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"One that would have the fruit must climb the tree."

Thomas Fuller (1608 – 1661)
English clergyman

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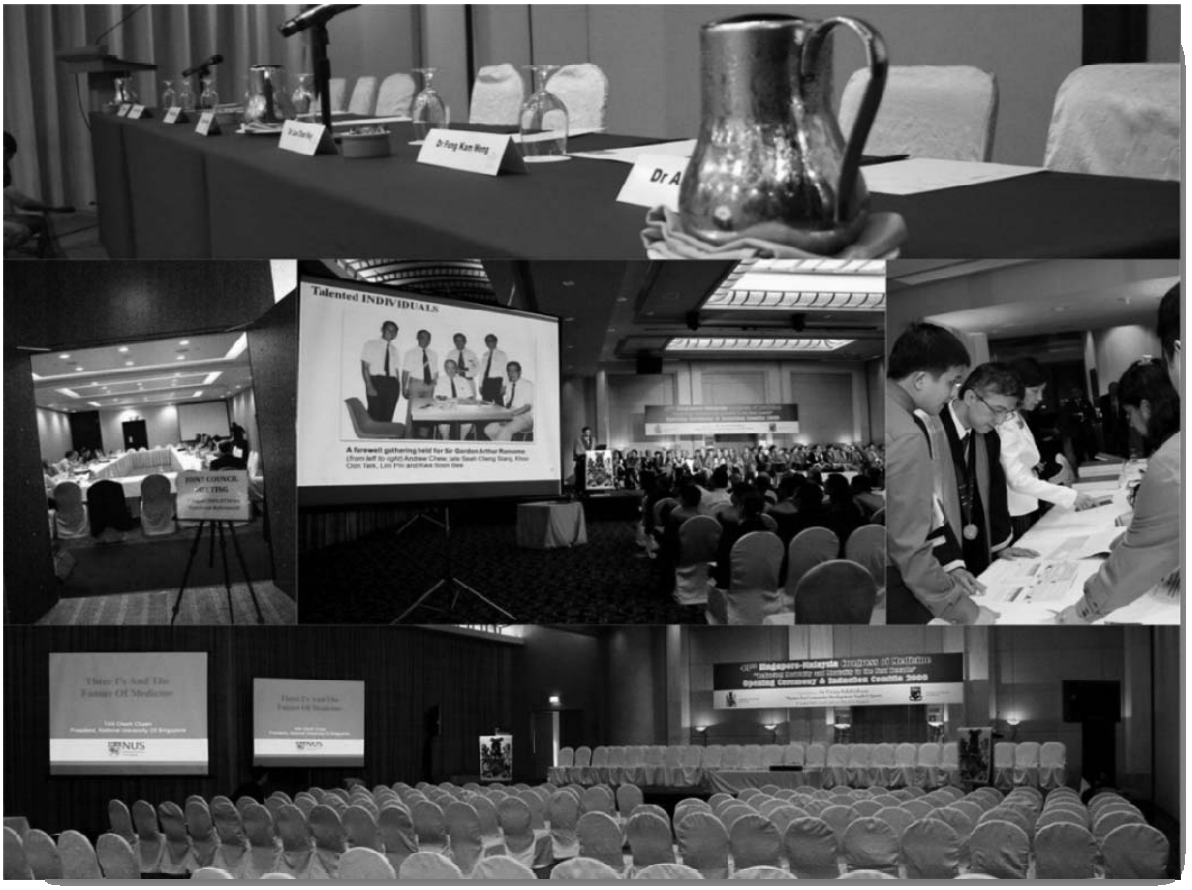

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Editorial

World Antibiotic Awareness Week

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World Antibiotic Awareness Week falls on 13 to 19 November this year, the fifth since its inception in 2013.[1] This World Health Organization (WHO) annual campaign had its genesis in 2 separate events that both began in 2008 – the European Antibiotic Awareness Day and the United States' Centers for Disease Control and Prevention's (CDC's) Get Smart About Antibiotics Week. It aims to increase public awareness of antibiotic resistance as well as antibiotics as a precious and finite resource.[1]

Alexander Fleming's serendipitous discovery of penicillin in 1928 helped to usher in a golden age of antibiotic discovery, which lasted until the late-1980s.[2] What is less well known is that he was also the first to warn the world about antibiotic resistance. In his Nobel Award lecture, Fleming described the ease with which he could make microbes resistant to penicillin in his laboratory,[3] and in a subsequent interview in the New York Times in 1945, sounded the alarm that "the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism". However, this warning went unheeded in the years of antibiotic plenty, and antibiotics have become almost a fundamental necessity in human society.

Antibiotics convey upon humanity the ability to prevent and treat most bacterial infections. They have been the bedrock without which many other modern medical interventions such as joint replacement surgery, cancer chemotherapy and organ transplantation will extract such a high toll in terms of death and disability that they will rightfully be attempted only for the most extreme of cases. They are also an important contributor towards the availability of cheap animal protein, upon which we are increasingly reliant.[4,5] When used in small quantities in animal feed, antibiotics act as growth promoters that increase daily growth rates by up to 10%, with meat containing less fat and increased protein.[4] Globally, more antibiotics are used in animals than in humans, and this difference is set to widen if current trends are not reversed.[6]

Over the past decades, the rates at which bacteria have become resistant to antibiotics have accelerated even as the antibiotic pipeline has slowed. In Singapore, our hospitals have seen rising rates of carbapenem-resistant Enterobacteriaceae since 2010,[7] as well as sporadic human cases of polymyxin-resistant *Escherichia coli* harbouring the *mcr*-1 gene first discovered in food animals in China.[8] A medical student community health project completed last year showed community carriage rates of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae that exceeded 25% (personal communication: A/Prof Alex Cook)—a marked jump from the 12.4% reported in an older study in 2006.[9]

A term first used in social policy planning, a "wicked problem" is an issue that is not easy to understand or resolve because of contradictory, variable and incomplete factors that may not be fully recognised. In this aspect, antimicrobial resistance is a classical "wicked problem"; there is no single solution to this crisis, and no perfect solution that comes without cost.[10] It is important to understand that antimicrobial resistance is an evolutionary response that cannot wholly be stopped or reversed, only slowed at best. The Global Antibiotic Research & Development Partnership (GARDP) was established last year by the WHO and the Drugs for Neglected Diseases Initiative (DNDi) to develop new antibiotic treatments,[11] but it will be at least a decade before these new antibiotics reach the market. Other measures include investments in new vaccines (one of the strategic initiatives of the Bill and Melinda Gates Foundation) and increasing their uptake, improving infection prevention practices and improving the appropriate prescription of antibiotics via antibiotic stewardship or healthcare worker education. In addition, there are now efforts to develop rapid diagnostics to differentiate between viral and bacterial infections within an hour, hence reducing the unnecessary use of antibiotics. Outside of the medical field, there are also measures to improve agricultural practices to reduce dependence on antibiotics, and incorporating concepts of antibiotics and antimicrobial resistance into the school education curriculum.

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Multiple studies have shown that 30% or more of antibiotic prescriptions are either unnecessary or the antibiotics were wrongly selected.[12] The optimal duration of treatment for most infections is also unknown, although the majority of newer studies suggest that the duration of treatment for many bacterial infections can be safely shortened.[12] The difficulty of crafting public messages or even those for healthcare workers based on such nuanced understanding has recently again been highlighted by the backlash to Dr Martin Llewelyn and co-workers' article in the British Medical Journal, provocatively titled, "The antibiotic course has had its day".[12] The deep divide even among healthcare workers and experts is most readily seen in the readers' responses to the article, which are helpfully available online.[12]

On a positive note, however, such debate is healthy and elevates the issue of antibiotic prescription and resistance temporarily into the public domain and consciousness. A path towards clearer messaging and education can hopefully be found in the future when better evidence is available and more minds are focused on the issue.

In summary, antibiotics remain a finite resource that underpins much of medical progress and capability, as well as cheap animal protein. The advent and increasing pressure of antimicrobial resistance has eroded some of the gains brought about by the easy availability of antibiotics, and threatens greater future human suffering and financial costs. Although no simple or clear solutions are available in the short term or perhaps even distant future, greater public awareness has resulted in more resources being directed to this global public health issue. This is a cause for optimism for the future.

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Editorial

Chronic Obstructive Pulmonary Disease (COPD): "Not a Cigarette Only Pulmonary Disease"

Augustine KH Tee, [1] *MBBS, FCCP, FRCP (Edin & Glasg)*

Since 2002, World COPD Day is celebrated yearly in November to raise awareness of Chronic Obstructive Pulmonary Disease (COPD) globally. 'The Many Faces of COPD' is the World COPD Day 2017 theme, chosen by The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a World Health Organization collaborative. This serves a simple and timely reminder of the multifaceted challenge faced by healthcare professionals, and more importantly by COPD sufferers and their caregivers. Even with the explosion of literature on COPD in the last two decades, much is still uncertain regarding its pathophysiology, diagnosis, optimal treatment and prognosis in a disease that is increasingly recognised as a heterogenous entity.

In 1971, the first description of COPD in Singapore had 54 Chinese opium smokers who were all cigarette smokers.[1] Their morbid anatomy, however, differed from pure cigarette smoking bronchitis and varied from bronchiectasis, emphysema to peri-bronchiolar fibrosis. Physiological abnormalities were varied among the individuals.

This early publication hinted at the non-uniform nature of the disease. Indeed, the standard definition of COPD by GOLD has changed every few years since the first GOLD report in 2001. GOLD 2017[2] defines COPD as "a common, preventable and treatable disease that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious gases or particles". Past definitions included terms such as 'chronic inflammation' and 'irreversible airway obstruction' which are inconsistently present in COPD, while demarcation into its two traditional distinct types of blue bloaters with chronic bronchitis versus emphysematous pink puffers appear too simplistic.[3]

Based on projections, COPD will be the third leading cause of death worldwide by 2030. Projected prevalence in Asia will be 3 times higher than the rest of the world. Despite this, accurate population prevalence rates have not been available to aid healthcare resource planning and guide government medical spending. Local data estimates prevalence to be between 3.5% to 5.9%.[4,5] Underdiagnosis is common, due to lack of public awareness and low usage of spirometry, which is an essential component of COPD diagnosis. A public survey[6] conducted locally in 2015 during World COPD Day revealed that 65% have never heard of COPD. Of those who have heard, 90% were unaware of what COPD is, 28% incorrectly identified the commonest symptoms, 25% incorrectly identified COPD as a contagious disease, and 12.5% had the misconception that current or ex-smokers are not at a higher risk of COPD. In the face of such figures, COPD continues to be among the top 10 commonest cause of death in Singapore, and is a significant burden to our public health system. In a study from two public health clusters here in 2011, mean total cost was approximately USD$9.9 million per year with inpatient admissions being the major/main cost driver, contributing an average of USD$7.2 million per year.[7]

Is the prevention of COPD solely a matter of controlling cigarette smoking in the population? Evidence suggests that although cigarette smoking is the main risk factor for developing COPD, it is by far not the only risk. Tobacco in the form of cigar, water pipe and marijuana may be associated with similar risk. Chronic exposures to noxious vapour, gas, dust or fumes, especially in "dusty trades"[8] are also associated. Cigarette smokers without COPD have higher prevalence of respiratory symptoms such as cough, and demonstrate mild lung function abnormalities. Conversely, less than 50% of smokers have COPD.

About 10% of COPD patients have never smoked cigarettes. These patients tend to have milder forms of COPD with lower symptom severity, but nevertheless have similar prognosis to smokers with COPD. Hereditary alpha-1 antitrypsin deficiency and indoor air pollution from biomass are less relevant in urban Singapore. The influence of gender, age, occupational exposure, low socioeconomic status, low birth weight and severe childhood respiratory infections are known to place an individual at risk of acquiring COPD in adult life. Previously, it was thought that COPD developed due to a risk factor triggered accelerated lung function decline, starting from a maximally acquired adult lung function. A 2015 study on three large independent cohorts had studied the Forced

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Expiratory Volume in 1st second (FEV_1) decline over about two decades. It shed light for the first time that lung function trajectories may follow different paths leading to COPD. Half of the patients followed a well described trajectory of accelerated decline in lung function, but about half of the patients started with a low FEV_1 in early adulthood followed by a normal rate of lung function decline.[9] Genetic and prenatal factors can also play a role in giving rise to the early origins of airflow limitation, as do severe childhood asthma theoretically depicted in a 3-phase lung function decline, consisting of a lower than predicted lung function at birth, early childhood FEV_1 decline due to poor asthma control, followed by a more physiological decline in later adult life.[10] These concepts imply that COPD as a disease may begin in early life. As we explore the possibilities of interventions in early life, let us not forget that smoking cessation continues to be an intervention that can positively impact survival of COPD patients.

The need to investigate evolving risk factors do not negate the importance of other aspects of COPD care. Managing exacerbations, evaluating for comorbidities, pharmacotherapeutic advances, inhaler device management, patient phenotyping and biomarker endotyping are all aligned towards a move to personalised and precision medicine in COPD. Innovations in big data management and real-world effectiveness studies are under way to better utilise the interconnectivity of information systems in our public institutions.[11] It is indeed an exciting time for the disease that is not "cigarette only".

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Original Article

Effectiveness of Diabetes Foot Screening in Primary Care in Preventing Lower Extremity Amputations

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Abstract

Introduction: The risk of lower extremity amputations (LEAs) in diabetics is 20 times higher than in non-diabetics. Clinical practice guidelines recommend that all diabetics should receive an annual foot examination to identify high-risk foot conditions. Despite this recommendation, there is little evidence in the literature to show its effectiveness in preventing LEA. This study aims to evaluate the effectiveness of diabetes foot screening in primary care in preventing LEA and to identify LEA risk factors. Materials and Methods: This is a retrospective cohort study of diabetic patients who visited the National Healthcare Group Polyclinics for the first time from 1 January 2008 to 31 December 2012. The intervention of interest was foot screening performed at least once during 2 years of follow-up, and the outcome of interest was LEA (major and/or minor) performed during 2 years of follow-up. Patients who did foot screening (n = 8150) were compared to a propensity score matched control group (n = 8150) who did not do foot screening. Logistics regression was done to identify factors associated with LEA. Results: Among those who underwent foot screening, there were 2 (0.02%) major amputations and 15 (0.18%) minor amputations compared with 42 (0.52%) and 52 (0.64%) among those who did not (P <0.001). Conclusion: Lack of diabetes foot screening, lower socioeconomic status, hip fracture, Malay ethnicity, chronic kidney disease, poorer glycaemic control, longer diabetes duration and male gender have been found to be associated with a higher risk of LEA.

