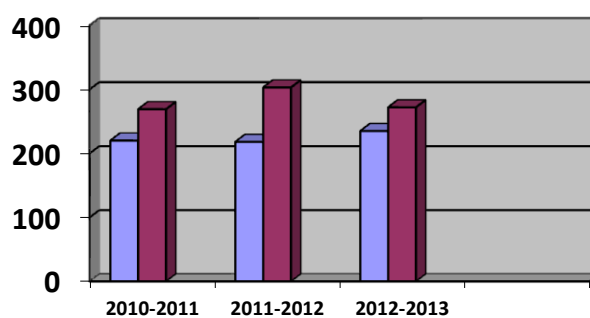
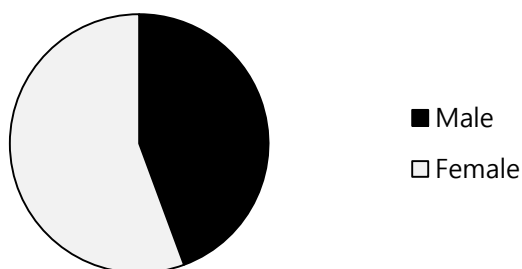
Percentage of patients per age group



B. Sex Wise Distribution of COPD Patients

The pie diagram below shows that the majority of the COPD patients (56%) are female. It may be due to the fact that there are many female smokers in our country and most of the rural females work in the kitchen with "smoking *chulhos* (wood and cowdung burning stoves) without proper ventilation.

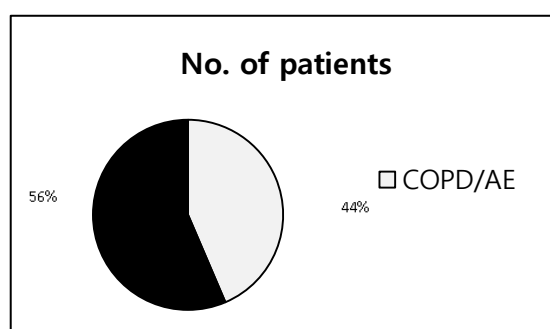
Sex Wise Distribution



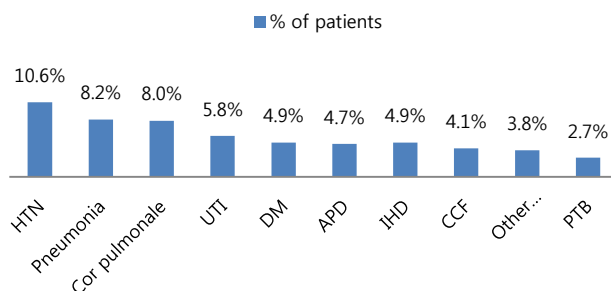
5) Patient Distribution According to Associated Conditions

As can be seen from the pie diagram below, the majority of the COPD patients (56%) came with some form of co-morbid conditions.

The pie diagram below shows that HTN, cor pulmonale, and pneumonia consist of the majority among all the conditions associated with COPD.



Associated Conditions



1. Interaction with policy makers and key stakeholders:

Nepal's general health policies give a low priority to Non Communicable Diseases (NCD). However, a national NCD policy and strategy has been drafted and awaits its government review and adoption. The Framework Convention on Tobacco Control (FCTC) was adopted. On this theme, a Smoking Prohibition and Control Act had been drafted in 2001, but has not yet been approved.

Tobacco control efforts point in right direction but have not yet yielded major results. The Ministry of Finance has set a tax on tobacco products. There is also a partial ban on tobacco advertising (applicable to electronic media only). Smoking has been banned in major public places. Anti-tobacco programs are implemented by a tobacco control cell within the Ministry of Health and Population (MoHP) and the National Health Education Information and Communication Center (NHEICC). The Ministry of Education also includes in the school curriculum elements on the ill-effects of tobacco consumption. Finally, the Nepal Health Research Council recently conducted a training program in alcohol and tobacco control.

Several other NCD-related programs are ongoing or under preparation. An NCD awareness program is under preparation for implementation in three districts. Implementation of the World Health Organization (WHO)'s Global Strategy on Diet, Physical Activity and health has also been started.

2. Interaction with medical professionals:

The chronic obstructive pulmonary disease (COPD) is one of the most common diagnoses at District Hospitals of Butwal—we've found little in the way of helpful guidelines designed for resource-limited settings. With the example of COPD, there are guidelines from the Global Initiative for Chronic Obstructive Lung Disease ([the GOLD guidelines](#)). However, they state that COPD should be diagnosed by spirometry, and only provide a tiny footnote for settings that do not have spirometry, providing the vague advice that clinicians should then "use all available tools."

We do not have a spirometer at our hospitals, nor is there one available anywhere in the district or any surrounding district. I've not seen one in any district hospital in Nepal. I would like to see us obtain a spirometer, but the present reality is that the vast majority of COPD patients in Nepal are diagnosed and cared for without spirometry, and we can provide them good care. Good clinical protocols are a necessary component.

Three decades ago Dr Mirgendra Raj Pandey with the help of young doctors and health workers showed that indoor pollution in the homes due to open hearths was a major cause of ill health in Nepal. Changes were made in constructing better chimneys and smokeless "chulos". People were able to breathe better as a result. However the problem of open fireplaces in homes persists and continues to wreak havoc. Nearly 2 million people die prematurely in the developing world due to indoor pollution.

Sadly, even today one of the most important problems we see in the hospitals in Nepal especially in the winter time is chronic obstructive lung disease (COPD). Visit any medical ward in Nepal and almost every other bed has a COPD patient. Once the patient has the full blown disease, it is game over because doctors cannot do much at that stage. Prevention is better than cure applies very clearly to COPD.

The most intriguing finding from Dr Pandey's early work in the villages in Jumla, rural Kathmandu, and the Terai was that women had significant amount of COPD which lead to early heart failure and death. This catastrophe happened notwithstanding the fact that women smoked far fewer cigarettes/bidis/tamakhu than men. In these women there was an obvious correlation of the excessively high prevalence of COPD and hours spent cooking with firewood and cow patties in soot filled kitchens. Relatively young women in their forties suffer from this disease if they cook in the smoky atmosphere year in and year out. Amazingly these women some of whom smoke only 3 or 4 cigarettes a day have lungs that resemble four pack a day smoker of a veteran's hospital in the US. This is the additive effect of using firewood and "guitha" for cooking.

This exposure to the deadly smoke in the home continues in Nepal. Cigarette smoking and atmospheric pollution have not helped. But women in Nepal as in many parts of the developing world continue to cook in open hearths. Besides COPD, a whole host of other problems are caused by smoky homes and open fireplaces: eye problems, heart problems, lung cancer, pneumonia, and burn injuries especially in children while playing.

Many villagers are averse to change because they feel the smoke filled homes provides warmth in the winter and termite prevention from eating away the roof of the house. So, dealing with these possible misperception and fears will be as important as installing a new stove or chimney. Otherwise projects of this kind are bound to fail regardless of their good intentions.

3. Interaction with COPD patients and their family members

This 79 year old female has suffered with what she describes as a bad chest for over ten years frequently experiencing dyspnoea and chest infections. She recalls suffering many exacerbations and put this down to experiencing asthma attacks. The patient admitted she had smoked 10 cigarettes a day for 64 years— a 32 pack year history. She was experiencing recurrent exacerbations of shortness of breath, inability to walk without fatigue and sputum production.

My initial thoughts were that she did not seem to be able to breathe well at all. This was quite alarming to me however she told me that this was usual for her. I felt somewhat reassured but I noticed that it was difficult to make conversation with her properly because of the degree of dyspnoea. She was diagnosed with COPD in 2000 A.D. and put on an inhaled corticosteroid and bronchodilator along with oral steroids. Her exacerbations were attributed to chest infections and she was given antibiotics to combat them. However, as the exacerbations kept coming back, the cause could be something more than respiratory infection. A cardiac cause was suspected, and more precisely— congestive cardiac failure. She showed symptoms of right sided or biventricular failure as she has peripheral oedema and symptoms of left sided heart failure such as, shortness of breath together with a reduction in mobility and fatigue. She was diagnosed with cardiac failure. She was prescribed a diuretic— Frusemide, it is possible that pulmonary oedema could have been triggering the attacks. She has received stents for ischaemic heart disease. The patient describes symptoms of paroxysmal nocturnal dyspnoea — unable to sleep lying down and needing the aid of pillows to prop her up. She reports sleeping with three pillows but is still unable to sleep well.

Conclusion

COPD is one of the leading causes of hospital admission in Lumbini Zonal Hospital (LZH). The number of admissions due to COPD is relatively stable, around 500 cases per year. The majority of patients are elderly females (60-69 age group), which is most likely due to the use of traditional wood and even cow patties burning stoves for cooking purposes for most of their lives. Most patients stay in the hospital for 2-4 days because most of them come due to acute exacerbation of COPD. 19% of patients admitted to the medical ward of LZH are admitted for COPD. Though that is a significant proportion, the actual prevalence of COPD is probably far higher as COPD is an "iceberg disease". So, preventive measures for COPD like smokeless cooking stoves, smoking control, and health awareness programs should be implemented in order to reduce the incidence and prevalence of COPD in the district.

Role of medical students:

Community education, involvement and organization around COPD issues.
Activities to foster community ownership and awareness of control programmes.
Coordination with all health-care providers (both public and private) for health awareness programmes.
Coordination with national and international partners for research based study.

LIMITATIONS OF THE STUDY

Association of COPD with smoking could not be found.

COPD being an "iceberg" disease, only the small proportion of cases seek hospital care. Hence only the "tip of the iceberg" were included in the study.

The patients coming for follow up were recorded more than once in the hospital register and hence counted more than once in our study.

The findings could not be compared to the district data as a whole due to inadequate record keeping about COPD in the peripheral health centres.

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SCIENTIFIC PAPER COMPETITION – PHILIPPINES

Chronic Kidney Disease in the Philippines- An Updated Situationer and the Impact of the Disease on the Quality of Life of Patients

Arcellana, Anna Elvira (University of the Philippines-College of Medicine); Bantolo, Alena (University of Santo Tomas); Bang-asan Meg (University of the East); Khan, Samina (Far Eastern University); Yang, Sheryl (Far Eastern University); Yang, Stephanie (Far Eastern University)

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ABSTRACT

Chronic kidney disease is a debilitating end-stage complication of most chronic illnesses such as diabetes mellitus, hypertension, glomerulonephritis, systemic lupus erythematosus, HIV, etc. Philippine data shows that it is already the ninth leading cause of death in the country (NKT, 2012). Chronic kidney disease also has increasing prevalence in the country, now affecting one in ten Filipinos. In the Philippines, the most common cause of chronic kidney disease requiring renal replacement therapy is diabetic nephropathy. Among patients with chronic kidney disease, 44.6% have diabetic nephropathy while 23% have hypertensive nephropathy (Amarga, 2013). This pattern of prevalence is also reflected in the results of the survey conducted by the investigators. Usually, by the time chronic kidney disease is diagnosed, the patient is already at stage V of chronic kidney disease, necessitating dialysis. This entails more vigilance and health prevention for patients with chronic illnesses at risk of developing renal failure.

This is a comprehensive qualitative research that involves a plethora of methods. This study involves a systemic review on international studies tackling the effect of chronic kidney disease on the quality of life of patients. A survey and key informant interviews using standardized questionnaires were conducted among patients on dialysis from two dialysis centers in the main island of the country. The objectives were to 1). document the experiences of chronic kidney disease patients when it comes to dealing with their illness; 2). describe impact of chronic kidney disease on the quality of life of Filipino patients; 4). recognize the needs and issues of chronic kidney disease patients to generate an action plan that will promote better quality of life for these patients.

The systemic review, survey, and key informant interviews all consistently demonstrated a deterioration in the quality of life of chronic kidney disease patients. Lack of access to financial resources, inadequate insurance coverage, lack of availability of dialysis centers or renal transplant centers, are just some of the struggles that they face. Most patients also suffer from depression because of the distressing physical symptoms, loss of employment opportunities, and inability to engage in public affairs. A multi-sectoral response is needed to address the plight of these patients.

