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"Faith is the strength by which a shattered world shall emerge into the light."

Helen Keller (1880 – 1968)
American author

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Professional Medical Congress Organisation for **Professionals**....

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Editorial

The 2016 Outbreak of Zika in Singapore

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The eponymous Zika virus (ZIKV) originated from Africa, and was discovered incidentally in rhesus macaques in the Zika forest in Uganda in 1947 as a result of Rockefeller Foundation-sponsored programmes on yellow fever.[1] ZIKV was not thought to be an important human pathogen, with a paucity of published clinical reports, until the explosive outbreak in the Americas. The Brazil 2015-2016 outbreak received international concern due to the association with alarming rates of microcephaly and the Guillain Barre Syndrome.[1,2] This led the World Health Organization (WHO) to declare Zika a "public health emergency of international concern" in February 2016, calling for a "coordinated international response" to address the pressing questions surrounding the lack of available knowledge about the virus and neuropathogenesis.[3]

Phylogenetic studies of ZIKV suggest that the virus was probably exported to Asia in the 1940s and then circulated throughout the region, forming a distinct Asian lineage (as opposed to the African lineage).[1,4] Human serosurveys of ZIKV in Southeast Asia from the 1950s—which must be interpreted with caution because of the different testing methodology and the cross-reactivity of ZIKV serological tests with other flaviviruses such as dengue—have found that 4% to 75% of the sample population tested had antibodies to ZIKV.[1] The epidemic in the Americas was caused by the Asian lineage ZIKV that crossed into Brazil via French Polynesia.[1]

Singapore had ZIKV on its radar as a re-emerging pathogen with local epidemic potential due to factors such as high volume of global travel, available *Aedes spp*. vector populations and a presumed Zika-naïve dense population in a dengue endemic area. The first case occurred in a permanent resident who had returned from Brazil in May 2016, and extended vector control coupled with active screening around the patient's home in Watten Estate found no further cases.[5] However, despite having initiated preparedness plans at the national level, the subsequent outbreak appeared to have caught everyone off guard, probably because Zika was anticipated to be associated with travel to the Americas. In brief, a group of general practitioners alerted the Ministry of Health (MOH) on 22 August 2016 that they had seen a spike of non-dengue febrile illnesses associated with rash at Sims Drive since the second week of August.[6] Although the initial cases were all from the construction site of the Sims Urban Oasis condominium, there are now almost 400 cases of laboratory-confirmed Zika infections at the time of writing, with multiple other clusters of cases beyond the original Aljunied/Sims Drive cluster.[7]

Confirmed Zika-infected patients have generally presented with a mild, brief illness consisting of fever, rash, myalgia and conjunctivitis as is widely reported, with a significant proportion of patients not having all the symptoms in the clinical case definition.[1] At the first notice of the outbreak, MOH and the National Environment Agency (NEA) attempted a trial of 'containment strategy' coupled with aggressive vector control measures akin to how chikungunya was contained in 2008.[8] From the outset however, it was clear that this was a far more challenging proposition. The ZIKV outbreak in August had already been ongoing for at least a couple of weeks before containment was attempted. Unlike chikungunya, approximately 80% of Zika-infected persons are asymptomatic but are still able to transmit the virus either via an *Aedes spp.* vector or rarely via sexual intercourse. ZIKV is also able to spread vertically (transovarial transmission) in the mosquito population, and thus technically does not require a susceptible primate population for maintenance.[9] When community transmission continued and new clusters arose after the initial week of containment, MOH stopped mandatory hospital quarantine of Zika viraemic patients. It is likely that Zika will become endemic in Singapore, but case numbers and associated complications will evolve with changing population immunity.

ZIKV is associated with Guillain-Barre syndrome, but this is reportedly rare, affecting 2.4 per 10,000 infected persons based on data from the French Polynesian outbreak.[1]

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The greatest concern regarding Zika infections has been the congenital Zika syndrome, in particular microcephaly. In vitro studies have shown that ZIKV can infect foetal neuroprogenitor cells by using the AXL receptor tyrosine kinase—which is found abundantly in neuroprogenitor cells but not in mature neurons—for entry.[10] The impact on pregnancy is highest during early trimesters of pregnancy, although later trimester infection may also cause foetal adverse events (growth restriction, bone dysgenesis) supposedly via placental infection and insufficiency.[1] The real risk of an infected pregnant woman (symptomatic or asymptomatic) giving birth to a baby with congenital Zika syndrome and microcephaly is not known at present. If the data from Bahia, Brazil is discounted, however, then the rates of congenital Zika syndrome would be closer to 1% than 13.2%, acknowledging inherent limitations in the variability of definitions and reporting among diverse countries.[2]

Whether Singapore will see cases of microcephaly and other adverse neonatal outcomes is unknown, although we should be prepared for them. Of importance, there can be manifestations of the congenital Zika syndrome such as hearing loss, impaired neurodevelopment, and loss of sight that may not be apparent in the neonatal stage, hence infants will need careful longitudinal follow-up.

There are several urgent areas of research with regard to Zika. At this time, there is a lack of a sensitive serological test that can reliably discriminate between Zika and dengue. There is also a need for a systematic approach to surveillance, case detection, monitoring and management of high-risk outcomes in both the pregnant and non-pregnant populations. The potential keys to the control of Zika and other flaviruses lie in effective vaccine(s) and mosquito control, for which novel strategies are needed. Candidate Zika vaccines will need to be studied and evaluated with respect to performance in a dengue endemic area such as Singapore in terms of efficacy and safety, especially for pregnant women.

In conclusion, each emerging and re-emerging disease pathogen will have its unique implications in terms of public health and clinical care, as well as new research questions that will arise. Singapore has long had an established public health infrastructure and vector control expertise to deal with dengue, but the re-appearance of Zika on our landscape has its own challenges which will need a multidisciplinary and concerted approach to address the concerns at hand, both for Singapore and the international community.

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Original Article

Diabetes Health Profile-18 is Reliable, Valid and Sensitive in Singapore

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Abstract

Introduction: The Diabetes Health Profile-18 (DHP-18) measures diabetes-related psychological well-being in patients with type 2 diabetes mellitus (T2DM). It includes 3 subscales: psychological distress (PD), barriers to activity and disinhibited eating. The psychometric properties of the DHP have not been evaluated in Asia. The aim of this study was to determine the psychometric properties of the DHP in multiethnic Singapore. Materials and Methods: Patients between the ages of 18 to 65 diagnosed with diabetes (either type 1 or type 2) for at least 1 year were recruited from a diabetes outpatient clinic in a tertiary hospital. They completed a set of self-administered questionnaires including sociodemographic information and the DHP. Validity of the DHP was evaluated using confirmatory factor analysis (CFA) and exploratory factor analysis (EFA). Reliability was assessed with internal consistency and sensitivity was determined by effect size, associated with detecting a statistically significant and clinically important difference between various patient subgroups. Results: A total of 204 patients with mean age 45.4 (11.9) years, comprising 64% males and 50% Chinese, 27% Indian and 12% Malay were studied. In CFA, model fit was poor. Forced 3-factor EFA supported the original 3-factor structure of the DHP. Convergent and discriminant validity was demonstrated (100% scaling success). DHP was sensitive across majority of social demographic, clinical and social-functioning determinants (i.e., effect size >0.3). Cronbach's alpha exceeded 0.70 for all subscales. Ceiling effects were negligible but large floor effects were seen for the PD subscale (23%). Conclusion: The DHP is valid, reliable and sensitive for measuring well-being in Asian patients with T2DM.

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Key words: Quality of life, Reliability, Sensitivity, Validity

Introduction

Type 2 diabetes mellitus (T2DM) is a global burden; in Asia, its prevalence will significantly increase in the next few decades.[1] In addition, it is a chronic disease that can have profound effects on the physical, psychological and social well-being of an individual. It is one of the most psychologically demanding chronic diseases as it is a lifelong condition with no cure;[2] it is a chronic disease that can lead to a multitude of complications associated with significant morbidity and mortality.[2,3] A significant part of the treatment is focused on self-management, which requires constant monitoring, diet change and lifestyle modifications.[4] Hence, to improve clinical outcomes, it is important that the psychological well-being of patients with T2DM be constantly monitored and discussed with patients, to prevent the onset of depression, which will limit treatment adherence and lead to poorer glycaemic control, increased risk for diabetes complications and increased health care costs.[5-7]

Diabetes-specific instruments such as the Problem Areas in Diabetes (PAID),[8] the Diabetes Quality of Life Measure (DQOL),[9] and the Diabetes Health Profile-18 (DHP-18)[4] are examples of questionnaires that measure the psychological well-being of patients with T2DM. A PubMed search on the

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3 questionnaires showed that PAID is the most published questionnaire to date (22 publications), followed by DQOL and DHP-18 with 4 publications each. Yet, there are several reasons why the DHP-18 is preferred over the PAID and DQOL: 1) DHP-18 is the shortest questionnaire, consisting of 18 items. Respondent burden is becoming the main cause of non-response.[10] Having a short questionnaire will reduce the burden on respondents and encourage participation; 2) DHP-18 measures multiple domains of psychological well-being, such as psychological distress (PD), barriers to activities (BTA) and disinhibited eating (DE); 3) In particular, the DE subscale is not covered by any other instruments despite studies showing that DE is a frequent struggle experienced by many patients with T2DM1;[11] and 4) Studies in European populations had shown that the psychometric properties of the DHP-18 achieved good internal consistency, validity and measurement equivalence.[4,12,13] To date, studies on the psychometric properties of the DHP-18 have been performed extensively in Western populations.[4,12,13] As such, there seems to be a lack of research conducted within the Asian population, whose cultures, values and beliefs are different from the West.[14]

Thus, the aim of this study was to determine the validity, reliability and sensitivity of the DHP-18 for the multiethnic population of Singapore. We hypothesise that: 1) we would obtain a 3-factor solution similar to the original design of the instrument; 2) validity would be achieved, where item-scale correlations will attain a correlation of ≥ 0.40[15] and items would have significantly higher correlation with its hypothesised scale than with scales measuring other constructs; 3) reliability would be met as item means and standard deviations (SDs) would be similar within each scale; 4) floor and ceiling effect would be minimal (<15%); and 5) known-groups validity, as guided by literature (e.g., those with complications will have poorer health-related quality of life [HRQoL] as compared to those without complications) would be met.

Materials and Methods

Study Design and Participants

This is a secondary analysis of the baseline data of a prospective longitudinal study on outcomes from a convenience sampling of patients with diabetes mellitus (PEAQ DM). This study was approved by the National Healthcare Group Domain Specific Review Board. English-literate patients aged between 21 and 65 years old, who were diagnosed with diabetes (type 1 or 2) for at least 1 year, were recruited from the specialist outpatient clinic of the National University Hospital from 2011 to 2012. Patients were selected at the clinic waiting area. Patients were excluded if there was self-reported or documented gestational diabetes, unstable and ongoing treatment of heart, kidney, liver and psychiatric conditions and gestational diabetes. The study terms and procedures were explained and written informed consent was obtained from all recruited patients. In the analysis, we only presented data on T2DM patients.

Data Collection

Data on demographic factors were collected from self-administered questionnaires. Ethnic group was classified as Chinese, Malay, Asian Indian or Others. Marital status was classified as "never married", "currently married" or "separated/divorced/widowed". Education level was determined based on the number of schooling years and was categorised into <7 (primary education), 7-10 (secondary education) and >10 years (tertiary education). Medical history of comorbidities (such as history of cardiovascular disease, retinopathy, nephropathy, peripheral vascular disease, anaemia, cerebrovascular disease and hepatic disease) was captured through self-reports. Glycaemic control (glycated haemoglobin test [HbA1c]) levels were collected either a few days before the clinic visit (along with the other blood tests) or on the day itself (as a standalone, finger prick test) at baseline at the National University Hospital.

Diabetes Health Profile (DHP)

The DHP-18 consists of 18 items covering 3 subscales: PD (6 items), BTA (7 items) and DE (5 items). Each item in DHP-18 is scored 0 to 3 ("Never" to "Very much") and subscales are rescored on a 0-100 scale by dividing the raw score for each subscale by the overall score range and multiplying this by 100.[16] High scores indicate poorer well-being. Since its development, the DHP-18 had been translated into 28 languages and could be completed via paper/pencil, interviewer-administered, self-administered, or electronically through handheld devices or internet. The DHP-18 will be referred to as DHP henceforth.

Definitions of Known-Group Variables

Several groups were created based on clinical, sociodemographic (age, gender and ethnicity), socioeconomic status (education and household income) and social functioning determinants for the purpose of evaluating the construct validity of DHP. Glycaemic control was determined by measuring HbA1c. We classified patients with good control of HbA1c as achieving the standard of HbA1c $\leq$7.0%.[17] Medications were classified into treatment types, such as oral, insulin or both. Presenteeism, which is a measure of the effectiveness of an individual who goes to

work despite having an illness, was measured using a single question: "On a scale of 0 to 10, how effective are you at work?" We considered a score ≤5 as not effective at work. PAID is a 20-item questionnaire measuring DM-specific psychological distress. PAID scores were dichotomised, with patients scoring 40 and above indicating severe DM-specific emotional distress.[18]

Statistical Analysis

For all questionnaires used, individual items were summed and transformed (where necessary) as recommended in the respective user manuals.[8,19,20] Participants with missing DHP item scores were excluded list-wise from the analysis. Continuous variables were presented as means +/- SDs unless otherwise stated and categorical variables were presented as percentages. Analyses were performed using Stata version 12 (StataCorp LP).

Validity

Construct validity assesses the degree to which an instrument measures what it was designed to measure. Factor analysis is a well-established method for assessing construct validity.[21] A confirmatory factor analyses (CFA) was conducted based on the factor structure suggested by the developer.[22] A conventional good model fit criteria includes Tucker-Lewis index (TLI) ≥0.9 or comparative fit index (CFI) ≥0.9. An unforced exploratory factor analysis (EFA) with varimax orthogonal rotation would be carried out if the model fit for the CFA was poor. Eigen value ≥1 was used to determine the number of factors in the unforced EFA.

Spearman rank correlations were performed to assess convergent and discriminant validity where convergent validity referred to high item-scale correlation exceeding 0.4 and be approximately equal within a scale[23] and discriminant validity referred to the item having higher correlation with its hypothesised scale rather than scales measuring other concepts. Scaling success was declared whenever an item correlated more strongly with its hypothesised scale than with a scale measuring a different construct.[15]

Reliability

The Cronbach's alpha coefficient was used to determine internal consistency of the subscales. Good reliability was defined as Cronbach's alpha ≥0.7 for group comparisons and ≥0.9 for individual assessments.[15] The percentage of respondents scoring at the floor (domain/total score = 0) and ceiling (domain/total score = 100) was also determined. A floor (ceiling) effect was defined as being present if >15% of the subjects scored at the minimum (maximum) level respectively.[24]

Sensitivity

Sensitivity was determined by effect size (ES), derived by dividing the differences in the mean scores between the 2 groups by the pooled standard deviation (PSD).[25] A sensitive instrument is able to detect a statistically significant and clinically important difference (ES >0.3) between various patient subgroups.[26-28] This measurement will concurrently measure known-groups validity, where we expect participants without complications to have lower DHP scores, indicating better psychological well-being.[29,30]

Results

In total, 406 T1DM and T2DM patients consented to participate in the study, leading to a response rate of 68.9% (Fig. 1). As T1DM and T2DM were confirmed against case notes after enrolment, the response rate could not be stratified by type of diabetes. However, after the various exclusions, the final number of patients with T2DM in the study was 217. Thirteen patients were excluded from the study due to missing information in the DHP and PAID questionnaires. Table 1 describes the sociodemographic and medical history of the 204 patients with T2DM included in the study. The mean SD age of the population was 45.4 (11.9) years with 64% males; 50% of the subjects were Chinese, followed by Indians (27%) and Malays (12%). Most of the subjects had at least one comorbidity with retinopathy (14%), cardiovascular (13%), followed by nephropathy (8%), to name a few. The PAID classified 32% as suffering from severe psychological distress.

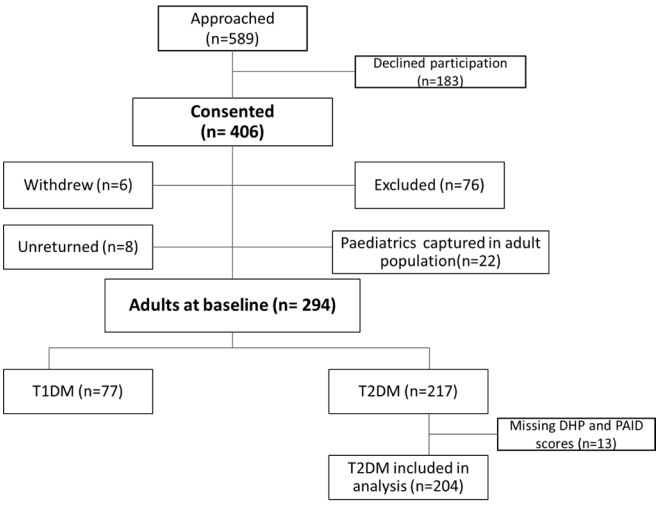

Fig. 1. Flowchart of the recruitment of patients with type 2 diabetes mellitus.

Table 1. Social Demographic of Sampled Patients with Type 2 Diabetes Mellitus

	All Races (n = 204)	
	n	%
Age (mean [SD], 95% CI)	45.4 (11.9)	43.8 – 47.1
Gender		
Male	131	64.2
Female	73	35.8
Ethnicity		
Chinese	103	50.5
Malay	24	11.8
Indian	57	27.9
Others	20	9.8
Education		
<7 years	16	8.5
7 – 10 years	65	34.4
>10 years	108	57.1
Marital status		
Single	41	20.1
Married	127	62.3
Divorced/widowed	20	9.8
Comorbidities (yes)		
Retinopathy	28	13.7
Cardiovascular disease	27	13.2
Nephropathy	17	8.3
Neuropathy	14	6.9
Cerebrovascular disease	12	5.9
Anaemia	12	5.9
PVD	6	2.9
Hepatic	5	2.5
Renal	1	0.5
Pyschological distress scales		
PAID (mean [SD], 95% CI)	28.8 (21.9)	25.8 – 31.9
Severe distress (yes)	66	32.4
DHP (mean [SD], 95% CI)		
Psychological distress	21.2 (22.0)	18.1 – 24.2
Barriers to activity	27.4 (19.7)	24.7 – 30.1
Disinhibited eating	42.1 (17.5)	39.7 – 44.5
Glycaemic Control		
Good (HbA1c ≤7%)	58	28.4
Poor (HbA1c >7%)	146	71.6

CI: Confidence interval; DHP: Diabetes Health Profile; HbA1c: Glycated haemoglobin; PAID: Problem Areas in Diabetes; PVD: Peripheral vascular disease; SD: Standard deviation

Validity

Table 2 provides the psychometric properties of the DHP subscales. Convergent validity was observed as all item-scale correlations exceeded 0.4 except the item, "Not easy to stop eating", from the DE subscale which achieved a correlation of -0.24. Nonetheless, the item achieved discriminant validity and hence scaling success for the DHP subscales was 100% for all items.

CFA (Table 3) showed that PD and the DE subscales both met the criteria for a good fit, but not the BTA subscale. This prompted the use of EFA to determine the factor structure of DHP-18 among Asians in Singapore. A 4-factor solution explaining 63% of the total variance of the data was obtained when the EFA was performed (Table 3). When a forced 3-factor EFA was performed, the original factor structure was reproduced (Table 4), accounting for 57% of the variance.

Reliability

Cronbach's alpha exceeded 0.70 for all subscales (Table 2). Ceiling effects were negligible but large floor effects were seen for the PD subscale (23%). As expected, item mean and SD were similar within the scale (Table 5). The only exception is the subscale BTA, which had a wider range of item means from 0.38 to 1.55.

Sensitivity

Table 6 shows the results of sensitivity and known-group validity. Among the social determinants, DHP subscales did not differentiate well between patients aged 45 years and over and patients younger than 45 years, men and women, across ethnicity and marital status (i.e., not sensitive), except DE which differentiated between the 2 age groups, ethnicity and marital status. The DHP subscales better differentiated across housing types and household income (i.e., more sensitive).

Among the clinical determinants, the subscale BTA was most efficient in differentiating among patients with and without chronic medical conditions (4 out of 6 chronic medical conditions studied: retinopathy, cardiovascular disease, nephropathy and neuropathy). DE was the least efficient (was sensitive in 2 out of 6 chronic medical conditions). All DHP subscales were able to differentiate well between good and poor glycaemic control.

Among the social functioning determinants, all subscales were sensitive across the 4 social functioning determinants studied except DE (sensitive in 2 of 4 determinants studied). Most importantly, DHP subscales were able to differentiate between known-groups based on PAID score and the effect sizes were large.

Table 2. Item Scaling Tests of the DHP in Singaporean Patients with Type 2 Diabetes Mellitus

	Floor (%) Ceiling (%)		Convergent Validity (Range of Correlations)	Discriminant Validity (Range of Correlations)	Cronbach's Alpha
DHP					
Psychological distress	23.53	0.98	0.68 – 0.82	-0.16 – 0.52	0.89
Lose temper over testing/diet					
More arguments at home because of diabetes					
Depressed because of diabetes					
Lose your temper/shout due to diabetes					
Touchy/moody about diabetes					
Lose temper over small things					
Barriers to activity	4.41	0	0.47 – 0.78	-0.05 – 0.52	0.78
Food controls life					
Difficulty staying out late					
Days tied to meal times					
Avoid going out if sugars on the low side					
Worry about colds and flu					
Frightened in busy/crowded shops					
Edgy when out and nowhere to eat					
Disinhibited eating	0	0	-0.24 – 0.80	0.15 – 0.52	0.78
Eat to cheer self up					
Hard saying no to food					
Not easy to stop eating					
Eat something extra when bored					
Wished not so many nice things to eat					

DHP: Diabetes Health Profile

Discussion

In this study to evaluate the psychometric properties of the DHP in Asia (among Chinese, Malay and Asian Indians), we found that the instrument was valid, reliable and sensitive in determining the psychological well-being of individuals with T2DM. Convergent validity with another well-studied diabetes-specific distress scale (PAID) was also supported. However, we found that the psychological distress subscale was limited insofar as the subscale had large floor effect and SD, which was a similar observation in the DHP Danish study and among those who were on oral medications- and diet-treatment in the United Kingdom study.[4]

Our study showed that Malays had the highest levels of psychological distress compared to Chinese, Indians and Others. This could be due to a greater proportion of Malays being older and less educated in our population. Research has shown that older and less educated individuals have lesser knowledge on the availability of resources and services to cope with their levels of distress.[31,32] This is in contrast to another study of depressive symptoms among Singaporeans with diabetes using the Center for Epidemiologic Studies Depression (CESD) Scale—the authors reported that Indians with T2DM tended to have higher levels of psychological distress as compared to the other ethnic groups.[33] Perhaps there is an ethnic difference in the prevalence of general depression (as measured by CESD) and diabetes-specific distress (as measured by DHP). This finding requires further investigation.