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Key words: Diabetes mellitus, Real-world, Singapore

Introduction

The prevalence of diabetes mellitus in Singapore has increased from 8.2% in 2004[1] to 11.3% in 2010[2] and is likely to increase to 15% in 2050.[3] Globally, the burden of diabetes both in terms of prevalence and number of adults affected has increased.[4] Diabetes mellitus is a disease known for its multifaceted complications, and foot ulceration, which often results in lower extremity amputations (LEAs)—one of the most common diabetes complications.[5] As the risk of LEAs in diabetics can be 20 times higher than in non-diabetics,[6] it is not surprising that there is an increasing trend in diabetes-related LEA in Singapore.[7] LEA can be further divided into major (ankle, through knee and up to hip amputations) and minor (foot and toes) amputations. LEA has high mortality (minor LEA: 1-year mortality 9.7% to 18.3%; major LEA: 1-year mortality 24.3% to 30.6%)[7] and substantial medical costs (minor LEA: S$5161; major LEA: S$9695),[8] highlighting the importance of primary prevention and early detection to prevent LEA.

Clinical practice guidelines recommend that all individuals with diabetes mellitus should receive an annual foot examination to identify high-risk foot conditions.[9,10] Despite this recommendation, there is weak evidence in the literature[11-13] to show that screening is effective in preventing diabetes-related LEA.

Since there is an increasing trend of diabetes-related LEA in Singapore,[7] our study aims to evaluate the effectiveness of diabetes foot screening in the primary care setting in preventing LEA and to identify risk factors for LEA.

Materials and Methods

Data Sources

National Healthcare Group (NHG) provides public healthcare services through an integrated network of 9 primary healthcare polyclinics, acute care and tertiary hospitals, national specialty centres and business divisions.[14] We obtained data from the NHG Diabetes Registry[15] which was launched in 2007. Details of how diabetic patients

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were identified have been described elsewhere.[15] In brief, patients with encounters in NHG from 2005 were identified for inclusion into the Diabetes Registry from existing stand-alone diabetes registries, ICD9CM diagnosis codes, anti-hyperglycaemic medication and laboratory confirmation.[15]

This was a retrospective cohort study. All resident diabetic patients residing in the central region of Singapore were eligible for the study. The study entry point for each patient was their first visit to any of the 9 NHG Polyclinics from 1 January 2008 to 31 December 2012. All patients were followed until their first LEA or 2 years from study entry, whichever is earlier. Patients with diabetes foot screening or LEA prior to study entry were excluded from the study. Patients with no LEA and who had died before the end of follow-up were also excluded.

Variables extracted from the NHG Diabetes Registry for the study included demographic data (age, gender and ethnicity), duration of diabetes mellitus, glycated haemoglobin (HbA1c), body mass index (BMI) and comorbid conditions. We also used Medifund (a medical endowment fund set up by the Singapore Government) status as a surrogate for low socioeconomic status as only needy patients who face financial difficulties with their medical bills will qualify for it.

Yearly diabetes foot screening in NHG Polyclinics comprised the following components: i) assessment of medical history and current symptoms (e.g. type of diabetes, date of diagnosis, latest HbA1c, history of ulceration or amputation, presence of paraesthesia or pins and needles, etc.); and ii) clinical examination (e.g. examination of the skin, vascular assessment, neurological assessment, presence of deformity).

Doppler reading of ankle-brachial index and toe-brachial index was done for all newly diagnosed diabetic patients at baseline and annually in patients with risk factors such as the following: i) age ≥50 years old; ii) history of smoking; iii) presence of ischaemic heart disease, transient ischaemic attack/cardiovascular accident, previous foot complications (ulcers, cellulitis); iv) presence of poor capillary refill (>3 seconds), absent pulses, intermittent claudication or rest pain; and v) presence of poorly controlled diabetes, hypertension or dyslipidaemia.

Based on the findings from the diabetes foot screening, patients would be risk stratified using the King's Classification[16] with low-risk patients seen yearly and patients with risk factors seen earlier (depending on their risk factors). Depending on the findings, patients may also be referred to the podiatrist for management of skin conditions, foot deformity or non-infected ulcer. For patients with more severe findings, they would be referred to the doctor for further management. This may lead to referral to specialists in tertiary hospitals, if necessary.

In this study, patients were assigned to the intervention group if they had at least one diabetes foot screening before any LEA during the 2 years follow-up period. Otherwise, they were assigned to the control group. As this was a retrospective study, we used propensity score matching[17,18] to balance the distribution of baseline characteristics between diabetic patients who went for foot screening and those who did not. We used baseline variables and logistic regression to obtain the probability of undergoing diabetes foot screening. From this, we predicted the probability for each diabetic patient to undergo foot screening (propensity score) and matched patients based on their propensity scores using a 1:1 matching and a caliper of width equal to 0.2 of the standard deviation of the estimated propensity scores.

After propensity score matching, multiple logistic regression analysis was then used to identify risk factors for LEA. We further divided LEA into major (above ankle, through knee and up to hip amputations) and minor (foot and toes) amputations as costs incurred for major and minor amputations were very different.

Statistical Analysis

Characteristics of the study population are described for categorical variables by n (%) and for continuous variable as the mean (standard deviation) if the distribution was normal and median (range) if the distribution was not normal. All analyses were conducted using STATA (StataCorp, College Station, TX, USA) statistical software, version 12.0.

Ethical Approval

The study was approved by the NHG's Domain-specific Ethics Review Board which is an independent committee constituting medical, scientific and non-scientific members. As this was a retrospective study using de-identified data, waiver of consent was granted.

Results

Description

A total of 26,173 patients were included in the analysis. Of these, 16,382 (62.6%) had undergone at least one diabetes foot screening during the follow-up period of 2 years while 9791 did not undergo any foot screening. Patients who underwent foot screening were younger, less likely to use Medifund subsidies, had shorter duration of diabetes mellitus and higher HbA1c compared to patients who did not undergo diabetes foot screening. In terms of comorbid conditions, those who underwent diabetes foot screening had higher prevalence of dyslipidaemia and hypertension, but lower prevalence of chronic kidney disease, coronary heart disease, stroke, asthma, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, osteoporosis, hip and spine fracture (Table 1).

Table 1. Patient Demographics

Variable	Foot Screening Done		*P* Value
	Yes (n = 16,382)	No (n = 9791)	
Age in years, mean (SD)	66.7 (12.0)	68.2 (14.5)	<0.001
Gender, n (%) Male	8229 (50.7)	5092 (52.1)	0.035
Ethnicity, n (%)			0.045
Chinese	12,659 (77.3)	7073 (72.2)	
Malay	1318 (8.1)	892 (9.1)	
Indian	1956 (13.2)	1494 (15.3)	
Others	781 (3.0)	332 (3.4)	
Medifund user, n (%)	1360 (8.3)	1393 (14.2)	<0.001
Duration of diabetes, median (range)	0.1 (0 to 45.4)	1.4 (0 to 43.5)	<0.001
HbA1c categories, n (%)			<0.001
Below 7.0	3804 (23.2)	1263 (12.9)	
7.0 – 7.9	1903 (11.6)	505 (5.2)	
8.0 – 8.9	898 (5.5)	266 (2.7)	
9.0 and above	1963 (12.0)	571 (5.8)	
Unknown	7814 (47.7)	7186 (73.4)	
BMI categories in kg/m^2, n (%)			<0.001
Risk of nutritional deficiency diseases and osteoporosis (<18.5)	198 (1.2)	164 (1.7)	
Low-risk (18.5 – 22.9)	2040 (12.5)	1130 (11.5)	
Moderate-risk (23.0 – 27.4)	4883 (29.8)	2086 (21.3)	
High-risk (≥27.5)	4364 (26.6)	1693 (17.3)	
Unknown	4897 (29.9)	4718 (48.2)	
Comorbid conditions, n (%)			
Dyslipidaemia	13,251 (80.9)	7261 (74.2)	<0.001
Hypertension	10,942 (66.8)	6408 (65.5)	0.026
Chronic kidney disease	2030 (12.4)	2011 (20.5)	<0.001
Coronary heart disease	2005 (12.2)	1897 (19.4)	<0.001
Stroke	1413 (8.6)	1073 (11.0)	<0.001
Asthma	502 (3.1)	493 (5.0)	<0.001
Atrial fibrillation	287 (1.8)	330 (3.4)	<0.001
Heart failure	278 (1.7)	518 (5.3)	<0.001
Chronic obstructive pulmonary disease	172 (1.1)	210 (2.1)	<0.001
Osteoporosis	179 (1.1)	184 (1.9)	<0.001
Transient ischaemic attack	155 (1.0)	117 (1.2)	0.055
Hip fracture	81 (0.5)	117 (1.2)	<0.001
Spine fracture	53 (0.3)	63 (0.6)	<0.001
Subarachnoid haemorrhage	9 (0.1)	6 (0.1)	0.836

BMI: Body mass index; HbA1c: Glycated haemoglobin

After propensity score matching, there were statistical differences in ethnicity, median duration of diabetes, HbA1c categories, BMI categories, prevalence of dyslipidaemia, hypertension and chronic kidney disease (Table 2).

Outcomes

During the follow-up period, there were a total of 111 LEAs. Major LEA (n = 44) accounted for 39.6% of LEA. Those who underwent diabetes foot screening had lower percentage of major LEA (0.02% vs 0.52%) and minor LEA

Table 2. Patient Demographics after Propensity Score Matching

Variable	Foot Screening Done		*P* Value
	Yes (n = 8150)	No (n = 8150)	
Age in years, mean (SD)	68.1 (12.4)	67.8 (14.4)	0.246
Gender, n (%) Male	4241 (52.0)	4226 (51.9)	0.814
Ethnicity, n (%)			0.045
Chinese	5904 (72.4)	6063 (74.4)	
Malay	735 (9.0)	688 (8.4)	
Indian	1228 (15.1)	1142 (14.0)	
Others	283 (3.5)	257 (3.2)	
Medifund user, n (%)	1016 (12.5)	950 (11.7)	0.112
Duration of diabetes, median (range)	0.2 (0 to 45.4)	1 (0 to 43.5)	<0.001
HbA1c categories, n (%)			0.003
Below 7.0	1128 (13.8)	1226 (15.0)	
7.0 – 7.9	437 (5.4)	493 (6.1)	
8.0 – 8.9	222 (2.7)	259 (3.2)	
9.0 and above	526 (6.5)	563 (6.9)	
Unknown	5837 (71.6)	5609 (68.8)	
BMI categories in kg/m^2, n (%)			<0.001
Risk of nutritional deficiency diseases and osteoporosis (<18.5)	137 (1.7)	127 (1.6)	
Low-risk (18.5 – 22.9)	1053 (12.9)	985 (12.09)	
Moderate-risk (23.0 – 27.4)	1777 (21.8)	1957 (24.0)	
High-risk (≥27.5)	1397 (17.1)	1594 (19.6)	
Unknown	3786 (46.5)	3487 (42.8)	
Comorbid conditions, n (%)			
Dyslipidaemia	5994 (73.6)	6185 (75.9)	0.001
Hypertension	5250 (64.4)	5384 (66.1)	0.028
Chronic kidney disease	1524 (18.7)	1400 (17.2)	0.011
Coronary heart disease	1459 (17.9)	1379 (16.8)	0.066
Stroke	893 (11.0)	847 (10.4)	0.243
Asthma	363 (4.5)	350 (4.3)	0.619
Atrial fibrillation	211 (2.6)	219 (2.7)	0.696
Heart failure	259 (3.2)	279 (3.4)	0.381
Chronic obstructive pulmonary disease	133 (1.6)	129 (1.6)	0.803
Osteoporosis	140 (1.7)	130 (1.6)	0.539
Transient ischaemic attack	98 (1.2)	97 (1.2)	0.943
Hip fracture	71 (0.9)	71 (0.9)	1.00
Spine fracture	46 (0.6)	43 (0.5)	0.750
Subarachnoid haemorrhage	8 (0.1)	6 (0.1)	0.593

BMI: Body mass index; HbA1c: Glycated haemoglobin

(0.18% vs 0.64%) compared to those who did not undergo foot screening (Table 3).

Risk Factors for LEA

Multivariate logistic regression analysis showed that patients who did not undergo foot screening had a 6.3-fold increased risk of a LEA compared to patients who underwent foot screening after adjustment for other risk factors. The other risk factors were Medifund user, hip fracture, chronic kidney disease, Malay ethnicity, male

Table 3. Lower Extremity Amputations by Screening Status

LEA	Foot Screening during Study Period	
	Yes (n = 8150)	No (n = 8150)
Major, n (%)	2 (0.02)	42 (0.52)
Minor, n (%)	15 (0.18)	52 (0.64)
Total, n (%)	17 (0.21)	94 (1.15)

LEA: Lower extremity amputation

gender, poor glycaemic control and increasing duration of diabetes (Table 4).

Discussion

Only 62.6% of diabetic patients had diabetes foot screening done at least once in 2 years. This figure is similar to another study done in Singapore that reported annual foot screening rates of 53% to 69.5%.[19] Internationally, diabetes foot screening rates in primary care environments vary from 50% to 86.7%[20-24] suggesting potential for increasing screening uptake.

There were differences in the percentage of both major and minor LEA between diabetic patients who underwent foot screening and diabetic patients who did not. From Table 3, we estimated that approximately 106 (95% CI, 84 to 145) patients need to be screened to prevent one LEA [(1/{1.15-0.21})*100]. Taking the unsubsidised cost of diabetes foot screening in Singapore to be S$50, the cost for screening 106 patients would be S$5300. The average cost for a minor LEA is S$5161 and the average cost for a major LEA is S$9695 in the local Singapore context. Thus, even if we screen 106 patients at a cost of S$5300 and avert one minor LEA, it would cost the healthcare system about S$139. However, if we can avert a major LEA (Table 5), we can save about S$4395. Thus it may be cost-saving to screen for diabetic foot from the healthcare providers' perspective, and this is also in accordance with current clinical practice guidelines.[9,10]

Table 4. Risk Factors for Lower Extremity Amputation

Risk Factor	Odds Ratio (95% CI)
No diabetes foot screening	6.3 (3.7 – 10.6)
HbA1c categories	
Below 7.0	Reference
7.0 – 7.9	2.1 (0.7 – 6.1)
8.0 – 8.9	3.9 (1.4 – 11.1)
9.0 and above	5.6 (2.3 – 13.2)
Unknown	2.0 (0.9 – 4.4)
Medifund user	4.0 (2.7 – 5.9)
Hip fracture	3.7 (1.1 – 12.5)
Ethnicity	
Chinese	Reference
Malay	2.2 (1.3 – 3.6)
Indian	1.0 (0.6 – 1.8)
Others	1.0 (0.3 – 3.2)
Chronic kidney disease	1.8 (1.2 – 2.8)
Duration of diabetes	1.1 (1.0 – 1.1)
Gender	
Male	Reference
Female	0.6 (0.4 – 0.9)

HbA1c: Glycated haemoglobin

Medifund status was associated with higher risk for LEA which is consistent with findings that lower socioeconomic status is associated with diabetes-related foot diseases and LEA.[25-28] Chronic kidney disease, poorer glycaemic control and longer duration of diabetes were associated with higher risk for LEA which is consistent with other studies.[29-33] Efforts can be made to improve glycaemic control and diabetes foot education in these high-risk groups to prevent LEA.

