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*“Home art gone and taken thy wages: golden lads and girls all must,
as chimney sweepers, come to dust.”*

In: Cymbeline, Act 4, scene 2
William Shakespeare (1564 – 1616)
English playwright

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Calculated Overhaul Versus Cultivating the Status Quo in Clinical Education

Shiva Sarraf-Yazdi, ^{1MD}, Sandy Cook, ^{1PhD}, Robert K Kamei, ^{1MD}

In an era of rapid healthcare evolution, complex challenges abound from changes in patient demographics, diseases, demand and delivery; to cost, technology, and setting.¹ Such transformations, bound by political, socioeconomic, cultural, and countless other hurdles, cannot be systematically and strategically met by a workforce whose pedagogy and preparation was intended for a different breed and generation of doctors.^{2,3} For decades, the approach to clinical education has not fundamentally changed, even as medical education literature has become inundated with calls for reform and restructuring.^{2,3} Despite a global shift towards shortened inpatient stays and increased ambulatory care, for example, the first clinical year of medical school has retained a block model in which students rotate through discipline-specific clerkships. Notwithstanding its history and tradition, the latter model is deemed “poorly aligned with society’s present and future needs”, leading to ill-prepared graduates.²

Among the block clerkship model’s shortcomings are arbitrary structure of largely inpatient rotations, limited outpatient experiences, discontinuous clinical skills development, and lack of continuity, be it with patients or faculty.² Evidence shows erosion of students’ ethical behaviour, moral reasoning, idealism, empathy, and patient-centred attitudes.⁴⁻⁶ These attributes are often undermined by unintended consequences of the hidden curriculum; one in which espoused and enacted elements of professionalism may be discordant.³ Years of formal training and acquisition of patient-centred skills are easily jeopardised in an environment in which such behaviours are not modelled, hindering development of students’ professional identity.³

Longitudinal Integrated Clerkships: Calculated Overhaul

In response to contextual challenges, medical schools in Australia, Canada, South Africa, and the United States have adopted a restructured model under the umbrella of *longitudinal integrated clerkships* (LIC).⁴⁻¹¹ Key features of this learner- and patient-centred approach are *longitudinal* continuity of learner relationships with faculty preceptors

and peers, *longitudinal* care of patients, and concurrent *integrated* exposure to multiple disciplines in tandem. A Consortium of Longitudinal Integrated Clerkships characterises the LIC as “the central element of clinical education whereby medical students (i) participate in the comprehensive care of patients over time, (ii) participate in continuing learning relationships with these patients’ clinicians, and (iii) meet the majority of the year’s core clinical competencies, across multiple disciplines simultaneously, through these experiences”.⁹ Another defining feature is the opportunity for learners to develop a meaningful connection with their “host community”.⁹

As each LIC programme caters to its own educational mission, there is no one-size-fits-all template. A programme may span from 6 months to longer than a year, involve a minority or the whole of a class, and emphasize rural vs urban clinical environments.⁴⁻⁹ An urban example is LIC at the University of San Francisco in which a portion of the class participates.^{6,7} The curricular makeup entails 50% discipline-specific clinical activities, 30% longitudinal patient follow-up and self-directed learning, 10% acute care, and 10% didactic curriculum.^{6,7} In a typical week, a student may go to medicine clinic on a Monday morning, followed by urgent care in the afternoon. On Tuesday, attend family medicine clinic, with time spent in the afternoon on self-directed learning and follow-up of patients. The following week will be structurally similar, incorporating gynaecology clinic instead of paediatrics, for example, and anaesthesia instead of surgery. This cycle continues throughout the year, underscoring continuity with panel of patients and clinical preceptors.

LIC preceptors, despite the time investment, report increased levels of professional satisfaction.^{5,8} Outcome studies from LIC programmes show more meaningful student relationships with patients, faculty, and peers, with less erosion of empathy.^{4,5} Academic performance is at least on a par with traditional clerkships, if not better, particularly in certain areas such as communication skills.^{4,6} In one study, graduates from LIC programmes in family medicine

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residency show at least equivalent performance to peers.¹⁰ In a collective review of LIC program outcomes, Walters et al⁵ conclude that with mounting supporting evidence, proof of academic non-inferiority no longer needs to be researched.

Plans at Duke-NUS: Cautiously Optimistic Overhaul?

At Duke-NUS Graduate Medical School, our educational values require that, among other skills, students be indoctrinated in teamwork, collaborative learning, and critical thinking. These are accentuated throughout the first year of basic sciences with team-based learning as a primary instructional strategy. Starting with clinical clerkships in year 2, however, educational shortcomings surface similar to those highlighted above; challenges likely to become more palpable with rising competition for clinical education resources.

In response to changing healthcare needs, we propose to create a hybrid, longitudinal integrated clerkship as a small pilot programme, with theory- and literature-based education reform proposals as its curricular framework.³ Far from a reactionary response, the overarching goal of this learner-centred programme will be to cultivate competencies to effectively and efficiently practice medicine in an evolving healthcare environment, facilitating students' longitudinal relationships with faculty, peers, and small panels of patients. Learners will be accountable for guided self-directed learning, focusing on disease progression, undiagnosed encounters in acute care and outpatient settings, chronic care, and exposure to information technology in healthcare. A cohort of interdisciplinary faculty will deliver a clinically integrated, yearlong developmental curriculum. Importantly, if LIC goals are to be realised, leadership support and concerted faculty development efforts will be instrumental,⁸ as faculty must "assume collective ownership of the entire clerkship experience"² and hone teaching skills aligned with a developmental, competency-based curriculum.

Amidst the magnitude of challenges within clinical education, a longitudinal, integrated approach employed within a collaborative community can enhance learning and by extension, eventually improve patient outcomes.² Notwithstanding considerable logistical efforts required, as well as unresolved "questions of efficacy", some view LIC as "the most significant educational innovation in clinical education to have occurred in our lifetimes".¹¹

We believe critical thinking skills are critical for our graduates; future doctors who are open to inquiry to the widest range of voices, question dogma, learn from mistakes, and deliberately seek out new possibilities. As educators and at times self-proclaimed role models, if we cannot be bothered to question assumptions underlying

our time-honoured educational practices, we must accept any unintended modeling effect on our learners, forego an expectation to foster critical thinkers, and optimistically hope for the best as we cultivate the status quo instead.

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Good Sleep and Good Health are Natural Bed Partners

Joshua J Gooley, ^{1,2}PhD

Sleep is time consuming. We spend nearly one-third of our lives asleep, but for what purpose? This is an important question to reflect upon, whether you are a scientist, philosopher, or a person who simply wants to know how to better spend his time. Sleep is generally considered a pillar of good health, yet it is increasingly common in modern society to shortchange oneself of sleep to partake in other activities. Sleep is considered by many as a low-priority health concern, but this is largely due to a failure to understand the importance of sleep for physical and mental health. Below we consider why sleep sometimes fails to get the respect that it deserves.

Firstly, sleep is often viewed as a time when the brain shuts down, when in fact sleep is an active process. The former view persists because we lose consciousness and become unresponsive to the environment during sleep. Not surprisingly, then, sleep has been used as a metaphor for death, in texts ranging from the Iliad to the Bible to works by Shakespeare and Robert Frost. On the face of it, sleep appears as a period of inactivity and lost productivity. In Thomas Edison's words,¹ "We are always hearing people talk about 'loss of sleep' as a calamity. They better call it loss of time, vitality, and opportunities." While it cannot be denied that sleeping less frees up more time to be awake, sleep does more than simply alleviate sleepiness. Sleep allows the brain to remove metabolic debris,² and also facilitates memory consolidation.³ Regarding the latter, in Greek mythology the Lethe, known as the river of forgetfulness, flowed around the cave of Hypnos, the personification of sleep—in hindsight, the river of remembering would have been a more apt description.

It is important to realise that sleep is not merely the antithesis of waking, but rather a complex behaviour that serves multiple functions. In addition to the roles already mentioned for sleep in brain-waste removal and transfer of memories to long-term storage, sleep plays a role in metabolic health. In the short term, sleep loss results in decreased glucose tolerance, and increased sympathetic tone and blood pressure.⁴ In the long term, short sleep is associated with a higher body mass index and increased

risk for diabetes mellitus and hypertension,⁵⁻⁸ which are predictors of cardiovascular disease. Short or disrupted sleep has also been linked to impaired immune responses, learning deficits, and mood disorders.⁹⁻¹¹ For better or for worse, sleep has its fingers in everything. Sleep is a basic physiologic need, and when removed, the body fails to function properly.

It is perhaps ironic that one of the reasons sleep is often overlooked is that it plays such a broad role in maintaining good health, as opposed to serving a singular function. Sleep mediates so many things, and yet seemingly does not explain any single thing. Sleep is the great facilitator working behind the scenes, operating under the cover of darkness. Since the negative effects of sleep loss on health are not usually immediate, advocates for sleep medicine and sleep research face the uphill battle of convincing others that a lifetime of short or poor quality sleep is costly in the long run. A similar scenario has played out for other behaviours that take decades to erode health, e.g. smoking and poor dietary choices. Smoking a cigarette or eating a high-fat meal has no measurable effect on long-term health, but decades of smoking greatly increases risk of lung cancer, and a lifelong history of poor eating habits can eventually lead to heart disease or stroke. To be sure, battles against tobacco and poor food choices have been difficult and are ongoing. The fight for sleep is just beginning, as the evidence continues to build that a lifestyle of short or disrupted sleep increases disease risk and mortality.

What, then, is the scope of the sleep problem in Singapore? That is difficult to answer, as there is little published data on sleep behaviour in Singaporean adults. Given that sleep duration and difficulty initiating and maintaining sleep (i.e. insomnia) are important health indicators, such information could be collected prospectively in the Singapore National Health Survey.¹² The last investigator-initiated study to examine the prevalence of insomnia was performed in a community sample nearly 20 years ago.¹³ Based on unpublished surveys of sleep habits that we and others have conducted, most Singaporean students attending junior college or university report sleeping less than 6

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hours per night on school nights, which is substantially less than the amount recommended by the National Sleep Foundation.¹⁴ The persistence of such sleep behaviours into later adulthood could contribute to the growing burden of metabolic disorders and heart disease in Singapore. In the Singapore Chinese Health Study, for example, the relative risk of coronary heart disease was significantly higher in individuals who reported sleeping ≤ 5 hours per night (relative risk = 1.57), relative to those who reported sleeping 7 hours.¹⁵ It appears that sleep is not only for the brain, but also for the heart.

In conclusion, it is important that health officials and physicians in Singapore promote good sleep habits for better health. Depriving oneself of sleep is tantamount to punishing the body, and over time the health consequences can be severe. Looking forward, more data are needed on sleep behaviour across all age groups to better understand how sleep modifies disease risk in the local context. Epidemiologic data collected in Singapore and elsewhere indicate that short sleep is associated with a higher rate of coronary heart disease.¹⁶ Also, shift work, which entails disrupted sleep and circadian rhythms, is associated with increased risk for stroke and some types of cancer.^{17,18} The aforementioned diseases account for more than half of all deaths in Singapore.¹⁹ Sleep is therefore on the shortlist of modifiable risk factors for diseases that impact the lives of Singaporeans. As such, let us work together to spread the gospel of good quality sleep—Singaporeans will be better off for it.

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Post Community Hospital Discharge Rehabilitation Attendance: Self-Perceived Barriers and Participation Over Time

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Abstract

Introduction: This study aimed to examine the attendance rates of post-discharge supervised rehabilitation as recommended by the multidisciplinary team at discharge among subacutely disabled adults and the barriers preventing adherence. **Materials and Methods:** Patients were from a community hospital, aged 40 years or older. They had been assessed by a multidisciplinary team to benefit from rehabilitation after discharge, were mentally competent and communicative. We used a sequential qualitative-quantitative mixed methods study design. In the initial qualitative phase, we studied the patient-perceived barriers to adherence to rehabilitation using semi-structured interviews. Emerging themes were then analysed and used to develop a questionnaire to measure the extent of these barriers. In the subsequent quantitative phase, the questionnaire was used with telephone follow-up at 3, 6, 9 and 12 months after discharge. **Results:** Qualitative phase interviews (n = 41) revealed specific perceived financial, social, physical and health barriers. At the start of the quantitative phase (n = 70), 87.1% of the patients viewed rehabilitation as beneficial, but overall longitudinal attendance rate fell from 100% as inpatient to 20.3% at 3 months, 9.8% at 6 months, 6.3% at 9 months and 4.3% at 12 months. The prevalence of physical and social barriers were high initially but decreased with time. In contrast, the prevalence of financial and perceptual barriers increased with time. **Conclusion:** Attendance of post-hospitalisation rehabilitation in Singapore is low. Self-perceived barriers to post-discharge rehabilitation attendance were functional, social, financial and perceptual, and their prevalence varied with time.

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Key words: Adult rehabilitation, Attendance, Barriers to rehabilitation, Mixed methods study

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Introduction

As Singapore faces a rapidly ageing population, the national burden of long-term disability is expected to correspondingly increase.^{1,2} Post-discharge rehabilitation of the newly disabled adults, especially during the subacute phase after an acute disabling event where functional recovery is most likely, is an important strategy to reduce the prevalence of severe disability.³ Besides maximising functional recovery, rehabilitation also improves their quality of life, reduces the costs associated with disability and years lost due to disability, translating into effective usage of limited resources.⁴⁻⁷ Community hospitals in Singapore function as one of the primary sites facilitating adult rehabilitation.⁸ Anecdotally, however, adherence

to supervised rehabilitation within the community, post-discharge, has been demonstrated to be low. Studies in the United States (US) and Australia have shown that the rates of rehabilitation service utilisation by stroke patients in the community is as low as 13% to 31%.^{9,10} A local study by Koh et al on the adherence rates (at day rehabilitation centres) in stroke patients discharged from community hospitals have estimated the rate to be about 28% at 1 year.¹¹

Studies have shown there are several factors which affect attendance for prescribed rehabilitation between different subgroups of patients. In one study in patients undergoing outpatient cardiac rehabilitation, common barriers to adherence to prescribed rehabilitation included

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financial cost and lack of motivation.¹² Another study done in a musculoskeletal outpatient clinic found that low adherence to rehabilitation was associated with low self-efficacy, depression, anxiety, helplessness, poor social support and greater perceived number of barriers.¹³ Attendance at rehabilitation appears to be a result of a complex interplay of knowledge, social, financial and physical barriers. A Cochrane review on the effectiveness of interventions in cardiac rehabilitation programmes found that well planned interventions targeted at important barriers significantly improved adherence.¹⁴ Articles regarding rehabilitation follow-up rates or analysing specific barriers in the context of rehabilitation in general were few, if any—demonstrating a definite knowledge gap in this aspect.

A mixed methods design was adopted to study the attendance rates at post-discharge supervised rehabilitation as recommended by the multidisciplinary team at discharge from a local community hospital among subacutely disabled adults and the barriers preventing adherence, with the aim to guide future development of interventions to improve adherence to rehabilitation.