Interestingly, despite the poor fit of the BTA subscale in the CFA, the forced 3-factors EFA was identical to that suggested by the developer. In fact, the variance accounted for by the forced EFA was higher than that reported by the developer. On closer scrutiny of the items from BTA subscale in the unforced EFA, it appears that items 11, 13 and 14 were more "psychologically" related, given their marginal loadings on the psychological distress factor (Table 4). A similar observation was seen only for item 13 in the study by Goddijn et al,[12] whereby item 13 loaded onto both BTA as well as PD. Nonetheless, since the forced 3-factor EFA replicated the suggested factors by the developer, there is no need to pursue this further.

Table 3. Confirmatory Factor Analyses (CFA) and Forced 3-Factor Exploratory Factor Analysis (EFA) of the DHP-18

Items	EFA Factor Loadings		CFA		
	Factor 1	Factor 2	Factor Loadings	TLI (≥0.9)	CFI (≥0.9)
Psychological distress					
DHP6: Lose temper over testing/diet	0.6285		0.6503858	0.9093	0.9456
DHP8: More arguments at home because of diabetes	0.5455		0.4813783		
DHP15: Depressed because of diabetes	0.7702		0.6290018		
DHP16: Lose your temper/shout due to diabetes	0.8544		0.6528133		
DHP17: Touchy/moody about diabetes	0.8664		0.7362633		
DHP18: Lose temper over small things	0.8494		0.6386526		
Barriers to activities					
DHP1: Food controls life	0.5362		0.4662655	0.693	0.7953
DHP2: Difficulty staying out late	0.7554		0.7004328		
DHP3: Days tied to meal times	0.8263		0.7963153		
DHP4: Avoid going out if sugars on the low side	0.6744		0.5576317		
DHP11: Worry about colds and flu		0.6205	0.3937982		
DHP13: Frightened in busy/crowded shops		0.7512	0.3074122		
DHP14: Edgy when out and nowhere to eat		0.7421	0.3875212		
Disinhibited eating					
DHP5: Eat to cheer self up	0.6757		0.8138619	0.9857	0.9929
DHP7: Hard saying no to food	0.6543		0.7432837		
DHP9: Not easy to stop eating	-0.7617		-0.3998019		
DHP10: Eat something extra when bored	0.7128		0.4920831		
DHP12: Wished not so many nice things to eat	0.5426		0.5310986		

CFI: Comfort fit index; DHP: Diabetes Health Profile; EFA: Exploratory factor analysis; TLI: Tucker-Lewis index

Just like Mulhern and Meadows[34] who showed that the DHP was able to discriminate between patients based on the presence/absence of comorbidities, we observed larger ES for the comorbidities that were more severe in nature. Importantly, it was noted that the largest ES were seen in the comparison between patients who had psychological distress with those who did not (as identified by PAID). This was also observed in the paper by Mulher and Meadows.[34] This did not come as a surprise for the PD subscale. However, BTA and DE also had the largest ES when comparing between patients who had psychological distress with those who did not. Studies had shown that social stigma was a limiting factor to social activities especially to patients with T2DM who had to inject insulin or refuse food at social gatherings.[35,36] Similarly, studies had found that distress often led to a loss of one's self control, which resulted in overeating.[11,37] All these help to explain the large ES observed between patients with no and serious psychological distress in the DHP subscales BTA and DE.

With the availability of DHP-18 on the internet and mobile versions, the DHP-18 can be easily completed while patients wait to see their doctor, with the results ready for clinicians to discuss with the patient during routine clinic session. The study by Chawla et al[38] had shown that when clinicians were able to address specific problem areas that patients face, the clinicians were able to improve patients' metabolic outcomes and satisfaction.

An important strength of this study lies in the consideration of the sensitivity of the DHP. Unlike most studies that focused on the reliability and validity of the instrument, studying the sensitivity of the DHP will provide information on the efficiency of the instrument in detecting differences between subgroups, which is critical in determining sample size requirement for future studies. A second strength lies in the variety of determinants used to assess the ability of the DHP instrument in discriminating various health states. Unlike previous studies that only used medication types,[4,12,13] we had used clinical (e.g., glycaemic control), social functioning (e.g., effectiveness at/outside work) as well as psychological variables (e.g., PAID questionnaire) to further assess the DHP. This gives us greater confidence on the measurement abilities of the DHP within the population.

This study has a few limitations. Firstly, due to the cross-sectional nature of this study, test-retest reliability and responsiveness of the DHP could not be evaluated. Secondly, we only captured English-speaking patients, thus limiting the generalisability of our findings. However, based on the Singapore Census 2010, 75% of the Singapore resident

Table 4. Factor Loading Patterns from the Forced Exploratory Factor Analysis Using Principal Component

Variable	Factor 1	Factor 2	Factor 3
Psychological distress			
DHP6: Lose temper over testing/diet	0.6173	0.2954	0.3465
DHP8: More arguments at home because of diabetes	0.5193	0.2921	0.2923
DHP15: Depressed because of diabetes	0.7919	0.2098	0.1538
DHP16: Lose your temper/shout due to diabetes	0.8637	0.1332	0.0997
DHP17: Touchy/moody about diabetes	0.8873	0.1324	0.1298
DHP18: Lose temper over small things	0.8302	0.058	0.1354
Barriers to activities			
DHP1: Food controls life	0.1567	0.4492	0.3707
DHP2: Difficulty staying out late	0.2083	0.742	0.2602
DHP3: Days tied to meal times	0.1032	0.8008	0.1052
DHP4: Avoid going out if sugars on the low side	0.2066	0.6733	-0.0784
DHP11: Worry about colds and flu	0.2968	0.5091	0.0896
DHP13: Frightened in busy/crowded shops	0.3824	0.4714	-0.1442
DHP14: Edgy when out and nowhere to eat	0.3771	0.447	0.127
Disinhibited eating			
DHP5: Eat to cheer self up	0.2998	0.3191	0.7147
DHP7: Hard saying no to food	0.3517	0.251	0.6687
DHP9: Not easy to stop eating	-0.0124	0.1027	-0.7513
DHP10: Eat something extra when bored	0.1322	-0.0595	0.6938
DHP12: Wished not so many nice things to eat	0.2912	0.3393	0.5184

DHP: Diabetes Health Profile

Table 5. Scale and Item Mean and Standard Deviation of DHP

	Score Range	Mean	SD
Psychological distress	0,100	21.16	22.01
Lose temper over testing/diet	0,3	0.73	0.95
More arguments at home because of diabetes	0,3	0.56	0.84
Depressed because of diabetes	0,3	0.64	0.78
Lose your temper/shout due to diabetes	0,3	0.51	0.75
Touchy/moody about diabetes	0,3	0.64	0.81
Lose temper over small things	0,3	0.73	0.81
Barriers to activity	0,100	27.38	19.70
Food controls life	0,3	1.55	0.93
Difficulty staying out late	0,3	0.67	0.86
Days tied to meal times	0,3	1.17	1.02
Avoid going out if sugars on the low side	0,3	0.83	1.00
Worry about colds and flu	0,3	0.62	0.88
Frightened in busy/crowded shops	0,3	0.38	0.76
Edgy when out and nowhere to eat	0,3	0.53	0.84
Disinhibited eating	0,100	42.12	17.53
Eat to cheer self up	0,3	1.10	1.00
Hard saying no to food	0,3	1.20	0.94
Not easy to stop eating	0,3	1.82	0.78
Eat something extra when bored	0,3	1.45	0.91
Wished not so many nice things to eat	0,3	0.75	0.93

DHP: Diabetes Health Profile; SD: Standard deviation

Table 6. Comparison of DHP Subscales across Social, Socioeconomic, Clinical, Social Functioning and Psychological Determinants

Social determinants	n	DHP								
		Psychological Distress			Barriers to Activities			Disinhibited Eating		
		Mean	SD	ES*	Mean	SD	ES*	Mean	SD	ES*
Age										
<45 years	86	23.00	23.62		27.80	17.89		45.27	16.59	
≥45 years	117	19.80	20.84	0.14	26.54	20.24	0.07	39.66	17.89	0.32
Gender										
Male	131	20.65	22.82		25.99	19.86		41.83	17.13	
Female	73	22.07	20.60	-0.06	29.88	19.30	-0.20	42.65	18.35	-0.05
Ethnicity										
Chinese	103	20.93	21.19		27.79	20.50		43.95	17.48	
Malay	24	25.69	25.94	-0.22	32.54	22.05	-0.23	41.67	15.39	0.13
Indian	57	18.71	22.11	0.10	25.31	18.40	0.12	38.60	17.98	0.30
Others	20	23.89	21.33	-0.14	25.00	15.82	0.14	43.33	18.67	0.03
Marital status										
Single	41	23.04	20.32	-0.09	26.83	17.65	0.03	48.29	15.55	-0.41
Married	127	21.04	22.47		27.37	19.89		41.05	18.31	
Divorced/widowed	20	21.39	22.02	-0.02	28.81	22.57	-0.07	37.67	15.93	0.19
Socioeconomic determinants										
Education										
<7 years	16	21.18	20.31		35.42	23.33		35.83	21.76	
7 – 10 years	65	26.24	23.08	-0.22	29.30	20.00	0.30	43.28	19.08	-0.38
>10 years	108	18.47	20.92	0.13	25.44	19.49	0.50	42.53	16.32	-0.39
Housing type										
HDB 1 – 4-room flat	88	22.73	21.54		30.09	18.83		43.64	18.36	
HDB 5-room/executive maisonette	63	22.31	24.00	0.02	28.34	23.27	0.08	42.75	17.99	0.05
Private housing	35	16.35	18.52	0.31	20.82	16.42	0.51	36.38	15.11	0.41
Household income										
Low (<4000)	73	23.90	22.64		31.05	21.18		46.67	19.37	
Middle (4000 to <8000)	53	19.39	22.53	0.20	23.72	18.34	0.37	38.74	15.25	0.45
High (8000 and above)	38	17.98	18.01	0.28	22.43	16.08	0.44	40.88	15.59	0.32
Clinical determinants										
None	57	19.01	22.05		25.31	18.82		42.57	17.22	
Retinopathy	28	22.02	18.61	-0.14	32.82	20.01	-0.39	41.90	16.62	0.04

DHP: Diabetes Health Profile; ES: Effect size; FFM: Family functioning measure; Hba1C: Glycated haemoglobin test; PAID: Problem Areas in Diabetes; SD: Standard deviation

*Calculated by dividing the differences in the mean scores by the pooled standard deviation ($sd_{pooled} = \sqrt{\left[\frac{(n1-1)s1^2 + (n2-1)s2^2}{n1+n2-2}\right]}$).

Table 6. Comparison of DHP Subscales across Social, Socioeconomic, Clinical, Social Functioning and Psychological Determinants (Con't)

Social determinants	n	DHP								
		Psychological Distress			Barriers to Activities			Disinhibited Eating		
		Mean	SD	ES*	Mean	SD	ES*	Mean	SD	ES*
Cardiovascular disease	27	29.42	25.77	-0.45	34.04	26.17	-0.41	41.23	20.26	0.07
Nephropathy	17	34.31	23.59	-0.68	40.34	21.04	-0.78	41.96	21.05	0.03
Neuropathy	14	37.70	21.15	-0.85	38.10	14.22	-0.71	44.29	17.85	-0.10
Cerebrovascular disease	12	25.00	23.03	-0.27	26.98	18.42	-0.09	37.22	15.16	0.32
Anaemia	12	14.35	13.91	0.22	28.17	16.30	-0.16	35.56	19.76	0.40
Control (Hba1C)										
Yes	58	13.12	14.93		20.61	17.26		37.82	15.36	
No	146	24.35	23.55	-0.52	30.07	20.01	-0.49	43.84	18.09	-0.35
Social functioning determinants										
Presenteeism										
Effective at work	168	18.95	19.91		25.71	17.33		41.31	16.22	
Not effective at work	24	35.42	30.73	-0.77	35.32	30.57	-0.49	45.56	24.05	-0.24
Effective outside work										
Yes	145	18.31	20.62		25.32	16.93		41.93	17.05	
No	50	29.33	24.90	-0.51	32.95	26.47	-0.39	42.80	18.72	-0.05
FFM (support)										
Good	180	20.34	22.32		26.67	19.63		41.48	17.36	
Poor	21	29.89	18.55	-0.43	34.47	20.31	-0.40	48.25	18.37	-0.39
Psychological determinants										
PAID (≥40)										
No problem	138	12.36	13.36		21.12	14.26		36.47	13.29	
Serious problem	66	39.56	25.06	-1.51	40.48	22.94	-1.10	53.94	19.45	-1.12

DHP: Diabetes Health Profile; ES: Effect size; FFM: Family functioning measure; Hba1C: Glycated haemoglobin test; PAID: Problem Areas in Diabetes; SD: Standard deviation

*Calculated by dividing the differences in the mean scores by the pooled standard deviation ($sd_{pooled} = \sqrt{\left[\frac{(n1-1)s1^2 + (n2-1)s2^2}{n1+n2-2}\right]}$).

population aged 25 to 65 was English-literate.[23] Lastly, patients with severe comorbidities were not included in our study, limiting the range of scores of the DHP. Nonetheless, we were able to detect large effect sizes, suggesting that the DHP was sensitive enough to detect significant and clinically important difference among various patient subgroups.

Conclusion

This paper has established important evidence on the validity, reliability and sensitivity of the DHP in a multi-ethnic Asian population. This adds to the repertoire of patient reported outcomes that have been validated to measure the psychological well-being of patients with T2DM in Singapore. Clinical trials and research may now consider the use of DHP when studying the psychological well-being of patients with T2DM. The findings may also be relevant to other Asian countries with ethnic Chinese, Malays or Indians, such as Malaysia, China, India, Taiwan and Hong Kong.

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Original Article

Predictors of Acute, Rehabilitation and Total Length of Stay in Acute Stroke: A Prospective Cohort Study

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Abstract

Introduction: The poststroke acute and rehabilitation length of stay (LOS) are key markers of stroke care efficiency. This study aimed to describe the characteristics and identify the predictors of poststroke acute, rehabilitation and total LOS. This study also defined a subgroup of patients as "short" LOS and compared its complication rates and functional outcomes in rehabilitation with a "long" acute LOS group. Materials and Methods: A prospective cohort study (n = 1277) was conducted in a dedicated rehabilitation unit within a tertiary academic acute hospital over a 5-year period between 2004 and 2009. The functional independence measure (FIM) was the primary functional outcome measure in the rehabilitation phase. A group with an acute LOS of less than 7 days was defined as "short" acute LOS. Results: Ischaemic strokes comprised 1019 (80%) of the cohort while the rest were haemorrhagic strokes. The mean acute and rehabilitation LOS were 9 ± 7 days and 18 ± 10 days, respectively. Haemorrhagic strokes and anterior circulation infarcts had significantly longer acute, rehabilitation and total LOS compared to posterior circulation and lacunar infarcts. The acute, rehabilitation and total LOS were significantly shorter for stroke admissions after 2007. There was poor correlation (r = 0.12) between the acute and rehabilitation LOS. In multivariate analyses, stroke type was strongly associated with acute LOS, while rehabilitation admission FIM scores were significantly associated with rehabilitation LOS. Patients in the short acute LOS group had fewer medical complications and similar FIM efficacies compared to the longer acute LOS group. Conclusion: Consideration for stroke type and initial functional status will facilitate programme planning that has a better estimation of the LOS duration, allowing for more equitable resource distribution across the inpatient stroke continuum. We advocate earlier transfers of appropriate patients to rehabilitation units as this ensures rehabilitation efficacy is maintained while the development of medical complications is potentially minimised.

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Key words: Functional Outcomes, Haemorrhagic, Ischaemic

Introduction

Stroke is a major cause of morbidity and disability worldwide. It is also the most common diagnosis for inpatient rehabilitation admission in Singapore and many developed countries.[1-3] Stroke comprises up to 4% of the direct costs of healthcare in developed countries due to its substantial physical, social and economic burdens.[4,5] Hence, in our healthcare system, the poststroke acute and rehabilitation lengths of stay (LOS) are utilised as key markers of cost and care efficiency.[1,5]

Evaluating the determinants of poststroke acute LOS are important due to the rising costs of early stroke management, with in-hospital acute stroke units accounting for more than 65% of total inpatient costs.[6] This may be attributed to the increasing costs of acute hospital beds and the aggressive use of neuroimaging, medications and paramedical resources, although the literature on predictors of poststroke acute LOS is scarce.[7]

Determining factors that impact the rehabilitation LOS are also important as they are directly associated with

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rehabilitation costs and are considered to be a primary proxy for many insurance and reimbursement systems.[3] The rehabilitation LOS further assumes particular importance in inpatient stroke rehabilitation as the LOS is longer than other common diagnoses admitted for rehabilitation including hip fractures and falls in the elderly.[1,8] Full recovery is the exception and the risk for extended inpatient stay is high.[8,9] Apart from cost efficiency, accurate LOS estimates are also important for patients and their families to plan for eventual community reintegration or resource utilisation in healthcare institutions and nursing homes.[9,10]

Significant efforts have been made recently to reduce the poststroke acute and rehabilitation LOS while maintaining care efficiency. For example, the institution of early supported discharge (ESD) programmes has provided planned and coordinated discharge from the hospital with continued rehabilitation in homes, which may shorten acute LOS.[11,12] Benchmarking strategies, where clinicians are made aware of and held accountable for rehabilitation LOS through the feedback of baseline resource utilisation, also reduce the LOS while maintaining functional outcomes.[4] Integrated stroke rehabilitation pathways with early caregiver identification, active multidisciplinary goal-setting and timely involvement of discharge liaison persons and social workers also shorten rehabilitation LOS.[9,13] There are further moves towards very early rehabilitation (VER) in stroke which impacts acute and rehabilitation LOS.[14-16] In VER programmes, specific stroke rehabilitation services are commenced within 48 hours of stroke onset.[15,16] This is because earlier rehabilitation results in better functional recovery generally.[14]

The poststroke total LOS (which summates the acute and rehabilitation LOS) has received recent attention. Moves towards an integrated care of chronic diseases such as stroke have been proposed, with per-episode (per-case) funding looking at rationalising resources across the entire inpatient episode rather than splitting them between acute and rehabilitation phases.[17,18] The literature on total LOS and the relationships between acute and rehabilitation LOS in stroke is scarce, if any.

In this prospective cohort study, we aimed to:

1. Describe postacute stroke, rehabilitation and total LOS, and examine the correlations and trends by year of admission as well as categories of stroke type. This provides an important baseline data for future comparative studies as there were no significant interventions such as ESD or VER programmes throughout the duration of this study.
2. Identify the predictors of both acute and rehabilitation LOS using a comprehensive set of sociodemographic, medical and functional variables. Predictors of prolonged LOS differ considerably between acute and rehabilitation hospital phases and are often reported separately with different cohorts.[6] The predictors were evaluated in the context of the same cohort that went through both acute and rehabilitation phases.
3. Further define a group of having less than 7 days of LOS of acute stroke as "short" acute LOS and a group that had 7 days or more of LOS as "long" acute LOS.[6] Using the median acute LOS of 7 days to divide patients into 2 equal groups for further study has been reported previously.[19] We analysed the short acute LOS group and hypothesised that there are differences in the development of medical complications and functional outcomes during the rehabilitation phase as compared to the long acute LOS group.[20]

Materials and Methods

The Department of Rehabilitation Medicine, Singapore General Hospital (SGH) is located within the acute hospital premises and admits patients across a wide spectrum of stroke severities. All stroke patients admitted to the inpatient rehabilitation unit of SGH between 1 February 2004 and 31 January 2009 were prospectively recruited.

Stroke was defined based on clinical features consistent with a stroke and supported by neuroimaging findings.[13] Criteria for admission to the inpatient stroke rehabilitation programme include recent haemorrhagic or ischaemic stroke, significant functional impairments that may benefit from comprehensive inpatient rehabilitation, sufficient medical stability to allow for care in a rehabilitation setting and ability to participate in a goal-directed programme.

The parameters charted were determined through a review of relevant literature by a multidisciplinary team, focusing on variables identified as predictors of LOS and functional outcomes. In addition, data pertinent to local social context which may impact rehabilitation outcomes, were also included.[2,9] The data collected were classified into 6 categories: 1) demographics, 2) social characteristics, 3) stroke type and neuroimaging findings, 4) cerebrovascular risk factors, 5) medical complications, and 6) functional outcomes. Demographic data included age, gender, race and marital status. Social characteristics included housing and the availability of a caregiver. Each stroke type was first categorised as either ischaemic or haemorrhagic stroke. Ischaemic stroke was further classified according to the Oxfordshire Community Stroke Project criteria as anterior circulation infarcts (ACI), posterior circulation syndrome or lacunar infarctions.[21,22] The total ACI and partial ACI categories were grouped into a single entity, as a diagnosis of hemianopia was difficult, especially in the presence of cognitive impairment. Medical complications

recorded during the rehabilitation stay included depression, nosocomial infections, falls and deep vein thrombosis.[5,9] Depression was diagnosed by consensus amongst the managing team based on patient-reported symptoms and clinician or caregiver observations.[2] Patients were also regarded as having received acupuncture if the service was delivered regardless of duration.