The strength of this study is as follows: we have a relatively large population of diabetic patients in a multiethnic Asian population with a follow-up period of 2 years. Our study entry period spans across 5 years, from 2008 to 2012.

This study has some limitations. This is a retrospective study and variables not captured at the start of the study such as smoking status, dietary habits and presence of foot ulcers would not be able to be used for analysis. Our diabetic patients might have gone for foot screening in private clinics and this would not be captured by our system. Similarly, they might have LEA performed in private hospitals and we would not have known about this. However, we expect these numbers to be small as we have restricted our study population to patients who were seen by our healthcare system and who were expected to utilise our healthcare system. We were unable to look at the link between diabetes foot screening and foot ulcers, as the presence and severity of foot ulcers were not captured in the database. Thus, we may have underestimated the cost savings for diabetes foot screening, if diabetes foot screening prevented foot ulcers as well.

We looked at the effect of missing variables on our analysis using complete case analysis. After removing patients with missing HBA1c and/or BMI readings, we redid the analysis using 1533 diabetic patients with foot screening and 1533 diabetic patients without foot screening. We found that the percentage of LEA remained statistically different ($P = 0.001$) between those who had foot screening (0.26%) and those who did not have foot screening (1.4%).

Table 5. Cost Savings Due to Foot Screening

Number Needed to Screen	Cost of Screening*	Cost Saving if Minor LEA is Averted†	Cost Saving if Major LEA is Averted†
106	$5300	-$138.51	$4395.20
Lower 95% CI : 84	$4200	$961.49	$5495.20
Upper 95% CI: 145	$7250	-$2088.51	$2445.20

LEA: Lower extremity amputation

*Unsubsidised cost of diabetic foot screening is $50 per patient.

†Average cost for minor LEA is $5161.49 and for major LEA is $9695.20 (source: Tan JH, Hong CC, Shen L, Tay E, Lee J, Nather A. Costs of Patients Admitted for Diabetic Foot Problems. Ann Acad Med Singapore 2015;44:567).

Note: All costs are in Singapore Dollars. Cost savings are from the healthcare providers' perspective.

Our propensity score matching narrowed the differences between the 2 groups but there were still differences between the 2 groups as shown in Table 2. We did a separate analysis using only patients who are well matched by using a caliper of width equal to 0.02 of the standard deviation of the estimated propensity score. A total of 0.34% of those who had foot screening had amputations, while 1.34% of those who did not have foot screening had amputations, and this was still statistically significant.

We have looked at the effectiveness of diabetes foot screening in the primary care setting and found that it could potentially prevent LEA, resulting in cost savings from the healthcare providers' perspective. We have also identified risk factors for LEA and more efforts can be made to improve glycaemic control in these high-risk groups and ensure they go for annual diabetes foot screening.

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Original Article

Selection and Short-Term Outcomes of Living Kidney Donors in Singapore – An Analysis of the Donor Care Registry

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Abstract

Introduction: Transplant rates in Singapore have been falling and there is limited information on baseline characteristics and clinical outcomes of living kidney donors nationally. This study aimed to determine the safety of living kidney donor transplant in Singapore by exploring the proportion of donors that meets international selection guidelines and describing short-term clinical outcomes. Materials and Methods: We analysed 472 donors who underwent nephrectomies from 1 January 2010 to 31 December 2014 from the Donor Care Registry. We described donor characteristics against 5 international guidelines and measured post-nephrectomy outcomes in 150 local donors for up to 24 months. A multivariate analysis was performed to determine the baseline variables associated with poorer outcomes. Results: There were more foreign than local donors, with differences in gender and hospital types. Selection was generally aligned with international recommendations although 3.0% (using the Chronic Kidney Disease Epidemiology [CKD-EPI] equation) to 8.5% (using radionuclide and creatinine clearance methods) of donors had inappropriate baseline estimated glomerular filtration rates (eGFR) for age. Post-procedure, many foreign donors were lost to follow-up. Over 24 months, eGFR decreased by 33.8% from baseline before recovering gradually to 29.6%. During this period, only 2 donors were admitted for renal or urological conditions and there were no cases of end-stage renal failure or deaths. A lower baseline eGFR (HR: 1.05; 95% CI, 1.02 to 1.09) and older age (HR: 1.04; 95% CI, 1.00 to 1.08) were associated with a post-nephrectomy eGFR of less than 60 mL/kg/1.73 m^2. Conclusion: Kidney donation is safe in Singapore. Donor selection is in keeping with international guidelines and short-term outcomes are comparable to other cohorts.

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Key words: Guidelines, Nephrectomy, Renal, Safety

Introduction

Persons with end-stage renal disease (ESRD) require either dialysis or a kidney transplant to survive. Transplant is preferred as it is considered a life-extending procedure; the typical patient lives an average of 10 to 15 years longer with a kidney transplant than if kept on dialysis.[1] In Singapore, data collected by the Singapore Renal Registry showed an increasing incidence of ESRD from 210.2 (1999) to 392.6 (2012) per million population. Yet transplant rates have fallen from 35.5 per million in 2006 to 16.2 per million in 2012.[2]

A cross-sectional study was conducted in 2012 to examine public attitudes to living kidney donation. It showed that only 48.4% of respondents expressed that they were willing to donate while alive. The main reasons given by those not willing to donate were fears of surgical risks (86.5%) and poorer health consequent to donation (87.5%).[3] There is presently limited published data regarding baseline characteristics and clinical outcomes of living kidney donors in Singapore at the national level.

There are currently a number of major guidelines used internationally for living kidney donation eligibility.

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The more commonly used are: i) the Amsterdam Forum on the Care of the Live Kidney Donor; ii) the British Transplantation Society/Renal Association United Kingdom guidelines for living donor transplantation; iii) the Guidelines for the Medical Evaluation of Living Kidney Donors by the United States (US) Organ Procurement and Transplant Network; iv) the Guidelines on Renal Transplantation by the European Association of Urology; and v) the Living Kidney Donor Guideline Caring for Australasians with Renal Impairment.[4-9]

In 2009, sub-legislation for the Donor Care Registry (DCR) of the National Registry of Diseases Office (NRDO), Ministry of Health (MOH), Singapore was established, mandating detailed reporting of all new and yearly follow-up information for living kidney donors. The aim of this study was to use data collected in the registry to determine the safety of living kidney donor transplantation in Singapore by exploring the proportion of donors that meets international selection guidelines and describing short-term clinical outcomes.

Materials and Methods

Living kidney donation in Singapore is governed through the Human Organ Transplant Act (HOTA) and the transplant ethics committee of each hospital. This is a retrospective case series which included all living donors reported to the DCR from 1 January 2010 to 31 December 2014 (inclusive).

Outcomes

The first primary outcome was the proportion of donors who met a list of parameters based on the 5 most commonly used international guidelines at baseline (Table 1). As there were variations in the absoluteness of contraindications, these were grouped into stronger and weaker relative contraindications. Conservative laboratory thresholds for haematuria and pyuria were used. Renal function at baseline was based on radionuclide glomerular filtration rate (eGFR) or urine creatinine clearance. eGFR was also calculated using serum creatinine using the 2009 Chronic Kidney Disease Epidemiology (CKD-EPI) formula. All laboratories had also indicated that their serum creatinine measurements were calibrated to isotope dilution mass spectrometry.

The second primary outcome was only performed for Singaporean citizens and permanent residents (locals) due to the likely high rate of loss to follow-up for foreign donors. These were clinical outcomes at less than 6 months, 6 to 12 months and 12 to 24 months of follow-up (Table 2). Complications and clinical complaints were documented as free-text and classified by an investigator (MZJ Ho) into mild (e.g. postoperative fever that resolved without antibiotics) as well as moderate and severe events (e.g. chest infections).

Table 1. Parameters for Baseline Analysis of Donors

	Baseline Parameters	Based On
Age	Less than 18 years old	USA, Europe: <18-year-old an absolute CI
	Less than 21 years old	USA: <21-year-old a relative CI
	More than 60 years old	No recommendations for upper limit
Hypertension	BP of >130/90 mmHg	USA: 130/90, Others: 140/90
	BP of >140/90 mmHg	>3 Absolute CI in USA guidelines
	On 3 or more anti-hypertensives	>3 Relative CI in UK guidelines
Dyslipidaemia	On hypolipidaemics	Generally not contraindicated
Diabetes	Diagnosed with DM	Absolute CI in European guidelines
	2-hour OGTT of ≥7.8 mmol/L	USA, Australia: ≥7.8 mmol/L
	2-hour OGTT of ≥11.1 mmol/L	Amsterdam: ≥11.1 mmol/L
Obesity	BMI of >30.0 kg/m^2	USA, Australia: >30 relative CI
	BMI of >35.0 kg/m^2	USA: >35 absolute CI
Renal function	Inappropriate eGFR for age	Amsterdam, USA, Australian, UK guidelines
Urine protein	24-hour urine protein >300 mg/24H	All guidelines
Urinary stones	Any stones on x-ray (size of stones not captured in registry)	USA: Any stones a relative CI
		Europe: >1 cm a relative CI
	Nephrocalcinosis or bilateral stones	Amsterdam: >1.5 cm a relative CI
		Amsterdam and Europe: Absolute CI
Anatomical abnormalities	Any significant abnormalities on x-ray	USA: Absolute CI
		European: Relative CI
Pulmonary issues	Any smoking history	Other pulmonary issues not directly captured

BP: Blood pressure; CI: Contraindication; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; OGTT: Oral glucose tolerance test; RBC: Red blood cell; UK: United Kingdom; USA: United States of America; WBC: White blood cell

Data Collection

Collection of data from new and follow-up donors was conducted by doctors and nurses within transplant clinics and hospitals. Although the extent and manner of data

gathering was left to clinicians, these were in accordance to structured electronic forms.[10,11] The National Organ Transplant Unit of MOH regularly generates a list of known donors and 2 NRDO renal transplant coordinators visited clinics and hospitals to record data using structured forms via an electronic database. Data was gathered through the access and review of clinical case notes, investigations and medication records.

On registration, basic demographic data, baseline pre-donation clinical state and investigations were collected. This was followed by nephrectomy details and complications noted during donors' hospitalisation. Registration of new donors to the registry was conducted ad-hoc, and not later than 3 months post-procedure. Donors were also followed-up annually, including documenting complications and clinical outcomes. At the first follow-up visit, clinical outcomes within the first 3 months post-transplant were also collected. Mortality data was obtained through the Singapore death registry.

Data Analysis

Demographics and clinical characteristics of patients were described using frequencies and percentages. Means and standard deviations were used for approximately normally distributed continuous variables, and medians and interquartile ranges (IR) for skewed distributions. Differences in demographics and clinical states between sub-groups of donors at the point of donation were examined. Paired sample t-test was used for differences in means while Fisher's exact test was used for differences in proportions.

Statistical analysis was performed using STATA, version 11.0. For all analysis, a two-sided *P* value of <0.05 was used as cutoff for statistical significance. Univariate analysis for renal function after donation was performed. Bivariate analysis for specific risk factors such as age, gender, baseline body mass index (BMI), baseline renal function and operative techniques, and association with changes in post-donation renal function were quantified using hazard ratios (HR) and 95% confidence intervals (CI). These are variables that had been previously shown to have had some effect on post-donation clinical outcomes in other cohorts.

Multivariate analysis was conducted through Cox proportional hazards regression analysis for 5 variables using an eGFR of <60 mL/min/1.73 m^2 as the outcome. Next, a receiver operating curve (ROC) was constructed with baseline eGFR as a predictor for postoperative eGFR of <60 per mL/min/1.73 m^2 to determine an optimal binary cutoff for baseline eGFR. This was followed by constructing a Kaplan-Meier curve for time to reach eGFR of <60 mL/min/1.73 m^2 based on the cutoff baseline eGFR.

Ethical Considerations

Collection of data and subsequent publication were covered by the 2009 National Registry of Diseases Act

Table 2. Clinical Outcomes for Follow-up Analysis

Outcomes	Definition
Post-donation renal function	eGFR (calculated using the 2009 CKD-EPI formula, as suggested by the 2012 KDIGO guidelines*); % change in GFR in each donor from baseline
Poor post-donation renal function	Last eGFR of less than 60 mL/min/1.73 m^2
Sign of possible end-stage renal failure	Last eGFR of less than 15 mL/min/1.73 m^2
Post-donation blood pressure	Systolic and diastolic blood pressure (in mmHg) compared to baseline
New onset hypertension	Use of blood pressure medications and not on medication pre-donation
New onset DM	Diagnosis of DM and did not have the diagnosis pre-donation
New onset proteinuria	Urinary protein of more than 300 mg/24 hours and did not have elevated urinary protein pre-donation
New onset elevated urinary RBC	RBC in urine of >2 RBC/hpf or RBC in urine of >3 RBC/u
New onset elevated urinary WBC	WBC in urine of >4 WBC/hpf OR WBC in urine of >6 WBC/uL
Complications and clinical complaints	Free text records of any significant clinical complaints during the admission of procedure, within 3 months post-donation and within 24 months post-donation
Readmission to Hospital	Any re-admission to hospital within 3 months and within 24 months post-donation
Death	Any deaths as recorded through clinical notes or registered in the National Death Registry

CKD-EPI: Chronic Kidney Disease Epidemiology; eGFR: Estimated glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; RBC: Red blood cell; WBC: White blood cell

*Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1-150.

Table 3. Demographic Characteristics of Donors at Baseline (n = 472)

	Number of Donors	%
Age		
Median age (IQR)	40 (31 – 50)	
Gender		
Male	255	54.0
Resident status		
Foreigners	322	68.2
Singapore citizens and PRs	150	31.7
Marital status		
Married	289	61.2
Single	143	30.3
Divorced/separated	31	6.6
Widowed	9	1.9
Education status		
No formal education	10	2.1
Primary/PSLE	54	11.4
Secondary/GCE N/O Level	183	38.8
Pre-university/ diploma	87	18.4
University and above	135	28.6
Unknown	3	0.6
Employment status		
Working full-time	358	75.8
Working part-time	8	1.7
Not working	10	2.1
Housewife	80	16.9
Retired	13	2.8
Student	3	0.6
Donor relationship status		
Biologically-related	247	52.3
Emotionally-related	221	46.8
Others	4	0.8

GCE: Singapore-Cambridge General Certificate of Education; IQR: Interquartile range; PR: Permanent resident; PSLE: Primary School Leaving Examination

which takes into consideration ethical issues. Data was anonymised by NRDO prior to analysis and the database was large enough to prevent inferential deduction of identities. Confidentiality was also maintained and the study did not influence clinical care nor provide direct benefits to donors.