Materials and Methods

Study Design

A sequential qualitative-quantitative mixed methods study was conducted in the 198-bedded Ang Mo Kio Thye Hwa Kwan Hospital (AMKH), one of the largest community hospitals in Singapore which are primary locations for continuation of care post-discharge from the acute hospitals. The study consisted of 2 phases: (i) an initial qualitative study involving semi-structured interviews of inpatients using a phenomenological approach to understand the self-perceived barriers to adherence to rehabilitation and to develop a quantitative questionnaire to measure the extent of self-perceived barriers to rehabilitation adherence, and (ii) a subsequent phase where the developed quantitative questionnaire was interviewer-administered on a new set of inpatients before discharge with repeated administration longitudinally via telephone interviews at 3, 6, 9 and 12 months after discharge to observe the trends in rehabilitation adherence and self-perceived barriers. The study was approved by the National University of Singapore Institutional Review Board.

Eligibility Criteria

For both the qualitative and quantitative studies, recruited subjects satisfied the following eligibility criteria: The subject must (i) be aged 40 years or older, (ii) have been assessed by a multidisciplinary team (consisting of a physician, nurse, physiotherapist, occupational therapist and medical social worker) to benefit from rehabilitation

after discharge during the pre-discharge multidisciplinary patient care conference (PCC), (iii) not have a history of mental incapacity (e.g. severe dementia) and (iv) be communicative (i.e. no dysphasia).

Qualitative Phase

For the first (qualitative) phase, available literature on the barriers to adherence to rehabilitation was reviewed and face-to-face discussions were conducted to develop a set of probing questions for the qualitative interview guide, as follows:

1. What do you understand by “rehabilitation”?
2. How do you feel about rehabilitation (e.g. good, not useful, etc.)?
3. Would you like to continue with rehabilitation after discharge? If yes/no, why?
4. If the hospital team recommends that you continue rehabilitation after discharge, would you do so? If yes/no, why?
5. Do you expect any barriers to rehabilitation after you go home? If yes/no, why?

Eligible subjects were identified at the PCCs within AMKH from June to July 2008. All eligible subjects were then interviewed with the above probing questions to explore their attitudes and beliefs towards post-discharge rehabilitation, with subsequent unstructured questions to clarify the context of their replies. As Singapore is a multiethnic population, multilingual interviewers (Abel W Chen, Yan Tong Koh, Sean WM Leong) conducted the interviews and translators were used when needed. To minimise inter-rater bias, all 3 interviewers were present during most of the interviews. At any given time, at least 2 interviewers were present. Subject interviews were audio-taped whenever possible and field notes were taken for those who refused audio-taping. Subjects who refused audio-taping were included in the study because this group formed nearly half of the surveyed population and excluding them would introduce significant bias. All audio-taped interviews were subsequently transcribed and translated into English where necessary. Thematic analysis using a phenomenological approach was then performed on the transcribed interviews and field notes.¹⁵ Specific quotes were identified which elucidated certain themes about the patients' experience with inpatient rehabilitation and their barriers to outpatient rehabilitation adherence. The themes elicited individually were then discussed as a group to reach a consensus regarding the themes identified. The qualitative study stopped after the research team (Abel W Chen, Yan Tong Koh, Sean WM Leong, Gerald CH Koh) felt that saturation of themes had occurred.

Quantitative Phase

For the second (quantitative) phase, themes about barriers to rehabilitation adherence identified from the initial qualitative phase were used to develop a questionnaire to quantify the proportion of subjects who cited these barriers. The quantitative questionnaire also captured data on patient demographics, medical diagnosis, presence of caregiver support, intention to attend rehabilitation before discharge and actual adherence to rehabilitation post-discharge. This questionnaire was interviewer-administered prior to discharge and administered over the telephone at 3, 6, 9 and 12 months after discharge. Like with the qualitative phase, the interviewers attended all PCCs in AMKH to identify subjects who satisfied the eligibility criteria from September 2008 to June 2009. During the follow-up period, details on which patients subsequently passed away or dropped out from rehabilitation were noted. We stopped recruitment in the quantitative phase when we reached 70 subjects because the attendance rates for post-discharge rehabilitation was so low that additional subjects would not have significantly altered the final percentages.

For the quantitative study, univariate analysis was used to describe the sample population and chi-square tests were used to evaluate differences in the proportions. In the computation of the adherence rate, those who died, were discharged from rehabilitation or were lost to follow-up were excluded from the denominator at each time point (Fig. 1). We used linear by linear association to determine the *P* value for trend for self-perceived barriers to non-adherence to rehabilitation across time points. We used Statistical Package for the Social Sciences (SPSS) version 18.0 for statistical analysis and statistical significance was set at the conventional *P* < 0.05.

Results

Qualitative Phase

Forty-one subjects participated in the qualitative study. Twenty-four subjects allowed the interview to be audio-taped and field notes were taken for the remaining 17 subjects. The majority of subjects were aged above 60 years (36/41, 90.3%) with 14.6% aged 80 years or above. The mean age was 69.8 (standard deviation = 9.8) years and the median age was 70 years (interquartile range, 63.6 to 7.65 years). The female to male ratio was 19:22 and the majority were of Chinese ethnicity (33/41, 80.5%). Thematic analysis identified 5 recurring domains as barriers to adherence to post-discharge rehabilitation: functional, social, financial, medical and perceptual.

Functional Factors

Twenty-six subjects (63.4%) reported that either their physical disability or home environment (both internal and external) were barriers to attending rehabilitation after discharge. As most subjects requiring rehabilitation inherently have disability, they were particularly susceptible to physical barriers to mobility and transportation. As 90% of Singaporeans live in public high-rise apartments (flats) with the lifts in older buildings serving only on a few floors, many subjects had difficulty climbing stairs without assistance.

“It’s very hard to get around... Upgrading works are in progress around my home at the moment. Now, I have to take a lift to the fifth floor before taking the stairs to the third storey where I live.”

[62-year-old Chinese female]

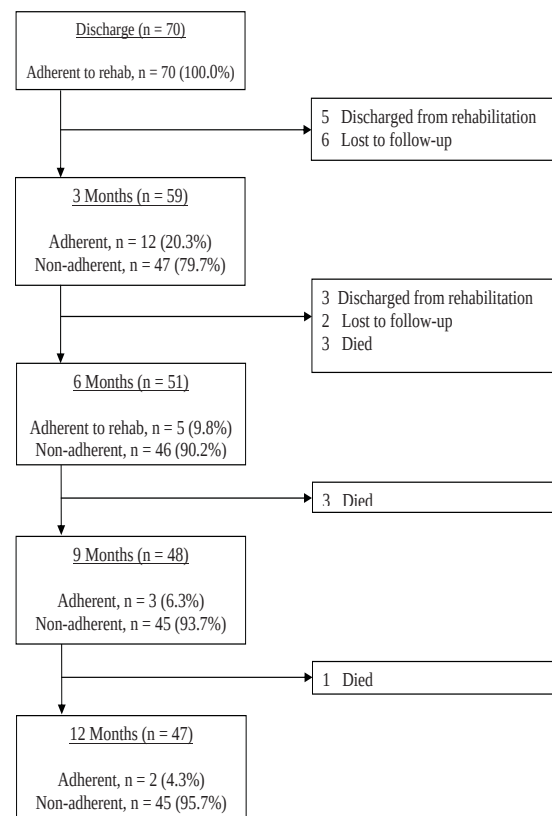


Fig. 1. Flowchart for quantitative study.

Even if subjects were able to reach the ground floor, they faced the challenge of being transported to the nearest day rehabilitation centre.

“I think that the burden of transport is the main problem. After all, my husband is already 70 years old and I am not young either.”

[64-year-old Chinese female]

“Yes, (the biggest problem is transportation). This is because my children don’t have a car to bring me there.”

[69-year-old Chinese male]

Social Factors

Nineteen subjects (46.3%) mentioned unavailability of caregivers to transport and accompany them for rehabilitation which is important as disabled persons need physical assistance and are at risk of falls.

“There is no one to bring me for my rehabilitation sessions if there will be any. However, I would like to continue rehabilitation if I am able to do so as I find it good and useful.”

[74-year-old Chinese female]

Subjects were also reluctant to inconvenience their caregivers, especially if they were working.

Interviewer: “The doctors have recommended that you continue day rehabilitation after your discharge. Would you go?”

Subject: “That depends on what my daughter feels about it.”

Interviewer: “Does your daughter have time to take you there?”

Subject: “She’s free once in a while, but not always. She has to work, you see.”

Interviewer: “So the main problem is just that there isn’t anyone to take you for physiotherapy, right?”

Subject: “Yes, I am afraid I might fall again if I go alone. However, I would like to continue rehabilitation if I am able to do so as I find it helpful.”

[69-year-old Chinese male]

“Although I am keen for rehabilitation, I do not want to burden my daughter.”

[68-year-old Chinese male]

Financial Factors

Eighteen subjects (43.9%) cited financial concerns as a barrier to attending rehabilitation centres. Subjects highlighted that rehabilitation could not be paid using their

medical savings account (Medisave) or national medical insurance (Medishield), and required personal out-of-pocket expenses.

“Money is an important factor. I am concerned that I cannot use Medishield or Medisave (government insurance) for physiotherapy and transport. I currently have no income, thus I cannot pay.”

[52-year-old Indian male]

Government subsidies for outpatient day rehabilitation are available for subjects who are eligible on means testing. However, subjects pointed out that although these subsidies helped to alleviate the cost of each therapy session, the cumulative cost of outpatient day rehabilitation was high. Subjects often needed 1 to 2 rehabilitation sessions per week over several months. Moreover, these costs did not include transportation and other medical costs.

“I think (the cost of rehabilitation) will be okay for the first few weeks but will be a problem if it goes beyond that. After all, I already have to pay for my (other medical) bills.”

[62-year-old Chinese female]

One subject was already so impoverished that he even felt rehabilitation was an extravagance and would be one of the first aspects of treatment he would dispense with.

“I am more worried about my financial situation. (In that light) I feel rehabilitation is a luxury.”

[73-year-old Malay male]

Medical Factors

Patients needing rehabilitation often have multiple comorbidities which limit their ability to tolerate rehabilitation. For example, patients with stroke often have risk factors like diabetes mellitus which often causes concurrent illnesses such as renal failure, ischaemic heart disease, heart failure and postural hypotension which pose challenges to adherence to rehabilitation.

“I can’t even walk now, how can I come? I’ll wait and see. Then again, I don’t think my condition permits me much exercise because of my long dialysis sessions. There was once I had to do physiotherapy after dialysis – I just couldn’t do it. Sometimes it’s not really fair to say that we patients don’t put our hearts into physiotherapy sessions. The fact remains that we are sick and are therefore (tire easily).”

[65-year-old Chinese male]

Perceptual Factors

Among patients who were not keen for rehabilitation, some felt their current functional status was already satisfactory, even when the multidisciplinary team advised them that they felt their functional status could improve with further rehabilitation.

Interviewer: "Will you still come back for physiotherapy after your discharge?"

Subject: "No, I don't think so. I feel I am fine and can walk now. I want to go home."

Interviewer: "So the only reason why you don't want to go for these sessions is because you don't want to come back?"

Subject: "Yes. I am totally fine."

Interviewer: "This is in spite that your doctors think you can improve further even after you're discharged?"

Subject: "Yes."

[74-year-old Chinese female]

One patient felt that rehabilitation to improve functional status was less important than caregivers learning to care for them at their current level of functional status.

"I feel that emphasis should be place on educating the caregiver instead on the patient going for day rehabilitation."

[90-year-old Malay female]

Another patient had an 'ageist' attitude towards functional independence: she felt she did not need rehabilitation as she was "supposed" to be functionally dependent because of her advanced age.

"I am so old already – I don't need to be functionally independent."

[75-year-old Chinese female]

Some patients were convinced that physiotherapy did not work, usually because of no self-perceived functional improvement during inpatient rehabilitation, preconceived notions, lack of understanding about rehabilitation or denial.

Interviewer: "Do you think the exercises are useful? Do you think they help you?"

Subject: "No, it's not useful. I cannot walk. It doesn't help me move. They just sit me down on a chair and then make me stand up."

Interviewer: "So you know that physiotherapy might take a long time. Do you think you will eventually start to improve?"

Subject: "No."

[85-year-old Eurasian female]

Quantitative Phase

The socio-demographic profile of respondents in the quantitative phase is detailed in Table 1. The median time from onset of acute disabling condition to admission into AMKH in our study population was 16 days (interquartile range, 11 to 25 days).

The majority of the respondents felt inpatient rehabilitation was beneficial ($n = 61/70$, 87.1%) and only 5.7% ($n = 4/70$) did not find rehabilitation beneficial, the rest being unsure. Although the majority of subjects acknowledged the benefit of inpatient rehabilitation, only 28 out of the 70 patients (40%) expressed an intention to continue with rehabilitation after discharge as recommended by the inpatient multidisciplinary team. Subjects who felt that inpatient rehabilitation was beneficial were not more likely to intend to continue with rehabilitation after discharge as recommended than those who did not [OR = 1.22 (95%CI, 0.54 to 2.78), $P = 0.68$].

Figure 1 is a flowchart detailing subjects discharged from rehabilitation, lost to follow-up and who died, as well as rehabilitation attendance rates at each 3-month period over the year of the quantitative study. The loss to follow-up rate in our study was 11.4% (8/70) at 1 year. By 3 months post-discharge, only 20.3% of subjects were adherent to recommended rehabilitation. This proportion decreased to 9.8% at 6 months, 6.3% at 9 months and 4.3% by 1 year. There were no associations between caregiver support, means test category, self-perceived benefit from inpatient rehabilitation and intention to continue with rehabilitation after discharge with the attendance at rehabilitation at all 4 time points post-discharge.

Table 2 details the self-perceived barriers for non-attendance at rehabilitation at discharge, 3, 6, 9 and 12 months, categorised into the 5 domains. At discharge, the main barriers to rehabilitation attendance were from the functional [problems with getting from home to rehabilitation centre (61.9%)] and social [(inconvenience for patient (57.1%) and no caregiver to accompany subject (31.0%)] barrier domains. However, from 6 months onwards, the main barriers to rehabilitation attendance were from the perceptual [satisfaction with current functional state and no interest in participating in rehabilitation] and financial [problems with out-of-pocket payments and high cost per session] barrier domains. Three barriers declined over time: problems with ambulating from home to rehabilitation centre ($P < 0.001$), inconvenience for subject ($P < 0.001$) and inconvenience for caregiver ($P = 0.105$) declined over time, although the last barrier was only borderline significant (Fig. 2). Two barriers increased over time: financial problems from long duration of rehabilitation ($P = 0.005$) and no interest in participating in rehabilitation ($P < 0.001$). Concurrent medical conditions were not perceived to be a major barrier to rehabilitation.