The primary outcomes for this study were acute and rehabilitation LOS. The acute LOS was defined as the number of days from admission to discharge from the acute stroke unit. Rehab LOS was defined as the number of days from admission to discharge in the dedicated inpatient rehabilitation facility.[3] The year of admission to the inpatient rehabilitation facility determined the year in which the individual was included.[3] The year of admission was divided into those admitted before or after January 2007, yielding 2 approximately equal groups for further analyses by time of admission.

The functional outcome measure for our stroke rehabilitation programme was the functional independence measure (FIM).[3,10,23] The FIM is collected prospectively at admission and upon discharge from the rehabilitation unit. It consists of 13 motor (Motor FIM) and 5 cognitive (Cognitive FIM) items rated on a 7-point Likert scale. Scores range from 1 (totally dependent) to 7 (totally independent) for each of the 18 items, with a maximum score of 126 indicating total functional independence. The FIM has well established content and construct validity, sensitivity and inter-rater reliability in stroke patients.[3,23,24] The FIM gain is the difference between the discharge and admission FIM scores and it measures functional improvement. The FIM efficiency, which measures the rate of functional improvement, is calculated by dividing the FIM gain against the LOS. FIM efficiency is further multiplied by 30 to obtain a value per 30 days as the absolute values were small. The FIM effectiveness is calculated by dividing the FIM gain by the difference between the maximum FIM score of 126 and the FIM at admission. It is then multiplied by 100% and the result indicates the percentage of potential functional improvement actually achieved.[1,3,25]

All subjects participated in a comprehensive rehabilitation programme that comprised medical, nursing, physical and occupational therapy.[2,9,23] Subjects received 2 to 3 hours of therapy per day. Appropriate patients were provided speech and language therapy, psychology and medical social work interventions. Weekly multidisciplinary rounds were conducted to review progress, goals, and further therapies, and to formulate discharge plans.

This study was approved by the SingHealth Centralised Institutional Review Board.

Statistical Analysis

A total of 1300 stroke patients were admitted to our rehabilitation unit over a 5-year period from 1 February 2004 to 31 January 2009. Twenty-three patients who had acute or rehabilitation LOS exceeding 3 standard deviations (SD) from its mean were treated as outliers and excluded from statistical analyses.[26] For comparison of variables between short and long acute LOS, participants were dichotomised based on the median value of acute LOS, which was defined as 7 days in our study.[19] Independent T-test was used to examine the differences for continuous variables between the 2 groups, while Fisher's exact test and chi-square test were used to examine the differences for categorical variables. The linear association between acute LOS and rehabilitation LOS was evaluated using Pearson's correlation coefficient. The linear relationship between predictors and acute or rehabilitation LOS was examined using the backward selection method as defined by the Akaike Information Criterion (AIC). AIC balances parsimony with goodness-of-fit models by penalising those models with a greater number of parameters, i.e. more complex models.[27] The model with a smaller AIC is preferred. We fitted our linear regression model adjusting for age, gender, ethnicity and recurrence of stroke. Statistical analyses were done using R version 3.0 and statistical significance was set at $P < 0.05$.

Results

Study Population

There were 1277 subjects in this stroke cohort; 753 (59.0%) were male patients with a mean (± SD) age of 64.2 ± 12.3 years (Table 1). Chinese patients comprised 80.9% of the cohort, followed by Malay (11.3%) and Indian patients (6.2%). There were 1019 (79.8%) ischaemic stroke subjects while the rest were haemorrhagic stroke subjects (Table 1). Among those with ischaemic stroke, 471 (46.2%) sustained a lacunar stroke, 353 (34.6%) had an anterior circulation stroke, while the rest had posterior circulation strokes (19.1%). Hypertension (78.4%) and diabetes mellitus (41.0%) were the 2 most common cerebrovascular risk factors. Urinary tract infection (UTI) (21.0%), depression (17.2%) and pneumonia (7.1%) were the 3 most common complications during rehabilitation. In the rehabilitation phase, the mean admission FIM scores were 67.9 ± 22.8 points, mean discharge FIM scores were 83.2 ± 23.4 points and mean FIM gain was 15.2 ± 12.0 points. The FIM efficiency was 28.5 ± 26.4 per 30 days and FIM effectiveness was 28.1 ± 22.8%. The large majority of patients (88.1%) were discharged home successfully.

Table 1. Demographics and Characteristics of the Study Population

Characteristics	All* (n = 1277)
Age (in years)	64.2 ± 12.3
Sex	
Female	524 (41.0%)
Male	753 (59.0%)
Race	
Non-Chinese	244 (19.1%)
Chinese	1033 (80.9%)
Admission year	
Before 2007	622 (48.7%)
After 2007	655 (51.3%)
Marital status	
Single/separated/divorced/widowed	336 (26.3%)
Married	940 (73.7%)
Caregiver	
Available	997 (78.1%)
No caregiver	280 (21.9%)
Type of stroke	
Lacunar	471 (36.9%)
Anterior circulation	353 (27.6%)
Posterior circulation	195 (15.3%)
Haemorrhagic	258 (20.2%)
Acupuncture	
No	1154 (90.4%)
Yes	123 (9.6%)
Laboratory parameters	
Albumin (g/dL)	35.1 ± 8.1
Haemoglobin (mg/dL)	13.9 ± 6.8
Low-density lipoprotein (mmol/L)	3.4 ± 1.3
Risk factors	
Hypertension	1001 (78.4%)
Diabetes mellitus	523 (41.0%)
Smoking	269 (21.1%)
Ischaemic heart disease	266 (20.8%)
AF	103 (8.1%)
Complications developed in rehabilitation stay	
Falls	31 (2.4%)
Deep vein thrombosis	16 (1.3%)
UTI	268 (21.0%)
Pneumonia	91 (7.1%)
Depression	220 (17.2%)
Functional measures	
Motor FIM	
Admission	43.2 ± 16.6
Discharge	56.7 ± 17.8
Cognitive FIM	
Admission	24.7 ± 8.5
Discharge	26.5 ± 7.7
Total FIM	
Admission	67.9 ± 22.8
Discharge	83.2 ± 23.4
FIM gain	15.2 ± 12.0
FIM efficiency (per 30 days)	28.5 ± 26.4
FIM effectiveness (%)	28.1 ± 22.8
Length of stay (in days)	
Acute	8.9 ± 7.2
Rehabilitation	18.1 ± 9.6
Total	27.0 ± 13.0

AF: Atrial fibrillation; FIM: Functional independence measure; UTI: Urinary tract infection

*Continuous variables are expressed in mean ± SD while categorical variables are expressed in count (%).

Acute, Rehabilitation and Total LOS

For the entire cohort, the mean (± SD) and median (interquartile range, IQR) acute LOS were 8.9 ± 7.2 days and 7 (IQR: 4 to 11) days, respectively. Meanwhile, the mean and median rehabilitation LOS were 18.1 ± 9.6 days and 17 (IQR: 11 to 24) days, respectively (Table 2). There was poor correlation between acute LOS and rehabilitation LOS (r = 0.178). The correlation was even weaker after controlling for age, gender, admission period and stroke type (r = 0.123). On comparing the admissions period between pre- and post-January 2007, there was a significant shortening of the acute, rehabilitation and total LOS for admissions after January 2007. The mean total LOS of subjects admitted post-January 2007 was about 7 days less than those admitted prior to January 2007 (23.8 ± 12.3 days vs 30.4 ± 12.8 days). We also compared the acute, rehabilitation and total LOS by the primary stroke subtype, adjusting for age, gender and admission period. For the acute LOS, haemorrhagic stroke had the longest adjusted mean (standard error, SE) LOS (12.3 [0.4] days), followed by anterior circulation strokes (9.4 [0.4] days), posterior circulation strokes (9.2 [0.5] days) and lacunar strokes (6.5 [0.3] days). For the rehab LOS, haemorrhagic strokes (19.1 [0.6] days) and anterior circulation strokes (21.0 [0.5] days) had rather similar adjusted mean LOS, but these were significantly longer than posterior circulation strokes (17.1 [0.7] days) and lacunar strokes (15.9 [0.4] days). In the total LOS analyses, the order of longest to shortest LOS followed that of acute LOS, with haemorrhagic

Table 2. The Acute, Rehabilitation and Total LOS (in Days) by Admission Period and Stroke Type

	n	Acute LOS	Rehabilitation LOS	Total LOS
Admission period (unadjusted)*				
Admission prior to January 2007	622	10.2 ± 7.3	20.3 ± 9.6	30.4 ± 12.8
Admission in January 2007 or after	655	7.7 ± 6.8	16.1 ± 9.2	23.8 ± 12.3
P value		<0.001	<0.001	<0.001
Stroke type (unadjusted)*				
Lacunar	471	6.4 ± 4.4	15.6 ± 8.6	22.0 ± 10.2
Anterior circulation	353	9.3 ± 6.6	20.8 ± 10.2	30.1 ± 13.3
Posterior circulation	195	9.1 ± 6.9	16.8 ± 9.1	25.9 ± 12.4
Haemorrhagic	258	12.9 ± 9.8	20.0 ± 9.7	32.9 ± 13.9
P value		<0.001	<0.001	<0.001
Stroke type (adjusted)†				
Lacunar	471	6.5 (0.3)	15.9 (0.4)	22.4 (0.6)
Anterior circulation	353	9.4 (0.4)	21.0 (0.5)	30.5 (0.6)
Posterior circulation	195	9.2 (0.5)	17.1 (0.7)	26.2 (0.9)
Haemorrhagic	258	12.3 (0.4)	19.1 (0.6)	31.4 (0.8)
P value		<0.001	<0.001	<0.001

LOS: Length of stay
*LOS values are unadjusted (crude) mean ± SD.
†LOS values are predicted mean (SE), after adjusting for age, gender and admission period.

stroke subjects having an adjusted mean total LOS of 9 days more (31.4 [0.8] days) as compared to lacunar stroke subjects (22.4 [0.6] days).

Predictors of Acute and Rehabilitation LOS

In multiple regression analysis of acute LOS, haemorrhagic stroke was strongly associated with longer acute LOS. In addition, anterior and posterior circulation ischaemic stroke subjects had longer acute LOS compared to lacunar stroke subjects (Table 3). Absence of hypertension, presence of atrial fibrillation, lower albumin levels, admission date prior to January 2007, females, non-Chinese and younger patients were also associated with a longer acute LOS. Marital status, diabetes mellitus, ischaemic heart disease, smokers, haemoglobin levels and absence of a caregiver were not predictive of acute LOS. In the multivariate model on the rehabilitation LOS, lower admission FIM motor scores were strongly associated with a prolonged rehabilitation LOS. Higher cognitive admission FIM scores were associated with a prolonged rehabilitation LOS (Table 3). Males, Chinese, non-smokers, younger patients, recurrent stroke, an admission date prior to January 2007, UTI, depression, acupuncture and the lack of a caregiver were also associated with a statistically significant increase in rehabilitation LOS. Marital status, acute LOS, stroke subtype, cardiovascular risk factors, haemoglobin or albumin levels and pneumonia were not associated with rehabilitation LOS.

Short Acute LOS Group and its Impact on Medical and Functional Outcomes

The results are detailed in Table 4. There were 591 (46.3%) patients in the short acute LOS group with a substantial 30% increase in patients with short acute LOS for those admitted after January 2007. In the short acute LOS group, the patients were significantly older and it had significantly more patients with lacunar strokes and less patients with haemorrhagic strokes compared with the long acute LOS group. There were no differences in gender proportions, racial distribution, marital status and caregiver availability in the 2 groups. The short acute LOS group was associated with significantly fewer UTI and pneumonia episodes, a lower incidence of clinical depression during the rehabilitation phase and had significantly higher albumin levels. The motor, cognitive and total admission FIM scores as well as the cognitive and total discharge FIM scores were significantly higher in the short acute LOS group. The motor discharge FIM score was also higher in the short acute LOS group but this was not statistically significant. The absolute FIM gain and FIM effectiveness were significantly lower in the short acute LOS group. However, the FIM efficiency was similar in

Table 3. Predictors of Acute and Rehabilitation LOS That Were Obtained Using Backward Selection Method by AIC

	Acute LOS* (Adjusted R^2 = 0.17)		Rehabilitation LOS† (Adjusted R^2 = 0.37)	
	β-Estimate (95% CI)	*P* Value	β-Estimate (95% CI)	*P* Value
Age	-0.06 (-0.10 to -0.02)	0.002	-0.07 (-0.12 to -0.03)	<0.001
Male	-0.48 (-1.45 to 0.50)	0.340	2.42 (1.31 to 3.53)	<0.001
Chinese	-1.41 (-2.61 to -0.21)	0.022	0.73 (-0.58 to 2.05)	0.274
Recurrence of stroke	0.10 (-0.93 to 1.13)	0.849	0.76 (-0.36 to 1.88)	0.182
Admission after 2007	-1.16 (-2.17 to -0.14)	0.026	-4.38 (-5.48 to -3.29)	<0.001
Anterior circulation stroke	2.38 (1.15 to 3.61)	<0.001		
Posterior circulation stroke	3.12 (1.69 to 4.55)	<0.001		
Haemorrhagic stroke	6.68 (5.33 to 8.02)	<0.001		
Hypertension	-1.17 (-2.35 to 0.003)	0.051		
AF	2.03 (0.26 to 3.80)	0.025		
Albumin	-0.16 (-0.22 to -0.10)	<0.001		
Admission motor FIM			-0.33 (-0.37 to -0.29)	<0.001
Admission cognitive FIM			0.10 (0.02 to 0.17)	0.013
No caregiver			2.18 (0.87 to 3.49)	0.001
Smoker			-2.01 (-3.31 to -0.72)	0.002
UTI			2.46 (1.17 to 3.75)	<0.001
Depression			1.80 (0.44 to 3.16)	0.010
Acupuncture			2.49 (0.70 to 4.29)	0.007

AF: Atrial fibrillation; AIC: Akaike Information Criterion; FIM: Functional independence measure; LOS: Length of stay; UTI: Urinary tract infection

*Age, gender, ethnicity and recurrence of stroke were included as base model. Marital status, caregiver, diabetes mellitus, smoking status, ischaemic heart disease and haemoglobin levels were not associated with acute LOS in this model.

†Age, gender, ethnicity and recurrence of stroke were included as base models. Marital status, stroke types, hypertension, diabetes mellitus, ischaemic heart disease, AF, pneumonia, acute LOS, albumin levels and haemoglobin levels were not associated with rehabilitation LOS in this model.

both groups. The proportion of patients discharged home was slightly higher in the short acute LOS group (89.8%) compared to the long acute LOS group (86.6%, $P = 0.08$).

Discussion

We highlight 3 important findings in this study. Firstly, for the same cohort of stroke patients, FIM scores rather than stroke subtype are a better predictor of rehabilitation LOS, even though the stroke type is strongly associated with acute LOS. Indeed, there is poor correlation between acute and rehabilitation LOS. Secondly, there is no difference between the FIM efficiency of the short acute and the long acute LOS groups. Thirdly, the short acute LOS group had fewer complications in the rehabilitation phase compared to the long acute LOS group.

Our entire stroke rehabilitation cohort is generally similar to those reported worldwide. The mean age of our cohort of stroke subjects was 64 years, which was in the lower end of the range reported in the literature.[21] Our unit does not have a lower age cutoff for admission compared to some geriatric stroke units. The racial distribution is similar to other cohorts reported locally, although the proportion of widowed patients and those with caregivers was lower, possibly due to the younger age.[1,9,13,28] The proportion of haemorrhagic strokes (20%) and the high prevalence of hypertension and diabetes mellitus are also similar to prior descriptions.[2,9] Patients admitted in the second half of the study had shorter LOS and this trend towards shortened LOS in recent years are also reported worldwide.[1,3,29] This has been attributed to a range of reasons including better quality of rehabilitation, more outpatient rehabilitation resources or even fiscal pressures from insurance and funding systems for shorter inpatient stays.[1,3,29]

The mean and median acute LOS of 8.9 ± 7.2 days and 7 (IQR: 4 to 11) days, respectively, is much shorter than that generally described in the literature.[19,29,30] Reported mean acute LOS was 13.9 days in a Spanish group, 27.3 days in a United States cohort and 37 days in a Canadian study.[20] In fact, an acute LOS of 30 days has been taken as a cutoff for early admission to inpatient rehabilitation previously.[19,20,31] Our acute LOS is similar to an Israeli study which defined a short acute LOS group at 7 days.[6] We believe our short acute LOS may be attributed in part to the rehabilitation unit being sited in the acute hospital, allowing for earlier transfers to inpatient rehabilitation.

Table 4. Comparison of Short Acute and Long Acute LOS Subgroups

	Short Acute LOS* (n = 591)	Long Acute LOS* (n = 686)	*P* Value
Age	66.3 ± 11.3	62.4 ± 12.9	<0.001
Sex			
Female	248 (42.0%)	276 (40.2%)	0.568
Male	343 (58.0%)	410 (59.8%)	
Race			
Non-Chinese	109 (18.4%)	135 (19.7%)	0.617
Chinese	482 (81.6%)	551 (80.3%)	
Admission year			
Before 2007	206 (34.9%)	416 (60.6%)	<0.001
After 2007	385 (65.1%)	270 (39.4%)	
Marital status			
Single/separated/divorced/widowed	156 (26.4%)	180 (26.3%)	1.000
Married	435 (73.6%)	505 (73.7%)	
Caregiver			
Available	461 (78.0%)	536 (78.1%)	1.000
No caregiver	130 (22.0%)	150 (21.9%)	
Type of stroke			
Lacunar	298 (50.4%)	173 (25.2%)	
Anterior circulation	150 (25.4%)	203 (29.6%)	<0.001
Posterior circulation	80 (13.5%)	115 (16.8%)	
Haemorrhagic	63 (10.7%)	195 (28.4%)	
Acupuncture			
No	543 (91.9%)	611 (89.1%)	0.106
Yes	48 (8.1%)	75 (10.9%)	
Laboratory parameters			
Albumin (g/dL)	36.1 ± 10.5	34.4 ± 5.9	0.005
Haemoglobin (mg/dL)	13.8 ± 1.8	13.9 ± 9.1	0.783
Low-density lipoprotein (mmol/L)	3.5 ± 1.2	3.4 ± 1.3	0.106
Risk factors			
Hypertension	462 (78.2%)	539 (78.6%)	0.892
Diabetes mellitus	267 (45.2%)	256 (37.3%)	0.005
Smoking	147 (24.9%)	122 (17.8%)	0.002
Ischaemic heart disease	120 (20.3%)	146 (21.3%)	0.679
AF	42 (7.1%)	61 (8.9%)	0.258
Complications developed in rehabilitation stay			
Falls	10 (1.7%)	21 (3.1%)	0.144
Deep vein thrombosis	4 (0.7%)	12 (1.8%)	0.128
UTI	79 (13.4%)	189 (27.6%)	<0.001
Pneumonia	19 (3.2%)	72 (10.5%)	<0.001
Depression	84 (14.2%)	136 (19.8%)	0.009
Functional measures			
Motor FIM			
Admission	45.5 ± 15.5	41.2 ± 17.2	<0.001
Discharge	57.4 ± 16.8	56.1 ± 18.5	0.191

AF: Atrial fibrillation; FIM: Functional independence measure; LOS: Length of stay; UTI: Urinary tract infection
*Continuous variables are expressed in mean ± SD while categorical variables are expressed in count (%).

Table 4. Comparison of Short Acute and Long Acute LOS Subgroups (Con't)

	Short Acute LOS* (n = 591)	Long Acute LOS* (n = 686)	*P* Value
Cognitive FIM			
Admission	26.1 ± 7.7	23.5 ± 8.9	<0.001
Discharge	27.3 ± 7.2	25.8 ± 8.1	<0.001
Total FIM			
Admission	71.6 ± 21.1	64.8 ± 23.7	<0.001
Discharge	84.7 ± 22.2	81.9 ± 24.3	0.031
FIM gain	13.1 ± 10.4	17.1 ± 13.0	<0.001
FIM efficiency (per 30 days)	27.5 ± 23.8	29.5 ± 28.5	0.170
FIM effectiveness (%)	26.3 ± 20.5	29.7 ± 24.5	0.008

AF: Atrial fibrillation; FIM: Functional independence measure; LOS: Length of stay; UTI: Urinary tract infection
*Continuous variables are expressed in mean ± SD while categorical variables are expressed in count (%).

This arrangement also allows remaining investigations or specialist reviews from the acute phase to continue in the rehabilitation unit, as compared to an off-site rehabilitation unit. Nosocomial infections (UTI and pneumonia) and poststroke depression were common complications during rehabilitation, similar to that reported in other studies.[9,21] The poor correlation between the acute and rehabilitation LOS suggests a difference in predictor variables between both, which needs to be evaluated separately.

It is clinically important that the difference in acute LOS is demonstrated through a simple classification of stroke types. Physicians could utilise this widely used classification, taking into account each individual's presenting stroke impairments and functional limitations, to develop a more comprehensive integrated rehabilitation plan across the inpatient continuum. There are existing reports stating that the acute LOS for haemorrhagic strokes is longer than that for ischaemic strokes, though this was not reflected similarly for rehabilitation LOS.[2,6] The reasons may be that haemorrhagic stroke patients are more disabled on admission, require more time for surgical interventions, or need further neuroimaging to elucidate underlying causes.[28] Conversely, lacunar stroke patients are less disabled than other ischaemic stroke types and their acute LOS is correspondingly shorter.[6,21] Admission functional status has been established as a major predictor of rehabilitation LOS, and this was reflected in our study.[2,21,23] Reasons include that patients with more severe disability may take a longer time to recover or the rehabilitation team had recommended a longer rehabilitation LOS for longer rehabilitation intervention. The poor correlation between acute and rehabilitation LOS is surprising.[32] A longer acute LOS is often a proxy for strokes with more severe disability and this in turn usually requires a longer rehabilitation LOS. This may be due to a more heterogeneous sample that included both haemorrhagic and ischaemic strokes. Further studies exploring this relationship should use a narrower homogenous cohort.