Results

Demographics

There were 472 persons who underwent living kidney donation from January 2010 to December 2014. There were more foreign than local donors and slightly more males than females. The median age of donors was 40 years (IQR: 31 to 50 years) with an almost equal proportion of biologically- and non-biologically-related donors (Table 3).

Most nephrectomies were between foreign donors and foreign recipients (65.7%), and between local donors and local recipients (30.9%). Majority of foreign donors underwent nephrectomies at private hospitals (89.8%), whereas local donors had majority of their procedures performed at public hospitals (74.0%). Gender distribution was also different – there were more females among local donors and more males among foreign donors (59.3% and 39.8% females, respectively). Relationships between donors and recipients were similar in both groups.

Selection of Kidney Donors

Pre-donation, there were 471, 459 and 47 donors with serum creatinine, urinary creatinine clearance and radionuclide eGFR data, respectively. Although there were few donors with stronger relative contraindications for living kidney donation, there were 8.5% of donors who fell below the recommended kidney function for their age based on radionuclide eGFR and urinary creatinine clearance. This was 3.0% based on the CKD-EPI formula (Table 4). All of these donors were more than 60 years of age, which may indicate increased caution among older donors. There were 3 donors who had a BMI of more than 35.0 kg/m^2 and another 3 who had a 24-hour urine protein of >300 mg in 24 hours.

The number of patients with weaker relative contraindications was higher, though none exceeded 10%. Although 7.5% of donors had a BMI of more than 30.0 kg/m^2, only 0.6% had a BMI of over 35.0 kg/m^2. There were 8.3% and 3.0% of donors with high systolic and diastolic blood pressure reading record, respectively, but none had 3 or more medications for chronic hypertension. Furthermore, there were 4.2% and 2.0% of donors with red and white cells detected on pre-donation urine microscopy, though 78% of these were female donors.

Quality of life, captured through the Euro-QoL 5 Dimensions (EQ-5D) questionnaire, was found to be generally good. Of 382 donors with data captured, only 2 reported moderate anxiety and depression, 1 reported some problems with self-care, and 1 reported some problems with mobility.

Table 4. Donors with Relative Contraindications and Other Indices

Stronger Relative Contraindications	**Donors with Data***	**No. of Donors**	**%**
Inappropriate eGFR for age (radionuclide eGFR or urinary creatinine clearance)†	459	39	8.5
Inappropriate eGFR for age (CKD-EPI)	471	14	3.0
Body mass index ≥35.0 kg/m^2	466	3	0.6
24-hour urine protein >300 mg/24H	373	3	0.8
Diagnosed with diabetes mellitus	472	1	0.2
Nephrocalcinosis or bilateral stones	465	1	0.2
Age less than 18 years	472	0	0
On 3 or more anti-hypertensives	472	0	0
2-hour OGTT of ≥11.1 mmol/L	58	0	0
Weaker Relative Contraindications	**Donors with Data**	**No. of Donors**	**%**
Systolic blood pressure ≥140 mmHg	472	39	8.3
Diastolic blood pressure ≥90 mmHg‡	472	14	3.0
Body mass index ≥30.0 kg/m^2	466	35	7.5
Red blood cells on urine microscopy§	452	19	4.2
White blood cells on urine microscopy‖	452	9	2.0
2-hour OGTT of ≥7.8 mmol/L	58	0	0
Other Indices	**Donors with Data**	**No. of Donors**	**%**
Other non-specific findings on x-ray¶	465	82	17.6
Current smoker	472	85	18.0
Age more than 60 years	472	30	6.4
On anti-hyperlipidaemia medication	472	26	5.5
Any stones on x-ray	465	18	3.9
Age less than 21 years	472	0	0

eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology; OGTT: Oral glucose tolerance test
*Differences in number of donors with data due to missing entries for some variables.
†Appropriate eGFR for age was based on the table for age-appropriate eGFR by the British Transplant Society.
‡Thirteen of these individuals also had high systolic blood pressure.
§Considered elevated if urine RBC >2 hpf or RBC >3 uL.
‖Considered elevated if Urine WBC >4 hpf or WBC >6 uL.
¶Any other x-ray findings apart from renal stones and cysts (e.g. double ureter).

Operative Techniques and Immediate Outcomes

There were more open surgeries in private hospitals (73.8% vs 9.0%), and more laparoscopic techniques in public hospitals. The median length of hospital stay was 5 days (IQR: 4,5). There were 10 (2.1%) and 6 (1.3%) donors respectively who had clinically moderate to severe events during their stay (chest infections, surgical site infections, acute urinary retention and pneumothorax) and there were no incidents of acute kidney failure or death. There were no differences in incidence of these events between public and private hospitals (P = 1.00) or operative techniques (P = 1.00).

Follow-up

There was high loss to follow-up for foreign donors (only 43.1% returned for any follow-up visit). In contrast, there were 96.4% of Singaporean citizens and permanent resident donors (locals) with at least 1 follow-up visit, and across the cohorts, an average of 72.8% (range: 65.5% to 87.9%) complied with annual follow-up.

Short-Term Kidney Function

Outcomes up to 24 months after transplant were thus only analysed for donors who were locals. Renal function decreased from pre-donation levels by a mean of 33.8% before recovering gradually to 70.4% of baseline renal function after 12 to 24 months post-nephrectomy (Fig. 1). Though 26.3% of the patients had an eGFR of <60 mL/min/1.73 m^2, there were no patients with eGFRs of <15 mL/min/1.73 m^2 or deaths.

Baseline renal function was higher in those less than 50 years of age (eGFR 108.4 mL/min/1.73 m^2 [SD: 12.7]

vs 95.5 mL/min/1.73 m^2 [SD 10.7]) and slightly higher among females (eGFR 105.9 mL/min/1.73 m^2 [SD 13.2] vs 99.7 mL/min/1.73 m^2 [SD 9.2]). Using the most recent post-nephrectomy eGFR result of <60 mL/min/1.73 m^2 as an outcome, multivariate analysis found a higher risk associated with lower baseline eGFR (HR: 1.05; 95% CI, 1.02 to 1.09) and to a lesser extent, older age (HR: 1.04; 95% CI, 1.00 to 1.08). There were no differences in gender, surgical approach and BMI (Table 5).

A baseline eGFR to predict postoperative eGFR of <60 mL/min/1.73 m^2 or ≥60 mL/min/1.73 m^2 yielded an area under the ROC curve (AUC) of 0.85 (95% CI, 0.78 to 0.93). An optimal sensitivity of 85.7% and specificity of 71.4% was achieved with a baseline eGFR cutoff value of 97 mL/min/1.73 m^2. Using this cutoff, a Kaplan-Meier curve was subsequently constructed. The probability of having a post-donation eGFR of <60 mL/min/1.73 m^2 was lower for patients with baseline eGFR ≥96.8 mL/min/1.73 m^2 (HR 0.18; 95% CI, 0.09 to 0.37; P <0.001) and the median time to reach post-donation eGFR of <60 mL/min/1.73 m^2 was shorter for baseline eGFRs lower than 96.8 mL/min/1.73 m^2 (424 days as compared to 693 days) (Fig. 2).

Other Outcome Measures

There were no significant differences in mean systolic (P = 0.843) and diastolic blood pressure (P = 0.200) in donors post-nephrectomy and there were no donors with newly diagnosed diabetes mellitus. Next, there were no donors with urinary protein above the upper limit of 300 mg/24 hours although a small number had new instances of elevated red (n = 8) and white blood cells (n = 9) in their urine. There were 10 donors (7.5%) who reported clinical complaints within 3 months of discharge, and of these, 4 required hospitalisation for reasons related to the procedure (e.g. surgical site infection) but not for poor renal function. Over a 24-month period, the proportion of patients hospitalised since their previous visit was 1.2%, 7.4% and 5.7% for within 6 months, 6 to 12 months and 12 to 24 months after donation, respectively. Of these, only 2 donors were admitted for renal or urological conditions.

Discussion

Donor Characteristics

This is the first study detailing baseline characteristics of living kidney donors in Singapore. The surprisingly high numbers of donations between foreign donors and foreign recipients suggest a strong medical tourism sector in keeping with overall trends seen during that period, and the difference in distribution between local and foreign donors in terms of hospital type may be due to subsidies available for locals at public hospitals.

Gender disparity among living kidney transplant has been a topic of much debate over the past few years. Among most cohorts, both in the West as well as a number of Asian countries such as China and India, it seemed that there was a female predominance.[12-14] The proportion of local female donors in Singapore is in keeping with these trends, whereas that of foreign donors seemed more akin to a handful of transplant centres from purportedly conservative societies such as Saudi Arabia, Iran and Korea.[15-17] Our study was unable to determine the cause for this difference, and it would necessitate further studies.

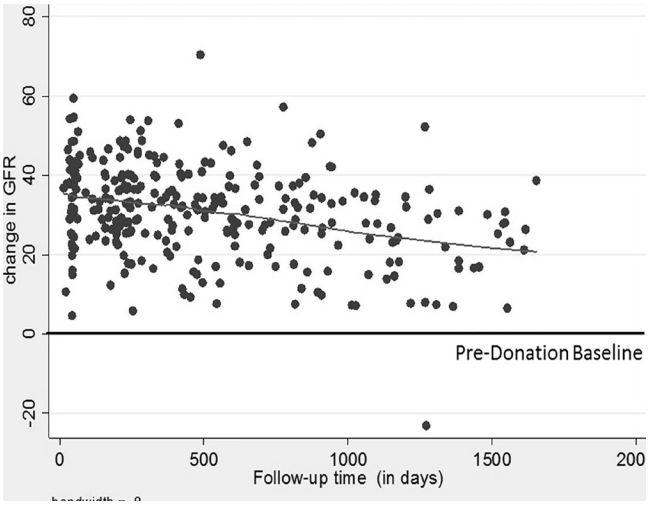

Fig. 1. Lowess plot of kidney function over time (locals).

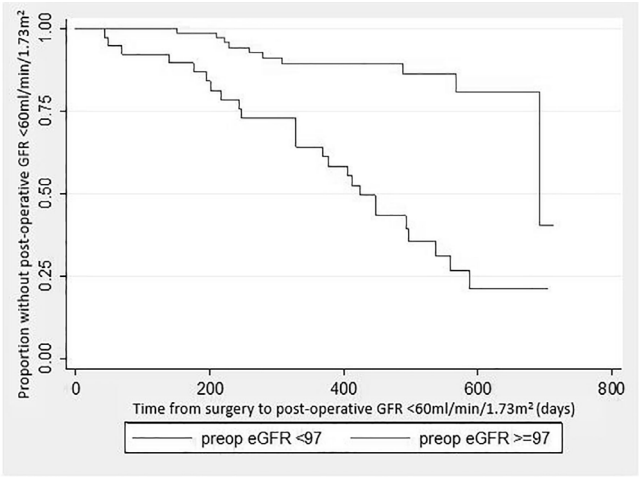

Fig. 2. Kaplan Meier curve for post-donation renal function of <60 mL/min/1.73m^2.

Table 5. Multivariate Analysis for Post-Donation Renal Function of <60 mL/min/1.73 m^2

	Post-Donation eGFR <60 mL/min/1.73 m^2 (n = 35)		Post-Donation eGFR ≥60 mL/min/1.73 m^2 (n = 98)		Crude Hazards Ratio			Adjusted Hazards Ratio		
	n	%	n	%	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Gender										
Male	20	57.1	33	33.7	1.00	-	0.068	1.00	-	0.388
Female	15	42.9	65	66.3	0.54	0.27 – 1.05	0.068	0.69	0.30 – 1.60	0.388
Surgical approach										
Laparoscopy	31	88.6	81	82.7	1.00	-	0.198	1.00	-	0.391
Open	4	11.4	17	17.4	0.50	0.18 – 1.43	0.198	0.61	0.20 – 1.89	0.391
	Mean	**SD**	**Mean**	**SD**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Baseline eGFR	90.8	12.1	107.6	11.5	1.06	1.04 – 1.10	<0.001	1.05	1.02 – 1.08	<0.001
Age at surgery	52.3	10.0	44.6	11.2	1.06	1.03 – 1.10	0.001	1.04	1.00 – 1.08	0.047
BMI	24.2	3.1	23.8	3.8	1.03	0.94 – 1.13	0.480	1.02	0.91 – 1.14	0.751

BMI: Body mass index; eGFR: Estimated glomerular filtration rate; HR: Hazards ratio

Selection of Donors

Donor selection in Singapore is aligned with international guidelines, with stringent adherence as compared to transplant centres overseas. In the United Kingdom, there were 70% and 86% of transplant centres that did not have lower and upper age limits, respectively; some (9%) did not have an upper limit for BMI, and only 30% collected 24-hour urine protein.[18] Similar variations were seen in transplant centres in the US.[19] Furthermore, in the US, 12.8% of donors had a BMI of ± 30 kg/m^2; there were 10.3% and 4.2% who were hypertensive and had a renal function of <60 mL/min/1.73 m^2, respectively, and 2.7% with more than one of these risk factors.[20] For direct comparison, only 0.4% of cases in our study fell below the more liberal cutoff of <60 mL/min/1.73 m^2. Selection of living kidney donors in Singapore is thus comparable, if not safer, than other countries.

Some donors would have required further workup. High blood pressure readings may have been due to natural fluctuations and the presence of red and white blood cells in urine may be due to physiological reasons (especially since majority with this abnormality were women). Unfortunately, details on any workup were not captured in the registry.

Clinical Outcomes

This is the first study detailing immediate and short-term outcomes of living kidney donors at a national level in Singapore. Immediate outcomes showed that surgical procedures were safe. A small number of donors had moderate to severe events during their admission post-surgery and the duration of their stay was fairly short and uniform.

Tan L et al conducted a study among 86 donors at a single public hospital in Singapore who had undergone nephrectomy from 1987 to 2008.[21] A significant proportion (55%) of donors had donated before the publication of the Amsterdam guidelines. Preoperative GFR was higher in our study (103.4 mL/min/1.73 m^2 vs 88.7 mL/min/1.73 m^2) and although this may have been due to differences in measurement techniques (Modification of Diet in Renal Disease [MDRD] formula was used), it may also suggest stricter selection of donors over time. Indeed, a more recent study by Han X et al among 82 prospectively recruited kidney donors noted a preoperative eGFR of 95.5 mL/min/1.73 m^2, which was closer to our findings.[22]

Tan L et al also found that 24.4% of donors had Stage 3 or worse chronic kidney disease (CKD) after an average of 6.4 years. Another study by Chen KW et al also found a mean postoperative eGFR of 68.9 mL/min/1.73 m^2 after an average of 52.9 months, with 24.1% of donors in Stage 3 CKD.[23] Both studies thus had similar results to our finding that 26.3% of donors had a last eGFR of less than 60 mL/min/1.73 m^2 within 24 months.

