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"Many a calm river begins as a turbulent waterfall, yet none hurtles and foams all the way to the sea."

Mikhail Lermontov (1814 – 1841)
Russian poet

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Editorial

Missed Appointments at a Diabetes Centre: Not a Small Problem

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Fundamental to optimal diabetes management is good patient self-care and regular follow-up with health professionals. Missed appointment may disrupt the continuity of diabetes care, thereby interfering with regular preventive screening and timely intervention.[1] It may also affect care for other patients due to interference with scheduling, poor use of resources and negative impact on doctor-patient relationship.[2]

The prevalence of missed appointment at diabetes clinics varied considerably. For example, it was reported in a review by Griffin SJ that the prevalence of non-attendance for at least a year from diabetes clinic in the United Kingdom was 4% to 8%.[2] A study by Karter AJ et al[1] showed that 64% of diabetic patients missed 1 or more appointments based on data from the Kaiser Permanente Diabetes Registry, whereas another study by Nuti LA et al[3] reported that 16.2% of diabetic patients missed their last scheduled appointment in a medical centre. The differences could be attributed to variations in settings and lack of common measures of missed appointment.

Studies have revealed a multitude of factors associated with missed appointments including age,[1,4] shorter duration of diabetes,[4] days from scheduling to appointment,[5,6] days of week and time of appointment.[5] However, information on missed appointments in patients with diabetes in Singapore remains limited. Hence, we assessed the magnitude and risk factors of missed appointments in the Diabetes Centre in our hospital, a dedicated one-stop multidisciplinary centre to provide more holistic care and where a short message service (SMS) appointment reminder system has been in place since inception. The findings will enable us to account for these factors when scheduling appointments and apply appropriate strategies to encourage attendance.

We conducted a retrospective cohort study of patients who first attended doctor's appointment at Diabetes Centre between 1 June 2010 and 31 May 2012. Their attendance for appointments was tracked till 31 December 2013. Missed appointments comprised scheduled appointments which were not attended nor cancelled. Data on patient and appointment characteristics were extracted or derived from the hospital administrative database. We analysed the data in 2 ways – 1) patients who missed most recent appointment as the primary analysis, using a study by Lee VJ et al[6] as reference, and 2) patients who missed >30% of scheduled appointments as a secondary analysis, using a study by Karter AJ et al[1] as reference.

In our study, there were altogether 13,244 appointments scheduled for 1645 patients at Diabetes Centre. Failed appointments accounted for 13.8% of these appointments. Of the 1645 patients, 53.7% missed one or more appointments. Of note, 229 patients (13.9% of the study population) who missed more than 2 appointments accounted for 53.5% of the missed appointments. After excluding 2 patients who died and 33 patients whose missed appointment occurred during hospitalisation, a total of 1610 patients were included in the analysis for most recent missed appointments. Of these, 25.5% had failed most recent appointment.

Our results showed that patients who missed most recent appointment tended to be younger, males, from Malay, Indian and Other ethnic groups and have fewer annual scheduled appointments. They were also more likely to have intrahospital referral, >20% of previous missed appointments, hospitalisation between previous and most recent appointments and repeated last scheduled appointment, with intervals 31 to 60 days and 61 to 90 days from previous appointment, and appointment during January-July (P <0.05 for all) (Table 1). In the multivariable model adjusted for age and gender, >20% of previously missed appointments, Malay, Indian and Other ethnic groups, appointment in January to September, intervals of 31 to 60 days and 61 to 90 days between previous and current scheduled appointments, age ≤40 years, and fewer annual scheduled appointments were significantly associated with missing most recent appointment (Table 2).The area under receiver operating characteristic (ROC) curve of the final model was 0.748 (95% CI, 0.720 to 0.776).

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Table 1. Characteristics of Patients by Missing Most Recent Appointment and Rate of Missed Appointments

Characteristic	All Patients (n = 1610)	Missed Most Recent Appointment			Rate of Missed Appointments		
		No (n = 1200)	Yes (n = 410)	*P* Value	0% to 30% Missed Appointment Rate (n = 1246)	>30% Missed Appointment Rate (n = 364)	*P* Value
Age (years)	56.0 ± 14.4	56.7 ± 14.0	53.7 ± 15.3	0.002	56.9 ± 14.0	52.7 ± 15.1	<0.001
Age group				<0.001			<0.001
≤30 years	92 (5.7)	50 (4.2)	42 (10.2)		57 (4.6)	35 (9.6)	
31 – 40 years	162 (10.1)	116 (9.7)	46 (11.2)		113 (9.1)	49 (13.5)	
41 – 50 years	275 (17.1)	207 (17.3)	68 (16.6)		207 (16.6)	68 (18.7)	
51 – 60 years	440 (27.3)	327 (27.3)	113 (27.6)		344 (27.6)	96 (26.4)	
61 – 70 years	379 (23.5)	301 (25.1)	78 (19.0)		312 (25.0)	67 (18.4)	
>70 years	262 (16.3)	199 (16.6)	63 (15.4)		213 (17.1)	49 (13.5)	
Gender				0.007			0.013
Female	787 (48.9)	610 (50.8)	177 (43.2)		630 (50.6)	157 (43.1)	
Male	823 (51.1)	590 (49.2)	233 (56.8)		616 (49.4)	207 (56.9)	
Ethnic group				<0.001			<0.001
Chinese	969 (60.2)	763 (63.6)	206 (50.2)		793 (63.6)	176 (48.4)	
Malay	222 (13.8)	153 (12.8)	69 (16.8)		158 (12.7)	64 (17.6)	
Indian	316 (19.6)	214 (17.8)	102 (24.9)		222 (17.8)	94 (25.8)	
Others	103 (6.4)	70 (5.8)	33 (8.1)		73 (5.9)	30 (8.2)	
Consultation type				0.118			0.063
Private	330 (20.5)	257 (21.4)	73 (17.8)		268 (21.5)	62 (17.0)	
Subsidised	1280 (79.5)	943 (78.6)	337 (82.2)		978 (78.5)	302 (83.0)	
First appointment				<0.001			
Yes	172 (10.7)	151 (12.6)	21 (5.1)				
No	1438 (89.3)	1049 (87.4)	389 (94.9)				
Referral source				<0.001			0.002
Polyclinic	370 (23.0)	276 (23.0)	94 (22.9)		293 (23.5)	77 (21.2)	
General practitioner	55 (3.4)	45 (3.8)	10 (2.4)		49 (3.9)	6 (1.7)	
Self	136 (8.5)	112 (9.3)	24 (5.9)		110 (8.8)	26 (7.1)	
Intrahospital	789 (49.0)	562 (46.8)	227 (55.4)		583 (46.8)	206 (56.6)	
Public institutions	196 (12.2)	165 (13.8)	31 (7.6)		166 (13.3)	30 (8.2)	
Others	64 (4.0)	40 (3.3)	24 (5.9)		45 (3.6)	19 (5.2)	
Month of the year				<0.001			
January	63 (3.9)	37 (3.1)	26 (6.3)				
February	66 (4.1)	39 (3.3)	27 (6.6)				
March	58 (3.6)	36 (3.0)	22 (5.4)				
April	90 (5.6)	52 (4.3)	38 (9.3)				
May	80 (5.0)	53 (4.4)	27 (6.6)				
June	92 (5.7)	54 (4.5)	38 (9.3)				
July	96 (6.0)	69 (5.8)	27 (6.6)				
August	119 (7.4)	89 (7.4)	30 (7.3)				
September	158 (9.8)	120 (10.0)	38 (9.3)				
October	253 (15.7)	210 (17.5)	43 (10.5)				
November	255 (15.8)	211 (17.6)	44 (10.7)				
December	280 (17.4)	230 (19.2)	50 (12.2)				

Table 1. Characteristics of Patients by Missing Most Recent Appointment and Rate of Missed Appointments (Con't)

Characteristic	All Patients (n = 1610)	Missed Most Recent Appointment			Rate of Missed Appointments		
		No (n = 1200)	Yes (n = 410)	*P* Value	0% to 30% Missed Appointment Rate (n = 1246)	>30% Missed Appointment Rate (n = 364)	*P* Value
Day of the week scheduled				0.629			
Monday	356 (22.1)	267 (22.3)	89 (21.8)				
Tuesday	267 (16.6)	206 (17.2)	61 (14.9)				
Wednesday	322 (20.0)	244 (20.4)	78 (19.1)				
Thursday	436 (27.1)	319 (26.6)	117 (28.6)				
Friday	227 (14.1)	163 (13.6)	64 (15.7)				
Time of scheduled appointment (hours)				0.240			
0700 – 0900	473 (29.4)	365 (30.4)	108 (26.3)				
1000 – 1200	645 (40.1)	469 (39.1)	176 (42.9)				
1300 – 1400	275 (17.1)	199 (16.6)	76 (18.5)				
1500 – 1700	217 (13.5)	167 (13.9)	50 (12.2)				
Days from previous appointment date to current appointment date (days)	97.0 (67.0 – 119.0)	98.0 (70.0 – 119.0)	91.0 (63.0 – 126.0)	0.254			
Days from previous appointment date to current appointment date (days)				0.003			
Up to 30 days	140 (9.5)	105 (9.8)	35 (8.6)				
31 to 60 days	170 (11.5)	109 (10.1)	61 (15.1)				
61 – 90 days	335 (22.6)	229 (21.3)	106 (26.2)				
More than 90 days	836 (56.5)	633 (58.8)	203 (50.1)				
Annual number of scheduled appointments	3.0 (2.0 – 3.8)	3.0 (2.0 – 3.8)	2.5 (2.0 – 3.3)	<0.001	3.0 (2.0 – 4.0)	2.3 (2.0 – 3.0)	<0.001
Percentage of previous missed appointments				<0.001			
Up to 20%	1159 (78.3)	890 (82.7)	269 (66.4)				
21% to 40%	198 (13.4)	128 (11.9)	70 (17.3)				
41% to 60%	99 (6.7)	47 (4.4)	52 (12.8)				
More than 60%	25 (1.7)	11 (1.0)	14 (3.5)				
Hospitalisation between previous appointment date and recent appointment visit date				0.012			
No	1429 (88.8)	1079 (89.9)	350 (85.4)				
Yes	181 (11.2)	121 (10.1)	60 (14.6)				

Table 2. Factors Associated with Most Recent Missed Appointment and Rate of Missed Appointment in Multivariable Logistic Regression Models

Characteristics	Odds Ratio (95% CI) *P* Value	
	Most Recent Missed Appointment*	More than 30% Missed Appointment Rate†
Age group		
Up to 40 years	1.59 (1.08 – 2.32) 0.018	2.40 (1.67 – 3.43) <0.001
41 to 60 years	1.00 (0.76 – 1.33) 0.982	1.32 (1.00 – 1.75) 0.049
More than 60 years	1.00	1.00
Gender		
Female	1.00	1.00
Male	1.14 (0.88 – 1.47) 0.332	1.25 (0.97 – 1.61) 0.079
Ethnic group		
Chinese	1.00	1.00
Malay	1.47 (1.02 – 2.13) 0.039	1.80 (1.27 – 2.55) 0.001
Indian	1.94 (1.41 – 2.67) <0.001	2.23 (1.64 – 3.03) <0.001
Other	2.43 (1.47 – 4.03) 0.001	2.09 (1.30 – 3.38) 0.003
Consultation type		
Private	1.00	1.00
Subsidised	0.95 (0.61 – 1.49) 0.827	1.40 (0.89 – 2.19) 0.148
First appointment		
Yes	1.00	
No	1.23 (0.59 – 2.53) 0.582	
Referral source		
Polyclinic	1.00	1.00
General practitioner	0.64 (0.26 – 1.58) 0.334	0.52 (0.19 – 1.42) 0.201
Self	0.64 (0.32 – 1.31) 0.223	1.09 (0.56 – 2.13) 0.805
Intrahospital	1.16 (0.85 – 1.60) 0.352	1.43 (1.05 – 1.96) 0.024
Public institutions	0.57 (0.35 – 0.93) 0.023	0.75 (0.47 – 1.22) 0.250
Others	1.29 (0.66 – 2.52) 0.451	0.93 (0.49 – 1.78) 0.835
Month of the year		
January – March	2.92 (1.88 – 4.53) <0.001	
April – June	2.59 (1.79 – 3.75) <0.001	
July – September	1.46 (1.05 – 2.03) 0.026	
October – December	1.00	
Days from previous appointment date to current appointment date (days)		
Up to 30 days	1.00	
31 to 60 days	2.19 (1.26 – 3.81) 0.005	
61 – 90 days	1.83 (1.11 – 3.02) 0.017	
More than 90 days	1.25 (0.78 – 1.99) 0.359	
Annual number of scheduled appoinments	0.72 (0.63 – 0.83) <0.001	0.73 (0.66 – 0.81) <0.001
Percentage of previous missed appointments		
Up to 20%	1.00	
21% to 40%	2.02 (1.41 – 2.90) <0.001	
41% to 60%	3.34 (2.08 – 5.38) <0.001	
More than 60%	3.81 (1.49 – 9.75) 0.005	
Hospitalisation between previous appointment date and recent appointment visit date		
No	1.00	
Yes	1.05 (0.71 – 1.55) 0.813	

*The multivariable model includes age, gender, ethnic group, consultation type, first appointment, referral source, month of the year, days from previous appointment date to current appointment date, annual number of scheduled appointments, percentage of previous missed appointments and hospitalisation between previous appointment date and recent appointment visit date.
†The multivariable model includes age, gender, ethnic group, consultation type, referral source and annual number of scheduled appointments.

The distribution of 1610 patients by missed appointments rate was as follows: 0% missed appointments, 46.8%; 1% to 30% missed appointments, 30.6%; >30% missed appointments, 22.6%. Patients who missed >30% appointments tended to be younger, males and from Malay, Indian and Other ethnic groups, had higher proportion of being referred from intrahospital source and fewer scheduled appointments annually than those with 0% to 30% of missed appointments (P <0.05 for all) (Table 1). In the multivariable model adjusted for age and gender (Table 2), Malay, Indian and Other ethnic group, younger age groups of up to 60 years, intrahospital referral and fewer appointments scheduled annually were significantly associated with >30% of missed appointments.

In our study, about 54% of patients missed one or more appointments and one-quarter missed most recent appointment. Only 14% of patients missed more than 2 appointments but accounted for about half of missed appointments. Similarly, an earlier study showed that a small group of patients failed 2 or more appointments but accounted for 59% of failed appointments at a Community Health Centre.[7] Furthermore, our results demonstrated that percentage of previous missed appointments is a strong risk factor of missing most recent appointment. Intensive measures can be taken to target patients with history of frequent defaults in order to reduce missed appointments substantially.

Similar to earlier research,[6] Malay, Indian and Other ethnic groups had higher odds of missing most recent appointment and frequent default in our study. The younger age group was more likely to miss most recent appointment or have poor appointment keeping behaviour than the older age groups in our study, in line with earlier studies.[3,4,6] The younger patients could have missed appointments due to commitments such as child care and employment. Secondly, they may tend to default when their condition improved.[8] Further research is needed to understand health-seeking behaviours and attitudes of patients by ethnic groups and age.

Longer interval between previous and current appointments increased the likelihood of missing most recent appointment. Forgetting appointment was cited as one of the top reasons for missing appointment.[9]

Fewer annual scheduled appointments was associated with missing most recent appointment and frequent default in our study. Patients who frequently defaulted appointment were more likely to make appointments and perceived less need to attend appointment when they felt better.[10]

To our knowledge, this is the first published study on missed appointments among patients attending a diabetes centre in Singapore. Our study reinforces earlier findings on the factors for missed appointment. Furthermore, the high area under the ROC curve for final model affirms the value of utilising routine hospital administrative data that is readily available without additional cost.

There are limitations in our study. Causality cannot be established in the retrospective observational design of our study. Secondly, our results cannot be extrapolated to the general population with diabetes or other clinical settings. As the administrative database is not designed for this study, we could not capture potential socioeconomic and clinical factors that may impact upon attendance.

In conclusion, a small group of patients contributed to a large proportion of missed appointments. Our study has shed light on the profile of patients at risk for frequent default. Using routine administrative database, we uncovered potential modifiable factors amenable to interventions.