Table 1. Characteristics of Quantitative Study Population (n = 70)

Characteristics	n (%)*
Age	
Mean (standard deviation)	73.3 (13.1)
Gender	
Female	37 (75.7%)
Male	33 (24.3%)
Ethnicity	
Chinese	61 (87.1%)
Malay	2 (2.9%)
Indian	6 (8.6%)
Others	1 (1.4%)
Marital status	
Single	14 (20.0%)
Married	23 (32.8%)
Divorced/separated/widowed	33 (47.2%)
Number of caregivers	
0	21 (30.0%)
1	14 (20.0%)
2	17 (24.3%)
3	13 (18.6%)
4	5 (7.1%)
Main caregiver	
None	21 (30.0%)
Spouse	12 (17.1%)
Child	14 (20.0%)
Sibling	2 (2.9%)
Maid	17 (24.3%)
Others	4 (5.7%)

Table 1. Characteristics of Quantitative Study Population (n = 70) (Con't)

Characteristics	n (%)*
Means test category†	
0%	40 (58.0%)
25%	5 (7.2%)
50%	6 (8.7%)
75%	18 (26.1%)
Primary diagnosis for admission	
Stroke	8 (11.4%)
Fractures	22 (31.5%)
Amputations	1 (1.4%)
Others	39 (55.7%)
Infection	11 (15.7%)
Trauma from falls	7 (10.0%)
Non-specific de-conditioning	5 (7.1%)
Postoperative de-conditioning	7 (10.0%)
Acute myocardial infarction	3 (4.3%)
Cancer	3 (4.3%)
Spinal stenosis	2 (2.9%)
End stage renal failure	1 (1.4%)
Barthel Index score on admission	
Median (interquartile range)	53.0 (42.5 – 66.5)

* Denominators vary slightly because of missing responses.

†Means testing is a policy introduced by Ministry of Health (Singapore) in 2001 to redistribute subsidies to different income groups through fixed parameters. After the test, the patients are allocated a percentage of subsidies, with the lower income group receiving more. At the time of study, the number of means testing categories was 4 but in 2010, the number increased to 9. More details can be found at <http://www.moh.gov.sg/mohcorp/hcfinancing.aspx?id=16072>.

Table 2. Self-Perceived Barriers to Non-Adherence to Rehabilitation at All Time Points

	n (%)					P value‡
	Discharge	3 months	6 months	9 months	1 year	
	(n = 42)*	(n = 47)†	(n = 46)†	(n = 45)†	(n = 45)†	
Functional barriers						
Problems with ambulating from home to rehabilitation centre	26 (61.9) ¹	10 (21.3)	12 (26.1)	11 (24.4)	8 (17.8)	<0.001
Problems with ambulating within the home	9 (21.4)	11 (23.4)	8 (17.4)	8 (17.8)	5 (11.1)	0.596
Social barriers						
Inconvenient for subject	24 (57.1) ²	11 (23.4)	6 (13.0)	6 (13.3)	8 (17.8)	<0.001
No caregiver available to accompany subject	13 (31.0) ³	13 (27.7) ³	11 (23.9)	11 (24.4)	8 (17.8)	0.687
Subject does not wish to burden caregiver	12 (28.6)	11 (23.4)	9 (19.6)	8 (17.8)	7 (15.6)	0.598
Inconvenient for caregiver	9 (21.4)	6 (12.8)	7 (15.2)	2 (4.4)	3 (6.7)	0.105
Caregiver is too busy	8 (19.0)	4 (8.5)	7 (15.2)	4 (8.9)	5 (11.1)	0.568
Subject is too busy	5 (11.9)	4 (8.5)	2 (4.3)	4 (8.9)	2 (4.4)	0.643
Financial barriers						
Financial problems from out-of-pocket payments	12 (28.6)	9 (19.1)	13 (28.3) ³	15 (33.3) ²	15 (33.3) ³	0.549
Financial problems from high cost per session	9 (21.4)	14 (29.8) ²	13 (28.3) ³	14 (31.1) ³	12 (26.7)	0.875
Financial problems from long duration of rehabilitation	2 (4.8)	6 (12.8)	14 (30.4)	13 (28.9)	14 (31.1)	0.005

Table 2. Self-Perceived Barriers to Non-Adherence to Rehabilitation at All Time Points (Con't)

	n (%)					P value‡
	Discharge	3 months	6 months	9 months	1 year	
	(n = 42)*	(n = 47)†	(n = 46)†	(n = 45)†	(n = 45)†	
Medical barriers						
Effects from medical conditions limiting rehabilitation participation	6 (14.3)	3 (6.4)	6 (13.0)	6 (13.3)	7 (15.6)	0.706
Perceptual barriers						
Satisfied with current functional state	13 (31.0) ³	15 (31.9) ¹	19 (41.3) ¹	16 (35.6) ¹	16 (35.6) ²	0.859
Not interested to participate in rehabilitation	5 (11.9)	11 (23.4)	18 (39.1) ²	18 (40.0)	21 (46.7) ¹	<0.001
Feels rehabilitation is not beneficial	7 (16.7)	9 (19.1)	5 (10.9)	8 (17.8)	7 (15.6)	0.849

Note: Superscript numbers represent the rank order of the top three barriers at the specified time point.

*Based on subjects who did not intend to continue with rehabilitation after discharge.

†Based on subjects who were non-adherent to rehabilitation at the specified time point.

‡Linear by linear association test for trend.

Discussion

In our study, only 40% of patients recommended for continuation of rehabilitation after discharge from an inpatient rehabilitation unit intended to adhere to the recommendation; by the third month after discharge, only 20% of patients were undergoing rehabilitation and this proportion decreased to less than 5% by 1 year. Our attendance rates at post-discharge rehabilitation are lower than data from the US and Australia studies which report that attendance at rehabilitation in the community is about 20% at 1 year.^{9,10} A previous local study on stroke patients reported that 28% of subjects were still participating in rehabilitation one year after discharge from 2 community hospitals.¹¹ The follow-up phase of our study was conducted during the global financial crisis in 2009 and as Singapore was also affected, financial barriers may have been felt more acutely during this phase and contributed to the lower rate

of rehabilitation attendance in our study.

Although Singapore is an urbanised compact city, ambulating to the nearby public transport (i.e. bus stop or subway) is still a physical challenge. Moreover, most local buses require passengers to climb stairs to board and alight, contributing another barrier for subjects. An alternative form of transport is to use a taxi but it is expensive for the majority of patients. For the severely disabled, especially the bedbound who cannot assume a sitting position, subjects pointed out that taxis were unsuitable and a non-emergency ambulance would be required. However, the cost of an ambulance for a one-way journey could cost 4 to 8 times the cost of a taxi fare. Another alternative would be to use a car but car ownership in Singapore is tightly regulated and is very expensive, and hence is not a viable option for most subjects.

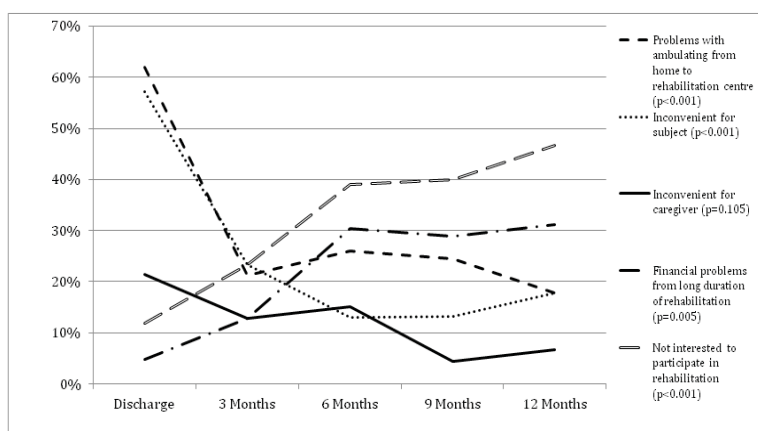


Fig. 2. Trends in self-perceived barriers which changed significantly with time.

A possible solution to environmental barriers, especially for the severely disabled, is home rehabilitation whereby therapists would visit the subject's home instead. However, home rehabilitation is currently not subsidised or eligible for use under Singapore's mandated medical savings account (Medisave) or medical insurance (Medishield), and is 3 to 5 times more expensive than day rehabilitation for 1 session. Hence, home rehabilitation is expensive and unaffordable for most subjects.

Singapore is a multicultural Asian society, and Asian values probably have an effect on the perceptions of the population on rehabilitation. In stark contrast to Anglo-American societies, the elderly in Chinese cultures gain social approval and social status from being dependent on their offspring, a phenomenon termed as 'generational dependency' by Hong and Liu, resulting in Chinese elderly being willing and even eager to become dependent on their offspring.¹⁶ This inclination to dependence could make these elderly less likely to be interested in rehabilitation and view it as an unnecessary chore. Their offspring would likewise be more inclined to look after them or employ domestic workers as an expression of filial piety, rather than encourage them to participate in rehabilitation to regain their functional independence, contributing to the increasing disinterest in rehabilitation with time.

Ageism is a societal phenomenon that has been observed all over the world, with the negative consequences of ageing being unconditionally unaccepted by both the elderly themselves and the people around them.¹⁷ As alluded to in the results of the qualitative phase, ageist attitudes towards health shown by the patients themselves were noted. These included a view that disability should be expected in old age and need not be alleviated even if interventions to do so exist. The ageism exhibited could again be influenced by misconceptions and a lack of information about healthcare and the benefits of rehabilitation.

Applying the conceptual framework of the Health Belief Model¹⁸ to structure our findings within a conceptual framework, newly disabled persons may not perceive continued dependency or failure to improve one's functional status as a consequence of non-adherence to rehabilitation (i.e. they do not consider themselves as susceptible to functional dependency because they viewed their disabling condition like stroke as a final endpoint). Yet, almost 90% of our study population acknowledged that inpatient rehabilitation was beneficial. Perhaps the issue is that although our subjects were convinced of the benefits of inpatient rehabilitation, they were less so with continuation of rehabilitation after discharge. There should also be greater public, patient and family education on the value and importance of subacute rehabilitation to maximise functional recovery, and the undesirable outcome of

unnecessary and irreversible disability with non-adherence with rehabilitation. Such education should also be coupled with peer group influence such as sharing of positive experiences by patients who benefited from post-discharge rehabilitation. Cues to action such as reminders to attend such as telephone reminders to subjects and caregivers may also aid in the promotion of rehabilitation adherence. Lastly, our study's focus on the barriers to rehabilitation adherence provides a rich contextualised understanding on the factors that facilitate or discourage adoption of post-discharge rehabilitation. The Housing Development Board (HDB) is already reconfiguring lifts in 5300 blocks built before 1990 to open on every level with blocks with higher proportions of elderly and disabled residents receiving priority.¹⁹ However, about 200 blocks will not qualify for the lift upgrading programme because of the high cost. The Land Transport Authority of Singapore has recently retrofitted all 4500 bus stops in Singapore to be wheelchair-accessible by replacing steps with ramps, removing potential obstacles and creating more space for wheelchairs to manoeuvre.²⁰ The government is also funding the capital cost of replacing steps in all buses with ramps by 2020. In the light of Singapore's low reproductive ratio, rising old dependency ratio, rising rates of singlehood and shrinking family sizes, social barriers are expected to escalate, and the need for social support services will correspondingly increase. Financial barriers such as transportation and day rehabilitation centre fees also need to be addressed to offset the cumulative cost of weekly rehabilitation sessions over months which can contribute to a significant amount in monthly out-of-pocket expenses. Subsidies for home rehabilitation, especially for the severely disabled and homebound, should also be considered.

Our study has several limitations, foremost being the relatively small sample size which probably accounted for the lack of statistically significant associations between caregiver support, means test category, perceived benefit from inpatient rehabilitation and intention to continue with rehabilitation after discharge. About half of our patients refused audio-taping and some data may have been lost from using field notes alone. Our study was limited to one community hospital and may not be generalisable to patients from other hospitals or other settings. Nevertheless, the qualitative themes identified and quantitative results are still useful for clinicians and policymakers. Also, the barriers identified were patient perceived and may not reflect true circumstances. Nevertheless, self-perceived barriers are important as they closely correlate with patient health-seeking behaviour. Lastly, in Figure 1, it should be noted that although we excluded patients who were lost to follow-up from the denominator when calculating attendance rates, these patients could have attended rehabilitation (but we could not contact them to verify whether they did).

Conclusion

In conclusion, only two-fifths of newly disabled older adult patients recommended for continuation of rehabilitation after discharge from an inpatient rehabilitation unit intended to adhere to the recommendation, one fifth were actually undergoing rehabilitation at 3 months, and this proportion decreased to less than 5% by 1 year. The barriers to post-discharge rehabilitation attendance were functional, social, financial and perceptual. Functional and social barriers were more frequently cited during the early post-discharge period but financial and perceptual barriers were more frequently cited during the late post-discharge period. These barriers must be addressed if we wish to improve attendance rates of post-discharge rehabilitation when recommended by healthcare professionals.

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Single Mothers Have a Higher Risk of Mood Disorders

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Abstract

Introduction: Previous research has shown single mothers to be at greater risk for both physical and mental health disorders as compared to married mothers. Psychiatric disorders, in particular depression, have been shown to be more prevalent in single mothers than married mothers. This study was aimed at comparing the prevalence of depression, other mood, and anxiety disorders in single and married mothers in a multiethnic Asian society. **Materials and Methods:** The Singapore Mental Health Study (SMHS) was a cross-sectional survey of the representative population of Singapore. The survey targeted Singapore residents aged 18 years and above. Trained interviewers established the diagnoses of mental disorders using the Composite International Diagnostic Interview version 3.0 (CIDI 3.0). Physical illnesses, social support and sociodemographic correlates were established using structured interviews. For the purpose of this study, single mothers were defined as unmarried, divorced/separated/widowed mothers who had children aged 21 years and below. **Results:** Face-to-face interviews were completed with 6616 respondents from December 2009 to December 2010. After controlling for sociodemographic correlates in multiple logistic regression model, single mothers had significantly higher odds of having mood disorders (OR = 5.28) as compared to married mothers. **Conclusion:** Our study found that single mothers in Singapore across ethnicities, experienced a higher risk for mood disorders as elsewhere in the world. Single motherhood was also associated with lower age and education. Our study identifies young, single mothers as a vulnerable group associated with mental illnesses that must be targeted with specific interventions to improve mental health and well-being.

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Key words: Anxiety disorder, Major depressive disorder, Single mother, Social support

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Introduction

Changing family structures over the last few decades have led to the emergence of the single parent household as a common “alternative” family form. Similar to the trend in other parts of the world, Asian societies too are facing an increasing number of single-parent households.¹ Single-mother families are of interest as relatively little work has been done to study problems or difficulties, especially health consequences specific to their circumstances in the Asian context.