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INTRODUCTION

Definition

Chronic kidney disease (CKD) – or Chronic Renal Failure (CRF), as it was historically termed - refers to an irreversible condition wherein there is gradual deterioration of renal function over a period of time. This condition can progress to not only end stage renal disease but as well complications of decreased kidney function and cardiovascular disease. The study of kidney diseases is facilitated by dividing them into those that affect the four basic morphologic components: glomeruli, tubules, interstitium, and blood vessels. Disease severity is assessed from glomerular filtration rate (GFR) and albuminuria, and clinical diagnosis (cause and pathology). Whatever the origin, there is a tendency for all forms of chronic kidney disease ultimately to destroy all four components of kidney, culminating in chronic renal failure and what has been called end stage kidneys. Before evident functional impairment, thus clinical manifestations were observed much damage was already occurring for the kidney is characteristically has large functional reserve.

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR).

Burden of Kidney Disease in the Philippines

In the Philippines, there is an estimated 120 Filipinos per million population each year who develop kidney failure, concluding about 10, 000 Filipinos are in need to replace their kidney function each year. Only around 86 percent, however, could undergo dialysis, while about 14 percent could afford transplantation, because of the high cost of treatment.

A study done by NIKTI showed that half the patients who start dialysis are dead within a year, presumably because they could not afford sufficient dialysis. In fact in a survey conducted by five kidney specialists on patients with chronic kidney disease from Bacolod City, Negros Occidental, from May to July 2002, only 46% of 182 patients prescribed dialysis were able to start treatment. Among those who started dialysis, 96% had inadequate treatment because they could not afford it.

Kidney transplantation would be one of the solutions for this condition but not all can afford and were given the opportunity. In fact in the country, based on the Philippine Renal Disease Registry Annual Report in 2008 about 510 Filipinos received a kidney transplant. But when compared to the number of people who were diagnosed with kidney disease only about 14% was given the option of a transplant.

Management of Chronic Kidney Disease

Treatment of chronic kidney disease (CKD) aims to slow progression to end-stage renal disease (ESRD) and to prepare for ESRD. The major causes of ESRD, hypertension, and type 2 diabetes can themselves be avoided to some degree by primary preventive measures such as diet, weight control, and exercise. Furthermore, once hypertension or diabetes are manifest, their renal complications can be mitigated by secondary prevention efforts aimed at blood pressure and glycemic control. Thus, treatment of CKD often represents an example of tertiary prevention in populations who have failed the first lines of prevention but who are still relatively asymptomatic. These features make CKD therapy a formidable task in practice. (Turner et.al 2011)

According to the National Kidney and Transplant Institute, therapeutic options for chronic renal diseases include medications, renal diet, fluid and salt restriction, hemodialysis, peritoneal dialysis, and kidney transplant.

Objectives of the Study

This study aims to present an updated situationer on the state of chronic kidney disease in the Philippines. Through the consolidation of relevant information on the burden of the disease in the country, management options, experiences of patients in dealing with this debilitating disease and forms of action implemented by the health sector as well as government and society in addressing this disease, the investigators will be able to spread awareness about an important disease. The information will also serve to guide health practitioners and policy-makers in formulating policies and programs that cater to the needs of patients with chronic kidney disease.

The main focus of this study is on the effect of chronic kidney disease on the quality of life of Filipino patients. Currently, there is a scarce pool of literature that looks into the quality of life of this type of patients. Through a systemic review, survey and key informant interviews, the investigators aim to document the impact of chronic kidney disease on the quality of life of Filipino patients. This study on chronic kidney disease patients can serve as a prime mover in pursuing initiatives that address the needs of these patients and improve their health outcomes.

Rationale of the Study

End stage renal disease is the seventh leading cause of death among Filipinos. Every hour, one Filipino develops chronic renal failure or about 120 Filipinos per million population per year (NIKTI, 2013). Chronic kidney disease is the terminal complication of a lot of diseases such as hypertension, diabetes mellitus, systemic lupus erythematosus, etcetera. Patients with poorly controlled hypertension or diabetes mellitus are at high risk for developing this debilitating disease. In the Philippines, 60% of dialysis patients have chronic renal failure because of diabetes mellitus or hypertension (NIKTI, 2013). Obstructive uropathy is also common in the Philippines and complications of this disease eventually lead to end stage renal disease (Dirks et al).

Distressing physical symptoms, emotional distress, and financial difficulties plague individuals with chronic kidney disease. Few studies have dealt with the impact of this physically, emotionally, and financially draining disease on the quality of life of Filipino patients. It is paramount to address the quality of life issues of chronic kidney disease patients. This study provides the groundwork for accomplishing that vital task. This study is also geared towards characterizing the over-all experience of patients when it comes to dealing with chronic kidney disease. The investigators also put together an updated situationer on the state of chronic kidney disease in the country in order to guide the health force directly involved in patient care as well as policy-makers in instituting reforms that will improve health outcomes for these patients.

Materials and Methodology

Systemic Review of Local and International Studies on Quality of Life of Chronic Kidney Disease Patients

A systemic review was conducted with the research question, "In patients with chronic kidney disease, how is their quality of life affected compared to individuals without chronic kidney disease?" The population of chronic kidney disease included both pediatric and adult patients with chronic kidney disease of any duration. Quality of life was defined as the general well-being of individuals. The effect on quality of life was qualified in terms of the impact of chronic kidney disease on physical and mental health, environment, education, recreation and leisure time, and social belonging. Study designs included were cohort studies, randomized controlled trials, multi-center studies, and qualitative research. Data from the studies included in the systemic review were synthesized and findings were interpreted. These relevant findings also contributed in the formulation of recommendations in the care of patients with chronic kidney disease.

Survey of Chronic Kidney Disease Patients on Dialysis

The study focused on the impact of chronic kidney disease on the quality of life of Filipino patients, particularly those on dialysis. The objectives of the survey were to: 1). generate an overview of the baseline characteristics of chronic kidney disease patients; 2). document the most distressing symptoms of chronic kidney disease from the point of view of Filipino patients; 3). obtain patterns of adherence to treatment and explore reasons for non-compliance to treatment; 4). recognize the needs of chronic kidney disease patients and how to address them; 5). analyze how chronic kidney disease affects the quality of life of these Filipino patients. Data on this was obtained through a survey employing a standardized questionnaire. The validated and standardized questionnaire sought the general data (age, location, diagnosis, availability of insurance), distressing symptoms experienced, effects of these distressing symptoms, difficulties in complying with dialysis schedule, sources of support, and other forms of support needed. This questionnaire also incorporated a validated quality of life scale, the 16-item Burckhardt quality of life scale, that has been constantly validated and utilized in the study of groups with chronic illnesses. Data from the survey was synthesized and analysed in order to come up with recommendations targeting Filipino patients. The respondents for the survey came from the dialysis unit in Premiere Medical Center, Cabanatuan City Nueva Ecija, and the dialysis center of the Philippine General Hospital. The study was approved by the Chief of the participating dialysis units in this study. Verbal consent was obtained from the twenty- six respondents before proceeding with the survey and the right to privacy of these patients were protected. This qualitative research utilized convenience sampling and the number of respondents was enough to reach saturation.

Key Informant Interviews of Chronic Kidney Disease Patients on Dialysis

The experiences of Filipino patients in dealing with chronic kidney disease were also scrutinized through key informant interviews of patients undergoing dialysis. The objectives of the key informant interviews were to 1). document the experiences of chronic kidney disease patients when it comes to dealing with their illness; 2). describe impact of chronic kidney disease on the quality of life of Filipino patients; 4). recognize the needs and issues of chronic kidney disease patients to generate an action plan that will promote better quality of life for these patients. The respondents for the key informant interviews came from the dialysis unit in Premiere Medical Center, in Cabanatuan City in Nueva Ecija, and the dialysis center of the Philippine General Hospital. The study was approved by the Chief of the participating dialysis units featured in this study. Verbal consent was obtained from the four respondents before proceeding with the survey and the right to privacy of these patients were protected. Such information obtained through the key informant interviews were correlated with the findings in the survey. This qualitative research utilized convenience sampling and the number of respondents was enough to reach saturation.

Results

Systemic Review

The systemic review consisted of an analysis of seven landmark articles tackling the effect of chronic kidney disease on the quality of life of patients. There are only a few international studies that dealt with this vital topic. The review covered cross-sectional and qualitative research studies.

In a study by Mazairac, et. al. which compared the effect of hemodiafiltration against hemodialysis on the quality of life, it was shown that over the span of five years, patients who underwent hemodialysis and hemodiafiltration had no significant differences in health-related quality of life (overall health, cognitive function, quality of social interaction, sleep, effects of kidney disease on daily life, and burden of kidney disease). However, in both dialysis modalities, the quality of life domain patient satisfaction declined over time. (1)

Perales-Montilla, et.al., meanwhile, used 36-item short form questionnaire (36-SF) to evaluate 39 CKD patients from four dialysis centers in Spain who have been on dialysis for at least six months. Analyses of the data showed lower levels of quality of life scores than the reference range and that depression is the main predictor of quality of life as it is associated negatively with its other components. The degree of concern as well as the use of passive coping strategies (ie helplessness-hopelessness and fatalism) are also associated with lower levels of quality of life. (2)

Pagels, et.al, performed a cross-sectional study on the health-related quality of life of 535 stage 2-5 CKD patients with glomerular filtration rates ranging from 69 to 2 ml/min/1.73², and 55 controls from the Stockholm region in Sweden. Also making use of 36-SF to assess the physical functioning, role physical, general health, physical summary scores, mental health, and pain of the patients, it was revealed that all dimensions deteriorated significantly in all CKD stages, with the lowest scores at stage 5. Patients in CKD stage 4 demonstrated deteriorated scores with a large magnitude in physical function, general health, and physical summary scores compared to patients with CKD stage 2-3. They concluded that CKD implied impaired health-related quality of life also in the earlier stages of the disease and that by the time dialysis is initiated, quality of life has already deteriorated substantially. Other powerful predictors of quality of life in CKD are presence of comorbidities such as inflammation and cardiovascular disease.(3)

SF-36 was also used by Santos on 166 patients who have been on hemodialysis for three months to assess for their quality of life. Depression was also assessed using the 10-item version of the Center for Epidemiologic Studies Depression scale. Results showed that 7.8% percent of the patients were depressed. When data from depressed patients were compared with those who were not, quality of life scores, particularly that concerning vitality, were lower among the depressed. Regression analysis showed that depression was a predictor of role-emotional. (4)

Research by Bayoumi, et.al., on 100 patients undergoing hemodialysis in Saudi Arabia also used 36-SF and the kidney disease quality of life scale short form to assess quality of life. Data showed that quality of life scores were negatively correlated with age and that there is a decreasing trend with increase of age and decreased education. Scores were also noted to be higher among female and working patients. Lower scores were also noted among patients who are male, older, and who have been on dialysis for a longer duration. (5)

Fukuhara, et.al., on the other hand, connected the quality of life of CKD patients not on dialysis in Japan with their daily activities. Using the vitality subscale of 36-SF, they were able to find that at baseline, higher vitality scores and younger age were associated with going out more often while sex and presence of diabetic nephropathy had no association with frequency of going out. Also, further data analyses revealed that greater changes in vitality scores were associated with greater frequency of going out. (6)

Belgian researchers Poppe, et.al., meanwhile, used self-report questionnaires to assess health-related quality of life, acceptance, and personality among 99 patients in the out-patient clinic of Ghent University Hospital Nephrology Department from January 2009 to August 2010. Results showed that acceptance had a significant positive contribution to the prediction of health-related quality of life and that neuroticism is negatively correlated with acceptance and quality of life. (7)

Quality of Life of Filipino Patients on Dialysis Based on Survey

A total of 26 patients diagnosed with Chronic Kidney Disease (CKD) undergoing dialysis at the Philippine General Hospital in the city of Manila or at the Premiere Medical Center in Cabanatuan City in the province of Nueva Ecija, were surveyed, ages ranged from 35 to 81 years old, 88.5% were from provinces in Luzon, the main island where both dialysis centers are located and 11.5% were from Metro Manila, the capital city of the country. Most (n=18 or 69.23%) declared that they were covered by the national social health insurance (PhilHealth). However, a significant number of respondents were not covered by any form of health insurance (n =9 or 34.61%).

Of the respondents, six patients were diagnosed with Chronic Kidney Disease Stage V, two patients have Stage IV Chronic Kidney Disease, eleven patients were diagnosed with diabetic nephropathy, seven patients had chronic kidney disease from hypertensive nephropathy and one patient had chronic kidney disease from chronic glomerulonephritis.