The LOS efficiency provides a good metric in programme evaluation as it encourages facilities to include more severely impaired patients while monitoring efficiency and effectiveness of rehabilitation.[1,3,23] It is significant that FIM efficiencies were maintained in the short acute LOS group, suggesting that earlier rehabilitation transfers may reduce risks of medical complications including nosocomial infections and depression, which was reflected in our study. Earlier rehabilitation commencement can also optimise the capacity for brain plasticity.[2,13-15] The FIM effectiveness in the short acute LOS group is statistically significantly lower than the long acute LOS group and this suggests a ceiling effect for further FIM gains as the admission FIM scores for the short acute LOS group is higher.[2,19] However, clinically, the absolute 7-point difference in the admission FIM scores and the 3% difference in FIM effectiveness between the short acute and the long acute LOS cohorts do not approach a minimally clinically important difference.[3] Sensible decisions regarding timing of transfers would still need to be individualised, though further research may elucidate subsets of patients who may benefit more through earlier rehabilitation transfers.

With regard to other independent variables associated with LOS, older age was associated with both shorter acute and rehabilitation LOS. This inverse relationship has been reported previously.[23] For the acute LOS group, younger patients may be subjected to a more rigorous pursuit of an underlying etiology and further investigations, hence resulting in a later rehabilitation transfer. Older patients may have a shorter rehabilitation LOS as the goals of rehabilitation may be more modest with a greater focus on compensatory approaches.[23,33] Lower albumin levels was associated with longer acute LOS and this generally reflects

poor general health due to a variety of causes, including poor nutrition, medical complications, dysregulation of hormones and elevated cytokines levels.[22,24] Atrial fibrillation has been associated with increased acute LOS and is associated with more extensive cortical strokes, severe disability and a general higher comorbidity burden.[6] We believe that that the time required for discussion with patients, initiation and titration of anticoagulation prior to rehabilitation transfer also contributed to increased acute LOS.

The relationship between a longer rehab LOS and the absence of a caregiver is not surprising. An extended stay is required for families to explore care options, await the arrival of a domestic helper, or nursing home placement.[9] Depression prolongs rehabilitation LOS as rehabilitation is less efficient due to diminished motivation, nutrition, poor sleep or concentration, limiting recovery.[5,13] Nosocomial infections including UTI and pneumonia also prolong rehabilitation LOS as rehabilitation programmes are often interrupted or reduced in intensity while infections are being treated.[2,5] Acupuncture is a treatment method popular with Asian patients and it may prolong rehabilitation LOS as patients often request to complete extended courses of acupuncture as inpatients, due to transportation difficulties once discharged.[2] The reasons for male patients having longer rehabilitation LOS remains to be studied. Our findings conflict with other studies that did not find any gender associations[5,10] or even longer rehabilitation LOS associated with the female gender.[3]

Our study has several strengths and weaknesses. Major limitations include firstly, selection bias as only stroke patients deemed able and willing to undergo rehabilitation were transferred to our unit.[2,30] Secondly, only a single hospital rehabilitation unit was involved and the results may not be reflective of other rehabilitation facilities locally or in other countries.[8,19,21] Thirdly, there are many other known and unknown latent variables that have an impact on LOS and FIM scores but were not available or controlled for, such as the patient's financial capacity, different intensities and techniques of stroke therapy delivered, and specific impairments such as balance or vision.[3,8] The strengths of this study include the large sample size and prospective study design. A large number of evidenced-based and socially specific independent variables were also evaluated. In addition, the analyses of the acute and rehabilitation LOS were performed on the same cohort of patients from the time of acute admission to rehabilitation discharge in a single study, which allows for meaningful conclusions in the context of the total LOS.[6,13]

Conclusion

This study provides an important baseline data on acute, rehabilitation and total LOS on the same cohort of patients. This will facilitate stroke programme planning and serves as a comparison for future interventions. Certain stroke types, particularly haemorrhagic stroke and anterior circulation infarcts, had longer acute LOS while lower admission FIM scores were associated with longer rehabilitation LOS. Correlation between the acute and rehabilitation LOS was poor, reflecting differences in predictors. There is a trend towards shorter acute and rehabilitation LOS in recent years, similar to that reported worldwide. A shorter acute LOS was associated with less medical complications but with similar functional efficacy scores compared to longer acute LOS patients. We advocate earlier rehabilitation transfers, where appropriate, to optimise stroke recovery, but all patients should have an integrated individualised plan throughout their entire inpatient stay.

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Original Article

Quality of Life in Obstructive Sleep Apnoea: A Role for Oxygen Desaturation Indices?

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Abstract

Introduction: This study aimed to determine the impact of obstructive sleep apnoea (OSA) on quality of life (QOL) and evaluate the utility of polysomnographic parameters in reflecting QOL. Materials and Methods: Eighty-eight patients who underwent polysomnography (PSG) between December 2010 and November 2012 consecutively were recruited and they completed the 36-Item Short-Form Health Survey (SF-36) and Epworth Sleepiness Scale (ESS) questionnaires. Based on the apnoea-hypopnoea index (AHI), patients were classified as primary snorers (AHI <5), suffering from mild (5 ≤15), moderate (15 ≤30) or severe OSA (≥30). Results: Seventy-nine male and 9 female patients with a mean age of 41 years were recruited. OSA patients scored significantly lower on 7 domains of SF-36 compared to the population. As AHI increased, only Physical Function (PF) and Physical Component Summary (PCS) but not ESS scores significantly worsened. PSG parameters correlated poorly with all QOL measures except PF, PCS and ESS. After adjusting for age, sex and body mass index (BMI), multiple linear regression revealed that only the oxygen desaturation parameters, but not sleep architecture indices or AHI were significant predictors of PF and ESS. For every fall in the lowest oxygen saturation (LSAT) by 1%, there was a decrease in PF by 0.59 points, and an increase in ESS by 0.13 points. Conclusion: OSA patients have a poor QOL compared to the population. The amount of physical impairment and daytime sleepiness they experience is better predicted by severity and duration of hypoxia and not AHI.

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Key words: Apnoea-hypopnoea index, Polysomnography, Sleep-disordered breathing

Introduction

Obstructive sleep apnoea (OSA) is a disease with significant morbidity affecting up to 10% of adults.[1] It is characterised by recurrent episodes of upper airway obstruction, leading to oxygen desaturations, arousals and sleep fragmentation.[2] This non-restorative sleep produces daytime symptoms of excessive sleepiness, poor concentration and memory, and mood changes, resulting in poorer productivity, job losses, disrupted social relationships and an increased risk of motor vehicle accidents.[3-5] The disease has also been associated with the development of hypertension, stroke and type 2 diabetes mellitus.[6-10] Collectively, patients experience a poor quality of life (QOL), which can be defined as the overall state of well-being that individuals experience as assessed by subjective and objective measures of functioning, health, and satisfaction with the important dimensions of their lives.[11]

The diagnosis of OSA requires both self-reported symptoms and polysomnography (PSG) evidence of an apnoea-hypopnoea index (AHI) of 5 or greater.[12] The absolute value of the AHI further indicates the severity of the disease.[13] However, PSG parameters are reported to be discordant with patients' reports of their symptoms.[14,15] Validated questionnaires have therefore been used to better reflect QOL. These include the 36-Item Short-Form Health Survey (SF-36) and the Epworth Sleepiness Scale

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(ESS).[16,17] The former, a generic questionnaire, permits the comparison of QOL among various diseases[18] whereas the latter, a disease-specific questionnaire, reflects the impact of a particular disease on functioning.[19]

To the best of our knowledge, studies evaluating QOL in OSA have mostly been performed in the Caucasian population,[15,20,21] with fewer studies being conducted in Asians,[22,23] in spite of the differences in disease epidemiology and manifestations between the 2 groups. Yamagishi et al reported that the prevalence of sleep-disordered breathing is lower among Japanese compared to white men.[24] Li et al suggested that for the same body mass index (BMI), Asians may have more severe disease compared to whites due to craniofacial skeletal characteristics.[25] The first aim of our study is therefore to determine the impact of OSA on QOL in Singaporeans using SF-36 and ESS.

In local clinical practice currently, patients with suspected OSA are worked up primarily via sleep studies with lesser attention being paid towards QOL. This is reasonable as the diagnosis of OSA requires PSG evidence of an elevated AHI. Ideally, we feel that QOL questionnaires should be routinely used to complement sleep studies in the initial investigation and follow-up of patients with OSA. Until this becomes common practice however, disease assessment will be principally limited to objective parameters. This then raises the question of whether PSG parameters can potentially be used as surrogate markers for QOL, despite them having been established to be imperfect.[14,15] The second aim of our study is therefore to evaluate the utility of PSG parameters in reflecting QOL in Singaporeans.

Materials and Methods

We conducted a retrospective study of patients who had PSG and completed SF-36 and ESS questionnaire in Singapore General Hospital Sleep Disorders Unit between December 2010 and November 2012.

Polysomnography

The PSG was conducted overnight in the hospital under monitoring. It recorded sleep architecture (4-lead electroencephalogram, bilateral electrooculogram, submental and bilateral leg electromyogram), breathing (oronasal airflow, thoracic and abdominal movement), pulse oximetry, electrocardiogram, infrared video, microphone and video. When split-night studies (combined diagnostic and continuous positive airway pressure titration) were performed (n = 3), only data from the diagnostic portion (mean ± SD, 132.3 ± 9.6 minutes) was analysed for the study.

PSG parameters were scored by trained sleep technicians and reviewed by a sleep physician. Sleep stages and respiratory events were defined according to the American Academy of Sleep Medicine 2007 guidelines.[26] The AHI was used to stratify patients as primary snorers (AHI <5), suffering from mild (5 ≤15), moderate (15 ≤30) or severe OSA (≥30).[13] Other PSG parameters studied included sleep architecture and the severity and duration of hypoxia. All the PSG parameters were analysed as continuous variables.

Questionnaires

Within 60 days prior to the PSG, patients completed a self-administered questionnaire that was distributed to them when they came for their booking visit for the PSG, consisting of the SF-36 and ESS.

The SF-36 is a validated 36-item generic questionnaire which evaluates QOL in 8 domains: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional health problems (RE), and mental health (MH).[16] It has been validated in Singaporeans, fulfilling assumptions for Likert scale scoring, internal consistency-reliability, test-retest reliability, factor structure and construct validity.[18,27] The results of these 8 domains can be represented by 2 measures, Physical Component Summary (PCS) and Mental Component Summary (MCS), without substantial loss of information.[28] Scores on all scales ranged from 1 to 100, with a higher score indicating a better QOL.

The ESS is a validated questionnaire that is commonly used for assessing the impact of sleep disorders.[17] It asks patients how likely they are to fall asleep in 8 different scenarios. Higher scores indicate greater sleepiness.

Statistical Methods

The 8 SF-36 scales were scored as recommended by the original distributor.[29] PCS and MCS scores were however calculated using scale means and factor coefficients for the Singapore population.[30] All scales and summary scales of SF-36 were analysed as continuous variables, and means compared against normative data for Singaporeans with adjustment for age, sex and ethnicity using the method proposed by Thumboo et al, except for PCS and MCS scales, which were adjusted only for ethnicity as data was unavailable.[18] Adjustment was necessary because age and male sex are risk factors for OSA, so comparing SF-36 scores directly between OSA patients and the Singaporean population may not be meaningful due to differing demographics. By a similar method, the scores of OSA patients were compared against that for patients with other chronic diseases.[18,31,32]

The ESS was analysed as a continuous variable and also as an ordinal variable. The latter implies stratification of patients into 3 clinical categories based on their ESS, with

Table 1. Sample Description

	Primary Snorer (n = 21)	Mild OSA (n = 22)	Moderate OSA (n = 15)	Severe OSA (n = 30)	*P* Value*
Age	38.1 (12.1)	38.5 (12.9)	41.8 (12.6)	45.2 (11.5)	0.142
BMI	26.2 (4.9)	26.6 (4.3)	26.2 (2.8)	30.2 (4.4)	0.001
Neck circumference	39.3 (3.9)	39.8 (3.6)	41.6 (2.5)	42.8 (3.3)	0.002
Sex					0.080
Male	17	18	15	29	
Female	4	4	0	1	
Race					0.174
Chinese	20	17	11	25	
Malay	0	0	1	2	
Indian	1	2	3	3	
Others	0	3	0	0	
AHI	1.8 (1.6)	9.5 (2.5)	21.0 (4.5)	64.3 (24.2)	-

AHI: Apnoea-hypopnoea index; BMI: Body mass index; OSA: Obstructive sleep apnoea
**P* value indicates the statistical difference across all 4 study groups.

those who score 0-10 being normal, 11-15 having excessive daytime sleepiness and 16-24 having severely excessive daytime sleepiness.[17]

Fisher's exact test and Kruskal-Wallis test were used to compare differences in categorical and continuous variables respectively across the patient groups. One-sample t-test was used to compare the difference in sample mean for SF-36 scores against the population mean.[18]

Spearman correlation coefficients between PSG parameters and QOL measures were also calculated. All associations with |r| >0.200, significant or otherwise, were further analysed using multiple linear regression or ordinal regression depending on the nature of the variable. For linear regression, the residuals were visually inspected to confirm that the assumptions of linearity and homoscedasticity were met. For ordinal regression, the proportional odds assumption was satisfied. All regression models were adjusted for age, sex and BMI. These co-variables were chosen based on their known association with OSA and QOL.[33] Regression analysis in which comorbidity was included as a fourth variable was also performed. Comorbidities were selected based on their association with OSA and have likewise been used by other authors.[20,34] The most prevalent comorbidities in our study were diabetes, cardiovascular diseases and musculoskeletal symptoms. However, given that visual inspection of the results revealed no significant differences

Table 2. SF-36 Scores of OSA Patients Compared Against the Population, Adjusted for Age, Sex and Ethnicity

SF-36 Scale	OSA Patients (n = 62)*		Singaporean Population (n = 5503)		Difference in Means	*P* Value‡
	Mean	SD	Mean†	SD		
PF	72.1	25.2	81.4	24.8	-9.3	0.003
RP	72.7	37.6	83.8	34.4	-11.1	0.012
BP	74.6	23.2	80.7	22.0	-6.1	0.021
GH	54.5	20.7	69.2	17.2	-14.7	<0.001
VT	53.2	19.5	63.7	16.9	-10.5	<0.001
SF	79.6	21.7	82.0	20.8	-2.3	0.198
RE	78.5	36.3	82.1	35.2	-3.7	0.214
MH	72.3	17.2	72.7	17.0	-0.4	0.433
PCS	27.3	0.9	52.4	-	-25.1	<0.001
MCS	15.2	2.3	49.7	-	-34.5	<0.001

BP: Bodily pain; GH: General health; MCS: Mental component summary; MH: Mental health; OSA: Obstructive sleep apnoea; PCS: Physical component summary; PF: Physical function; RE: Role emotional; RP: Role physical; SF: Social functioning; VT: Vitality
*For this analysis, primary snorers were excluded so as to demonstrate the effect of OSA on QOL. Additionally, only OSA patients aged 21 to 65 years who were Chinese, Malay and Indians were considered. This is because SF-36 scores for the Singaporean population are only available for these subgroups.
†Adjusted for age, sex and ethnicity except for PCS and MCS scales, which were only adjusted for ethnicity as data was unavailable.
‡One-tailed.

Table 3. SF-36 Scores of OSA Patients Compared Against Patients With Other Chronic Diseases

SF-36 Scale	OSA (n = 62)*	Systemic Lupus Erythematosus (n = 69)†	Differentiated Thyroid Carcinoma (n = 144)‡	Anxiety Disorders (n unreported)§
PF	-9.2	-13.9	-5.8	-8.3
RP	-11.0	-21.0	-12.8	-35.8
BP	-6.0	-14.8	-5.6	-22.7
GH	-17.7	-20.0	-7.3	-18.4
VT	-10.5	-11.0	-6.4	-19.2
SF	-2.3	-12.6	3.6	-29.3
RE	-3.6	-14.4	-10.0	-47.1
MH	-0.4	-6.3	-4.5	-23.4
PCS	-25.0	-	-	-
MCS	-34.4	-	-	-

BP: Bodily pain; GH: General health; MCS: Mental component summary; MH: Mental health; OSA: Obstructive sleep apnoea; PCS: Physical component summary; PF: Physical function; RE: Role emotional; RP: Role physical; SF: Social functioning; VT: Vitality

*For this analysis, primary snorers were excluded so as to demonstrate the effect of OSA on QOL. Additionally, only OSA patients aged 21-65 years who were Chinese, Malay and Indians were considered. This is because SF-36 scores for the Singaporean population are only available for these subgroups.

†Thumboo J, Chan SP, Machin D, Soh CH, Feng PH, Boey ML, et al. Measuring health-related quality of life in Singapore: normal values for the English and Chinese SF-36 Health Survey. Ann Acad Med Singapore 2002;31:366-74.

‡Tan LG, Nan L, Thumboo J, Sundram F, Tan LK. Health-related quality of life in thyroid cancer survivors. Laryngoscope 2007;117:507-10.

§Luo N, Fones CS, Thumboo J, Li SC. Factors influencing health-related quality of life of Asians with anxiety disorders in Singapore. Qual Life Res 2004;13:557-65.

between whether adjustment was performed for 3 or 4 variables, and the rule of thumb that 1 coefficient in the model needs a sample size of 20 to reduce fitting bias, only results adjusted for age, sex and BMI are presented.[35] Data was analysed using SPSS version 20 software. A *P* value less than 0.05 was considered significant.

Results

Eighty-eight patients were recruited, most of whom were middle-aged Chinese males (Table 1). OSA patients scored lower on all domains of SF-36 compared to the average Singaporean (Table 2). The score differences were significant in all domains except for SF, RE and MH.

The QOL of OSA patients was comparable to that of patients with other chronic diseases, such as systemic lupus erythematosus (SLE), differentiated thyroid carcinoma (DTC) and anxiety disorders (Table 3). OSA patients perceived their VT and GH domains as being impaired to the same extent as SLE patients did. As OSA severity increased, PF ($P = 0.011$) and PCS ($P = 0.036$), but not ESS scores, worsened (Fig. 1).

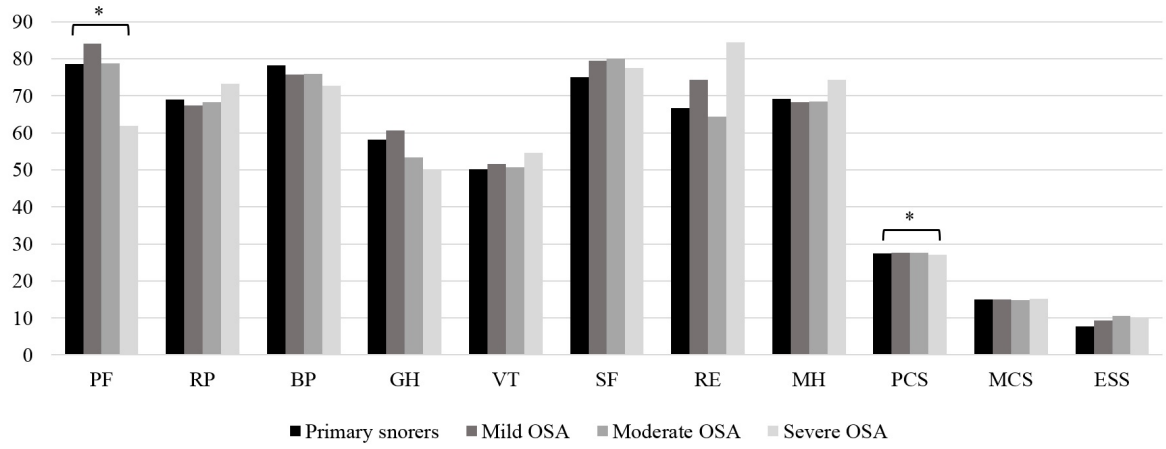

Fig. 1. SF-36 scores of primary snorers and OSA patients.
OSA: Obstructive sleep apnoea

Table 4. Correlation between PSG Parameters and QOL Measures

	Sleep Architecture		Respiratory Events		Oxygen Desaturation			
	N3	REM	ArI	AHI	LSAT	O_2 <95*	O_2 <90*	O_2 <85*
SF-36								
PF	0.316†	0.218†	-0.282†	-0.352†	0.397†	-0.441†	-0.399†	-0.439†
RP	-0.022	0.113	-0.021	0.065	0.059	-0.110	-0.034	-0.077
BP	0.008	0.035	0.014	-0.078	-0.002	-0.181	-0.067	-0.046
GH	0.218†	0.132	-0.119	-0.203	0.148	-0.248†	-0.202	-0.164
VT	0.045	-0.023	0.045	0.051	-0.029	0.019	0.053	0.045
SF	0.000	0.101	0.085	0.038	-0.063	-0.057	0.028	-0.001
RE	-0.023	0.047	0.108	0.156	-0.135	0.068	0.159	0.081
MH	-0.025	0.066	0.061	0.078	-0.063	0.056	0.081	0.067
PCS	0.148	0.103	-0.184	-0.231†	0.307†	-0.357†	-0.300†	-0.366†
MCS	0.081	0.051	0.017	-0.004	-0.011	-0.036	0.001	0.016
ESS	-0.051	-0.001	0.078	0.150	-0.255†	0.063	0.233†	0.233†

AHI: Apnoea-hypopnoea index; ArI: Arousal index; BP: Bodily pain; ESS: Epworth sleepiness scale; GH: General health; LSAT: Lowest oxygen saturation; MCS: Mental component summary; MH: Mental health; N3/REM: Percentage of total sleep time (% TST) spent in N3/REM sleep respectively; O_2: Oxygen; PCS: Physical component summary; PF: Physical function; RE: Role emotional; RP: Role physical; SF: Social functioning; VT: Vitality

*O_2 <95/90/85: percentage of total sleep time (% TST) for which SpO_2 <95/80/85% respectively.