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Original Article

Smartphone Imaging in Ophthalmology: A Comparison with Traditional Methods on the Reproducibility and Usability for Anterior Segment Imaging

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Abstract

Introduction: This study aimed to determine the reproducibility and usability of anterior segment images taken from a smartphone stabilised on a slit-lamp with those taken from a custom-mounted slit-lamp camera. Materials and Methods: This was a prospective, single-blind comparative digital imaging validation study. Digital photographs of patients with cataract were taken using a smartphone camera (an iPhone 5) on a telescopic mount and a Canon EOS 10D anterior segment camera. Images were graded and compared according to the Lens Opacification Classification System III (LOCS III). Results: A total of 440 anterior segment images were graded independently by 2 ophthalmologists, 2 residents and 2 medical students. Intraclass correlation (ICC) between the iPhone and anterior segment camera images were fair for nuclear opalescence (NO) and nuclear colour (NC), and excellent for cortical (C) and posterior subcapsular (PSC) (NO: ICC 0.40, 95% CI, 0.16 to 0.57; NC: ICC 0.47, 95% CI, 0.16 to 0.66; C: ICC 0.76, 95% CI, 0.71 to 0.81; PSC: ICC 0.81, 95% CI, 0.76 to 0.85). There was no difference in grader impression of confidence and images usability between both cameras (*P* = 0.66 and *P* = 0.58, respectively). Conclusion: Anterior segment images taken from an iPhone have good reproducibility for retro-illuminated images, but fair reproducibility for NO and NC under low light settings. There were no differences in grader confidence and subjective image suitability.

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Key words: Cataract, Clinical Ophthalmology, iPhone

Introduction

There is an increasing trend amongst medical professionals in recent years to incorporate smartphones as an informal clinical tool.[1,2] The ubiquity and accessibility of smartphones have prompted many ophthalmologists to use them as a clinical tool, and several studies have described the techniques on how to utilise smartphone cameras during ophthalmic examinations.[3,4]

Several studies have demonstrated qualitatively the ease of capturing ophthalmic images including fundus imaging using smartphones.[3,5] The smartphone is also a suitable platform for reviewing images taken remotely, as demonstrated in a retinopathy of prematurity (ROP) screening study in India.[6] However, to our knowledge, there are no studies that quantitatively compares the quality of images taken of patients' eyes in a clinical setting using a smartphone with those taken with a custom-mounted slit-lamp camera. Ye et al has concluded recently that the image spatial resolution of custom-mounted slit-lamp cameras was better than that of smartphones (iPhone 4 and 4S), though both were inferior to direct ocular viewing through the slit-lamp.[7] However, there are no published studies on the clinical reproducibility of smartphone images as compared to those taken with an anterior standard camera. This study describes a relatively simple method of obtaining stabilised slit-lamp images of eyes with cataract using a smartphone, and attempts to quantify its reproducibility using the validated Lens Opacification Classification System III (LOCS III), which covers important components in an anterior segment examination, namely slit examination (colour, opalescence) and retro-illumination.[8]

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Materials and Methods

Study Design

This was a single centre, clinic-based, and single-blind comparative digital imaging validation study. Eligible patient subjects were recruited from the general eye clinic after their clinical consultation. Patient subjects had to be at least 21 years old, willing and able to give informed consent, and have no concurrent intraocular or lid pathologies that might obscure photo-taking. Inclusion criteria for graders were as follows: at least 21 years old, willing and able to give consent, had undergone at least 1 clinical ophthalmology posting, and familiar with grading cataract images through LOCS III. This study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki and had ethics approval from the National Healthcare Group Domain Specific Review Board. Informed consent was obtained from all participating subjects.

Image Capturing Protocol

As part of the routine examination, image capture was performed in the same room for 1 or both eligible eyes of the patient after dilation with 1.0% tropicamide. For images taken using the anterior segment camera, a slit-lamp BP 900® (Haag-Streit, USA) with custom-mounted 6.3-megapixel Canon® EOS 10D digital single-lens reflex camera (Canon, Japan) was used; images were taken at a resolution of 3072 x 2048 pixels. For images taken using a smartphone, an iPhone 5 (Apple, Cupertino, CA) on a telescopic mount (Orion SteadyPix Universal Camera Mount, USA) was used; images were taken at 2448 x 3264 pixels using ProCam application (ProCam, Apple Store) which allows an autofocus lock for easier focusing.

Four simultaneous images of each eligible eye were taken for each instrument: 1 diffusely illuminated image, 1 slit image of the anterior segment, and 2 retro-illuminated images focused on cortex and posterior subcortex respectively.[8] Appropriate cropping was performed to retain only elements necessary for LOCS III grading (Fig. 1). Two anterior segment images were used to assess nuclear opalescence (NO) and nuclear colour (NC), while the remaining 2 images were used to grade cortical (C) and posterior subcapsular (PSC), respectively. Room settings and slit-lamp settings were modelled after standard conditions for LOCS III image grading, as described in greater detail elsewhere.[9]

Image Grading Protocol

Digital images were randomised separately for subject identity and for instrument used. To minimise response error, the images were shuffled through a simple random sampling (without replacement) using a computer software. A 10-minute briefing on LOCS III grading protocol was given prior to grading.[10] Graders individually graded all images on a standardised questionnaire. Images for grading were displayed on a 13-inch MacBook Pro laptop (Apple, Cupertino, CA) with a display resolution of 2560 x 1600 and maximum screen brightness. A LOCS III grading chart was also shown on the same screen for reference. Graders were blinded to the type of instrument being used for image capturing, but were informed that 2 separate instruments were used. All gradings were completed over a minimum of 3 sessions; each session did not exceed 1 hour and involved a maximum of 40 eyes.

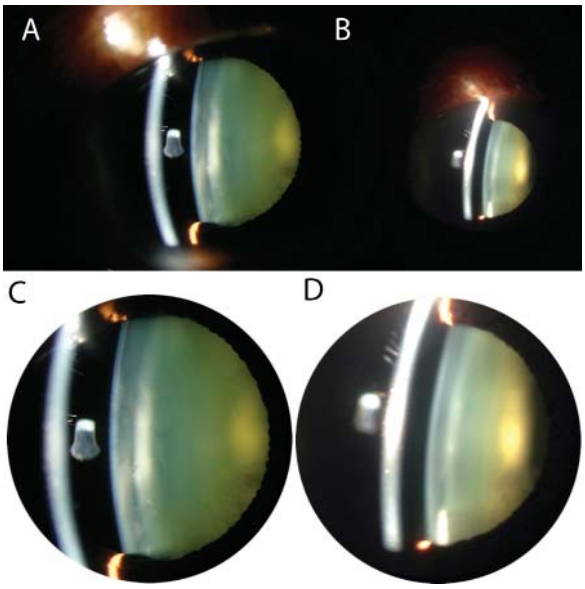

Fig. 1. Digital images taken from the anterior segment camera and the iPhone 5. Anterior segment image of the same patient taken with the anterior segment camera (A) and the iPhone 5 (B). Images were edited and cropped appropriately for both the anterior segment camera (C) and the iPhone 5 (D) to retain only necessary components for grading without giving away the source of image capture.

A standardised questionnaire and the LOCS III grading protocol were used to grade the cataract.[8] Each image also had an option for "Can't grade", when image quality was too poor for grading, or when 1 region of the lens obscured another region.[11] In addition, 2 subjective 5-point Likert scale questions were asked for each eye and assessed holistically i.e. based on NO, NC, C and PSC images of the same eye. One question assessed grader confidence, "I am confident of the pathologies I identified on this image", while another assessed subjective image suitability, "The quality of the image is suitable for identification of pathology".

Outcome Measures

The primary outcome measure of this study was the reliability of LOCS III grading in assessing images taken from an iPhone and those taken from anterior segment camera.

Table 1. Agreement between 6 Graders for Images Taken with the iPhone 5 and the Anterior Segment Camera

	Inter-Rater Agreement (iPhone 5)		Inter-Rater Agreement (Anterior Segment Camera)	
	Mean (SD)	ICC Coefficient (95% CI)	Mean (SD)	ICC Coefficient (95% CI)
Nuclear opalescence images (NO)	3.93 (0.35)	0.317 (0.193, 0.468)	3.38 (0.47)	0.391 (0.252, 0.539)
Nuclear colour images (NC)	4.07 (0.24)	0.485 (0.357, 0.625)	3.44 (1.12)	0.548 (0.392, 0.687)
Cortical images (C)	2.10 (0.15)	0.741 (0.638, 0.833)	1.91 (0.16)	0.847 (0.775, 0.906)
Posterior subcapsular images (PSC)	1.64 (0.40)	0.742 (0.619, 0.970)	1.80 (0.50)	0.691 (0.547, 0.810)

CI: Confidence interval; ICC: Intraclass correlation; SD: Standard deviation

Secondary outcome measures included the number of non-gradable images taken from an iPhone and anterior segment camera, inter-rater variability in grading iPhone images as well as anterior segment camera images, and grader confidence and image suitability for LOCS III grading.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (SPSS Inc, Chicago, Illinois). To achieve an expected agreement of kappa value (Κ) of at least 0.8 with a minimum power of 80%, images from 51 eyes with cataract were required. Intraclass correlation (ICC) was used to assess the between-graders and between-instrument reproducibility of the LOCS III for NO, NC, C, and PSC images. ICC interpretation was as follows: poor reproducibility if ICC <0.4, fair if 0.4 ≤ ICC ≤0.75, and excellent if ICC >0.75.[12] Bland-Altman plot was also used to assess agreement between LOCS III measurements.[13] Pearson's Chi-square test or Fisher's exact test was performed to determine associations between categorical variables and paired t-test was used to test for any difference between repeated continuous measurements. A *P* value of less than 0.05 was considered statistically significant in this study.

Results

Image Grading

A total of 440 digital images (iPhone: 220 images, anterior segment camera: 220 images) were taken from 55 eyes of 32 patients. Images were graded by 6 separate healthcare personnel independently (2 ophthalmologists, 2 ophthalmology residents, 2 medical students), over 3 separate sessions each. All graders completed all images. Out of the 440 images, 421 images (95.7%) were gradable by 1 rater (iPhone, n = 211, 95.9%; anterior segment camera, n = 210, 95.5%, *P* = 0.82). The cumulative percentage of non-gradable images for all raters was 6.3% (166 out of 2640 images; NS: n = 14, 2.1%; NC: n = 14, 2.1%; C: n = 61, 9.2%; PSC: n = 77, 11.7%).

Reproducibility between Graders

Intraclass correlation between graders for images taken by an anterior segment camera was poor for NO, fair for NC and PSC, and excellent for C images (Table 1). Intraclass correlation between graders for images taken by iPhone was poor for NO images and fair for the other subtypes (Table 1).

Reproducibility between Instruments

The reproducibility of images taken from the iPhone, when compared to those taken by the anterior segment camera, is shown in Table 2. Compared with the anterior segment camera, images taken by the iPhone were graded with significantly higher scores for NO and NC, and significantly lower scores for PSC. However, the scores were not significantly different

Table 2. Agreement between the iPhone 5 and the Anterior Segment Camera

Test Modality	Instrument Used	Mean (SD)	*P* Value*	ICC Coefficient (95% CI)
Nuclear opalescence images (NO)	Anterior segment camera	3.41 (0.94)	<0.001	0.399 (0.162, 0.567)
	iPhone 5	4.02 (0.98)		
Nuclear colour images (NC)	Anterior segment camera	3.45 (0.95)	<0.001	0.471 (0.156, 0.659)
	iPhone 5	4.09 (0.97)		
Cortical images (C)	Anterior segment camera	1.91 (1.46)	0.37	0.760 (0.705, 0.805)
	iPhone 5	1.85 (1.54)		
Posterior subcapsular images (PSC)	Anterior segment camera	1.74 (1.71)	0.002	0.805 (0.756, 0.845)
	iPhone 5	1.54 (1.58)		

CI: Confidence interval; ICC: Intraclass correlation; SD: Standard deviation
*Paired t-test.

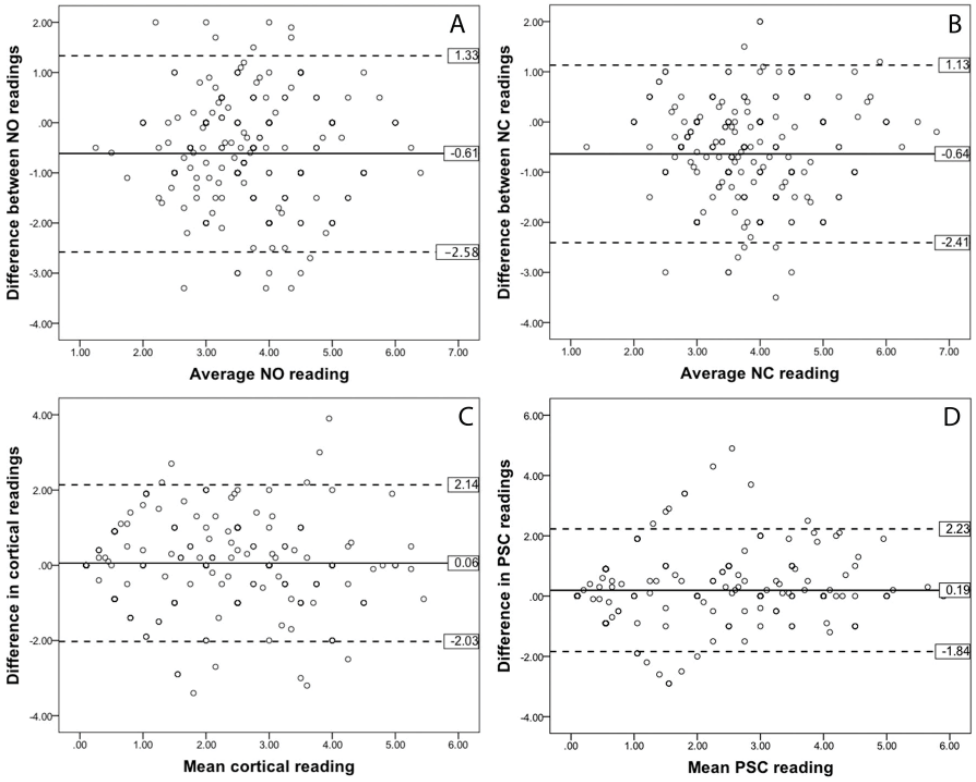

Fig. 2. Bland-Altman plot comparing images from the iPhone and from the anterior segment camera. Difference in measurement between instruments is calculated as: anterior segment camera – iPhone (where anterior segment camera represents images taken from the anterior segment camera, and iPhone represents images taken from the iPhone 5). Solid horizontal line represents the mean difference between instruments in each plot; dashed horizontal lines represent the upper and lower limits of 2 standard deviations from the mean difference.
NC : Nuclear colour images; NO: Nuclear opalescence images; PSC: Posterior subcapsular images

for C images. These findings were similar and consistent for all cataract subtypes among the graders and were also reflected in the Bland-Altman plots (Fig. 2).

Overall, reproducibility for iPhone images was fair for NO and NC images, and excellent for C and PSC images. These findings were consistent with those by ophthalmologists and ophthalmology residents. Medical students found that there was poor reproducibility for NO images, and fair reproducibility for NC, C and PSC images.

Subjective Scores

Cumulative responses to the 2 subjective Likert scale questions were collected. Graders expressed their confidence in grading images for 243 (73.6%) eyes that were taken using the anterior segment camera, and for 238 (72.1%) eyes taken using the iPhone ($P = 0.66$). On the other hand, graders felt that the images of 216 (65.5%) eyes taken by the anterior segment camera and the images of 197 (59.7%) eyes taken by the iPhone were suitable for grading ($P = 0.13$). Of the 3 grader categories, medical students responded the most positively to both questions, with more than 70% choosing "Agree" or "Strongly agree" to either question (Table 3).

Discussion

This study evaluated and compared the reproducibility of images taken using an iPhone with those captured by

Table 3. Confidence and Suitability by Proportion of Disagree (Stratified by Grader Categories)

Question	Grader Category	n (%)	
		Anterior Segment Camera	iPhone 5
"I am confident of the pathologies I identified on this image" – Agree/strongly agree	Ophthalmologist	64 (58.2)	72 (65.5)
	Resident	89 (80.9)	83 (75.5)
	Medical student	90 (81.8)	83 (75.5)
"The quality of the image is suitable for identification of pathology" – Agree/strongly agree	Ophthalmologist	60 (54.5)	63 (57.3)
	Resident	72 (65.5)	57 (51.8)
	Medical student	84 (76.4)	77 (70.0)

an anterior segment camera, using the validated LOCS III grading system on patients with cataract. The overall intraclass correlation between these 2 instruments ranged from fair to excellent, with the best reproducibility coming from the images of C and PSC cataract. Greater reproducibility was produced when graded by ophthalmologists or ophthalmology residents, while reproducibility was poorer overall when graded by medical students. Intraclass correlation between graders for anterior segment camera images ranged from poor to excellent depending on the type of image graded, and poor to fair for iPhone images. There was no significant difference in terms of grader confidence and subjective image suitability between anterior segment camera and iPhone, as measured through the 2 Likert scale questions.