Singapore enjoys a status on par with other highly developed countries in terms of socioeconomic growth and demographic trends. The majority of Singapore residents belong to 1 of 3 Asian races; Chinese, Malay and Indian.² These societies traditionally favour the dual-parent family structure, with the family as the pillar of Asian society.³ Government policy in Singapore also supports dual-parent

households over single-parent families. This is manifest in uneven benefits and subsidies accorded to “normal families” vs single-parent families in taxation, housing, welfare schemes and programmes aimed at improving fertility.⁴

Previous research has shown single mothers to be at greater risk for both physical and mental health disorders as compared to married mothers.⁵⁻⁷ Psychiatric disorders, in particular depression, have been shown to be more prevalent in single mothers than married mothers.⁸⁻¹² Single mothers have also been found to have higher risk for other mood and anxiety disorders.¹³⁻¹⁶ This may be attributed to risk factors that predispose to depression, such as gender, socioeconomic disadvantages, social support, etc., which are also associated with single parenthood.¹⁷

Single mothers have been found to experience greater levels of financial hardship than other family types.^{8,18,19}

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Low educational levels and low income have also been associated with depressive symptoms in single mothers.^{20,21} The association between employment and single mother status is somewhat unclear. In 1997, Brown and Moran found that among their sample of women from Islington, UK, single mothers were more likely to have full time employment than married mothers.⁸ In contrast, Cairney et al found that single Canadian mothers were more likely to be unemployed.¹⁰ Increased attention is also being paid to the health-related impacts of perceived social support on mothers. Single mothers have also been found to lack social support²²⁻²⁴ and lack of social support has been associated with depression.²⁵⁻²⁷

Few epidemiological studies have compared the prevalence of psychiatric disorders in single and married mothers in Asia. Although it is now well established in many parts of the world that single mothers have an increased risk for psychiatric disorders, it is yet unclear whether similar differences occur in Asian societies and which factors contribute to it. The traditional cultural values of the 3 dominant ethnicities in the face of a “modern”, economically thriving metropolis like Singapore make for a unique experience of single motherhood; one that has not been explored much thus far. This study aims to: (i) compare the prevalence of depression, other mood and anxiety disorders in single and married mothers in Singapore, and (ii) determine the effect of sociodemographic correlates and perceived social support on the association of these psychiatric disorders among single mothers.

Materials and Methods

Sample

The Singapore Mental Health Study (SMHS) was a cross-sectional survey of the representative population of Singapore. The survey targeted Singapore residents (Singapore Citizens and Permanent Residents) aged 18 years and above. The sample size was calculated by estimating statistical power for single and two proportions to determine sample sizes required overall, as well as for subgroups (i.e. age and ethnicity) to produce a precise estimate with a margin of error equal to 0.05 for different disorders. Those of Malay and Indian ethnicity as well as those aged 65 years and above were oversampled to ensure that sufficient sample size would be achieved to improve the reliability of estimates for the subgroup analyses. Thus, a disproportionate stratified sampling (by age groups and ethnicity) was used where the 3 main ethnic groups (Chinese, Malays, and Indians) were sampled in equivalent proportion of about 30% each. The weighted data were then adjusted to represent the Singapore population based on the 2007 census. Face-to-face interviews were completed with 6616 respondents from December 2009 to December 2010. The

survey response rate was 75.9%. The sample for this study was selected from SMHS to include mothers who were single/unmarried (n = 10), married (n = 1510), divorced/separated (n = 97) and widowed (n = 21) with children aged 21 years and below (21 years is the year of majority in Singapore). The detailed methodology of the study has been described in a previous article.²⁸ The study was approved by the ethics committee (National Healthcare Group, Domain Specific Review Board) and all respondents and parents/guardians of respondents aged 18 to 20 years gave written informed consent for participating in the study.

Measures

Trained interviewers established the diagnoses of mental disorders using the Composite International Diagnostic Interview version 3.0 (CIDI 3.0)²⁹ based on Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (APA, 2000)³⁰ criteria. The psychiatric disorders included in this study were mood disorders including major depressive disorder (MDD), dysthymia and bipolar disorder; anxiety disorders including generalised anxiety disorder (GAD), and obsessive compulsive disorder (OCD); and alcohol use disorders i.e. alcohol abuse and alcohol dependence. Lifetime and 12-month prevalence of each disorder were established using hierarchy rules.

Health-related quality of life (HRQoL) was established using the Euro-QoL-5D (EQ-5D). The EQ-5D is a self-reported generic HRQoL instrument developed by the EuroQoL Group.³¹ EQ-5D comprises a descriptive system and a visual analogue scale (VAS). The descriptive system assesses 5 domains (i.e. mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and respondents were asked to rate their health on a 3-point severity scale (no problem/moderate problem/extreme problem). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' (100) and 'Worst imaginable health state' (0). The information can be summarised as a single score which represents 'health utilities' which are anchored at 0 (equal to death) and 1 (health state of full health). We used the UK time trade-off values³² to convert the states to health utility scores.

Data on social support were collected using the CIDI Social Network module. This included questions on social network and perceived social support. Frequency of social contact was analysed using 2 questions that measured average number of contacts that the respondent had: (i) with relatives who do not live with them, and (ii) with friends. The questions to the respondents were, “How often do you talk on the phone or get together with relatives who do not live with you/friends”? The categories for answers were: Most every day, a few times a week, a few times a month,

once a month and less than once a month. Perceived social support was analysed using 4 questions: (i) How much can you rely on your relatives who do not live with you/friends for help if you have a serious problem and (ii) how much can you open up to relatives who do not live with you/friends if you need to talk about your worries. The categories for answers were: A lot, some, a little, or not at all. The scale was dichotomised with choices ‘a lot’ and ‘some’ indicating good social support and those that indicated ‘a little’ or ‘not at all’ were assumed to have poor social support. The paper and pencil version of the CIDI-3.0 (used for interviews in Bahasa Melayu language) combines the information on friends and relatives into a single question. Hence, the computer assisted personal interviewing (CAPI) data was combined for the 2 questions ie. perceived social support was computed as ‘good’ if the respondent endorsed at least ‘2’ (i.e. some) for either friend or relative for each domain.^{33,34}

Disability was assessed with the Sheehan Disability Scale (SDS) which examined functioning in work, household, relationship, and social roles in the worst month of the past year. Responses were scored with a 0-to-10 visual analogue scale having response options labeled: none (0), mild (1 to 3), moderate (4 to 6), severe (7 to 9), and very severe (10). Respondents were also asked an open-ended question to estimate the number of days in the past 365 days when they were “totally unable to work or carry out your normal activities” because of depressive symptoms.

Sociodemographic data was collected using a structured interview. Data on age (at interview), gender, ethnicity, marital status, educational qualifications, employment, income and number of children was captured. Chronic physical conditions were assessed using a checklist adapted from the CIDI checklist of chronic medical disorders and the respondents were asked to report any of the disorders listed in the checklist.

Statistical Analyses

Statistical analyses were carried out using the Statistical Analysis Software (SAS) System version 9.2 (SAS Institute, Cary, NC). To ensure that the survey findings were representative of the Singapore population, the data were weighted to adjust for oversampling and poststratified by age and ethnicity distributions between the survey sample and the Singapore resident population in 2007. Descriptive analyses were performed to establish the prevalence of lifetime and 12-month disorder as well as describe the sociodemographic profile of the study population. Analysis of variance was used to compare EQ-5D scores between 2 groups. We performed multiple logistic regression analyses to examine odds of having lifetime mental disorders and social correlates among single mothers versus married mothers after controlling for sociodemographic variables

including age, ethnicity, education, employment, income and number of children. Standard errors (SE) and significance tests were estimated using the Taylor series linearisation method. Multivariate significance was evaluated using Wald χ^2 tests based on design-corrected coefficient variance-covariance matrices. Statistical significance was evaluated at the 0.05 level using two-sided tests.

Results

Only 0.4% (n = 10) women in our sample reported that they were unmarried mothers, while 6.3% (n = 97) women reported that they were divorced/separated and 1.2% (n = 21) reported that they were widowed mothers with children aged 21 years and below. Given the small numbers of these groups, we combined them into a single category—‘single mothers’ with children aged 21 and below at the time of the study.

The sociodemographic characteristic of single and married mothers with children aged 21 and below is presented in Table 1. The study sample comprised 1638 respondents; with married mothers (92.2%) constituting the majority of the sample. Most of the single and married mothers were Chinese (73.7% and 74.3%), followed by Malays (17.2% and 15.3%), Indians (6.5% and 8.3%) and only 2.6% and 2.2% belonged to the ‘others’ ethnic groups. There was significant difference in terms of education and employment status between the 2 groups. The proportion of pre-university/junior college/diploma and university qualifications, were significantly higher in married mothers as compared to single mothers. Married mothers were significantly more likely to belong to the economically inactive group as compared to single mothers.

Table 2 shows the weighted prevalence of lifetime and 12-month mood, anxiety and alcohol disorders among single mothers and married mothers with children aged 21 and below. Lifetime and 12-month mood disorders were significantly higher among single mothers than married mothers. The prevalence of anxiety and alcohol disorders were also relatively more common among single mothers than the married mothers. After controlling for sociodemographic correlates in multiple logistic regression model, single mothers had significantly higher odds of having mood disorders (OR = 5.28) as compared to married mothers. There were no significant differences in the prevalence or odds of having any physical illness between the 2 groups (data available on request).

The proportion of single mothers who reported that they “open up” to relatives/friends (64%) was significantly lower as compared to married mothers. After controlling for sociodemographic correlates in multiple logistic regression model there were no significant differences between the 2 groups (Table 4). There were also no significant differences

Table 1. Sociodemographic Characteristics of Single Mothers and Married Mothers with Children Aged 21 and Below in the Singapore Mental Health Study (n = 1638)

	Single* Mothers 128 (7.81%)			Married Mothers 1510 (92.19%)			X ²	P value
	n	%	SE	n	%	SE		
Age (years)								
18 to 34	29	18.35	4.40	363	19.80	0.37	0.117	0.943
35 to 49	75	64.68	5.75	917	64.41	0.49		
50 to 64	24	16.97	4.61	230	15.80	0.39		
Ethnicity								
Chinese	35	73.68	3.75	418	74.28	0.31	1.161	0.762
Malay	60	17.23	2.73	629	15.30	0.22		
Indian	29	6.52	1.36	419	8.26	0.13		
Others	4	2.57	1.25	44	2.16	0.11		
Education								
Pre-primary	7	5.61	2.99	34	1.25	0.34	31.790	<0.0001
Primary	33	26.07	5.63	240	13.99	1.26		
Secondary	57	43.03	6.34	599	39.44	1.81		
Vocational	11	8.43	3.51	76	3.94	0.66		
Pre-U/Junior college/Diploma	15	14.88	4.64	251	18.72	1.47		
University	5	1.97	0.98	310	22.66	1.55		
Employment								
Employed	102	85.59	4.20	890	68.32	1.70	27.951	<0.0001
Economically inactive	16	8.32	3.14	545	30.71	1.69		
Unemployed	9	6.09	3.01	29	0.97	0.28		
Personal Income (Annual)								
S\$19,999 and below	82	56.08	6.54	901	56.12	1.92	1.567	0.457
S\$20,000 to 49,999	32	33.24	6.27	360	27.58	1.73		
S\$50,000 and above	9	10.68	4.31	146	16.31	1.50		
Number of Children								
1 to 4	124	97.05	2.12	1459	98.47	0.30	0.787	0.375
5 and above	4	2.95	2.12	51	1.53	0.30		

*Includes women who are single, separated, divorced and widowed.

Table 2. Weighted Prevalence of Lifetime and 12-Month Mood, Anxiety and Alcohol Disorders Among Single Mothers and Married Mothers with Children Aged 21 and Below (n = 1638)

	Single Mothers 128 (7.81%)			Married Mothers 1510 (92.19%)			P Value
	n	%	SE	n	%	SE	
Lifetime Mood Disorder	29	26.74	5.80	102	6.86	0.93	<0.001
Lifetime Anxiety Disorder	9	6.11	3.01	76	4.98	0.81	0.692
Lifetime Alcohol Use Disorder	4	1.46	0.81	10	0.64	0.28	0.2338
Any Lifetime Mental Disorder	34	30.23	5.96	159	10.25	1.11	<0.001
12-Month Mood Disorder	13	14.44	4.78	52	2.69	0.57	<0.001
12-Month Anxiety Disorder	5	3.14	2.13	34	2.46	0.59	0.7369
12-Month Alcohol Use Disorder	2	0.54	0.39	-	-	-	-
Any 12-Month Mental Disorder	16	17.06	5.07	74	4.44	0.76	<0.001

Table 3. Odds Ratios for Lifetime Mood, Anxiety and Alcohol Use Disorders of Single Versus Married Mothers Controlling for Sociodemographic Factors

	Mood		Anxiety		Alcohol		Any Mental Disorder	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Married Mothers	Ref.		Ref.		Ref.		Ref.	
Single Mothers	5.28	(2.47, 11.27)*	1.1	(0.33, 3.67)	1.52	(0.4, 5.69)	3.66	(1.83, 7.32)*
Number of Children	1.19	(0.87, 1.62)	0.69	(0.46, 1.06)	0.59	(0.18, 1.89)	1.07	(0.81, 1.42)
Age (years)								
18 to 34	2.92	(1.1, 7.72)†	1.86	(0.44, 7.99)	3.39	(0.38, 30.08)	2.26	(0.97, 5.31)
35 to 49	1.33	(0.56, 3.17)	1.73	(0.47, 6.42)	4.64	(0.44, 49)	1.32	(0.62, 2.81)
50 to 64	Ref.		Ref.		Ref.		Ref.	
Ethnicity								
Chinese	Ref.		Ref.		Ref.		Ref.	
Malay	0.68	(0.39, 1.17)	1.19	(0.67, 2.11)	2.0	(0.59, 6.85)	0.88	(0.56, 1.38)
Indian	0.96	(0.54, 1.68)	1.41	(0.78, 2.55)	1.98	(0.37, 10.52)	1.07	(0.67, 1.7)
Others	1.69	(0.58, 4.97)	0.46	(0.05, 3.86)	.	.	1.86	(0.73, 4.79)
Education								
Pre-primary	0.48	(0.07, 3.19)	0.51	(0.05, 5.49)	8.22	(0.77, 87.52)	0.56	(0.11, 2.99)
Primary	0.37	(0.1, 1.4)	1.26	(0.32, 4.89)	1.51	(0.17, 13.66)	0.54	(0.19, 1.57)
Secondary	0.74	(0.28, 2.01)	0.94	(0.32, 2.77)	2.76	(0.56, 13.57)	0.77	(0.34, 1.74)
Vocational	0.74	(0.21, 2.61)	0.27	(0.06, 1.19)	0.96	(0.07, 14.14)	0.62	(0.21, 1.86)
Pre-U/Junior college/Diploma	0.87	(0.35, 2.17)	0.73	(0.25, 2.09)	3.37	(0.27, 42.74)	0.78	(0.36, 1.66)
University	Ref.		Ref.		Ref.		Ref.	
Employment								
Employed	Ref.		Ref.		Ref.		Ref.	
Economically inactive	0.7	(0.33, 1.49)	0.59	(0.24, 1.48)	0.05	(0.01, 0.61)†	0.66	(0.35, 1.24)
Unemployed	1.68	(0.43, 6.54)	0.89	(0.17, 4.55)	.	.	1.62	(0.44, 5.99)
Personal Income (Annual)								
S\$19,999 and below	Ref.		Ref.		Ref.		Ref.	
S\$20,000 to S\$49,999	0.67	(0.32, 1.43)	1.82	(0.76, 4.34)	0.77	(0.14, 4.22)	1.01	(0.55, 1.88)
S\$50,000 and above	1.08	(0.4, 2.91)	1.47	(0.45, 4.87)	.	.	1.11	(0.48, 2.58)

**P* value <0.01; †*P* value <0.05

Table 4. Weighted Prevalence and Odds Ratio of Social Correlates Among Single Mothers and Married Mothers with Children Aged 21 and Below (n = 1638)

	Single Mothers			Married Mothers			Single Mothers vs Married Mothers			
	n	%	SE	n	%	SE	<i>P</i> Value	OR*	95% CI	<i>P</i> value
Frequency of Contact										
Contact with Family Members	97	81.39	4.79	1315	86.86	1.28	0.214	0.64	0.30, 1.39	0.261
Contact with Friends	105	85.56	4.50	1141	76.19	1.61	0.0951	1.92	0.89, 4.14	0.094
Social Support										
Rely on Relatives/Friends	76	60.32	6.25	1050	71.60	1.68	0.0624	0.78	0.42, 1.43	0.418
Open up to Relatives/Friends	84	63.98	6.19	1078	76.56	1.53	0.0281	0.66	0.36, 1.20	0.170
Poor Interaction with Relatives/Friends	61	53.65	6.37	663	45.37	1.86	0.2115	1.34	0.74, 2.40	0.332

*Multiple logistic regression controlled for sociodemographic factors include number of children, age, ethnicity, education, employment and income.

found between single mothers and married mothers with respect to EQ-5D VAS score and EQ-5D index score.