Tan L et al also found that the baseline eGFR rate of less than 82 mL/min/1.73 m^2 was an independent risk factor for post-donation CKD.[21] This cutoff was higher in a separate study by Tsai SF et al among 105 donors in Taiwan (90.2 mL/min/1.73 m^2), than the cut-off of 96.8 mL/min/1.73 m^2 in our study.[24] These may again be due to differences in measurement techniques (MDRD formula vs CKD-EPI formula used by our study). Another possible reason was that the time to follow-up in our study was still short (2 years, as compared to 6.4 years and 5.4 years in studies by Tan L

et al and Tsai SF et al respectively)[21,24] and some donors' renal function may have improved further. Another study by Tan RY et al similarly found a 6% risk reduction for each unit increase in pre-nephrectomy eGFR, pointing towards high pre-nephrectomy eGFR conferring protection against low post-donation eGFR.[25]

Baseline eGFR thus continues to play an important role in the safe selection of living kidney donors in relation to donors' eventual risk of developing CKD. International guidelines continue to be useful in laying out minimum acceptable standards to which transplant centres should adhere to. However, many use a single or range of stratified cutoffs and it is important to keep in mind that such risks to otherwise healthy donors actually exist on a continuum.

The decrease in renal function of 33.8% from baseline is in keeping with local studies and other international cohorts. Of note, this is less than the 50% that would have been expected after removing 1 of 2 kidneys. At a local institution, Han X et al noted a fall in postoperative eGFR to 71.0 mL/min/1.73 m^2 (a decrease of 25.7%) over a median follow-up of 7.8 years. Furthermore, 43.1% of donors regained 75% of more of preoperative eGFR after 5 years.[22] Kasiske BL et al showed that donors had a drop in renal function post-nephrectomy of 33.6%, with a gradual rise over the subsequent 3 years.[26] We found a similar trend, with gradual recovery to 29.6% by 24 months.

Guerra J et al showed that donor kidney function was 32% lower post-nephrectomy as compared to baseline, with 21% having an eGFR of less than 60 ml/min/1.73m^2, influenced by age and baseline eGFR.[27] Among Japanese donors, eGFR dropped by an average of 37% and was negatively associated with older age and lower preoperative eGFR.[28] Our study likewise showed these associations as well.

Although earlier studies had shown equal longer-term mortality among kidney donors as compared to the general population,[29] more recent studies showed that mortality was still higher than matched healthy non-donors. These were accompanied by increases in blood pressure, proteinuria, and ESRD.[30-35] None of these changes were observed in our cohort, although a longer period of follow-up and future studies would be required to draw more definitive conclusions.

Limitations and Strengths

The retrospective nature restricts the amount of information available for analysis as data that was not collected or poorly recorded could not be analysed. In addition, recorded data were assumed to be accurately captured. For example, we were unable to ensure that adequate urine was collected by clinicians when determining urine creatinine clearance as this depended on individual practice protocols. During follow-up visits, certain portions deemed less important were sometimes not assessed by clinicians. Medical visits in other settings would also not be captured. Furthermore, there was also a high rate of loss to follow-up for foreign donors, thus results may not be generalisable to this group. Intervals of follow-up visits were dependent on clinician preference; as such, not all donors had results within each time bracket, thereby reducing the amount of data available for analysis.

The presence of legislation ensured that data capture of all living kidney donors in Singapore was generally expected to be good. There were also relatively good follow-up rates among local donors. The use of trained coordinators for data collection reduces interpersonal variability and a structured form to record findings would lower the need for subjective interpretation. Majority of outcome indicators were also derived through investigation results (e.g. serum creatinine), hospitalisation events and medication data, thus providing more objective data.

Conclusion

The demand for renal donations in Singapore is expected to continue, driven by the increase in persons with end-stage renal failure. The enactment and subsequent revisions of HOTA have sought to improve organ donation numbers; however, these have not resulted in an increase in kidney transplants that commensurates with demand. Deceased donor transplants are also not without downsides, with studies showing that graft survival was lower as compared to living transplants.[36]

Since fear of surgical complications and postoperative outcomes were found to be the main barriers to living kidney donations in Singapore, presenting an accurate reflection of these risks is important to help allay some of these concerns.[4] Findings from our study show that after 24 months of post-donation monitoring, although there is some expected decrease in renal function, transplant operating procedures in Singapore remain safe. As long as clinical practice adheres rigorously to internationally accepted guidelines, kidney donation in Singapore will be as effective and free of adverse outcomes as other high-performing transplantation programmes.

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Commentary

Rate or Rhythm Control of Atrial Fibrillation – Pearls for the Internist

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Abstract

Atrial fibrillation is an epidemic in Asia that is increasingly prevalent. Apart from stroke risk stratification and management of anticoagulation, physicians managing this group of patients also need to determine an optimal strategy in terms of rate or rhythm control. With new techniques of catheter ablation to maintain patients in sinus rhythm, patients with atrial fibrillation now have more options for treatment, on top of pharmacological methods. This paper aims to review the current evidence for rate and rhythm control in both general patients and subgroups of interest commonly encountered in clinical practices such as obesity, heart failure and thyroid disease.

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Key words: Ablation, Anti-arrhythmic drugs, Stroke

Introduction

Atrial fibrillation (AF) is the most commonly sustained cardiac arrhythmia. The prevalence rate of AF in the adult population is 1% in most Asian countries, with an estimated 72 million patients in Asia affected by 2050.[1]

Stroke Prevention in Atrial Fibrillation

Risk stratification systems like the CHA_2DS_2-VASc score help determine annual stroke risk to aid understanding and discussion of anticoagulants in non-valvular AF. This risk scoring system is not applicable to patients with rheumatic mitral stenosis and conditions like hypertrophic cardiomyopathy where AF confers elevated stroke risks regardless of CHA_2DS_2-VASc score and when anticoagulation should be commenced. Aspirin alone should not be offered for stroke risk prevention in AF.[2,3]

Current options of anticoagulation for non-valvular AF include warfarin and non-vitamin K antagonist oral anticoagulants (NOACs); only dabigatran, rivaroxaban and apixaban are currently available in Singapore.

Warfarin is effective if good quality anticoagulation control—defined by the time in therapeutic range (TTR) of over 70%—is achieved. However, achieving a good TTR can be difficult, particularly in Asian populations.[4] Hence, NOACs offer a therapeutic alternative. A meta analysis[5] of 4 landmark NOAC trials revealed a significant 19% stroke risk reduction, driven by the reduction in haemorrhagic stroke, and a 10% reduction in all-cause mortality relative to warfarin, at the expense of a slight increase in gastrointestinal bleeding. The efficacy and safety of NOACs over warfarin seem to be even greater in East Asians compared with non-Asians.[6]

Percutaneous left atrial appendage occlusion might be an alternative for patients who are at high risk but have contraindications to oral anticoagulants; this should be considered a secondary option and patients still require dual antiplatelets for at least 6 weeks after the procedure.

Symptom Management: The Controversy of Rate or Rhythm Control

The 2 main treatment strategies for symptom management are rate and rhythm control. These 2 strategies are not exclusive; rate control is central to AF management, even for patients who ultimately require rhythm control.

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Several large clinical trials have been performed to compare the risks and benefits of rate versus pharmacological rhythm control strategies in patients with AF,[7-9] and rate control was not shown to be inferior to rhythm control in terms of cardiovascular mortality and morbidity. The lack of superiority of rhythm control in these trials may be due to the modest ability to maintain sinus rhythm using pharmacological rhythm when compared to rate control agents, with sinus rhythm ranging from 26% to 63% in the rhythm control arm; a more effective rhythm control therapy might have resulted in greater benefit.

Rate Control

Ventricular rate control in AF can help reduce symptoms and enable exercise. However, the target ventricular rates for AF are unclear. Few trials look at this issue in AF. In the RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation: a comparison between Lenient and Strict Rate Control II) study,[9] comparing lenient rate control of <110 beats per minute (mean heart rate in study 93 ± 9 beats/minute) versus strict rate control of less than 80 beats per minute, there was no difference in the composite clinical outcome of cardiovascular mortality and morbidity and also no differences in patient reported outcomes. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) study in elderly AF patients with preserved ejection fraction and subanalysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) also failed to demonstrate better outcomes with stricter heart rate control of less than 80 beats per minute.[10,11]

Lenient rate control is easier to accomplish for both physician and patient, with significantly fewer hospital visits and lower dosages of drugs necessary to achieve the target heart rate. Drugs commonly used for rate control and their characteristics are summarised in Table 1.

Rate control in every patient requires consideration of their activity level and symptoms, the type of AF (paroxysmal, persistent and permanent), age, underlying disorders, the presence of heart failure, and previous attempts at medical management. However, if one condition remains symptomatic despite initial lenient rate control measures, stepping up on rate control needs to be balanced with risks of symptomatic bradycardia and pauses. Alternatively, pharmacological rhythm control or AF ablation can be considered. In cases of drug refractory

Table 1. Common Rate Control Agents Used in Atrial Fibrillation

Type of Agent	Example of Medications	Benefits	Side Effects	Comments
Beta blockers	Metoprolol, bisoprolol, nebivolol, carvedilol, esmolol	Widely available and safe to use in patients with low LVEF. Intravenous formulation available for metoprolol and esmolol (convenient when patients are fasted). Esmolol has minimal effect on blood pressure with rapid half-life.	Most common adverse symptoms are lethargy, headache, peripheral oedema, upper respiratory tract symptoms, gastrointestinal upset and dizziness. More serious adverse effects include bradycardia, atrioventricular block and hypotension.	Beta 1 selective agents are preferred, especially in the setting of bronchospasm and severe asthma. Carvedilol should be avoided in such circumstances.
Calcium channel blockers	Verapamil, diltiazem	Consistent atrioventricular nodal blockade. Both are available in intravenous forms. Safe to use in reactive airway disease.	Adverse effects include heart block, hypotension and myocardial depression. Use in patients with low LVEF suggestive of increased death, re-infarction and heart failure.	Use with caution in Wolfe-Parkinson-White syndrome. Need to be careful when in combination with beta blockers. Reduce dose with hepatic impairment and tart with smaller dose in renal impairment.
Cardiac glycosides*	Digoxin	Available in intravenous and oral forms. Systematic review suggests no increase in mortality in concomitant heart failure and AF. Can be used in combination with beta blockers and calcium channel blockers.	Gastrointestinal upset, dizziness, blurred vision, headache and rash. In toxic states (serum levels >2 ng/mL), digoxin is pro-arrhythmic and can aggravate heart failure, particularly with coexistent hypokalaemia.	Contra-indicated in patients with accessory pathways, ventricular tachycardia and hypertrophic cardiomyopathy with outflow obstruction. Need to monitor digoxin level and use with caution in patients with renal impairment; higher risk of toxicity.

AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction
*Na+/K+ pump inhibitor, increases intracellular calcium.

symptomatic-persistent AF, physicians may need to consider atrioventricular nodal ablation with implantation of a permanent pacemaker to provide better ventricular rate control.

Rhythm Control

Catheter Ablation of AF

Catheter ablation is an invasive procedure which isolates the pulmonary veins and eliminates triggers for AF. A review of 7 studies directly comparing catheter ablation and drugs confirmed that sinus rhythm is better maintained following catheter ablation,[12] with improved patient reported outcomes over anti-arrhythmic drugs (AADs). The profile of patients enrolled in these studies tends to be younger with symptomatic paroxysmal AF and this partly contributes to better sinus rhythm maintenance postablation.

Cardioversion

Termination of AF can be achieved by direct current or pharmacological cardioversion. For electrical cardioversion, pretreatment with AAD increases the probability of restoring sinus rhythm. Anterior posterior electrode placement has also been shown to be more effective than the anterolateral placement in clinical trials. Otherwise, pharmacological cardioversion with bolus administration of AAD can be attempted with success rate of approximately 50% within 15 to 120 minutes. Examples of common drugs used for pharmacological cardioversion are: intravenous flecainide, propafenone, ibutilide and amiodarone.

Other drugs used for maintenance of sinus rhythm besides those listed are summarised in Table 2. Drug selection for patients largely depends on the presence of any structural heart disease such as coronary artery disease, congestive cardiac failure or left ventricular ejection fraction of less than 35%, left ventricular hypertrophy >1.4 cm.

AADs have significant drug-related toxicities. Amiodarone, the most effective AAD, has up to 6% risk of adverse events, including hepatic toxicity, peripheral neuropathy, hyper- and hypo-thyroidism and pulmonary toxicity. Overall complication rate for AF ablation also approximates 6%, and the most feared complication of

Table 2. Common Pharmacological Rhythm Control Agents Used in Atrial Fibrillation

Type of Agent	Example of Medications	Benefits	Side Effects	Comments
Class Ia*	Procainamide, quinidine, disopyramide	Procainamide is available in intravenous dosing, and is useful in patients with Wolfe-Parkinson-White syndrome with AF and normal LVEF.	Can cause QT prolongation and arrhythmia. Procainamide and quinidine have frequent gastrointestinal side effects and procainamide can cause a lupus-like syndrome and hypotension.	Dosage of procainamide and disopyramide need to reduce dose for patients with hepatic and renal impairment; metabolism is via CYP3A4 and hence, there is a need to be aware of possible drug interactions.
Class Ic†	Flecainide, propafenone	Available in oral and intravenous dosing and can be used for acute pharmacological conversion of AF.	Adverse effects include hypotension, atrial flutter with 1:1 conduction, QRS prolongation. Will need concomitant beta blockade. Avoid use in ischaemic and structural heart diseases.	Flecainide used in patients post myocardial infarction increases mortality. Propafenone can precipitate decompensated heart failure, particularly in CYP 2D6 slow-metabolisers.
Class III‡	Amiodarone, dronedarone, dofetilide, ibutilide, sotalol	Amiodarone, dofetilide and ibutilide can be used for pharmacological conversion of AF. Amiodarone and dofetilide can be used in structural heart disease.	QT prolongation with increased risk of ventricular arrhythmias. Amiodarone can worsen sinus node dysfunction and cause hepatotoxicity, hypo/hyperthyroidism and pulmonary fibrosis. Dronedarone is associated with increased mortality In patients with heart failure.	Sotalol and dofetilide need to be used with caution in patients with renal impairment; latter is contraindicated if CrCl <20 ml/min. Dofetilide requires inpatient stay for loading due to risk of torsades.

AF: Atrial fibrillation; CrCI: Creatinine clearance rate; LVEF: Left ventricular ejection fraction
*Prolong conduction, slow repolarisation and block fast inward Na+ channels.
†Block myocardial Na+ channels.
‡Potassium channel blockers and prolong phase 3 of action potential.

catheter ablation—atrio-oesophageal fistula often leading to fulminant sepsis and death—is estimated to be 0.03%-1.5%.

With current evidence, for patients with few or no symptoms attributable to their AF, the risks of currently available AAD or catheter ablation outweigh the modest effectiveness of these agents in the maintenance of sinus rhythm. However, rhythm control still holds value for symptomatic patients despite optimal rate control therapy.