This is the first study of its kind that uses ICC to grade anterior segment images through cataract assessment. Previous studies on photo grading was performed by describing the presence and absence of pathology.[14,15] From this study, it appears that iPhone images are more reliable for estimating areas of C and PSC cataract as compared to images captured by the anterior segment camera. However, reproducibility between images taken by the iPhone and anterior segment camera for NC and NO images was only fair, with the Bland-Altman plot demonstrating a consistently higher rating for the iPhone (Fig. 2). This could possibly be due to lighting issues—the standard LOCS III setting requires a dimly lit room for image capture. As a result, the auto-ISO and auto-white balance effects of the iPhone could have been artificially increased in the absence of an external flash, resulting in oversaturation of image colour and consequently, opacification. To compensate for the phone's form factor, the iPhone 5 uses a 4.54 mm x 3.42 mm CMOS sensor while the Canon EOS 10D uses a 22.7 mm x 15.1 mm CMOS sensor, and this could explain the superior performance of the latter under lower light settings. Interestingly, this phenomenon did not appear to affect retro-illuminated images (i.e. C and PSC images), suggesting that retro-illuminated images are well taken and may benefit from auto-ISO adjustments from the iPhone even in dim lighting. In view of such lighting issues, iPhone images may not necessarily be inferior to anterior segment camera images; rather, users should be mindful of ambient lighting while taking ophthalmic images using the iPhone, and provide a sufficiently well lit environment whenever possible.

In addition, we noted that there was considerable inter-rater variability in this study. There was fair to good reproducibility for retro-illuminated images, but grader agreement for NO and NC was poor and fair, respectively. This relatively poor agreement between graders manifested in the grading for both anterior segment camera and iPhone images (Table 1), suggesting that there is great subjective variability when grading despite using the LOCS III. Previous studies have demonstrated good inter and intrarater reliability on LOCS III; however, those studies were conducted on 35 mm film photographs instead of digital images.[8] A study by Tan et al which compared inter-rater variability between junior and senior ophthalmologists demonstrated moderate to substantial agreement in inter-rater agreement, though the study was conducted through slit-lamp observation.[10] This could imply that digital still images may not be ideal for LOCS III grading, and an alternative standardised photographic grading system such as the Wisconsin system could be used, though it may vary substantially with LOCS III measurements.[16] Alternatively, the variability found in this study may be due to the small number of raters used.

The technique used to capture images from the smartphone—by securing the smartphone on a slit-lamp through a telescopic mount—significantly reduced shake and improved photo usability. At the same time, live image transmission through a high resolution screen facilitated image focus and capture, and could potentially be used for live demonstrations. However, despite the high screen resolution, the relatively small screen size of the iPhone 5 limited the eventual image focus as some images which had appeared sharp on the iPhone screen eventually turned out unfocused when enlarged on a 13-inch screen. During the image capture, we found that such focusing issues could be reduced by predetermining the camera focus settings, and manually focusing the slit-lamp, while requesting patients to hold as steady as possible.

Several authors have previously described ways to utilise the smartphone for ophthalmology in a clinical setting.[3-5] The ubiquity and portability of the smartphone could prove to be a useful tool for clinical teaching. In this study, we found that medical students were equally confident when grading images taken from the iPhone and the anterior segment camera as measured through the 2 Likert scale questions, and there was fair agreement between images taken from both instruments in all categories. However, grading reproducibility between instruments ranged from fair to poor for the same group of students. This could be due to non-ideal light settings for the iPhone as explained above, though it could also be due to a poorer understanding of LOCS III grading scale in general. More experience in grading cataract images would certainly aid in enhancing reproducibility, and we believe in the potential of using the iPhone as a clinical education tool. Further studies could be conducted to evaluate the educational value of the smartphone in clinical ophthalmology.

We acknowledge the limitations of this study. Test-retest reliability was not assessed, and this could have made it

more difficult to compare intrarater reliability. Nonetheless, the purpose of this study was not so much to evaluate the best way to assess cataract, but to compare anterior segment images taken from smartphones with an anterior segment camera, using the LOCS III as a validated and standardised questionnaire. This study also confined itself to examining the graders' ability to grade photos for 1 type of pathology only, and it remains uncertain whether results could be extrapolated to other pathologies of the eye. A previous study by Kumar et al to validate digital images suggests such a possibility for smartphone images.[14] Similarly, given the encouraging performances of the iPhone in capturing fundus images, as presented by Bastawrous previously using the iPhone 4,[5] we remain very positive on the utility of the smartphone as a clinical adjunct for educational purposes or photo documentation.

Conclusion

This study has demonstrated that the iPhone has good reproducibility for retro-illuminated images, but tends to produce oversaturation of the anterior segment under low light settings. Graders reported similar levels of confidence when grading photos taken from the iPhone and the anterior segment camera. Images taken from the iPhone could be of adequate quality for teaching purposes, but further studies would be necessary to evaluate the suitability of iPhone images in demonstrating specific anterior segment pathologies, and for evaluating its utility in fundus photographs.

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Original Article

Comparison of Medication Adherence and Treatment Persistence between New Oral Anticoagulant and Warfarin among Patients

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Abstract

Introduction: This study aimed to compare medication adherence and treatment persistence of patients on warfarin versus rivaroxaban in Singapore. A secondary objective was to identify significant covariates influencing adherence. Materials and Methods: A retrospective cohort study was conducted where data from September 2009 to October 2014 was retrieved from the hospital electronic databases. Prescription records of rivaroxaban patients with 3 months or more of continuous prescription were extracted and compared against those of patients on warfarin. Primary outcome of adherence was determined based on the medication possession ratio (MPR), while treatment persistence was determined by outpatient clinic appointment gaps. Results: A total of 94 rivaroxaban and 137 warfarin users were analysed by complete case analysis. The MPR of warfarin patients was lower than rivaroxaban patients by 10% (95% CI, 6.4% to 13.6%; *P* <0.0001). Also, there were more warfarin patients who had gaps in treatment persistence compared to those prescribed rivaroxaban (8.0% vs 1.1%; *P* = 0.03). Significant factors affecting medication adherence were age and duration of anticoagulant use. For every 10-year increase in age, MPR increased by 1.7% (95% CI, 0.7% to 2.8%). Similarly, for every year increase in duration of use, MPR increased by 1.8% (95% CI, 0.6% to 3.0%). Race, gender, concomitant medication and type of residence were not found to be significant covariates in the multivariable analysis. Conclusion: Patients on rivaroxaban are likely to be more adherent to their prescribed oral anticoagulant with increasing age and duration of treatment influencing adherence.

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Key words: Compliance, Medication possession ratio, Oral anticoagulation, Rivaroxaban

Introduction

Rivaroxaban is a non-vitamin K oral anticoagulant (NOAC) approved for use in Singapore since 2008 for the prevention of venous thromboembolism in patients undergoing total hip and knee replacement surgery. In March 2012, the registered indication was expanded to include prevention of stroke and systemic embolism in subjects with non-valvular atrial fibrillation, treatment of deep vein thrombosis (DVT), and the prevention of recurrent DVT and pulmonary embolism (PE).[1]

Clinical trials and meta-analysis have demonstrated rivaroxaban's equivalent efficacy and similar major bleeding rates as compared to warfarin.[2-4] Additionally, rivaroxaban has fewer drug interactions and do not require dose titration in routine use. In practice, patients are recommended for annual re-evaluation of renal function to ensure continued safe use of the drug.[5] This is in contrast to warfarin which requires frequent monitoring and dose titration.

The advantage of less frequent visits to healthcare centres in routine care has ironically been reported to translate to poorer medication adherence.[6-8] Unlike patients taking warfarin whose compliance can be gauged from measured international normalised ratios (INRs), patients taking NOACs will typically have no objective measures of their state of compliance.

A number of studies on this matter have shown conflicting

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medication adherence results.[9-11] Warfarin is currently classified as a "standard drug" in Singapore, costing around S$0.10 per dose, whereas rivaroxaban, a "non-standard drug", costs about S$5 per dose. In an in-house survey conducted in 2010 among 93 anticoagulation clinic patients in Singapore General Hospital (SGH), 81.7% of the patients were not willing to switch from warfarin to NOACs if given a choice, and the top reason for this was higher drug costs of proprietary NOACs compared to generic warfarin (92.1%).[12] Culturally, with Asians' limited risk-taking and thrift mentality, the 50-fold difference in drug price was hypothesised to discourage patients from taking rivaroxaban regularly. Coupled with the lack of regular monitoring and reminders during clinic or pharmacy visits, these factors may translate into poorer medication adherence.

The sum effect of these factors on NOACs adherence and persistence among our patients treated for acute venous thrombosis is currently not known. We therefore studied a group of patients who had been anticoagulated for venous thrombosis to determine if there were important differences in medication adherence and treatment persistence between patients taking NOACs and warfarin. This paper reports our findings.

Materials and Methods

Study Design

This retrospective, single centre, cohort study was conducted in SGH, a Joint Commission International (JCI) accredited 1700-bed acute care academic medical centre in Singapore. Prescription and dispensing records from October 2009 to October 2014 were retrieved electronically from patients who were prescribed the 2 commonly used oral anticoagulants—warfarin and rivaroxaban. The index anticoagulant of each patient was determined based on the first prescription of either warfarin or rivaroxaban. Patients satisfying the following criteria were included in the analysis: 1) anticoagulated for treatment of DVT or PE; 2) at least 3 months of continuous anticoagulation on either warfarin or rivaroxaban; 3) anticoagulant therapy managed in SGH. Exclusion criteria included: 1) patients with incomplete demographic data in electronic record; 2) patients whose anticoagulation therapy was stopped for medical reasons; 3) lost to follow-up.

Statistical Analysis and Sample Size Calculation

Using Lehr's approximation and Cohen's standardised effect size of 0.5, with α at 0.05 and β at 0.10, a minimum of 84 patients in each group were required to detect the anticipated difference, assuming 1:1 allocation ratio. Patient demographics, type of anticoagulant prescribed and adherence were summarised using frequency and percentages for categorical variables, and means and standard deviation for continuous variables which were normally distributed. Where the data were skewed, median and range were presented. Independent sample t-test was used for comparing mean differences of continuous data if they were approximately normal; otherwise, the Mann-Whitney U test was applied. Fisher's exact test was used for comparing differences in proportions between the 2 treatment arms with respect to baseline demographics. To identify factors affecting adherence, multivariable linear regression was performed, and the following patient demographics—age, gender, ethnicity, duration of anticoagulant used, housing type and number of concomitant medicines—were considered for inclusion in the model. These factors were chosen as they are known surrogates affecting general medication adherence.[13-15] All the analyses were performed using STATA Version 13.1 (College Station, TX: StataCorp LP) assuming a 2-sided test at the conventional 5% level of significance.

Data Collection

Prescription records of rivaroxaban and warfarin were obtained from the institution's computerised physician order entry system (CPOE) (Sunrise Clinical Manager; Eclipsys, Atlanta, Georgia). Pharmacy refill records of patients were extracted from the electronic dispensing system (MaxCare; iSoft, Adelaide, South Australia). The records of patients taking rivaroxaban were then compared with patients taking warfarin to estimate differences in adherence.

The Singhealth Centralized Institution Review Board (CIRB) approved this study protocol. The study also conforms to the provisions of the Declaration of Helsinki and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Outcome Measures

The primary outcome measure of this study is medication adherence and treatment persistence. Medication adherence is generally defined as the extent to which patients take the medications as prescribed. In this study, it was calculated using the medication possession ratio (MPR) as follows:

$$MPR = \frac{\textbf{Duration of refills collected from pharmacy}}{\textbf{Duration of intended treatment or follow-up}}$$

As for treatment persistence, it is defined as the absence of gap in follow-up medical appointments. Presence of appointment gap, regardless of the duration or reason, is considered as treatment non-persistence. Secondary objective is to determine if there are any other variables that may have contributed to the difference in the adherence between the 2 regimes apart from anticoagulant choice.

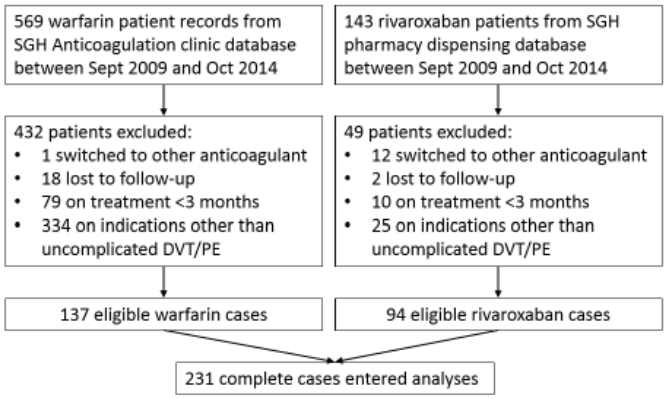

Fig. 1. Screening and enrolment flowchart.

Results

Of the 896 patients screened between September 2009 and October 2014, 231 met the inclusion criteria and were included in the data analysis (Fig. 1). Of these, 94 were on rivaroxaban and 137 were taking warfarin for treatment of DVT and/or PE for at least 3 months. Their characteristics are presented in Table 1.

The median time in therapeutic range (TTR) of the warfarin patients included in the study was 60%, with a median duration of use of 6.5 months and 6 clinic visits. The mean age and gender distributions of warfarin users did not differ significantly from those in the rivaroxaban arm. Rivaroxaban patients had a significantly higher median number of concurrent regular medications compared to those on warfarin (7.5 vs 6.5; $P = 0.0001$). More rivaroxaban users resided in 5-room flats, executive units, condominiums and landed properties (23.4% vs 12.4%) while most warfarin users resided in 1-room to 4-room flats (87.6% vs 76.6%). However between both groups, the distribution of patients across the housing types was not significantly different ($P = 0.149$).

Table 2 details the MPR of the warfarin and rivaroxaban users, along with the non-persistence of therapy. The MPR in the rivaroxaban arm was significantly better than that of the warfarin user arm (0.904 ± 0.094 vs 0.804 ± 0.159). On average, rivaroxaban users have 0.100 (95% CI, 0.064 to 0.136; $P < 0.0001$) higher MPR than warfarin users.

There were also significantly more people failing to adhere to outpatient appointments in the warfarin group compared to the rivaroxaban group (8.03% vs 1.06%; $P = 0.030$).

In the linear regression analysis performed to predict factors affecting MPR, effect of drug choice (warfarin vs rivaroxaban) on MPR was assessed in the presence of other significant covariates. We observed that using rivaroxaban

Table 1. Baseline Characteristics of Study Subjects

Characteristics	Warfarin (n = 137)	Rivaroxaban (n = 94)	*P* Value
Mean age in years (SD)	62.33 (1.44)	63.32 (1.60)	0.654
Gender, n (%)			
Male	59 (43.1)	49 (52.1)	0.183
Female	78 (56.9)	45 (47.9)	
Ethnicity, n (%)			
Chinese	90 (65.7)	69 (73.4)	0.231
Indian	22 (16.1)	7 (7.5)	
Malay	15 (11.0)	12 (12.8)	
Eurasian	8 (5.8)	3 (3.2)	
Others	2 (1.5)	3 (3.2)	
Mean duration of anticoagulant used, months (SD)	11.10 (1.85)	10.47 (0.79)	0.788
Median number of concomitant medicines (range)	6.5 (2 – 10)	7.5 (0 – 18)	0.0001
Housing type, n (%)			
1- or 2-room flat	16 (11.7)	7 (7.5)	0.149
3-room flat	36 (26.3)	21 (22.3)	
4-room flat	68 (49.6)	44 (46.8)	
5-room flat/executive/condominium/ landed	17 (12.4)	22 (23.4)	

SD: Standard deviation

Table 2. Univariate Analysis of the Association of MPR and Persistence with Warfarin or Rivaroxaban

	Warfarin	Rivaroxaban	Effect Estimate (95% CI)	*P* Value
Mean MPR (SD)	0.804 (0.159)	0.904 (0.094)	0.100 (0.064 – 0.136)	<0.0001
Non-persistence	11 (8.03%)	1 (1.06%)	0.123 (0.003 – 0.880)	0.030

MPR: Medication possession ratio; SD: Standard deviation

as the choice of anticoagulant resulted in 10% increase in medication adherence (95% CI, 6.4% to 13.6%; P <0.001), while every 10-year increase in age and every year increase in duration of use improved adherence by 1.7% (95% CI, 0.7% to 2.8%, P = 0.001) and 1.8% (95% CI, 0.6% to 3.0%, P = 0.003) respectively (Table 3).

