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*"We get wise by asking questions... for a well-packed question carries
its answer on its back as a snail carries its shell."*

James Stephens (1882–1950)
Irish poet

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Too Much Medicine: Time to Stop Indiscriminate Cancer Screening

Raymond CH Ng, ¹MBChB, FRACP, MPH

Like most industrialised countries in the world, cancer has now become the leading cause of mortality in Singapore. Approximately 1 in 3 deaths in Singapore today is as a result of cancer.¹ It is therefore unsurprising that cancer screening has become an integral part of health screening in primary health care today. The current Singapore's Ministry of Health as well as Academy of Medicine's guidelines are in keeping with most screening guidelines in the world in their recommendations of routine screening for breast, cervical and colorectal cancers in those with average risks based on appropriate age cutoff,^{2,3} as well as screening for additional cancers based on elevated risks such as family history. Nowhere in the guidelines are serum tumour markers recommended as a method of routine screening. Despite this, every day in primary health care setting in Singapore, serum tumour markers such as carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), CA153, alpha-fetoprotein (AFP), Epstein-Barr virus (EBV) serology are commonly included in packages of health screening. Indeed, an entire industry surrounding this concept of healthy living and early disease detection has sprung up locally in which one can spend a day in a spa-like "health screening centre" where health screening packages can be selected from a menu by a consumer. These packages are often dressed up in attractive sounding hyperboles such as "Premium", "Executive", "Deluxe", "Luxury" as well as the rather bland and less persuasive sounding "Basic" package. The last of which, ironically, is often the only one that is usually driven by guidelines. To compound this further, many of these health screening endeavours are not truly individualised according to personal risk factors despite their claims as such. In fact, the only personalised aspect of the screening appears to be based primarily on consumer request and how much he or she is willing to spend. Indeed, a healthy 30-year-old with no risk factors or symptoms can request and undergo a package that will include among them, a colonoscopy, an oesophago-gastroduodenoscopy and all the various serum tumour markers despite the fact that the likelihood of him being harmed far outweighs any potential miniscule benefit that may arise.

Just as troubling, is that these practices appeared to have also filtered across to many primary health practitioners as well as government hospitals in Singapore. Furthermore, third party health screening industries now also frequently contact business and educational institutions to sell health screening packages to their staff personnel.

In this issue of *Annals*, Tan et al⁴ described in a letter to the editor, 5 cases of medullary thyroid carcinoma detected through raised CEA from general health screening. They naturally concluded that the presence of a raised CEA should therefore prompt one to search for an underlying medullary thyroid carcinoma, with the inference that subsequent treatment will ultimately benefit the patient. However, a careful appraisal of the report and available data suggests that perhaps a very different conclusion should be made. In the 5 cases reported, the time it took from the detection of a raised CEA to the diagnosis of medullary thyroid carcinoma ranged from almost 2 to as long as 9 years. And despite this protracted interval, all of the cancers were still confined to the thyroid and none had metastasised to the lymph nodes. This suggests that there is a high probability that in fact, some of these tumours are incidental indolent cancers that would probably have never been detected or indeed become clinically relevant if it was not for the raised CEA. That is to say, that some, if not all, of the patients presented in the report would probably have died from other causes unrelated to thyroid cancer without ever having been diagnosed with the condition.

This seeming paradox is a well recognised phenomenon in screening known as overdiagnosis. Overdiagnosis occurs when a condition is diagnosed that would otherwise not go on to cause symptoms or death. Cancer overdiagnosis may have of 1 of 2 explanations: 1) The cancer never progresses or in fact, regresses, or 2) the cancer progresses so slowly that the patient dies of other causes before the cancer becomes symptomatic.⁵ Although the notion of an indolent cancer may be alien to many, the best example can be illustrated in prostate cancer. Autopsy series in men who have died from conditions unrelated to prostate cancer have demonstrated the presence of prostate cancer in as high as

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80% of 70-year-olds whom were not known to have this diagnosis previously.⁶ Yet for many, the probability of dying from prostate cancer remains significantly lower. This means that many men in their old age will develop prostate cancer but few will ever be aware of it or be clinically affected by it. But by screening for the disease in an asymptomatic elderly man, there is a high chance that the condition will be diagnosed. This phenomenon of overdiagnosis is now also well documented in multiple other malignancies including breast, lung, thyroid, neuroblastoma and kidney cancers.⁵

It is timely to revisit and understand the objectives of cancer screening. Screening aims to find a cancer earlier and therefore provide timely treatment with the ultimate goal of reducing long-term relapse and prolonging survival. However, if screening does not achieve the latter goals but merely finds the cancer earlier (known as lead time bias) or worse, just finds more cancers (overdiagnosis bias); then that screening itself is clearly undesirable. Overdiagnosis can be estimated through studies such as ecological, cohort and randomised control trials.⁷ Many randomised trials in cancer screening have been instrumental in allowing us to measure the benefits and harms of screening.

Take for example, ovarian cancer screening. CA125 is a serum tumour marker associated with ovarian cancer and a common test included in many of the health screening packages available in Singapore today. However, a recent trial of ovarian cancer screening provided some sobering results. In this study, close to 80,000 women aged 55 to 74 were randomised to receive annual CA125 blood test as well as transvaginal ultrasound compared to no screening,⁸ with the primary goal of demonstrating a reduction in mortality. Unfortunately the results showed no difference in the 2 groups in terms of number of ovarian cancers detected, the stages of cancer detected nor any differences in deaths from ovarian cancers or otherwise. Moreover, in women that were screened, 10% of them had a false positive result i.e. being told that they had cancer when they did not. Of these, one-third had to undergo major surgery and 15% suffered a major complication. These highly disappointing results underscore the importance of the necessity to base rational screening decisions on available evidence. Recent results from a separate randomised trial that interpreted serial CA125 change through a risk algorithm have shown more promising outcome in detecting ovarian cancers. However, final results on mortality outcome are still pending and eagerly awaited.⁹ Till then, it remains difficult for one to justify the utility of ovarian cancer screening. Indeed, based on the aforementioned study, not only is ovarian cancer screening with serum CA125 and ultrasound useless, it is actually potentially detrimental. To put this in another manner, if one were to submit to the reader for consideration, a new antihypertensive that does not actually reduce blood

pressure but has potential side effects that mimic cancer which may result in unnecessary surgery with resultant major complications; it is clear that no sane-minded readers, let alone the health funding authorities, will ever allow this medication to be included in the prescription list. Yet every day in Singapore right now, serum CA125 blood tests are being offered and performed in women as part of cancer screening despite clear evidence confirming these very detrimental harms.

Finally, it is perhaps pertinent in this editorial prompted by thyroid cancer to heed a cautionary tale from a neighbouring country, South Korea. The leading cancer diagnosed in South Korea today is thyroid cancer. The age-adjusted incidence rate of thyroid cancer per 100,000 persons soared astronomically from 7.2 in 1999 to 61.9 in 2010.¹⁰ There is no clear environmental reason for this rapid surge in thyroid cancer cases. Disturbingly, the root for this disconcerting epidemic appears to be iatrogenic. Many hospitals in South Korea market “health check-up” programmes that include thyroid cancer screening with ultrasonography and many general practitioners also have ultrasonography machines in their offices and routinely perform thyroid scanning.¹¹ With such a large increase in number of cases, one would naturally expect the death rate from thyroid cancer to fall correspondingly since one is detecting these cancers at an earlier stage and hence, treating and curing it. Yet despite this surge in diagnosis, the actual mortality from thyroid cancer has remained virtually unchanged in the country over the same time period. This suggests very strongly that all these excess cases are in fact, overdiagnosed, indolent and clinically irrelevant cancers. This disconcerting data rightfully led to concerns expressed by physicians in South Korea with calls for the screening to be banned in the country. Unfortunately, these pleas have been largely ignored¹² and with thyroid cancer now being the leading cancer in the country, this vicious cycle looks unlikely to abate with consumers and health providers seeing the cancer’s position on the league table alone as justification to continue this approach.

As much as 1.5 trillion won (S\$1.8 billion) is estimated to be spent annually on thyroid ultrasounds in Korea¹³ and the Korean National Health Insurance Service spent 260 billion won (S\$315,000,000) on treating thyroid cancer alone in 2012.¹⁴ It is not difficult to see who the eventual true beneficiaries from all these indiscriminate screenings are.

In conclusion, it is imperative for us to recognise that all screening endeavours cause harm. Some also generate good as well and it is only those that create more good than harm that should be considered for adoption in clinical practice. Although the aim of health providers in providing screening may have been well intended, failure to adhere to guidelines may inadvertently result in unfortunate

harms. Our supposedly noble profession is founded on the principle of *Primum non nocere*: First do no harm. We owe it to ourselves and the larger community to reconsider this current practice of potentially harmful, indiscriminate and non-evidence based cancer screening.

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Unipolar versus Bipolar Hemiarthroplasty for Displaced Femoral Neck Fractures in the Elderly: Is There a Difference?

Dennis ZW Ng, ¹MBBS (Singapore), MRCS (Edinburgh), Kevin BL Lee, ¹MRCS (Edinburgh), MMed (Ortho), FRCS (Ortho)(Edinburgh)

Abstract

Introduction: Hip hemiarthroplasties are commonly performed for displaced femoral neck fractures. Considerable differences of opinion exists regarding the choice between unipolar and bipolar designs. The main theoretical advantage of a bipolar over a unipolar prosthesis is the reduction of acetabular erosion due to movement taking place within the implant rather than at the acetabular implant interface. It is thus hypothesised that bipolar prostheses lead to better long-term functional outcomes with less complications. In this study, we aimed to compare unipolar (Moore's) and bipolar hemiarthroplasty looking specifically for differences in 1) pain and functional hip scores; 2) rates of acetabular erosion, component migration and revision surgery; and 3) rates of postoperative morbidity. **Materials and Methods:** Inclusion criteria were 1) age more than or equal to 65 years; 2) displaced femoral neck fracture of non-pathologic origin; 3) normal cognitive function; 4) ambulatory with or without assistive devices prior to the fracture; and 5) treated with a primary prosthetic replacement. Of the 193 patients that were available for review, 118 were in the Moore's group and 75 in the bipolar group. Postoperatively, patients were assessed with regards to pain, satisfaction, Modified Harris hip score and Oxford hip score. Standard anteroposterior pelvis and lateral hip radiographs were obtained at regular intervals. These were analysed specifically with regards to acetabular erosion and component migration. **Results:** There was no significant difference between a Moore's and a bipolar prosthesis regarding hip pain, functional hip scores, rates of acetabular erosion, component migration, revision surgery and complications rates. **Conclusion:** Use of the more expensive bipolar prosthesis in elderly and premorbidly ambulant patient is not justified.

Ann Acad Med Singapore 2015;44:197-201

Key words: Hip fracture

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Introduction

Hip hemiarthroplasties are commonly performed for displaced femoral neck fractures. The advantages of hemiarthroplasty over internal fixation include earlier mobility, less reoperations and better functional outcome at 1 year.^{1,2}

Considerable differences of opinion exists regarding the choice between unipolar and bipolar designs. The main theoretical advantage of a bipolar over a unipolar prosthesis is the reduction of acetabular erosion due to movement taking place within the implant rather than at the acetabular implant interface. It is thus hypothesised that bipolar prostheses lead to better long-term functional

outcomes with less complications. However, evidence from the literature so far has not been supportive of this theory.³⁻⁷

All studies so far have found that bipolar implants have a significantly higher cost compared to unipolar implants.^{5,8} In our price-sensitive population, we wonder whether the higher costs associated with the use of bipolar implants are justified. The purpose of this study is to compare unipolar (Moore's) and bipolar hemiarthroplasty with the following aims: 1) Are there any differences in terms of pain and functional hip scores?; 2) What are the rates of acetabular erosion, component migration and revision surgery?; and 3) Are the rates of postoperative morbidity similar?

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Materials and Methods

All patients who underwent hemiarthroplasty for displaced neck of femur fractures between 1 January 2004 and 31 December 2007 were analysed from a log of all operative procedures. Inclusion criteria were 1) age more than or equal to 65 years; 2) displaced femoral neck fracture of non-pathologic origin; 3) normal cognitive function; 4) ambulatory with or without assistive devices prior to the fracture; and 5) treated with a primary prosthetic replacement. Patients with a pre-existing hip abnormality requiring total hip replacement or a pathological fracture secondary to malignant disease were excluded.

Patient characteristics examined included age, gender, prefracture ambulatory status, and number of associated comorbidities. Prefracture ambulatory status was classified into the following categories: 1) independent community ambulatory; 2) community ambulant with assistive devices; and 3) home ambulant. General health status was defined by the number of pre-existing significant comorbid conditions, which included diabetes mellitus, congestive heart failure, cardiac arrhythmias, ischaemic heart disease, previous cerebrovascular accident, renal disease, Parkinson's disease, hypertension, chronic obstructive pulmonary disease, and the need for ongoing anticoagulation. These comorbidities were chosen as the most important ones based on those reported in the literature.^{9,10}

Between 1 January 2004 and 31 December 2007, 317 patients underwent hemiarthroplasty for displaced neck of femur fracture. Of these, a total of 270 patients met the selection criteria and were included in this study; 164 patients received a Moore's and 106 patients received a bipolar prosthesis. Demographic data and preoperative ambulatory status are summarised in Table 1. The 2 groups did not differ with regards to age, gender, prefracture ambulatory status and number of medical comorbidities.

Table 1. Demographic Data and Preoperative Ambulatory Status

	Moore's (n = 164)	Bipolar (n = 106)
Age (years)*	74.3 (65 – 85)	72.5 (65 – 85)
Female (%)	143 (87.2)	90 (84.9)
Prefracture ambulatory status		
Independent community ambulator	67	47
Community ambulant with assistive devices	47	31
Home ambulant	50	28
Number of comorbidities		
0 – 2	134	87
>2	30	19

*Values given as mean, with range in parenthesis.

At the time of review, 38 patients were lost to follow-up and 39 patients had died; 24 (14.6%) from the Moore's group and 15 (14.2%) from the bipolar group. There were no statistically significant differences in mortality between the 2 groups of patients. In the group of 38 patients who were lost to follow-up, the prosthetic hips were minimally symptomatic as of the last follow-up. In the group of 39 patients who died, all the deaths were attributed to other medical conditions not related to the hip replacement surgery. According to telephone interviews with family members, all prosthetic hips were also minimally symptomatic till the time of death. No revision procedures were performed in both groups of patients. Mean age at time of operation was 75.4 years (range, 67 to 84) and mean duration between the primary procedure and death was 1.2 years.

A minimum of 2 years of follow-up was available for 193 of the surviving patients who were available for review; 118 in the Moore's group and 75 in the bipolar group. Mean age at time of operation was 73.7 years (range, 65 to 85). Mean duration of follow-up for this group of patients was 4.1 years (range, 2.1 to 5.2).

Postoperatively, a series of subjective assessments were made including pain, satisfaction with the operation, the Modified Harris hip score¹¹ and Oxford hip score.¹² The final score is multiplied by a factor of 1.11 to obtain a percentage. A score of 90 to 100 is considered excellent, 80 to 90 good, 70 to 80 fair and <70 poor. The Oxford hip score is a patient-centred questionnaire designed to assess functional ability and pain from the patient's perspective. It is calculated from responses to 12 questions on activities of daily living (ADL). The minimum score of 12 indicates normal function and the maximum of 60 the most severe disability. Other variables obtained included length of stay and postoperative complications.

The patients were reviewed postoperatively at 2 weeks, 6 weeks, 3 months, 6 months, 1 year and then annually after that. Average follow-up for the unipolar and bipolar groups were 4 and 4.25 years respectively. Standard anteroposterior pelvis and lateral hip radiographs were obtained at each visit. These were analysed specifically with regards to acetabular erosion and component migration. Acetabular erosion was evaluated radiographically by the grading system shown in Figure 1. This measures the change in thickness of the acetabular cartilage compared with the immediate postoperative radiograph. Vertical and horizontal acetabular migration was assessed by measuring the vertical distance from the center of the uni or bipolar head to the interteardrop line and the horizontal distance from the centre of the cup to the ipsilateral teardrop, respectively.¹³ Patients were also evaluated for dislocation rate and need for any revision procedure.