Discussion

Consistent with other studies done around the world, single mothers had a significantly higher prevalence of mood disorders.⁸⁻¹² The prevalence of mood disorders was also found to be associated with age: younger mothers (aged 18 to 34 years) having nearly 3 times the risk than older women aged 50 to 64 years. This may be explained by the higher prevalence of MDD in younger women in general as reported in an earlier study.³⁵ Single motherhood may also present a greater challenge to younger women because of the lack of experience and maturity that comes with age. Additionally, they probably have a relative lack of resources and wealth while raising very young children. These combined factors could result in a decline of mental well-being not seen in older women. Though the prevalence of anxiety and alcohol disorders was higher among the single mothers, it was not significantly so. Studies on the association between anxiety disorders and single mothers are inconsistent, while some have shown significantly higher risk of anxiety disorders in single mothers,^{12,16,18} other studies have failed to do so. Alcohol use disorder has not been studied to a great extent in single mothers. Cairney et al did find that previously married women (divorced/separated/widowed) had a higher prevalence for alcohol disorders than never married mothers.¹² However this (and other substance disorders) may be an interesting area to explore especially in comparison with single fathers who have been found to have higher prevalence in some cases.¹⁶

It was interesting to note that though married mothers were more highly educated on average than single mothers, they were more likely to belong to the economically inactive group. This is in line with the idea that single mothers as the only earning member of the household are required to be more economically productive than their married counterparts.^{13,17} Brown and Bifulco³⁶ found that full time working mothers were at higher risk of having clinical depression than non-working mothers especially among single mothers as they more often experienced 2 or more measures of 'work strain' (measured by 'work overload', 'identity destructiveness', 'enjoyment', 'security diminishing characteristics' and 'unsatisfactory relationships') than married mothers, adding to the challenges of motherhood.

The assessment of severity of disability due to MDD (the most prevalent mood disorder in SMHS)³⁵ among the 2 groups using SDS revealed no significant differences between single and married mothers. However, we found that single mothers on an average reported lesser days in the last year when they were completely unable to work due to MDD (5.6 days in single mothers vs 35.1 days in married

mothers). This further corresponds with the need for single mothers to remain economically and functionally active in spite of serious health problems as the sole breadwinner, and, the lack of support from a partner or spouse.

The limitations of our study includes the small number of single mothers in the sample, necessitating the use of a single category to capture never married, as well as widowed, and divorced/separated mothers. Some studies have suggested that single mothers are a diverse group,¹⁸ with never-married mothers occupying an intermittent position between married and separated/divorced mothers with regard to psychopathology¹⁴ and that combining may lead to under/over estimation of risk factors. We also used the broad diagnostic category of mood disorder and did not separate those with MDD, dysthymia and bipolar disorder into three separate groups. As this was a cross-sectional study, we were unable to establish any causal relationships. While it is possible that the stress of single parenting leads to mood disorder, alternatively it is also possible that early onset of mood disorder prevented transition into marriage or recurrent episodes of the disorder lead to separation or divorce. We did not study distal stressors such as childhood abuse and other childhood traumas that may have a role in the association between single mothers and MDD.^{9,18} As the information obtained was based on self-report, it was subject to recall bias on part of the respondents. However, the strengths of our study are that we used a structured instrument to establish the diagnosis of mood disorders and other psychiatric illnesses. This is also the first study examining the association of single mothers and psychiatric disorders in a multiethnic Asian country, and the relatively high response rate of 75.9% ensures the generalisability of our findings.

Conclusion

In conclusion, our study found that single mothers in Singapore across ethnicities, experienced a higher risk for mood disorders as elsewhere in the world. Single motherhood was associated with lower age and education. The factors that moderate/mediate the relationship between single motherhood and mood disorders are not very clear, but it is reasonable to assume that sole-parenting responsibilities and the associated potential lack of resources (social and economic) would have a role to play. This has policy implications as it clearly identifies young, single mothers as a group for targeted intervention to improve mental health and well-being. The National Council of Social Services in Singapore runs Single-Parent Family Support Services, with the objectives of "supporting and promoting the psycho-emotional well-being of single-parent families towards stability, growth and acceptance of the new family unit". However, more needs to be done both in terms of

creating awareness, early detection and provision of client centred services for this group. Further research is needed both among larger samples, that could help tease out and identify mental health problems within subgroups of single mothers (never married, widowed, divorced/separated) and in longitudinal cohorts that could help us understand the relationship between the natural history of psychiatric disorders and family structures. This could also contribute to our understanding of the role of a major life event (divorce or bereavement) in the health and coping mechanisms of these women.

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Immunophenotypic, Cytogenetic and Clinical Features in Chinese Adult Acute Lymphoblastic Leukaemia (ALL) Patients

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Abstract

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Key words: Biological characteristics, Cytogenetics, Immunophenotype

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Immunophenotypic, Cytogenetic and Clinical Features in Chinese Adult Acute Lymphoblastic Leukaemia (ALL) Patients

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Abstract

Introduction: This study sought to investigate the immunophenotypic subtype profiles of 110 Chinese adult patients with acute lymphoblastic leukaemia (ALL) and its association to cytogenetics and the clinical features. **Materials and Methods:** A total of 110 adult patients with ALL were immunophenotyped by CD45/SSC double parameters and 4 colour flow cytometry. Seventy-three cases were also subjected to karyotype analysis by R-banding technology. The clinical and laboratory data of 110 ALL patients were retrospectively analysed. **Results:** Of all the patients, 21.8% were identified as T-ALL, 78.2% as B-ALL. Abnormal karyotypes were detected in 37 out of 73 (50.7%) cases and the most common cytogenetic abnormality was the Philadelphia (Ph) chromosome, which was found in 23.3% (17/73) of the cases. Myeloid antigen (MyAg) expression was documented in 47.3% of the 110 adult ALL cases analysed and CD13 was the most commonly expressed MyAg in ALL patients (32.1 %). No difference was observed in the expression of MyAg between the groups of patients with T-ALL (45.8%) and B-ALL (47.7%). Our data showed that older age, higher CD34 positivity and lower proportion of patients with splenomegaly were found to be correlated with MyAg+ ALL, and that patients with Ph+ B-ALL were older, presented with higher haemoglobin level and higher CD34 expression. No statistical difference was noted in complete remission (CR) rate, relapse rate, induction mortality or total death rate among My+ and My-, Ph+ and Ph-, or B-ALL and T-ALL patients. **Conclusion:** Our results indicate that the distribution of ALL in Chinese adult patients was similar with the general distribution pattern in the other countries, and the expression of MyAg in patients with T-ALL and B-ALL was comparable. Both the expression of MyAg and the presence of Ph chromosome in adult ALL were significantly associated with median age and CD34 expression while not with the response to induction treatment.

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Introduction

Acute lymphoblastic leukaemia (ALL) is a malignant disease resulting from the accumulation of genetic alterations of B or T lymphoid precursor cells.^{1,2} Immunophenotyping, cytogenetic-molecular studies, and more recently, high resolution genome-wide screening are characterising ALL as a heterogeneous disease with distinct manifestations and prognostic and therapeutic implications.³ Of the many variables that influence prognosis, genetic subsets, initial white blood cell count (WBC), age at diagnosis, and early treatment response are the most important.⁴ ALL is the most

common leukaemia in children and accounts for 20% of acute leukaemias in adults, and it remains one of the most challenging adult malignancies, especially with respect to therapy. The 5-year event-free survival is over 80% for children but only approximately 40% for adults with ALL.¹ Though the outcome of patients with ALL has improved with intensification of therapy and complete remission (CR) can now be achieved in majority of adults with ALL, only 30% to 40% of them are cured with varying proportion according to clinical and biological risk factors.⁵⁻⁹

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Because leukaemic lymphoblasts lack specific morphologic and cytochemical features, the assessment of immunophenotype by flow cytometry and the identification of distinct cytogenetic-molecular abnormalities have become essential and are part of the World Health Organization classification of neoplastic diseases of hematopoietic and lymphoid tissues.¹⁰ In this study, we have investigated the clinical and biologic features of 110 adult patients with ALL and analysed the correlations between immunophenotype, cytogenetic abnormalities and clinical features of these patients. One of the most important aims of this study was to investigate the prevalence of the expression of the myeloid associated antigens in adult ALL and to relate their presence to the initial clinical and biologic features as well as to early response to therapy. Expression of myeloid antigen (MyAg) was a common aberrancy in ALL and reports vary widely on the degree of MyAg expression.¹¹⁻¹⁴ Consequently, the clinical significance of MyAg expression is unclear. One potential reason for this variation is differences in the binding characteristics of different monoclonal antibody clones.¹⁵ Different thresholds for antigen positivity and different flow cytometry methods, instruments, and reagents may also have a role. Some scholars indicated that ALL patients with MyAg expression had poor prognosis.^{16,17} However, most reports indicate that MyAg expression in ALL patients is not associated with adverse presenting clinical and biological features and prognosis.^{14,18} The relatively small numbers of patients in ALL series and differences in the treatment protocols have led to divergent results. Although the presence of MyAg lacks prognostic significance, it can be useful in distinguishing leukaemic cells from normal hematogones and in monitoring patients for minimal residual disease (MRD).¹⁹

Materials and Methods

Study Population and Treatment Protocols

A total of 110 adult patients with newly diagnosed ALL were enrolled in this study and their bone marrow (BM) were collected from January 2007 to July 2010 in our hospital. Of these subjects, there are 60 males and 50 females with a median age of 31 years, ranging from 15 to 77 years old. The only inclusion criterion was the availability of a full immunophenotypic profile.

Patients received remission-induction and consolidation therapy, followed by risk-directed continuation treatment. The main remission-induction programme is VDLP regimen (vincristine 2 mg, day 1; daunomycin 40 mg/day, days 1 to 3; L-asparaginase 10,000 U/day, days 14 to 25 and dexamethasone 10 mg/day, days 1 to 20, then dexamethasone 5 mg/day, days 21 to 25). Once remission was achieved, patients received consolidation therapy and continuation treatment as scheduled: VDLP-EA-high dose

methotrexate-VMLP-EA-high dose methotrexate-VDLP, repeat from VDLP for 5 cycles. EA (etoposide + Ara-C) regimen: etoposide 40 mg/m²/day, days 1 to 5; cytosine arabinoside 2g/m²/day, days 1 to 5. Methotrexate 3 to 5 g/m², 24 hours. VDLP regimen: vincristine 2 mg, day 1; daunomycin 60 mg/day, days 1 to 3; cyclophosphamide 800 mg/day, days 1,3 and dexamethasone 10 mg/day, days 1 to 20, then dexamethasone 5 mg/day, days 21 to 25. VMLP regimen: vincristine 2 mg, day 1; mitoxantrone 10 mg/day, days 1 to 3; L-asparaginase 10,000 U/day, days 14 to 25 and dexamethasone 10 mg/day, days 1 to 20, then dexamethasone 5 mg/day, days 21 to 25.

Morphologic CR was defined as less than 5% blast cells in a regenerated BM aspirate, absence of extramedullary leukaemia, and peripheral blood (PB) neutrophil and PLT counts of $>1.5 \times 10^9$ and $>100 \times 10^9/L$, respectively. Clinical relapse was defined as detection of at least 5% blast cells in BM or detection of leukaemic cells extramedullary. The study was approved by the ethics committee in our hospital with written informed consent from the parents or guardians, as well as from the patients.

Immunophenotype Detection of Leukaemia Cells

Immunophenotype was determined for ALL cases using 4 colour flow cytometry profiles with fluorescein isothiocyanate (FITC), phycoerythrin (PE), allophycocyanin (APC) or peridinin chlorophyll-protein (Per-CP) labeled monoclonal antibodies, including CD45, CD34, CD10, CD19, CD2, CD13, HLA-DR, CD33, CD7, CD38, CD20, CD22, CD15, CD9, CD117, CD14, CD3, CD5, CD4, CD8, CyCD3, CyIgM, and CyCD79a. The reagents and 12 × 75 mm Falcon™ capped polystyrene test tubes were provided by Becton-Dickinson Bioscience in the United States. Cells were acquired and analysed with Cell Quest and Paint-A-Gate software in FACS Calibur flow cytometer (BD Bio). Abnormal populations were recognised by CD45/SSC gating, which was the base of calculating the positive rate of leukaemia-related antigens expressed on the abnormal cells. Cell populations were designated as positive for a particular antigen if more than 20% of the leukaemic lymphoblast events stained beyond an appropriate isotypic cutoff (set at 98% of isotypic control staining); otherwise they were designated as negative. We regarded $\geq 10\%$ of cell expression in a tube as positive for CyIgM, CyCD79a or CyCD3.

Cytogenetic Analysis

BM cells were cultured for 24 hours to prepare for conventional chromosome detection, and karyotype was analysed with R-banding technique. Each karyotype was named according to International Human Chromosomes Nomenclature (ISCN 1995).