Discussion

Poor medication adherence is common in clinical settings and may not be evident in the absence of objective laboratory monitoring. Contrary to our initial hypothesis, it was found that adherence as measured by MPR was better among rivaroxaban patients despite the higher treatment costs and lower monitoring intensity. The result is in line with some existing studies that reported better adherence in NOAC including rivaroxaban.[16-18] Also, rivaroxaban patients in this study were more persistent with their therapy compared with those using warfarin. Several reasons could potentially explain these observations.

Firstly, patients prescribed with rivaroxaban were a select group of patients. Rivaroxaban is currently listed as a non-standard medication in our institution and is not entitled to subsidy. As such, it tended to be prescribed to those of higher economic status who were willing to pay the price premium. Prior to prescription, the physicians would normally discuss cost of treatment with their patients and respect their choices. Importance of medication adherence was also constantly reinforced by physicians and pharmacists at the point of prescribing and dispensing rivaroxaban. This combination of factors may have limited the impact of cost on adherence among rivaroxaban patients.

Secondly, rivaroxaban is taken once a day like warfarin and offers additional advantages like not requiring routine blood tests, along with fewer interactions. These conveniences could have paradoxically led to better adherence as patients are more assured of its efficacy and less concerned with side effects. In a survey on the use of warfarin and dabigatran in patients with atrial fibrillation, patients reported higher satisfaction (e.g. no need for dietary restrictions, ease of handling missed doses, less checkups, less concerns with possible interactions with other concurrent medications or supplements) with the use of dabigatran than warfarin therapy.[19] This is despite the greater incidences of adverse effects as they believed that the convenience and benefits of NOAC outweighed the marginal increase in risks and thus were more willing to take their medications consistently. This may similarly be expected in our patients on rivaroxaban.

Thirdly, socioeconomic status and a medical co-payment system have been reported to affect medication adherence.[20] In our study, we used housing type as a surrogate marker for the socioeconomic status of patients, as in other studies on chronic conditions.[21-23] These studies have found an association between community dwelling type and medication adherence in patients; it was reported that patients at the lower end of the social economic ladder, based on the type of residence, were more likely to have poorer medication adherence as this group of patients had limited access to healthcare monitoring and treatment, or fail to adhere to their medication regimens as a result of their inability to acquire adequate supply of medications. While many aspects of such studies are not applicable in Singapore, our co-payment system of healthcare did influence the selection of patients who chose to use rivaroxaban. In our sampling distributions, we noted that patients on rivaroxaban were economically better-off than patients on warfarin. Aspects of socioeconomic status which

Table 3. Factors Affecting MPR

Factors	Coefficient	95% CI	*P* Value	R^2
Rivaroxaban vs warfarin	0.099	0.064 – 0.133	<0.001	0.180
Age	0.00174*	$6.99x10^{-4}$ – $2.80x10^{-3}$	0.001	
Duration of use	0.00149†	$5.01x10^{-4}$ – $2.48x10^{-3}$	0.003	

*Coefficient is presented in terms of per year increase for age.

†Coefficient is presented in terms of per month increase for duration of use.

MPR: Medication possession ratio

are known to influence adherence invariably contributed to adherence difference.

Treatment persistence was notably higher in rivaroxaban group in our study, which is consistent with studies performed overseas with other NOACs.[24,25] As warfarin patients have more clinic visits, the likelihood of missing some of their appointments intentionally or otherwise was likely to be higher.

In this study, it was found that the choice of drug (warfarin vs rivaroxaban) alone explained about 11.5% of the variation in MPR. When age and duration of use were added into the regression model, they explained 18% collectively. It echoes the findings of many previous studies that medication adherence is a multifaceted problem involving the interplay of many varying factors. Screening by doctors and pharmacists during prescribing and dispensing counselling together with other usual safeguards, may potentially help to further reduce the risk of medication non-adherence among this group of patients in our care setting.

There are several strengths in this study. Firstly, this is a focused local study to evaluate adherence to rivaroxaban as compared to warfarin, and the results of this study can provide insights into differences in adherence between NOACs and warfarin among our patients in Singapore. This can potentially be applied to other conditions requiring anticoagulation like atrial fibrillation. Secondly, results from the secondary analysis may help physicians assess and select the most appropriate patients who are likely to be older and been taking anticoagulants for longer periods.

There are a number of limitations in this study. Firstly, given the retrospective nature of the study, the allocation of patients into either warfarin or rivaroxaban arm was not at random but based on physicians' subjective assessment of patients' ability to afford the medications and perceived adherence at the point of treatment prescription. This clearly represented a selection bias which could influence the study findings. However, this selection bias also best reflect real world practice in our care setting and yielded findings that are devoid of the controlled environment of a randomised study. The results may, in turn, have higher relevance and applicability. Secondly, the presence of refills in the electronic database does not necessarily mean that the patient actually consumed the medications. Therein lies the assumption that patients are adherent to their medications as long as they return for a refill, which may thus lead to an overestimation of adherence. Thirdly, we did not have, for instance, sufficient data on possible confounders such as education status, personal income data, occupation, mobility and caregiver availability. As a result, we cannot rule out the possibility of residual confounding from unmeasured causal factors that were unevenly distributed between treatment groups and this could have influenced our results. Besides, sample size of the study was calculated to detect differences in MPR between the warfarin and rivaroxaban arm. Failure to detect significant differences among some suspected factors could potentially be due to insufficient power to detect them. Though inconclusive, the exploratory findings do provide important insights into other possible influencing factors that may warrant investigating in future studies.

Conclusion

The results of this study suggest that adherence with rivaroxaban may be superior to warfarin for the treatment of DVT/PE in Singapore despite it being more costly. Indicators of medication non-adherence need to be evaluated apart from other clinically relevant parameters like renal function and full blood count when deciding on the choice of anticoagulant to be administered to patients to optimise treatment outcome.

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Original Article

Prevalence, Presentation, and Outcome of Heart Failure with Preserved Ejection Fraction among Patients Presenting with Undifferentiated Dyspnoea to the Emergency Room: A 10-year Analysis from a Tertiary Centre

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Abstract

Introduction: We assessed the local prevalence, characteristics and 10-year outcomes in a heart failure (HF) cohort from the emergency room (ER). Materials and Methods: Patients presenting with acute dyspnoea to ER were prospectively enrolled from December 2003 to December 2004. HF was diagnosed by physicians' adjudication based on clinical assessment and echocardiogram within 12 hours, blinded to N-terminal-pro brain natriuretic peptide (NT-proBNP) results. They were stratified into heart failure with preserved (HFPEF) and reduced ejection fraction (HFREF) by left ventricular ejection fraction (LVEF). Results: At different cutoffs of LVEF of ≥50%, ≥45%, ≥40%, and >50% plus excluding LVEF 40% to 50%, HFPEF prevalence ranged from 38% to 51%. Using LVEF ≥50% as the final cutoff point, at baseline, HFPEF (n = 35), compared to HFREF (n = 55), had lower admission NT-proBNP (1502 vs 5953 pg/mL, *P* <0.001), heart rate (86 ± 22 vs 98 ± 22 bpm, *P* = 0.014), and diastolic blood pressure (DBP) (75 ± 14 vs 84 ± 20 mmHg, *P* = 0.024). On echocardiogram, compared to HFREF, HFPEF had more LV concentric remodelling (20% vs 2%, *P* = 0.003), less eccentric hypertrophy (11% vs 53%, *P* <0.001) and less mitral regurgitation from functional mitral regurgitation (60% vs 95%, *P* = 0.027). At 10 years, compared to HFREF, HFPEF had similar primary endpoints of a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and rehospitalisation for congestive heart failure (CHF) (HR 0.886; 95% CI, 0.561 to 1.399; *P* = 0.605), all-cause mortality (HR 0.663; 95% CI, 0.400 to 1.100; *P* = 0.112), but lower cardiovascular mortality (HR 0.307; 95% CI, 0.111 to 0.850; *P* = 0.023). Conclusion: In the long term, HFPEF had higher non-cardiovascular mortality, but lower cardiovascular mortality compared to HFREF.

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Key words: Acute heart failure, Asian, Prognosis

Introduction

Heart failure (HF) with preserved ejection fraction (HFPEF) occurs in almost half of HF population and the prevalence is rising.[1-4] Detecting the abnormalities associated with diastolic dysfunction in HFPEF using echo- and tissue-Doppler techniques requires expert acquisition and interpretation.[5] No echo parameter has emerged that is pathognomonic of diastolic HF, and definition of HFPEF largely depends on an agreed, albeit arbitrary, left ventricular ejection fraction (LVEF) cutoff value. The threshold for normal LVEF is set at 50% in the 2012 European Society of Cardiology guidelines,[5] although cutoff values of LVEF ranging from 40% to 50% have been used in various clinical studies.[3,4,6,7]

Given the above issues regarding the choice of LVEF threshold, it is not unexpected that the proportion of HFPEF compared with HF with reduced ejection fraction (HFREF) has been variably observed in HF registries.[3,4,6,7] Diverse practice settings;[3,4,8] burden of comorbidities; regional characteristics including social, economic and genetic (ethnic) difference all may impact on HFPEF prevalence in registry data. Unlike HFREF whose outcome has gradually improved with evidence-based medical therapy, optimal treatment of HFPEF is still unresolved[9,10] and data for long-term outcomes are limited, especially in Asian populations.[11]

The objectives of this analysis were to assess the prevalence, presenting features and outcomes of HFPEF

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among patients presenting to the emergency room (ER) with undifferentiated dyspnoea, and to compare these with HFREF patients, in the local population.

Materials and Methods

Patients and Study Design

Between December 2003 and December 2004, a single centre prospective study was performed in which consecutive patients presenting with undifferentiated dyspnoea to the ER had N-terminal-pro brain natriuretic peptide (NT-proBNP) (which was not standard of care in local hospitals at that time) performed to validate its diagnostic accuracy for HF in local population. HF diagnosis was based on consideration of Framingham's criteria for congestive HF, response to diuretic treatment and echocardiographic findings. Exclusion criteria were patients less than 40 years old; whose dyspnoea was clearly not a result of HF (eg. pneumothorax, asthma, malignant pleural effusion); and patients with definite acute coronary syndrome, as determined by electrocardiogram changes and cardiac enzymes.[12] Patients with known systolic HF, evidenced by documented LVEF <50% demonstrated by echocardiogram within 12 months were deliberately excluded in order to ensure recruitment of more subjects whose diagnosis of HF was less immediately apparent, and which could potentially have been aided by the then novel NT-proBNP biomarker.

Diagnosis of HF were adjudicated by pairs of doctors comprising one each of cardiologists, internists or emergency physicians, based on all medical records pertaining to the patient, including: (a) Framingham's criteria for congestive heart failure (CHF) (2 major or one major and 2 minor criteria);[13] (b) response to treatment directed towards HF[14] and (c) echocardiographic findings (eg. reduced LVEF or diastolic dysfunction). All adjudicators were blinded to the NT-proBNP levels.

For the patients who were diagnosed to have dyspnoea not due to CHF, confirmation on the basis of the following observation will be attempted: (a) presence of fever and cough with yellowish sputum, (b) absence of heart enlargement and pulmonary venous congestion on chest radiography, (c) abnormal lung function test, response to treatment with nebulizers corticosteroids or antibiotics and (d) absence of admission to the hospital for CHF in the following 6 months. Patients assessed to have both HF and other contributing non-HF presentations, were categorised into the HF group.

Routine electrocardiogram, chest radiograph, laboratory results (full blood count, cardiac enzymes, renal panel) were recorded on admission. Blood sampling for NT-proBNP were taken after 10 minutes of supine rest. Echocardiograms were performed within 12 hours of blood sampling of NT-proBNP. The following measurements were recorded: left ventricular end diastolic dimension, left ventricular end systolic dimension, fractional shortening, ejection fraction (by biplane Simpson's method), wall thickness, transmitral flow profiles E (early wave), A (atrial contraction), deceleration time (DT), E/A ratio and valvular abnormalities.

Patients were admitted or discharged and managed at the discretion of the treating physicians. The treating physicians were blinded to the results of NT-proBNP. At that time, NT-proBNP was not standard of care.

N-terminal-pro Brain Natriuretic Peptide

Immunoassay for the quantitative determination of NT-proBNP was performed using Elecsys proBNP II STAT assay (Roche Diagnostics). The measurement range of this assay is 5 to 35,000 pg/mL (defined by the Limit of Detection and the maximum of the master curve). Values above the measuring range were reported up to 70,000 pg/mL for 2-fold diluted samples.

Ethics

The study protocol was approved by the local hospital ethics committee in our hospital. All subjects gave written informed consent to participate in the study.

Echocardiogram

At baseline, study participants underwent standard echocardiography with Doppler measurements. Left ventricular (LV) chamber dimensions were measured by M-mode according to the American Society of Echocardiography (ASE) recommendations.[15] LV mass (LVM) and relative wall thickness (RWT) were calculated using ASE recommended formulas.[15] Based on LV mass and geometry, participants were classified into normal, concentric remodelling, concentric hypertrophy and eccentric hypertrophy patterns.[15]

Outcomes

The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and rehospitalisation for CHF events. Secondary endpoints were individual components of the primary endpoint as well as all-cause death.

Events were ascertained from review of case records linked to the Hospital Care Inpatient Discharge Care and Electronic Medical Record Exchange system of hospitals in Singapore. In addition, information on deaths was obtained

from death certificates issued by the National Registry of Births and Deaths.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) for parametric, and median (quartile range) for non-parametric data. Dichotomous variables are presented as number and percentage. Baseline features of patients with HFPEF and HFREF were compared. Dichotomous variables were compared by Pearson Chi-square test. Continuous variables were compared by Student's t-test for parametric and Mann Whitney U test for non-parametric data. Survival time was measured from date of study registration to the date of outcome or date of last contact. The Kaplan-Meier survival curves were constructed, the significance of which was tested by the log-rank Cox regression test. Sensitivity tests were performed using different thresholds of LVEF for HFPEF (≥45%, ≥40%), as well as comparing only extreme phenotypes by omitting those LVEF between 40% and 50%. Notably, patients in the latter group possess distinctly different physiological and prognostic behaviours.[11] Sensitivity analysis using a different gold standard to diagnose HF (Framingham's criteria plus elevated NT-proBNP >900 pg/mL) was performed to determine the robustness of the survival relationship pertaining to LVEF. Statistical analysis was performed using SPSS statistical software package (version 21; SPSS Inc., Chicago, IL) for all analyses. A P value of <0.05 was considered to indicate statistical significance.

Results

Clinical Characteristics

A total of 152 consecutive patients with undifferentiated dyspnoea presenting to the ER agreed to participate in the study; 90 (59%) patients were diagnosed to have HF by physician adjudication; 3 patients who were initially adjudicated not to have HF had subsequent HF hospitalisation within 6 months. Two of these had fluid overload states which were initially thought to be attributable to proteinuria and endstage renal failure, respectively, and were subsequently adjudicated into HF group upon review at 6-month postinitial presentation. The third subject, whose breathlessness was due to thyrotoxicosis, remained classified in the non-HF group.

Using LVEF ≥50% as the cutoff, 35 (39%) and 55 (61%) were classified into HFPEF and HFREF groups, respectively. Sensitivity test was performed using different diagnostic criteria for HF. Among 86 (57%) patients who were diagnosed HF by a combination of Framingham's criteria plus elevated NT-proBNP >900 pg/mL for HF, HFPEF and HFREF prevalence was 35 (41%) and 51(59%), respectively.

Subjects were followed up to 10 years. Follow-up was 96% complete. Among 90 HF patients, 2 were lost to follow-up at 2 weeks (non-residents); and another 2 were lost to follow-up at 18 months and 23 months, respectively.