Data was analysed using Statistical Package for the Social



Fig.1. Grading system for acetabular erosion.

Sciences package (SPSS, Chicago, Illinois). The chi-square test was used to compare the groups with respect to hip pain and patient satisfaction. The Mann-Whitney U test was used to compare Modified Harris hip score and Oxford hip score. Fisher exact test was used to assess mortality, revision and complication rates. The student t-test was used to assess acetabular migration. The level of significance was set at $P < 0.05$.

Results

Sixty-six percent of patients who had a bipolar prosthesis reported minimal or no pain at follow-up compared to 65% of patients who had a Moore's prosthesis. This is however not statistically significant at the 5% level. Clinical outcome in terms of patient satisfaction, Modified Harris hip score and Oxford hip score did not differ significantly as well (Table 2). Analysis of data was on an 'intention-to-treat' basis. The outcomes of pain and satisfaction with operation were categorised as yes or no; patients that died or who were lost to follow-up were included in the 'yes' group with regards to pain and the 'no' group with regards to satisfaction.

Table 2. Outcome and Functional Scores

	Moore's (n = 164)	Bipolar (n = 106)	P Value
No or mild pain (%)	107 (65.2)	70 (66.0)	0.77 [†]
Satisfied with operation (%)	110 (67.1)	73 (68.9)	0.65 [†]
Harris hip score*	78.7 (55 – 92)	79.3 (54 – 90)	0.45 [‡]
Oxford hip score*	25.8 (12 – 48)	24.9 (12 – 48)	0.23 [‡]

*Values are given as mean, with range in parenthesis.

[†]Chi-square test.

[‡]Mann-Whitney U test.

To determine whether the results were influenced by age, gender and prefracture ambulatory status, we performed logistic regression to adjust for these potential confounding factors. After adjustment for these factors, there were still no significant differences between the 2 groups for pain, satisfaction, Modified Harris hip score and Oxford hip score.

Acetabular erosion was observed in 3 patients belonging to the Moore's group but not in the bipolar group. Of these 3 patients, 2 required a revision arthroplasty for severe pain associated with acetabular erosion. Duration between surgery and revision were 2.4 and 2.7 years for these 2 patients. After the revision procedure, they had markedly improved Modified Harris hip scores and Oxford hip scores. One patient from the bipolar group required revision for periprosthetic fracture 1.5 years postoperatively. The Moore's group showed a mean cranialisation of 2.5 mm (range, 0 to 5) and mean medialisation of 2.1 mm (range, 0 to 4) of the prosthesis head compared to a mean cranialisation of 1.7 mm (range, 0 to 2) and a mean medialisation of 1.5 mm (range, 0 to 2) for the bipolar group. No cases of femoral stem loosening were noted in both groups. There were no significant differences with respect to acetabular erosion, component migration and revision rates between the 2 groups.

Postoperative complications and length of stay were identical as well (Table 3).

One patient who underwent a Moore's hemiarthroplasty suffered a dislocation in the early postoperative period after turning awkwardly in bed. There was no additional instability after a successful closed reduction. There were no cases of dislocation in the bipolar group.

Discussion

Hemiarthroplasty is the most commonly performed operation for displaced femoral neck fractures in the elderly. The aim of our study is to compare unipolar (Moore's) and bipolar hemiarthroplasty looking specifically for differences in 1) pain and functional hip scores; 2) rates of acetabular

Table 3. Postoperative Complications

	Moore's (n = 164)	Bipolar (n = 106)	P Value*
Dislocation	1	0	0.375
Deep vein thrombosis	9	5	0.446
Pulmonary embolism	1	1	0.714
Wound infection	3	2	0.725
Pneumonia	4	2	0.318
Urinary tract infection	5	4	0.217
Myocardial infarction	1	2	0.146
Pressure sores	1	2	0.324

*Fisher's exact test.

erosion, component migration and revision surgery; and 3) rates of postoperative morbidity. Patients with significant cognitive impairment and those who were non-ambulant prefracture were specifically excluded because many studies have shown that these patients have a poor prognosis with respect to survival and function.^{10,14,15}

There are several limitations to this study. First, it is a retrospective study with all the problems associated with this methodology. Although the 2 groups appear similar in terms of demographic data, the patients were not randomly assigned to one of the implant groups. Hence, unmeasured confounders may exist that could have biased the results. Second, a fairly large number of patients were either lost to follow-up or had passed away. Third, the mean duration of follow-up was only slightly more than 4 years. Clearly, a longer follow-up is required to determine rates of acetabular erosion, component migration and revision surgery.

No significant differences in terms of pain, patient satisfaction and functional hip scores can be demonstrated between patients treated with a Moore's or bipolar hemiarthroplasty in our study. Evidence in the literature so far supports our findings. To date, both retrospective^{5,6} and prospective studies^{3,16,17} have not demonstrated a significant difference in functional outcome between the 2 groups.

One of the major complications associated with hemiarthroplasty is painful acetabular erosion. In theory, the second articulation in a bipolar arthroplasty would increase the range of motion and decrease native acetabular wear. The polyethylene may also result in the release of wear debris, which may lead to osteolysis and subsequent component migration. However, our study did not demonstrate a significant difference in the incidence of acetabular erosion or component migration between the 2 groups of patients. The theoretical advantages of a bipolar implant also have not been borne out by other clinical studies.^{4,18} Reported rates of acetabular erosion ranged from 2.2% to 36% for unipolar designs and 0% to 26% for bipolar designs.¹⁹ Dalldorf et

al reviewed the histologic specimens in patients who were having a revision of a hemiarthroplasty and compared them with age-matched controls. Progressive degeneration was found to correlate directly with the duration of articulation of the implant with the acetabulum but not the type of implant. The fate of the cartilage that had articulated with the unipolar prosthesis was similar to that of the cartilage that articulated with the bipolar prostheses.²⁰ In our series, we had no cases of symptomatic or radiographic loosening. No revisions were required in either group for loosening.

Rates of postoperative morbidity were comparable between the 2 groups with no statistically significant differences (Table 3). Many studies in the literature also support our findings. Hudson et al, in an 8-year retrospective review of 90 unipolar and 48 bipolar hemiarthroplasties showed no statistically significant differences in the rates surgical or medical complications.⁴ Calder et al, in a prospective and randomised 2-year trial comparing unipolar and bipolar prosthesis in octogenarians, found no difference in the complication rates as well.³

All studies have found that bipolar hemiarthroplasty has a higher cost than unipolar hemiarthroplasty.^{5,8} With rising medical costs, this adds to the economic burden of caring for hip fracture patients. Our results have not shown a significant difference between a Moore's and a bipolar prosthesis regarding hip pain, functional hip scores, rates of acetabular erosion, component migration, revision surgery and complications rates. Studies conducted thus far concur with our findings. In addition, an evidence-based review of this topic conducted by Parker and Gurusamy concluded that the present literature demonstrated no difference between unipolar and bipolar hemiarthroplasty.²¹ This suggests that the use of the more expensive bipolar prosthesis in elderly and pre-morbidly ambulant patient is not justified, particularly in our price sensitive population.

In recent years, there is also an increasing trend towards total hip arthroplasty for displaced femoral neck fractures.^{19,22} In a study by Gebhard et al²³ involving 166 displaced femoral neck fractures, total hip arthroplasty demonstrated superior longevity when compared with hemiarthroplasty with and without cement. Revision rates were lower as well. In a prospective study of 89 patients with a displaced neck of femur fracture, Dorr et al²⁴ found that function improved with time after total hip replacement but not after hemiarthroplasty.

Conclusion

Use of the more expensive bipolar prosthesis in elderly and pre-morbidly ambulant patient is not justified. In view of the increasing life expectancy of the local population, further studies are required to determine long-term outcomes.

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Fasting during Ramadan and Associated Changes in Glycaemia, Caloric Intake and Body Composition with Gender Differences in Singapore

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Abstract

Introduction: Millions of Muslim patients with diabetes mellitus (DM) fast during Ramadan. However, little is known about the metabolic impact of Ramadan fasting. We aimed to study the changes in body composition and metabolic profile in this group of patients. **Materials and Methods:** We studied 29 Southeast Asian Muslim patients with type 2 diabetes; all underwent pre-Ramadan education. Study variables were weight change, body composition (using multifrequency bioimpedance method, InBody S20®, Biospace, South Korea), blood pressure (BP), glycated haemoglobin (HbA1c), fasting lipid profile, and caloric intake assessment using FoodWorks® nutrient analysis software. **Results:** Twenty-three subjects fasted ≥ 15 days; mean $\pm$ SD: 57 ± 11 years; 52% were males. HbA1c improved significantly ($8.6 \pm 2.4\%$ pre-Ramadan vs $8.0 \pm 2.3\%$ end-Ramadan, $P = 0.017$). Despite similar body weight, there was reduction in body fat mass (BFM) (30.9 ± 11 kg vs 29.2 ± 12.2 kg, $P = 0.013$). Multivariate analysis suggested that the reduction in HbA1c was attributed by reduction in BFM ($\beta = -0.196$, $P = 0.034$). There was no change in visceral adiposity (visceral fat area (VFA)) but stratification by gender showed a reduction amongst females (137.6 ± 24.5 cm² to 132.5 ± 25.7 cm², $P = 0.017$). These changes occurred despite similar total caloric intake (1473.9 ± 565.4 kcal vs 1473.1 ± 460.4 kcal, $P = 0.995$), and proportion of carbohydrate ($55.4 \pm 6.3\%$ vs $53.3 \pm 7.5\%$, $P = 0.25$) and protein intake ($17.6 \pm 4.1\%$ vs $17.3 \pm 5.4\%$, $P = 0.792$), before and during Ramadan respectively, but with increased proportion of fat intake ($11.9 \pm 2.4\%$ vs $13 \pm 11.7\%$, $P = 0.04$). Seven out of 23 patients had medications adjusted to avert symptomatic hypoglycaemia but none of the patients developed severe hypoglycaemia. **Conclusion:** Ramadan fasting can be practiced safely with prior patient education and medication adjustment. It also confers modest benefits on metabolic profile and body composition, especially among females.

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Key words: Diabetes, Education, Muslims

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Introduction

Muslim individuals worldwide participate in obligatory abstinence from oral consumption of medications, food and liquid during the fasting month of Ramadan. Fasting during Ramadan is one of the 5 pillars of Islam. However, Islam exempts individuals whose health may be significantly affected from fasting. Despite this, up to 80%¹ of Muslim individuals with diabetes mellitus (DM) choose to fast during Ramadan and it is estimated that this figure is approximately 50 million Muslims globally. Singapore, a multi-ethnic country, has diverse religious beliefs and practices, and Muslims account for ~15% of the resident population.²

The Epidemiology of Diabetes and Ramadan (EPIDIAR) study, a large epidemiological study of Muslims with diabetes in 13 Muslim countries with over 12,000 participants, showed that severe hypoglycaemic episodes were significantly more frequent during Ramadan compared with other months, and less than half of the population changed their treatment dose when fasting.¹ Although having no overtly harmful effects, fasting during Ramadan has been observed to be associated with changes in lipid profile and body composition even in healthy individuals, which has been postulated to be due to either a change in nutritional habits during Ramadan or a response to

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starvation.^{3,4} Notwithstanding its worldwide practice, the effect of fasting during Ramadan on metabolic profile and body composition in individuals with diabetes remains understudied with conflicting evidence in the literature.

The aim of our study was to assess the impact of Ramadan-associated fasting on glycaemic control, caloric intake, and body composition in people with diabetes in Singapore. In addition, we aim to evaluate the safety of fasting in this group of people with the provision of physician and dietician-guided advice on safe practices in fasting based on the recommendations by the American Diabetes Association.⁵

Materials and Methods

This prospective cohort study was conducted at a single-centre outpatient clinic. The protocol for the research project was approved by the ethics committee of our local Institutional Review Board and conforms to the provisions of the Declaration of Helsinki. All adult subjects (age ≥ 18 years) with type 2 diabetes by accepted criteria,⁶ who expressed intention to fast for at least 15 days during the month of Ramadan, in addition to being deemed eligible for fasting during Ramadan based on the recommendations of their primary physician, were eligible for recruitment. Subjects with end-stage kidney disease, acute illness during Ramadan, and pregnancy were excluded from the study.

All subjects underwent educational sessions with a physician and a dietician according to the recommendations of the American Diabetes Association on management of diabetes during Ramadan.⁵ These education sessions included advice on frequent monitoring of blood glucose levels and acute management of hypoglycaemia and hyperglycaemia. Adjustment in dosage and timing of medications was individualised to the patient and at the discretion of the physician. Nutritional advice and methods of estimation of portion sizes were taught by the dietician in order to have an estimation of daily caloric intake.

Subjects were provided with glucometers and blood glucose strips and instructed to chart their blood glucose readings 5 times per day: before pre-dawn meal (suhoor); 2 hours post suhoo; between 12 pm to 2 pm; before breaking fast (iftar); and 2 hours post-iftar to guide diabetes management. Hypoglycaemia was assessed via review of symptoms and these readings. Severe hypoglycaemia was defined as hypoglycaemia requiring third-party assistance or hospitalisation.⁷

Study variables included weight change, body composition as analysed by multifrequency tetrapolar bioelectrical impedance method (InBody S20®, Biospace, Seoul, South Korea), blood pressure (BP), glycated haemoglobin (HbA1c), and fasting lipid profile. Daily meal and snack intake was determined via a 3-day food diary

with information on portion sizes, frequency of eating, and food preparation. Caloric assessment was performed using FoodWorks® nutrient analysis software (Xyris Software, professional version 6.0.2539, Brisbane, Australia). These study variables were obtained pre- (within 1 month) and at the end (final week) of Ramadan.

Biochemical analyses on blood investigations were carried out at our institution's referral laboratory, which is accredited by the College of American Pathologists. Plasma glucose was obtained by enzymatic methods using blood collected in fluoride oxalate tubes. Serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were measured using an automated analyser (Roche COBAS INTEGRA 700).

Statistical analyses with SPSS version 19.0 software (SPSS, Chicago IL, USA) were conducted using paired t-test (pre- and end-Ramadan parameters) and multiple-linear regression (dependent variable: end-Ramadan parameters e.g. HbA1c; independent variables: corresponding pre-Ramadan parameters and predictor of interest e.g. change in body fat mass). When subjects were stratified by gender, non-parametric Wilcoxon signed-rank test was used. A *P* value < 0.05 was considered statistically significant.

Results

A total of 29 subjects were recruited. Twenty-three subjects (80%) fasted for at least 15 days and had complete follow-up data. Four subjects were lost to follow-up and the remaining 2 subjects did not complete Ramadan-fasting due to acute illness. Table 1 shows the baseline demographics of the study population.

Mean age of the subjects was 57 ± 11 years. Fifty-two percent were men and 87% were of Malay ethnicity. The majority (58.6%) of subjects were treated with oral anti-diabetic agents alone, whilst the remainder was on insulin therapy with or without combination oral antidiabetic agents. A significant proportion of our study population had long diabetes duration; duration of diabetes was less than 10 years in 37.9%, between 10 to 20 years in 31%, and longer than 20 years in 27.6% of subjects.

There was no severe hypoglycaemia or complications of hyperglycaemia in our study group. Medications were adjusted in 7 subjects during Ramadan, primarily to avert symptomatic hypoglycaemia, which was self-treated in all. In the 2 subjects who fasted for < 15 days, one was hospitalised for urinary tract infection and the other had an upper respiratory tract infection that did not require hospitalisation.