Statistical Methods

Statistical analysis was performed taking into account gender, age, WBC count, haemoglobin (HB) level, PLT count, BM blasts, presence or absence of hepatomegaly, splenomegaly and lymphadenopathy, immunophenotype, cytogenetics and the patients's response to treatment. Data analysis was carried out using SPSS software (version 13.0, SPSS, Chicago, IL, USA). Statistical differences of various clinical and laboratory parameters between groups were analysed by the Kruskal-Wallis H test, Mann-Whitney U test, chi-Square or Fisher's Exact tests. *P* values of less than 0.05 were considered significant.

Results

Immunophenotype and MyAg Expression in ALL Patients

CD45 staining and side scatter (SS) properties were used to isolate the leukaemic cell populations, referred to as the bulk of the leukaemia and usually defined by a weak CD45 expression (CD45dim) and low SS (SSlow) (Figs. 1 to 3). B-lineage markers: CyCD79a, CD19, CD10, and CD22 were expressed in the vast majority of B-ALL samples. No more than a single T-cell antigen was expressed in any 1 case, and expression of CD3 was not observed. Thus, T-cell/B-cell biphenotypic leukaemias were not observed in this patient cohort. Of 24 T-ALL cases, CD7 was the only surface T-cell

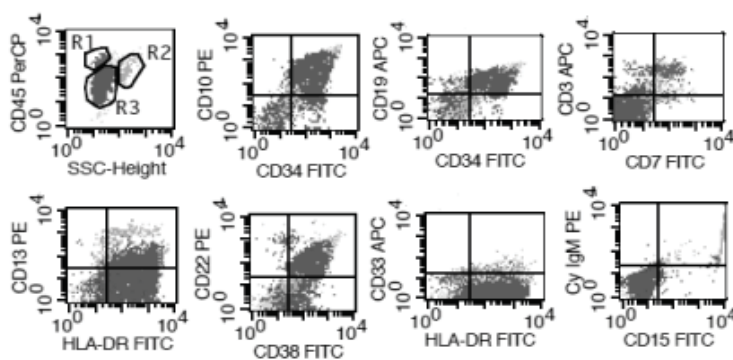


Fig. 1. Com-B ALL. The abnormal blasts (R3) are positive for CD34, CD10, CD19, CD13, HLA-DR, CD38 and CD22.

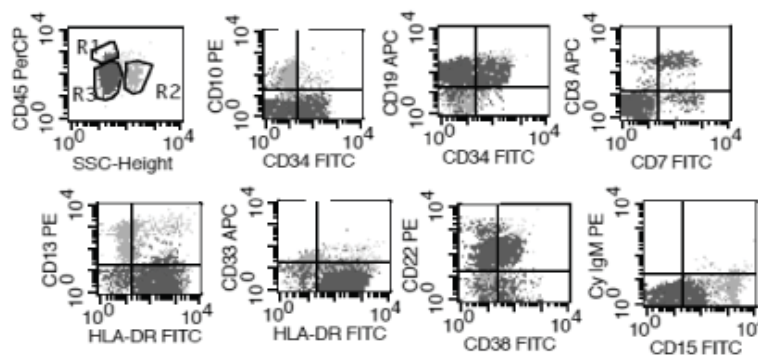


Fig. 2. Pro-B ALL. The abnormal blasts (R3) are positive for CD34, CD19, CD38, HLA-DR, CD22 and CD15.

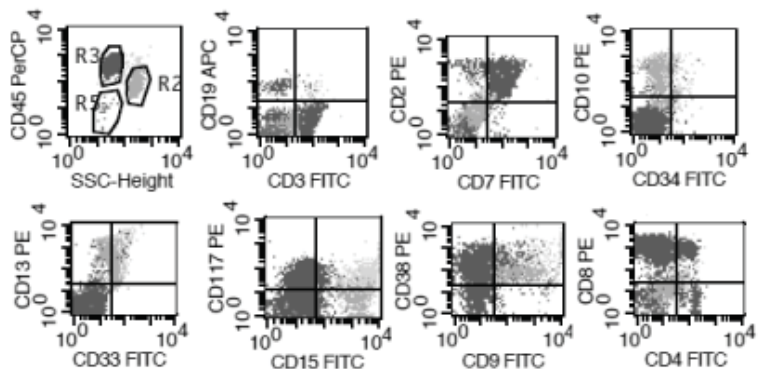


Fig. 3. T-ALL. The abnormal blasts (R3) are positive for CD3, CD2, CD7, CD38, CD8 and CD117.

antigen expressed by all T-ALL cases (100%), followed by CD5 (65.2%), CD2 (65.2%), CD3 (54.2%), CD8 (47.8%) and CD4 (26.1%). The positive rates of CD34 and HLA-DR were much lower in T-ALL than those in B-ALL (25% vs 74.4%, 41.7% vs 100%, $P = 0.000$).

MyAg expression was documented in 47.3% of the 110 adult patients analysed. CD13 was the most commonly expressed MyAg (32.1%) (Fig. 1), followed by CD15 (15.1%) (Fig. 2), CD33 (6.4%) and CD117 (5.7%). CD14 was negative in all ALL patients, and CD117 was negative in all B-ALL patients but positive in 30% T-ALL patients (Fig. 3). CD13 expression was found most commonly in Com B-ALL (42.6%) than CD15 (13.5%) and CD33 (8.5%) ($P = 0.004$, $P = 0.000$), and CD15 expression was found most frequently in ProB-ALL (60%) than that in Com B-ALL (13.5%) and Pre B (3.7%) ($P = 0.008$, $P = 0.001$). The myeloid antigens were detected and seen in the same population as the leukaemic blasts (Figs. 1 to 3). Furthermore, no difference was observed in the expression of MyAg between the groups of patients with T-ALL (45.8%) and B-ALL (47.7%) ($P = 0.873$). MyAg expression was also compared in the subtypes of B-ALL, and MyAg positivity in Com B-ALL (53.2%), Pro B-ALL (58.3%) and Pre B-ALL (50.0%) was comparable.

Cytogenetics

A total of 73 cases were subjected to karyotype analysis, including 59 cases of B-ALL and 14 cases of T-ALL, and the karyotype studies showed that a total of 37 (50.7%) had an abnormal karyotype. Numerical abnormality of chromosome was found in 12 cases, including 7 cases of hyperdiploid and 5 cases of hypodiploid. Structural abnormality of chromosome was found in 25 cases, and 17 cases of $t(9;22)(q34;q11)$ were found in Com-B and Pre-B, 1 case of $t(4;11)(q21;q23)$ were found in Pro-B, and 1 case of $t(10;14)(q24;q11)$, 2 cases of $del(6q)$ were found in T-ALL.

Clinical and Biological Features in ALL Patients

On the basis of the positivity for at least one myeloid marker, we stratified the patients into 2 groups: MyAg+ and MyAg-. The clinical and biological characteristics of the patients were presented in Table 1. No differences were found between the MyAg+ and MyAg- groups with regard to proportion of females/males, median WBC count, haemoglobin level and PLT count, percentage of patients with high WBC count ($>50 \times 10^9/L$), percentage of BM blasts, proportion of B/T-lineage ALL patients and cytogenetic abnormalities. However, the median age in MyAg+ was older than that in MyAg- ALL ($P = 0.016$), and CD34 expression was found in 75.0% of MyAg+ and in 53.4%

of MyAg- cases ($P = 0.019$). In addition, the percentage of patients with splenomegaly in MyAg+ group was much lower than that in MyAg- group (25.5% vs 55.6%, $P = 0.002$), but there was no significant difference between the 2 groups with regard to cases with hepatomegaly or lymphadenomegaly ($P = 0.108$, $P = 0.937$).

Twenty-five ALL patients stopped treatment after diagnosis while the remaining 85 ALL patients received treatment. Seven patients died during remission-induction therapy. We failed to observe any statistical difference between the 2 groups in induction mortality (10.3% vs 6.5%, $P = 0.819$) and total death rate (25.6% vs 21.7%, $P = 0.673$). Seventy-eight ALL patients who received

Table 1. Clinical and Biological Features in MyAg+ and MyAg- ALL Patients

Features	MyAg+	MyAg-	P values
Gender (male/female)	27/25	33/25	0.601
Age (years)	37.0	28.5	0.016
(range)	(24.0 to 49.0)	(17.3 to 42.0)	
WBC count ($\times 10^9/L$)	16.8	19.9	0.834
(range)	(6.2 to 57.5)	(4.2 to 52.1)	
Haemoglobin (g/L)	84.0	84.5	0.867
(range)	(62.0 to 108.0)	(58.8 to 113.8)	
PLT count ($\times 10^9/L$)	41.0	38.0	0.623
(range)	(21.0 to 94.0)	(17.5 to 72.5)	
BM blasts (%)	78.1	84.5	0.544
(range)	(66.8 to 89.9)	(67.4 to 90.6)	
WBC count ($\times 10^9/L$)			
(>50 / <50)	17/35	18/40	0.852
CD34 ($\pm$)	39/13	31/27	0.019
Cytogenetics (normal/abnormal)	18/21	18/16	0.563
Ph ($\pm$)	10/29	7/27	0.610
B-ALL/T-ALL	41/11	45/13	0.873
Hepatomegaly (%)	9/47 (19.1)	18/54 (33.3)	0.108
Splenomegaly (%)	12/47 (25.5)	30/54 (55.6)	0.002
Lymphadenomegaly (%)	24/47 (51.1)	28/54 (51.9)	0.937
CR rate after the first induction (%)	23/35 (65.7)	33/43 (76.7)	0.282
Overall CR rate (%)	29/35 (82.9)	38/43 (88.4)	0.486
Relapse rate (%)	13/29 (44.8)	16/38 (42.1)	0.824
Induction mortality (%)	4/39 (10.3)	3/46 (6.5)	0.819
Total death rate (%)	10/39 (25.6)	10/46 (21.7)	0.673

BM: Bone marrow; CR: Complete remission; MyAg: Myeloid antigen; Ph: Philadelphia; PLT: Platelet; WBC: White blood count

remission-induction therapy were evaluated for response. No differences were found between the 2 groups in terms of CR rate after the first induction (65.7% vs 76.7%, $P = 0.282$) and overall CR rate (82.9% vs 88.4%, $P = 0.486$). The presence of aberrant MyAg did not affect the cumulative incidence of relapse (44.8% vs 42.1%, $P = 0.824$) and the median relapse (4.8 vs 7.5 months, $P = 0.221$). We separately analysed the presence of MyAg in T and B lineage ALL cases, and failed to find any difference in CR achievement, relapse or death rate between MyAg+ and MyAg− cases in the different ALL subgroups (data not shown).

Analysis of the clinical and laboratory findings in different B-ALL subtypes and T-ALL failed to establish significant association for mean age, mean PLT count, cytogenetic abnormalities, MyAg positivity and percentage of BM blasts, as well as hepatomegaly and splenomegaly (Table 2). However, among different B-ALL subtypes, the proportion

of male patients in Com B-ALL was higher than that in Pre B-ALL ($P = 0.008$). Higher percentage of patients with WBC count ($>50 \times 10^9/L$) and higher median WBC count were both found in Pro B-ALL than those in Com B or Pre B-ALL ($P = 0.030$, $P = 0.004$, $P = 0.029$, $P = 0.001$). Higher CD34 positivity was found in Com B -ALL than that in Pre B -ALL ($P = 0.025$). The total death rate in Pro B-ALL was higher than that in Com B or Pre B-ALL ($P = 0.003$, $P = 0.032$). Besides, compared with B-ALL, higher percentage of male patients ($P = 0.003$), higher percentage of patients with WBC count ($>50 \times 10^9/L$) ($P = 0.002$) and lymphadenomegaly ($P = 0.030$), higher median WBC count ($P = 0.017$) and haemoglobin level ($P = 0.010$), lower CD34 positivity ($P = 0.000$) seem to be the typical features of T-cell ALL subtype. No statistical differences were noted between the 2 groups with regard to CR rate, relapse rate, induction mortality and total death rate.

Table 2. Clinical and Biological Features in Adult Patients with B-ALL and T-ALL

Features	Pro-B	Com-B	Pre-B	Total-B	T-ALL
Gender (male/female)	3/9	29/18†	8/19	40/46*	20/4
Age (years)	37.0	26.5	40.0	32	30.5
(range)	(28.3 to 54.0)	(17.3 to 44.3)	(22.0 to 55.0)	(20.0 to 46.0)	(23.0, to 48.8)
WBC count ($\times 10^9/L$)	51.6†	17.0†‡	7.1	11.5*	51.2
(range)	(14.1 to 190.5)	(6.2 to 49.5)	(3.8 to 13.5)	(4.2 to 49.9)	(16.8 to 123.0)
Haemoglobin (g/L)	67.5	86.0	67.0	77.0*	108.0
(range)	(57.3 to 83.3)	(61.0 to 120.0)	(57.0 to 91.5)	(58.0 to 100.0)	(76.0 to 125.0)
PLT count ($\times 10^9/L$)	42.0	31.0	38.0	36.0	61.5
(range)	(9.0 to 94.5)	(17.0 to 2.0)	(12.0 to 71.3)	(16.0 to 72.0)	(21.3 to 110.8)
BM blasts (%)	92.6	80.1	77.0	81.2	84.5
(range)	(71.8 to 94.9)	(68.0 to 88.4)	(66.7 to 88.5)	(67.0 to 89.3)	(69.2 to 95.0)
WBC count ($\times 10^9/L$)					
(>50 / <50)	7/5	12/35‡	3/24‡	22/64*	14/10
CD34 ($\pm$)	9/3	39/8†	16/11	64/22*	6/18
Cytogenetics (normal/ abnormal)	7/2	14/16	9/11	30/29	6/8
MyAg ($\pm$)	7/5	25/22	9/18	41/45	11/13
Hepatomegaly (%)	3/10 (30.0)	9/44 (20.5)	8/23 (34.8)	20/77 (26.0)	7/24 (29.2)
Splenomegaly (%)	4/10 (40.0)	18/44 (40.9)	8/23 (34.8)	30/77 (39.0)	12/24 (50.0)
Lymphadenomegaly (%)	4/10 (40.0)	20/44 (45.5)	11/23 (47.8)	35/77 (45.5)*	17/24 (70.8)
CR rate after the first induction (%)	3/7 (42.9)	29/37 (78.4)	15/19 (78.9)	47/63 (74.6)	9/15 (60.0)
Overall CR rate (%)	5/7 (71.4)	32/37 (86.5)	17/19 (89.5)	54/63 (85.7)	13/15 (86.7)
Relapse rate (%)	3/5 (60.0)	12/32 (37.5)	8/17 (47.1)	23/54 (42.6)	6/13 (46.2)
Induction mortality (%)	2/9 (22.2)	1/38 (2.6)	1/20 (5.0)	4/67 (6.0)	3/18 (16.7)
Total death rate (%)	6/9 (66.7)	5/38 (13.2) ‡	4/20 (20.0) ‡	15/67 (22.4)	5/18 (27.8)

BM: Bone marrow; CR: Complete remission; MyAg: Myeloid antigen; PLT: Platelet; WBC: White blood count

* $P \leq 0.05$, compared with T-ALL group.