Baseline characteristics of patients with HFPEF versus HFREF are shown in Table 1. There was a trend towards prevalence of female gender in HFPEF (52%) compared to HFREF (36%), but no statistically significant difference was found. HFPEF patients had lower baseline NT-proBNP compared to HFREF. Numerically, but not statistically significantly, HFPEF had higher numbers of prior obstructive lung disease, and lower numbers of prior myocardial infarction with less previous use of angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers, nitrates, diuretics, digoxin and antiplatelets compared to HFREF. Notably, the prevalence of diabetes was high in both groups. Clinical presentations (lung rales, cardiomegaly, elevated jugular venous pressure, presence of pleural effusion or pulmonary oedema on chest radiograph, ankle oedema and paroxysmal nocturnal dyspnoea) were similar in general, except HFPEF patients were less tachycardic, had lower diastolic blood pressures (DBPs) at baseline, and less LV hypertrophy by voltage criteria on electrocardiogram compared to HFREF. There was no statistically significant difference between HFPEF and HFREF in number of patients requiring intravenous diuretics as well as dosage of the diuretics given in ER. Other than 1 in HFPEF and 3 in HFREF patients who require intravenous nitrates, none of the patients in this study require intravenous inotropic support in ER.

Echocardiographic Features

Echocardiographic measurements are shown in Table 2. HFPEF had smaller LV end diastolic dimensions than HFREF. Mean LV mass was raised in both groups. HFPEF patients tended to present with concentric LV remodelling compared to HFREF (20% vs 2%, $P = 0.003$). In contrast, eccentric LV hypertrophy was more common in HFREF compared to HFPEF (53% vs 17%, $P <0.001$). On Doppler measurements, deceleration time was longer in HFPEF compared to HFREF.

In patients with more than moderate degree of valvular heart disease, mitral valve regurgitation (MR) was the most common condition in both HFPEF (17%) and HFREF (41%) patients. In terms of aetiology, MR subjects with HFPEF had lower proportion diagnosed with functional MR (60% vs 95%, $P = 0.027$) compared to HFREF group.

Outcomes

The primary composite outcome occurred in 31 and 48

Table 1. Baseline Clinical Characteristics

	HFPEF (n = 35)	HFREF (n = 55)	*P* Value
Age, years	72 ± 9	72 ± 11	0.806
Female sex, n (%)	18 (52)	20 (36)	0.158
Comorbidities			
Prior diabetes, n (%)	20 (57)	33 (60)	0.788
Prior hypertension, n (%)	43 (78)	27 (77)	0.908
Prior atrial fibrillation, n (%)	11 (31)	17 (31)	0.959
Prior heart failure, n (%)	10 (29)	17 (31)	0.813
Prior myocardial infarct	2 (6)	9 (16)	0.133
Prior stroke, n (%)	3 (9)	8 (15)	0.399
Prior chronic obstructive lung disease, n (%)	5 (14)	2 (4)	0.066
Prior chronic kidney disease, n (%)	4 (11)	4 (7)	0.499
Medications at presentation			
Dihydropyridine, n (%)	5 (15)	7 (13)	0.817
Betablockers, n (%)	5 (14)	9 (16)	0.791
ACEI/ARB, n (%)	6 (17)	17 (31)	0.144
Diuretics, n (%)	8 (23)	18 (33)	0.238
Nitrates, n (%)	8 (23)	19 (33)	0.640
Digoxin, n (%)	1 (3)	6 (11)	0.164
Antiplatelet, n (%)	4 (11)	15 (27)	0.073
Medications in ER			
Intravenous furosemide in ER, n (%)	27 (77)	43 (78)	0.908
Mean IV furosemide dosage, mg	45 ± 37	46 ± 32	0.866
IV GTN, n (%)	1 (3)	3 (6)	0.560
Biochemistry			
NT-proBNP at ER (pg/mL)	1502 (164 – 4885)	5953 (3390 – 14393)	<0.001
NT-proBNP on discharge (pg/mL)	868 (127 – 3504)	2541 (1439 – 6891)	0.002
Change in NT-proBNP (pg/mL)	353 (26 – 2011)	3298 (875 – 6540)	0.004
Haemoglobin (g/L)	12 ± 2	13 ± 2	0.053
Anaemia, n (%)	21 (60)	26 (47)	0.239
Glucose (mmol/L)	8 ± 4	10 ± 4	0.051
Sodium (mmol/L)	136 ± 4	137 ± 4	0.444
Hyponatraemia (<135 mmol/L), n (%)	8 (23)	12 (22)	1.000
Urea (mmol/L)	10 ± 7	9 ± 5	0.456
Creatinine (μmol/L)	142 ± 92	126 ± 67	0.341
Urea/creatinine ratio* (SI unit)	19 ± 7	19 ± 6	0.602
NYHA functional classification			
Class I and II, n (%)	20 (51)	27 (49)	0.456
Class III, n (%)	11 (31)	21 (38)	0.514
Class IV, n (%)	4 (11)	7 (13)	0.855
Systolic blood pressure (mmHg)	142 ± 29	150 ± 33	0.260
Diastolic blood pressure(mmHg)	75 ± 14	84 ± 20	0.024
Heart rate (bpm)	86 ± 22	98 ± 22	0.014

ACEI: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin II receptor blockers; HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; JVP: Jugular venous pressure; NT-proBNP: N-terminal-pro brain natriuretic peptide; S3: Third heart sound; NYHA: New York Heart Association; ECG: Electrocardiogram; ER: Emergency room; LVH: Left ventricular hypertrophy; QRS: Time from the start of Q wave to the end of S wave on electrocardiogram; QTc: Corrected QT interval; IV: Intravenous; GTN: Glyceryl trinitrate

*Normal range for urea-to-creatinine ratio is 40-100:1, >100:1 indicates prerenal cause and <40:1 is suggestive of intrarenal cause.

Table 1. Baseline Clinical Characteristics (Con't)

	HFPEF (n = 35)	HFREF (n = 55)	*P* Value
Initial ECG characteristics			
Presence of LVH, n (%)	2 (6)	13 (24)	0.026
QRS width (ms)	95 ± 22	97 ± 19	0.714
QTc duration (ms)	433 ± 34	445 ± 34	0.160

ACEI: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin II receptor blockers; HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; JVP: Jugular venous pressure; NT-proBNP: N-terminal-pro brain natriuretic peptide; S3: Third heart sound; NYHA: New York Heart Association; ECG: electrocardiogram; ER: Emergency room; LVH: Left ventricular hypertrophy; QRS: Time from the start of Q wave to the end of S wave on electrocardiogram; QTc: Corrected QT interval; IV: Intravenous; GTN: Glyceryl trinitrate

*Normal range for urea-to-creatinine ratio is 40-100:1, >100:1 indicates prerenal cause and <40:1 is suggestive of intrarenal cause.

patients in the HFPEF and HFREF groups, respectively. Over 10 years' follow-up, 64 deaths occurred (71%). The median survival was 3.2 and 2.2 years in the HFPEF and HFREF cohort, respectively. At 10 years, all-cause death occurred in 27 and 37; and cardiovascular death in 5 and 15 patients in HFPEF and HFREF groups, respectively (Table 3). Kaplan-Meier survival curves showed no difference in rates of primary endpoints and all-cause mortality between the 2 groups (Figs. 1 and 2). Cardiovascular mortality was higher in HFREF versus HFPEF group (27% vs 14%, *P* = 0.023) (Fig. 3).

Using different thresholds of LVEF for HFPEF (≥45%, and ≥40%, >50% plus excluding LVEF between 40% and 50% inclusive), yielded different proportions of HFPEF versus HFREF (Fig. 4). Sensitivity testing of outcomes using different thresholds of LVEF for HFPEF showed no

Table 2. Echocardiographic Parameters

	HFPEF (n = 35)	HFREF (n = 55)	*P* Value
LVIDd (cm)	4.7 ± 0.9	5.8 ± 0.9	<0.001
IVSd (cm)	1.1 ± 0.3	1.1 ± 0.2	0.081
PW thickness (cm)	1.1 ± 0.2	1.1 ± 0.2	0.442
RWT (cm)	0.5 ± 0.1	0.4 ± 0.1	<0.001
LVM (g)	199 ± 69	256 ± 77	0.004
LV geometry*			
Normal geometry, n (%)	13 (37)	13 (24)	0.168
Concentric remodelling, n (%)	7 (20)	1 (2)	0.003
Concentric hypertrophy, n (%)	11 (31)	12 (22)	0.308
Eccentric hypertrophy, n (%)	4 (11)	29 (53)	<0.001
Mitral inflow			
E (mm/s)	95 ± 45	99 ± 33	0.615
A (mm/s)	83 ± 28	74 ± 36	0.350
E/A	1.1 ± 0.8	1.6 ± 1.0	0.066
DT (ms)	210 ± 92	151 ± 44	0.001
M-mode LA diameter (cm)	4.4 ± 0.9	4.4 ± 0.9	0.786
TR velocity (mm/s)	290 ± 41	316 ± 67	0.200
Mitral regurgitation (MR)† n (%)	5 (17)	21 (41)	0.028
Ischaemic MR, n (%)	3 (60)	20 (95)	0.027

HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; LVIDd: Left ventricular end diastolic dimension; RWT: Relative wall thickness (measured by 2 x posterior wall thickness divided by LV diastolic diameter); LVM: Left ventricular mass; E: Early diastolic mitral inflow velocity; A: Late diastolic mitral inflow velocity; DT: E wave deceleration time; LA: Left atrium; TR: Tricuspid regurgitation

*Definition of elevated LVM (female ≥162 g and male ≥224g). Normal geometry (LVM normal and RWT <0.42), concentric remodelling (LVM normal but RWT ≥0.42), eccentric hypertrophy (LVM elevated but RWT <0.42), and concentric hypertrophy (LVM elevated and RWT ≥0.42).

†Mitral regurgitation only accounts for regurgitation of more than moderate degree.

Table 3. Comparison of Outcomes between HFPEF and HFREF

	HFPEF (n = 35)	HFREF (n = 55)	HR (95%CI)	*P* Value
Composite endpoint, n (%)	31 (89)	48 (87)	0.886 (0.561 – 1.399)	0.605
Non-fatal myocardial infarction, n (%)	1 (3)	8 (15)	0.168 (0.021 – 1.344)	0.093
Non-fatal stroke, n (%)	1 (3)	2 (4)	0.672 (0.061 – 7.439)	0.746
HF hospitalisation, n (%)	20 (57)	32 (58)	0.843 (0.480 – 1.481)	0.553
Cardiovascular mortality, n (%)	5 (14)	15 (27)	0.307 (0.111 – 0.850)	0.023
All-cause mortality, n (%)	27 (77)	37 (67)	0.663 (0.400 – 1.100)	0.112
Non-cardiovascular death, n (%)	22 (63)	22 (40)	1.048 (0.515 – 2.135)	0.896
Sepsis, n (%)	9 (26)	11 (20)	0.699 (0.266 – 1.679)	0.392
Cancer, n (%)	3 (9)	3 (5)	1.160 (0.233 – 5.772)	0.856
Lung disease, n (%)	3 (9)	0 (0)	NA	NA
Kidney disease, n (%)	0 (0)	0 (0)	NA	NA
Others*, n (%)	7 (20)	8 (15)	NA	NA

HF: Heart failure; HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; HR: Hazard ratio

*Other causes of death: 1 case died from subarachnoid hemorrhage in HFPEF group, 1 case died from hypoxic ischaemic brain injury in HFREF group, and the rest were unknown causes of death.

difference in outcomes. Sensitivity testing using different method for HF diagnosis as mentioned above did not alter the conclusions.

Discussion

The prevalence of HFPEF was reported to be 36% to 61% based on various LVEF cutoffs ranging from 40% to 50% in western populations.[3,4,16-20] We observed a prevalence of HFPEF at 39% at LVEF cutoff of 50%, which is similar to another Asian HF registry ATTEND (43%).[2] However, differing LVEF cutoffs of ≥50% and ≥40% were used in our and ATTEND studies, respectively. The choice of LVEF threshold can alter HFPEF prevalence significantly, and may limit direct comparison between studies. In our study, by shifting the LVEF threshold from 50% to 40%, HFPEF prevalence increased from 39% to 51%, which was very similar to western cohorts (using LVEF thresholds ranging from 40% to 50%).[3,16,20]

In large clinical trials, compared to HFREF, HFPEF patients were usually older, more frequently female, and more likely to have history of atrial fibrillation, diabetes, hypertension, renal insufficiency, and pulmonary disease.[1,6,7,9] We found a similar trend towards female gender, more chronic pulmonary disease, and less prior myocardial

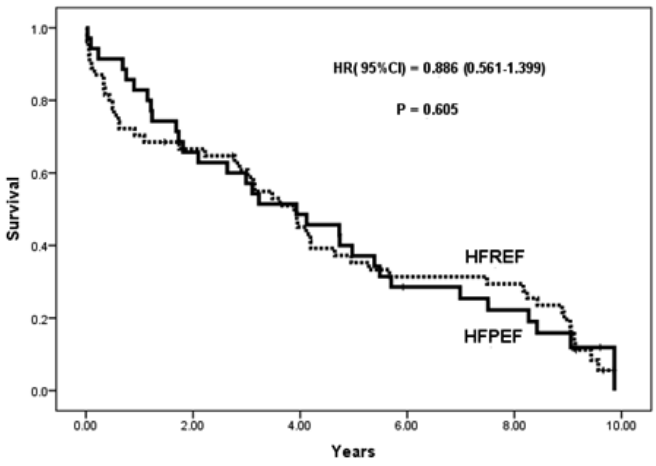

Fig.1. Kaplan-Meier analysis of composite primary endpoints among patients with HFPEF vs HFREF over 10 years. HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; HR: Hazard ratio.

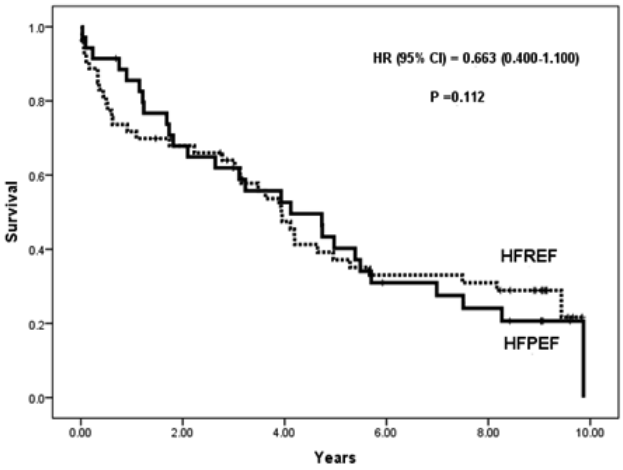

Fig.2. Kaplan-Meier analysis of overall survival among patients with HFPEF vs HFREF over 10 years. HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; HR: Hazard ratio.

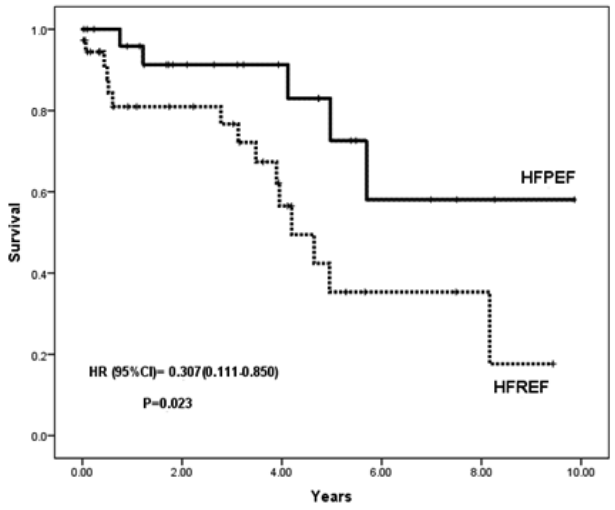

Fig.3. Kaplan-Meier analysis of cardiovascular mortality among patients with HFPEF vs HFREF over 10 years. HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; HR: Hazard ratio.