Duration since CKD diagnosis spanned from 8 months to 12 years before the time of interview, while duration of dialysis treatment also varied, from 0 (first dialysis) to 7 years since diagnosis. Patients were advised by their doctor to undergo dialysis 2-3 times a week. Nineteen respondents or 73% were able to adhere to their prescribed treatment plan (i.e., how many times a week they are required to undergo dialysis). Among those who failed to adhere to their prescribed treatment plan, four were not covered by any form of health insurance while only one was covered by PhilHealth or the social health insurance program of the Philippines.

Patients ranked fatigue or weakness (24%), easy fatigability (16%), nausea or vomiting (12%) and pruritus (11%) as the four (4) most distressing symptom of CKD (Figure 1). These symptoms affect their quality of life mostly by impairing their ability to work and interact with others. Some patients have also described feelings of discomfort, not being able to eat well, and not being able to think straight.

Reasons for non-compliance to treatment were explored in this study. Lack of money (53%) was a significant difficulty experienced in complying with the dialysis schedule; dialysis center being too far away from home (19%) and physical discomfort and distressing symptoms after dialysis (19%) were second in frequency in terms of the reasons for non-adherence to treatment (Figure 2). Primary sources of financial support for treatment were family members (50%) and health insurance (30%) (Figure 3). When asked about the form of support that they need during this time of illness, financial support (77%) was placed as the most needed form of support; support groups (10%) were a distant second (Figure 4).

In order to standardize the responses of the patients on dialysis, the Burckhardt (16-item) quality of life scale was used. The range of the scale is from 1 to 7 (1 = terrible, 2 = unhappy, 3 = mostly dissatisfied, 4 = mixed, 5 = mostly satisfied, 6 = pleased, 7 = delighted). The validated scale encompasses the various factors that determine quality of life such as physical and mental health, environment, economic security, education, recreation and leisure time, and social belonging. In their quality of life, patients were mostly satisfied (42%) with financial security and access to material comforts, such as home and food. On the other hand, 23% were mostly dissatisfied and another 23% had mixed feelings about their current state of health (Figure 5). In terms of relationships, majority of the respondents were delighted- 38% for relationships with parents, siblings and relatives, 31% with children, 38% with spouse or significant other, 38% with close friends. An equal percentage of respondents (27%) had mixed feelings and were pleased about their own ability to help and encourage others and to give advice. Patients were mostly dissatisfied because they were not able to socialize (31%), and participate in organizations and public affairs (27%). Respondents largely had mixed feelings toward expressing themselves creatively (35%), gaining more knowledge (31%), and their independence (27%). They had mixed to good impressions regarding knowing their assets and limitations (23%) and in being able to work on the job or at home (23%). Most patients (31%) were delighted about their ability to read, listen to music, or observe entertainment. A significant percentage (27%) were pleased about their ability to participate in active recreation. In summary, Filipino patients find chronic kidney disease debilitating because their current state of health suffers, and their ability to socialize, and participate in organizations and public affairs is impaired.

Quality of Life of Chronic Kidney Disease Patients Based on Key Informant Interviews

Interviewees commonly held a negative impression towards chronic kidney disease, with majority stating severity and irreversibility in their knowledge of the disease. Most of the respondents were aware that chronic kidney disease is the end-stage complication of other diseases such as diabetes and hypertension. A significant number of respondents also thought that there is no real cure for chronic kidney disease and that dialysis is only a means of controlling the symptoms of the disease, but does not really prolong their life.

All of the participants of the key informant interviews reported a lower quality of life relative to their pre-morbid condition. Chronic kidney disease has many distressing symptoms such as fatigue and weakness, dyspnea, nausea and vomiting, pruritus, bone pain, numbness, tingling sensation, restless leg syndrome, and edema among others. These distressing symptoms constantly make them uncomfortable and hamper their ability to perform the activities of daily living. Such bothersome symptoms also dampen their mood and make them irritable or despondent. The interviewees also reported that chronic kidney disease is not only physically debilitating but also economically draining because of the sheer expense of the treatment and the loss of employment opportunities because it is hard to find a regular job when one is weak or when one has to have absences in order to undergo dialysis. The patients also expressed that even if social health insurance like PhilHealth can partially cover the cost of dialysis, there are other hidden costs such as transportation expenses and lost employment opportunities.

The interviewees recognized the lack of financial resources as a primary factor affecting their ability to adhere to treatment. Their quality of life is also adversely affected by their inability to acquire basic needs.

Discussion

An Updated Situationer

Chronic kidney disease is a debilitating end-stage complication of most chronic illnesses such as diabetes mellitus, hypertension, glomerulonephritis, systemic lupus erythematosus, HIV, etc. Philippine data shows that it is already the ninth leading cause of death in the country (NKT, 2012). Chronic kidney disease also has increasing prevalence in the country, now affecting one in ten Filipinos. In the Philippines, the most common cause of chronic kidney disease requiring renal replacement therapy is diabetic nephropathy. Among patients with chronic kidney disease, 44.6% have diabetic nephropathy while 23% have hypertensive nephropathy (Amarga, 2013). This pattern of prevalence is also reflected in the results of the survey conducted by the investigators. Usually, by the time chronic kidney disease is diagnosed, the patient is already at stage V of chronic kidney disease, necessitating dialysis. This entails more vigilance and health prevention for patients with chronic illnesses at risk of developing renal failure.

Most chronic kidney disease patients are also in need of more assistance especially because of the high cost of this disease. Currently, PhilHealth or the social health insurance system has coverage for renal replacement therapy in the form of hemodialysis and renal transplant. However, the full cost of the treatment is still financially debilitating and many patients are lost to follow-up.

Impact of Chronic Kidney Disease on the Quality of Life of Filipino Patients

Both the systemic review, survey and key informant interviews echo the adverse effects of chronic kidney disease on the quality of life of Filipino patients. Depression over the severity and chronicity of the nature of the illness is a major determining factor in shaping quality of life. Most patients lament the loss of employment opportunities, the distressing nature of the physical symptoms, and the inability to attend social functions and participate in societal and organizational affairs.

Multi-sectoral Role in Treatment and Prevention of Chronic Kidney Disease

Patients with chronic kidney disease have self-reported a marked deterioration in their quality of life. Various sectors of society have unique roles to play in uplifting the state of these suffering patients. For instance, medical students, with their comprehensive knowledge on the pathophysiology and treatment of chronic kidney disease, can take on a more active role in public education by conducting public forums and producing educational materials on the renal diet and lifestyle. Government is pivotal in terms of increasing coverage and providing increased financial assistance to indigent patients. Society at large can improve the plight of patients with chronic kidney disease. Support groups play a big role in providing much needed psychosocial support and improving quality of life through sustained participation in organizations and public affairs.

Conclusion

Quality of life is impaired in patients with chronic kidney disease. The management of this chronic disease has economically and socially debilitating consequences. It is within the purview of the health sector to enact programs to increase financial assistance for these patients and to provide psychosocial support and participation in public affairs for these patients.

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Figures

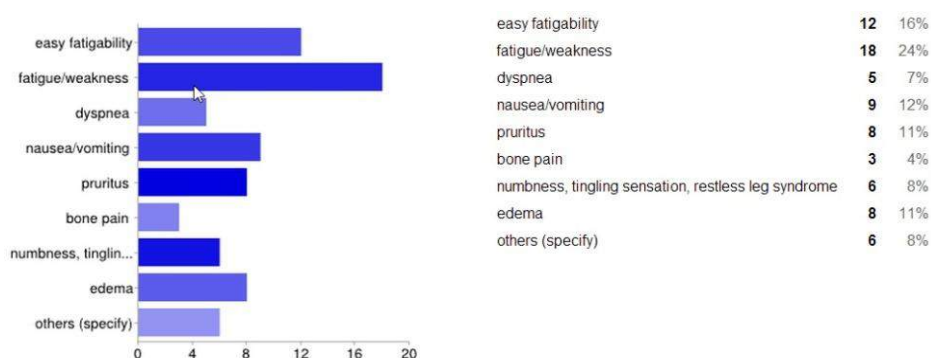


Figure1.

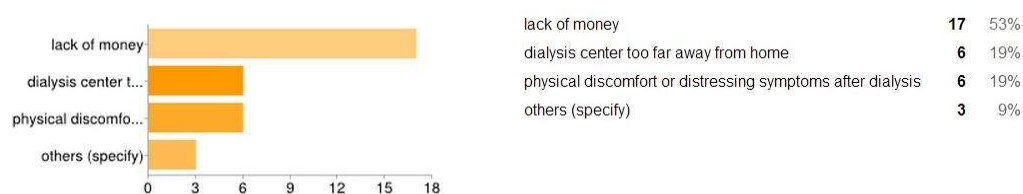


Figure2.

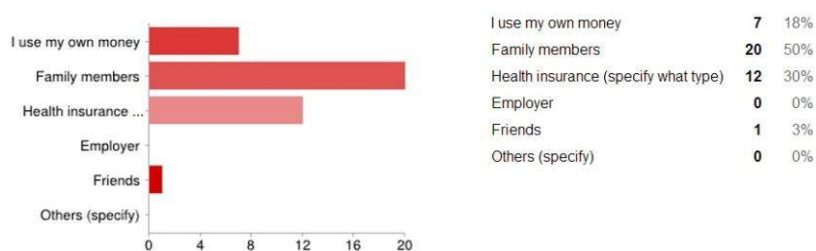


Figure3.



Figure4.

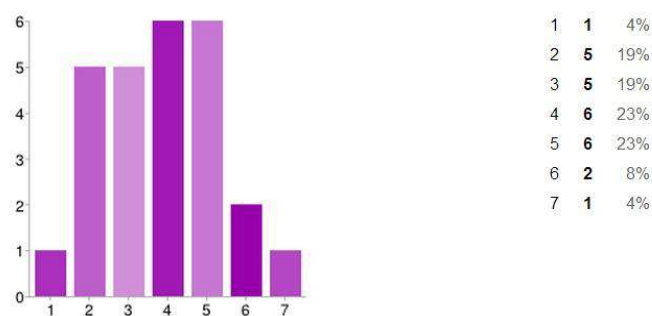


Figure5.

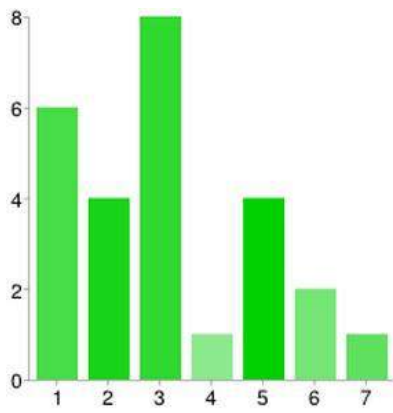


Figure6.

1	6	23%
2	4	15%
3	8	31%
4	1	4%
5	4	15%
6	2	8%
7	1	4%

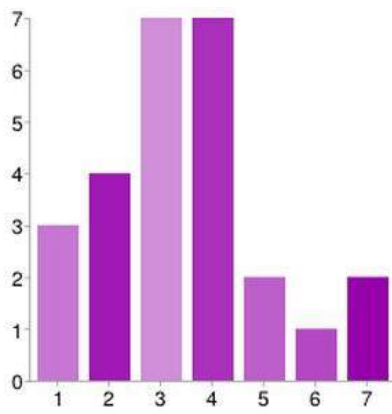


Figure7.

1	3	12%
2	4	15%
3	7	27%
4	7	27%
5	2	8%
6	1	4%
7	2	8%

SCIENTIFIC PAPER COMPETITION – SINGAPORE

Patients' Perspectives on Thromboprophylaxis in Atrial Fibrillation

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1. Abstract

Introduction: Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide with significant chronic health ramifications, including an increased risk of thromboembolic stroke. Though oral anticoagulation (OAC) treatment with warfarin is widely accepted as a pharmacologic standard for the management of stroke risk in AF patients, the rate of OAC use remains suboptimal across the globe, standing at only 40.7% in Singapore. This low rate of OAC use can be attributed to both patient and physician factors. While past research has focused on physician factors that influence the prescription of OAC treatment, this paper will explore the impact of patient's perspectives on the rate of thromboprophylaxis in Singapore.