†P <0.05.

PSG parameters generally correlated poorly with QOL measures (Table 4). However, PF correlated significantly with all the PSG parameters studied. PCS correlated significantly with AHI and the severity and duration of hypoxia. ESS correlated significantly with the severity and duration of hypoxia but not with AHI.

Multiple linear regression revealed that only the severity and duration of hypoxia remained as significant predictors of QOL measures (Table 5), especially PF and to a lesser extent ESS. For every fall in lowest oxygen saturation (LSAT) by 1%, there was a decrease in PF by 0.59 points, and an increase in ESS by 0.13 points. Ordinal logistic regression showed that the severity of hypoxia was a marginally significant predictor of one's ESS score (P = 0.053). For every increase in LSAT by 1%, the odds of moving up one clinical category decreases by 5%. In other words, every percentage increment in LSAT makes one 5% less likely to have excessive daytime sleepiness (ESS score 11-15) compared to being normal (ESS 0-10). One is also 5% less likely to have severely excessive daytime sleepiness (ESS 16-24) compared to having excessive daytime sleepiness (ESS 11-15). The duration of hypoxia below 95% (P = 0.088) and 90% (P = 0.082) were marginally significant predictors of the ESS score. For every increase in the duration of total sleep time for which SpO_2 <95% by 1 minute, the odds of moving up one clinical category increases by 2%.

AHI was not a good predictor of any QOL measure. Although AHI initially correlated significantly with PF and PCS (Table 4), these associations failed to achieve statistical significance after performing linear regression (Table 5).

Table 5. Regression Results

	AHI	LSAT	O_2 <95*	O_2 <90*	O_2 <85*
Linear Regression					
PF	B = -0.124	B = 0.588†	B = -0.158	B = -0.496‡	B = -0.669†
PCS	B = -0.002	B = 0.015	B = -0.006	B = -0.010	B = -0.016
ESS	B = 0.012	B = -0.129†	B = 0.034	B = 0.074	B = 0.080
Ordinal Regression					
ESS	OR = 1.009	OR = 0.954§	OR = 1.02	OR = 1.03	OR = 1.03

AHI: Apnoea-hypopnoea index; ESS: Epworth sleepiness scale; LSAT: Lowest oxygen saturation; O_2: Oxygen; PCS: Physical Component Summary; PF: Physical Function

*O_2 <95/90/85: percentage of total sleep time (% TST) for which SpO_2 <95/80/85% respectively.

†P <0.05.

‡P ≤0.01.

§P = 0.053.

The previously observed lack of correlation between AHI and ESS (Table 4) was again noted on regression analysis (Table 5), when AHI failed to predict ESS, regardless whether a linear or ordinal model was used.

Finally, BMI (P = 0.001) and neck circumference (P = 0.002) were noted to be significantly different across OSA severity groups (Table 1). Patients with severe OSA had significantly different BMIs from primary snorers (P = 0.007), mild OSA (P = 0.032) and moderate OSA (P = 0.023) groups. They also had significantly different neck circumferences from primary snorers (P = 0.004) or mild OSA (P = 0.014), but not moderate OSA (P = 0.683) groups. There were no significant differences in age, sex or ethnicity across the groups.

Discussion

OSA Patients Have Lower QOL Compared to the Population – Impairment Appears More Physical than Mental

It has been well established that sleep-disordered breathing negatively impacts QOL. Gliklich et al found that both primary snorers and OSA patients scored significantly worse than the population for all SF-36 domains, with the largest decrease being in RP and VT.[20] Bennett et al reported that their study group comprising both primary snorers and OSA patients had significantly lower PF and VT scores than the population.[21] Weaver et al noted that OSA patients have a significant deficit in MH score compared to the population and are at a higher risk of depression, although their group did not use the entire SF-36.[15] Banhiran et al found that primary snorers and OSA patients only had significantly lower scores than the Thai population in the RP and GH domains.[22] Wang et al reported that OSA patients scored significantly lower in all SF-36 domains compared to the Taiwanese population.[23] In our study, we found that OSA patients scored significantly lower than the average Singaporean in all domains of SF-36 except the SF, RE and MH domains (Table 2). OSA patients were therefore not at a higher risk of having mood disturbances. Given that the PF and RP domains reflect physical health and activity limitations, and MH and RE reflect mental health and activity limitations, it appears that OSA impairs patients more in the physical, rather than mental health aspect, at least locally. It is not entirely clear why only some of our results overlap with those of other studies, but this may be attributable to differences in sample characteristics, in particular age, sex and ethnicity. In our study, the mean age was 41 years, males comprised 89.8% of the sample and our patients were mostly Chinese (83.0%). These demographics are more similar to those reported by Wang et al, whose patients had a mean age of 44.8 years, were mostly male (86.2%) and all of Chinese ethnicity.[23] In contrast, the Caucasian studies tended to have a higher average age[15,21] and a lower proportion of males.[15,20]

QOL Decline is Similar to Patients with Other Diseases

VT reflects energy and fatigue levels and has been suggested as the domain most relevant to sleep disorders.[4] It asks participants if they "have a lot of energy, feel worn out or tired".[29] Bennett et al reported that out of the 8 SF-36 scales, it exhibited the greatest improvement after nasal continuous positive airway pressure (CPAP) treatment.[21] We found that OSA patients had significantly lower VT scores compared to the general population. The magnitude of this decrease was comparable to that observed in SLE (Table 3).

As AHI Increases, Physical Impairment and Daytime Sleepiness Do Not Increase

Yang et al noted that OSA patients fared poorer on the PF, RP and VT scales compared to primary snorers.[34] They did not analyse the PCS and MCS domains. Gliklich et al stated that a higher AHI was significantly correlated with poorer PF scores.[20] We initially found that as OSA severity increased, patients had worse PF and PCS but not ESS scores (Fig. 1, Table 4). This inability of ESS to correlate well with AHI in clinical studies but not population-based studies has been previously described.[3,15,36-40] Pack et al suggested that there may be a component of inter-individual variation, with different individuals requiring different amounts of sleep to feel refreshed.[41] Weaver et al posited that this may be due to the presence of selection bias in clinical cohorts and the fact that there are many other factors contributing to excessive daytime sleepiness for which complete adjustment may be difficult.[15] After performing regression analysis, we found that AHI was not a significant predictor of PF, PCS or ESS (Table 5).

Hypoxia Severity and Duration Better Predict Physical Impairment and Daytime Sleepiness

The inability of AHI to reflect QOL effectively in clinical populations has led to the search for other PSG parameters as an indicator of a patient's health. Guilleminault et al reported that patients with Multiple Sleep Latency Test <5 minutes have more sleep fragmentation (higher arousal index) and less rapid eye movement (REM) and slow wave sleep.[42] Hypoxemia is also known to be associated with impaired cognitive function.[43-45] Our study revealed that the severity and duration of hypoxia exhibit better correlation with and prediction of PF and ESS than AHI (Tables 4 and 5). Similarly, Gliklich et al reported that the number of oxygen desaturations to below 85% correlates more strongly with PF than AHI does.[20] Weaver et al noted that self-rated health

was significantly correlated with the percentage of sleep time for which oxyhaemoglobin saturation was less than 90% (r = 0.24, *P* = 0.02) but not AHI.[15] Collectively, these findings imply that oxygen desaturation indices may be more appropriate than AHI in the use of objective parameters as surrogate markers of QOL. Weaver et al suggested that OSA may produce 2 relatively different types of effects: one on daily functioning, and one on long-term health risk.[15] AHI may therefore be a better indicator of morbidity in the long run[6-9] and LSAT a better reflection of day-to-day QOL.

PF Complements ESS in Evaluation of QOL

Our regression analysis (Table 5) revealed that hypoxia severity and duration are useful predictors of both ESS and PF. This suggests that apart from ESS, PF may also be useful in evaluating QOL. Firstly, patients with OSA are known to have elevated basal and sleep energy expenditure, possibly secondary to increased sympathetic output and work of breathing.[46-48] Consequently, this may result in them having less energy available to perform activities such as "carrying groceries, climbing stairs" which are assessed by the PF domain of SF-36. Secondly, among studies that have used SF-36 to assess QOL, differences in PF scores between primary snorers and OSA patients have been consistently noted.[20-23,34] Thirdly, a fraction of OSA patients who undergo CPAP also exhibit an improvement in their PF scores following therapy. Tsara et al found that after using CPAP, the SF-36 scores of 120 patients with severe OSA improved significantly in all domains except pain, and their scores were now similar to that of the Greek population.[49] However, in 15 patients with mild to moderate OSA, SF-36 scores only increased in the PF domain, and this was not statistically significant. They attributed this to the smaller sample size in this subgroup. Hida et al noted that after CPAP therapy, obese OSA patients exhibited an improvement in scores in all domains of SF-36 whereas in non-obese OSA patients, all domains except for PF and RE significantly improved.[50] Banhiran et al reported that there was improvement in all domains of SF-36 after CPAP treatment.[22]

Given that OSA is a cardiovascular risk factor, it could be argued that the decline in PF with more severe disease may be attributable to comorbidities. However, adjusting for comorbidity in our regression analysis did not change our results (data not shown).

Obesity and Neck Circumference are Strongly Associated with OSA

We also found that patients with more severe disease were more likely to have higher BMI and wider neck circumference (Table 1). These are known risk factors for OSA.[33]

Limitation 1 – Time Interval between Questionnaire Distribution and PSG

One limitation of this study is the interval of 60 days between questionnaire distribution and PSG. This is because the severity of OSA might worsen with time. Patients with severely deranged AHI might have therefore under-reported their deterioration in QOL initially. However, we undertook this protocol because based on experience, patients who turn up for PSG are often anxious given the new environment and not particularly keen to fill up lengthy questionnaires. A compromise was thus made to ensure data integrity.

Limitation 2 – Questionnaire Validity

Despite ESS being the most commonly used questionnaire in sleep research, Kendzerska et al reported that it still suffers from problems of redundancy and vague item descriptions.[51] Abma et al found that there was conflicting evidence for the internal consistency of the ESS and suggested that OSA-related QOL questionnaires such as the Maugeri Obstructive Sleep Apnea Syndrome (MOSAS), the Obstructive Sleep Apnea Patient-Oriented Severity Index (OSA-POSI), the Quebec Sleep Questionnaire (QSQ) and the Sleep Apnea Quality of Life Index (SAQLI) should instead be adopted because the target population (patients with OSA) was involved in the development of these 4 questionnaires.[52]

Despite the SF-36 fulfilling assumptions for Likert scale scoring, internal consistency-reliability, test-retest reliability, factor structure and construct validity in the Singaporean population,[18,27] Abma et al noted that the mental health component, in particular the vitality domain (VT) may be more useful for measuring outcomes in OSA patients.[52] The authors also favoured the use of disease-specific questionnaires over generic ones in clinical practice where available.[52] Moving forward, it may therefore be more prudent to restrict the use of SF-36 to academic comparisons in QOL between diseases. ESS and 1 of the 4 aforementioned OSA-related QOL questionnaires should instead be utilised routinely in the clinical setting to evaluate the impact of OSA on daily functioning.

Conclusion

OSA patients have a poor QOL compared to the population. The amount of physical impairment and daytime sleepiness they experience is better predicted by severity and duration of hypoxia and not AHI. Ultimately, assessment of QOL is best achieved through OSA-related QOL questionnaires and not PSG findings. However, until the use of these questionnaires becomes routine in local clinical practice, disease assessment will be chiefly limited to objective parameters, in which case there should be a move towards considering oxygen desaturation indices and not just AHI in the appraisal of sleep studies.

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Commentary

A Brief History of the Biology of Sleep

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Glaswegian physician, Dr Robert Macnish, was half right when he stated in 'The Philosophy of Sleep' that "sleep exists in two states; in the complete and incomplete."[1] His postulation that incomplete sleep was "the active state of one or more of the cerebral organs while the remainder are in repose" beared some vague semblance to our current concept of rapid eye movement (REM) sleep. However, his concept of complete sleep being "characterised by a torpor of the various organs which compose the brain" typified the erroneous perception of sleep being a state of passivity.

This philosophical proposition of sleep being a passive state was seemingly demonstrated in the 1930s by Frederick Bremer who conducted electroencephalography (EEG) on cats' brains (encéphale isolé) preparations and concluded that sleep was a consequence to the brain being "turned off."[2] Subsequently in 1970, when it was proven by others that active stimulation at the "basal optic focus" and "bulbo-pontine area" produce slow wave sleep through direct inhibition of the reticular activating system (RAS),[3] Bremer performed stimulation studies on cat encéphale isolé in the basal preoptic area which resulted in EEG synchronisation and sleep.[4] This debunked his previous theory that sleep was due to de-afferentisation.

Research into the anatomy and physiology of the brain has revealed that sleep is an active process. One of the earliest evidence that sleep is an "activated" state originated from Constantin von Economo.[5] He studied histological sections of brains of influenza-afflicted patients who had encephalitis lethargica and discovered that cell loss in the anterior hypothalamus and preoptic regions was linked to profound insomnia in a small group of these patients. It was postulated that the activation of these regions of the brain was required to effect sleep.

The discovery of the EEG in 1928[6,7] allows for non-invasive recording of brain activity during sleep and sets the stage for further demonstration that sleep is, indeed, an active process. Loomis et al demonstrated that trains of "spontaneous" bursts of waves – "spindles", "trains", "saw-tooth waves" and "random waves" occurred at certain hours of sleep.[8] He also described the locations and transitions of such waves as sleep progressed.[9] Analysis of 84 records of 30 subjects during sleep allowed the authors to conclude that there was a "continual shift of a person from one state of sleep to another."[10]

The discovery of REM sleep and its association to dreams sets another milestone in establishing sleep as an active process.[11] The discovery of REM by Aserinsky and Kleitman in 1953 reinforced the concept of an activated state in sleep.[12] The authors correlated electrooculograms (EOG) recordings with EEG, respiratory rates and the presence of dreams in normal adult subjects and found that REM was linked to a distinct pattern of EEG recordings, autonomic nervous system activation and probably, dreaming and concluded that this state of REM sleep was a manifestation "of a particular level of cortical activity which is encountered normally during sleep".

Shortly after, in 1959, Jouvet coined the term "paradoxical sleep"[13] which corresponds to the current REM sleep. He was referring to the paradoxical state of cortical activation and REM in the presence of muscle atonia in sleeping cats. The modern day sleep profile in adults is characterised by non-rapid eye movement (NREM) stage 1, NREM 2, NREM 3 and REM sleep. Each stage is characterised by a unique set of EEG, EOG and electromyogram (EMG) manifestations.[14] Transitions between these sleep stages form the sleep cycle. If sleep were a passive process, then we would expect brain processes to be quiescence, i.e. in a "turned-off" state. On the contrary, in NREM and REM sleep, neurons in the ventrolateral preoptic (VLPO) nucleus are in an active state and cause active inhibition of the awake activating neurons in the tuberomammillary nucleus (TMN), locus coerulus (LC) and dorsal raphe nucleus (DRN).[15] Destruction of the VLPO disrupts sleep. Similarly, REM sleep is associated with high level of brain activity. One of

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the postulations was that REM-on cholinergic neurons in the lateral dorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) exerts a positive feedback on itself and on the REM-off neurons in the TMN, LC and DRN. When this excitatory effect on the REM-off neurons reaches a threshold, the REM-off neurons will inhibit the REM-on neurons, thereby terminating the REM episode.[16] Yet another sign of brain activation in REM sleep is the emergence of ponto-geniculo-occipital (PGO) waves[17-20] in EEG. PGO waves are generated from the pons, and these waves project to the lateral geniculate nucleus (LGN) and visual occipital cortex. The nucleus subcoeruleus had been shown, in rats, to be the origin of these waves.[21] The pontine reticular formation (PRF) was found to be central in the generation and maintenance of REM sleep.[22] Neurons in the PRF remained polarised throughout REM sleep.

Also pivotal to the concept of the active state of sleep is the presence of dreams. Following the discovery of REM in sleep in 1953 and its possible relationship with dream,[12] Dement tested the relationship between REM and dreaming in 9 subjects and found that there was a high incidence of dream recall after REM versus NREM awakening.[23] Interestingly, eye movements, i.e. vertical, horizontal etc. that occurred during sleep while in the state of dream corresponded with those in the awake state when the respective dreams were "re-enacted". Dreams are known to occur in NREM sleep though they are often more frequent and bizarre in REM sleep.[24]

Recent advances in neuroimaging has extended our understanding of the functional neuroanatomy of sleep and brain activity during sleep. Positron emission tomography (PET) was employed to map the metabolically active areas of the brain during REM, namely the brainstem, the limbic system and the cingulate cortex.[25] Functional MRI (fMRI) had demonstrated the active anatomical origins of the slow and fast spindles during NREM sleep.[26] The same technology also revealed significant activity in the parahippocampal gyrus, cerebellum and brainstem during slow wave sleep illustrating that it is not a period of cerebral quiescence or passivity.[27]

There were, previously, philosophical vascular theories relating the "passive" state of sleep to the redistribution of blood from the brain to the digestive system.[28] This was debunked by Reivich et al in 1967 who showed that there was an increase in cerebral blood flow during the state of REM which signified increased brain activity and metabolism.[29] A recent study in mice had demonstrated a 60% increase in convective clearance of β-amyloid, one of the proteins implicated in neurodegeneration, from the cerebrospinal fluid to the interstitial fluid through the glymphatic system during sleep.[30]

Sleep is postulated to be essential for brain processing and memory consolidation. Studying subjects with narcolepsy, Scrima et al demonstrated that recall of prior tasks consisting of anagrams and trigrams was the most accurate after isolated REM sleep. Recall was also significantly better after NREM sleep than after an awake state.[31] Hence, it was concluded that there were active processes in REM sleep that were essential for memory consolidation. The sequential hypothesis of the function of sleep postulates that the information acquired during the awake state will undergo the processing stage in slow wave sleep and consolidation takes place during REM sleep.[32]

The active state of sleep is also evidenced by extracranial manifestations. Haemodynamic changes reflecting an increase in sympathetic drive had been observed in REM sleep. Transient increases in heart rate, predominantly in phasic REM sleep, results in increases in blood pressure.[33,34] Excitatory inputs to the respiratory system during REM sleep resulted in tachypnoea and irregular breathing.[35] These were clearly atypical of passivity.

Sleep also represents a state of active development and tissue restoration. Growth hormone surges occur at sleep onset and during slow wave sleep in prepubertal children.[36] Sexual maturation in boys is facilitated by peaking testosterone and luteinising hormone levels during sleep in pubertal boys.[37] Bone growth and increase mitotic rate of lymphoctyes had been shown to be enhanced during sleep.[38]

Though controversial, sleep has been postulated as a modulator of immune function. Lymphocyte activity and antibody synthesis had been shown to be lower after sleep deprivation.[39] Brown et al reported that there was inferior clearance of influenza virus and lower virus specific antibody in sleep-deprived immunised mice.[40] Similar effects were demonstrated in sleep-deprived humans who were given influenza vaccinations.[41]

Hence, sleep is an active process. And as illustrated above, certain processes in the brain and body can be more active in sleep than awake.

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Implementation of a Proactive Nutrition Protocol Improves Enteral Nutrition in Mechanically Ventilated Patients Admitted to the Neuro-Intensive Care Unit

Dear Editor,

The enteral mode of nutrition delivery in the critically ill confers gastrointestinal, immunologic and survival advantages over parenteral nutrition (PN), especially when initiated early. Intensive care unit (ICU) patients with traumatic brain injury (TBI) exhibit hypercatabolism, needing higher energy requirements. The focus of TBI management is cardiorespiratory resuscitation (CPR) and neuroprotective strategies, often resulting in the neglect of nutrition as an important physiologic requirement.

A retrospective study was performed to determine the effectiveness of an evidence-based proactive nutrition protocol in improving the nutrition of mechanically ventilated neurosurgical patients admitted to the neuro-ICU (NICU).

Materials and Methods

In 2010, a multidisciplinary workgroup consisting of neurointensivists, nurses and dieticians developed an enteral nutrition protocol aiming to reduce inadequate nutrition amongst NICU patients. Before implementation, ICU staff were briefed and relevant information were made readily accessible on the ICU intranet. This protocol comprised 4 different interventions.

1. Electronic Nutrition Charting

Electronic nutrition charting with clear display of hourly and cumulative caloric intake per day was introduced (Fig. 1).

2. Protocolised Management of Enteral Nutrition (Early Intiation and Minimising Interruptions)

Previously, preprocedure fasting was often excessive and timely resumption of feeding postprocedurally was often forgotten. Figure 2 illustrates the stepwise workflow to circumvent both delays in starting and interruptions to enteral nutrition. Advisory alerts on the electronic charts were introduced to remind physicians to resume feeding 2 to 4 hours following procedure or successful extubation.

3. Consensus Definition and Practice Guideline on Management of High Gastric Residual Volumes

There had been no clear definition and management guideline for patients with gastric residual volume (GRV) in neurocritical, ventilated patients, but following the Ministry of Health (MOH) nursing best practice guidelines promulgated in 2010, the workgroup recommended patients who developed feeding intolerance (defined GRV as ≥150 mLs) to be actively managed by the intensivist as outlined in Figure 3. Enteral feeding, provided via oro-nasogastric route, was 1 kcal/mL, high protein, fibre-containing, polymeric formula (Jevity as default) via closed-system given continuously over 24 hours.

4. Dietician Review

The protocol mandated a dietician review within 24 hours of admission of all newly admitted NICU patients receiving mechanical ventilation to optimise the nutrition prescription.