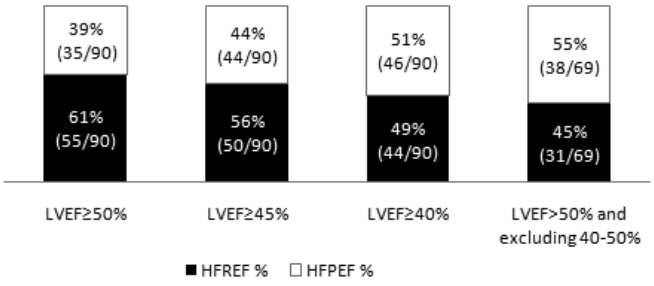

Fig.4. Chart showing the prevalence of HFPEF at different cutoff points of LVEF. HFPEF: Heart failure with preserved ejection fraction; HFREF: Heart failure with reduced ejection fraction; LVEF: Left ventricular ejection fraction.

infarction in HFPEF, although there was insufficient power to demonstrate statistical significance.

Diabetes is a global health concern and important cause of systolic and diastolic HF. In Singapore, 1 out of 9 people aged 18 to 69 has diabetes. That's about 11.3% of our population or more than 400,000 people.[21] Notably, the prevalence of diabetes in our cohort was extremely high in both HFPEF (57%) and HFREF (60%) compared with contemporaneous global data in acute (32% to 47%)[2,3,22] and chronic (20% to 32%) HF cohorts.[1,5,18,23] Microvascular disease, in particular, associated with diabetes, has been invoked as a putative pathophysiological and aetiological explanation for HFPEF.[24] With rising diabetes prevalence,[25] HF can be expected to rise commensurately.

In contrast to some other studies,[17,26] significantly lower heart rates and diastolic arterial pressure were observed in HFPEF compared to HFREF in our study; proportion of hyponatremia was similar in HFPEF and HFREF (Table 1). Of note, our study recruited acute HF subjects, whereas most other trials enrolled chronic ambulatory HF patients. HFPEF subjects may have impaired chronotropicity[27] and may exhibit lower heart rates and arterial DBPs,[28] especially in stress situations (like in our acute HF cohort). In the acute HF study RELAX-AHF, a similar trend was observed in which DBP was significantly lower in HFPEF compared to HFREF patients (79.6 ± 13.9 vs 82.6 ± 13.6 mmHg, P = 0.0015).[29]

In our HFPEF subjects, we observed higher prevalence of concentric LV remodelling on echocardiography compared with HFREF. In contrast, in HFREF, the eccentric hypertrophy pattern is more prevalent. Such LV remodelling differentiation is similar to other HF studies.[30,31] This higher prevalence of concentric LV remodelling, and potential attenuation of coronary perfusion due to lower DBP, may result in increased myocardial oxygen consumption and subendocardial ischaemia.[32]

We observe lower baseline NT-proBNP level in HFPEF than HFREF. Despite lower NT-proBNP levels, HFPEF patients have been reported to exhibit similar levels of renin-angiotensin-aldosterone system (RAAS) activation and clinical severity of HF compared to HFREF. It was postulated that HFPEF is associated with relative NT-proBNP deficiency which was induced by renal impairment, RAAS activation, sodium retention and vasoconstriction.[28]

Anaemia, particularly iron-deficient anaemia, is common in chronic HF patients, and is associated with worse symptoms and outcomes in both HFPEF and HFREF.[33] In this study, a trend towards higher prevalence of anaemia was present in HFPEF (60%) compared with HFREF (47%) (P = 0.239), which is consistent with other studies of chronic HF[17,18,28] as well as acute HF.[3,28] The reason for this is unclear. Most likely, the high prevalence of anaemia in HFPEF is a surrogate marker of the higher burden of comorbidities (in our cohort, prevalence of prior chronic obstructive lung disease and chronic kidney disease, but not diabetes, were numerically higher in HFPEF).

Substantial mortality in HFPEF, similar to HFREF, has been reported in both epidemiological and clinical trials. In population-based studies, unadjusted 5-year all-cause mortality rates of 52% to 76% versus 54% to 73% for HFPEF and HFREF, respectively, have been reported.[4,8,17,19] On the other hand, randomised clinical trials reported lower all-cause mortality rates. For instance, in the placebo-control arms in I-PRESERVE[34] and CHARM-Preserved,[7] cumulative all-cause mortality were 21% and 25% at 4 years and 3 years, respectively. However, the subjects in the above trials were largely ambulatory and were not required to have

been hospitalised at the time of recruitment, which may explain the difference in mortality results from our cohort.

Our study is based on patients recruited from the ER, all of whom were subsequently hospitalised. Median survival was 3.2 years and 2.2 years in HFPEF and HFREF cohorts, respectively. As mentioned, discrepancies of mortality rates between different studies may be due to differences in baseline patient characteristics and the burden of comorbidities. Indeed, our patient group comprised older subjects, many with comorbidities.

High proportions of non-cardiac deaths ranging from 24% to 61% have been observed in other HFPEF studies.[19,35,36] In our study, patients with HFPEF were similarly more likely to die from non-cardiovascular causes including sepsis (26%), cancer (9%), chronic obstructive lung disease (9%) (Table 3). This is in keeping with the principal non-cardiac causes of death in Singapore general population which includes cancer (30.5%), sepsis such as pneumonia (18.5%) and urinary tract infection (2.6%), nephritis, nephrotic syndrome and nephrosis (2.4%), and chronic obstructive lung disease (1.6%) reported by the Ministry of Health in 2013.[37]

On the other hand, in Singapore, ischaemic heart disease (15.5%) is still the leading cause of cardiovascular death, followed by cerebral vascular disease (8.9%) and hypertensive heart disease (3.1%).[37] In our study, HFPEF subjects had less cardiovascular death events and a trend towards less HF rehospitalisation rate. This is perhaps in keeping with the lower biomarker (NT-proBNP) burden in HFPEF compared with HFREF. The burden of non-cardiovascular death appears to be inversely related to the extent of coronary artery disease (CAD) in HFPEF population.[38] Patients with HFPEF, who are more likely to be free from epicardial CAD, are conceivably more likely to be spared from cardiac deaths, and only to die from non-cardiovascular causes.[36]

Studies have shown that older age, higher NT-proBNP, and burden of comorbidities such as cancer, pulmonary disease, and diabetes were independent predictors of mortality.[17,36] Unfortunately, our cohort is too small to permit multivariable analysis of these relevant risk predictors.[22]

Limitations

This is a relatively small study conducted in a single centre and results of this study may not be generalisable. Nevertheless, it comprises a hitherto relatively unstudied group of Asian patients presenting with undifferentiated dyspnoea to the ER. The very long follow-up allows meaningful analyses of outcomes despite the small numbers. While we primarily used LVEF ≥50% as the threshold for HFPEF, this is not universally applied across all studies, which limited comparison. However, sensitivity analyses performed for different cutoff ranging from 40% to 50% did not alter the conclusions regarding primary outcome events and mortality rates. Neither does sensitivity analysis using a combination of Framingham's criteria plus elevated NT-proBNP for HF diagnosis alter the analysis.

One of our study objectives then was to evaluate the diagnostic accuracy of NT-proBNP assay for HF diagnosis in a local population. This necessitated the exclusion of patients with known recent systolic dysfunction. There is thus a possibility overt HFREF might have been under-represented in our study. However, we believe the effect is minor. We obtained similar balance of HFPEF versus HFREF subjects as other contemporaneous registries. Importantly, we believe that comparisons of clinical characteristics and outcomes between HFPEF and HFREF remain valid.

Conclusion

This prospective single centre Singapore cohort study demonstrated that all-cause mortality in HFPEF and HFREF did not differ significantly. HFPEF had significantly higher non-cardiac mortality but lower cardiovascular mortality at 10 years. Diabetes is extremely prevalent in both HFPEF and HFREF, and may be an important driver of burgeoning HF incidence.

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Special Article

Time for Action on Viral Hepatitis

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Abstract

The recent outbreak of hepatitis C virus (HCV) at Singapore General Hospital (SGH) has highlighted the dangers of viral hepatitis. In this case, infection control and environmental contamination were the culprits, particularly, a drop of blood containing 5 million IU HCV. From a broader perspective, there has been a revolution in HCV therapy with the recent rapid evolution of short-term (12 weeks) safe, all oral directly-acting antiviral (DAA) therapy leading to cure rates of 90% to 100%, even in previously difficult to treat patients with liver cirrhosis, previous treatment failure and those on immunosuppression. Consequently, treating HCV in risk groups such as renal dialysis and haemophiliacs can eliminate a pool of infected patients to prevent future outbreaks. A seroprevalence study is needed to identify a possible "birth cohort" effect that could aid screening. For HBV, vaccination has reduced prevalence to 3.8%, but these patients are prone to complications such as HBV flares. Since 2014, 13 patients developed liver failure and were listed for liver transplantation at National University Hospital (NUH) but 6 died beforehand. This avoidable catastrophe is due to undiagnosed HBV infection or patients who did not return for follow-up. Good antiviral therapy is available, but the issues are similar to HCV, identification of patients and linkage to care. A cure seems likely in the future as pharmaceutical companies are developing new agents. Singapore has joined in this initiative with a recent award of a national research translational grant to better understand the pathophysiology and the processes needed for a cure of HBV.

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Key words: Eradication, Hepatitis C, Linkage to care, Outbreaks, Screening, Treatment

The recent hepatitis C virus (HCV) outbreak in the renal ward at Singapore General Hospital (SGH) brought to public attention a little known virus. Little known to the public in Singapore largely due to the relatively low local prevalence, a revolution was occurring in hepatitis C therapy. Up to 2010, the standard treatment was a combination of injectable pegylated interferon and orally taken ribavirin. Although Asians responded to this very well with cure rates (defined as sustained virological response or SVR) of 70% to 90%,[1] the treatment usually took at least a year and was accompanied by significant side effects which led to the discontinuation of therapy in 9.6% to 13% of patients.[2] Outside Asia, response rates were even lower—around 40% due to the unfavourable polymorphisms of the *IL28B* interferon response gene,[3] unlike Asians who have the good response genotype. All this changed in the last 5 years with the rapid evolution of all-oral therapy (called direct-acting antivirals or DAAs) leading to SVR rates of >90%, even in previously difficult to treat patients such as those with cirrhosis, liver failure, immunosuppression and prior treatment failure.[4] In the latest treatment regimens, SVR of 97% to 100% after only 12 weeks of therapy using a combination of sofosbuvir and velpatasvir across all genotypes, can be achieved.[5] Noteworthy is the finding that most of the DAAs are relatively free of side effects and well tolerated, although drug interactions need to be monitored.[6] While there are many possible combinations of antiviral therapy available that are highly efficacious, some confusion remains on the choice of therapy. A roadmap of HCV treatment in Asia provides a guide to clinicians on therapeutic choices.[4]

With this background in mind, it is timely to reflect back on the HCV outbreak at the SGH renal unit. HCV is a relatively asymptomatic infection testified by the millions

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of chronically infected patients globally, many of whom are unaware they have HCV. The lack of symptoms also explains the difficulty of reporting and detecting acute infection, and consequently, the difficulties in recognising an outbreak. Looking forward, we should be aware that 2 or more cases of acute HCV in a healthcare setting is sufficient to be an outbreak, based on the United States (US) Centers for Disease Control and Prevention (CDC) definition.[7] The salient points of the outbreak have been well documented in the Independent Review Committee (IRC) report[8] and a subsequent editorial in the Straits Times including the write up by Professor Paul Tambyah.[9] There are some important issues from a medical perspective. The first is that HCV virus seems to be highly resilient in the environment, being able to be detected in dried blood spots even after 1 year[10] and may remain as infective virus on formites for as long as 6 weeks,[11] in contrast to hepatitis B virus (HBV) which cannot be detected after 14 days[12] and human immunodeficiency virus (HIV) which lasts about 1 week.[13] Secondly, the environmental contamination was by extremely high levels of virus, with as much as 5 million IU of virus per 50µl drop of blood, likely increasing the risk of parenteral transmission. Secondly, we need to view this outbreak in the correct perspective. Unlike outbreaks like influenza, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV),[14] which are primary infective agents transmitted by airborne means and close exposure, HCV is transmitted by parenteral means, hence transmission can only occur by contaminated syringes and needles, contaminated injection contents and now also by environmental contamination. Thirdly, is the issue of environmental contamination broadly applicable to all infectious agents? Patients infected by hepatitis B and C and HIV fall into this category and outbreaks have been reported with these agents, and when such patients are identified, higher infection safety precautions should be taken. The resilience of HCV in the environment and high levels of virus imply that added attention to this is important.

While infection control is one approach to preventing outbreaks, another approach gathering momentum is to try to eradicate the pool of patients that harbour chronic infection. In the USA, a notion that treating prisoners[15] and intravenous drug user (IVDU) patients[16,17] may be a good approach towards reducing the pool for potential transmission, and seems to have some success in HIV.[18] While such risk groups may not be significant in Singapore, the pool of patients who are on renal dialysis is significant. Data from the National Registry of Diseases Office (NRDO) indicates that as of end 2014, HCV prevalence in renal dialysis patients in Singapore nationally is 3.8%. A report from SGH in 2000 indicated that the prevalence of HCV in haemophiliacs was as high as 46%.[19] Such patients are potential sources for future outbreaks. With such highly efficacious HCV therapy available today that is safe, it is no longer necessary to warehouse these patients, thus removing a potential source of transmission and outbreaks. Of course, it would be wise to still continue vigilance in infection control and monitoring. Eradicating HCV from risk groups is one strategy while in other countries, eg Georgia, where the prevalence of HCV is 6.7%, there is a commitment by the government to eradicate the virus completely in the entire country.[20] This is a matter that could be considered for Singapore since the burden of disease is relatively small.

The size of the HCV disease burden in Singapore is an issue that has not been well evaluated; the only study in 1991 showed 1.9% prevalence of anti-HCV using a first-generation assay[21] and 0.54% in a blood donor population using a second-generation kit.[22] Internal estimates from the Ministry of Health (MOH) put an approximate prevalence of 0.1% based on blood donor screening data and cumulative notifications of HCV cases to MOH. It may now be timely to conduct a community-based survey in the same manner as that of hepatitis B so we are better able to estimate the seroprevalence of hepatitis C in the community. This for instance will determine whether there is a "birth cohort" effect as was found in the USA, and is now the foundation of their screening strategy for HCV.[23] A "birth cohort effect" identifies higher seroprevalence in certain age groups that that would make that age group a risk factor for HCV screening. In the SGH outbreak, the phylogenetic analysis showed that the strain was unrelated to known strains from SGH patients, leading to the possibility of community acquisition, and potential danger of a community acquired infection getting into an at-risk population.

We should look at the recent HCV outbreak as a learning experience. Acute HCV often leads to chronicity in 70% to 80% but the outcomes of cirrhosis and liver cancer occur only after decades,[24] giving ample time to eradicate the virus thus preventing these serious complications. However, those who are immunosuppressed have a higher risk of developing fibrosing cholestatic hepatititis (FCH),[25] an atypical form of liver failure, because coagulopathy and encephalopathy tend to be late events, and the syndrome is characterised by severe cholestasis, with typical liver biopsy findings. Recognition and diagnosis is crucial as the prognosis is very poor but can now be rescued with appropriate therapy, at least in post-liver transplant patients,[26] provided it is given early.[27] In renal transplant patients, a recent report indicates that the DAAs are safe and efficacious[28] but there is little data on FCH.

The good news is that we are now much more aware of the serious dangers posed by HCV in immunosuppressed patients, of infection control measures in such patients,

and in ensuring that we have coordinated recognition and outbreak response measures. The Ministry of Health is now examining the formation of such a "SWAT" team.[29] More importantly, treatments today lead to such good cure rates that eventually HCV will be significantly less of a threat than today.