At the end of Ramadan, HbA1c improved significantly (8.6 ± 2.4 to $8 \pm 2.3\%$, $P = 0.017$). Despite not having

Table 1. Baseline Characteristics of Study Participants

Parameter	Whole Cohort	Men	Women	P Value
Population (n, %)	29 (100)	15 (52)	14 (48)	NA
Age (years)	57 ± 11*	61 ± 11*	54 ± 10*	0.095
Diabetes duration (%)				
Less than 10 years	39.2	26.7	53.9	0.499
10 to 20 years	32.1	40.0	23.1	
More than 20 years	28.6	33.3	23.1	
HbA1c (%)	8.6 ± 2.4*	8.6 ± 2.7*	8.6 ± 2.0*	0.988
BMI (kg/m ²)	30.3 ± 5.6*	30.7 ± 6.7*	29.9 ± 4.7*	0.734
Treatment (%)				
Oral agents	58.6	60.0	57.2	0.442
Insulin therapy	41.4	40.0	42.8	

BMI: Body mass index; NA: Not available

*Data are expressed as mean ± SD.

significant change in body weight ($P = 0.837$), we observed a modest but significant reduction in body fat mass (BFM) (30.9 ± 11 to 29.2 ± 12.2 kg, $P = 0.013$). Multivariate analysis suggested that the reduction in HbA1c was partly attributable to reduction in BFM ($\beta = -0.196$, $P = 0.034$). Table 2 shows the biochemical and body composition variables pre- and post-Ramadan.

As a group, visceral adiposity (visceral fat area (VFA)) did not change throughout Ramadan ($P = 0.273$). However, when stratified by gender, a significant reduction in VFA was seen amongst women ($P = 0.017$). There was no

appreciable change in caloric intake between the fasting (1473.1 ± 460.4 kcal) and non-fasting (1473.9 ± 565.4 kcal) period ($P = 0.995$) although when stratified by gender, total caloric intake was ~20% lower in women compared to men during Ramadan (1599.2 ± 492.5 in men vs 1277 ± 342.9 kcal in women, $P = 0.102$) and women consumed ~9% less calories during Ramadan as compared to pre-Ramadan (1408.5 ± 529.2 pre-Ramadan vs 1277 ± 342.9 during Ramadan, $P = 0.441$), although these were not statistically significant. There was no significant change in proportion of carbohydrate and protein intake before and

Table 2. Biochemical and Body Composition Variables of Study Participants Pre- and End-Ramadan Fasting

Parameter	Men			Women			P Value [§]	P Value	P Value [†]
	Pre-Ramadan (mean ± SD)	End-Ramadan (mean ± SD)	P Value [†]	Pre-Ramadan (mean ± SD)	End-Ramadan (mean ± SD)	P Value [†]			
BMI (kg/m ²)	30.7 ± 6.7	30.4 ± 6.7	0.332	29.9 ± 4.7	29.8 ± 4.5	0.028*	0.734	0.814	0.023*
BFM (kg)	30.7 ± 12.9	28.6 ± 14.5	0.092	30.4 ± 8.6	30.0 ± 9.0	0.058	0.946	0.807	0.013*
VFA (cm ²)	148.0 ± 33.3	148.0 ± 38.5	0.534	137.6 ± 24.5	132.5 ± 25.7	0.017*	0.388	0.337	0.273
SBP (mmHg)	150.2 ± 18.9	148.3 ± 16.4	0.100	158.6 ± 26.5	147.6 ± 18.7	0.721	0.337	0.925	0.174
DBP (mmHg)	84.2 ± 9.3	87.2 ± 6.3	0.833	87.0 ± 10.8	81.8 ± 6.3	0.313	0.462	0.066	0.500
HbA1c (%)	8.6 ± 2.7	8.0 ± 2.8	0.059	8.6 ± 2.0	8.0 ± 1.6	0.066	0.988	0.976	0.017*
LDL-c (mmol/L)	2.62 ± 0.80	2.65 ± 0.78	0.299	2.98 ± 0.74	2.94 ± 0.84	0.678	0.215	0.399	0.741
TG (mmol/L)	2.09 ± 1.03	2.04 ± 1.33	0.826	2.00 ± 1.19	1.67 ± 0.95	0.050	0.831	0.471	0.361
HDL-c (mmol/L)	1.15 ± 0.30	1.19 ± 0.26	0.530	1.22 ± 0.33	1.26 ± 0.36	0.677	0.567	0.598	0.475

BFM: Body fat mass; BMI: Body mass index; DBP: Diastolic blood pressure; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; SBP: Systolic blood pressure; TG: Triglyceride; WHR: Waist-hip ratio; VFA: Visceral fat area

*Indicates statistical significance, P value < 0.05.

[†]Pre- and end-Ramadan comparison within men.

[‡]Pre- and end-Ramadan comparison within women.

[§]Pre-Ramadan comparison between gender.

^{||}End-Ramadan comparison between gender.

[†]Mean changes as a group (including both men and women) pre and end-Ramadan.

during Ramadan although there was a significant increase in proportion of fat intake overall, with women having a higher proportion as compared to men during Ramadan ($P = 0.018$). Table 3 shows the dietary variables pre- and post-Ramadan.

A decrease in serum triglycerides was observed in women at end-Ramadan (near statistical significance, $P = 0.05$), which was not present in men ($P = 0.826$). There were no significant changes in blood pressure and other lipid parameters.

Discussion

Our observation shows that daylight fasting during the month of Ramadan appears to confer benefits on glycaemia and body composition, especially among women with type 2 diabetes, with improvement in HbA1c and a reduction in VFA. In addition, fasting during Ramadan is safe in a group of individuals who have received prior education on dietary counselling, glucose monitoring, and adjustment of medication dosage and timing.

Improvement in glycaemic control with HbA1c reduction was observed in the presence of decreased meal frequency, despite no appreciable change in overall total caloric intake. Total caloric intake during Ramadan has been shown to be similar to non-fasting periods in some studies despite the reduction in meal frequency,⁸ whilst other studies have shown a decrease⁹ or increase¹⁰ in total caloric intake. These

differences can be attributed to distinctive dietary habits in different countries and customs during the month of Ramadan.⁹ Similarly, variable changes in glycaemic control have been reported;¹¹ with some showing no significant changes,¹² while others had improved⁹ or worsened glycaemic control. Similarly, the increase in fat intake found in our study is concordant to previous findings,¹¹ where the decrease in carbohydrate intake is compensated for with an increase in fat intake without any appreciable change in daily caloric intake. Despite the reduction in meal frequency due to fasting, it is a common observation that people often overeat during the breaking fast meal.

Interestingly, our study found a gender-specific difference in the associated changes; with a higher fat intake, decreased BFM, and a significant reduction in VFA in women. These differences may be hypothesised to be due to increased fat oxidation in women during the fasting period,¹³ supported by decreased serum triglycerides^{11,14} at the end of Ramadan.

None of the subjects required hospitalisation for any of the acute complications of diabetes, such as hyperglycaemic emergencies (diabetic ketoacidosis or hyperosmolar hyperglycaemic state), hypoglycaemia or dehydration. Symptomatic hypoglycaemia occurred in 30% (7/23) of the subjects, and these were self-managed by the subjects with subsequent adjustment of medication dose by the physician. It is possible that the provision of patient education, active glucose monitoring, dietary counselling, and the review and adjustment of medication dosage and timing before

Table 3. Dietary Variables of Study Participants Pre- and End-Ramadan Fasting

Parameter	Men			Women			P Value [§]	P Value	P Value [¶]
	Pre-Ramadan (mean $\pm$ SD)	End-Ramadan (mean $\pm$ SD)	P Value [†]	Pre-Ramadan (mean $\pm$ SD)	End-Ramadan (mean $\pm$ SD)	P Value [‡]			
Daily energy intake (kcal)	1515.9 $\pm$ 603.1	1599.2 $\pm$ 492.5	0.510	1408.5 $\pm$ 529.2	1277.0 $\pm$ 342.9	0.441	0.667	0.102	0.995
Carbohydrates (gram)	222.0 $\pm$ 69.4	233.2 $\pm$ 86.6	0.636	189.6 $\pm$ 66.6	164.0 $\pm$ 48.3	0.260	0.281	0.041*	0.826
% of total energy intake	56.6 $\pm$ 5.2	55.3 $\pm$ 7.6	0.802	53.7 $\pm$ 7.6	50.3 $\pm$ 6.6	0.314	0.294	0.128	0.250
Protein (gram)	68.9 $\pm$ 28.0	66.0 $\pm$ 25.9	0.683	65.1 $\pm$ 27.2	56.7 $\pm$ 14.1	0.441	0.755	0.338	0.365
% of total energy intake	17.5 $\pm$ 4.6	16.9 $\pm$ 6.5	0.683	17.9 $\pm$ 3.5	17.9 $\pm$ 3.4	0.833	0.834	0.633	0.792
Fat (gram)	48.6 $\pm$ 26.8	51.5 $\pm$ 18.1	0.530	45.4 $\pm$ 17.6	46.0 $\pm$ 15.5	0.859	0.759	0.461	0.692
% of total energy intake	11.4 $\pm$ 2.5	12.3 $\pm$ 1.3	0.221	12.6 $\pm$ 2.1	14.0 $\pm$ 1.8	0.110	0.289	0.018*	0.040*

BFM: Body fat mass; BMI: Body mass index; DBP: Diastolic blood pressure; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; SBP: Systolic blood pressure; TG: Triglyceride; WHR: Waist-hip ratio; VFA: Visceral fat area

*Indicates statistical significance, P value <0.05 .

[†]Pre- and end-Ramadan comparison within men.

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[§]Pre-Ramadan comparison between gender.

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and during the fasting month contributed to this positive outcome. The Ramadan Prospective Diabetes Study showed a similar observation that the majority of patients did not have any serious acute complications of diabetes during Ramadan with a reduction in frequency of hypoglycaemic episodes.¹⁵ Similarly, the Ramadan Education and Awareness in Diabetes (READ) programme showed that a structured education programme about physical activity, meal planning, glucose monitoring, hypoglycaemia, dosage and timing of medications prevented weight gain in the group of patients who attended the programme as compared to a group that did not; along with a decrease in the total number of hypoglycaemic events.¹⁶ Our study supports the findings of these studies that people with diabetes intending to fast during Ramadan should receive structured education. Healthcare professionals should also actively ask about the intention to fast among their Muslim patients with diabetes.

The limitations of our study include the small sample size, the absence of a control group, and the lack of physical activity quantification. The provision of diabetes education related to fasting may also contribute to the improvement in glycaemic control seen. Despite these limitations, this study presents important findings in view of a high prevalence of fasting in Ramadan among patients with DM.

Future studies involving larger sample sizes will be useful to confirm our findings and elucidate the determinants of these changes in body composition and metabolic profile as well as gender differences. It is tempting to speculate that these benefits may be attributable to changes in circadian rhythm¹⁷ and physical activity with intensive prayer activity performed during the month of Ramadan.

Clinical practice indications of this study include promoting the provision of structured education for Muslims with diabetes in Singapore intending to fast during the month of Ramadan. Nutritional and dietary counselling is an essential component in the education package. Healthier alternatives to sugary fluids and sweet foods traditionally used to break fast should be advised to Muslims with diabetes along with avoidance of high saturated fat meals. In addition, it may be advisable to spread the daily caloric allowance over the non-fasting period to mitigate hyperglycaemic swings.

Conclusion

Ramadan fasting confers metabolic and glycaemic benefits (albeit modest) and can be practiced safely with appropriate patient education, blood glucose monitoring, adjustment of medication dose, and timing among Muslims with diabetes.

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How do English-speaking Cancer Patients Conceptualise Personhood?

Rayan Alsuwaigh, ¹*MBBS*, Lalit Kumar Radha Krishna, ¹*MBChB, FRCP, PhD*

Abstract

Introduction: Understanding personhood or “what makes you, you” is pivotal to the provision of person-centred care. Yet the manner that personhood is conceived amongst patients varies significantly. This study aims to investigate conceptions of personhood in a multiracial, multicultural, multireligious setting. **Materials and Methods:** A mixed-methods study was conducted at National Cancer Centre Singapore, from January 2013 to April 2013. We used a validated questionnaire where English-speaking oncology patients rated the importance of 26 features of “personhood” on a 10-point Likert scale from 0 to 9, with 9-points being extremely important. This was followed by a semi-structured interview. Analysis of transcripts using the Grounded Theory revealed original data that inspired novel ideas about the nature of personhood, which precipitated a further study in April 2014. **Results:** Our initial study of 100 patients revealed that personhood is conceived in a unique and novel manner. To study this, we interviewed a further 40 patients using a supplemental question to our original questionnaire. Our data affirmed our initial findings and evidenced a change in conceptions of personhood. **Conclusion:** Our evidence supports the Ring Theory of Personhood, which suggests that personhood is defined by innate, individual, relational, societal elements. It also evidences that personhood is temporally and contextually sensitive allowing for better appreciation of the evolving goals of care that frequently occur at end-of-life. Most importantly, this study reminds healthcare professionals on the importance of “treating persons” and looking beyond familial interests in maintaining the interests and dignity of the patient.

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Key words: End-of-life, Oncology, Palliative care, Person-centred care

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Introduction

Understanding the way personhood or “what makes you, you” is conceptualised is pivotal to the practice of medicine.¹⁻⁶ Conceptions of personhood determine the moral and legal status of an individual, is central to the protection of rights and privileges and is pivotal to the maintenance of the distinctiveness of the individual at times of illness and incapacity.¹⁻⁶ Bishop Merrill states that, “A clearer notion of what constitutes personhood will produce better arguments for moral decisions and actions in clinical settings and in public policy. It will also shed light on issues as far-ranging as abortion, euthanasia, and quality assurance in clinical care.”⁶

Yet despite its vital role, personhood is poorly understood.¹⁻⁶ This need is particularly evident within the end-of-life setting where provision of patient-centred care, the maintenance of dignity and issues pertaining to a “good death” revolve around appropriate understanding of personhood.⁷⁻¹⁰ Indeed the charge of explicating this concept has been brought into sharp focus with suggestions that a loss of personhood ought to be considered indifferentiable from biological death.¹¹ Extrapolations of LiPuma’s position could be seen to relegate many terminally ill patients who are naturally delirious or sedated as a result of their ongoing disease process or as a result of treatment, to a state devoid of personhood and akin to death.¹¹ This worrying posture

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drawn from a conception of personhood that pivots on conscious ability and social interaction explains the exigency to better explicate conceptions at the end-of-life given the repercussions to care.¹¹⁻¹³

Such “consciousness-led” definitions of personhood are but one of many prevailing views of personhood, each with a significant impact upon end-of-life care.¹⁴⁻¹⁹ Resonating with personalist concepts, Polkinghorne, Himma and Beckwith suggest that personhood is tied to ensoulment, whilst Nelson notes that humanist views sees personhood endowed to all by virtue of being human.¹⁴⁻¹⁹ These concepts of innate personhood are held to be lost only with the demise of the individual.² The impact upon palliative care given this belief that personhood is preserved irrespective of the state of the patient provides little impetus to protect the dignity and values of the unconscious patient nor to ensure a “good death”.^{2,20}

This notion of personhood however has been rejected by some philosophers who suggest instead that the crux of personhood lies in the presence of self awareness.^{4,21-26} Fletcher’s 15 “criteria or indicators” of personhood expand upon pre-existing theories of personhood that revolve upon consciousness-dependent factors and the centrality of rational thought.²⁶ Farah and Heberlein, Fins et al and Rich on the other hand have defined personhood by one’s ability to think and appreciate one’s own existence.²¹⁻²⁶ The impact upon end-of-life care where sedation and delirium are common is inescapable.^{12,13}

Tsai’s 2-dimensional concept of Confucian personhood, on the other hand, refutes this atomistic view.⁵ This concept which continues to dominate local thinking holds to the view that a “person” exists within a network of social and familial interrelatedness.⁵ The impact to end-of-life care is inescapable in the denigration of individual rights of patients in favour of the wishes and values for family.^{5,27-29}

Influenced by growing clinical evidence and case reports of a wider concept of personhood in the form of the Ring Theory of Personhood and Hughes’s statement that our notion of the “person” must square with clinical experience, we undertook to study local conceptions of personhood to better inform our practice.^{7,8,9,30-33} We aimed to understand how personhood is conceptualised and defined amongst cancer patients in multicultural, multireligious Singapore.