ICU Flowsheet	29/03/2011 09:00	10:00	11:00	12:00	13:00	14:00	15:00
Estimated Target kcal/day	1500	1500	1500	1500	1500	1500	1500
⊞ Enteral Feeds kcal/hr	0	30	30	30	30	30	30
⊞ Parenteral kcal/hr				0	50.4	50.4	50.4
Total kcal/hr	0	30	30	30	80	80	80
Cummulative kcal (24hrs)	0	30	60	90	170	250	330
Deficit kcal (24hr)	1500	1470	1440	1410	1330	1250	1170
Cumulative kcal (LOS)	0	30	60	90	170	250	330

Fig. 1. Caloric deficits were computed on a daily basis and flagged up as a reminder to the physicians on the electronic chart.

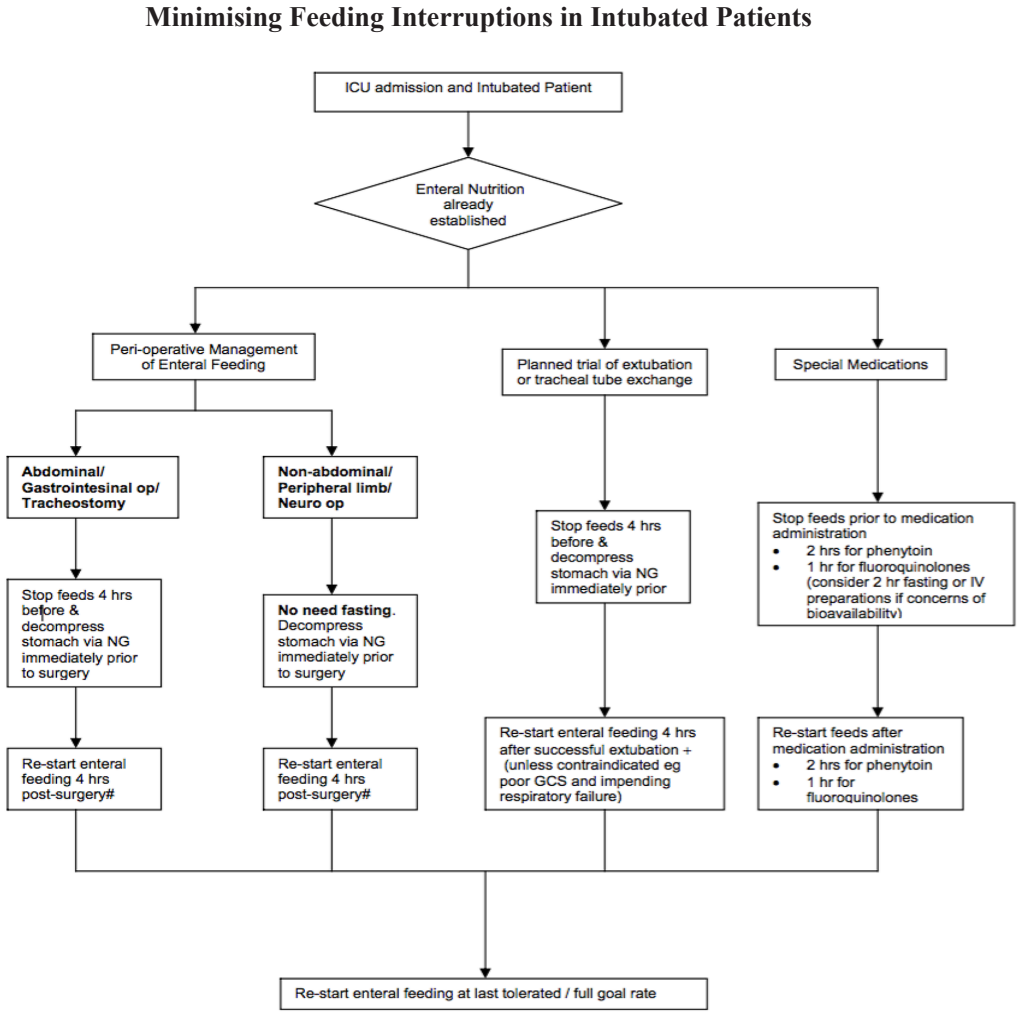

Fig. 2. The protocol recommended at most 6 hours of fasting prior to tracheostomy or trial of extubation. Intubated patients undergoing non-airway, non-abdominal procedures necessitated only 2-hour fasting with gastric decompression via aspiration of feeding tube prior to procedure.

After approval from the local ethics committee, power analysis was performed using a power of 80% and alpha value of 0.05 to detect a 50% improvement in the incidence of adequate feeding after protocol implementation. A sample size of 74 per group was required, with an additional 10% added to sample size in order to account for loss to follow-up. In total, 169 consecutive neurosurgical patients admitted to our NICU from July 2010 to June 2011 were studied. Of these, 83 patients were admitted 6 months before protocol implementation and 86 patients were admitted 6 months postimplementation. Inclusion criteria include: 1) mechanical ventilation ≥48 hours, 2) ≥18 years of age, and 3) suitable for enteral nutrition. Exclusion criteria include contraindications to enteral nutrition, such as gastrointestinal haemorrhage.

Statistical Analysis

The primary outcome was the incidence of adequate feeding as defined by the proportion of patients who met ≥80% of their energy goal requirements (25 kcal/kg/day) during their stay in NICU or till cessation of enteral nutrition and conversion to oral diet, or discharge from NICU or death. Secondary outcomes include the average caloric intake (kcal/kg/day), time to initiation of enteral nutrition, ICU and hospital length of stay (LOS) and mechanical ventilation days. Reasons for underfeeding and incidence of infection (as diagnosed by positive bacteriology and clinical correlation) were studied.

The independent sample t-test was used for normally distributed data, Mann-Whitney U test for non-normally distributed data and Pearson chi-square tests for categorical variables.

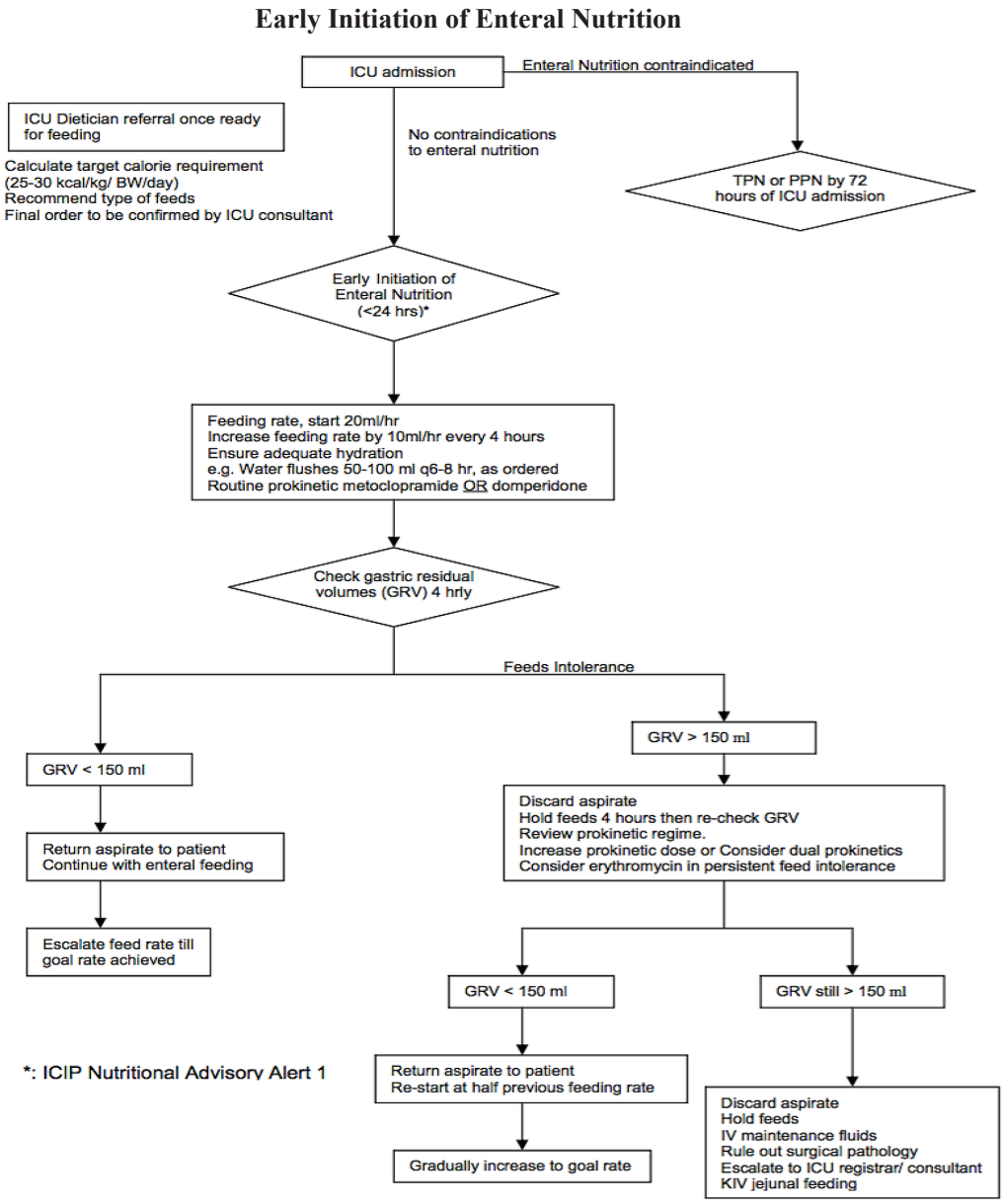

Fig. 3. Workflow which addresses early enteral nutrition initiation, intensive care unit (ICU) dietician review and management of high gastric residual volume (GRV).

Multivariate logistic regression model using a backwards stepwise elimination method was used to identify factors affecting enteral nutrition. Two-sided P value <0.05 was considered statistically significant for all comparisons. Stata v.10.1 (Statacorp, College station, Texas) was used in the statistical analysis of the results.

Results

There were no significant differences in patient demographics between the pre and postimplementation groups (Table 1).

There was significant improvement in the primary outcome of incidence of adequate feeding in the postimplementation group (39.5%) compared to the preimplementation group (25.3%), $P = 0.048$. No significant differences in secondary outcomes were detected (Table 2).

Pre/postimplementation, patient's weight, postsurgical status, ICU LOS and ICU mortality were significant factors that affected nutrition in the study population.

Patients from postimplementation period (OR = 3.71; 95% CI, 1.42 to 9.62) and greater ICU LOS (OR = 1.28; 95% CI: 1.14 to 1.43) were more likely to have adequate

Table 1. Baseline Patient Characteristics by Implementation Groups

Patient Characteristics	Preimplementation (n = 83)	Postimplementation (n = 86)	*P* Value
Age (years)†	55.6 (17.1)	59.7 (15.0)	0.10
APACHE score‡	24.7 (5.11)	24.3 (5.21)	0.58
Admission Glasgow Coma Scale (GCS)†	4 (4)	4 (4)	0.60
Gender*			
Male	49 (59.04%)	48 (55.81%)	0.76
Female	34 (40.96%)	38 (44.19%)	
Weight†	58.0 (10.0)	56.8 (10.8)	0.46
Postsurgical*			
Yes	52 (62.65%)	56 (65.88%)	0.75
No	31 (37.35%)	29 (34.12%)	
Neurological diagnosis*			0.51
Subarachnoid haemorrhage	22 (28.57%)	27 (32.53%)	
Spontaneous cerebral haemorrhage	35 (45.46%)	27 (32.53%)	
Traumatic brain injury	12 (15.58%)	16 (19.28%)	
Brain tumour	5 (6.49%)	4 (4.82%)	
Ischaemic stroke with haemorrhagic conversion	3 (3.9%)	8 (9.64%)	
Arteriovenous malformation	0 (0%)	1 (1.2%)	

*Frequency (%) for categorical variables.
†Mean standard deviation (SD) for normally distributed data.
‡Median interquartile range (IQR) for non-normally distributed data.

Table 2. Primary/Secondary Outcomes by Implementation Groups

Patient Characteristics	Preimplementation (n = 83)	Postimplementation (n = 86)	*P* Value
Adequate feeding*			
Yes	21 (25.3%)	34 (39.53%)	0.048
No	62 (74.7%)	52 (60.47%)	
Kcal/kg/day†	15.6 (8.36)	17.5 (7.1)	0.12
Days of ICU stay‡	6.9 (8)	7.35 (6)	0.96
Days of mechanical ventilation‡	4.6 (4.7)	5.2 (5.4)	0.80
Feed lapse time (days)‡	0.95 (0.9)	0.8 (0.7)	0.1
Infection*			
No infection	29 (55.77%)	29 (50%)	0.19
Airway/lung	13 (25%)	8 (13.79%)	
Wound	0 (0%)	2 (3.45%)	
Urinary tract	8 (15.38%)	17 (29.31%)	
Blood	2 (3.85%)	2 (3.45%)	
ICU mortality*			
Yes	25 (30.12%)	29 (33.72%)	0.616
No	58 (69.88%)	57 (66.28%)	
Glasgow Coma Scale (GCS) at end of study†	7 (4.29)	6 (3.82)	0.65

ICU: Intensive care unit
*Frequency (%) for categorical variables.
†Mean standard deviation (SD) for normally distributed data.
‡Median interquartile range (IQR) for non-normally distributed data.

feeding. Patients with lower body weight (OR = 0.89; 95% CI, 0.84 to 0.93), having postsurgical status (OR = 0.14; 95% CI, 0.05 to 0.39), and those who died in ICU (OR = 0.21; 95% CI, 0.06 to 0.70) were more likely to be underfed. Receiver operating curve (ROC) analysis with the area under the curves (AUC) 0.91 (95% CI, 0.86 to 0.95) indicated the final model exhibited excellent discriminatory property to differentiate between patients with and without adequate feeding.

Amongst the reasons for underfeeding, the 2 commonest were fasting for surgical procedures and investigations (37.5%) and patients deemed too ill to initiate enteral nutrition (22%) (Fig. 4).

Discussion

This study showed that implementation of a proactive nutrition protocol improved the delivery of enteral nutrition in mechanically-ventilated NICU patients. These findings were consistent with others. For example, Mackenzie showed that nutrition support protocol implementation in their adult ICU improved patients achieving their predetermined caloric goal from 20% preimplementation to 60% postimplementation.[1]

Delay in enteral nutrition initiation is commonly perceived to cause underfeeding. However, the time to initiation of enteral nutrition was ≤24 hours across the study population. This was compatible with the European Society For Clinical Nutrition And Metabolism (ESPEN) guideline of early enteral nutrition initiation within 24 hours of admission.[2] Frequent interruption of feeding was the most common reason for underfeeding. This highlights a unique aspect in the management of neurosurgical patients who often require fasting for repeated neuro-imaging and procedures including placement of external ventricular drain(s) or tracheostomy. Although these procedures were crucial to neurocritical care, 52% of these patients had unjustified reasons for delayed resumption of feeding. Common reasons include either physicians forgetting to re-order enteral feeding postprocedure or allowing excessive periods of fasting to monitor patients' condition postprocedure.

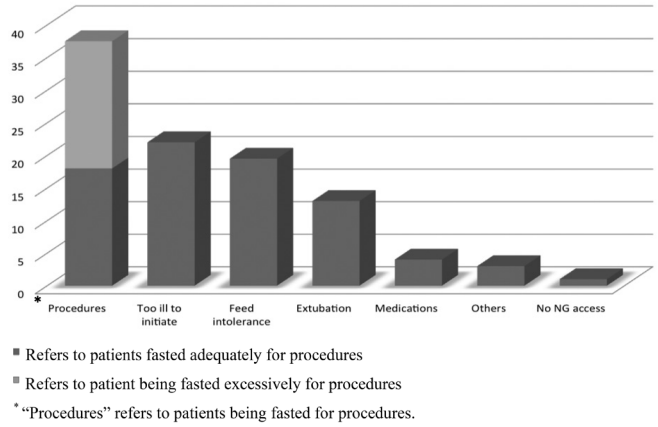

Fig. 4. Reasons for underfeeding in NICU.

A significant proportion of underfed patients were deemed too ill to commence enteral nutrition. These include multitrauma patients with severe TBI and/or concurrent abdominal/visceral injuries, or those receiving barbiturate coma therapy thus potentially developing ileus. Another group of patients suffered severe spontaneous intracranial haemorrhage with demise shortly after admission before enteral nutrition could be initiated.

Multivariate analysis showed that patients from post-implementation period and those with greater ICU LOS were more likely to have adequate feeding. This supported the finding that the nutrition protocol implementation improved EN in our patients. Also, patients who stayed in ICU for a longer time period were likely to allow more time for physicians to catch up with their nutrition requirements. Conversely, patients having postsurgical status (requiring perioperative fasting), lower body weight and those who died in NICU were more likely to be underfed.

Despite the protocol implementation, the rate of adequate feeding remained challengingly low at 40%. Similarly, Spain found that enteral nutrition delivery was improved with a nutrition support protocol but the compliance rate by physicians was only 58%.[3] Continued education and raising awareness amongst ICU staff regarding the importance of nutrition in improving patient outcome is instrumental in enhancing protocol compliance.

The threshold of ≥150 mLs as high GRV in our protocol may be deemed too conservative. The North American Summit on Aspiration in the Critically Ill Patient advocated defining 400 mLs to 500 mLs as high GRV.[4]

Despite evidence of benefits of early enteral nutrition in the critically ill,[5,6] our study detected no difference in secondary outcomes such as infection rates and mortality. This could be due to the study not being powered to detect a difference in secondary outcomes and being a retrospective observational study without randomisation, there may be confounders not accounted for between the groups.

Conclusion

Implementation of a proactive nutrition protocol has improved nutrition delivery in ventilated neuro-ICU patients. However, the success of protocol implementation can be further enhanced with the continued education of ICU staff, accompanied by a mindset change that nutrition support in ICU patients is no longer merely an adjunctive care but rather proactive therapy that can improve patient nutrition.

Acknowledgement

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Duodenal Mass from Heterotopic Pancreas: A Unique Cause of Septic Shock

Dear Editor,

Heterotopic pancreas is defined as pancreatic tissue found outside the pancreas without any anatomical or vascular connection with the main pancreas.[1] Heterotopic pancreas is also known as the ectopic pancreas, aberrant pancreas and accessory pancreas.[2] It can occur at any part of the gastrointestinal tract with 90% encountered in the stomach, duodenum and the jejunum.[3-5] The entity is usually found as incidental finding.[6,7]

Case Report

A 62-year-old Siamese lady presented with abdominal pain associated with early satiety, loss of appetite, loss of weight and repeated vomiting after a meal for 1 week. She was lethargic, afebrile but with no signs of peritonism. Full blood count, liver and renal functions were within normal range. There was a slight raise in the serum amylase level. Serum carcinoembryonic antigen (3.8 U/mL), alpha-fetoprotein (4.4 ng/mL) and cancer antigen-19-9 (38 U/mL) were all within normal ranges. Ultrasound showed the presence of fluid collection in the abdomen. Computed tomography (CT) scan of the abdomen revealed thickening at the first part of the duodenal wall (D1) and normal pancreas (Fig. 1). Subsequent oesophagogastroduodenoscopy (OGDS) revealed circumferential mass at D1 with few nodules and ulcer that caused narrowing of the lumen (Fig. 2). She showed some improvement and was discharged home.

However, she presented again several days later due to fatigue and poor oral intake. Physical examination revealed that she was lethargic with impaired conscious level, having a blood pressure of 90/70 mmHg and pulse rate of 120/min. A biopsy that was taken from previous OGDS site showed an inflamed heterotopic pancreas (Fig. 3). It is composed of lobules of acinar cells, pancreatic ducts and a few small foci of the islet of Langerhans cells that could be highlighted by neuroendocrine markers (chromogranin and synaptophysin). In areas, there was marked neutrophilic activity noted for attacking the glands. Her condition then deteriorated and showed clinical evidence of disseminated intravascular coagulation (high level of D-dimer and deranged clotting profiles). She was admitted to intensive care unit, intubated and developed hospital-acquired pneumonia with type I respiratory failure. Unfortunately, she died after several days in intensive care unit due to multi-organ failure. An autopsy was not performed.

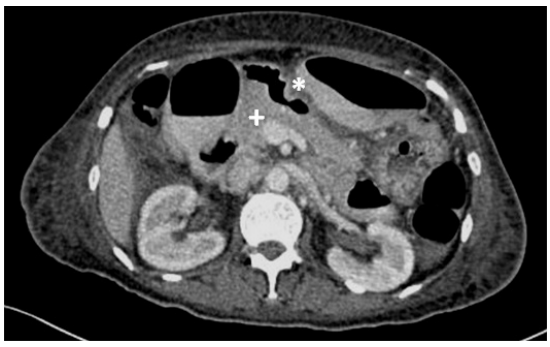

Fig. 1. Radiological finding: Contrast-enhanced CT scan at the level of pancreas shows normal homogenous pancreas enhancement (+) with adjacent thickened duodenal wall (*).

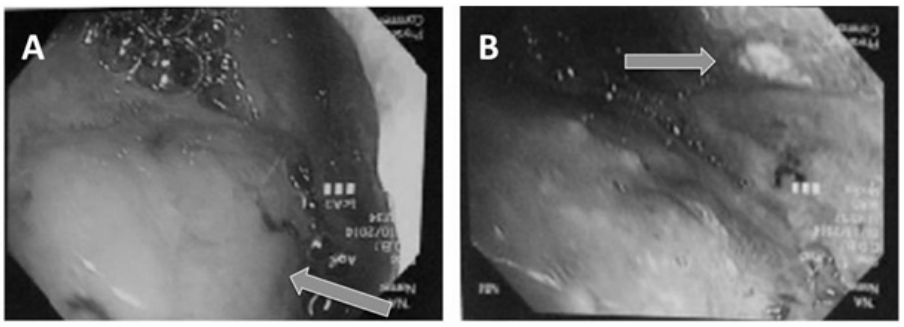

Fig. 2. Oesophagogastroduodenoscopy (OGDS) findings: In A) a circumferential pushing mass at D1 (arrow) is seen, and in B), an ulcer (arrow) is seen.