Methodology: From October to November 2013, a cross-sectional survey study was performed on 100 patients with AF warded at the National University Hospital (NUH), Singapore. Investigators administered a modified version of the validated Anti-Clot Treatment Scale (ACTS) questionnaire, which was translated verbally into local languages and dialects. The data was then analyzed by stratifying the patients into two groups based on anticoagulation status, and comparing the two groups according to each ACTS item, as well as the overall Burdens and Benefits subscales. Epidemiological data was analyzed in a similar fashion.

Results and Discussion: Of the 100 patients surveyed, 64 were on OACs, while 36 were on antiplatelet therapy. Overall, 75% of the patients were aged ≥ 65 years, 57% made their own medical decisions, and 91% had a CHA₂DS₂-VASc score of ≥ 2 . There were no statistically significant differences between the two groups in the mean scores of each ACTS item, as well as the overall burden and benefit scores. Of all the ACTS items, routine blood tests garnered the highest burden score (2.27 out of 5), while burden scores were lower for limitations in alcohol intake and work life (1.0 and 1.3 out of 5 respectively). Notably, patients' knowledge of anticoagulation therapy was found to be uniformly lacking, with 51% unaware of the reason behind their need for anticoagulation treatment, though satisfaction with information delivery was found to be high (84%). Our data also revealed a significant influence of the physician's and family's opinions on a patient's decision-making, with 99% and 67% indicating that it would influence their decision respectively.

Conclusion: This study has revealed several significant trends that require further discussion and evaluation, including patients' perception of the most burdensome aspects of anticoagulation therapy, a lack of informed decision-making that is prevalent amongst patients, and the strong influence of the physician and family on patients' decision-making.

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Patients' Perspectives on Thromboprophylaxis in Atrial Fibrillation

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1. Introduction

1.1 AF is an Important Chronic Disease

Atrial fibrillation (AF) is the most common cardiac arrhythmia^{1, 2} with a global prevalence of 4.7% in patients aged ≥ 65 and up to 9% in the 80-90 age group³. In Singapore, an estimated 1.5% of the population suffers from AF, and that number rises to 5.8% in those > 80 years old⁴.

AF has significant health ramifications, with thromboembolic events being the most common⁵. Ischemic stroke secondary to AF is more severe (41% of patients with AF-related stroke become bedridden compared to 23% of non-AF-associated stroke patients⁶) and close to 20% of strokes are attributable to AF⁷. Accordingly, AF not only increases the risk of stroke by 5 times, but also independently predicts poorer clinical outcomes⁸.

In Singapore, stroke is among the top 10 causes of hospitalization and is the fourth leading cause of death⁹. With our greying population¹⁰, stroke as a deleterious consequence of AF poses a significant healthcare burden to Singapore. Stroke prevention in AF is therefore crucial.

1.2 Pathological Basis of Atrial Fibrillation

AF is defined as a phenomenon of rapid, chaotic electrical impulses in the atria, where the regular electrical impulses generated by the sinoatrial node are overwhelmed by rapid electrical discharges produced in the atria and adjacent pulmonary veins.

Consequently, atrial excitation is disordered, and they no longer contract in a coordinated fashion thus entering into fibrillation. Also, the concurrent disordered conduction across the atrioventricular node to the ventricles results in ineffective ventricular filling, thereby compromising cardiac output.

The lack of organized atrial contraction leads to stasis of blood within the atria, which predisposes to thrombus formation, and any subsequent embolism of thrombi through downstream arteries to the brain will culminate in a stroke^{11, 12, 13}.

1.3 Management of Atrial Fibrillation

The cornerstones of AF management involve rate control or rhythm control, and anticoagulation¹⁴. Rate control is achieved by dromotropic drugs (e.g. beta-blockers, calcium channel blockers, digoxin) which control conduction across the atrioventricular node¹⁵. Rhythm control is primarily achieved with antiarrhythmics such as amiodarone.

Oral anticoagulants (OACs) play a quintessential role in mitigating AF-related stroke by preventing thrombus formation. Multiple randomized controlled trials have demonstrated the effectiveness of anticoagulation in the management of AF related stroke risk. Long-term OAC therapy with warfarin reduces the relative risk of thromboembolic stroke in AF patients by approximately 65%¹⁶. Antiplatelet agents like aspirin and clopidogrel have been found to be somewhat efficacious, although much less so as compared to OACs. Moreover, novel oral anticoagulants (NOACs) introduced in recent years, including rivaroxaban, dabigatran, and apixaban, promise a similar efficacy to warfarin with the added benefits of enhanced safety and ease of use¹⁷. However, given warfarin's lower cost and significant clinical experience from being utilized worldwide, it is likely to remain a mainstay of antithrombotic therapy in the near future.

1.4 Current Trend of Under-Anticoagulation

Medical evidence and guidelines internationally and locally suggest that OACs play a key role in the management of AF-related stroke risk. In Singapore, anticoagulation use in AF is "strongly recommended in most circumstances without reservations"¹⁸. Despite this recommendation, Lim *et al* noted that 40.7% of patients (n=1826) were discharged without anticoagulation despite their high thromboembolic risk¹⁹. This is an international phenomenon, paralleled also in the United Kingdom where 40% of AF patients eligible for anticoagulation were actually not on such therapy²⁰.

This trend of under-anticoagulation is arguably multifactorial, and can be mainly attributed to patient and physician factors²¹. Much research in recent years has focused on elucidating factors that affect physicians' willingness to prescribe anticoagulation, with minimal emphasis on patient factors. For example, in a study of the GARF IELDS registry, Kakkar *et al* noted that ineffective anticoagulation in 48% of the cases could be attributed to physician decisions²².

As warfarin treatment is associated with a small but significant increase in the risk of major bleeding²³, physicians must necessarily weigh its potential benefits (stroke prevention) against potential risks (increased risk of bleeding) in consultation with the patient. To aid the decision-making process, several scoring tools such as CHA₂DS₂-VASc²⁴, CHA₂DS₂-VASc²⁵ and HASBLED²⁶ have been developed in addition to several international guidelines such as the ACCP²⁷, ESC²⁸, and Canada²⁹ anticoagulation guidelines. The most recent guidelines from the ACCP also assessed evidence related to patients' preferences and recommend that a ratio of stroke versus GI bleeding risk in the range of 2:1 to 3:1 should prompt the physician to recommend oral anticoagulation³⁰. However, these are international guidelines unspecific to Singapore's context, and this may have an effect on the physician's confidence in prescribing warfarin treatment locally.

Furthermore, warfarin treatment imposes a significant burden on the patient in terms of the dosing regimen, countless interactions with drugs and food, and the need for constant follow-up to monitor INR; therefore, there are significant challenges in ensuring compliance and keeping treatment within the therapeutic range in patients³¹. The treatment burden on patients may be a contributing factor to the state of under-anticoagulation, though such patient factors have not been evaluated adequately to date.

1.5 Research aims

Evidence based medicine is an amalgamation of physician expertise, patient values and expectations, as well as clinical evidence that improves patient outcomes. Physician factors that influence the prescription of antithrombotic therapy and clinical evidence about the efficacy of different types of antithrombotic treatment have been explored in preceding studies¹⁹, while there have been no prior studies of patient factors to date in the local context. Thus, this paper aims to elucidate patients' perspective of anticoagulation therapy in view of its ramifications on the treatment of AF.

2. Methodology

2.1 Survey Administration

We performed a cross-sectional survey study of 100 patients with AF in the National University Hospital (NUH), Singapore. Patients were recruited over a two-month period from October to November 2013. The following inclusion criteria were used: patients (I) who have been diagnosed with AF, and (II) who were warded in NUH during the study period.

A modified version of the Anti-Clot Treatment Scale (ACTS) questionnaire was administered. The original ACTS³² is a 17-item survey assessing patient satisfaction with OAC treatment, comprising 13 questions that assess the burden and 4 questions that assess the benefit of anticoagulation, and scored on a 5-point Likert scale. It has been validated in numerous international studies^{32, 33, 34}, and has also been included as an outcome in several large-scale longitudinal AF patient registries^{35, 36}.

To study patients in the Singapore context, the ACTS survey was modified slightly. 3 questions were added to the Burden subscale to assess the impact of anticoagulation therapy on patients' work life and on their families and caregivers (important in the local setting as the family is often heavily involved in caregiving). Also, 2 questions were added to assess the influence of the physician's opinion on patients' decisions to accept anticoagulation treatment, and how the patients' quality of life has been affected in general.

We administered this modified ACTS survey by translating it verbally into various locally spoken languages and dialects – English, Mandarin, Malay, Tamil, Hokkien and Cantonese – to suit the patients' language abilities. The rationale for an investigator-administered approach was to standardize the results across the study population, given that a number of the patients studied were either illiterate or spoke only dialects which have no unitary standardized writing systems.

2.2 Statistical Analysis

We analyzed our data using IBM SPSS Statistics Version 21. The data was first analyzed as a whole to identify common epidemiological and behavioral trends in the patient population. Patients were then stratified into two groups – those currently taking oral anti-coagulants and those not – and analyzed separately, with special attention paid to the patients' demographics, knowledge of anti-coagulation and perception of anti-coagulation therapy.

From the ACTS survey results, the ACTS Burden and Benefit scores were calculated. The Burden score is the sum of all the responses on the Likert scale to the questions assessing burden, subtracted from 65. The Benefit score is the sum of all the responses on the Likert scale to the questions assessing benefit. The possible Burden scores range from 0 to 52, with a higher score indicating less perceived burden. The possible Benefit scores range from 3 to 15, with a higher score indicating greater perceived benefit.

3. Results

Of the 100 respondents, 64 patients (64%) were prescribed OACs and the remaining 36 patients (36%) were receiving anti-platelet therapy. Several of the latter group had previously taken OACs, but had since stopped for various reasons including non-compliance and side-effects of bleeding. For the purposes of the study, they have been grouped with those who have never received OACs.

The demographics of the surveyed population are displayed in Table 1. The majority of the population can be considered geriatric, with 75% being 65 years of age or above. 98% of those surveyed were Singaporeans, and the ethnic distribution of the respondents roughly corresponds to that of the local population (74.1% Chinese; 13.4% Malay; 9.2% Indian, 3.3% others³⁷). Most were retired (70%) and lived with others, usually the family, with only 10% living alone.

The patients had CHA₂DS₂-VASc scores ranging from 0 to 9 (maximum) with a median score of 4 as shown in Fig. 1. 91% of the respondents had a CHA₂DS₂-VASc score of 2 and above, which is the cut-off at which anti-coagulation therapy ought to be given as per ACCP guidelines. The most common risk factor for stroke among the patients was hypertension (85%), followed by diabetes mellitus (41%). In addition, 34% of those surveyed had already experienced a previous stroke or transient ischaemic attack.

Table 2 summarises patients' awareness of their risk of stroke and knowledge of anti-coagulation. None of the patients knew what the CHA₂DS₂-VASc score, a predictor of stroke risk, was and what their personal score was. 51% of the patients were unaware of the reason they ought to be on anti-coagulation.

Table 3 is a summary of the responses to the ACTS questionnaire, with a comparison between the group on OACs and the group that is not. Overall, there are no significant differences between the responses of the two groups. This may suggest that the main factor determining whether patients are anti-coagulated or not is the physician's decision.

The mean population Burden score is 42.54 out of 52 and the mean population Benefit score is 10.13 out of 15, with no significant difference between the two groups.