Materials and Methods

Two mixed-methods studies were conducted at the National Cancer Centre Singapore (NCCS) from January to April 2013 (2013 study) and March to April 2014 (2014 study). Both studies were identical other than an additional question being used in the 2014 study. English-speaking patients over the age of 21 attending the centre for outpatient

chemotherapy were invited to participate in a questionnaire and semi-structured interview on personhood. They were recruited via convenient sampling on a voluntary basis. There was no predetermined sample size. The sample size was eventually determined at the end of the study when data saturation from the qualitative analysis was reached. Data saturation was attained at 90 patients in the 2013 study and 16 in the 2014 study. The subsequent 10 interviews in the 2013 and 2014 studies respectively did not add further value to the data accrued nor reveal any disconfirming data. The decision was then made by the study team to stop at 100 in the 2013 study and 40 in the 2014 study.

Thematic analysis of the data collected in the 2013 study that revealed the notion that concepts of personhood evolved with time and context provided the rationale for the 2014 study and the impetus for the design of a further question to scrutinise changes in personhood. Both study protocols were reviewed and approved by the institutional review board.

The Questionnaire

Following informed consent, participants completed a short personhood questionnaire that is based on Sarah Bishop Merrill’s questionnaire from her study, ‘Defining Personhood’.⁶ A list of 26 features were presented to participants who were asked to rate how important each feature was to “being a person” on a 10-point Likert scale from 0 to 9. This list of features is shown in Figure 1. No statistical software was used for the quantitative analysis of the data.

Qualitative Interviews

Following the questionnaire, participants engaged in a face-to-face semi-structured interview based on Krishna et al’s 2013 questionnaire on personhood.^{7,31} This began with the question: ‘What other features make you who you are as a person?’^{7,31} Subsequent questions were based on scenarios surrounding hypothetical characters in various health states.^{7,31} These hypothetical situations offered a less threatening method to explore sensitive subjects.^{10,34,35} The questions and hypothetical scenarios were discussed and developed with an expert panel to minimise researcher bias. A single trained interviewer completed all interviews in each study and in both studies, our data analysis was carried out in a similar manner. In both studies the average interview length was 30 minutes, but ranged from 20 to 90 minutes. Responses were transcribed during the interview process. The interviewer was tasked to accurately transcribe verbatim all relevant comments during each interview, as the interview sessions were not audiotaped. A member of the expert panel who evaluated the design of the study tool was invited to sit in for multiple interview sessions to evaluate

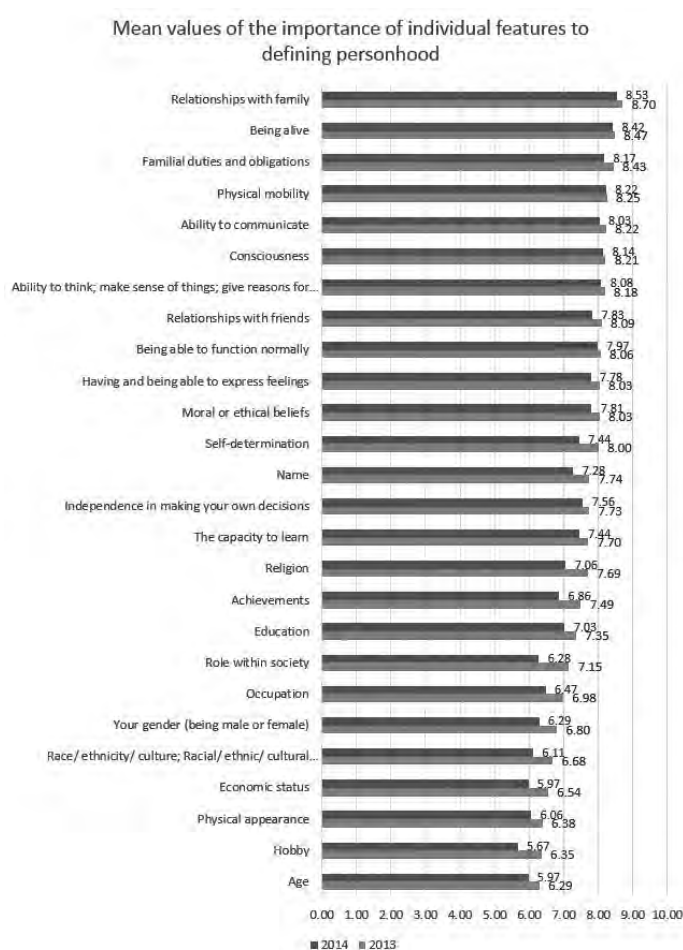


Fig. 1. Mean values of the importance of individual features to defining personhood – a comparison between data from 2013 and 2014.

the interview and transcription process. Interviewer field notes were kept throughout the data collection process.

Data analysis took place simultaneously with ongoing data collection. Transcripts were analysed using the Grounded Theory method in the following stages: 1) Open coding; initial familiarisation of the data; 2) Delineation of emergent concepts; 3) Conceptual coding; 4) Refinement of conceptual coding schemes; 5) Clustering of concepts to form analytical categories; 6) Searching for core categories; 7) Core categories led to identification of core theory; and 8) Testing of emergent theory.¹⁰

The data was constantly revisited throughout the analysis with a constant attempt to challenge developing theories. Close attention was paid to deviant cases. A minimum of 2 researchers were involved in the qualitative data analysis process at any point in time. Where there were differing codes and analyses, these were anonymously presented to external qualitative researchers to reach consensus.

The Grounded Theory method as developed by sociologists Glaser and Strauss (1967) was used as the nature of the study was broad and exploratory with aims to generate theory about “personhood” and the way it is understood, allowing these theories to be tested across a range of settings.³⁵

Concepts that emerge from early stages of the data analysis were compared with subsequent concepts and categories emerging from the next (constant comparative method). This process of constant comparison went on until no new significant concepts emerged – ‘theoretical saturation’. The study team was constantly reminded to maintain a reflexive awareness of the research process and the researcher’s role. Apart from being open and reflexive about the methodology, theoretical assumptions and starting points were addressed by each researcher before the analysis began.

Design of the Question to Study Change in Conceptions of Personhood

One emergent theme not fully captured within Krishna et al’s original 2013 questionnaire employed in our 2013 study was the issue of change in conceptions of personhood as patients progressed through their illness.^{7,31} To study this element, a further question was to be added to Krishna et al’s questionnaire.^{7,31}

Design of this questionnaire was inspired by a number of factors highlighted in Table 1.³⁶ We were particularly cognisant of the characteristics of the patients, their physical, emotional and practical limitations as well as the overall time constraints given our need to limit discussions to less than 30 minutes. We were also aided in our design by the data and experiences studying personhood amongst local oncological patients, a review of similar studies, our debrief notes from previous studies and refining the focus of study to the issue of change in personhood.^{7,31} Our third question was, ‘Do you think you have changed as a person over the course of your illness?’

Results

Participant Characteristics

A total of 100 patients completed the questionnaire and semi-structured interviews in our 2013 study, and 40 patients participated in our 2014 study which included our new question on change of conceptions of personhood. Table 2 shows the basic demographics of participants. There was an even distribution of male (55%) and female (45%) participants in the 2013 study. In our 2014 study, 70% of our participants were males; 78% of the participants were Chinese in both studies. Representation of the other key ethnic groups in both studies closely mirrored their

Table 1. The Key Elements that Helped Guide the Design of the Question on Changes in Personhood

Debriefing	• Prior debriefing experience in previous studies on personhood • Comments of students, social workers, physicians, nurses and physiotherapists • Relevant theories • Previous study findings • Prevailing sociocultural, philosophical and religious/spiritual views • Prevailing practises
Psychological factors	• Pressure • Stress • Anxiety • Low mood
Physical considerations	• Reduced concentration • Tiredness • Weakness • Lethargy • Sedation
Participants	• Prior knowledge • Knowledge built on preceding questions • Own experiences • Motivations • Personal characters
Data-driven considerations	• Refined key issues brought up in analysis of the initial study results

respective societal representation within Singapore fairly well.³⁶ Singaporean citizens dominated both studies. The marital status and age of participants in both studies were similar (Table 2).

General Review of the Study Results

The overall results from both our 2013 and 2014 studies were very similar (Table 3).

Review of the 26-item Questionnaire

Participants were asked to rate the importance of each feature with respect to “being a person” on a 10-point Likert scale from 0 to 9. Zero-point was defined as not important, 1-point as minimally important and 9-points as extremely important. The mean scores for individual features for both studies are shown in Figure 1.

‘Relationships with family’ had the highest mean score. Nine features were similarly ranked within the top 10 considerations in both studies (Fig. 1). ‘Relationships with family’ and ‘familial duties and obligations’ had the lowest standard deviations in both studies—demonstrating the least variance among patients for these 2 features.

Table 2. Demographics of Respondents from the 2013 and 2014 Studies

Characteristics		n = 100 (%)	n = 40 (%)
		2013	2014
Gender	Male	55 (55%)	28 (70%)
	Female	45 (45%)	12 (30%)
Median age (range)		55 (35 – 82)	57.5 (17 – 81)
Ethnicity	Chinese	78 (78%)	31 (77.5%)
	Malay	6 (6%)	4 (10%)
	Indian	8 (8%)	2 (5%)
	Others	8 (8%)	3 (7.5%)
Religion	Christianity	32 (32%)	8 (20%)
	Buddhism	9 (9%)	14 (35%)
	Islam	11 (11%)	5 (12.5%)
	Hinduism	10 (10%)	1 (2.5%)
	Roman Catholic	9 (9%)	5 (12.5%)
	Taoism	2 (2%)	0 (0%)
	Free Thinker	27 (27%)	2 (5%)
	No Religion	0 (0%)	5 (12.5%)
Nationality	Singaporean	96 (96%)	36 (90%)
	Others	4 (4%)	4 (10%)
Marital status	Married	81 (81%)	32 (80%)
	Divorced	0 (0%)	3 (7.5%)
	Never married	19 (19%)	5 (12.5%)

The mean scores ranged from 8.7 for ‘relationships with family’ to the ‘age’ at 6.29 in our 2013 study and 8.53 for ‘relationships with family’ to the ‘hobby’ at 5.67 in our 2014 study. No statistical tests for significance were performed as mathematical calculations for *P* values were deemed to be inappropriate in the context of these studies. Instead, to further contextualise these results and investigate if the differences in mean scores between individual features were significant, we went on to analyse qualitative data from subsequent semi-structured interviews in both studies.

The Emergent Concepts from Grounded Theory Analysis of Qualitative Data: Personhood is Represented by the Sum of Individual Features

The first emergent concept was that all 26 features in both studies were believed to contribute to personhood equally with no absolute preference for 1 feature over another in defining one’s personhood.^{7-9,31-33} Disregarding the interviewer’s attempt to get him to rate each feature from zero to 9, Patient 44 (2013 study) stated: “The sum is greater than its parts... It is not just about having individual features on a checklist. It is the summation of all that we have—that makes us who we are”. Patient 49 (2013 study)

Table 3. Rankings and Mean Values of the Importance of Individual Features to Defining Personhood – a Comparison between Data from 2013 and 2014

Feature	2013		2014	
	Mean	Rank	Mean	Rank
Relationships with family	8.70	1	8.53	1
Being alive	8.47	2	8.42	2
Familial duties and obligations	8.43	3	8.17	4
Physical mobility	8.25	4	8.22	3
Ability to communicate	8.22	5	8.03	7
Consciousness	8.21	6	8.14	5
Ability to think; make sense of things; give reasons for what you do and don't do	8.18	7	8.08	6
Relationships with friends	8.09	8	7.83	9
Being able to function normally	8.06	9	7.97	8
Moral or ethical beliefs	8.03	10	7.81	10
Having and being able to express feelings	8.03	10	7.78	11
Self-determination	8.00	12	7.44	13
Name	7.74	13	7.28	15
Independence in making your own decisions	7.73	14	7.56	12
The capacity to learn	7.70	15	7.44	14
Religion	7.69	16	7.06	16
Achievements	7.49	17	6.86	18
Education	7.35	18	7.03	17
Role within society	7.15	19	6.28	21
Occupation	6.98	20	6.47	19
Your gender (being male or female)	6.80	21	6.29	20
Race/ethnicity/culture; Racial/ethnic/cultural characteristics	6.68	22	6.11	22
Economic status	6.54	23	5.97	24
Physical appearance	6.38	24	6.06	23
Hobby	6.35	25	5.67	26
Age	6.29	26	5.97	25

stated: “I cannot think of anything that does not make me who I am, or a person. Everything—every feature or trait I have makes me a person. Having to list features will suggest that if I lose any of these, I become less of who I am—this is not true”. This concept of personhood being the sum total of a diverse set of individual features is mirrored in both studies and is represented diagrammatically in Figure 2.

Innate Personhood

A recurrent theme stressed throughout the discussion of personhood was the notion of minimal criteria sufficient for the endowment of personhood (Table 4). In both studies nearly all patients (96% in 2013 and 100% in 2014) in our study population believed that an embryo was endowed with personhood from the moment of conception. The key reasons given were that it was alive and possessed his or her distinctive physical appearance despite a lack

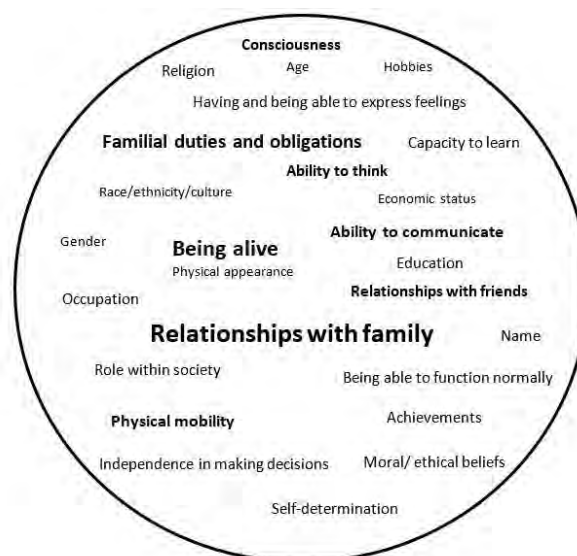


Fig. 2. Personhood is represented by the sum of present features.

Table 4. Summary of Responses to Vignettes

Vignette Questions	Response	n = 100 (%)	n = 58 (%)
		2013	2014
At the point where Jane becomes pregnant, do you consider the embryo to be a person?	Yes	96 (96%)	40 (100%)
	No	4 (4%)	0 (0%)
	No answer	0 (0%)	0 (0%)
What features make the embryo a person?*	Being alive	75 (78.12%)	16 (40%)
	Relationships with family (Acknowledgement from parents)	36 (37.5%)	7 (17.5%)
	Physical appearance	12 (12.5%)	4 (10%)
The baby is born unconscious. Is the baby a person?	Yes	97 (97%)	39 (97.5%)
	No	1 (1%)	0 (0%)
	No answer	2 (2%)	1 (2.5%)
Ben, the baby, grows up and marries Lisa. Lisa suffers a stroke and is left unconscious. Is Lisa still a person?	Yes	98 (98%)	39 (97.5%)
	No	0 (0%)	0 (0%)
	No answer	2 (2%)	1 (2.5%)
Does Lisa, being unconscious, change Ben's "person" (her husband)?	Yes	70 (70%)	25 (62.5%)
	No	28 (28%)	6 (15%)
	No answer	2 (2%)	9 (22.5%)
Does Lisa, being unconscious, change her children's "person"?	Yes	72 (72%)	27 (67.5%)
	No	26 (26%)	7 (17.5%)
	No answer	2 (2%)	6 (15%)
Lisa suffers a second stroke and is left in a permanent vegetative state. Is Lisa still a person?	Yes	97 (97%)	34 (85%)
	No	1 (1%)	6 (15%)
	No answer	2 (2%)	0 (0%)
Lisa dies. Is Lisa still a person?	Yes	47 (47%)	10 (25%)
	No	50 (50%)	30 (75%)
	No answer	3 (3%)	0 (0%)
If yes, what makes Lisa a person?*	Relationships with family	34 (72.3%)	3 (30%)
	Memories	18 (38.3%)	1 (10%)
	Religion	0 (0%)	1 (10%)
Does Lisa's death change Ben's "person"?	Yes	82 (82%)	28 (70%)
	No	15 (15%)	5 (12.5%)
	No answer	3 (3%)	7 (17.5%)

*A single participant may have mentioned more than one response. Not all participants gave an answer. Percentages shown are with reference to only those who answered 'Yes' to the related question preceding it.

of consciousness.^{7-9,31-33} Personhood also existed even if consciousness is never attained or is lost in various health states.^{7-9,31-33} "It is about what is sufficient and not what is necessary" (Patient 32, 2013). In discussing the personhood of a hypothetical character, Lisa, who was in a permanent vegetative state, 97 participants in our 2013 study and 34 participants from our 2014 study reported that "she is still a person" as a result of being alive and her physical appearance. This concept of a maintained personhood by certain features despite the loss of others is represented by Figure 3.