For hepatitis B, it is a different story. Singapore has an admirable record in the control of chronic hepatitis B, bringing the seroprevalence down from 5% to 6% in the 1980s[30] to 3.6% in 2010, the most recent seroprevalence study.[31] This was largely due to the rapid adoption of universal vaccination,[31] initially with a plasma-derived vaccine before the current yeast-derived vaccine. This programme has been tremendously successful and we owe much to this early initiative. With the development of antiviral drugs and the subsequent wide availability of top line antiviral agents such as tenofovir and entecavir,[32] control of chronic hepatitis B seems more than adequate, and eventual eradication only a matter of time but this may take another 50 to 60 years as the oldest vaccinees are now only about 30 years old, and most complications of chronic hepatitis B occurs in 50 to 70 age groups. The World Health Organization (WHO) estimates that 20% to 40% of chronic hepatitis B patients over their lifetime may develop these complications.[33] With the higher prevalence of HBV in Singapore and the larger burden of disease, this will remain an important health problem for the immediate future, and already, some signals that all is not right have been emerging. Flares of chronic hepatitis B leading to liver failure and requiring liver transplantation have featured recently, with 13 cases evaluated for liver transplantation at National University Hospital (NUH), but only 4 were transplanted, and 6 deaths since 2014. These patients were not on therapy and not on follow-up, making them an unrecognised risk for complications. A study performed a few years ago from NUH showed that 67% of patients with chronic hepatitis B were not on follow-up.[34] Multiple reasons for this include lack of knowledge, lack of reminders and lack of time.[35,36] Although sentiments from patients are for a cure of chronic hepatitis B,[37] we are still some way from this event. However, recently, experts are increasingly believing that this is an achievable goal.[38] In concurrence, the National Medical Research Council-National Research Foundation (NMRC-NRF) awarded a Translational Clinical Research Grant for $25 million for the eradication of hepatitis B in 2015. This consortium of 29 investigators across major research and healthcare instituitions in Singapore, is one of the first major international grants awarded that is focused on HBV eradication. The current treatments with nucleos-(t)ide analogues or immunomodulators are not able to achieve HBsAg seroclearance in most patients, the marker of a cure of chronic hepatitis B. Consequently, the grant focuses on understanding the immunology and virology of the disease, examining new treatment targets and evaluating new classes of agents. Already new classes of agents such as a core inhibitor, TLR7 agonist, HBV receptor blocker, and siRNA are being evaluated in clinical trials[39] by multiple pharmaceutical companies that are pouring resources into this disease such that a cure for hepatitis B could be achieved in the near future. Consequently, for chronic hepatitis B, treatments today can control the disease and prevent complications, and although a cure is desirable, this will need to wait for new classes of therapies. The same issues arise as with HCV i.e. in identifying, testing and treating the vast pool of yet unrecognised patients.

In conclusion, although HCV can be cured much more easily today, and HBV can be controlled with oral therapy, there is no time for complacency as the warning bells show they can still cause problems. Singapore potentially has the resources, infrastructure, and capability to lead the way to eradicate and control these dangerous diseases. In order to be successful, we need to convene a working group to complement the "SWAT team" focussed on outbreaks, bringing together medical professionals, epidemiologists and the MOH to create a multipronged strategy that involves screening, testing and linkage to care,[5] and monitoring outcomes. However, we have to be cognisant of the costs of intervention and explore innovative methods to address these. Globally, the WHO resolution on viral hepatitis[40] provides the framework for action to be taken on eradication of viral hepatitis.

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Transvaginal Drainage of Pelvic Collections: a 5-year Retrospective Review in a Tertiary Gynaecology Centre

Dear Editor,

Imaging-guided aspiration and drainage is a feasible alternative to surgery in the treatment of pelvic collections.[1-10]

Traditionally, interventional radiologists access the pelvic collections via transabdominal, transgluteal and endorectal approaches. The transabdominal approach usually entails long distances to the pelvic lesions and risks transgression of intervening viscera. The transgluteal approach risks damaging the nerves and vessels, and is occasionally obstructed by the pelvic bones.[11] The endorectal approach is useful for accessing collections adjacent to the rectum[12] but it is non-sterile.

Transvaginal approach was initially described in the early 1990s.[7,11] The approach allows accurate, real time ultrasound-guided needle and drain placement, but has often been overlooked by interventional radiologists, owing to unfamiliarity and lack of data to guide case selection. The Royal College of Obstetricians and Gynaecologists (RCOG) noted that ultrasound-guided aspiration of pelvic fluid collections may be equally effective as surgery, and this has been incorporated into the United Kingdom national guideline for the management of pelvic inflammatory disease since June 2011.[12]

The aim of this study was to retrospectively review the indications, complications and success rates of transvaginal ultrasound-guided aspiration and catheter drainage of pelvic collections at our institution.

Materials and Methods

The hospital institutional review board approved this retrospective study and waived requirement for consent. The KK Women's and Children's Hospital's (KKH) radiology database from 2008 to 2012 identified 65 patients who underwent ultrasound-guided transvaginal drainage procedures. We defined pelvic collection as a cystic collection in the lower abdomen or pelvis that could not be safely or adequately treated with conventional percutaneous transabdominal drainage. Collections that were located caudal to the levator ani were excluded.

There are 2 interventional radiologists who routinely perform the transvaginal aspiration and drainage procedures at our institution. To facilitate the transvaginal ultrasound and visualisation of pelvic structures, patients were asked to empty their bladder prior to the procedure or had an in-and-out urinary bladder catheterisation. The patients were positioned in the lithotomy position and preliminary localisation with transabdominal and transvaginal scan were performed. Intravenous fentanyl and midazolam were administered for analgaesia and sedation. The perineum and vagina were prepared with 10% povidone iodine and chlorhexidine. Topical lignocaine (10%) spray was used to anaesthetise the cervix and vagina. The transvaginal probe was placed in the vaginal fornix and the needle route was scrutinised for bowels, bladder and vessels. Upon confirmation of the needle route, the probe was advanced to stretch the vagina over the transducer head, and a 17 to 18 gauge needle was advanced into the collection under direct ultrasound guidance. If a drain is indicated, a stiff 0.035 inch guidewire was inserted coaxially through the needle. The track was dilated and an 8 French pigtail drainage catheter was inserted. The drain was taped to the thigh and attached to a urinary collection bag or a vacuum bottle. In an aspiration-only procedure, the targeted fluid collection was syringed by hand till emptied. All fluid specimens were sent for microbiologic or cytological examination as indicated by the requesting clinicians. The catheter was removed once the output was less than 10 ml or at the clinical team's discretion.

The number of days patient stayed after the procedure were collated and analysed.

Statistical Analysis

Clinical success was defined as avoidance of surgery during the duration of the patient's admission. Complications were classified according to Society of Interventional Radiology (SIR) criteria.

Results

A total of 34 aspirations and 31 catheter drainage procedures were performed on 65 patients. The patients were women attending KKH hospital, ranging from 23 to 86 years old, with an average age of 45.9 years.

The indications for the procedures and success rates are summarised in Table 1. The clinical success rates are

Table 1. Indications for Aspiration and Drainage

Aetiology of Pelvic Collection	No. of Patients (n)	Percentage (%)	Aspiration	Drainage
Tuboovarian abscess	23	35	11	12
Pelvic collections	30	46	14	16
Endometriotic cysts	6	9	4	2
Symptomatic ovarian cysts	4	6	4	0
Haematocolpos	1	2	0	1
Haematometra	1	2	1	0
Total	65	100	34	31

summarised in Table 2. An example of ultrasound-guided transvaginal drainage is illustrated in Figure 1.

The patient with haematocolpos due to uterine diadelphys was excluded as surgery was preplanned and aspiration was for temporary relief of symptoms. The overall success rate for avoiding surgery during the duration of the patient's admission was 88% (56 of 64 patients), including 83% (19 of 23 patients) with tuboovarian abscesses refractory to medical therapy.

In total, there were 13% (9 of 65) of patients who needed surgery, including 4 cases of unremitting tuboovarian abscesses, 1 case of mixed ovarian tumour, 1 case of serous cystadenoma, 1 case of unremitting pyometria, 1 case of endometriosis and 1 case of haematocolpos.

One patient developed a minor complication according to SIR criteria, requiring nominal therapy without significant long term consequence. The patient underwent a combined transvaginal and transabdominal drainage for tuboovarian abscesses, with the transabdominal approach resulting in an abdominal wall haematoma. The patient was treated with manual compression and was well enough for discharge the following day.

There were 2 mortalities within the study group during the course of hospital admission. The mortalities were due to complications of advanced pelvic malignancy and were unrelated to the interventional drainage procedures. One patient suffered asystolic collapse secondary to overwhelming sepsis. The second patient succumbed to intestinal obstruction from peritoneal metastases. Both patients underwent transvaginal drainage for symptomatic relief of large pelvic cystic collections related to pre-existing pelvic malignancies.

Thirty-seven percent of the patients were discharged on the same day and 66% were discharged up to 2 days post-aspiration, demonstrating good patient tolerability of the transvaginal procedure.

Discussion

Standard treatment of pelvic fluid collection refractory to medical therapy has been laparotomy or laparoscopy. Image-guided drainage procedure obviates general anaesthesia, surgical wounds and associated surgical morbidity. Ultrasound-guided drainages are feasible due to advances in ultrasound technologies and refinement in techniques.[5-8]

The pelvic collections group comprises the largest group of patients in our study. This group is heterogeneous comprising postsurgical collections, infected pelvic collections, malignant pelvic collections and other cystic pelvic lesions. Transvaginal ultrasound-guided aspiration or drainage had therapeutic role in selected benign or postsurgical pelvic collection and was a valuable adjunct to surgery.

Table 2. Clinical Success Rates

Aetiology of Pelvic Collection	No. of Cases (n)	Surgery	No Surgery	Success
Tuboovarian abscess	23	4	19	83%
Pelvic collections	30	4	27	90%
Endometriotic cysts	6	0	6	100%
Symptomatic ovarian cysts	4	0	4	100%
Haematocolpos	1	1	0	0%
Haematometra	1	0	1	100%
Total	65	9	56	86%
Adjusted Total*	64	8	56	88%

*After exclusion of haematocolpos due to uterus didelphys.

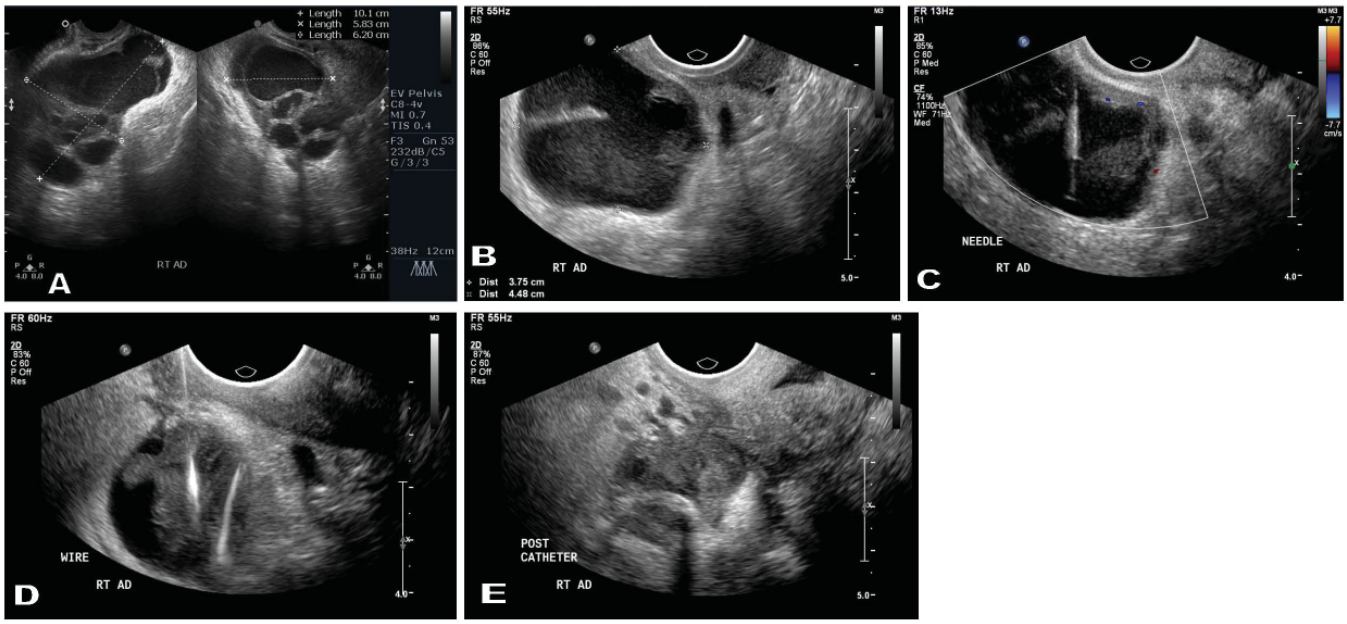

Fig. 1. Right tuboovarian abscess in a 29-year-old woman with pelvic inflammatory disease, presenting with fever and lower abdominal pain. (A) Ultrasound pelvis shows a 10.1 x 5.8 x 6.2 cm multiloculated cystic mass in the right adnexa containing internal echoes and prominent vascularity in its internal septations, consistent with a tuboovarian complex. Patient underwent transvaginal ultrasound guided drainage 2 days after initial ultrasound. (B,C,D) The transvaginal probe, equiped with a needle adapter, was inserted into the vagina. Under direct ultrasound guidance, a 18G needle was advanced into the right adnexal cystic lesion via the needle adapter. A 0.035 guidewire was then advanced into the collection. (D) A 8F drainage catheter was then inserted over the guidewire with pigtail deployed into the collection. The catheter was then connected to a vacuum drainage bottle and secured with adhesive dressing to the thigh. (E) A post-drainage ultrasound image with the catheter in situ.

In our study, tuboovarian abscesses refractory to medical therapy is the second largest group of patients. Transvaginal ultrasound-guided aspiration or drainage was frequently feasible with minimal risk. Ultrasound-guided drainage of tuboovarian abscesses helped majority of our study group patients avoid surgery.

Transvaginal ultrasound-guided aspiration of symptomatic ovarian cysts led to symptom improvement for all patients. Although there are concerns raised about missed malignancy[13,14] and the possibility of recurrence, the clinical efficacy, low morbidity and low risks associated with transvaginal ultrasound-guided drainage makes it a reasonable alternative to surgery in carefully selected patients.

Conclusion

In our study, transvaginal ultrasound-guided drainage is efficacious and demonstrates high clinical success rate. The clinical success rate for tuboovarian abscesses, pelvic collections and overall pelvic collections were 83%, 90% and 88%, respectively. Transvaginal approach to drainage of pelvic collections is a useful technique to add to the repertoire of the interventional radiologist, and can help patients with deep pelvic collections circumvent the need for general anaesthesia, open surgery and risks of surgical complications.

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Letter to the Editor

Demographics of Multiligamentous Knee Injuries at a Level 1 Trauma Centre

Dear Editor,

Multiligamentous knee injuries account for 0.02 % to 0.2% of all orthopaedic injuries[1,2] and can result in significant functional disability. The aim of this study is to review the aetiology, characterise the injury patterns and present our management of multiligamentous knee injuries.

Materials and Methods

A case review was performed for 18 consecutive patients who presented with multiligamentous knee injuries. These patients were managed over a 34-month period from 2010 to 2013 by the senior author who managed majority of the cases in our centre. Our institution is a 1300-bed Level 1 trauma centre that manages the highest number of trauma patients in our locality.[3] A multiligamentous knee injury was defined as an injury to 2 or more knee ligaments. These included the anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), lateral collateral ligament (LCL), posteromedial (PMC) and posterolateral complexes (PLC). Assessment of the injured knee involved clinical examination and imaging modalities including x-rays and magnetic resonance imaging (MRI).

Results

Epidemiology and Mechanism of Injury

Eighteen patients were identified from an injury database. The average age was 36 years old (range, 19 to 60 years) and 94% (17 patients) were male. High-energy trauma accounted for 72% of the injuries. These included motorcycle collisions (33%, 6 patients) and motorcyclists who self-skidded (22%, 4 patients), fall from height (11%, 2 patients) and a pedestrian who was hit by car (1 patient). Low-energy trauma accounted for 28% of the cases. These included sports injuries (11%, 2 patients) and low-energy falls (17%, 3 patients).

Timing of Presentation and Associated Injuries

Fourteen patients (78%) presented acutely and 4 patients (22%) were referred for management following resolution of the more emergent injuries. Associated injuries in the ipsilateral lower extremity were present in 5 patients (28%) as follows: 2 open fractures of the tibia shaft with one of them having compartment syndrome at presentation, 1 chip fracture of the fibula head, 1 tibia plateau avulsion fracture and a metatarsal fracture. All the patients with associated fractures sustained high-energy trauma except 1 patient.

Injury Patterns of the Knee

The extent of injury was classified according to the ligaments involved (Table 1). The most common injury pattern involved the anterior cruciate ligament, posterior cruciate ligament, and medial collateral ligament complex (33%, 6 patients). The majority of injuries were closed except 1 patient who presented with an open knee dislocation.

Initial Management

All patients that presented following high-energy trauma underwent a full trauma evaluation in the emergency department. Four patients (22%) required emergent surgery at time of their initial presentation including debridement of open knee dislocation, intramedullary nailing, external fixation and fasciotomy.