Special Conditions: Obesity

In the Framingham Heart Study, every unit increase in body mass index correlated with a 4%-5% increase in AF risk.[13] Obesity and related obstructive sleep apnoea are the few modifiable risk factors for AF that have been identified. Weight loss modifies AF substrate including diastolic function, inflammation, and pericardial fat,[14] which are important players of AF mechanism in obesity.

Significant weight reduction reduces AF burden and symptom severity, and has shown to decrease interventricular septal thickness and left atrial area.[15] This suggests that cardiac remodelling with sustained weight potentially benefits obese patients with difficult-to-control, symptomatic AF, on top of pharmacological and ablation therapies.

Hyperthyroidism

AF is a common arrhythmia in the thyrotoxic state. The prevalence of AF in this disease ranges between 2% and 20%. Successful treatment with either radioiodine or thioureas is associated with a reversion to sinus rhythm in a majority of patients within 2 to 3 months. First line treatment for AF in thyroid disease is beta-adrenergic blockade. Digitalis may be less effective due to the increased rate of digitalis clearance as well as the decreased sensitivity of the heart in hyperthyroid state.[16] Treatment with calcium channel blockers, especially when administered parenterally, should be avoided because of the potential unwanted effects of blood pressure reduction through effects on the smooth muscle cells of the resistance arterioles as hyperthyroid patients may already be in a vasodilated state. Amiodarone, which is iodine-rich, should also be used with caution in a thyrotoxic state due to potential iodine organification and iodine-induced exacerbation of thyrotoxicosis.

Heart Failure

Although subgroup data suggests that sinus rhythm is associated with improved outcomes in patients with AF (including all-cause survival), clinical trials have failed to demonstrate superiority of either a rate or rhythm control strategy. There are several reasons why rhythm control has failed to improve survival in clinical trials, including limited efficacy and adverse effects of available treatments such as AAD (in which choices are further limited in the setting of heart failure), or delayed intervention such that the cumulative effects of AF are already unable to be reversed. Sinus rhythm can be difficult to achieve and maintain, particularly in patients with heart failure. For example, recurrence of AF after successful cardioversion is a frequent problem (>50% at 6 months), particularly in patients with heart failure.

While the older studies mainly used AAD to maintain patients in sinus rhythm, recent trials that used catheter ablation seemed to have more promising outcomes[17-19] (Table 3). Larger and more definitive trials are underway

Table 3. Randomised Controlled Trials Comparing Rhythm and Rate Control in Heart Failure

Trial	Year	n	Type of AF	Rhythm Control Method	Outcome	Follow-up
AF CHF*	2008	1376	Permanent/ paroxysmal AF with LVEF <35%	DC cardioversion and anti-arrhythmic therapy	No difference in cardiovascular mortality (hazard ratio in the rhythm-control group, 1.06; 95% confidence interval, 0.86 to 1.30; $P = 0.59$ by the log-rank test). No significant difference in secondary composite outcome of death from cardiovascular causes, stroke, or worsening heart failure.	37 months
CAFÉ-II	2009	61	Permanent	DC cardioversion and amiodarone	NYHA class ($P = 0.424$) and 6MWT distance ($P = 0.342$) were similar between groups. Patients assigned to rhythm control had improved LV function ($P = 0.014$), NT-proBNP concentration ($P = 0.046$) and QOL ($P = 0.019$) compared with those assigned to rate control.	12 months

AF: Atrial fibrillation; DC: Direct current; EF: Ejection fraction; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; QOL: Quality of life; 6MWT: Six-minute walk test

*Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667-77.

†Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, et al. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. J Am Coll Cardiol 2013;61:1894-903.

‡Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, et al. A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). Circ Arrhythm Electrophysiol 2014;7:31-8.

Table 3. Randomised Controlled Trials Comparing Rhythm and Rate Control in Heart Failure (Cont'd)

Trial	Year	n	Type of AF	Rhythm Control Method	Outcome	Follow-up
MacDonald, et al	2011	41	Persistent AF, LVEF <35%	Pulmonary vein isolation ± linear and focal complex fractionated atrial electrogram ablation	Fifty percent AF-free survival in the ablation group at 6 months; no significant increase in LVEF, functional capacity, and QOL between ablation and rate control group. However, patient who remained in sinus rhythm had significant increase in LVEF.	6 – 14 months
ARC-HF†	2013	52	Persistent AF, LVEF <35%	Pulmonary vein isolation ± linear and focal complex fractionated atrial electrogram ablation	Eighty-eight percent AF-free survival in ablation group at 12 months; peak oxygen consumption significantly increased in the ablation arm compared with rate control (difference +3.07 ml/kg/min, $P = 0.018$). Significant improvements in Minnesota Score ($P = 0.019$) and B-type natriuretic peptide ($P = 0.045$), and trend towards improvement in EF ($P = 0.055$).	12 months
CAMTAF‡	2014	50	Persistent AF, LVEF <50%	Pulmonary vein isolation ± linear and focal complex fractionated atrial electrogram ablation	LVEF in ablation group was 40 ± 12% compared with 31 ± 13% in the rate control group ($P = 0.015$). Significantly improved peak oxygen consumption (22 ± 6 versus 18 ± 6 mL/kg per minute; $P = 0.014$) and Minnesota living with Heart Failure Questionnaire Score (24 ± 22 vs 47 ± 22; $P = 0.001$) compared with rate control.	6 months

AF: Atrial fibrillation; DC: Direct current; EF: Ejection fraction; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; QOL: Quality of life; 6MWT: Six-minute walk test

*Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667-77.

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to help clarify whether ablation leads to improved cardiovascular outcomes in patients with AF and heart failure.

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An Unusual Infection in a Child with Congenital Heart Disease – *Trichosporon asahii* Infection with Rapid Diagnosis by 18s Ribonucleic Acid (RNA)

Dear Editor,

We report a case of a 12-year-old boy with cyanotic heart disease and Klippel-Feil syndrome, palliated with a left-sided Blalock-Taussig (BT) shunt in infancy, and complicated by multiple revisions secondary to thrombosis and subsequent right-sided BT shunt insertion at 4 years of age. At 11 years, he underwent staged insertion of a right ventricle to pulmonary artery (RV-PA) valved conduit (12 mm Hancock), and augmentation of the branch pulmonary arteries.

He, however, presented 6 days after discharge with fever and a purulent sternal wound discharge. He was empirically managed for presumed wound infection with ceftriaxone and vancomycin. Wound and blood cultures were unremarkable and he recovered well. Subsequently, he was admitted a further 5 times within the first year after discharge for suspected infection, managed with several courses of antibiotics including intravenous ceftriaxone, vancomycin and cloxacillin and antifungals including liposomal amphotericin. Wound surface swabs and blood cultures for bacteria and fungi during each episode were consistently negative with no significant findings on computed tomography (CT) thorax, blood biochemistry or immunology, except during the last episode, when coagulase-negative *Staphylococcus aureus* (CONS) was identified from a swab of a chest wall sinus.

The patient presented again after 14 months with fever and purulent wound discharge. Although his fever settled with intravenous vancomycin, ceftriaxone and voriconazole, repeat CT thorax revealed a large, progressive thrombus in the supra-valvular region of the RV-PA conduit, with a wedge-shaped infarct of the right lower lobe (Fig. 1). In view of the progressive nature of the thrombus, and failure to respond to antimicrobial treatment, decision was made for surgical intervention to remove the infected thrombus.

The RV-PA conduit was changed at surgery, and intraoperative findings revealed pustular debris with a large thrombus within the conduit, and friable, infected tissue in the surrounding mediastinum. Histology of the tissue revealed a granuloma with spore-forming fungus (no hyphae).

In view of multiple inconclusive previous cultures, the tissue samples were subjected to a next-generation

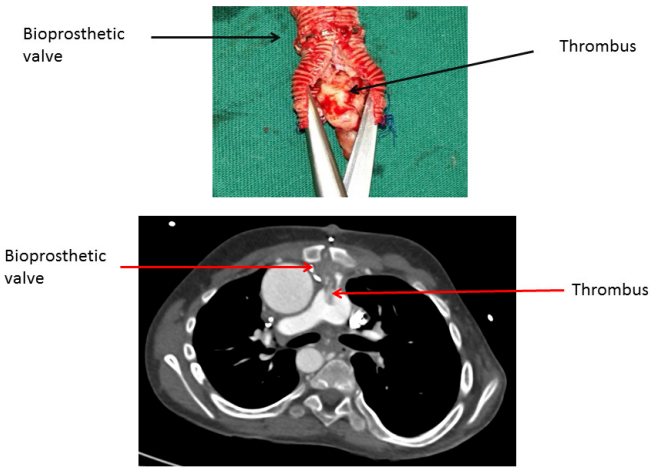

Fig. 1. Computed tomography of thorax.

sequencing (NGS), pipeline-based approach using primers targeting the 18S ribosomal ribonucleic acid (RNA) (rRNA) gene, details of the primers[1] and the NGS data obtained are provided in Table 1. This molecular analysis revealed fungal deoxyribonucleic acid (DNA), matching *Hortaea werneckii*, *Hypocreales* or *Trichosporon* species (Figs. 2 and 3). From the 18S reads shown in Figure 2, excluding the human reads, the remaining reads were from fungi and not from bacteria, indicating that contamination from skin or commensals would be unlikely. The phylogenetic tree diagram in Figure 3 showed that the majority of fungi reads were from *Hortaea werneckii*, *Aspergillus, Hypocreale* or *Trichosporon spp*. Three contigs assembled from the *Trichosporon* reads showed the closest match to *Trichosporon asahii*, at the species level. When compared, the contigs were 99% similar, which suggests that there was only one species of *Trichosporon*, i.e., *T. asahii* in the tissue samples.

The results from the molecular NGS studies preceded subsequent positive cultures from tissue samples of the pericardium, conduit and thrombus which all grew *Trichosporon asahii*. This was most sensitive to voriconazole, and a lesser degree to fluconazole and amphotericin. In addition, cultures from the explanted pacing wire and sternal wound tissue demonstrated CONS resistant to methicillin. He was therefore managed with a combination therapy including intravenous voriconazole,

Table 1. 18S and Fungi ITS-Specific Primer Pairs Used for Next-Generation Sequencing of Patient Tissue Samples and Observed Results

Primer Pairs	Expected PCR Band (bp)	Observed	Sequencing Successful
Forward primer: ITS1F -CTTGGTCATTTAGAGGAAGTAA Reverse primer: ITS2 -GCTGCGTTCTTCATCGATGC	250	250, 350 and 400 bp bands	Yes
Forward primer: 18S_0067a_deg -AAGCCATGCATGYCTAAGTATMA Reverse primer: NSR 399 -TCTCAGGCTCCYTCTCCGG	350	350 bp band	Yes
• Total number of reads = 56,692 -Number of reads mapped to human = 4433 (7.8%) -Number of reads mapped to fungi = 38,270 (67.5%) -Number of unmapped reads = 13,989 (24.7%)			
• Top 20 BLAST hits to fungi -Accounted for 23,825 reads (42%) -*Hortaea werneckii*, *Aspergillus caesiellus*, *Trichosporon spp**, *Hypocreales spp.* identified			

BLAST: Basic Local Alignment Search Tool

*The reads for *Trichosporon species* accounted for 31.0% of the 42% BLAST hits for fungi.

ceftriaxone and vancomycin.

Initial treatment for the *Trichosporon asahii* infection comprised intravenous voriconazole; however, he developed hepatotoxicity on day 12 and was switched to liposomal amphotericin with fluconazole. Because of amphotericin nephropathy, treatment was changed back to voriconazole on day 33, which henceforth was tolerated well. The patient completed 4 months of intravenous antifungal therapy, of which the last 3 months were on intravenous voriconazole, and has since been continued on oral voriconazole. His deep-seated CONS infection of the sternal wound and pacing wire was managed with 3 months of intravenous vancomycin and 6 weeks of oral co-trimoxazole and minocycline, with no further evidence of sternal wound infection.

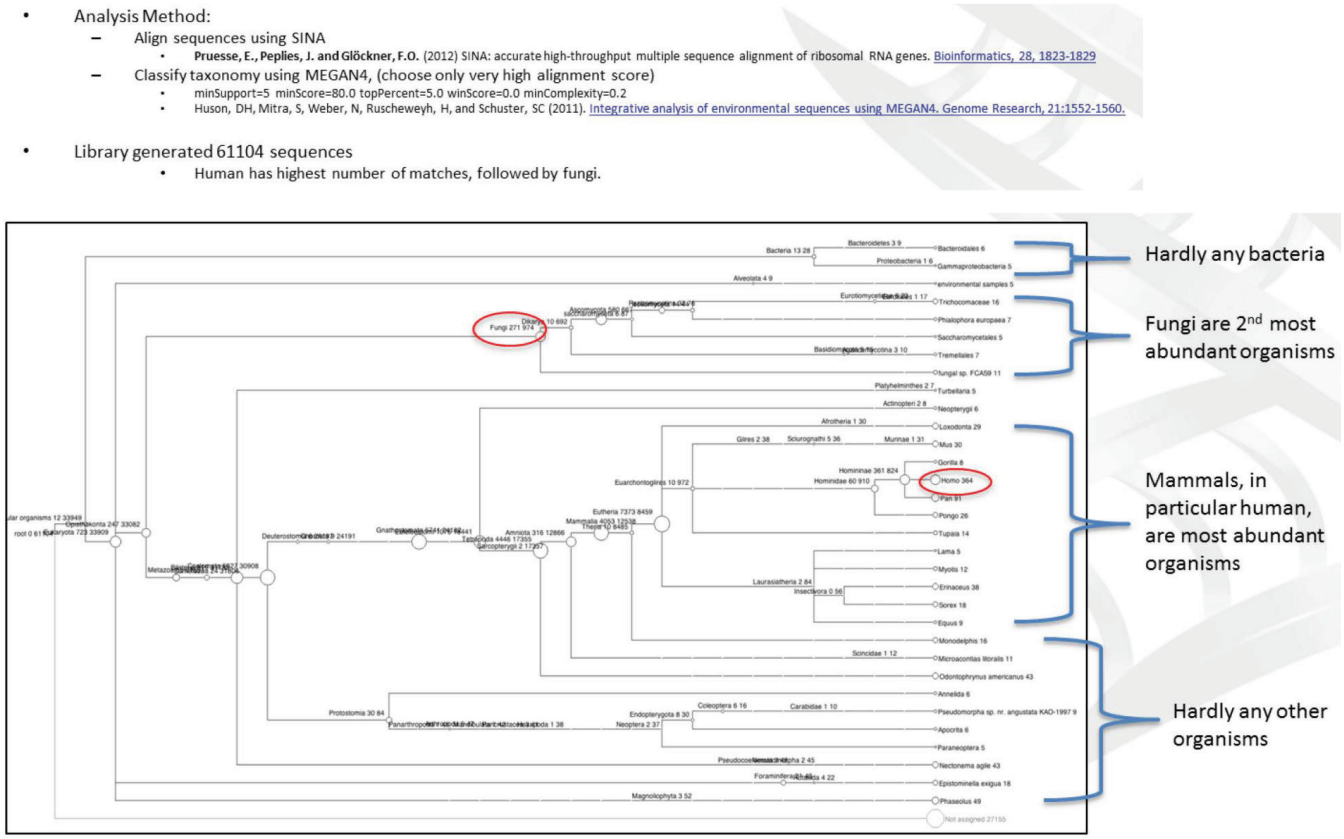

Fig. 2. 18S sequencing results (04V-9, IonXpress010).