Characteristic	%, Total	%, on OAC	%, no OAC
Age			
Below 65	25	25.0	25.0
65 to 74	33	37.5	30.6
75 and above	42	37.5	44.4
Gender			
Male	52	53.1	50.0
Female	48	46.9	50.0
Ethnicity			
Chinese	80	75.0	88.9
Malay	15	17.2	11.1
Indian	4	6.3	0.0
Others	1	1.6	0.0
Own decision maker	57	56.3	58.3
> 65 years old	84	-	-
< 65 years old	48	-	-
Patient's education level			
Below PSLE	14	9.5	22.2
PSLE	41	44.4	36.1
Above PSLE	24	28.6	16.7
Others	21	17.5	25.0
Employment status			
Working	17	20.3	11.1
Not working	83	79.7	88.9
Marital status			
Married	74	76.6	69.4
Not married	26	23.4	30.6
Living arrangement			
Living alone	10	7.8	13.9
Not living alone	90	92.2	86.1
Alcohol			
Abstinent	83	84.4	80.6
Not-abstinent	17	15.6	19.4
Smoking			
Never smoked	68	68.8	66.7
Former smoker	25	25.0	25.0
Current smoker	7	6.2	8.3

Table 1. Demographics of patient population

Characteristic	%, Total	%, on OAC	%, no OAC
Co-morbidities			
CCF	28	28.1	27.8
Hypertension	85	84.4	86.1
Stroke / TIA	34	32.8	36.1
Vascular Disease	39	35.9	44.4
Diabetes Mellitus	41	42.2	38.9
CHA ₂ DS ₂ -VASc score			
Aware of score	0.0	0.0	0.0
Aware of own score	0.0	0.0	0.0
Anti-coagulation			
Aware of term 'anti-coagulation'	64	70.3	52.8
Aware of need for anti-coagulation	77	81.3	69.4
Aware of reason for anti-coagulation	51	57.8	38.9
Satisfied with information delivery	84	87.5	77.8
Gave consent or would give consent to anti-coagulation	83	87.5	75.0
Already on anti-coagulation	64	100.0	0.0

Table 2. Risk factors and awareness of patient population

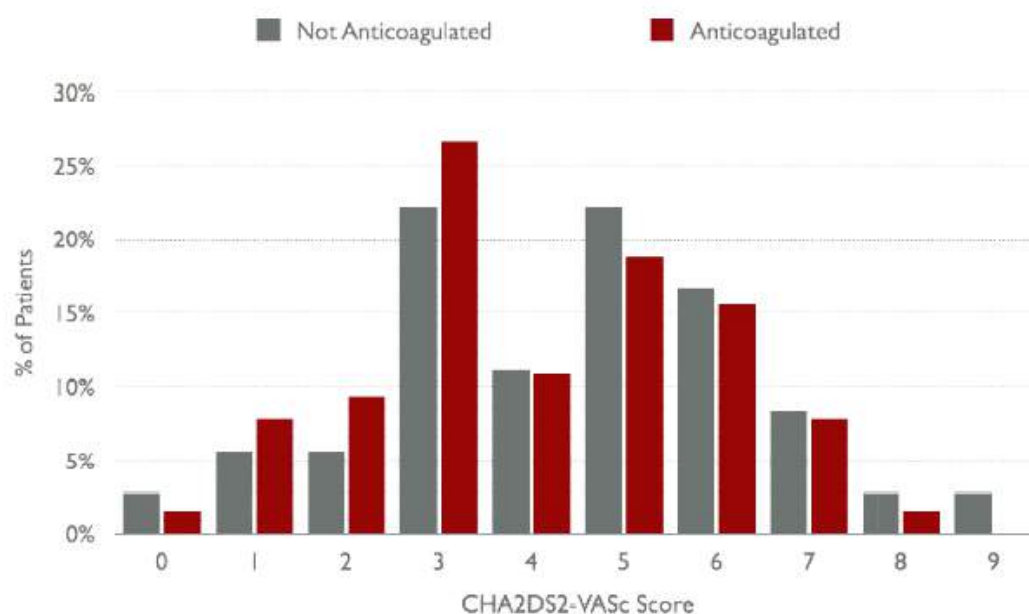


Fig 1. CHA₂DS₂-VASc Score of Surveyed Population

Question	Mean $\pm$ SD, on OAC	Mean $\pm$ SD, no OAC
1. Does the possibility of bleeding due to anti-clot therapy limit the patient from engaging in physical activities? (sports, cycling, leisure activities)	1.7 $\pm$ 0.99	1.7 $\pm$ 1.1
2. Does the possibility of bleeding due to anti-clot therapy limit the patient from performing in his/her work life?	1.3 $\pm$ 0.82	1.4 $\pm$ 0.96
3. Does the possibility of bleeding due to anti-clot therapy limit the patient from taking part activities of daily living(eg: shopping, housework)	1.7 $\pm$ 1.1	1.9 $\pm$ 1.3
4. Does the possibility of bruising easily bother the patient?	1.9 $\pm$ 1.1	1.8 $\pm$ 0.98
5. Do the limitations in diet due to anti-clot therapy bother the patient?	1.7 $\pm$ 1.2	1.9 $\pm$ 1.2
6. Do the limitations in alcohol intake due to anti-clot therapy bother the patient?	1.1 $\pm$ 0.28	1.0 $\pm$ 0.17
7. Are the daily aspects of anti-clot therapy an inconvenience to the patient? (eg: remembering to take medication at a certain time, taking the correct dose of medication, following a specific diet etc...)	1.6 $\pm$ 0.90	1.8 $\pm$ 0.94
8. Are routine blood tests whilst on anti-clot therapy an inconvenience to the patient? (eg: arranging appointments, travelling to and from hospital, waiting time etc...)	2.2 $\pm$ 1.3	2.4 $\pm$ 1.2
9. Does the patient find it difficult to follow and be adhere to the anti-clot treatment?	1.6 $\pm$ 0.96	1.5 $\pm$ 0.77
10. Does the patient find time consuming to follow and adhere to the anti-clot treatment?	1.6 $\pm$ 0.95	1.9 $\pm$ 1.3
11. Does the patient find the anti-clot treatment to be frustrating?	1.8 $\pm$ 1.0	1.9 $\pm$ 1.1
12. How much of a burden is the anti-clot treatment?	1.9 $\pm$ 1.1	2.1 $\pm$ 1.2
13. How much of a burden is the anti-clot treatment to the patient's family/caregiver?	2.0 $\pm$ 1.2	2.1 $\pm$ 1.1
14. How much of a negative impact has the anti-clot treatment have on the patient's life?	1.6 $\pm$ 0.86	2.1 $\pm$ 1.1
15. Is the patient confident that the anti-clot treatment will prevent thromboembolic events (eg: blood clots, stroke, DVT etc...)	3.5 $\pm$ 1.2	3.0 $\pm$ 1.4
16. Does the patient feel reassured whilst on anti-clot treatment?	3.4 $\pm$ 1.2	3.2 $\pm$ 1.3
17. Does the patient feel satisfied whilst on anti-clot treatment?	3.5 $\pm$ 1.2	3.6 $\pm$ 1.3
18. How much of a positive impact does the anti-clot treatment have on the patient's life?	3.1 $\pm$ 1.2	2.8 $\pm$ 1.1
19. Did the physician's opinion influence your decision?	4.7 $\pm$ 0.63	4.3 $\pm$ 1.1
20. Ultimately, has the anti-clot treatment changed the patient's quality of life?	2.7 $\pm$ 1.0	2.6 $\pm$ 1.2
ACTS Burden Score (Questions 1-13, reverse-coded)	43.06 $\pm$ 7.220	41.61 $\pm$ 7.028
ACTS Benefits Score (Questions 15-17)	10.33 $\pm$ 3.381	9.78 $\pm$ 3.522

Table 3. Responses to ACTS questionnaire

4. Discussion

The results derived from the survey can be broadly classified into 2 categories – 1) demographic data and 2) patients' views on anticoagulation therapy. Through analyzing both categories using a variety of statistical analytical tools including reliability and regression analysis, conclusions regarding patients' perspectives on antithrombotic therapy and key factors that influence the decision-making process to commence with antithrombotic therapy were drawn.

4.1 Individual Agency with Family Influence

Compared to Western cultures, Asian societies, which largely embody a collectivist culture, place a much higher emphasis on the nuclear and extended family unit, where familial interdependence, filial piety, and togetherness are oft-emphasized and children are expected to care for their elderly parents in old age³⁸. Thus, in Singapore's largely Asian society, one may expect many elderly patients to have their medical decisions made by their family on their behalf.

AF is a chronic disease with a high prevalence in the elderly which imposes a higher disease burden on the geriatric population, by virtue of multiple comorbidities that afflict them³⁹. While it is understandable that a large proportion of the patients under 65 years old (84%) made their own medical decisions given that they are likely to be more independent and have a greater degree of control over their personal lives, it is surprising that almost half (48%) of the elderly patients surveyed also claimed to be the primary decision maker. This purported "independent decision making" must however be considered in the cultural context of Singapore where decisions are likely to have been made in consultation with patients' family members. Accordingly, the role of the family in decision-making cannot be belittled as 67% of the patients consulted their families' opinions, and up to 42% listed family concerns as among their top 3 considerations when making medical decisions. Furthermore, in the local context where medical concepts are usually explained to accompanying family members during the consult due to either language barriers between the doctor and the elderly patient, or the family's preference to spare the patient unnecessary details, the doctor inadvertently places the onus of communicating the facts of the disease and management on the patients' family members.

Nevertheless, the family being an important stakeholder in the consult process notwithstanding, the patient must necessarily be cognizant of the facts of the consultation given that they are the ones making the final decisions.

4.2 Reliance on the Physician in Decision Making

An overwhelming 85% of those surveyed indicated that their physician's opinion is one of the three most important factors that influence their medical decision-making, considerably ahead of other factors such as family opinion (42%) and their own view of their health issues (76%). Also, for 99% of the patients, their physician's opinion counted and formed the cornerstone of the decision-making process. In other words, even if they may have reservations about the management options offered, patients do have trust in their physician's professional advice and believe that physicians have their best interests at heart. This is further emphasized by the point that 82% of the patients derived their knowledge of antithrombotic therapy solely from the physician and did not actively seek further information from any other sources such as the Internet.

This submissive attitude can possibly be attributed to the fact that most patients regard their "laymen's understanding" of their condition as unlikely to be superior to that of the physician. Although this relatively passive attitude may stem from the lower educational qualifications of elderly patients, our results prove otherwise; this trend seems to be pervasive regardless of the education level of the patient or the designated decision maker. Also, there was no statistically significant correlation between the education level and the level of understanding of the reason for anticoagulation (Chi-square = 4.685, $p = 0.585$).

The strong reliance that patients have on their physicians suggests that physician factors would naturally form an important determinant of the take-up rate of antithrombotic treatment in AF patients, and could partially account for the current state of under-anticoagulation of AF patients in Singapore. A review of the literature regarding the influence of physician factors on utilization rates of antithrombotic treatment reveals a lack of standardization, such as varying thresholds of individual physicians in offering antithrombotic therapy. Notably, Turakhia *et al* pointed to the finding that cardiologists are more likely to offer warfarin to their patients than doctors from other specialties, even after accounting for comorbidities and age among other factors⁴⁰. Hence, better standardization of the AF treatment protocol may be warranted in the local context to better guide physicians with regard to when antithrombotic therapy should be initiated. This would contribute towards ensuring that AF patients who should be on thromboprophylaxis are indeed receiving it.

4.3 Lack of Informed Decision-Making

Our results have also shown that of the 83% of patients who indicated that they consented to the anticoagulation treatment, only a mere 54% were actually aware of the medical reasons behind their treatment; none of the patients knew about the CHA₂DS₂-VASc scoring system, and a corresponding 0% knew what their own score was. This glaring paucity in patient awareness of the reason for anticoagulation translates to the fact that 46% of the patients who had consented to anticoagulation treatment did so without fully understanding the reasons behind it. These statistics suggest the disquieting fact that patients in this study made medical decisions without a clear knowledge of what they are consenting to – either due to inadequate information delivery about the risks and benefits of treatment, or a relative subservience to the doctors' word without feeling the impetus to know more about their condition – thus constituting uninformed decision-making. This is especially worrying in the context of anticoagulation treatment by warfarin, where awareness and precaution are required on the patient's part in order to minimize potential complications such as excessive bleeding.

Interestingly, of those who reflected that they do not understand the reasons behind anticoagulation treatment (49%), 77.6% claimed that they were satisfied with the way the information on anticoagulation treatment was delivered. This could be attributed to the fact that patients in the local context have an implicit trust in the veracity of their doctors' word, and although the patients may not fully grasp the content delivered, they were satisfied with either the non-medical aspects of information delivery (for example concern that the doctor showed) or with the mere fact that their family members were present at the consultation and understood the information delivered.

The lack of informed decision making in this study population is glaring, and this once again points to the physician's duty to ensure that patients are on a suitable treatment regime.

4.4 Warfarin and its Burden on Patients

Anticoagulation treatment by warfarin is notably accompanied by well-documented medical side-effects and social burdens, which include the need for frequent blood tests, dietary restrictions and activity limitations secondary to the high risk of uncontrolled bleeding when injured.