† $P < 0.05$, compared with Pre-B group.

‡ $P < 0.05$, compared with Pro-B group.

Clinical and Biological Features of Ph+ and Ph- Precursor B-cell ALL

The clinical and biological characteristics of the 59 B-ALL patients with Philadelphia (Ph)+ and Ph- are summarised in Table 3. In this study, 28.8% of the adult patients with B-ALL were identified as Ph+. Almost all Ph+ ALL cases have a precursor B-cell phenotype and most expressed CD19, CD10 and CD34 in our patients, which is similar to that reported elsewhere.²⁰ There was no difference in gender distribution between Ph+ and Ph- patients but the median age was significantly higher in the Ph+ group (35- vs 25-year olds, $P = 0.025$). The Ph+ patients were also characterised by higher median haemoglobin levels (110.5 g/L vs 66.5 g/L, $P = 0.001$). The WBC counts, platelet (PLT) counts and BM blast infiltration were found to be similar in both Ph+ and Ph- patients. Higher CD34 positivity was observed in Ph+ B-ALL than that in Ph- B-ALL (94.1 vs 64.3%, $P = 0.044$). While no statistical significance was observed for expressing of MyAg, organomegaly (lymphadenomegaly, hepatomegaly and splenomegaly), CR rate, death rate, relapse rate and the median relapse among Ph- and Ph+ patients.

Discussion

Of all the adult patients, 21.8% were identified as T-ALL, 78.2% as B-ALL, and comparison of different subtypes of B-ALL in this study has demonstrated a higher frequency of Com-B subtype (54.7%) followed by Pre-B (31.4%) and Pro-B (14.0%) subtype, which was consistent with earlier reports.^{21,22} The dissimilarities observed among various studies could largely be due to the small sample size of the patients in many studies and methodological differences in classification of ALL. We confirmed the close association between T-cell phenotype with higher frequency of males, higher median WBC count and haemoglobin level, higher percentage of patients with WBC count ($>50 \times 10^9/L$) and lymphadenomegaly, and lower CD34 positivity, which was also demonstrated by other reports.^{23,24} Many groups have confirmed the superior outcome of T-ALL as compared to B-ALL in adults,²⁴ while others reported that T-cell immunophenotype tended to be associated with a poorer outcome,²⁵ and adult patients in the B-ALL subgroup did fairly well.²¹ It was similar to an early report that CR was achieved in 85.9% patients, with no significant difference in CR rate between B- and T-ALL in our study.²⁶ Meanwhile, no differences were found between the 2 groups with regard to relapse rate, induction mortality and total death rate.

It has been thought that ALL cells with expression of MyAg originate from initial stem cells earlier than lymph-directional stem cell and progenitor cell. In our study, the overall incidence of MyAg expression in adult ALL patients was 47.3% and CD13 was the most commonly

Table 3. Clinical and Biological Features of Ph+ and Ph- B-ALL

Features	Ph+	Ph-	P values
Gender (male/female)	8/9	15/27	0.418
Age (years)	35.0	25.0	0.025
(range)	(27.5 to 49.5)	(18.8 to 38.8)	
WBC count ($\times 10^9/L$)	16.4	10.3	0.408
(range)	(6.1 to 88.0)	(4.2 to 50.5)	
Haemoglobin (g/L)	110.5	66.5	0.001
(range)	(72.5 to 126.5)	(54.5 to 84.3)	
PLT count ($\times 10^9/L$)	39.0	39.5	0.900
(range)	(19.8 to 67.8)	(19.3 to 72.5)	
BM blasts (%)	83.4	84.8	0.795
(range)	(74.7 to 90.5)	(66.6 to 90.2)	
WBC count ($\times 10^9/L$)			
(>50 /<50)	4/13	12/30	0.943
CD34 ($\pm$)	16/1	27/15	0.044
MyAg ($\pm$)	10/7	20/22	0.436
Hepatomegaly (%)	3/17 (17.6)	10/35 (28.6)	0.609
Splenomegaly (%)	5/17 (29.4)	17/35 (48.6)	0.190
Lymphadenomegaly (%)	6/17 (35.3)	16/35 (45.7)	0.476
CR rate after the first induction (%)	10/13 (76.9)	23/31 (74.2)	1.000
Overall CR rate (%)	11/13 (84.6)	26/31 (83.9)	1.000
Relapse rate (%)	5/11 (45.5)	10/26 (38.5)	0.728
Induction mortality (%)	0/13 (0.0)	2/33 (6.1)	1.000
Total death rate (%)	3/13 (23.1)	7/33 (21.2)	1.000

BM: Bone marrow; CR: Complete remission; MyAg: Myeloid antigen; PLT: Platelet; WBC: White blood count

expressed MyAg, which was in line with the data reported in the literature.²³ It was noted by Saxena A et al²⁷ that precursor B cells co-expressing CD13 showed higher in vitro proliferation compared to that of CD13-CD19+ B cells. By blocking their cell surface CD13 in leukaemic blasts with monoclonal antibody, they were able to inhibit their proliferation, so they hypothesised that CD13 may thus be an important target for novel molecular therapy of early stage acute B-cell leukaemia. It was different from an earlier report that MyAgs were not significantly more frequently associated with B-ALL than with T-ALL.^{14,28} The differences observed are probably due to the criteria used to define a “percent positive” cell, the number of antigens tested and the relatively small numbers of T-ALL cases analysed in our study. Our data showed that patients with older age, higher CD34 positivity and lower proportion of patients with splenomegaly were found to be correlated with MyAg+ ALL, but no differences were found with regard to other clinical features, which was different from an earlier

report.¹⁴ It may be due to the relatively small numbers of adult ALL patients in our study. Further analysis of MyAg expression in ALL on the impact of treatment response suggested that no differences were found between the MyAg+ and MyAg- groups with regard to CR rate, relapse rate, induction mortality and total death rate. In conclusion, our findings demonstrated that the presence of MyAg in the surface of blasts from adult ALL patients cannot predict worse outcome, which was consistent with earlier report.²⁹

Chromosomal abnormalities in adult ALL had important significance related to diagnosis, management and prognosis. The absence of CD10 expression has been correlated with rearrangements of the MLL gene at 11q23, which is commonly seen in infants and older adults.³⁰ In our study, CD15 positivity was the highest in Pro B-ALL (60%), and the 1 case with t(4;11)(q21;q23) was an older woman patient with CD10-CD15+, which was consistent with the previous report that 11q23/MLL translocation occurred in CD10-/CD15+ Pro-B ALL.³¹ In this study, the most common cytogenetic abnormality was the t(9;22) translocation, resulting in the Ph chromosome and the formation of BCR-ABL fusion transcripts, which was found mainly in B-ALL and none in T-ALL. The karyotype studies showed that 28.8% (17/59) of our B-ALL patients had Ph chromosomes, which was lower than what Bao L et al reported.³² The difference observed was mainly due to the fact that we analysed the cases only by routine conventional karyotyping but not fluorescence in situ hybridisation and the relatively small numbers of B-ALL cases analysed in our study. Several clinical characteristics observed among Ph+ B-ALL patients in this series, such as older age, higher haemoglobin level, and higher CD34 expression are similar to those reported elsewhere.³²⁻³⁵ However, unlike their studies, we fail to observe higher white blood cell and blast counts, and higher expression of MyAg in Ph+ B-ALL. No statistically significant differences in initial CR rate, relapse rate and the median relapse were observed between Ph+ and Ph- groups and this was different from a previous study that BCR-ABL positivity is associated with a worse prognosis resulting from a lower initial CR rate and an earlier occurrence of relapse.²⁰ The presence of Ph chromosome in adults is associated with a very unfavourable prognosis.^{9,36,37} Even though CR could be achievable with standard chemotherapy regimens, without an allogeneic stem cell transplant, cures are uncommon. Recent combinations of tyrosine kinase inhibitors (TKIs) with chemotherapy have produced promising results, although the impact on long-term disease-free survival remains unclear.

Our results indicate that the distribution of ALLs in Chinese adult patients was similar with the general distribution pattern in the other countries. Unlike previous studies, we found that the expression of MyAg in patients with T-ALL

and B-ALL was comparable. Our data suggest that MyAg expression is significantly associated with median age, CD34 expression and splenomegaly, but is not associated with adverse presenting clinical and biological features, and that response to treatment and prognosis is comparable in MyAg+ and MyAg- adult ALL patients with regards to CR rate, relapse rate and death rate. In addition, we also found that patients with Ph+ B-ALL were older, presented with higher haemoglobin level and higher CD34 expression, but no differences were observed in other clinical or biological parameters between Ph+ and Ph- groups. In conclusion, ALL is a success story for paediatric cancer therapy but not adult ALL. The poor outcome of chemotherapy in adults with ALL as compared to children relates to multiple factors, including poor tolerance of intensive courses of chemotherapy and a higher incidence of poor prognostic subtypes of ALL such as Ph chromosome-positive ALL. Therapy for adult ALL will remain complex, and progress ultimately depends on effective crossbreeding between drug development, understanding of ALL biology, and sophistication of prognostic systems.

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Single Centre Experience of Transjugular Liver Biopsy in 152 Patients

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Abstract

Introduction: Liver biopsy is considered the definitive investigation in the diagnosis and management of liver disease. This study describes the experience of performing transjugular liver biopsy (TJLB) over the last 9 years in a local single centre. **Materials and Methods:** A retrospective review of consecutive TJLB procedures performed at our institution was conducted. A total of 152 patients (74 males and 78 females), with a mean age of 47.4 years (range, 13 to 83 years) underwent a total of 154 TJLB procedures at our institution between March 2003 and November 2011. The principal indication for TJLB was severe coagulopathy in over 80% of patients. The technical success, number of passes, histological adequacy and complication rates were analysed. **Results:** The procedural success rate was 98.7% (152 out of 154 procedures). Adequate material for diagnosis was obtained in 149 out of 152 (98.0%) technically successful procedures. There was procedure related morbidity in 8 patients (5.2%) of which all but one were self-limiting requiring no further intervention. We also performed hepatic venous pressure gradient (HVPG) measurements in 19% of patients at the time of TJLB. **Conclusion:** TJLB performed at our institution is a safe and reliable technique in patients in whom traditional percutaneous liver biopsy may be hazardous. TJLB has a high technical success rate as well as a high diagnostic yield with a low complication rate. TJLB also has the added benefit of performing HVPG, which is of increasing importance in management and prognostication of chronic liver disease.

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Key words: Indications, Safety, Singapore, Transjugular Liver Biopsy

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Introduction

The first reported case of liver biopsy was recorded in 1883 by Ehrlich.¹ Since then, the technique of liver biopsy has been modified tremendously with major advances over the last 50 years, allowing safer and more reliable methods of performing liver biopsy.

Liver biopsy is a commonly performed procedure and is the investigation of choice in the diagnosis and investigation of liver disease. The most common method of biopsy is by the percutaneous route, either with or without image guidance. Percutaneous liver biopsy (PLB) has a small but inherent risk even in the most experienced hands, and it should therefore only be performed when the benefits of knowing the histology outweigh the risks to the patient.² PLB under image guidance, most often ultrasound, is currently considered the standard method of procuring tissue for histological assessment. This can be performed

relatively safely in patients without pre-existing deranged coagulation or ascites. PLB is a fast and technically simple procedure.³ The most common complication, which is a major limitation of PLB is post-procedure haemorrhage. Significant haemorrhage (indicated by a reduction in haemoglobin of >2g/dL) occurs in up to 0.3% to 0.5% of patients.⁴ It has been reported that subclinical haemorrhage occurs at a much higher rate, with up to 23% of patients having intrahepatic or subcapsular haematomas detectable by ultrasound 24 hours after biopsy.⁵

It has been demonstrated that taking more than one core of liver at biopsy can increase the diagnostic yield, but this may have an effect on morbidity. It has been clearly shown that making more passes increases the incidence of bleeding complications with PLB.^{4,6}

Transjugular liver biopsy (TJLB) was first reported

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experimentally in 1964 by Dotter.⁷ It was subsequently utilised as a clinical tool in 1974.⁸ Since its introduction, TJLB has been most commonly performed in patients in whom the risks of conventional PLB were deemed unacceptable. TJLB is considered safer in these patients as the needle exits the hepatic vein into the liver parenchyma and then cuts the tissue. Any bleeding complication from TJLB is usually into the hepatic vein, theoretically making the procedure safer in these patients compared to PLB, which breaches the liver capsule. Bleeding from TJLB has been shown not to change significantly with increasing passes.⁹ The most common indications for using the transjugular route are coagulopathy (congenital or acquired), ascites, liver transplant recipients and acute liver failure.³

In this study, we reported our single centre experience of TJLB in 152 patients encompassing a total of 154 procedures over the last 9 years.

Materials and Methods

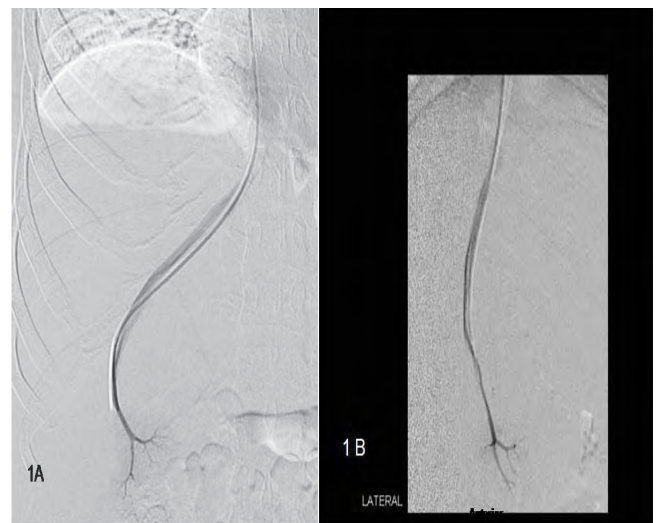
A retrospective review of consecutive TJLB procedures performed between March 2003 and November 2011 at our institution was conducted. Institutional Review Board approval was obtained. The patients were identified using our hospital Radiology Information System. Thereafter, the procedural and histological reports were reviewed as well as the clinical indications and laboratory results.

Technique

Prior to the procedure, the most recent cross-sectional imaging of the liver was reviewed to assist in pre-procedural planning, particularly with respect to hepatic venous anatomy. Informed and written consent was obtained for all patients undergoing TJLB.

All TJLB procedures were performed in the angiography suite in our Interventional Radiology Centre under conscious sedation. Continuous monitoring of heart rate, oxygen saturation and electrocardiographic readings was performed.

The right internal jugular vein (IJV) was the principal access point for the vast majority of patients. The left IJV was used in one patient due to occlusion of the right IJV. The IJV was accessed under ultrasound guidance after infiltration of local anaesthetic. Using a Seldinger technique, a guide wire was introduced and under fluoroscopic guidance was manipulated into the inferior vena cava. A 9 Fr vascular sheath was inserted. An angiographic catheter, most commonly a MPA-1 catheter (Cordis, New Jersey, USA), and a hydrophilic guide wire (Terumo, Tokyo, Japan) were manipulated into the hepatic vein, usually the right, and hepatic venography was performed (Figs. 1A and 1B). Hepatic venous pressure gradient (HVPG) measurements were performed at this stage if clinically indicated.