Personhood Beyond its Innate Form: Individual, Relational and Societal Personhood

Once again, the findings in both studies were similar and analysis of both sets of results revealed 3 further domains that built upon the innate elements of personhood (Fig. 3). Firstly, there are the features related to consciousness.^{7-9,31-33} These were the basis of one's individualism or distinctness—forming an "individual personhood".^{7-9,31-33}

The next domain revolved around one's relational links. Significant emphasis was placed on "relational personhood"

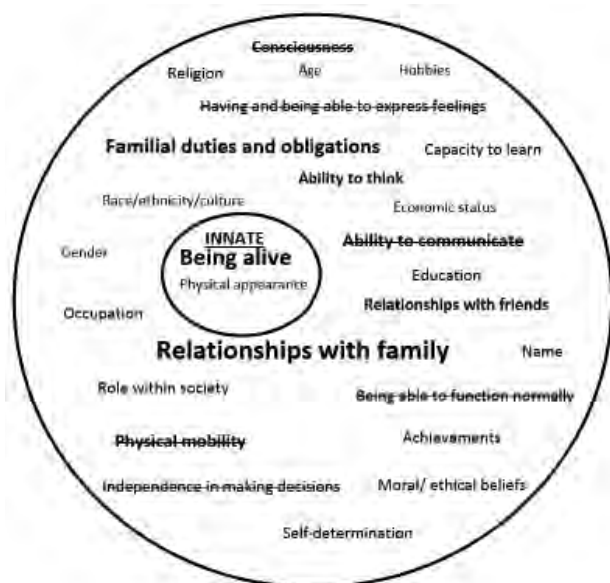


Fig. 3. Certain “innate” features form the core of personhood. The loss of certain features in various health states does not affect the overall integrity of one’s personhood.

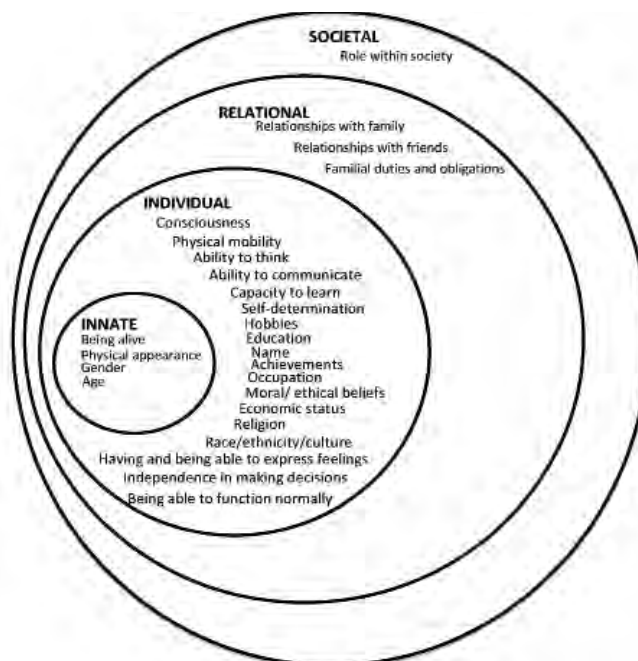


Fig. 4. Personhood beyond its innate form: the idealised forms of individual, relational and societal personhood.

which built upon “individual personhood”—personal and important relationships with loved ones.^{7-9,31-33} These relationships included both family and close friends.^{7-9,31-33}

Lastly, the impact of social, cultural, religious and political factors upon the practises, character, values, beliefs and interest of the patient are also acknowledged as the standards, expectations, obligations and laws they are subject to.^{7-9,31-33} This categorised view of a developed personhood is illustrated in Figure 4.

Features of Personhood are Interrelated, Interdependent, and Amenable to Change

In the majority of interviews in both studies, the “distinct” features of personhood were found to be interrelated, interdependent and amenable to change over time.^{7-9,31-33} Figure 5 conceptualises this aspect of personhood that in effect makes discrete domains unlikely.

Seventy-two participants in our 2013 and 30 participants in our 2014 study emphasised that relationships are dependent on the presence of conscious function. In the hypothetical scenario of a mother’s loss of consciousness, it was found that the effects upon her relationship with her husband and children affected her personhood. Participants also acknowledged that features such as culture and age also influenced the manner personhood was conceived. Patient 13 (2013 study) stated: “Lisa’s loss of consciousness may not affect her relationship with her children if they are too young to understand.”

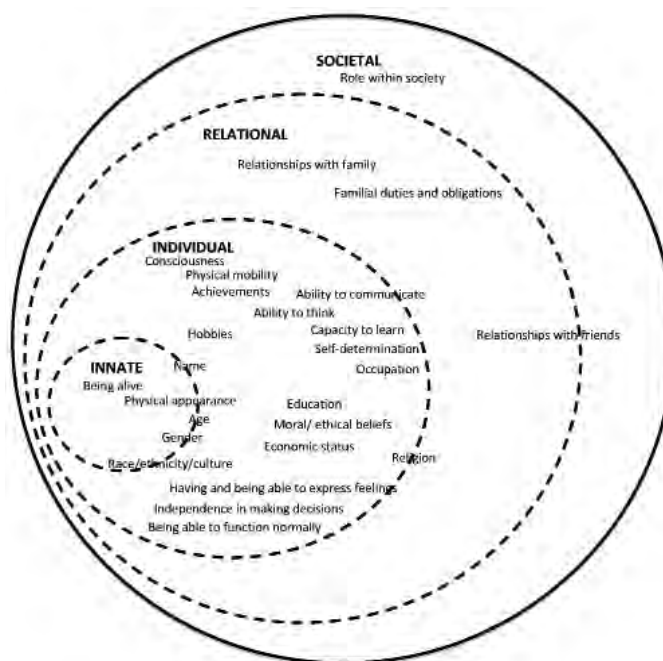


Fig. 5. Individual features overlap between domains, influence one another and are amenable to change.

In keeping with this theme of change, it emerged that personhood was perceived to be context dependent, transforming over time and with experiences particularly with illness experiences.^{7-9,31-33} “This “list” will always change and remold and reshape the person that I am” (Patient 49, 2013 study). All 140 interviewees in both studies acknowledged this aspect of change in personhood. The idea that certain features strengthen and grow in importance while others weaken was found to recur across transcripts. There was no identifiable pattern as to how personhood changes. Rather, this was depicted as a dynamic process.^{7-9,31-33} While some believed relational personhood to disintegrate as a result of unconsciousness, others saw it strengthening: “Lisa’s relationship with her family may paradoxically strengthen when she is sick... just like how my own experience with battling cancer has brought my family closer” (Patient 22, 2013 study).

The final theme identified builds upon the shifting features of the 4 domains highlighting the influence they have upon one another.^{7-9,31-33} Participants in both studies noted that weakening cognitive function for instance is seen to strengthen relational ties, whilst relational ties are found to be subject to societal and cultural oversight for instance in the form of filial piety. This is overlap of rings is illustrated by the porous rings delineating each domain.^{7-9,31-33} Indeed it was the presence of this notion of change in conceptions of personhood expressed in so many of participants in our initial study that precipitated our second study of changes in the conceptions of personhood throughout the course of a cancer sufferer’s disease journey.

Changing Conceptions

Twenty-six (65%) (Fig. 6) of our 40 participants reported a change in personhood when asked, “Do you think you have changed as a person over the course of your illness?” (Table 5) These changes affected patient’s innate individual, relational and societal personhood as revealed in Figure 7. This represents the first empirical evidence of changes in conceptions of personhood amongst terminally ill patients. Grossly, we note that change in conceptions of personhood tends to be global, affecting more than just the patient’s innate, individual, relational and societal personhood. Second, change in conceptions of personhood does not occur in a linear fashion or at specific points. Third, change in one dimension is affected by and causes evolution in the other dimensions of personhood. Fourth, the size of the change need not be congruent with the significance attributed to it by the patient. Fifth, significance of change is determined by the patient and is influenced by contextual and temporal factors. Sixth, change of the dimension of personhood need not necessarily be seen as an involution and can in fact be an expansion of a specific element of personhood. Seventh,

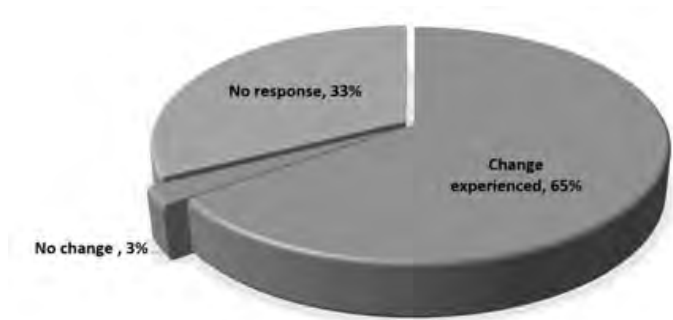


Fig. 6. Percentage of patients who experienced a change in personhood in the course of illness.

Table 5. Percentage of Respondents who Experienced Changes in the Individual, Relational and/or Societal Rings of Personhood

Any Change Experienced	Domain/Ring		
	Individual	Relational	Societal
Yes	65%	40%	17.5%
No	20%	38%	35%
Unsure/No response	15%	23%	48%

determination of the impact of change upon personhood can only be determined by a holistic review of the patient’s specific circumstances.

These findings are congruent with the conclusions drawn from our 2 studies and re-emphasise the need for patient-centred case specific holistic review.

Discussion

Analysis of the emergent themes reveals a dynamic more holistic concept of personhood than prevailing concepts of personhood suggest.^{3-9,11-26, 31-37} This data reveals that local conceptions of personhood do not pivot solely upon the presence of either social interactions nor conscious function negating fears that loss of either function would be tantamount to “social death”.^{8,9,11} Critically such a finding circumnavigates suggestions that an irreversible loss of consciousness could be deemed undifferentiable to biological death.^{8,9,11} Instead, personhood in these unconscious patients are seen to persevere through the presence of family and close relationships.^{7-9,31-33}

However, rather than perpetuate family-centric practises that stem from a “synergistic dualist” perspective of personhood of a patient simultaneously being a distinct autonomous individual and a member of a family who must protect and advance familial interests, the data suggests an equal importance placed on preserving one’s

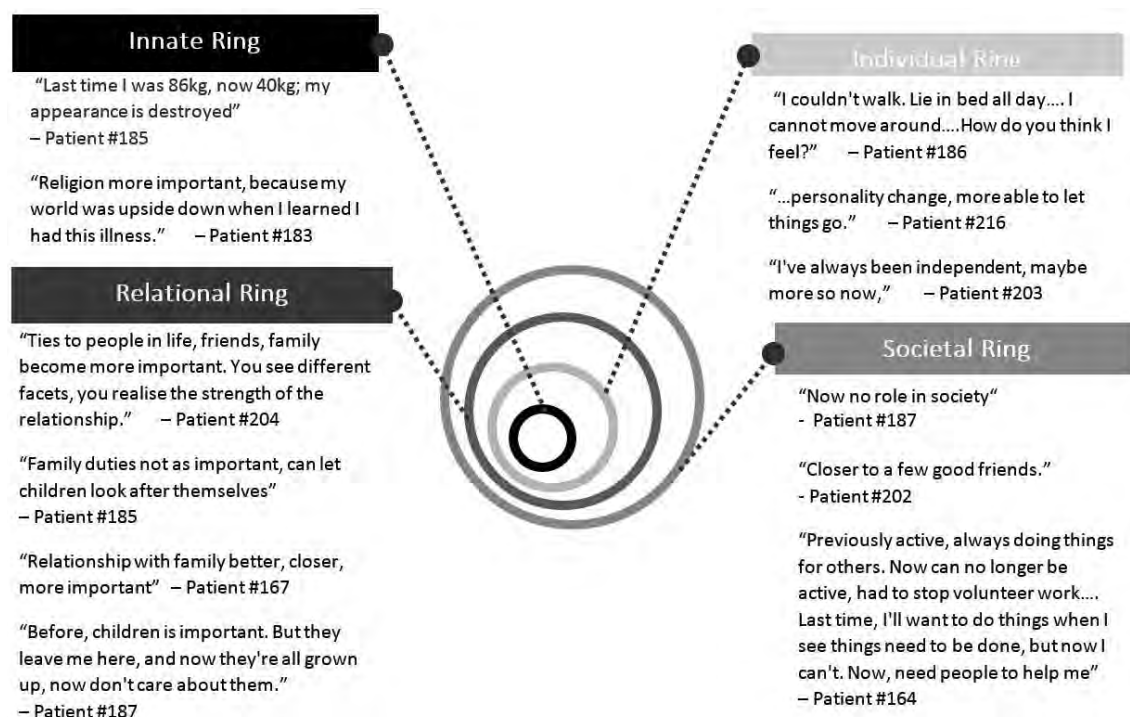


Fig. 7. Quotes from respondents on how their personhood has changed in the course of their illness.

unique identity and legacy that is not easily trumped by familial interests.^{7-9,31-33} These findings have far reaching implications to a society that is still immersed in family-centric determinations drawn from its long embrace of Confucian beliefs that has seen the usurping of autonomous choice, overriding of previously stated wishes in a now incompetent patient and the circumnavigation of direct patient involvement in care determination.³⁸⁻⁴³

Our results validate Krishna et al's Ring Theory of Personhood (Ring Theory) that proffers a clinically relevant, culturally appropriate perspective of personhood that will better inform health care professionals of how best to provide patient-centred care within their respective clinical, cultural and social setting.^{7-9,31-33} The Ring Theory can be seen to explain our findings as to the presence of the innate, individual, relational and societal rings (Fig. 8).

As with Krishna et al's findings, we note that our data supports the presence of an innate ring constructed on the belief that personhood is bestowed on living human beings "irrespective of their stage of development or deterioration" whilst the individual ring does represent conscious function and a continuing identity over time.⁸ The relational ring houses "those personal relationships that the patient considers important", whilst the outermost ring, the societal ring contains "the social, professional and familial ties that are not felt to warrant a place in the relational ring by the patient" and "the societal, professional

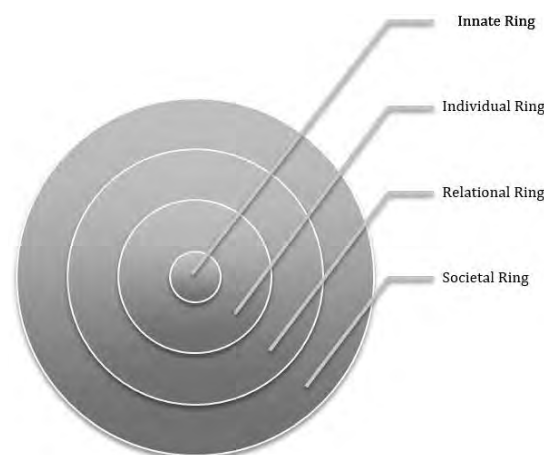


Fig. 8. The Ring Theory of Personhood

and familial expectations and standards that the patient and those within their various rings are subject to".^{7-9,31-33} The synergistic interactions between these 4 rings are clearly focused upon maintaining the integrity of individual identity in response to changing psychosocial, clinical and contextual circumstances.^{7-9,31-33}

Aside from affirming the Ring Theory, data from our 2014 study does provide the first insight into the manner that personhood changes throughout the course of an illness and calls for a holistic case by case review of each patient's

situation by a multi-professional team in keeping with the key practises of a palliative care approach, if patient-centred care is to be achieved.^{7-9,31-33,37} This blueprint to patient-centred care in oncology and palliative care settings reminds us that it is only through understanding, “what makes you, you” can health care professionals hope to provide patient-centred care that is consistent with the particular interests, values and wishes of patients, regarding them as persons and protect their welfare.