According to the survey results, patients pointed to the routine blood tests as the most burdensome aspect of therapy (mean score of 2.27 out of 5), ascribing the burden to the pain associated with regular blood drawing, as well as the inconvenience experienced by family members who need to sacrifice time to accompany elderly patients (who are unable to travel independently) for appointments.

Interestingly, although Coleman *et al* (2013) reported that patients "perceived that they had limitations on both the physical activity they could engage in and regarding their diet", these factors were not significant in our local population. A plausible explanation for this is that many of the surveyed patients were either non-community ambulant or were not physically active, and that a considerable number of respondents claimed to be unaware of the food restrictions. Also, as 81% of respondents are already retired or unemployed, the impact of anticoagulation treatment on their work life is minimal.

4.5 Financial Considerations

Financial considerations are not however a major concern for these patients. This is likely because warfarin is a cheap medication in Singapore, not costing more than a few cents per tablet. At the same time, most of these patients are under social support schemes and thus healthcare costs are likely to be low.

However, in the study 27% of patients actually placed financial burden among their top three considerations in making medical decisions. While not explicitly studied in this survey, from the surveyor's experience it was found that these cost concerns were more related to the overall cost of hospitalization than that of the anticoagulant itself, especially since most of the patients surveyed had multiple comorbidities and required long hospitalizations. At the same time, some patients in the surveyed sample were actually on NOACs but were not stratified from those on warfarin. In such a case cost may indeed be a poignant concern as these NOACs come at a cost many times that of warfarin. The affordability of warfarin in relation to other alternatives can also be a significant reason as to why NOACs have seen a relatively slow pick-up rate in Singapore.

4.6 Satisfaction with Anticoagulation Therapy

Patients surveyed seem to be ambivalent about any positive impact their anticoagulation treatment has on their lives, a finding that appears to be consistent across both patient groups. The ACTS Benefits Score was comparable between the two patient populations – 10.3 for those on warfarin, and 9.8 for those not on warfarin, out of a total possible score of 15, without any statistically significant difference (p -value = 0.44). This could possibly be attributed to the problem of inadequate information delivery and lack of informed consent as previously discussed, resulting in patients not being fully aware of the potential benefits and reduction in the risk of stroke associated with anticoagulation therapy.

4.7 Recommendations

There however remain drawbacks in our survey which should be followed up on in the future.

While many physicians in the surveying hospital have already begun to prescribe NOACs to their patients with AF, this is not reflected in the survey where patients are stratified as being on warfarin-containing or non-warfarin-containing anticoagulation treatment regimes. Therefore, certain concerns such as dietary restrictions and financial considerations may have been confounded by patients on NOACs as such concerns are vastly different in their case.

5. Issues with OAC Therapy: Way Forward

5.1 Difficulties in Management of Chronic AF

The management of chronic AF in Singapore's context is neither straightforward nor simplistic, as different stakeholders in the healthcare setting face different challenges.

Firstly, the patient may unknowingly suffer from information asymmetry, either due to a lack of information delivery by the physician or a passive attitude in their disease management, and are thus predisposed to making uninformed decisions regarding anticoagulation therapy. Moreover, the relative burden of warfarin treatment experienced or preconceived notions of the dangers of warfarin may dissuade both current and potential patients from warfarin therapy.

Secondly, from the physician's perspective, an apprehension to prescribe warfarin therapy due to the lack of unequivocal local guidelines that balance benefits against risks of treatment, and attitudes toward risk aversion, are barriers in ensuring suitable anticoagulation treatment in eligible patients with AF.

Finally, the long-term ramifications of thromboembolic strokes secondary to inadequate anticoagulation therapy in patients with AF will impose a heavy burden on government resource allocation and the healthcare budget, especially in the chronic care of patients with residual disability.

5.2 Looking Ahead: Overcoming Obstacles in Chronic AF Management

5.2.1 Role of Medical Students

Medical students can play an indispensable role in conducting health campaigns and education programs that aim to improve patient understanding of the disease facts and management of AF. The risks, benefits and considerations (dietary restrictions, importance of INR trending etc.) of anticoagulation treatment by warfarin can be presented clearly in brochures, which can be written in different languages to cater for our multi-ethnic population and distributed to patients and family members. Education campaigns have a wide reach and can potentially level the information asymmetry, thus empowering patients to make informed decisions about their treatment.

Also, medical students at our medical school organize various large-scale health screenings (Public Health Screening, Neighborhood Health Screening etc) throughout the year; in addition to the traditional focus on chronic diseases like diabetes, hypertension and dyslipidemia, opportunistic screening for AF and education can possibly be incorporated as well.

5.2.2 Role of Patients

With an increasingly educated and enlightened population, patients and their family members can be encouraged to take a more active role in the management of their health issues and equip themselves with the necessary knowledge about AF. They can be enabled in this proactive information gathering process by the provision of websites that are targeted at the understanding of the patient by their healthcare provider.

5.2.3 Role of Physicians

Most importantly, physicians have to play a part in eradicating the information asymmetry by providing information that is adequate, comprehensive and understandable, about AF and its management to their patients. It is quintessential for physicians to ensure informed consent in starting anticoagulation treatment, because any attempt to begin or withhold treatment otherwise is ethically misguided.

5.2.4 Role of Government

At the national level, Singapore can adopt measures to improve the experience of patients on long-term anticoagulation treatment. For example, the Community Health Assist Scheme (CHAS) which subsidizes medical treatment of chronic diseases at polyclinics and general practitioners' clinics for lower income Singaporeans can be a possible avenue to lessen the perceived burden of warfarin treatment. As of 1 Jan 2014, the CHAS only covers 15 chronic diseases that do not include AF; if AF can be covered by the scheme, blood tests for INR monitoring can be done more conveniently and will be more accessible and affordable to patients. Perhaps by reducing what patients report to be the largest burden in our study, the take-up rate of warfarin treatment as a suitable antithrombotic therapy will increase.

6. Conclusion

In Singapore, patients largely engage in personal decision-making regarding antithrombotic treatment, though physician advice and family opinion influence the decision-making process ostensibly. Yet, the glaring paucity of informed decision-making in this study population suggests that physicians need to level the information asymmetry and shape patients' understanding of anticoagulation treatment.

There was no significant difference in the perceived burden and benefit of anticoagulation treatment in patients on warfarin compared to those on antiplatelet treatment, signifying that the onus is upon the physician to adequately prescribe anticoagulation therapy in AF patients who are suitable for it.

7. Acknowledgements

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SCIENTIFIC PAPER COMPETITION – TAIWAN

Genetic Variations in miR-196a2 Determine Endometriosis Development and are Associated with Malignant Transformation Potential

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Abstract

Background Endometriosis is a gene-related chronic disease which may cause menstrual cramps, pelvic pain, and infertility; however, cure for this disease has not been found out yet. Conducting experiments at molecular level is essential to realize the etiology and thus prevent deterioration and endometriosis-associated ovarian carcinoma. MicroRNAs (miRNAs) are a set of short non-coding RNAs, regulating gene expression post-transcriptionally. Aberrant miRNA expressions were reported in endometriosis and studies found several miRNA polymorphisms are involved in cancer development. We summarized and investigated whether cancer-related miRNA polymorphisms are also associated with endometriosis development and what pathogenic cellular function they may exert to link both diseases.

Material and methods Seven single-nucleotide polymorphisms (SNPs) within cancer-related miRNA genes were genotyped in 197 endometriosis patients and 204 healthy controls. Associations with endometriosis and clinical phenotypes were analyzed by χ^2 test. The most highly related miR-196a2 polymorphism (rs11614913) was selected for transfection into endometrium cells, and gene expression profile was analyzed by microarray. Selected targets of miR-196a2 and differentially expressed genes identified by microarray were further validated by quantitative reverse-transcriptase PCR (qRT-PCR).

Results Polymorphism in miR-196a2 was found significantly associated with endometriosis in higher odds of susceptibility, infertility and severer pain. Small nucleolar RNAs (snoRNAs) and ribosomal proteins (RPs) were identified as the target of miR-196a2 in endometrium cells. The alteration of snoRNAs and RPs are associated with breast and lung cancers and therefore suggest the relation between endometriosis with those cancer.

Conclusion Polymorphism rs11614913 in miR-196a2 may serve as a biomarker to estimate the progression of endometriosis and to predict the potential of contracting lung or breast cancer. Government can establish public health policy to include this examination into healthcare, and promote examination campaigns as well.

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Genetic Variations in miR-196a2 Determine Endometriosis Development and are Associated with Malignant Transformation Potential

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Introduction

Endometriosis is a gynecological chronic disease affecting 6-10% women of reproductive age which genetic predisposition plays a role in (Bullett, Coccia, Battistoni, & Borini, 2010). It occurs when tissue from the uterine lining attaches to organs in the pelvis and begins to grow outside the uterine cavity. This displaced endometrial tissue may cause dysmenorrhea – or severe menstrual cramps – pelvic pain, and infertility. Dysmenorrhea can affect work of female labors, which number more than 5 million in Taiwan (Manpower Survey Results in October 2013, 2013). To address this problem that may also influence every family and even our society, the revision earlier in last November gives women employees three extra days of menstrual leave. ("The Act of Gender Equality in Employment," 2013)

Endometriosis is classified into one of four stages (I-minimal, II-mild, III-moderate, and IV-severe) depending on location of endometriosis implants, severity of adhesions, and size of ovarian endometriomas. Endometriosis may be resulted from the deficiency to clear uterine lining and blood entering the pelvis during each menstrual period; however, the exact etiology of endometriosis remains unknown. (Endometriosis: A Guide for Patients, 2012)

Since there is no cure for endometriosis, what interventions currently practiced are treatment of pain and infertility. Managements are the following. First, surgery such as laparoscopy excise ectopic endometrium (Endometriosis and Infertility: Can Surgery Help?, 2012). However, pregnancy might not occur after laparoscopic treatment, so *in vitro* fertilization would be an option to improve fertility (Yeung, Shwayder, & Pasic, 2009). Second, hormonal medication such as Progesterone inhibits the growth of the endometrium, and oral contraceptives reduce the menstrual pain (Harada, Momoeda, Taketani, Hoshiai, & Terakawa, 2008). Last but not least, opioid painkillers and anti-inflammatory drugs provide pain control (Endometriosis: A Guide for Patients, 2012).

Though endometriosis is a benign lesion, its pathological characteristics that attach to, invade and damage affected tissues resembles cancer (Jiang & Wu, 2012; Vlahos, Economopoulos, & Fotiou, 2010; Vlahos, Kalampokas, & Fotiou, 2010). Furthermore, numerous epidemiologic studies have shown an increased risk of women with endometriosis to develop epithelial ovarian cancer (EOC), which is the most frequent cause of gynecologic malignancy-related mortality in women (Brinton, Gridley, Persson, Baron, & Bergqvist, 1997; Kobayashi et al., 2007; S. Kumar et al., 2011; Melin, Sparen, Persson, & Bergqvist, 2006; Ogawa et al., 2000; Vercellini et al., 1993; Vlahos, Economopoulos, et al., 2010; Yang et al., 2008). Recent research in the relation between endometriosis and ovarian cancer proved that there is a prevalence of ovarian cancer in 2.0-17.0% of women with endometriosis. Conversely, the prevalence of endometriosis in women with ovarian cancer ranged from 3.4 to 52.6% (Heidemann, Hartwell, Heidemann, & Jochumsen, 2013). However, the pathway of endometriosis-associated ovarian carcinoma (EAO) developing remains scarcely understood.

Normal life and well-being of patients is deprived by endometriosis, though little can they do to prevent suffering or to avoid susceptibility to EAO. On the other hand, medical professionals could try their best to find out the correct treatment for individual and clearly explain the usage of drugs, yet, they still can't cure endometriosis so far. Moreover, unable to stop the development of endometriosis means considerable costs of drugs, injections, and more surgeries are needed. Treatment of EAO even costs more. Those are burdens for the expenses of healthcare in Taiwan and meanwhile our government. The vital key to cure endometriosis and make clear the relation between endometriosis and malignancies lies in scientific research. Thus, we try to find out factors involved in deterioration of endometriosis and associated ovarian tumorigenesis at molecular level.