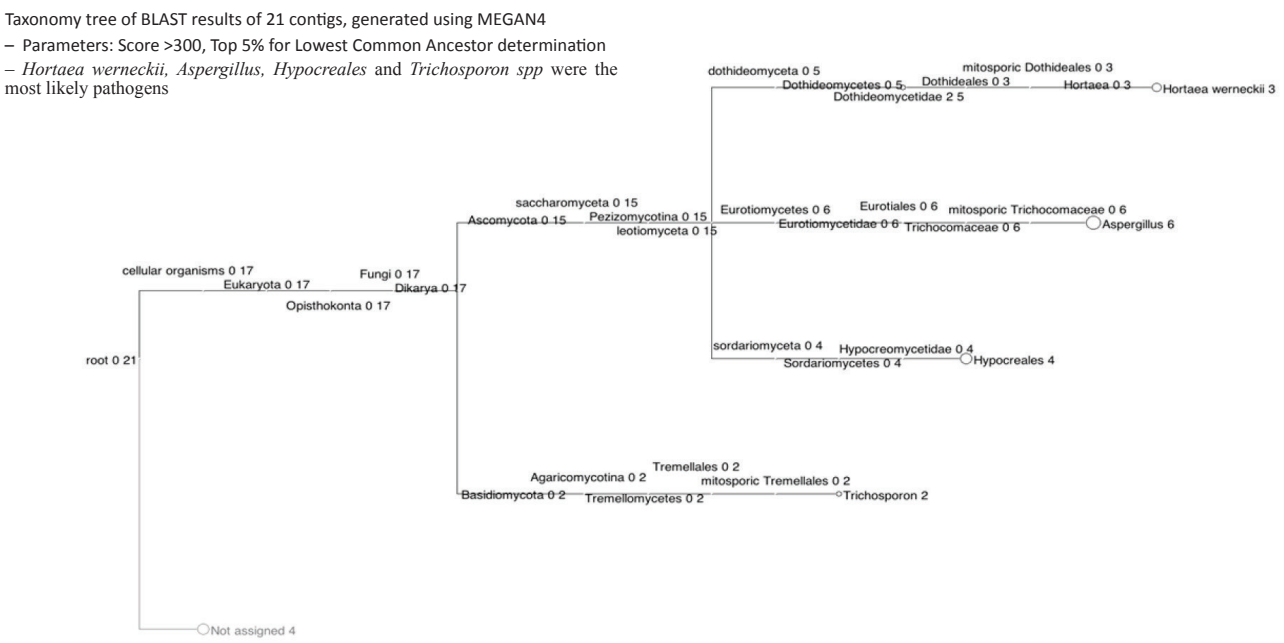

Fig. 3. Fungi ITS sequencing results (02V-20, IonXpress013).

The patient has since kept well and all repeat cultures were negative. Repeat cardiac CT has revealed a patent RV-PA conduit with no evidence of thrombus or collection.

Discussion

Trichosporon asahii has been recognised as a re-emerging pathogen. A recent systematic review[2] showed that infection occurs in 28% of non-immunocompromised patients, often postoperatively, following broad spectrum antibiotic therapy or in association with catheters and implants. Mortality was very high in earlier cases (64%-83%),[3,4] but has improved to 44.3%[2] since azoles are used more commonly. The association of trichosporonosis with cardiac patients is limited to transplanted patients,[5] although there are case reports of *Trichosporon asahii* and *Trichosporon beigelii* infective endocarditis.[6,7] Of 11 cases of endocarditis secondary to *Trichosporon spp*,[7] 9 had infected prosthetic valves. Management included surgical and antifungal therapy, but with poor prognosis and high mortality rate of 82%. However, all but one of these patients were treated with amphotericin B, an antifungal agent now known to have poor in-vitro activity towards *Trichosporon beigelii*.

We describe this case of postoperative *Trichosporon asahii* infection involving the patient's endocardium, prosthetic material with thrombus, and surrounding mediastinal tissue to highlight the importance of a re-emerging pathogen, and propose a rapid NGS molecular test as an alternative screening strategy for those with suspected deep-seated culture-negative infections, which could save vital time in initiating the correct treatment, given the still very high mortality of infections with this organism. The tissue samples in our case showed hyphae and spores, indicative of proliferation in the tissues rather than contamination. Good communication among surgeons, cardiologists, infectious disease specialists and microbiologists was crucial in managing the patient's infection effectively. Surgical removal of as much infected tissue was imperative, as there is a potential of failure to clear and recurrence of infection. The NGS-based molecular diagnosis of fungal infection allowed for a targeted antimicrobial treatment before the culture result was available.

There are no controlled trials about the duration of antifungal treatment in such cases. Once trichosporonosis has established in tissue, recurrence is common even with prolonged antifungal treatment of up to 2 years.[8,9] In this case, duration of intravenous antimicrobial treatment was guided by clinical improvement and monitoring of inflammatory markers; we switched intravenous to oral treatment approximately 1 month after all inflammatory markers (C-reactive protein [CRP], procalcitonin, erythrocyte sedimentation rate [ESR]) in our patient had normalised. Treatment in this case was complicated by initial intolerance to voriconazole, requiring a switch to a regimen that was potentially less effective (amphotericin and fluconazole). We did not see signs of recurrence; reasons that could be hypothesised include this patient never having blood stream infection, tissue growth of *Trichosporon* is slow, and the combination of amphotericin with fluconazole may have had the effect of at least keeping fungal growth at bay.[4] As prevention of any recurrence is essential, the

plan is to continue oral voriconazole indefinitely. The question remains as to duration of management and ultimate long-term outcome, as we are unable to confidently document clearance.

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Correlates of Online Game Play Motivations, Social Anxiety and Psychological Distress

Dear Editor,

Online gaming is a popular pastime among children and adults alike, and research on its impact on behaviour has increased in recent decades. With growing concerns over problematic gaming, Internet Gaming Disorder was introduced in Section 3 of the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), prompting necessary research before including it as a diagnostic category.

Massively multiplayer online role-playing games (MMORPGs) is the game genre most often studied with regard to online gaming behaviour. Whang and Chang[1] described the online world of MMORPGs as virtual "living" places and described players as having different "lifestyles" in-game, with different reasons and ways of playing. Yee[2] proposed 10 motivations describing reasons MMORPG players feel motivated to play and these are commonly used to assess gaming motivations. One of the motivations described is 'escapism' which involves playing games to relax, escape from real life and avoid real life problems; and was found to be a predictor of internet addiction and problematic internet use. Other studies[3] have cited achievement and socialising to be predictors as well.

Though some develop problematic use, not all gamers become addicted. Researchers have proposed that online games are used as a method of coping with psychosocial problems or unmet needs and that excessive use may not necessarily indicate addiction but something termed 'compensatory internet use'.[4]

Psychosocial distress is thought to have both direct and mediated effects on addictive gaming[5] and may even precede it.[6] Some psychosocial stressors which are ostensible causes of compensatory internet use or addiction use are loneliness, low self-esteem, depression, anxiety, body dissatisfaction, social phobias and stress.[6,7,8] With escapism and socialising being two motivations of play,[2] it is arguable that distress in these areas can motivate people to play games beyond normal levels of use as a means of compensation.

These studies demonstrate that motivations could be indicators of unmet psychosocial needs. Thus, the authors explored the sociodemographic factors relating to motivations of play and investigated the relationship between motivations of play, social phobia and psychological distress. Data was collected as part of a study on internet gaming disorder in Singapore.[9]

Participants aged 13-40 years old, residing in Singapore at the time of the study were recruited through convenience sampling. Responses were collected via an anonymous online survey which took approximately 10-15 minutes to complete. Informed consent was obtained from all participants online before beginning the survey.

Sociodemographic data including age, gender, ethnicity, education level and employment status was obtained. Yee's[2] Motivations To Play Inventory (MTPI) scale that measures 10 different motivations of online game-play that fall under 3 main components, was used to measure participants' motivations of play. Details of the different motivations are provided in Table 1. The Social Phobia Inventory (SPIN)[10]

Table 1. Gaming Motivations*

Component	Subcomponent	Description
Achievement		
	Advancement	The need to progress or advance in the game in terms of gaining points or other achievements.
	Mechanics	Seeking to analyse and understand the system as a way of maximising their performance in the game.
	Competition	The need to compete or vie with an opponent.
Social		
	Socialising	Perceiving it as a social interaction that involves chatting and interacting with other players.
	Relationship	Forming important and relevant relationships with other players.
	Teamwork	Perceiving the game as a team-effort and gaining fulfillment from it.
Immersion		
	Discovery	Unearthing novel events or approaches in the game.
	Role-playing	Creating, assuming and acting out the role of a fictional character.
	Customisation	Customising their character based on personal preferences.
	Escapism	Using the game as a means to seek distraction and escape unpleasant realities.

*Described by Yee N. Motivations for play in online games. Cyberpsychol Behav 2007;9:772-5.

was used to measure social anxiety symptoms. The General Health Questionnaire (GHQ-12)[11] was used to measure psychological distress.

Multiple linear regression was conducted to explore the relationship between MTPI scores, sociodemographic factors, SPIN scores and GHQ-12 scores. Responses from 737 respondents who played MMORPGs were included in the analysis. Sample characteristics are shown in Table 2. Overall, the results revealed sociodemographic differences in motivations of play as well as correlations between social phobia, psychological distress and select motivations.

Gender was significantly associated with more motivations than any other sociodemographic factor and was similarly identified as a significant factor in Yee's[2] study. These gender differences are different to those found by Yee.[2] Males scored higher than females on the motivations for achievement (advancement, mechanics and competition) in both studies. However, Yee[2] found females to be more motivated by the relationship subcomponent while the opposite was found in this study. Males were more motivated by the relationship and socialising subcomponents while females were motivated by teamwork. This is not to say that females in our study were not motivated by relationships and socialising, but perhaps the contrasting findings reflect an interaction between culture and gender. Yee also found no gender differences in the role-playing and escapism subcomponents though males in our sample scored higher in these motivations than females. Studies from Taiwan reported gender differences in game-play habits suggesting that males were more motivated to play video games[12] and that certain factors including distress such as "lower self-esteem and lower satisfaction with daily life were associated with more severe addiction among males, but not females".[13] Gender differences in gaming behaviour could be more prominent in Asian countries, but more cross-cultural research is needed to explore this possibility.

Table 2. Sample Characteristics (n = 737)

		n	%
Gender			
	Male	447	60.7
	Female	290	39.3
Age group			
	13 – 20 years	252	34.2
	21 – 25 years	286	38.8
	26 – 30 years	122	16.6
	31 – 40 years	77	10.4
Education level			
	Primary	27	3.7
	Secondary	17	2.3
	O/N levels	135	18.3
	A levels	103	14
	Vocational	23	3.1
	Diploma	206	28
	University	225	30.5
Employment status			
	Student	395	53.6
	Employed	293	39.8
	Unemployed	24	3.3
	Homemaker	2	0.3
	Conscription	23	3.1
Ethnicity			
	Chinese	695	94.3
	Malay	22	3
	Indian	13	1.8
	Others	7	0.9

Similarly, further cross-cultural research could elucidate the ethnic differences found in our sample. Malays scored higher for competition, while Indians and those of Others ethnicity scored higher in escapism than Chinese participants. As our results and previous studies have shown escapism to be related to psychological distress, social phobia and problematic use, one must be cognisant of the higher scores in certain ethnic groups. To our knowledge, no other studies have explored ethnic differences in motivations of play and it is difficult to explain these differences. Future research is required to investigate ethnic differences in motivations and their relationship to problematic game-playing to clarify if higher escapism in different ethnic groups is a cause for concern.

Significant correlations found between motivations and age, education level and employment status are interesting but difficult to explain. These differences may simply be different MMORPG playing lifestyles as described by Whang and Chang,[1] with different groups playing for different reasons.

As both the teamwork and socialising subcomponents fall under the overarching social motivation, it is interesting to note that social phobia was negatively correlated with teamwork but positively correlated with socialising. Those with higher SPIN scores being motivated to play for socialising reasons appears congruent with Kardefelt-Winther's[5] theory of compensatory internet use. While socialising online despite fear of social interactions may seem counter-intuitive, researchers have acknowledged the ostensible safety of anonymity that online communication grants which allows individuals to practise social interactions in a safe environment.[14] With regard to the discrepancy

between socialising and teamwork subcomponents, this may be explained by the versatility of MMORPGs. The teamwork motivation is related to interacting during game-play to achieve a common goal, whereas socialising involves interacting with other players simply for the sake of interaction. MMORPGs are often versatile enough that in-game goals may be completed alone, and that interaction with other players need not be related to in-game goals. Perhaps this describes a different playing style of MMORPG players who endorse social anxiety symptoms.

Playing for customisation of the player's character was associated with higher social phobia scores and psychological distress scores. Previous research suggests the use of game characters as means of achieving an ideal self. Discrepancies between one's actual self and ideal self may cause distress and customisable game characters are used to reduce this discrepancy, particularly in those with lower psychological well-being.[15] Thus, the process of customising and playing as an ideal character can reduce distress and enhance the sense of escaping problems during game-play. This may explain why MMORPGs are popular among gamers as well as researchers investigating the basis of problematic game use. Similarly, the anonymity provided by online interactions and the ability to present a more ideal, "customised" self through game characters may facilitate socialising online since those with higher SPIN scores are motivated by both customisation and social subcomponents.

Finally, in line with the extant literature,[2,4] escapism was positively associated with social phobia and psychological distress in our study. While the different motivations are not direct signs of psychosocial problems in gamers, unusually high levels of motivation to play, particularly for escapism, may be an indicator of the unmet needs in gamers with internet gaming addiction or other psychological distress. Although there was no specific motivation associated with social phobia or psychological distress, it appears that those with higher levels of social phobia and distress are generally more motivated to play online games than those without. The DSM-5 proposes excessive play and using games to escape or relieve negative mood as part of the criteria for internet gaming disorder. However, our findings are in line with a recent longitudinal study on online game-play which suggested that psychosocial problems may be the cause rather than the consequence of excessive use.[7]

Playing for what some may consider long hours or to escape problems is not sufficient for a diagnosis but may indicate compensatory internet use. This has implications for the treatment of those with problematic gaming as reducing social phobia and distress may also reduce motivation for game-playing and by extension, the time spent playing games. This may also improve the individual's overall mental well-being and support treatment for internet gaming addiction. Thus, the holistic treatment and differential diagnosis of internet gaming disorder should consider whether other psychosocial problems are a confounding factor and treat them accordingly.