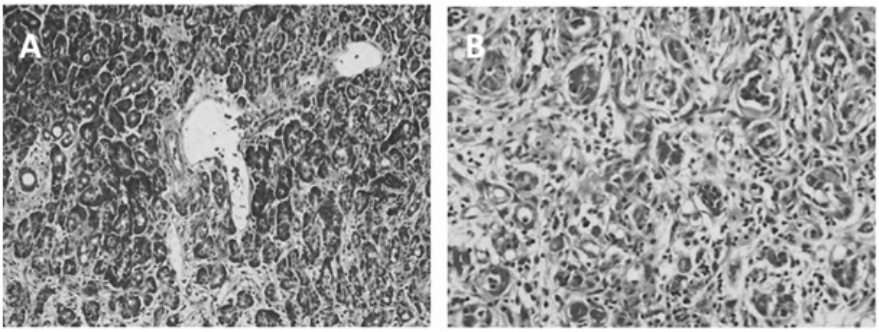

Fig. 3. Histological finding: A) shows lobules of acinar cells with occasional pancreatic duct typical of a pancreas, haematoxylin & eosin x 40, and in B), marked neutrophilic infiltration is also noted, haematoxylin & eosin x 200.

Discussion

In the literature, symptoms related to heterotopic pancreas are usually related to complications including intestinal or common bile duct obstruction, mucosal ulcer with haemorrhage, intussusception, gastrointestinal bleeding and abdominal mass. Rarely, the symptoms related to pathological conditions of the ectopic pancreas itself, such as acute or chronic pancreatitis,[8-10] pancreatic cyst[4] or neoplasm.[11] Non-specific gastrointestinal symptoms mainly occur with heterotopic pancreas in the upper gastrointestinal tract such as abdominal pain, nausea, vomiting, regurgitation, and anorexia or weight loss, etc.[7] The current patient is the first case reported of an inflamed heterotopic pancreas complicated with shock and multiple organ failures.

Diagnosis of heterotopic pancreas is difficult even with the advancement in imaging, endoscopy and routine biopsy procedure. It is prone to misdiagnosis and missing diagnosis due to its scarceness, variations of anatomical location, small size and non-specific clinical symptoms.[7] All these contributed to the rarity of preoperative or clinical diagnosis of heterotopic pancreas.[3,7]

On OGDS, ectopic pancreas could be hinted by the presence of a firm, round, sub-epithelial mass having a central depression that represents the opening of the pancreatic duct. In the present case, the central depression was not observed, but an ulcer was noted.[10]

The radiological findings were also not much help due to several limitations. On CT scan /MRI (magnetic resonance imaging), small ectopic pancreas could be differentiated from other gastrointestinal submucosal tumour by their location, prominent enhancement, ill-defined border, endoluminal growth pattern and the longest/shortest diameter ratio (LD/SD).[2] However, these characteristic features may not be present. Specifically, in this case, the contrast CT scan showed only focal thickening of duodenal mucosa with the adjacent normal pancreas. In contrast, the presence of multiple nodules detected on endoscopic examination as well as the clinical presentation gave the false impression of malignancy.

In recent years, endoscopic ultrasound (EUS), a combination of endoscopy and ultrasonographic images of high resolution together with fine needle aspiration biopsy (FNAB) are of increasing use for detecting gastrointestinal and peri-gastrointestinal diseases. Ectopic pancreas in stomach has been reported to be diagnosed by EUS-FNAB.[12,13]

Management of heterotopic pancreas remains controversial. Some recommended no further investigation and management; others recommended local resection to avoid any future complication. Surgical resection is the best choice when dealing with symptomatic patients.[6,11] Benign asymptomatic lesions generally do not require surgical intervention.[6] To improve diagnosis rate and to avoid misdiagnosis or unnecessary extensive operations, endoscopic resection with intraoperative frozen section could be considered.[5]

Overall, the rarity of the presentation of heterotopic pancreas makes the diagnosis a great challenge. Though the majority of the cases are asymptomatic, there is potential for lethal complications when acute inflammation is noted in the heterotopic pancreas.

Acknowledgement

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Validation of the Use of a Point-of-Care Device in Monitoring the International Normalised Ratio in Postoperative Cardiac Patients

Dear Editor,

Warfarin is prescribed for various conditions including mechanical heart valves, atrial fibrillation and venous thromboembolism. Prevention of bleeding and thromboembolic complications require maintenance in a tight therapeutic range. The use of patient self-testing has been well documented in the United Kingdom and Europe in prospective and retrospective studies.[1-5]

CoaguChek® XS (Roche Diagnostics, Basel, Switzerland) prothrombin coagulation monitoring system[6,7] provides point-of-care (POC) monitoring with a measurement range of 0.8 to 8.0 international normalised ratio (INR) and consists of a CoaguChek® XS monitor and test strips.

To date, validation studies have been limited to stable outpatient anticoagulation clinic cohorts,[7] with studies done in cardiac patients perioperatively.[8-10] However, these used arterial or whole blood samples and evaluated patients in the immediate perioperative period. Therefore, there is a void of data in the validity of such devices using capillary blood samples in cardiac patients during the recuperative in-hospital phase.

The study aimed to validate the POC testing (POCT) device with capillary samples in an Asian cohort during the postoperative phase. By introducing the concept and validity of POC self-testing in patients, it would help to empower the patient to participate in his or her care, laying ground for developing an outpatient self-testing programme. The authors believe that this period is a window of opportunity for the implementation of self-POCT as patients are under closer supervision and more motivated.

Materials and Methods

Study Population

Consecutive adult patients, between the age of 21 and 80, who had undergone open heart surgery at the National Heart Centre Singapore (NHCS) from February 2014 to May 2014 and initiated on warfarin therapy were recruited (Table 1). Patients on additional heparin coagulation were not excluded to reflect real-life situations.

Patients with anti-phospholipid antibodies,[11] haematocrit outside the range of 25% to 55%, triglyceride level of more than 7 mmol/L, absence of previous unhaemolysed renal panel assay or serum bilirubin of more than 513 mmol/L were excluded, as recommended by the manufacturer in accordance with their device insert.[12]

Table 1. Demographic and Clinical Characteristics of Patients Participating in the Study

Patient characteristics	
Male	33 (35.3%)
Female	18 (64%)
Mean age (years)	58
Indication for anticoagulation	
Valve replacement	20 (39.2%)
Valve repair	14 (27.5%)
Atrial fibrillation	11 (21.6%)
Valve repair and atrial fibrillation	3(5.9%)
Valve replacement and atrial fibrillation	2 (3.9%)
Left ventricular assist device	1 (2.0%)
Concurrent anticoagulation	
IV heparin	4 (7.8%)
Subcutaneous enoxaparin	1 (2%)
None	46 (90.2)

IV: Intravenous

For validation tests, venous blood samples were drawn in 3.5 mL sodium citrate tubes and prothrombin time (PT) was obtained by Diagnostica Stago's STart® 4 analyser using the Neoplastine C1 Plus 5 thromboplastin. The international sensitivity index (ISI) for the batch used was 1.26. For the POCT, capillary blood is obtained by lancing the side of the patient's fingertip. A drop of blood was expressed onto the test strip within 15 seconds. The meter performed a quality control test on the test strip before displaying the result on the screen of the device.

CoaguChek® XS

This device uses a human recombinant thromboplastin with an ISI value of 1.0 to activate the coagulation cascade in the blood. Thrombin[7] cleaves peptide substrate on the test strip to generate an electrochemical signal. The time elapsed from sample application to signal generation is used to calculate the INR value. INR results are obtained within 1 minute. The test strips also include an internal quality control system. This has been validated in multiple reports.[13]

Recruited patients were initiated on warfarin postoperatively as per managing clinician's discretion. A randomisation list was created by a statistician. Patients were randomised to receive POCT testing from day 1 to 8 of commencement of warfarin in order to capture a range of INR readings. On the randomised day, both venous and capillary INR readings were within a median of 5.4 hours of each other by a physician.

Ethical approval was granted by Centralised Institutional Review board (CIRB) and patients were recruited from the NHCS Department of Cardiothoracic Surgery and gave informed consent (CIRB protocol number 2013/758/C).

Statistical Analysis

All statistical data analysis was performed using SPSS version 21.0 (IBM Corp 2012). Baseline demographic and clinical characteristics of the study population were expressed as an average with standard deviation. Statistical significance was defined as P <0.05. The linear regression and correlation of the 2 methods of assay were analysed, and a scatter diagram and regression line of the 2 were plotted. The Bland-Altman analysis was used to plot a scatter diagram with the deviation and mean INR measured obtained with the 2 methods of assay.

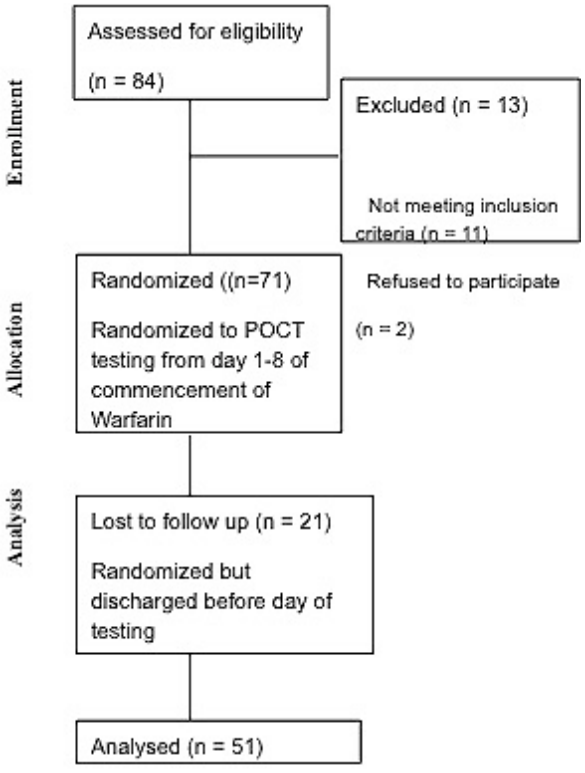

Fig. 1. Participant flow diagram.

Results

A total of 84 patients underwent open heart surgery from February 2014 to May 2014. Two patients declined to participate, 11 patients had a haematocrit <25%. Twenty-one patients were discharged before their scheduled POCT and were excluded (Fig. 1). The remaining 51 patients with their baseline characteristics as shown in Table 1 underwent venous and capillary INR testing.

Indications for anticoagulation included valve repair, valve replacement, atrial fibrilation postoperatively and left ventricular assist device implantation (Table 1).

Comparison of Venous laboratory and CoaguChek® XS INR

Venous and CoaguChek® XS INR were obtained from 51 patients (Table 1).

A significant regression equation was found (F [1,49] = 711.082). There is good correlation between the measured INR values obtained through both assays with an R^2 of 0.93 (P <0 .05) (Fig 2). The degree of bias can be observed in the Bland-Altman plot of CoaguChek® XS INR and venous INR (Fig. 2). The gap between the measured value from the CoaguChek® XS INR and the venous INR is 0.168 ± 0.176, proving good consistency between the 2 groups.

Discussion

This is the first prospective cohort study looking at the reliability of the CoaguChek® XS device in an Asian cohort during the recuperative hospital phase of cardiac surgery, using capillary blood.

This study shows that the capillary INR obtained through the CoaguChek® XS device is reliable. Though the cost between the 2 methods is similar,[14] the availability of a POCT device with a result that is instantaneous allows

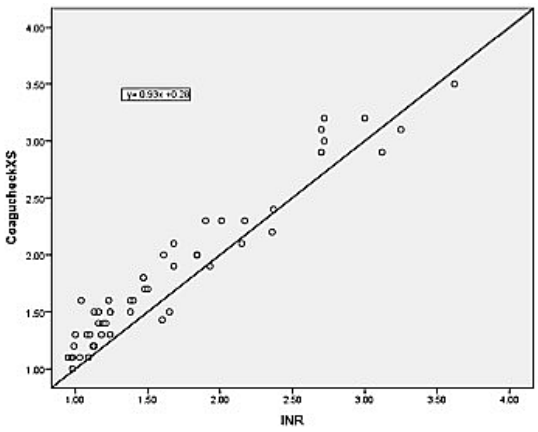

Fig. 2. Bland-Altman plot of CoaguChek® XS INR and venous laboratory INR.
INR: International normalised ratio

doctors to prescribe the appropriate dose of warfarin during morning rounds in a timely manner, without having to wait for laboratory results. There have been situations where the time to target INR, and hence hospitalisation stay, has been delayed as a result of omitting warfarin while awaiting the results of laboratory samples.

Patients can be trained to use a POCT device. With purchase or home loan services, and the setup of a physician infrastructure to follow up postdischarge, the number of visits to the anticoagulation clinic can be reduced. This empowers patient to be proactive in their own care and can also translate to cost and time saving and freeing up of slots within the anticoagulation clinic in addition to increased safety.

Study Limitations

The results of this POCT device are limited to venous INR up to 3.5. However, the range of INR depicted parallels real life where the risk of bleeding due to an raised INR, is a real concern.

While there was significant time delay between venous and capillary INR monitoring (Table 3), results still showed a strong correlation between both readings despite the time difference. The difference between the 2 INRs has a mean of 0.168 which we feel while being statistically significant, is not significant clinically.

Conclusion

The strong correlation coefficient between laboratory-obtained INR values and CoaguChek® XS values suggests that CoaguChek® XS is suitable for use in the recuperative in-hospital phase. This will help in initiating patients to self-testing programmes during this period.

Acknowledgment

The authors would like to thank the NHCS Department of Cardiothoracic Surgery, the Pharmacy department, and the nursing staff. The authors would also like to thank Roche Diagnostics for their kind support during this study.

Disclosure

Roche Diagnostics provided the CoaguChek® XS coagulometer as well as the test strips used in the study. The conception, design and implementation of the study as well as the preparation of the manuscript and conclusions were independent of industry support.

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"Do Not Touch": An Uncommon Benign Fatty Bone Tumour

A 27-year-old male with no medical illness presented to the orthopaedic clinic with left knee pain since 1 week. There was no history of trauma. There was no tenderness or swelling on physical examination and the range of motion of the left knee was normal. Frontal and lateral radiographs of the left knee (Fig. 1) were obtained, which showed an eccentric and well defined radiolucent lesion with a thin sclerotic rim located in the proximal metadiaphysis of the left tibia. The lesion had a narrow zone of transition. There was no cortical destruction, periosteal reaction or any soft tissue swelling. The left knee joint was normal. The radiographic findings were in keeping with a non-aggressive bone lesion of the tibia.

What is the most likely diagnosis?

A. Fibrous dysplasia
B. Non-ossifying fibroma
C. Simple bone cyst
D. Chondroid tumour
E. Intraosseous lipoma

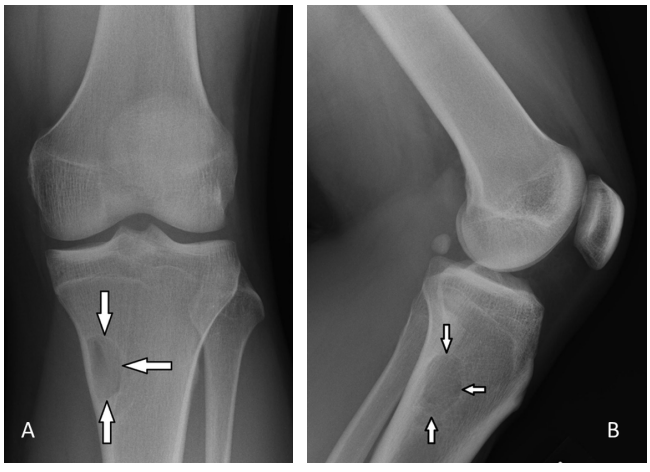

Fig. 1. A) Frontal and B) lateral radiographs of the left knee show an eccentric radiolucent lesion with a thin sclerotic rim (arrows) located in the proximal metadiaphysis of the left tibia.

Findings and Diagnosis

Radiographically, the common differential diagnosis of non-aggressive lucent lesion affecting the tibia in patients less than 40 years of age includes fibrous dysplasia, non-ossifying fibroma, simple bone cyst, aneurysmal bone cyst, and chondroid tumours like chondromyxoid fibroma and enchondroma.

Subsequently, magnetic resonance imaging (MRI) of the left knee was performed on the patient. The MRI showed that the lesion was hyperintense, with signal intensity similar to that of the subcutaneous fat on coronal T1-weighted MRI image (Fig. 2A). It had a thin hypointense rim that corresponded to the sclerotic margin seen on radiographs. On the coronal T2-weighted fat-suppressed MRI image, the lesion appeared largely hypointense, consistent with the suppression of fat signal (Fig. 2B). The lesion also showed an irregular internal low signal intensity area on the T1-weighted image which appeared hyperintense on T2-weighted fat-suppressed image. The diagnosis was intraosseous lipoma. The patient has been asymptomatic since then. Hence, no follow-up investigation was done.

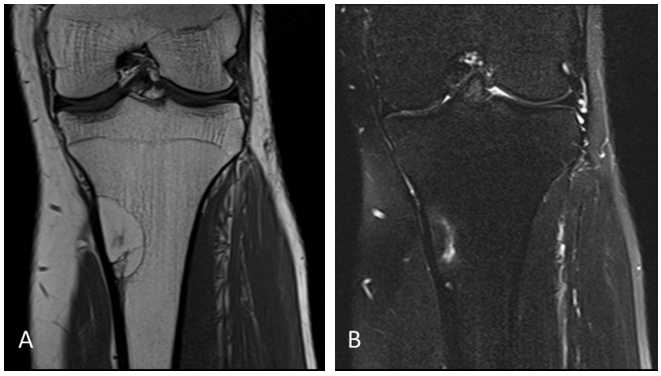

Fig. 2. A) Coronal T1-weighted MR image shows a well defined hyperintense lesion, with signal intensity similar to that of subcutaneous fat, in the medial proximal tibia. It has a thin hypointense rim corresponding to the sclerotic margin and an irregular internal low-signal-intensity area corresponding to fat necrosis. B) Corresponding coronal T2-weighted MR image with fat suppression shows a largely hypointense lesion consistent with suppression of fat signal. The central hyperintense area within the lesion is consistent with fat necrosis.

Answer: E

Discussion

Intraosseous lipoma was first described in 1880.[1] It is a rare primary bone tumour accounting for only 0.1% cases of all primary bone tumours.[1-4] With the increasing use of computed tomography (CT) and MRI, intraosseous lipomas are now diagnosed more often than before.[1,2] It can affect both sexes of any age group; however, it is most commonly discovered in the fourth and fifth decades of life.[2,3]

It is generally intraosseous but can be cortical or parosteal.[3] It may affect any skeletal bones due to normal marrow fat content.[2] In the appendicular skeleton, the common sites are the intertrochanteric and subrochanteric regions of femur, calcaneum, ilium, proximal tibia, and fibula.[5] In the axial skeleton, the craniofacial bones, pelvis, spine and ribs are more commonly involved, in decreasing order of frequency.[2,5] It usually affects the metadiaphysis of long bones.[3]

Clinically, pain might be the presenting symptom in 70% of patients.[5] Others are asymptomatic and discovered incidentally.[5] The exact cause of the pain is unclear but it may be due to expansile bone remodelling.[2,3] Some patients may present with swelling or pathological fractures.[1,2]

Milgram proposed a 3-stage classification system for intraosseous lipomas based on their histological appearances (Table 1).[2] The appearances on radiographs, CT and MRI often correspond to the histological stage of the lesion. The stage I lesions are radiolucent, with or without bony expansion, and represent viable, non-necrotic fat with resorption of bony trabeculae. On CT, the lesion shows fat attenuation ranging from -60 to -100 HU.[3] On MRI, the lesion has signal intensity similar to that of subcutaneous fat on all sequences including the fat-suppressed sequence.[1,3,4] Stage I lesions may show a peripheral rim of sclerosis on radiographs and CT images which appear as rim of low signal intensity on T1- and T2-weighted MRI images.[2-4] In stages II and III, intraosseous lipomas appear as an expansile lucent lesion with peripheral sclerotic rim and central area of increased density on conventional radiographs and CT. This finding is due to fat necrosis followed by dystrophic calcification. Stage III lesions are more radiodense with thicker peripheral zone of reactive sclerosis than stage I or II lesions, due to extensive areas of fat necrosis and calcification, and greater cystic changes.[2,3] On MRI images, areas of fat necrosis reveal variable signal on T1-weighted images and increased signal on T2-weighted images.[1,4] The areas of calcification have low signal intensity on both T1- and T2-weighted images.[1,4] Cysts are seen as well defined areas of intermediate signal intensity on T1-weighted images and high signal on T2-weighted images.[5] Stage III lesions are most confusing and difficult to diagnose due to fat necrosis, calcification, cystic changes and reactive ossification closely mimicking bone infarcts and chondroid lesions. Other lesions which may closely mimic lipomas on radiographs are fibrous dysplasia, simple cysts, non-ossifying fibroma, chondromyxoid fibroma and aneurysmal bone cysts. Hence, identification of fat signal on CT and MRI is crucial and helps confirm the diagnosis of intraosseous lipoma.[4]

Table 1. Milgram's Histological Classification for Intraosseous Lipoma

Stage	Histopathological Classification
I	Non-necrotic viable fat with resorption of bony trabeculae.
II	Partial necrosis of the fat together with viable lipocytes.
III	Extensive fat necrosis with variable grade of dystrophic calcification and cyst formation.

Management in an asymptomatic patient involves conservative treatment with regular follow-up scanning. Pain and swelling suggest a complication such as pathological fracture or malignant transformation, which can be treated with surgical curettage and bone grafting.[1,2] MRI may be useful in the follow-up of treated lesions. Malignant transformation or recurrence after surgery is very rare.[1] Milgram reported 4 cases of presumed malignant transformation in which lipoma developed into malignant fibrous histiocytoma or liposarcoma. If a stage I lipoma shows rapid bone destruction associated with pain, malignant transformation of lipoma should be suspected. [6]

Conclusion

Although lipomas are an uncommon bone neoplasm, they may not be as rare as the literature suggests. Hence, it is important to recognise the characteristic radiographic, CT or MRI appearances of intraosseous lipomas in guiding appropriate management and preventing unnecessary biopsy and surgery.