MicroRNAs (miRNAs) are a set of short non-coding endogenous RNAs, which act as post-transcriptional regulators. Targeting mRNAs by miRNAs may accelerate degradation of these mRNAs or repress their translation, depending on the extent of complementarity between the target site and the miRNA (Bagga et al., 2005; Giraldez et al., 2006; Hutvagner & Zamore, 2002; Lim et al., 2005; Rehwinkel, Behm-Ansmant, Gattfield, & Izaurralde, 2005). Previous microarray and functional studies have revealed that miRNA expression levels are related to benign conditions, malignant diseases or fertility disorders in female reproductive tract (Carletti & Christenson, 2009; Nagaraja et al., 2010; Pan & Chegini, 2008; Teague, Print, & Hull, 2010; Zhang et al., 2010). In addition, single-nucleotide polymorphisms (SNPs) in miRNA sequences that may affect miRNA biosynthesis is associated with various cancer susceptibilities as well (M. S. Kumar, Lu, Mercer, Golub, & Jacks, 2007; Landi et al., 2008; Lowenberg, 2008; Peng et al., 2010; Sethupathy & Collins, 2008; Yu et al., 2007).

Until now, no study has yet established a link between polymorphisms within miRNA genes and endometriosis. Given previous strong indication of genetic predisposition of endometriosis (Hadfield, Mardon, Barlow, & Kennedy, 1997; Kennedy, 1998; Simpson & Bischoff, 2002; Teague et al., 2010), we believe that certain miRNA polymorphisms might be a crucial epigenetic factor presetting susceptibility to endometriosis. Our study reveals an endometriosis-related SNP and its novel function in regulating the production of small nucleolar RNAs, which may lead to malignant transformation.

Small nucleolar RNAs (snoRNA) are suggested to mediate post-transcriptional editing of ribosomal RNAs (rRNAs) or spliceosomal RNAs (Kiss, 2002). SnoRNAs are divided into two major classes with distinct their signature sequences: box C/D or box H/ACA snoRNAs (Kiss, 2001). The box C/D and box H/ACA snoRNAs engage 2'-O-methylation and pseudouridylation of rRNAs through their complementary recognition sequences, as guiding components of small ribonucleoprotein particles (snoRNPs) (Reichow, Hamma, Ferre-D'Amare, & Varani, 2007). Ribosome biogenesis is especially crucial for cell cycle progression coming with extensive protein translation activities, thus perturbation of ribosome assembly can cause proliferation arrest, which had been implicated in malignant diseases (McMahon, Ayllon, Panov, & O'Connor, 2010). Our study unveiled a subgroup of rather novel small non-coding RNAs may have been working behind the scene during endometriosis development.

Material and Methods

Study population. The study population consisted of 194 individuals who were pathologically diagnosed with endometriosis and underwent laparotomy or laparoscopy at China Medical University Hospital in Taiwan. Disease-related fertility status was verified by clinical report from all the cases. Definition of endometriosis stage was based on the classification of the American Society of Reproductive Medicine. The control group consisted of 202 women with matching age profile, who received regular physiological check and proved to be healthy based on examines conducted. This study was approved by the Institutional Review Board at China Medical University with patient consent from each individual.

Genotyping of single nucleotide polymorphisms. Genomic DNA was extracted from peripheral blood leukocytes according to standard protocols (Genomic DNA kit; Qiagen, Valencia, CA, USA). DNA fragments containing the SNP sites were amplified by PCR using the *Taqman* SNP genotyping assay system (Applied Biosystems Inc., Carlsbad, CA, USA). The probe IDs for the 8 SNPs tested were listed in Supplementary Table 1. A perfect match between the probe and the tested DNA fragment generated a positive signal. Genetic variations were detected by reading the fluorescence signals of the PCR products.

Statistical analysis. The allelic frequency and genotype frequency distributions for the 8 SNPs of endometriosis patients and controls were performed by χ^2 analysis using SPSS software (version 10.0, SPSS Inc. Chicago, IL, USA). Allelic and genotypic frequencies are expressed as percentages of the total number of alleles and genotypes. Odds Ratios (ORs) were calculated for allelic and genotypic frequencies with 95% confident interval (95% CI), using the most frequent allele as references. Adherence to the Hardy-Weinberg equilibrium constant was checked by χ^2 test with one degree of freedom by PLINK program (Purcell et al., 2007). Combined risk analysis for abnormal CA125 levels were analyzed by one-way ANOVA, and plotted by using GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA, USA, www.graphpad.com).

Cell culture, transfection and sorting. Vector pCMV-MIR (Origene, Rockville, MD) including a green fluorescent protein (GFP) reporter gene was used to construct the miR-196a2-C plasmid. A C to T mutation was introduced to the miR-196a2 plasmid at rs11614913, generating miR-196a2-T, by using the QuikChange II site-directed mutagenesis kit (Agilent Technologies, Inc.; Santa Clara, CA). Sequence of the resultant vector was verified by sequence analysis. For transfection analysis, 5×10^6 HEC-1-A cells were seeded in 6-cm dish and transfected with each plasmid, using the Lipofectamine system (Invitrogen) directed by manufacturer's protocol. G418 (Sigma-Aldrich, St. Louis, MO) were added to culture medium at 24h post-transfection to select positively transfected cells.

For quantitative reverse transcription polymerase chain reaction analysis (qRT-PCR), cells were sorted by their GFP levels via flow-cytometry, retaining over 90% positively transfected cells for RNA extraction. At 48h post-transfection, cells were removed, washed and resuspended in PBS and selected by GFP fluorescence using a FACS Canto flow cytometer (Becton Dickinson, San Jose, CA) with a retaining ratio of about 15%. The transfection efficiencies were rechecked by counting fluorescent cells under microscope before and after cell sorting. To measure cell growth, 5×10^6 cells were plated at 48h post-transfection and maintained for five days with G418 in medium.

Microarray experiment. Total RNA was prepared from the sorted cells with TRIzol Reagent (Invitrogen) following manufacturer's protocol. The quality of extracted RNA was assessed by the Agilent Bioanalyzer (Agilent Technologies). 150ng of total RNA from each sample was processed for reverse transcription, fragmentation and hybridization onto GeneChip® human gene 1.0 ST Array (Affymetrix Inc, Santa Clara, CA) according to the manufacturer's protocol and scanned. Raw gene expression data in the generated CEL files were then normalized and processed by using dChip (Li & Wong, 2001). Further clustering and visualization were performed by using TM4 (Saeed et al., 2003).

Results

Association between risk and SNPs. Seven SNPs located within either pri-miRNA or pre-miRNA regions are known to be associated with various cancers (Supplementary table 1). We genotyped the patients and control population in these seven SNPs to analyze their correlation with endometriosis. Two of these SNPs, namely rs11614913 located in pre-miR-196a2 and rs7372209 in pri-miR-26a-1, were found to be significantly associated with endometriosis risk (Table 1). The C allele of rs11614913 within pre-miR-196a2 is associated with increased endometriosis risk (OR = 1.63, 95% CI = 1.23-2.17, $p = 5.0 \times 10^{-4}$), even after the correction of multiple comparisons ($p = 3.5 \times 10^{-3}$) (Table 1). Further analysis of it linked patients with CC or CT genotypes to higher risk of endometriosis (OR = 2.45, 95% CI = 1.54-3.91, $p = 1.4 \times 10^{-4}$), suggesting a dominant way of its influence on endometriosis susceptibility (Table 2). The T allele of rs7372209 in pri-miR-26a1 is also associated with increased endometriosis risk (OR = 1.42, 95% CI = 1.06-1.92, $p = 0.018$) (Table 1), but the risk is significantly reduced for individuals with at least one protective C allele (OR = 0.43, 95% CI = 0.25-0.86, $p = 0.014$) (Table 2).

Association between clinical phenotype and SNPs. Four common phenotypes associated with endometriosis were analyzed with SNPs, including infertility, stages, CA125 levels and pain scores (Table 3). The C allele of rs11714913 within pre-miR-196a2 is significantly associated with higher odds of infertility (OR 95% CI = 1.14-3.84, $p = 0.016$) and severe pain (OR 95% CI = 1.13-2.69, $p = 0.012$) (Table 3).

Polymorphism in miR-196a2 affects the expression on snoRNAs and RPs. To understand the downstream effects, miR-196a2 with either C or T allele was transfected into HEC-1-A cell line. The expression profile of transfected cells was measured by microarray. A number of snoRNAs underwent high level of fold change, with most of them overexpressed (fold change > 1.5) in miR-196a2 with C allele (Fig. 1 A). Interestingly, the corresponding expressions of 32 ribosomal proteins (RPs) in this cell line were moderately elevated (fold change > 1.3), which represented nearly half of human ribosomal protein family (Fig. 1 B).

Validating expressions of snoRNAs and RPs. The result of microarray was confirmed by qRT-PCR with specific primers. The validation appears to be consistent with the patterns in microarray data in general, with less fold change of SNORD45A, SNORD 54 and RPS29 (Fig. 2 A & B).

Discussion

The Polymorphism rs11614913 in pre-miR-196a2 locates within the stem of the pre-miRNA, implying a chance to influence on the production of the mature miRNA (Iwai & Naraba, 2005). In the results, there is a significant correlation between miR-196a2 and endometriosis. The polymorphism leads to a certain fold change in snoRNA and RPs expression. The overall increase of snoRNA and RPs may enhance ribosome activity, alter cell proliferation and expansion of endometrium and then cause deterioration in endometriosis, although their tissue specificity and detailed function is still unidentified.

The CC genotype of miR-196a2 rs11614913 polymorphism is also found associated with an increased breast cancer risk in homozygote comparison and dominant model (Gao et al., 2011). Several independent signs of evidence have indicated that these non-coding RNAs might play crucial roles in controlling cell behavior, and snoRNA dysfunction could consequently contribute to oncogenesis in previously unsuspected ways (Williams & Farzaneh, 2012). Therefore, these changes in our data could be linked to cancer. For instance, SNORD44 is known as a tumor suppressor in breast cancer and found down-regulated in C allele of miR-196a2 (Gee et al., 2011); SNORD33 and SNORD76 serve as oncogenes in non-small cell lung cancer (NSCLC) and appear to be significantly up-regulated in C allele (Liao et al., 2010). To sum up, snoRNA is affected by miR-196a2 polymorphism and the alteration of snoRNA leads to higher chance of cancer, which is consistent with the previous study on miR-196a2 polymorphism, suggesting it to be a candidate mechanism of carcinogenesis resulted from the miR-196a2.

Because breast and ovary are both gland, their mechanisms of carcinogenesis may be similar. Throughout the experiment results, however, the way how endometriosis develops into ovarian cancer still remains unclear. Studies in epidemiology support the correlation between them, but our analysis of CA125 is not able to confirm it, suggesting that there might be other factors for malignant transformation. Noteworthy, CA125 parameter in early screening of early stage in ovarian cancer is unspecific (Sarsari, Coukos, & Scholler, 2009), and thus the result cannot be viewed as an opposite evidence of our postulate that endometriosis is associated with ovarian tumorigenesis. Other analytic methods might be needed for further validation.

Considering the high relation among endometriosis, its deterioration, risk of various cancer and polymorphism in miR-196a2, it is suggested for patients with endometriosis to conduct genotyping in rs11614913 polymorphism. With this information provided, medical professionals can provide personal medication based on different genotypes of endometriosis patients.

Conclusion

Polymorphism rs11614913 in miR-196a2 plays a role in network of progression and malignant transformation. With the correlation among endometriosis, its deterioration, and risk of various cancers, the polymorphism might be able to serve as a biomarker for endometriosis patients to estimate the progression of the disease and to predict the potential of suffering lung or breast cancer. After more experiments are conducted to prove our findings, specific probe can be designed to examine genes of patients. Medical professionals can suggest that their patients with endometriosis should do gene examination. Then, patients of endometriosis can take gene examination and seek medical advice on the best treatment for them. Besides, government can establish public health policy to include this examination into healthcare, and promote examination campaigns as well. Furthermore, society should give patients more understanding and practical help such as menstrual leave. Last but not least, as medical students, we can not only master clinical knowledge, but also devote ourselves to medical research to help solving clinical problems.