Limitations

We recognise the limitations of our study. Participants were recruited by convenient sampling and this may bias findings. This is particularly evident in the second study where there was a preponderance of males and patients who report no specific religious affiliations that could have potentially biased results. Future studies should be aimed at collecting data via varied methodologies to test the findings of this study. This includes purposive sampling to include a diversified group of participants from different ethnic, religious and language backgrounds, as well as random sampling to minimise selection or participation bias.

Our exclusion of non-English-speaking poses a particular drawback to the generalisability of these findings as does the small sample size of both studies. Future studies on the wider population particularly non-English-speaking patients are being planned as studies focused upon conceptions of personhood in various settings and stages of life.

We recognise that the results are not based on direct behavioural observations. Ethnographic studies on how patients behave and make medical decisions (with their personal values; family’s contributions etc.) may also play a role in validating the results of this study.

Conclusion

Our studies serve to re-emphasise the necessity for careful holistic appreciation of the needs of patients particularly in times of significant psychosocial and physical distress. Our data confirms longstanding suspicions that personhood and thus individual conceptions of dignity, moral rights and patient-centred goals evolve requiring an ongoing multidisciplinary team trained in holistic care to meet the holistic needs of patients in a practical manner that complies with societal expectations, professional standards and institutional guidelines. We hope this study will usher in the advent of more patient-centric care at the end-of-life.

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Epidemiology and Clinical Evolution of Liver Cirrhosis in Singapore

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Abstract

Introduction: Liver cirrhosis is a common cause of morbidity and mortality and an important burden on the healthcare system. There is limited literature on liver cirrhosis in Singapore. We aimed to describe the epidemiology and clinical characteristics of cirrhotic patients seen in an ambulatory setting in a tertiary referral centre. **Materials and Methods:** This is a retrospective observational cohort study of cirrhotic patients attending the ambulatory clinic of Singapore's largest tertiary hospital over 5 years. Cirrhosis was diagnosed on characteristic radiological features and/or histology. Aetiology of cirrhosis was determined by history, serology, biochemistry and/or histology. Data on decompensation events and death were retrieved from computerised hospital records. **Results:** The study included 564 patients with median follow-up of 85 months. Mean age was 60.9 ± 12.5 years with 63.8% males. Main aetiologies of cirrhosis were chronic hepatitis B (CHB) (63.3%), alcohol (11.2%), cryptogenic (9%) and chronic hepatitis C (CHC) (6.9%). CHB was the predominant aetiology in Chinese and Malays whereas alcohol was the main aetiology in Indians. CHC cirrhosis was more common in Malays than other races. Majority had compensated cirrhosis with 76.8%/18.3%/5%; Child-Pugh A/B/C respectively. Decompensation events occurred in 155 patients (27.5%) and 106 of them (18.8%) died. Diagnosis of cirrhosis via surveillance ultrasound was associated with improved 10-year survival. Age at diagnosis, portal vein thrombosis, Child-Pugh class and decompensation within 1 year of diagnosis were independent predictors of mortality. **Conclusion:** CHB is the primary cause of liver cirrhosis in Singapore. The major aetiologies of cirrhosis vary amongst the different ethnic groups. Cirrhotics with advanced age, portal vein thrombosis, poorer liver function and early decompensation have a higher mortality risk.

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Key words: Aetiology, Ambulatory, Clinical characteristics, Ethnic group, Mortality

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Introduction: Liver cirrhosis is a common cause of morbidity and mortality and an important burden on the healthcare system. There is limited literature on liver cirrhosis in Singapore. We aimed to describe the epidemiology and clinical characteristics of cirrhotic patients seen in an ambulatory setting in a tertiary referral centre. **Materials and Methods:** This is a retrospective observational cohort study of cirrhotic patients attending the ambulatory clinic of Singapore's largest tertiary hospital over 5 years. Cirrhosis was diagnosed on characteristic radiological features and/or histology. Aetiology of cirrhosis was determined by history, serology, biochemistry and/or histology. Data on decompensation events and death were retrieved from computerised hospital records. **Results:** The study included 564 patients with median follow-up of 85 months. Mean age was 60.9 ± 12.5 years with 63.8% males. Main aetiologies of cirrhosis were chronic hepatitis B (CHB) (63.3%), alcohol (11.2%), cryptogenic (9%) and chronic hepatitis C (CHC) (6.9%). CHB was the predominant aetiology in Chinese and Malays whereas alcohol was the main aetiology in Indians. CHC cirrhosis was more common in Malays than other races. Majority had compensated cirrhosis with 76.8%/18.3%/5%; Child-Pugh A/B/C respectively. Decompensation events occurred in 155 patients (27.5%) and 106 of them (18.8%) died. Diagnosis of cirrhosis via surveillance ultrasound was associated with improved 10-year survival. Age at diagnosis, portal vein thrombosis, Child-Pugh class and decompensation within 1 year of diagnosis were independent predictors of mortality. **Conclusion:** CHB is the primary cause of liver cirrhosis in Singapore. The major aetiologies of cirrhosis vary amongst the different ethnic groups. Cirrhotics with advanced age, portal vein thrombosis, poorer liver function and early decompensation have a higher mortality risk.

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Key words: Aetiology, Ambulatory, Clinical characteristics, Ethnic group, Mortality

Introduction

Cirrhosis is the common end result of chronic damage to liver parenchyma caused by a variety of liver diseases. It results in replacement of liver tissue by fibrotic scar tissue and regenerating nodules, leading to progressive liver dysfunction and clinical complications such as portal hypertension, hepatocellular carcinoma (HCC), liver failure and death. Cirrhosis is a major cause of mortality and morbidity worldwide and represents an important burden on healthcare resources.¹

The epidemiology of liver cirrhosis varies with geographical location and socioeconomic conditions. The major aetiologies of cirrhosis in Western countries are

chronic hepatitis C and alcoholic liver disease.²⁻⁴ In the East, there are variations in epidemiology of liver cirrhosis within different Asian countries. Chronic hepatitis C is the prevalent cause of liver cirrhosis in Japan, whereas chronic hepatitis B is the main aetiology of cirrhosis in China, Korea and parts of Southeast Asia.^{5,6} In Nepal and Thailand, alcohol-related cirrhosis is the predominant aetiology.^{7,8}

To date, there is little published data on the epidemiology of liver cirrhosis in Singapore. Most were case series involving small numbers of patients and were published more than 25 years ago.⁹⁻¹³ There is an important need to fill the knowledge gap with regards to the current epidemiology of liver cirrhosis in Singapore. The aim of this study was

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to describe the aetiology and clinical evolution of liver cirrhosis in a cohort of multi-ethnic Asian patients attending an ambulatory liver clinic at a large tertiary care hospital in Singapore.

Materials and Methods

We performed a retrospective observational cohort study of cirrhotic patients attending the ambulatory clinics of the Singapore General Hospital's Department of Gastroenterology and Hepatology between September 2006 and August 2011. Cases of liver cirrhosis were identified from the department's outpatient cirrhosis registry. Cirrhosis was diagnosed by radiology (presence of coarse echoes and nodular outline of the liver on either ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) or by histology. The date of diagnosis of liver cirrhosis was based on the earliest record of radiological or histological evidence of liver cirrhosis. Patients' clinical and laboratory data were retrieved from computerised hospital records. The study was approved by the hospital's centralised institutional review board.

Aetiology of cirrhosis was determined by the primary physician and was based on clinical history, serology, biochemistry and/or histology. Cirrhosis was classified as due to chronic hepatitis B (CHB) or chronic hepatitis C (CHC) based on the presence of hepatitis B surface antigen (HBsAg) or anti-HCV IgG, respectively. Alcoholic liver cirrhosis was diagnosed if the patient consumed more than 20 units of alcohol per week for males or 14 units per week for females. Non-alcoholic fatty liver disease (NAFLD) was diagnosed based on presence of hepatic steatosis on imaging or histology, in the absence of significant alcohol consumption and co-existing causes for chronic liver disease. Primary biliary cirrhosis (PBC) was diagnosed based on positive anti-mitochondrial antibodies or corroborative histology. Autoimmune hepatitis (AIH) was diagnosed based on the presence of anti-liver antibodies, raised globulin fraction and/or histological evidence suggesting AIH. Wilson's disease was diagnosed based on a combination of clinical features, low serum caeruloplasmin, positive Kayser-Fleischer rings, elevated 24-hour urinary copper and histology, where available. Patients were considered to have cryptogenic liver cirrhosis when all the above tests were negative, in the absence of significant alcohol intake and the absence of radiological features of hepatic steatosis. Dual aetiologies were considered when there was equal contribution of 2 aetiological factors. Otherwise, the predominant cause of liver cirrhosis was recorded based on the definitions above.

Compensated cirrhotics were followed up every 6 months and decompensated cirrhotics were reviewed every 3 months

or less in the ambulatory clinic. During each clinic visit, patients were evaluated for signs of decompensation and development of new complications. Abdominal ultrasound and alfa-fetoprotein (AFP) were performed every 6 months for HCC surveillance. Outcome parameters recorded were development of decompensation events (jaundice, ascites, spontaneous bacterial peritonitis (SBP), variceal bleeding, hepatic encephalopathy), HCC and death. Mortality data were retrieved from hospital records and was censored on 31 August 2011. Deaths from complications of cirrhosis, progressive liver failure and HCC were considered to be liver-related. Patients who had a record of a recent clinic attendance within 6 months of the census date were deemed to be alive. Patients who had no record of a recent clinic attendance within 1 year of the census date and no record of death were deemed to be lost to follow-up and were excluded from the survival analysis. We were unable to determine if these patients were still alive or may have passed away outside of our hospital.

Statistical analysis was performed using SPSS version 19 (Chicago, USA). Continuous variables were compared between groups using unpaired t-test and Mann-Whitney U test. Categorical variables were compared using chi-square test (or Fisher's exact test where applicable). Survival from time of diagnosis of cirrhosis was analysed using the Kaplan-Meier method and compared by the log-rank method for variables of interest. Logistic regression analysis was performed to identify factors associated with mortality. Multivariate analysis was performed using Cox's proportional hazard regression model to evaluate for independent factors predictive for patient survival. Missing data was addressed by using the population means. A *P* level of less than 0.05 was taken to be significant.

Results

Our study included 564 patients with a median follow-up period of 85 months (range, 3 to 273). The baseline characteristics of the study cohort are described in Table 1. Majority of the subjects were Chinese (89.7%) and 76.8% had Child-Pugh A cirrhosis.

Aetiology of Liver Cirrhosis

CHB was the most common cause of liver cirrhosis in Singapore, accounting for almost two-thirds of the entire cohort (63.3%). This was followed by alcohol (11.2%), cryptogenic (9%) and CHC (6.9%).

Comorbid Conditions

Hypertension was present in 42.9%, diabetes mellitus in 34.6% and hyperlipidaemia in 22.7% of the cirrhotic cohort

Table 1. Baseline Characteristics of the Study Cohort (n = 564)

Variable		Mean $\pm$ SD/n (%)
Age	Mean age (years)	60.9 $\pm$ 12.5
Gender	Male	360 (63.8%)
Race	Chinese	506 (89.7%)
	Malay	27 (4.8%)
	Indian	25 (4.4%)
	Others	6 (1.1%)
Aetiology	Chronic hepatitis B	357 (63.3%)
	Alcohol	63 (11.2%)
	Cryptogenic	51 (9%)
	Chronic hepatitis C	39 (6.9%)
	Primary biliary cirrhosis	21 (3.7%)
	Non-alcoholic fatty liver disease	10 (1.8%)
	Autoimmune hepatitis	9 (1.6%)
	Wilson disease	2 (0.4%)
	Hepatitis B + hepatitis C	4 (0.7%)
	Hepatitis B + alcohol	2 (0.4%)
	Hepatitis C + alcohol	1 (0.2%)
	Others	5 (0.9%)
Comorbidities	Diabetes mellitus	195 (34.6%)
	Hypertension	242 (42.9%)
	Hyperlipidaemia	128 (22.7%)
	Coronary artery disease	68 (12.1%)
	Renal impairment	94 (16.7%)
	Smoking	65 (11.5%)
Laboratory tests	Albumin (G/L)	35.3 $\pm$ 6.8
	Bilirubin (μ mol/L)	28.1 $\pm$ 39.2
	Alkaline phosphatase, ALP (U/L)	106.7 $\pm$ 73.3
	Alanine transaminase, ALT (U/L)	69.6 $\pm$ 152.9
	Aspartate transaminase, AST (U/L)	72.3 $\pm$ 137.1
	Gamma glutaryltransferase, GGT (U/L)	126.7 $\pm$ 165.4
	Prothrombin time, PT (seconds)	12.6 $\pm$ 2.3
	International normalised ratio, INR	1.2 $\pm$ 0.3
	Haemoglobin, Hb (g/dL)	12.8 $\pm$ 2.2
	Platelets ($\times 10^9$ /L)	150 $\pm$ 75
Child-Pugh class	Alfafetoprotein, AFP (μ g/L)	294 $\pm$ 3761
	A/B/C	433 (76.8%)
		103 (18.3%)
		28 (5%)

(Table 1). Diabetes, hypertension and hyperlipidaemia were significantly more common in patients with cryptogenic liver cirrhosis and NAFLD-related cirrhosis compared to those with CHB, CHC and alcoholic cirrhosis. There was

no significant difference in the frequency of coronary artery disease amongst the different aetiologies. Renal impairment was more common amongst patients with CHC cirrhosis. Smoking was significantly more common in patients with alcoholic cirrhosis (data not shown).

Ethnic Differences in Aetiology of Liver Cirrhosis

The aetiologies of liver cirrhosis were different between ethnic groups (Table 2). In Chinese, CHB was the commonest aetiology of cirrhosis, followed by alcohol and cryptogenic cirrhosis. In Malays, CHB was likewise the most common aetiology, followed by CHC and cryptogenic cirrhosis. Among Indians, however, alcohol was the predominant cause of liver cirrhosis, followed by cryptogenic cirrhosis and CHB. We observed a high rate of CHC cirrhosis in Malays compared to Chinese and Indians ($P < 0.001$ for both comparisons). We also observed that the prevalence of cryptogenic cirrhosis was higher in Malays and Indians compared to Chinese. There were no significant differences in the prevalence of PBC and NAFLD-related cirrhosis amongst the different ethnic groups.

Clinical Presentation

Eighty-three percent of the study cohort had compensated disease at diagnosis (Table 3). Amongst these, the most common mode of diagnosis of cirrhosis was via surveillance ultrasound in patients on regular follow-up for chronic viral hepatitis (CHB and CHC). Conversely, compensated patients with alcoholic cirrhosis, cryptogenic cirrhosis and NAFLD were more commonly diagnosed through evaluation of abnormal liver function tests, low platelet counts or incidentally on imaging for unrelated indications (Fig. 1).

A small proportion (17%) of this ambulatory cohort of cirrhotics presented with decompensated cirrhosis (Table 3). Of these, the most common clinical presentations were elevated bilirubin and ascites. A greater proportion of alcoholic cirrhotics presented with decompensated disease at initial diagnosis compared to other aetiologies of cirrhosis. They were more frequently jaundiced and had a higher incidence of ascites and variceal bleeding. HCC was diagnosed in 52 patients (9.2%) at the time of diagnosis of cirrhosis and was more common in CHB compared to other aetiologies.