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Paradoxical Worsening of Truncal Acne with Doxycycline

An 18-year-old Chinese male was referred to our hospital for severe chest acne. He had mild truncal acne for the last 2 years and was started by his general practitioner on oral doxycycline and topical 4% sulphur and 2% resorcinol for 1 application twice a day, 3 weeks before his condition worsened acutely. He presented to us with inflammatory papulopustular acne with ulceration over the anterior chest (Fig. 1). He did not have similar acneiform lesions on the scalp, axillae or groin. No polyporous comedones were present. He did not report any fever, musculoskeletal pain or other systemic symptoms.

Laboratory investigations such as full blood count, erythrocyte sedimentation rate and liver function test were normal. Histopathology from the ulcer edge incisional biopsy was performed.

What is the most likely diagnosis?

A. Pseudo-acne fulminans
B. Acne fulminans
C. Acne conglobata
D. Pityrosporum folliculitis
E. Ecthyma

Discussion

Lesional biopsy showed mixed inflammatory granulation tissue with foreign body giant cell reaction. No follicles, foreign bodies, fungi or acid-fast bacilli were seen.

Doxycycline was stopped by the patient after the initial 3 weeks due to worsening of his truncal acne. Oral prednisolone was commenced at 30 mg per day and gradually tapered off over 6 weeks. Oral isotretinoin was introduced after 10 days of prednisolone at 10 mg/day, and the patient showed remarkable response to this treatment (Figs. 2 and 3). At the latest clinic follow-up visit 18 weeks after presentation, the patient was on 30 mg of isotretinoin with marked improvement overall.

Acne fulminans (AF) is a severe variant of acne vulgaris associated with systemic symptoms such as fever, weight loss and musculoskeletal pain. Lesions consist of acneiform papules or nodules, some of which break down to form haemorrhagic ulcers with overhanging borders. The absence of systemic symptoms in a patient with characteristic lesions of AF represents a subtype called "AF sine fulminans" or "pseudo-AF". Acne conglobata (AC) can present similar to AF but polyporous comedones and non-inflammatory cysts,

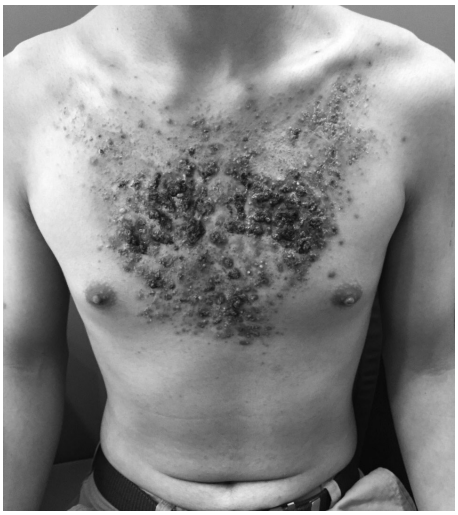

Fig. 1. On the patient's first visit, it was observed that multiple open and closed comedones were present.

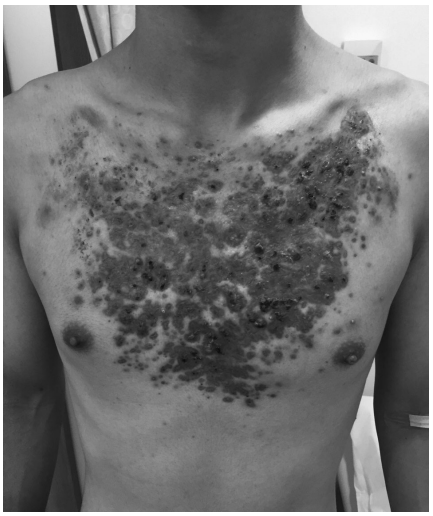

Fig. 2. The patient, 10 days after starting oral prednisolone.

Answer: A

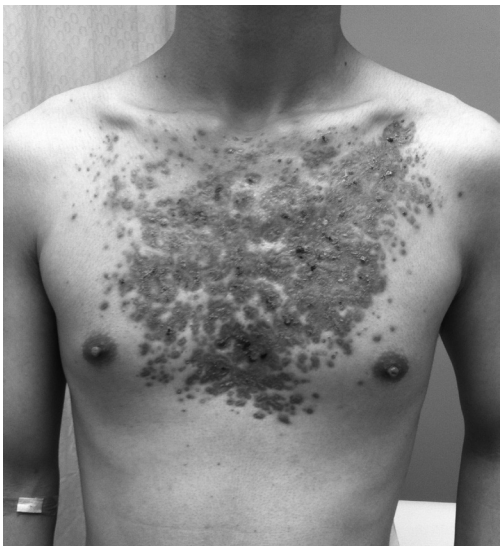

Fig. 3. The patient, 7 days after starting oral isotretinoin while still on oral prednisolone.

not seen in AF,[1] are present. In addition, patients with AC do not have systemic involvement unlike AF.

This patient had the typical cutaneous findings of AF without the associated systemic involvement, making this a case of pseudo-AF triggered by doxycycline. Pityrosporum folliculitis typically presents with erythematous monomorphic pustules on the chest and back, while ecthyma is a deep bacterial infection of the skin that presents with discrete lesions consisting of erythematous purulent ulcers with an overlying thick crust. The features of these 2 conditions were not seen in our patient.

AF has been associated with the commencement of isotretinoin and rarely, with doxycycline.[2] There are 3 kinds of acne flare-up with isotretinoin that may occur: inflammatory attacks in the first month which should resolve; recurring inflammatory attacks in the following months which are associated with the presence of open or closed comedones; and inflammatory attacks in the second and third month in which the clinical picture is of AF.[3]

Promoting factors for patients developing a flare of acne during initiation of isotretinoin therapy include young age, male gender, presence of large closed comedones[4] and truncal nodules, and isotretinoin administered at a starting dose of 0.5 mg/kg. We hypothesise that macrocomedones are also a risk factor for acne flare-up with doxycycline. Recognising predictive factors for severe flare may help in anticipating and ameliorating severe flares which may result in permanent scars.

A commonly proposed pathophysiological mechanism for AF would be a hypersensitivity reaction to bacterial antigens of *P. acnes* released during treatment with oral isotretinoin.[2] Similarly, we postulate that treatment with doxycycline could possibly result in a release of *P. acnes* bacterial antigens with subsequent hypersensitivity reaction in those predisposed.

The treatment of patients with pseudo-AF consists of a combination of oral isotretinoin and corticosteroids. Patients who previously received isotretinoin should have this stopped or reduced to 0.2 mg/kg/day while concurrent prednisolone at a dose of 0.5 to 1.0 mg/kg/day is implemented and gradually tapered according to the patient's response. Patients who did not receive prior isotretinoin can be started on a low dose of this after 2 weeks' treatment with prednisolone. Long-term low dose isotretinoin is frequently required thereafter.[5] Macrocomedonal extraction prior to starting isotretinoin may prevent severe flares during the initiation phase of isotretinoin.

This case brings to attention that an entity of pseudo-AF exists, and that conventional acne treatment with doxycycline can possibly trigger an attack.

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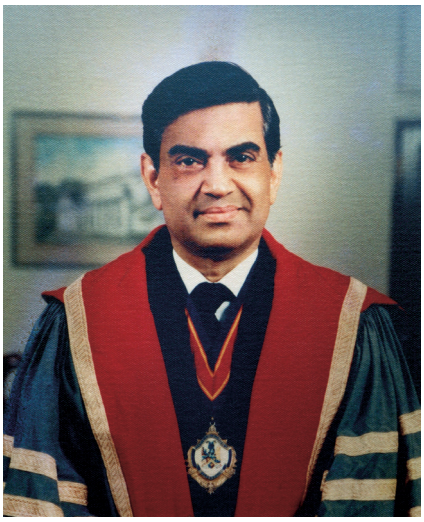
An Interview with Prof Raj Nambiar

Dialogue between Prof Pierce Chow, President of the College of Clinician-Scientists and his teacher Prof Raj Nambiar, previous Master of the Academy of Medicine, Singapore.



PC: The Academy of Medicine was established during a very different time. How far do you think it has fulfilled its original aims? Moving forward, what do you think would be the continuing role of the Academy?

RN: When it was established in the 1950s, the Academy's main aims were to advance postgraduate medical education, research and promote high standards for professional and ethical practice for its members.

However, during the first 10 years, the Academy was just finding its feet and progress was rather slow. At the beginning, it had less than 50 medical specialists, a small office in the basement of the old Alumni Association Building and one administrative secretary in charge. You probably do not remember the old Alumni building across the present one, do you?

PC: Probably not (laughs).

RN: Several years later, a lecture room on the ground floor was furnished and named Academy lecture theatre. Besides organising occasional postgraduate lectures, the most important activity for the Academy was the Annual Scientific Congress. It later became the Singapore Malaysia Congress of Medicine and was the major scientific meeting for specialists in Malaysia and Singapore. Since then, the Academy has come a long way in its 60 years in trying to fulfill its original aims.

PC: And there wouldn't have been many specialists then as now?

RN: There were only a small number of specialists in the major specialties. Doctors interested in specialty training then had to go overseas for their examinations as there was no local organisation for it. The Australasian Colleges were the first to offer their help in our postgraduate education.

PC: The Australians came here and were quite active?

RN: Yes. I think it was in the late '50s that the Australasian College of Surgeons and the College of Physicians offered to conduct postgraduate courses and examinations under the Colombo Plan in Singapore. The first primary course and examination was held by the Royal Australasian College of Surgeons in 1957. Those who passed had to go to Australia for final fellowship examinations.

PC: So they did their Primary here and the Finals there. But not as a training attachment, just the exam?

RN: I think there was also a training attachment. I know Drs James Murugasu and NC Tan were among the early ones in this scheme. Much later, advanced surgery courses and final fellowship examinations were also held in Singapore, both a first for the Australian College of Surgeons to hold their examinations in Southeast Asia.

The Academy was the prime mover in the formation of the School of Postgraduate Medical Studies. It was following many memoranda and representations by the Academy that the Government finally agreed and established the School of Postgraduate Medical Studies in 1970. It was started as an independent School under the University. The Director was appointed by the Vice Chancellor and the membership had equal representation from Academy and University and DMS representing the MOH.

The School was responsible for organising courses and the local postgraduate examination for the M.Med degree. Initially it was in 4 disciplines: Internal Medicine, Surgery, Paediatrics and O&G. Later it was expanded to include 10 specialties. From the very beginning, the School had maintained high international standards for our examination and so we had external examiners from the Royal Colleges. I remember that for M.Med Surgery, it was pitched equal (if not higher) than the fellowship examinations.

PC: It has always been seen as being more intense (laughs).

RN: Yes. Although the format was similar to fellowship examinations, more time was allocated, especially for clinical examinations. So it allowed for a more thorough assessment of candidates. We also had the Chairman or the Chief Examiner from the Royal Colleges to participate as external examiner.

In recognition of our high standards, the Royal College of Surgeons of Edinburgh decided to hold Joint Examination with the School to award the FRCS Edinburgh together with M.Med Surgery. After the first joint examination in 1985 in surgery, joint examinations were started in many other specialties.

Another important role that the Academy played is in certification of specialist training. It happened with rapid growth of specialties and subspecialties when the training and assessment in basic specialty was recognised as inadequate. So an advanced training in specialties was introduced. A Joint Committee for Advanced Specialist Certification (JCAST) was started in which Academy had major responsibility.

PC: So, it came back to the Academy, so to speak?

RN: Yes, Academy was the initiator of specialists' certification long before the Specialist Certification Board was formed. Academy had a standing committee on specialist certification that formulated the criteria for specialist training in all recognised specialties.

PC: Which year did this occur?

RN: I think it was pretty early, in the 1980s. But the Specialist Accreditation Board (SAB) under the MOH was formed much later, after the MRA in 1997. The SAB, as you know, is now the overall charge of specialist certification in Singapore.

PC: I believe in Australia and some other places, until today, the Colleges themselves can decide who is a specialist.

RN: Yes, but these colleges have a charter from the government whereas here, the MRA is by an act of parliament.

PC: So, in a way, this diminished the role of the Academy?

RN: Not really. I think Academy is now involved in a lot more activities than before. Since the SAB was formed, the Academy has had greater responsibility through the Joint Committee for Specialist Training (JCST). The Master of the Academy is co-chair with the Director of graduate division of the Faculty of Medicine. The JCST has oversight for the training in all specialties and subspecialties except the 10 specialties that continues to have an M.Med Examination.

PC: So the role of the Academy since its beginning has mainly been in the training of specialists?

RN: Indeed, it has evolved over the years. You know, Academy also has had a major part in starting the Continuing Medical Education (CME) for specialists? Academy initiated it as a voluntary arrangement. Specialists who were Academy members were requested to sign attendance at accredited CME lectures and courses to show that they have been actively involved in learning and updating their knowledge. However, the programme was not a success because there was no regulatory pressure. Later, the Singapore Medical Council (SMC) made CME a compulsory requirement for all medical practitioners in Singapore to get licence to practice.

PC: Where do you see the role of the Academy as we move forward in this sense?

RN: I believe, in general, the Academy has done well and it continues to be active in postgraduate education and training of specialists. Moving forward, I would like to see Academy playing an increasing role in professional development in order to assure that specialists practising in Singapore are current in their knowledge and skills and uphold high moral and ethical values.

PC: What can the Academy do in this?

RN: Well, now that the Academy has many specialty Colleges and Chapters under its wings, it is important to formulate programmes that are essential for all specialists and cut across specialties. Structured courses and lectures for professional development are useful to all specialists and I am glad to see Academy organising relevant courses on medical ethics, medical expert evidence etc. Since we started our CME programme more than 10 years ago, we have not made much progress. The practice of merely signing in at lectures and collecting the required number of credit points is no assurance of continued learning or improvement in practice. Even the current maintenance of certification (MOC) programme may not go far enough.

PC: One of the challenges the Academy faces now is that not all specialists wish to be Fellows. They think they are quite okay without that and which is why it is a struggle for Academy to get new members.

RN: Yes, I am afraid this will continue to be a big problem.

Prof Pierce Chow (right) seeking the views of Prof Raj Nambiar in an exclusive interview for Annals.

Although SMC has recognised Fellowship of Academy (FAMS) a registrable qualification, it is not a requirement to practice as a specialist in Singapore.

PC: So, the Academy needs to create value in their recertification?

RN: Exactly. Many other countries have introduced recertification in the last 10 years. The American Boards have had it for a long time as a requirement for MOC. The American Board of Surgery (ABS) recertification is every 10 years and requires a medical licence and institutional privileges, CME activity, practice assessment and an MOC examination in the specialty. If and when we start this process, I believe the Academy will have a major role to play and that will provide ample opportunity to create value for its members.

PC: Surgical training has undergone very significant changes recently. Although we have adopted a North American system of training, it has been observed that surgical teachers continue to teach as they used to under the UK collegial system. There is discussion now that we need to add another year and return the required period back to 6 years in order to produce competent surgeons. What are the pros and cons of the North American system of surgical training? Do you think it works in Singapore?

RN: Yes, you are right about surgical training that has undergone major changes in the last 25 years. Even in UK, it is no longer the traditional apprentice system in which the number of years spent in surgical service was counted as training and passing fellowship examination the hallmark of a specialist. The American system, on the other hand, has been known for being well structured with a curriculum, close supervision, competency-based progression and formative assessments during training. Perhaps it is important to understand that over the years, the UK and Australasian systems have also made major changes and also incorporated competency-based training and assessments in their training programmes.

All training systems, however good they are, will require changes with times. With the introduction of the current residency training, we now have an improved training system and organisation in hospitals with institutional director, education office, programme director and protected time for teaching.

You mentioned that surgical teachers are continuing to teach in the same old way. Clinical teachers who have had their own training in the old ways cannot be expected to change unless they undertake specific courses in new teaching methods and become familiar in using them. Even then, I would think it may take a few years to see the change. Close supervision of trainees in all clinical activities and regular assessment and feedback are critical for success and require much time and commitment of teachers.

I understand that a major problem is the difficulty for trainees obtaining sufficient clinical experience within 5 years of residency training. Unlike in the USA, our residents have to fulfill medical registration requirements in the first year after graduation and get very little operative experience in the first year. So, to complete 750 major operations in the remaining 4 years is not practical for most residents.

PC: This is a very important conversation (laughs). You have identified where the problem is and have hit the nail on the head.

RN: And of course the patients, the type of diseases, surgical techniques and care delivery have all changed. It's a phenomenal change that has occurred from the 1960s to '90s.

Most elective surgical patients do not require hospital stay for complete investigation or even for preoperative care. They are admitted, operated and discharged either on the same day or within a couple of days. The use of interventional radiology and wide use of minimally invasive surgical techniques have made open procedures infrequent in general surgery and patient stay shorter in hospitals.

The downside of this development is that residents have less opportunity to interact with patients and fully understand and take care of pre and postoperative care and complications. Furthermore, the mandatory time off and restriction of duty hours have also had a negative impact on training.

PC: So, for the same number of patients, the training is different now?

RN: Certainly. The training also must change because of

limited time and new techniques of endoscopic, laparoscopic and robotic surgery. In the present day, it is not practical to learn these skills on patients in the operating room. Fundamental abilities such as psychomotor skills, visuo-spatial ability and depth perception can be learnt and practised in skills laboratory. Perhaps, we have to make greater use of simulation to teach surgical skills like in the US centres.

One of the concerns we hear often is the lack of sufficient specialists and teachers. I think it is not in terms of number but certainly specialists who are able, willing and enthusiastic to teach the next generation. Unfortunately in Singapore, we have a divide between those who are in public hospitals and those outside and there is little integration of the two.

I wonder if the Academy of Medicine would have a role in coordinating better integration of all specialists in Singapore for the common purpose of teaching and training of future specialists. As this would involve major policy changes and sacrificing both time and income of specialists, I am not too optimistic of the outcome!

PC: The ethos has changed?

RN: In the 1960s, I remember teaching of medical students and junior doctors was considered part of normal duties of a specialist in public hospitals. In fact, many among those pioneers were passionate teachers and did not expect any remuneration. They were also not accorded any academic titles either. Now, the scenario is totally changed!

PC: It's no longer so altruistic?

RN: It is unfortunate but true. There was a time when the Academy was expanding its activities through the formation of various Chapters. But many specialists then did not want to join as member of the Academy and those who were members then were reluctant to serve on committees. In many other countries, the fellows or members of their professional Colleges would gladly come forward and consider it a privilege to be on college committees.

I have always thought that being a professional is a unique privilege for you to spare time for teaching and training others and also volunteer in activities of professional colleges. It can improve the public perception of the profession as a whole and promote professional standing.

PC: Although the concept of Academic Medicine and of Academic Medical Centres in Singapore to drive translational and clinical research was first mooted in 2007 (almost 10 years ago), many would say we have not seen much evidence of Academic Medicine on the ground. In General Surgery specifically, it appears that a lower proportion of surgeons and surgical trainees do any form of academic research, receive grants or publish, in spite of more abundant funding available. Anecdotally fewer surgeons seem interested in teaching. Do you think that the culture in General Surgery has changed to one that is less aligned with research and academic surgery? If so, what is the reason and how can these be reversed?

RN: I would agree that until the 1990s, there was very little medical research in Singapore. There was no leadership with research experience, no facilities, no funding and no such thing as a research culture. The Academy of Medicine in order to promote the culture then had formed a research committee and later established the Seah Cheng Siang and Yahya Cohen lectureships and Johnson and Johnson, Roche and Glaxo fellowships.

It is remarkable that clinicians like Professor SS Ratnam still achieved outstanding international reputation for clinical research. During that time, there were just very few notable clinicians who sacrificed their time and published papers based on their clinical experiences. However in the last 20 years, the whole environment has changed. The formation of Academic Medical centres and the 3 medical schools have spurred great academic activity in Singapore. So if you don't see much evidence of academic medicine on the ground, I would think perhaps 10 years is too short a time.

I believe the main reason for the lack of academic research in General Surgery was the lack of interest, facilities and surgeon leaders with clinical research experience. In contrast, during my training years in UK, research publications were essential for those aspiring for consultant positions in University or teaching hospitals. It was not uncommon then for many young surgeons in England to go to USA for further research experience. In Singapore, publication was perhaps desirable but was not a requirement for promotion even in the University.

PC: Surgical leadership is particularly important. When you were HOD in the Department of Surgery at SGH, that department was perceived as a highly academic department although it was not a University Department. To what extent do you think the philosophies and qualities of the surgical leadership important to academic surgery? What would these philosophies and qualities be?

RN: No one will dispute that leadership is critical in any organisation. After having worked abroad and in the Surgical unit at the General Hospital, Singapore (SGH) for many years I have had a fair idea of what makes a good teaching surgical unit (not using the term academic). Later,

it was at Thomson Road Hospital (renamed as Toa Payoh Hospital) when I was HOD that I first introduced these ideas and later in SGH in 1985.

The basic philosophy is simple and familiar to all. Clinical excellence in patient care combined with good teaching and training and encouraging clinical research. Of course that is easily said than done! How well you put these in practice will determine whether or not your department is perceived as an academic department. That's where leadership matters.

I would say that we achieved a few important things: with new innovations in clinical care and surgery, the surgical bed occupancy soon increased to maximum capacity, overall mortality and morbidity in high risk operations were significantly reduced, and patient and staff satisfaction very much improved. The department at Toa Payoh Hospital became popular for training of postgraduates and the trainees consistently obtained success in their examinations. Evaluation of clinical work and presentation of papers at clinical meetings became routine for trainees, some of whom published papers for the first time.

The leadership is not about creating a chart of so-called academic activities and names of people in charge but motivating all levels of staff to do their best and pull the cart forward together to your goal. It means ensuring certain amount of discipline at work, maintaining high standards, accountability and integrity and a commitment or passion in work. I think it is most important for the leader to set the tone not by threats but by personal example.

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