Table 1. Patterns of Multiligamentous Knee Injury

Injury Pattern	No. of Knees (n = 18)	Percentage
ACL-PCL-MCL	6	33
ACL-PCL-PLC	4	22
ACL-PCL	2	11
PCL-PLC	2	11
ACL-PCL-MCL-LCL	1	6
ACL-PCL-PLC-PMC	1	6
PCL-MCL	1	6
PCL-PLC-MCL	1	6

ACL: Anterior cruciate ligament; PCL: Posterior cruciate ligament; MCL: Medial collateral ligament; LCL: Lateral collateral ligament; PLC: Posterolateral corner; PMC: Posteromedial corner

Subsequent Management

Seven patients (39%) underwent definitive multiligamentous knee reconstruction (Table 2). Four patients underwent surgery at an average of 12 weeks after injury (range, 8 to 16 weeks) while the remaining 3 patients underwent surgery at 10 months and 3 years after the initial injury due to delayed presentation and patient preference for a trial of non-operative treatment. Eleven patients (61%) were managed non-operatively (Table 3).

The ACL was reconstructed using a transportal technique, while transtibial outside-in technique was used for PCL reconstruction, and a fibular-based reconstruction technique for PLC reconstruction. The sequence of graft tensioning was as follows: PCL, ACL, PLC/LCL, MCL. Postoperatively, all patients underwent a standardised rehabilitation protocol with their knee brace locked in extension for the first 6 weeks, except during therapy where passive range of motion from 0° to 45° was allowed. From 6 to 12 weeks postoperatively, the knee brace is unlocked and active range of motion is allowed. In the presence of a PCL reconstruction, patients were advised to avoid active hamstring contraction for 12 weeks and to sleep in a prone position to minimise the posterior directed forces on the tibia.

Discussion

Epidemiology and Injury Pattern

Multiligamentous knee injuries are complex extremity injuries that may be associated with neurovascular injuries and concomitant fractures of the involved limb. They may result in significant functional disability.

High-energy trauma is the most common cause of multiligamentous knee injuries. Wascher et al[4] reported 80% (40 patients) of cases were due to high-energy trauma involving motor vehicle accidents. Similarly, 76% (13 patients) in our series were due to high-energy trauma with a high proportion (10 patients, 59%) attributed to motorcycle accidents. A systematic review done to compare globally the distribution of road traffic deaths by road user group found that in Southeast Asia, motorcyclists contribute more to road traffic fatalities (up to 50%) compared to Europe and America (3% to 21%).[5] In our locality, motorcycles formed 15% of the total vehicles registered in 2011,[6] yet were implicated in 46% to 54% of all road traffic fatal accidents.[7,8]

Fractures of the ipsilateral extremity (12% to 58%)[9] are commonly associated with the multiligamentous injured knee. In our cohort of patients, 28% (5 patients) had associated ipsilateral limb fractures. In the polytrauma setting, the diagnosis of multiligamentous knee injury may be delayed as the management of life and limb threatening conditions will take precedence. In our series, 22% (4 patients) presented more than 3 months after the initial injury. Three of them were referred after the more emergent injuries were treated. This highlights the need to be vigilant for concomitant joint injuries in the setting of polytrauma. The initial knee dislocation may have spontaneously reduced and the injury to the knee is underestimated.[10]

Management

The surgical management of multiligamentous knee injuries is complex and controversial. Two approaches had

Table 2. Timing of Definitive Ligamentous Reconstruction

Case	Surgery	Timing from Injury
1	ACL, PCL reconstruction with partial lateral menisectomy and medial meniscus repair	2 months
2	ACL, PCL reconstruction with partial lateral menisectomy	3 months
3	ACL, PCL, MCL reconstruction	3 months
4	LCL repair	3 weeks
	Staged reconstruction of ACL, PCL, PLC	4 months
5	ACL, PCL, MCL reconstruction*	10 months
6	PCL, MCL reconstruction*	3 years
7	PCL, PLC reconstruction†	3 years

ACL: Anterior cruciate ligament; PCL: Posterior cruciate ligament; MCL: Medial collateral ligament; LCL: Lateral collateral ligament; PLC: Posterolateral corner; PMC: Posteromedial corner

*Delayed surgery due to patients' request for trial of non operative treatment.

†Delayed surgery due to late presentation.

Table 3. Reasons for Non-operative Management

Reason	No. of Patients	Injury Pattern
Functional stability	3	Patient 1: PCL/MCL Patient 2: PCL/PLC Patient 3: ACL/PCL/MCL
Comorbidities/low functional demand/ functionally stable	3	Patient 1: ACL/PCL/PLC Patient 2: ACL/PCL/MCL Patient 3: ACL/PCL/PLC
Stable after acute MCL bony avulsion repair	1	Patient 1: MCL/PCL
Delayed presentation	1	Patient 1: PCL/MCL/PLC
Transfer to country of origin for treatment	3	Patient 1: ACL/PCL/MCL/LCL Patient 2: ACL/PCL/LCL Patient 3: ACL/PCL/PLC

ACL: Anterior cruciate ligament; PCL: Posterior cruciate ligament; MCL: Medial collateral ligament; LCL: Lateral collateral ligament; PLC: Posterolateral corner; PMC: Posteromedial corner

been adopted include the early, single stage reconstruction and staged reconstruction. Early surgery is defined as surgical repair or reconstruction performed within 3 weeks of the injury. In a systematic review by Levy et al,[11] early surgical treatment resulted in higher knee outcome scores than delayed surgery. There was no significant difference in mean range of motion or flexion loss. However, patients who underwent early surgery had higher sports activity scores. Staged reconstruction involves performing extra-articular ligamentous reconstruction in the early phase followed by intra-articular reconstruction subsequently. A systematic review by Mook et al[12] reported superior subjective outcomes in the staged treatment group when compared with both early and late surgery. Liow et al[13] highlighted that the advantages of performing a staged procedure are that of lower operative time as well as a lower risk of arthrofibrosis.

We adopted a staged surgical approach to the management of multiligamentous knee injuries due to associated risk of iatrogenic compartment syndrome during arthroscopy in the acute phase of injury.[14,15] Thirty-nine percent of our patients (7 patients) underwent definitive multiligamentous knee reconstruction. Four patients had surgery at an average of 12 weeks after injury (range, 8 to 16 weeks) while the remaining 3 patients underwent surgery 10 months to 3 years after the initial injury due to late presentation and patient preference for a trial of non-operative treatment (Table 3). Other factors that affect surgical timing are concomitant injuries such as open fractures, extensive soft tissue injury and other systemic medical conditions.

In a systematic review of studies[11] comparing operative and non-operative management, the Lysholm scores of the operative group was statistically significantly better than that of the non-operative group. There was also a high rate of return to work and sport in the group treated operatively. In our series, 11 patients (61%) were managed non-operatively, most commonly due to good functional stability of the affected knee, and/or low functional demand of the individual, medical comorbidities or returned to their country of origin for management (Table 3). This highlights the need for an individualised treatment approach for these complex knee injuries.

Conclusion

The majority of our patients with multiligamentous knee injury were high-energy motorcycle accidents. The most common pattern of injury involved the ACL, PCL and MCL complex. An individualised and staged surgical approach was adopted in the management of this complex knee injury.

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Professor Feng Pao Hsii (1936 – 2015)

In Memoriam: By the Chapter of Rheumatologists; and Singapore Society of Rheumatology

Prof Feng obtained his MBBS from the University of Malaya, Singapore Division in 1960. In 1964, he was awarded the Singapore Government Colombo Plan Scholarship to the University of Glasgow where he passed the membership examination of the Royal College of Surgeons and Physicians of Glasgow within 6 months. In 1969, he was awarded the World Health Organization Research Fellowship to Israel. By the early 1970s, Prof Feng's passion had gradually switched from Nephrology to Rheumatology, and in particular lupus. He was promoted Physician Grade G in 1971, then Senior Physician Grade D by 1985. During this time, he had worked at Singapore General Hospital and Toa Payoh Hospital before taking over from Prof Chew Chin Hin in 1979 as Head of Department of Medicine IV, Tan Tock Seng Hospital (TTSH).

In 1986, Prof Feng proposed to Prof Chew, who was then Deputy Director of Medical Services at the Ministry of Health, to develop Rheumatology and Clinical Immunology further as "it had advanced from a specialty dealing with 'aches and pains' to one dealing with the 'diverse nature of autoimmunity' like lupus". His request was fully acceded to and the proposal approved. He subsequently established the first Department of Rheumatology & Immunology in Singapore at TTSH and became its founding Head. Thirty years after the birth of Rheumatology in Singapore, we now have 57 accredited rheumatologists working in both the private and public sectors. He also had the foresight in the mid-1990s to develop paediatric rheumatology in Singapore. We now have paediatric rheumatologists at the KK Women's and Children's Hospital and National University Hospital who help look after children with childhood arthritis and rheumatic diseases like lupus.

In 1989, while he was Chairman Medical Board at TTSH, Prof Feng laid the groundwork for formal Infectious Diseases training in Singapore. Like Rheumatology, Infectious Diseases which started off as a small department in TTSH, now has 69 accredited Infectious Diseases physicians in private practice and the public sector in Singapore.

Prof Feng Pao Hsii (left) shares a light-hearted moment at a dinner lecture in 2000. Photo courtesy of Dr Leong Khai Pang.

Apart from his many portfolios in TTSH, Prof also contributed significantly to the regional and international scene in rheumatology, with the highest honour being President of the Asia Pacific League of Associations for Rheumatology (APLAR) from 1996 to 1998. He also had a passion for lifelong learning, including organising congresses to ensure that rheumatology education remained "without borders", and helping the younger rheumatologists to forge clinical and research collaborations. The International League of Associations for Rheumatology (ILAR) Congress in Singapore in 1997, and the Ten Topics in Rheumatology (Asia) series from 2011 to 2013 remain the most memorable. As a patient advocate, he strongly believed in the importance of patient education and empowerment. This was evident through his work as Chairman of the National Arthritis

Foundation, where he actively helped raise funds for adults and children with arthritis who needed expensive medications like biologics to keep them going at work and at school.

Prof Feng was actively involved with the Academy of Medicine (Singapore) (AMS) from the 1970s – 1990s; where he was Censor (1973 – 75) and Bedel (1975 – 77) of the AMS Council, Chairman of Chapter of Physicians (1977 – 79), Scribe (1979 – 84), Assistant Master (1984 – 1988) and Censor (1988 – 1990). The Academy organised a highly successful 3rd Congress of the South East Asia and Pacific League Against Rheumatism (SEAPAL) in 1976. Many of the members of the organising committee later founded the Singapore Society of Immunology and Rheumatology that same year, among whom Prof Feng was President from 1981 – 1993. He delivered the Galloway Memorial Lecture in 1983 entitled "Systemic Lupus Erythematosus in Singapore—A Decade of Study", and the Seah Cheng Siang Memorial Lecture in 2000 entitled "Going Places—A Rheumatological Odyssey".

Despite his busy schedule, Prof still made time to contribute to the Singapore Medical Association (SMA) where he was Editor of the Singapore Medical Journal (SMJ) from 1978 – 1987. He delivered the SMA Lecture in 2000 entitled "Medicine in the Digital Era—Opportunities & Challenges." For his contributions to the SMA and Medicine in Singapore, he was awarded the SMA Honorary Membership in 2014.

With over 150 publications in international, regional and local journals, and his MD thesis entitled "Systemic Lupus Erythematosus in Singapore—A Clinical Study", he was appointed Adjunct Professor at the Faculty of Medicine, National University of Singapore. For his numerous contributions, dedication to service and country, Prof Feng was awarded the Public Administration Medal (Silver) in 1986, the Public Administration Medal (Gold) in 1997, and the National Healthcare Group Lee Foundation Lifetime Achievement Award in 2002.

It takes a tough character to overcome challenges and Prof Feng certainly has overcome several challenges in his career. Each letter of the word TOUGH spells out a character trait of Prof Feng that we all can learn from. He was "tenacious". Starting specialties such as Rheumatology, Infectious Diseases and Medical Intensive Care from scratch is no easy task. Prof was "outstanding". This attitude of excellence helped to put Rheumatology on the world map. He has published or inspired those he trained to publish extensively in reputable journals and he has organised world congresses on SLE and Rheumatology. He dared to be "unique". When treatment of lupus nephritis was bleak, he together with Prof Seah Cheng Siang were the first to use cyclophosphamide, which made a great difference to lupus patients. With those he worked with, Prof Feng was "generous". He did literature searches for his registrars and consultants knowing their pet interests in Rheumatology. He kept in touch with them when they were on their Health Manpower Development Plan (HMDP) training overseas. Above all, he was not threatened by his staff who would bring back new skills, knowledge and expertise. He nurtured and groomed those under him to flourish in their own right. Finally, he was "humble". Many great people are self-absorbed and serve their own interests. The truly great are humble and seek the good of others. Prof Feng did his life's work not to seek his own glory but he sought to serve the needs of others.

Prof ended his Seah Cheng Siang Lecture in 2000 with these words: "With the beginning of a new millennium, the medical profession faces unprecedented pressures and challenges that jeopardise our ability to care for patients. To be effective, physicians must work together. We must be vigilant about threats to high standards, research, education and ethics and seize opportunities for improvement. We need to ensure that relationships with patients, students, colleagues and other healthcare professionals are marked by trust and mutual respect. The pursuit of excellence, caring for our patients with compassion and a sturdy resolve to retain the valued fundamentals of our profession must never change. Our patients and Professor Seah expect nothing less."

Prof Feng is indeed the Father of Rheumatology in Singapore and we will truly miss him.

Dr Bernard Thong
Chairman, Chapter of Rheumatologists

Dr Keng Hong Leong
Board Member, Chapter of Rheumatologists

Dr Khai Pang Leong
President, Singapore Society of Rheumatology

In Memoriam: By the Chapter of Infectious Disease (ID) Physicians; and Society of Infectious Disease (Singapore)

The Chapter of Infectious Disease (ID) Physicians and members of Society of Infectious Disease (Singapore) would like to acknowledge Prof Feng for starting ID as a recognised specialty in Singapore. He was a unique individual who saw a need and had the vision and drive to

Prof Feng Pao Hsii at the Western Pacific Congress of Chemotherapy and Infectious Diseases held in 1996. Photo courtesy of Dr Brenda Ang.

create something out of nothing in not 1 but 2 specialities. This vision was broad and inclusive. He saw that in order for his own specialty, Rheumatology, to progress, with the widespread use of immunosuppression, there was a pressing need for ID specialists to look after vulnerable immunocompromised patients. He brought in Dr Lowell Young as Health Manpower Development Plan (HMDP) visitor to Rheumatology in the late 1980's who supported this call. The beginnings of ID practice in Singapore in its present form then took root with David Allen's arrival in 1989. With the support of Prof Feng and the leadership of Dr David Allen, the Department of Infectious Diseases in Tan Tock Seng Hospital was started in 1992 and slowly in the beginning, but steadily thereafter, it grew to become a national and regional reference centre for infectious diseases and emerging infections.

Prof Feng also formed the Society of Infectious Disease (Singapore) in 1990, with support from his rheumatology colleagues, microbiologists, venerealogists, and Dr David Allen. He was the Founding President of the society which organised the 1st Singapore San Francisco Conference on Infectious Diseases in 1991, the forerunner of our popular Annual Practice Updates. SID(S) went on to organise the Western Pacific Conference on Infectious Diseases in 1996, which remains one of the most successful infectious diseases conferences in the region to date. Part of the proceeds from the conference were used to start the Communicable Diseases Centre (CDC) Endowment Fund which was used to fund training of healthcare staff in infectious diseases and microbiology, as well as treatment for human immunodeficiency virus (HIV) patients at a time when there was no subsidy for antiretrovirals and the financial support meant the difference between life or death for these patients.

The subspecialty of Infectious Diseases would not have flowered without his insight, strategic support, intellectual provocation, and willingness to break with the past. His friendship and his collegiality were valued by the first and second generation of infectious disease physicians in Singapore. He was a pragmatist who worked discretely behind the scenes to look beyond existing patient care and medical education paradigms for new approaches to better care for our patients, prepare our trainees and overall to advance the profession of Medicine in Singapore.

Singapore's ID physicians acknowledge Prof Feng as the founding father of ID in Singapore. We are grateful to him as protector, friend and mentor to many and we all mourn his passing.

Dr Brenda Ang

Chairman, Chapter of Infectious Disease Physicians

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