Development of Decompensation during Follow-up

A total of 155 patients (27.5%) developed clinical decompensation during the follow-up period. Of those who presented with compensated cirrhosis at diagnosis, 102 patients (21.8%) experienced their first decompensation

Table 2. Comparison of Major Aetiologies of Liver Cirrhosis Based on Ethnic Groups

Aetiology	Chinese (n = 506)	Malays (n = 27)	Indians (n = 25)	Others (n = 6)
Chronic hepatitis B (CHB)	336 (66.4%)	12 (44.4%)	4 (16%)	5 (1.4%)
Alcohol	52 (10.3%)	0 (0%)	10 (40%)	1 (1.6%)
Cryptogenic	38 (7.5%)	6 (22.2%)	7 (28%)	0
Chronic hepatitis C (CHC)	33 (6.5%)	6 (22.2%)	0 (0%)	0
Primary biliary cirrhosis (PBC)	20 (4%)	0 (0%)	1 (4%)	0
Non-alcoholic fatty liver disease	7 (1.4%)	2 (7.4%)	1 (4%)	0

Table 3. Clinical Presentation of Cirrhosis Based on Different Aetiologies of Liver Disease

	Overall (n = 564)	HBV (n = 357)	HCV (n = 39)	Alcohol (n = 63)	NAFLD (n = 10)	Crypt (n = 51)
Compensated cirrhosis	468 (83%)	319 (89.4%)	30 (76.9%)	34 (54%)	8 (80%)	45 (88.2%)
Abnormal liver function tests	77 (13.7%)	24 (6.7%)	4 (10.3%)	9 (14.3%)	3 (30%)	17 (33.3%)
Thrombocytopenia	26 (4.6%)	10 (2.8%)	1 (2.6%)	5 (7.9%)	1 (10%)	8 (15.7%)
Incidental diagnosis on imaging	81 (14.4%)	41 (11.5%)	6 (15.4%)	12 (19%)	3 (30%)	16 (31.4%)
Screening for chronic liver disease	283 (50.2%)	244 (68.3%)	19 (48.7%)	8 (12.7%)	1 (10%)	3 (5.9%)
Decompensated cirrhosis	96 (17%)	38 (10.6%)	9 (23.1%)	29 (46%)	2 (20%)	6 (11.8%)
Elevated bilirubin	55 (9.8%)	19 (5.3%)	4 (10.3%)	23 (36.5%)	1 (10%)	0 (0%)
Variceal bleeding	27 (4.8%)	7 (2%)	3 (7.7%)	8 (12.7%)	1 (10%)	4 (7.8%)
Ascites	39 (6.9%)	22 (6.2%)	2 (5.1%)	9 (14.3%)	0 (0%)	3 (5.9%)
Hepatic encephalopathy	3 (0.5%)	1 (0.3%)	0 (0%)	1 (1.6%)	1 (10%)	0 (0%)
Hepatocellular carcinoma	52 (9.2%)	43 (12%)	2 (5.1%)	2 (3.2%)	0 (0%)	4 (7.8%)

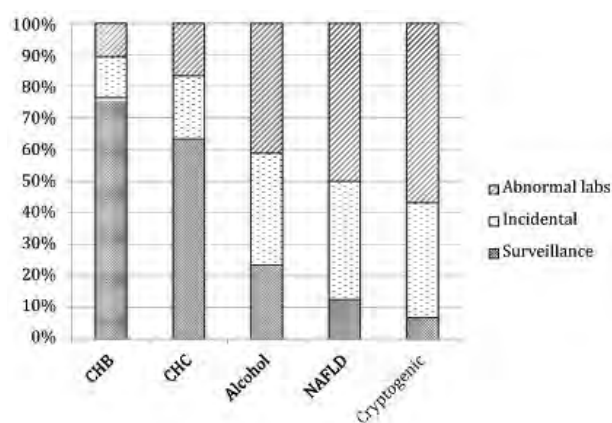


Fig. 1. Graph showing the mode of diagnosis in patients with compensated cirrhosis (n = 468).

event during follow-up. In the group who presented with decompensated cirrhosis at diagnosis, 53/96 (55.2%) experienced a further decompensation event. The most common decompensation events were development of ascites (16.8%) and hepatic encephalopathy (14.4%). Variceal bleeding (9.8%), jaundice (6.7%) and SBP (4.6%) occurred less often. Median time to the first decompensation event was 32 months (range, 0 to 244), and was significantly shorter in Child-Pugh C patients (6 months) versus Child-Pugh B (17 months) and Child-Pugh A (43 months), $P < 0.001$ by log-rank comparison. There was no significant difference in the time to first decompensation based on different races or aetiologies of cirrhosis.

Survival Data

A total of 106 cirrhotic patients died (18.8%) over a median follow-up period of 85 months (range, 3 to 273). The cause of death was related to liver cirrhosis and/or HCC in 74.5%. Majority of the liver-related death were due to advanced HCC and hepatic decompensation complicated by sepsis. Patients who died from non-liver related causes

of death were excluded from the survival analysis.

A total of 388 patients (68.8%) remained compliant to follow-up and attended the ambulatory clinic within 6 months of the census date. A further 70 patients (12.4%) were deemed to be lost to follow-up as they had not visited the hospital in the 1 year prior to the census date and had no record of death. These patients were excluded from the survival analysis. In a comparative analysis of baseline characteristics of patients who were lost to follow-up versus those who completed the study, the former had a significantly higher proportion of alcoholic cirrhosis and more advanced cirrhosis.

The median survival of the cohort was 17.5 ± 5 years, with a 5-year survival rate of 90% and a 10-year survival rate of 73%. There was no difference in survival based on gender or ethnic group, but we observed significant differences in survival based on aetiology. Patients with alcoholic cirrhosis had significantly poorer survival compared to other aetiologies of cirrhosis with a median survival of 11.1 years versus 17.5 years respectively, $P = 0.005$ by log-rank comparison (Fig. 2).

The 10-year survival rate of cirrhotics diagnosed through surveillance ultrasound was significantly better compared to those who presented with abnormal laboratory findings such as abnormal liver function and low platelet count (Fig. 3). Cirrhotic patients with diabetes mellitus had significantly reduced survival compared to non-diabetics (OR 2.32, 95% CI, 1.53 to 3.52). A similar reduced survival trend was seen in cirrhotic patients who actively smoked (OR 2.62, 95% CI, 1.58 to 4.35) (Table 4).

Mean survival of Child-Pugh A cirrhotics (16.5 ± 0.9 years) was significantly better compared to Child-Pugh B (9.8 ± 0.6 years) and Child-Pugh C (8.6 ± 0.8 years) patients. There was no significant difference in the survival between Child-Pugh B and C patients, even after excluding 11 patients who underwent liver transplantation. Patients with compensated cirrhosis had a 10-year survival rate of 82% compared to 59% in those with decompensated disease at diagnosis (Fig. 4).

On multivariate analysis, only age at diagnosis of cirrhosis, presence of portal vein thrombosis, Child-Pugh class and decompensation within 1 year of diagnosis were identified as independent predictors for mortality (Table 4).

Discussion

Our study is the first to provide comprehensive data on the epidemiology and clinical evolution of liver cirrhosis in Singapore. The main aetiology of liver cirrhosis in Singapore is CHB infection, which accounted for 63%

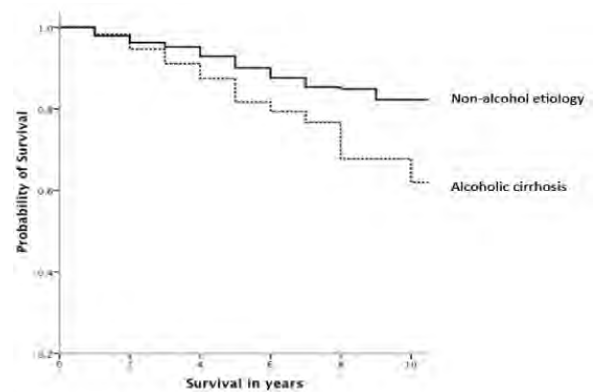


Fig. 2. Graph showing the Kaplan-Meier analysis of survival between patients with alcoholic cirrhosis (dotted line) and other aetiologies of liver cirrhosis (solid line), adjusted for age and race.

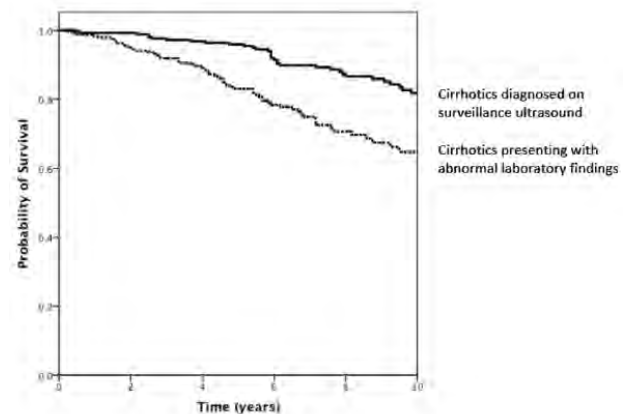


Fig. 3. Graph showing the comparison of 10-year survival between compensated cirrhotics diagnosed through surveillance (solid line) versus those presenting with abnormal laboratory findings (dotted line), $P < 0.001$ by log-rank comparison.

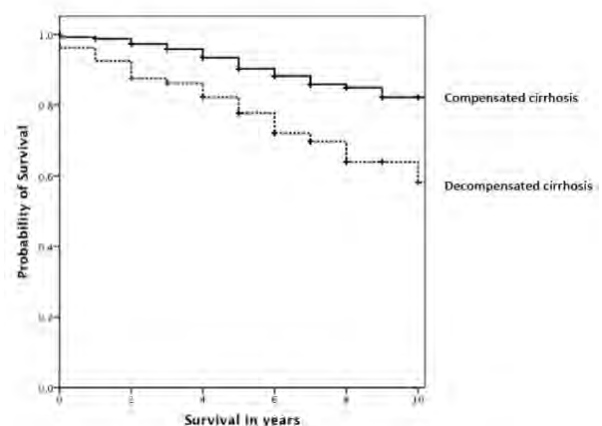


Fig. 4. Graph showing Kaplan-Meier analysis of 10-year survival between patients diagnosed with compensated cirrhosis (solid line) and decompensated cirrhosis (dotted line), $P < 0.001$ by log-rank comparison.

Table 4. Univariate and Multivariate Cox Regression Analysis of Factors Associated with Survival in Cirrhotic Patients

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.04 (1.02 – 1.06)	<0.001	1.04 (1.02 – 1.06)	0.001
Alcohol aetiology	2.34 (1.40 – 3.90)	0.001	-	NS
CHB aetiology	0.53 (0.35 – 0.81)	0.003	-	NS
Diabetes mellitus	2.32 (1.53 – 3.52)	<0.001	-	NS
Active smoking	2.62 (1.58 – 4.35)	<0.001	-	NS
ALT	0.99 (0.99 – 1.00)	0.048	-	NS
Platelet count	0.99 (0.99 – 1.00)	0.011	-	NS
Portal vein thrombosis	4.51 (1.81 – 11.19)	0.001	10.94 (3.62 – 33.06)	<0.001
HCC at diagnosis of cirrhosis	2.69 (1.52 – 4.77)	0.001	-	NS
Child-Pugh A vs Child-Pugh B/C	0.33 (0.22 – 0.51)	<0.001	0.41 (0.21 – 0.78)	0.006
Decompensated at presentation	2.39 (1.49 – 3.83)	<0.001	-	NS
Cirrhosis diagnosed on surveillance	0.55 (0.36 – 0.84)	0.006	-	NS
Decompensation within 1 year	6.77 (4.37 – 10.48)	<0.001	4.60 (2.74 – 7.74)	<0.001
New HCC on follow-up	2.39 (1.57 – 3.64)	<0.001	-	NS

ALT: Alanine transaminase; CHB: Chronic hepatitis B; HCC: Hepatocellular carcinoma

of cases identified from the largest tertiary referral centre in the country. The high proportion of CHB cirrhosis reflects the endemicity of CHB in the region. In Singapore, approximately 4% to 6% of the population is chronically infected with hepatitis B.¹⁴ However, the hepatitis B carrier rate in adults has steadily declined from 9.1% in 1975 to 4.1% in 1999 and 2.7% in 2005 as a result of a compulsory nationwide hepatitis B virus (HBV) immunisation programme.¹⁵ Nonetheless, the prevalence of CHB-related liver cirrhosis remains a significant challenge as a significant proportion of the adult hepatitis B carriers diagnosed in the 1970s would have developed cirrhosis by now.

Our data are similar to that reported by neighbouring Asian countries such as Hong Kong, Taiwan and Malaysia where hepatitis B is the predominant aetiology of liver cirrhosis.^{16–18} The epidemiological pattern of liver cirrhosis is likely to be related to the ethnic profile of the various Asian populations. Countries in which a substantial proportion of the populations comprise of immigrants originating from Southern China have a high CHB prevalence.¹² The results of our study thus contribute towards the growing body of data on the epidemiology of liver cirrhosis in Asia. Information regarding aetiology of liver cirrhosis in different countries and different populations is important for optimal distribution of national healthcare resources.¹⁹

We observed significant differences in the predominant aetiology of liver cirrhosis amongst different ethnic groups. Singapore is a multi-ethnic country with 74.2% Chinese, 13.3% Malays and 9.2% Indians, based on the latest national population statistics. We observed that the ethnic

distribution in the cirrhotic cohort was different from that of the general population, with a higher proportion of Chinese (89.7% vs 74.2%) and a corresponding lower proportion of Malays (4.8% vs 13.4%) and Indians (4.4% vs 9.2%). The prevalence of CHB cirrhosis was significantly higher in Chinese whereas alcoholic cirrhosis was significantly higher in Indians. CHC cirrhosis was more common in Malays compared to the other ethnic groups.

Alcoholic liver cirrhosis was the second commonest aetiology of cirrhosis in our study, accounting for 11% of the cohort. While significantly lower than rates in the West, this rate is comparable to data from neighbouring Asian populations.¹⁸ In Singapore, alcoholic cirrhosis was most prevalent among Indians, in keeping with data from the Singapore National Health Survey on trends in alcohol consumption.²⁰ The Muslim religion forbids the consumption of alcohol, thus explaining the absence of alcoholic cirrhosis amongst Malays. The high incidence of CHC cirrhosis amongst the Malay population may be related to a higher incidence of intravenous drug abuse among young Malay males in Singapore.²¹

Our findings on the racial distribution of specific aetiologies of liver cirrhosis validate those published by Qua et al in a similar multiracial Asian population.¹⁸ However, while theirs was a point-in-time prevalence study, our study provides long-term follow-up data on the clinical evolution and survival of the different ethnic and aetiological cohorts. Our study confirms that there is no significant difference in the rate of decompensation or overall survival amongst the different ethnic groups. However, the underlying aetiology

of cirrhosis appears to affect long-term outcome. We showed that patients with alcoholic cirrhosis have poorer survival compared to cirrhosis from other aetiologies. On multivariate analysis however, alcohol aetiology was not found to be an independent predictor for mortality in cirrhosis. The poor outcome in alcoholic cirrhosis is related to delayed presentation, as shown in our study by a significantly higher rate of decompensation, large esophageal varices and poorer liver function at diagnosis.

The 5-year survival rate of 90% in our study cohort exceeds the rate reported in similar studies on the natural history of cirrhosis.^{22,23} The favourable survival profile is likely because our study focused on an ambulatory cohort of cirrhotics, in which a large proportion had compensated, Child-Pugh A cirrhosis. Half the cohort was diagnosed via surveillance ultrasound during regular follow-up for chronic viral hepatitis. Secondly, we used ultrasound features of echogenicity and surface nodularity to diagnose cirrhosis in our study. Transient elastography was not routinely available for confirmation of cirrhosis at the time and liver biopsy for histological confirmation of cirrhosis was not routinely performed. Given that the accuracy of ultrasound for diagnosis of cirrhosis is only 65%,²⁴ it is plausible that a proportion of the cohort may not have had true cirrhosis but advanced fibrosis. This may explain the longer than expected survival rates observed in our study. However, our observational study is based on routine clinical practice, in which ultrasound is routinely used for diagnosis of cirrhosis. We thus believe that the results reflect the true, “on-the-ground” survival rates seen in patients diagnosed with liver cirrhosis via ultrasound. Our study highlights that the use of ultrasound to diagnose cirrhosis is not ideal due to poor specificity. When the clinical pretest probability of cirrhosis is low, we recommend that ultrasound findings of cirrhosis be confirmed with the use of transient elastography before a diagnosis of cirrhosis is conclusively made. In situations of ambiguity, liver biopsy should be performed to make a confirmatory diagnosis of cirrhosis.