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Visual Outcomes after Cataract Surgery in Diabetic Patients: A Meta-Analysis

Dear Editor,

Diabetic retinopathy is a common complication of diabetes which can result in blindness. Studies have generally shown that visual outcomes after cataract surgery in patients with diabetes are worse than in non-diabetics, especially those with diabetic retinopathy.[1-3] In patients with diabetic retinopathy, a major cause of unfavourable outcomes after cataract surgery is macular oedema.[4] Factors associated with significant macular oedema include the duration of diabetes, glycaemic control, degree of retinopathy, and macular oedema at the time of surgery.[4,5] Increased retinopathy progression and increased incidence of macular oedema after cataract surgery have been reported in patients with diabetes,[1] while other studies have not reported these findings.[6] Some authors suggested that the findings are due to the natural course of diabetes.[5,7]

To this end, we performed a meta-analysis to determine outcomes of cataract surgery in diabetic patients with diabetic retinopathy as compared to those without retinopathy.

Materials and Methods

Medline, Cochrane, and Google Scholar databases were searched from inception until January 30, 2015 using combinations of the following keywords: visual outcome, cataract surgery, diabetes, diabetic retinopathy. Inclusion criteria for the meta-analysis were: 1) two-arm studies; 2) one group of eyes that had diabetic retinopathy and another that did not; 3) that both groups of eyes had undergone cataract surgery; 4) quantitative outcomes that had been reported. Single-arm studies and those with patients receiving medical treatment (enoxaparin, ranibizumab, or triamcinolone, etc.) in addition to cataract surgery to prevent macular oedema were excluded. Letters, comments, editorials, case reports, proceedings, and personal communications were also excluded. Studies were identified by the search strategy via two independent reviewers.

Information/data extracted from studies that met the inclusion criteria were: the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, presence of retinopathy and the major outcomes. The method described by Hayden et al[8] was used to assess the quality of the included studies.

Outcome measures were: 1) percentage of eyes with postoperative newly developed macular oedema; 2) percentage of eyes with progressive retinopathy; 3) percentage of eyes with visual acuity reaching 6/12. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to represent the effect size of associations between diabetic retinopathy and outcomes. An OR >1 indicated that patients with diabetic retinopathy had greater odds of developing macular oedema and progressive retinopathy compared to those without diabetic retinopathy, and that patients with diabetic retinopathy had greater odds of visual acuity improvement than those without diabetic retinopathy. Heterogeneity among the studies was assessed by the Cochran Q and the I^2 statistic. A Q statistic P <0.10 was considered to indicate statistically significant heterogeneity. An I^2 statistic ≥50% was considered to indicate large to extreme heterogeneity. Random-effects models were used if heterogeneity was detected (I^2 >50% or Q statistics P <0.10). Otherwise, fixed-effects models were used. A two-sided P <0.05 was considered statistically significant. Meta-analysis sensitivity was assessed with the leave-one-out approach. Statistical analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Results

A total of 370 articles were identified, and 330 remained after duplicates were removed. After screening by abstracts and titles, 283 were excluded and the full-texts of 47 articles were reviewed. Thirty-nine articles were excluded for not meeting the inclusion criteria. Ultimately, 8 studies were included in the meta-analysis.[1,2,4,9-13] The number of patients in the 8 studies ranged from 30 to 119, and number of eyes ranged from 30 to 180. The mean or median age ranged from 66.4 to 76 years, and the proportion of males ranged from 32% to 79% (Table 1).

There was no evidence of heterogeneity across 3 studies that reported outcomes of newly developed macular oedema. Patients with diabetic retinopathy had higher odds of developing macular oedema than those without diabetic retinopathy (pooled OR = 5.912, 95% CI: 2.723 to 12.839, P <0.001) (Fig. 1a).

There was no evidence of heterogeneity across 5 studies that reported outcomes of progressive retinopathy. Patients

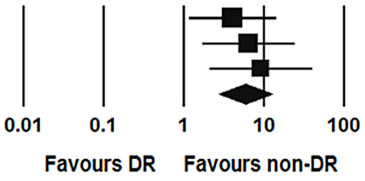
Table 1. Characteristics of Studies Included in the Meta-Analysis

First Author (Publication Year)	Study Design	No. of Patients	Length of Follow-up	Group	No. of Eyes in Each Group	Cataract Surgery	Age (Years)	Male	Retinopathy Subgroup	No. of Patients in Retinopathy Subgroup
Cunliffe (1991)	Retrospective	60	2.6 years	Non-diabetics	66	Extracapsular cataract extraction	70.5	42%	Non-diabetics	66
				Diabetics	66		73.9	42%	Without retinopathy	33
									Background	23
									Proliferative	10
Pollack (1992)	Retrospective	79		Non-diabetics	25		71.2	40%	Non-diabetics	25
				Diabetics	44		66.7	32%	Without retinopathy	28
									With retinopathy	16
Antcliff (1996)	Retrospective	63	12 months	Without retinopathy	24	Phacoemulsification and intraocular lens implantation	67	41%	Without retinopathy	24
				With retinopathy	50				Background	23
									Proliferative	27
Tsujikawa (1997)	Retrospective	102	6 months	Diabetics	140	Extracapsular cataract extraction	68.6	43%	Without retinopathy	83
									Background	42
									Preproliferative	3
									Quiescent proliferative	9
									Active proliferative	3
Borrillo (1999)	Retrospective	119	10 months	Without retinopathy	56	Phacoemulsification	62.2	34%	Without retinopathy	56
				With retinopathy	94				Non-proliferative	49
									Proliferative	45
Zaczek (1999)	Prospective		12 months	Non-diabetics	22	Uncomplicated, phacoemulsification	Median:76	55%	Non-diabetics	22
				Diabetics	52		Median:73	39%	No/mild-moderate	27
									Proliferative	25
Sadiq (1999)	Retrospective			Non-diabetics	28	Phacoemulsification	69.3	32%	Non-diabetics	
				Diabetics	28		66.4	50%	Without retinopathy	14
									Background	8
									Maculopathy	5
									Proliferative	1
				Non-diabetics	90	Extracapsular cataract extraction	72.3	46%	Non-diabetics	
				Diabetics	90		74.4	42%	Without retinopathy	78
									Background	8
									Proliferative	1
									Maculopathy	3
Chatterjee (2004)	Retrospective	30	12.4 months	Without retinopathy	22	Phacoemulsification	68.9	50%	Without retinopathy	22
				With retinopathy	8				Non-proliferative	5
									Proliferative	3

(a) Newly developed macular oedema

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value
Zaczek (1999)	4.062	1.166	14.154	2.200	0.028
Tsujikawa (1997)	6.377	1.691	24.042	2.736	0.006
Pollack (1992)	9.148	2.072	40.386	2.922	0.003
Pooled	5.912	2.723	12.839	4.491	0.000

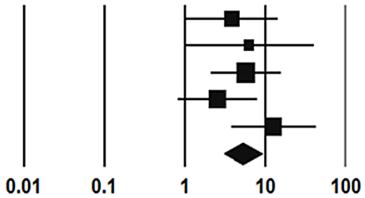
Test for heterogeneity: Q = 0.69, *P* = 0.708, I^2 = 0%



(b) Progressed retinopathy

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value
Pollack (1992)	3.857	1.044	14.247	2.025	0.043
Chatterjee (2004)	6.333	1.001	40.071	1.961	0.050
Borrillo (1999)	5.780	2.105	15.874	3.404	0.001
Antcliff (1996)	2.533	0.813	7.890	1.604	0.109
Cunliffe (1991)	12.880	3.853	43.060	4.150	0.000
Pooled	5.282	3.051	9.144	5.944	0.000

Test for heterogeneity: Q = 3.99, *P* = 0.407, I^2 = 0%



(c) Visual acuity reaching 6/12

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value
Pollack (1992)	0.124	0.031	0.498	-2.944	0.003
Antcliff (1996)	0.467	0.136	1.600	-1.212	0.225
Cunliffe (1991)	0.190	0.059	0.612	-2.782	0.005
Sadiq (1999)	0.195	0.076	0.502	-3.385	0.001
Pooled	0.217	0.122	0.385	-5.208	0.000

Test for heterogeneity: Q = 2.21, *P* = 0.531, I^2 = 0%

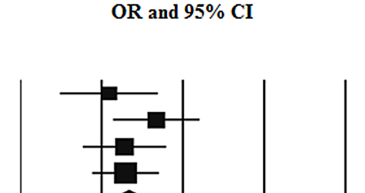


Fig. 1. Forest plots for association of diabetic retinopathy on (a) newly developed macular oedema, (b) progressive retinopathy and (c) visual acuity reaching 6/12.

with diabetic retinopathy had higher odds of developing progressive retinopathy than those without diabetic retinopathy (pooled OR = 5.282, 95% CI: 3.051 to 9.144, *P* <0.001) (Fig. 1b).

There was no evidence of heterogeneity across 4 studies that reported visual acuity outcomes. Patients with diabetic retinopathy had lower odds of visual acuity reaching 6/12 than those without retinopathy (pooled OR = 0.217, 95% CI: 0.122 to 0.385, *P* <0.001) (Fig. 1c).

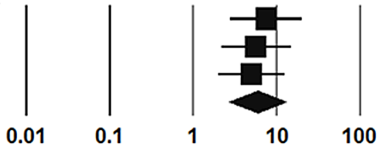
Sensitivity analyses showed that the magnitude and direction of the outcomes did not change considerably, indicating that there was no single study that had a significant impact on the pooled results of any of the outcomes (Fig. 2). Quality assessment demonstrated a low risk of bias in both study participation and study attrition. A moderate risk was estimated in prognostic factor measurement, outcome measurement and analysis. All the studies showed a high risk of bias in confounding measurement and account.

Discussion

This meta-analysis showed that patients with diabetic retinopathy had higher odds of developing macular oedema, progressive retinopathy, and lower odds of achieving visual acuity of 6/12 after cataract surgery. Only one prior meta-analysis performed in 1995 examined outcomes of

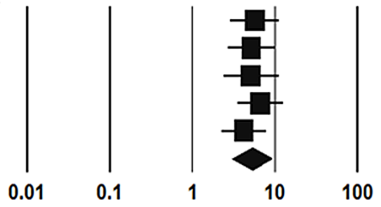
(a) Newly developed macular oedema

Study name	Statistics with study removed					OR and 95% CI with study removed
	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value	
Zaczek (1999)	7.485	2.783	20.135	3.987	0.000	
Tsujikawa (1997)	5.685	2.186	14.782	3.564	0.000	
Pollack (1992)	5.020	2.022	12.462	3.477	0.001	
Pooled	5.912	2.723	12.839	4.491	0.000	



(b) Progressed retinopathy

Study name	Statistics with study removed					OR and 95% CI with study removed
	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value	
Pollack (1992)	5.689	2.870	11.277	4.980	0.000	
Chatterjee (2004)	5.191	2.675	10.072	4.869	0.000	
Borrillo (1999)	5.138	2.402	10.987	4.220	0.000	
Antcliff (1996)	6.606	3.530	12.363	5.904	0.000	
Cunliffe (1991)	4.187	2.261	7.754	4.555	0.000	
Pooled	5.282	3.051	9.144	5.944	0.000	



(c) Visual acuity reaching 6/12

Study name	Statistics with study removed					OR and 95% CI with study removed
	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value	
Pollack (1992)	0.243	0.129	0.458	-4.383	0.000	
Antcliff (1996)	0.175	0.091	0.335	-5.250	0.000	
Cunliffe (1991)	0.226	0.114	0.450	-4.235	0.000	
Sadiq (1999)	0.230	0.109	0.487	-3.847	0.000	
Pooled	0.217	0.122	0.385	-5.208	0.000	

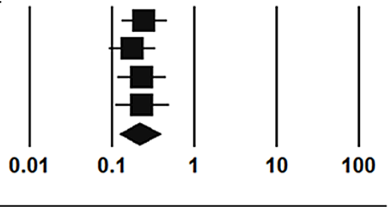


Fig. 2. Sensitivity analysis for association of diabetic retinopathy on (a) newly developed macular oedema, (b) progressive retinopathy and (c) visual acuity reaching 6/12.

cataract surgery in patients with diabetes, and the study found that the severity of retinopathy and maculopathy prior to cataract surgery were the major factors affecting postoperative visual acuity.[3]

Dowler et al[14] reported that phacoemulsification was associated with better visual outcomes, less need for capsulotomy, and less inflammation as compared to extracapsular extraction in patients with diabetes. While visual outcomes in diabetic patients with or without minimal retinopathy are similar to those without diabetes, postoperative visual acuity may be less than optimal in patients with significant retinopathy.[13] In eyes without macular oedema at the time of surgery, the occurrence of postoperative macular oedema tends to resolve spontaneously. In cases where macular oedema persists, it may represent the natural course of diabetes rather than the effect of surgery.[5] Clinically significant macular oedema at the time of cataract surgery, however, is unlikely to resolve postoperatively.[5] Krepler et al[7] reported poorer visual outcomes in patients developing macular oedema after phacoemulsification and posterior chamber lens implantation. Eriksson et al[15] reported final visual outcomes in eyes with mild to moderate retinopathy without previous macular oedema were as good as that in normal eyes.

Diabetic retinopathy can progress after intracapsular and extracapsular cataract extraction.[16] On the other hand, some studies have shown similar results with phacoemulsification, while others have reported no effect on retinopathy as a result

of phacoemulsification.[7] Differences in outcomes may be attributable to different criteria used to define progressive retinopathy. Two prospective studies of phacoemulsification in patients with diabetes indicated the procedure does not accelerate diabetic retinopathy, and progression is likely the result of the natural course of the diabetes.[5]

The results of this study must be interpreted with caution due to a number of limitations. The number of studies was only 8 and the total number of patients was small. All 8 studies did not address all outcomes, and all the studies were performed in the 1990s with the exception of one performed in 2004. Data from older studies may not necessarily reflect current outcomes due to advances in surgical techniques. The surgical approach and patient grouping and selection varied between studies, and different surgical approaches are associated with different results. We did not distinguish between proliferative and non-proliferative diabetic retinopathy, or examine confounding factors. Lastly, we did not stratify retinopathy, account for glucose control, or consider prior treatments as the number of studies were so limited.

Conclusion

In conclusion, worse outcomes are seen in diabetic patients with retinopathy after cataract surgery than in those without retinopathy. The results, however, should be interpreted with caution due to a lack of recent studies.

Acknowledgements

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