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Figures and Tables

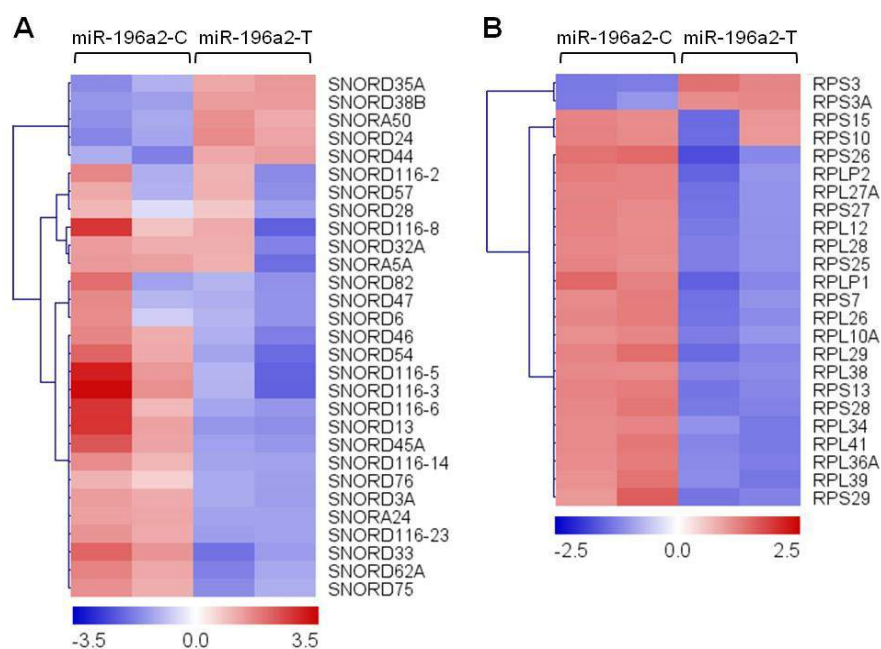


Figure1.

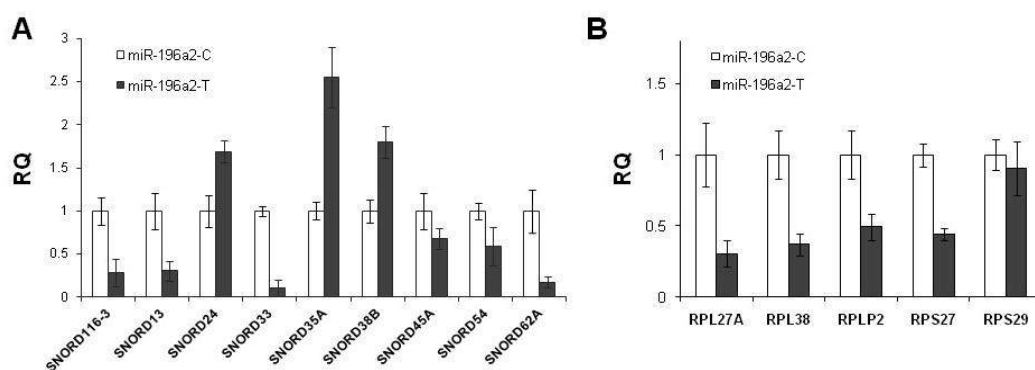


Figure2.

Table 1. Allele distributions of miRNApolymorphisms in Taiwanese endometriosis patients and controls

miRNA	SNP	MAF ^a		OR ^a	95% CI ^a	Nominal P-value ^b	Corrected P-value ^c
		cases (n=194)	control (n=202)				
miR-100	rs1834306	42.2	47.5	0.81	0.61-1.07	0.13	0.91
miR-146a	rs2910164	38.5	41.0	0.80	0.47-1.38	0.49	1.00
miR-196a2	rs11614913	55.2 ^d	42.8 ^d	1.63 ^d	1.23-2.17	5.0×10 ⁻⁴ *	3.5×10 ⁻³ *
miR-26a1	rs7372209	36.2	28.5	1.42	1.06-1.92	0.018*	0.13
miR-27a	rs895819	24.2	27.7	0.83	0.60-1.15	0.27	1.00
miR-423	rs6505162	21.2	19.6	1.08	0.76-1.52	0.56	1.00
miR-499	rs3746444	20.6	19.4	1.08	0.76-1.53	0.68	1.00

^aMAF, minor allele frequency; OR, odds ratio of minor alleles with reference to major alleles;

95% CI, 95% confidence interval.

^bP-values were calculated by χ^2 test.

^cBonferroni method was applied for multiple test correction.

^dThe minor C allele of rs11614913 in Chinese Han population is defined as the reference allele by HapMap and the corresponding OR shown above is estimated for C allele.

*Statistical significant ($P < 0.05$).

Table 2. Genotype distribution of miRNA polymorphisms in Taiwanese endometriosis patients and controls

SNP (miRNA)	Genotype	No. (%) of patients	No. (%) of control	P-value ^a	OR(95% CI)
rs1834306 (miR-100)	AA	33 (17.2)	42 (20.8)	0.27	0.65 (0.36-1.16)
	AG	96 (50.0)	108 (53.5)		0.73 (0.46-1.16)
	GG	63 (32.8)	52 (25.7)		1.00
	AA+AG	129 (67.2)	150 (74.3)	0.12	0.71 (0.46-1.10)
	GG	63 (32.8)	52 (25.7)		1.00
rs2910164 (miR-146a)	GG	38 (19.9)	32 (15.9)	0.41	1.43 (0.81-2.53)
	CG	76 (39.8)	76 (37.8)		1.21 (0.78-1.87)
	CC	77 (40.3)	93 (46.3)		1.00
	GG+CG	114 (59.7)	108 (53.7)	0.23	1.27 (0.85-1.90)
	CC	77 (40.3)	93 (46.3)		1.00
rs11614913 (miR-196a2)	CC	55 (28.7)	42 (20.9)	6.1×10 ⁻⁴ *	2.66 (1.62-4.35)
	CT	102 (53.1)	88 (43.8)		2.35 (1.43-3.86)
	TT	35 (18.2)	71 (35.3)		1.00
	CC+CT	157 (81.8)	130 (64.7)	1.4×10 ⁻⁴ *	2.45 (1.54-3.91)
	TT	35 (18.2)	69 (35.3)		1.00
rs7372209 (miR-26a-1)	TT	32 (16.6)	17 (8.4)	0.042*	2.28(1.17-4.44)
	CT	76 (39.4)	82 (40.6)		1.12(0.73-1.72)
	CC	85 (44.0)	103 (51.0)		1.00
	CC+CT	161 (83.4)	185 (91.6)	0.014*	0.43 (0.25-0.86)
	TT	32 (16.6)	17 (8.4)		1.00
rs895819 (miR-27a)	CC	15(7.7)	16 (8.0)	0.42	0.85 (0.39-1.85)
	CT	60 (34.5)	81 (40.7)		0.75 (0.49-1.15)
	TT	112(57.7)	102 (51.3)		1.00
	CC+CT	82 (42.3)	97 (48.7)	0.20	0.77 (0.52-1.15)
	TT	112 (57.7)	102 (51.3)		1.00
rs6505162 (miR-423)	AA	12 (21.7)	9 (4.5)	0.74	1.43 (0.56-3.65)
	AC	58 (42.0)	61 (30.2)		1.02 (0.66-1.58)
	CC	123 (36.4)	132 (65.3)		1.00
	AA+AC	70 (36.3)	79 (34.7)	0.74	1.07 (0.71-1.62)
	CC	123 (63.7)	131 (65.3)		1.00
rs3746444 (miR-499)	CC	31(21.7)	26 (17.6)	0.44	1.47 (0.78-2.77)
	CT	60 (42.0)	58 (39.2)		1.22 (0.76-2.13)
	TT	52(36.4)	64 (43.2)		1.00

Table 3. Association between polymorphisms in miRNAs and endometriosis clinical phenotypes^a.

SNP	<i>Infertility</i>		<i>Stage 1/2</i>		<i>CA125 >35</i>		<i>Pain score ≥5</i>	
	<i>VS. non-infertility</i>		<i>VS. stage 3/4</i>		<i>VS. CA125 ≤35</i>		<i>VS. pain score <5</i>	
	<i>P-value^b</i>	<i>OR 95%CI^b</i>	<i>P-value^b</i>	<i>OR 95%CI^b</i>	<i>P-value^b</i>	<i>OR 95%CI^b</i>	<i>P-value^b</i>	<i>OR 95%CI^b</i>
rs11614913 (miR-196a2)	0.016*	1.14-3.84	0.86	0.46-1.92	0.094	0.93-2.55	0.012*	1.13-2.69
rs7372209 (miR-26a1)	0.84	0.51-1.74	0.22	0.22-1.43	0.15	0.36-1.17	0.18	0.86-2.23

^aAssociation tests are based on allele distributions.

^b*P*-values were calculated by χ^2 test. 95% confidence intervals of odd ratios are calculated for minor alleles with reference to major alleles.

*Statistical significant (*P* < 0.05).

Supplementary table 1. Summary of previously reported cancer-related miRNA polymorphisms.

SNP	Location in miRNA	Associated cancer type	PubMed ID	Allele frequencies ^a (%)	ABI probe ID
rs1834306	Pri-miR-100	Colon	20585341	A: 43 G: 57	C__11483095_10_F
rs2910164	Pre-miR-146a	Gastric	22455393	G: 43 C: 57	C__15946974_10
		Lung	22818121		
		Breast ^a /ovarian	18660546		
rs11614913	Pre-miR-196a2	Breast ^a	19567675	C: 45 T: 55	C__31185852_10
		Lung	19293314		
		liver	21692953		
rs7372209	Pri-miR-26a1	Colon	20585341	T: 32 C: 68	C__29123986_10
rs895819	Pre-miR-27a	Gastric	20666778	C: 29 T: 71	C__11483095_10_F
		Breast	19921425		
rs6505162	Pre-miR-423	Breast	22593246	A: 16 C: 84	C__11613678_10
rs3746444	Pre-miR-499	Head and neck	20549817	C: 17 T: 83	AHQIU1L ^b
		Breast	18634034		

^a Allele frequencies provided by HapMap database for Han Chinese in Beijing.

^bCustom designed probe.

SCIENTIFIC PAPER COMPETITION – THAILAND

THAILAND

DIALYSIS PATIENTS' CONCERNS ON WELL-BEING, AND MEDICAL STUDENTS': ARE WE ON THE SAME PAGE?

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ABSTRACT

Background

With the universal health coverage regime in Thailand on the rise, the country has invested a large amount of money on renal replacement therapy. Most patients fall under either peritoneal dialysis or hemodialysis, both of which are known to have great effects on their quality of life. Nephrologists, internists are the main care providers for specific and technical support, but general practitioners, consisting of newly graduated medical students, also play a vital role in improving the patients' quality of life. This study aims to identify if the concerns medical students have, in regards to dialysis patients' quality of life, match the problems identified by the patients themselves.

Methodology

In 2013, a self-administered questionnaire developed by the researchers was given to year-5 and year-6 medical students practicing at King Chulalongkorn Memorial Hospital to evaluate their opinions on 11 different areas of dialysis patients' quality of life according to KDQOL-SFTM. Ranking of these areas were done to reflect the level of concerns by medical students. The final ranking was then used for comparison with the already-existing PhD dissertation on dialysis patients' quality of life to detect any similarities or discrepancies.

Results

A total of 213 questionnaires were obtained and analyzed (year-5 47.85%, year-6 51.17%). In comparison to KDQOL-SFTM done by dialysis patients prior to this study¹, the medical students' concerns and the patients' problems did not match. Among the 11 areas of quality of life in compliance with KDQOL-SFTM, top three problems identified by the patients were 'work status', 'burden of kidney disease' and 'sexual function'. For the medical students, the first three were 'effects of kidney disease', 'symptoms' and 'social support', while 'work status', 'burden of kidney disease' and 'sexual function' came seventh, third and eleventh, respectively. The correlation between the 2 rankings was 0.055 with a *p*-value of 0.873.

Conclusion

Medical students expressed significantly different concerns, which could result in ineffective improvement of dialysis patients, with reference to the quality of life. In order to prepare new generations of general practitioners, patients' concerns and problems on quality of life should be incorporated into the curriculum or new teaching strategies.

1. Srisubat, A. (2012). *Cost-effectiveness analysis of microalbuminuria screening in type 2 diabetic patients*. (Doctoral dissertation).