We observed a poorer survival in cirrhotic patients with diabetes mellitus and in those who actively smoked. Both factors have been shown to be associated with higher risk of progressive fibrosis and development of HCC.²⁵⁻²⁹ Screening of cirrhotics with oral glucose tolerance test has been shown to predict prognosis of cirrhotics.³⁰ However, neither factor was an independent predictor of mortality on multivariate analysis.

We acknowledge that the retrospective nature of our study is a limitation to the validity of the observations made. However, approximately 70% of the study cohort remained compliant to follow-up through to the end of the study period. Hence, despite being identified retrospectively, the high compliance to follow-up allowed us to collect

comprehensive data on the clinical evolution of the study cohort. Secondly, this study was designed as an observational study of a cohort of cirrhotics identified from an ambulatory clinic. Expectedly, a majority of the patients included in the cohort had early-compensated cirrhosis and were diagnosed on surveillance. As such, the conclusions derived from this study are not applicable to advanced cirrhotics who are inpatients or too ill to attend clinics. Thirdly, the prevalence of non-alcoholic steatohepatitis (NASH) is likely to be under-reported in this study. A large number of patients were diagnosed more than decade ago at a time when the role of NASH in liver cirrhosis was not routinely recognised. The observation that concomitant diabetes mellitus, hypertension and hyperlipidaemia were significantly more common in the cryptogenic group suggests that some of these patients were likely NASH patients who were misclassified as cryptogenic cirrhosis.

Conclusion

In conclusion, CHB is the major aetiology of liver cirrhosis in Singapore, accounting for almost two-thirds of the cirrhotic population. The prevalence of specific aetiologies of cirrhosis varies amongst the various ethnic groups, reflecting different exposures to cirrhosis risk factors due to inherent hereditary, socioeconomic and cultural differences. Overall survival in this ambulatory cohort of cirrhotics is excellent, owing to early diagnosis of compensated Child-Pugh A patients through active surveillance. Advanced age, Child-Pugh class, presence of portal vein thrombosis and development of decompensation within 1 year of diagnosis are independent predictors of mortality in patients with liver cirrhosis.

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Five Patients with Medullary Thyroid Carcinoma Presenting as Asymptomatic Elevation of Carcinoembryonic Antigen Level

Dear Editor,

Early detection of malignancies is not easy. Few methods of health screening have been proven to be of value. The use of carcinoembryonic antigen (CEA) in health screening has never been proven to result in early detection of cancers¹ but requests to test tumour markers continue to be made.

A raised CEA is not an uncommon finding and there are no established protocols on how to approach this issue. We report 5 cases where a raised CEA was the initial finding that later led to the diagnosis of medullary thyroid carcinoma (MTC).

Summary of the Five Patients

The patients (3 males and 2 females) ranged in age from 36 to 52 years at the time of presentation (Table 1). All had presented for a general health screen, which revealed no significant pathology apart from a raised CEA. None were smokers. The time from presentation to diagnosis of MTC ranged from 19 months (Patients 1 and 3) to 8 years (Patients 2 and 4) and 9 years (Patient 5).

The CEA level at presentation ranged from 5.5 to 58 ug/L. All the patients were referred for endoscopy within 1 month except for 1 (Patient 5, whose CEA was only 5.5 ug/L). This last patient had a mild elevation of CEA and the CEA even returned to normal before rising again gradually over a period of 3 years. After 3 years, Patient 5's CEA rose to 9.98 ug/L and she was referred for endoscopy.

All the patients (except Patient 1) had a repeat endoscopy as their CEA remained elevated without any clear cause established. Patients 2 and 4 had many endoscopic procedures performed yearly over a period of 8 years (until the diagnosis of MTC was made).

Three patients had a computed tomography (CT) scan of the thorax and abdomen within 3 months of presentation and in 1 patient (Patient 1), a thyroid nodule was detected. This was further investigated but the needle biopsy of the thyroid nodule was reported as a colloid nodule. Patient 3 had a second CT scan 17 months after presentation and this detected thyroid nodule (which was biopsied) was found to be positive for MTC.

Table 1. Summary of Patient Characteristics and Investigation Results

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Male	Male	Female	Male	Female
Age at presentation	52	38	48	44	36
Smoker	Previous	Previous	No	No	No
Initial CEA (ug/L)	58	Not known	6.5	38	5.5
Colonoscopy, time from presentation	Yes, 1 month	Yes, 1 month	Yes, 1 month	Yes, 1 month	Yes, 3 years
Repeat colonoscopy, time from presentation	No	Yes, 1 – 2 yearly after presentation	Yes, 1 year	Yes, Once yearly after presentation	Yes, 5 years
CT scan, time from presentation, thyroid nodule detected	Yes, 3 months, Yes	No	Yes, 1 month, No	No	Yes, 1 month, No
Repeat CT scan, time from presentation, thyroid nodule detected	No	No	Yes, 17 months, Yes	No	No
PET scan, time from presentation, thyroid nodule detected	Yes, 4 months, Yes SUV 2.5	Yes, 4 years, Yes SUV 2.8	No	Yes, 6 years, No	Yes, 3 years, Yes SUV 1.8
Repeat PET scan, time from presentation, thyroid nodule detected	No	Yes, 8 years, Yes SUV 3.2	No	Yes, 8 years, Yes SUV 3.5	Yes, 9 years, Yes SUV 2.8
Thyroid FNAC	Yes, benign	Yes, medullary carcinoma of thyroid	Yes, medullary carcinoma of thyroid	Yes, atypical cells	No
Time to final diagnosis	19 months	8 years	19 months	8 years	9 years
Size of tumour	2 cm	2.8 cm	1 cm	2 cm	1.5 cm

CEA: Carcinoembryonic antigen; CT: Computerised tomography; FNAC: Fine-needle aspiration cytology; PET: Positron emission tomography

Four patients (except Patient 3) had a positron emission tomography (PET) scan. In 3 of these patients, a thyroid nodule with focal uptake of fluorodeoxyglucose (FDG) was detected but SUV was in the low or equivocal range. Only Patient 1 proceeded to surgery after PET scan. The other 2 (Patients 2 and 5) continued to be observed and only when a second PET scan noted an increase in SUV of the thyroid nodule was biopsy or surgery performed. Patient 4 had thyroid nodule noted only in the second PET scan and this led to biopsy and later surgery of the thyroid nodule.

At the diagnosis of MTC, the size of tumour ranged from 1 cm to 2.8 cm. All the patients were negative for RET oncogene mutation. CEA levels returned to normal for 4 out of the 5 patients. Patient 5 had a persistently elevated CEA and is being further evaluated for malignancy.

Discussion

Carcinoma of the colon is a well-known cause for elevation of the CEA and invariably all these patients are referred for endoscopy. Lim YK in 2009, reported that out of 217 asymptomatic patients with raised CEA, a total of 20 patients were found to have primary and 8 to have metastatic cancers.² Of the 20 cases with primary cancers, only 11 were colonic cancers. The level of CEA was not found to correlate with the likelihood of detecting a malignancy in that study.

CEA can be raised in many malignancies apart from colonic cancer and also in benign tumours as well as other conditions like infections. CEA is often raised in smokers up to 2 times the upper normal range.³

The detection of incidental thyroid nodule on PET scan is not uncommon and estimated by Bertagna to be 2.46% of which malignancy occurred in 34.6% of those with focal hypermetabolic activity.⁴

Nodules that have diffused hypermetabolic activity were less likely to have malignancy (4.4%) in comparison with nodules that had focal hypermetabolic activity (34.8%).⁵ Soelberg further reported that the SUV max was 4.8 for benign nodules as compared to 6.9 for malignant ones. The doctors investigating Patients 2 and 5 may have considered the nodule an incidental benign nodule and did not investigate further. Subsequently, Patient 2 had a repeat PET scan which showed that the nodule had increased in size and SUV max rose to 3.5. SUV max does not discriminate well between benign and malignant thyroid nodules and with hindsight thyroid biopsy should be done when there is a thyroid nodule and elevated CEA.

Our cases demonstrated that although there was a difference between malignant SUV max and benign SUV max (e.g. 7.04 versus 3.85 in Boeckman's study),⁶ it is not sufficient to depend on this method to know whether

a nodule is malignant. The thyroid nodules discovered on PET scan with focal uptake in Patients 2 and 5 should have been evaluated by ultrasound and fine needle aspiration.

Conclusion

The sequence of investigations and the time frame of investigations of these 5 patients demonstrate a high degree of variation. Different doctors appear to investigate this problem differently. All considered endoscopy within a short time of presentation but had different thresholds to ordering CT or PET scans.

In a patient with persistently elevated CEA, after negative endoscopy, CT scan or PET scan should be considered. If an incidental thyroid nodule is discovered, this should be further evaluated with a fine needle aspiration for cytology.

MTC is a relatively uncommon thyroid cancer forming about 4% of all thyroid cancers.⁷ MTC is an established cause of CEA elevation and has been previously reported^{8,9} but not all practitioners may be aware of this. This could have led to some delay in the diagnosis. In spite of the long delay of about 8 to 9 years in Patients 2, 4 and 5, the tumour was still confined to the thyroid with no lymph node involvement. Patient 5 still has an elevated CEA of uncertain aetiology but Cases 2 and 4 suggest a possibility that these tumours may be incidental and may not be as clinically significant as medullary carcinoma detected in other clinical settings.

Awareness and a high degree of suspicion is required in order not to miss an uncommon cancer like MTC.

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An Alternative Diagnosis: *Bartonella* Neuroretinitis

Dear Editor,

We refer to the letter 'Lyme Neuroretinitis in Singapore: A Diagnostic Dilemma' published in the April 2012 Vol. 41 No. 4 issue of the Annals, Academy of Medicine. We propose a differential diagnosis of *Bartonella* neuroretinitis for the case reported.

The authors described a 59-year-old Chinese man who had neuroretinitis with a macular star on retinal examination. Syphilis serology was negative. Enzyme-linked immunosorbent assay (ELISA) serology for Lyme disease showed a positive IgG titre. A repeat Lyme serology showed no rising titre and a confirmatory test using western blot was negative. The patient responded to treatment with intravenous ceftriaxone followed by oral amoxicillin. A weaning dose of oral steroid was also given for anti-inflammatory effect. Direct questioning of the patient revealed positive contact history with his dog that had a previous history of ticks. No significant travel history outside of Singapore was mentioned.

Discussion

The unique finding of a macular star on the retinal examination should prompt physicians to investigate for infective causes such as *Bartonella*, syphilis, Lyme disease and toxoplasmosis.^{1,2} As mentioned by the authors, there have been no reported cases of Lyme disease acquired in Singapore to date. The cases of Lyme disease are largely centred in North America and Europe.³

The Centers for Disease Control and Prevention (CDC) recommends a two-tiered approach to testing for Lyme disease, which consists of initial IgM and IgG quantitative ELISA, followed by confirmation of all indeterminate or positive ELISA test with separate IgG and IgM western blots. Without a significant travel history, it is possible that the initial Lyme serology was a false positive.

Bartonella infections have been reported in the Asian population. Pets, particularly cats and dogs, represent a large reservoir of hosts of *Bartonella* species. In Singapore, seroprevalence of *Bartonella henselae* in cats has been reported as 47%,⁴ although there is no data on the incidence in dogs. *Bartonella henselae* is more commonly described to cause cat scratch disease and while it is also found in

dogs, other subspecies such as *Bartonella vinsonii* is more commonly associated with dogs. In Singapore, brown dog ticks (*Rhipicephalus sanguineus*) are the most common ticks found on dogs. Brown dog ticks can carry *Bartonella* species.⁵ The treatment for both Lyme disease and *Bartonella* infection is similar, with both organisms responding to ceftriaxone. Further laboratory investigation to rule out other infectious causes such as *Bartonella* should be sent for the patient.

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Re: An Alternative Diagnosis: *Bartonella* Neuroretinitis

I would like to thank the authors for the reply to our case report.¹ The differential diagnosis of *Bartonella* neuroretinitis in this patient was considered, but it would definitely not be on the top of my list due to the following reasons.

The role of dogs as reservoir hosts of *Bartonella* spp. is less clear, as compared with cats and they are also accidental hosts.² The cat scratch disease caused by *Bartonella* can manifest in the eye with unilateral eye redness, foreign body sensation, and epiphora, while mild cases present lid swelling.^{3,4} Our patient did not have pain, skin lesions or a lymph node enlargement.

A case report⁵ mentioned that serologies were positive for both *B. henselae* and *B. burgdorferi*. That patient was treated with oral antibiotics for coverage of both aetiologies, and her condition improved.

Another factor was the financial issues involved for our patient doing additional serology tests. In cat scratch disease, serology results are also not standard. Some patients produced high levels of both IgG and IgM, others produced only high levels of IgM, and a few patients produced only low levels of antibodies.⁶

As the suggested treatment is similar,⁵ establishing an alternative diagnosis was not considered. As with Lyme's disease, there are no reported cases of *Bartonella* neuroretinitis in Singapore based on the literature search.

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Associate Professor Dr Vijayan Appasamy (1953 – 2015)

It was with much sadness that we learnt of the passing of A/Prof Vijayan Appasamy, or “Prof V” as he was fondly known to all, on 20 March 2015. He was in Chicago, USA, representing Singapore at a surgical educators’ meeting, doing what he liked best, when he suffered a massive heart attack. He leaves behind his wife and 2 daughters.



Vijayan graduated from the University of Madras in 1979 and came over to Singapore in 1982. After finishing his housemanship, he chose to sign on as a regular with the Naval Diving Unit, where he obtained his basic and advanced Diving and Hyperbaric Medicine certificates.

He was responsible for writing naval medicine doctrines and reorganised the Diving Unit and Hyperbaric Medicine Centre. He was also an instructor for the Advanced Trauma Life Support (ATLS) course and the Advanced Medical Officer Course (AMOC) for the Navy, and rose to the rank of lieutenant colonel, before making a mid-career switch to general surgery in 1996.

He joined the Department of General Surgery in Tan Tock Seng Hospital (TTSH) and obtained his double Fellowship of the Royal College of Surgeons (FRCS) in 1998. He chose to specialise in trauma and acute care surgery and was instrumental in setting up the trauma service at TTSH, along with his “partner-in-crime” Dr Chiu Ming Terk. Under his leadership, the service attained international recognition when it was appointed the training centre for the ATLS course.

He was the “doer”, while Ming Terk was the “dreamer”, in their own words.

He then pursued his passion of surgical education, making his mark rapidly in this field. He was a very popular and passionate teacher, who led by example. Those at his memorial service in TTSH will remember the numerous tributes from his students and residents, which moved many to tears. He

moved with them, as one of them, friend and mentor.

A tireless worker and achiever, he wore many hats, including Director for the General Surgery Residency Program at National Healthcare Group; Assistant Head, Education and Training, Department of General Surgery; Adjunct Associate Professor with the Lee Kong Chian School of Medicine; Senior Lecturer with Yong Loo Lin School of Medicine; Member, International Residency Review Committee, ACGME-I; Reviewer with the Division of Graduate Medical Education of Yong Loo Lin and NHG schools of medicine, and served as an examiner for the Bachelor of Medicine and Bachelor of Surgery (MBBS) and Master of Medicine (MMed) (Surgery) exams, to name just a few. He also served in the executive committee of Joint Committee on Specialist Training (JCST) and later was appointed member of the review committee for residency programmes.

He also found time to serve in the College of Surgeons, Singapore, first in the Chapter of General Surgeons, rising to General Secretary, Vice President and eventually President Elect. He was, in fact, due to take office in May 2015. With his untimely passing, the College has lost a visionary leader.

Many may not know that he was also a volunteer with the Drug Rehabilitation Centre Review Committee of the Ministry of Home Affairs, for which he received 10-year and 15-year Long Service Awards. His list of awards and commendations is lengthy, of which his Public Service Medal (PBM) and Public Service Star (Bintang Bakti Masyarakat) (BBM) deserve special mention, being National Day honours.

But perhaps the greatest of honours is the legacy he leaves behind, in the form of the medical students and residents he helped train, who will bear testament to the inspiring teacher, mentor and friend that he was.

May his soul rest in peace.

Ikshuvanam Swaminathan
College of Surgeons, Singapore