Figs. 1(A) and 1(B). Right hepatic vein venogram—Anteroposterior (AP) and lateral projection.

After cannulation of the target vein, exchange for a superstiff guide wire (Amplatz, Cook Medical Inc, Bloomington, USA) was performed, and the 7 Fr long and metal cannula of the TJLB set (Liver Access Biopsy Set – LABS 100, Cook) were slowly introduced. Through the sheath, the 60 cm long 18G (2 cm throw) biopsy needle was inserted co-axially through the 7 Fr sheath and under fluoroscopic guidance positioned in the proximal segment of the hepatic vein. The cannula was then rotated, usually anteriorly and the hepatic vein wall was then traversed and the tip of the needle advanced into the liver parenchyma (Fig. 2A). Biopsies were then performed (Fig. 2B). The number



Fig. 2(A). Biopsy needle within the right hepatic vein prior to biopsy.



Fig. 2(B). Core biopsy needle advanced into the liver parenchyma prior to biopsy.



Fig. 3. Right hepatic venogram completed.

of passes required was determined by the radiologists' macroscopic assessment of the specimens obtained. A post-biopsy venogram was performed to exclude any haemorrhagic complications (Fig. 3). The vascular sheath was then removed and manual compression applied to the access site on the neck until haemostasis was achieved. Following the procedure, all patients were closely monitored in the ward for 6 hours, and then discharged only after 24 hours.

Technical failure of TJLB was classified as the failure to obtain a liver sample for any reason. The specimen was considered adequate if it allowed a histological diagnosis to be made in the given clinical context. Minor and major

complications were classified according to the Society of Interventional Radiology criteria.¹⁰

Results

The study group comprised 74 males and 78 females with a mean age of 47.4 years (range, 13 to 83 years). The most common indication for TJLB was coagulopathy (82.4%) followed by ascites and post-liver transplantation (Table 1). In 4 patients, HVPG measurements were required as well procurement of liver tissue, hence TJLB biopsy was performed concurrently, obviating the need for PLB. All patients with an abnormal coagulation profile received pre- and intra-procedural transfusions of fresh frozen plasma and/or pooled platelets as per our departmental protocol (Table 2). A total of 154 TJLB procedures were performed over the review period on 152 patients. Two postoperative liver transplant recipients underwent TJLB twice to assess for rejection.

The overall technical success rate was 98.7% (152/154 procedures). In one patient, it was not possible to perform the biopsy due to the failure to achieve a stable sheath/cannula

Table 1. Indications for Performing TJLB

Indication for TJLB	No. of Patients	%
Coagulopathy	127	82.4
[Platelets]	55	
[APTT and/or PT]	34	
[Platelets and APTT/PT]	38	
Ascites	13	8.4
Ascites and coagulopathy	1	<1
Post-liver transplant	4	2.6
HVPG (principal)	4	2.6
Unknown	5	3.2

TJLB: Transjugular liver biopsy; APTT: Activated partial thromboplastin time; PT: Promthrombin time; HVPG: Hepatic venous pressure gradient

Table 2. Departmental Parameters for Abnormal Coagulation

	Normal range	Indication for TJLB
Activated partial thromboplastin time (APTT)	27.0 – 36.1 seconds	>40.1 seconds
Prothrombin time (PT)	9.2 – 11.2 seconds	>3.2 seconds
Platelets	140 – 440 x 10 ⁹ /L	<100 x 10 ⁹ /L

position. The technical failure was attributed to a very shrunken cirrhotic liver resulting in unfavourable hepatic venous anatomy. A specimen was subsequently obtained at a later date via the percutaneous route after infusion of clotting factors to partially reverse the coagulopathy. In another patient with known cryptogenic liver cirrhosis, who required a repeat biopsy and HVPG measurements, the biopsy needle could not penetrate the liver. This was felt to be due a very hard liver as a result of the underlying severe cirrhosis.

The right hepatic vein was the most commonly cannulated vein, being used in 140/153 procedures (91.5%) with the middle hepatic (12/152) and accessory right hepatic vein (1/152) being used for the remainder of cases.

The number of passes varied amongst patients from 1 to 7. The average number of passes was 3.5. Only 12 patients had 5 or more passes.

Of the specimens obtained in 152 patients, histological assessment in 149 patients was deemed adequate for histological diagnosis. The specimens in 3 patients were assessed to be either too small or too fragmented.

The average specimen length could not be determined as this was not routinely reported. However, the range of specimen lengths obtained was stated in all 149 (adequate quality) biopsy reports. The mean range of specimen length was 5.7 mm to 10.6 mm (range, 1 to 18 mm). The number of complete portal tracts (CPTs) was only reported numerically in only 36 patients, with the vast majority being reported from 2009 onwards. The average number of CPTs in this group was 6.9 (range, 1 to 18).

Repeat biopsy was subsequently performed in 2 of the patients via the percutaneous approach (with attempted correction of coagulation with clotting factors). One of these patients developed a small subcapsular haematoma after PLB, which was managed conservatively. In a few cases, more than one aetiological feature was described in the histological report (e.g. cholestasis with features compatible with primary biliary cirrhosis). In such cases, the primary aetiological pathology (i.e. primary biliary cirrhosis) was given as the diagnosis. The principal histological diagnoses are detailed in Table 3.

Complications

There were 8 (5.3%) procedure related complications, of which 7 were classified as minor in terms of severity (Table 4). The single major complication resulted in procedure related mortality. A 40-year-old woman with a history of systemic lupus erythematosus presented with fulminant acute hepatitis and acute renal failure as well as deranged coagulation. At presentation, her liver function tests were severely deranged. The patient was in established multiorgan

Table 3. Histological Diagnosis for 152 Technically Successful Procedures

Histology	No. of Patients
Acute/chronic hepatitis	53
Cirrhosis (all aetiology)	21
Cholestasis	15
Haemosiderosis	14
Steatosis	11
Malignancy	9
Drug induced hepatitis	5
Autoimmune hepatitis	3
Regenerative hyperplasia	3
Fibrosis	3
Primary biliary cirrhosis	2
Graft versus host disease	2
Rejection	2
Cystinosis	1
Myelofibrosis	1
Citrullinaemia	1
Normal	3
Non diagnostic	3
Total	152

Table 4. Minor Complications of TJLB

Type of Minor Complication	No. of Patients
Small subcapsular haematoma / self limiting capsular rupture	2
Portal vein penetration	1
Biliary tree penetration	1
Entanglement of Amplatz guide wire within right ventricle	1
Small self-limiting haematoma at IJV puncture site	1
Contrast allergy	1

TJLB: Transjugular liver biopsy; IJV: Internal jugular vein

failure, requiring ventilatory support as well as artificial extracorporeal liver support and renal replacement therapy by way of continuous veno-veno haemofiltration. At the time of TJLB, one week after initial presentation, her coagulation remained impaired with an APTT of 63.3 seconds, PT of 18.5 seconds and platelets of $48 \times 10^9/L$. The patient underwent TJLB via the right hepatic vein (5 passes) without immediate complication. No evidence of extravasation was demonstrated on the post-biopsy venogram. Approximately 6 hours after the procedure, the patient became hypotensive and dyspnoeic. Her haemoglobin level reduced from 10.8 to 3.5 g/dL. An emergency CT scan showed active contrast extravasation from the right lobe of the liver with a large

amount of haemoperitoneum. Initial hepatic angiography failed to show any active bleeding. The patient then developed disseminated intravascular coagulopathy with an APTT >180 seconds and PT >120 seconds. Due to deterioration of her condition, repeat emergent hepatic angiography was performed with successful coil embolisation of the bleeding point from a segment 5/6 artery. Despite cessation of bleeding, the patient continued to deteriorate despite maximum intensive care therapy and passed away 48 hours after TJLB.

Overall, 5 complications were liver-puncture related (3.3%) and 3 were non-liver puncture related (2.0%). All minor complications (Table 4) were self-limiting with no further subsequent intervention necessary in any of the patients.

Discussion

TJLB is usually indicated when PLB is contraindicated most commonly due to severe coagulopathy, and also in patients with ascites. Patients with chronic liver disease often have impaired synthesis of coagulation factors, which may result in prolongation of the APTT and PT. In addition, thrombocytopenia as well as platelet dysfunction is a common finding in patients with portal hypertension and cirrhosis, due to hypersplenism and splenic sequestration of platelets.

Several advantages of TJLB over PLB have been described. One such advantage is the relative safety of using the transjugular approach. In both percutaneous and transjugular approaches, the overall complication rate has been stated as 7.1% (6.6% minor and 0.5% major).¹¹ The major concern with any visceral biopsy, particularly with regards to liver biopsy is that of haemorrhage. Taking into account that patients who are referred for TJLB invariably have some degree of coagulopathy (and therefore are at high risk of bleeding), it can be inferred that TJLB is seen as a relatively safe procedure. It is well known that in PLB, the risk of haemorrhage-related complications increases with the number of passes made.⁴ With TJLB, however, it has been shown that increasing the number of passes does not have a significant effect of increasing haemorrhage-related complications.⁹ Importantly, although the complication rates of both TJLB and percutaneous liver biopsy are similar, with the more stringent demand for larger specimens it is likely that the complication rate from percutaneous biopsies may increase as more passes will be required to obtain a larger amount of tissue. Conversely, TJLB offers the feasibility of several passes without necessarily increasing the complication rate.¹¹

Another advantage of the transjugular approach is the ability to perform HPVG measurements, which

has prognostic value as well as allowing assessment of pharmacological treatment response of portal hypertension.¹² In our series, we performed HPVG in 19% (29/154) of our patients who underwent TJLB. Furthermore, recent research suggests that HPVG might be a better endpoint than histology for the assessment of therapeutic benefit of antiviral treatment in patients with chronic hepatitis C infection.^{13,14} As such, it has been mooted that in this subgroup of patients TJLB together with HPVG measurements may be the standard approach and therefore negate the increased cost of performing TJLB over PLB.¹²

In our series, we performed an average of 3.5 passes per procedure, slightly more than stated in the literature (average of 2.7),¹¹ however, we did not feel that this impacted significantly on our complication rate of 5.3%. Our liver puncture related complication rate was 3.3%, the same as stated in the literature of 3.3%.¹¹ In particular, in these patients, the average number of passes was 3.8. The increase in the average number of passes in this subgroup may have possibly contributed to the development of haemorrhagic complications, but this is difficult to prove due to the small numbers involved. We routinely perform biopsies in a more proximal segment of the hepatic vein rather than peripherally. Performing proximal rather than peripheral biopsies has been shown to be safer and is associated with fewer capsular perforations/haematomas.¹¹

Traditionally, TJLB specimens have been considered comparatively smaller and more fragmented, resulting in reduced diagnostic yields. This has often been cited particularly in specimens obtained in patients with liver fibrosis or cirrhosis, with the smaller size of the needle being the cause of such.^{15,16} In our practice, both our TJLB and PLB core biopsy needles are 18G in size with a 2 cm throw. Several studies have assessed the minimum length and number of portal tracts necessary for optimal histological evaluation.³ It has been accepted that a specimen of >15 mm in length as well as containing 6 to 8 CPTs should be present for the diagnosis in chronic liver disease. A large systematic review assessing the quality of liver biopsy showed that the length of specimens obtained by the transjugular route are on average 4.2 mm shorter compared to the percutaneous method (13.5 mm vs 17.7 mm). More significantly, the number of CPTs obtained were almost similar (6.8 vs 7.5).¹⁷ In our study, it was difficult to accurately ascertain the average specimen length. Our average ranges were 5.7 to 10.6 mm. However, the number of CPTs obtained averaged 6.9. Interestingly, subgroup assessment of average specimen ranges in the 36 patients where the number of CPTs was stated was 4.8 to 9.8 mm. The recent trend has been towards staging and grading of chronic liver disease for prognostication purposes, particularly in the assessment of fibrosis in patients with chronic hepatitis C and NASH. In

these patients, specimens of 20 mm to 25 mm in length or with 11 CPTs or more have been considered to be necessary for reliable histological evaluation.¹⁸ However, more recent studies assessing the adequacy of biopsy specimens using the newer generation cutting biopsy needles, including a large systematic review of over 7000 TJLB procedures,¹¹ has shown that the quality of specimens obtained using the transjugular approach is comparable, if not better,³ to those obtained via the percutaneous approach.

A limitation of our study was the inconsistent description of specimen length, which was often described in terms of the range of sizes of specimens received. This precluded detailed assessment of specimen fragmentation. Also, our study was retrospective and spanned nearly 9 years. As the importance of assessing the number of CPTs has only come to light recently, complete analysis of this parameter could not be performed. In addition, no comparative assessment with PLB procedures performed over the same period of time was made.

Conclusion

TJLB is a safe and reliable method of liver biopsy in our patients and has a high diagnostic yield and low complication rate. Although more time consuming and technically more difficult compared to PLB, in a selected group of (higher risk) patients, the benefit of performing TJLB outweighs these technical factors. TJLB should be considered as a complimentary procedure to PLB with the added benefit of performing HVPG at the time of biopsy. In our institution, TJLB is now considered the first line approach to obtaining a histological diagnosis in those groups of patients suspected of having liver disease with impaired coagulation or ascites.

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External Validation of the Cham Score for Ordering of Blood Cultures in Emergency Department Patients with Non-Hospital Acquired Pneumonia

Mark Patterson, ¹*MBBS*, Anne-Maree Kelly, ²*MD, FACEM, FCCP*, Sharon Klim, ²*BN*

Abstract

Introduction: The aim of this study was to externally validate the Cham score for the prediction of bacteraemia in emergency department (ED) patients with non-hospital acquired pneumonia. **Materials and Methods:** This is a secondary analysis of a dataset collected to identify independent predictors of bacteraemia in adult ED patients with non-hospital acquired pneumonia. The primary outcome of interest was the predictive performance (sensitivity, specificity, negative predictive value) of the score with respect to bacteraemia. Secondary outcomes included the performance of the score in patients not known to be intravenous (IV) drug users, the predictive performance of pneumonia severity index (PSI) class IV/V and PSI class IV/V or IV drug use as predictors and the clinical impact of score application on test ordering. Data analysis was by clinical performance and receiver operator characteristic curve analysis. **Results:** A total of 200 patients were studied; 14 true positive blood cultures (7%, 95% CI, 4% to 11%). The Cham score had a sensitivity of 92.9% (95% CI, 64.2% to 99.6%), specificity of 26.3% (95% CI, 20.3% to 33.4%) and negative predictive value (NPV) of 98% (87.0% to 99.9%). Area under the receiver operating characteristic (ROC) curve was 0.71 (95% CI, 0.56 to 0.86). Using PSI class IV/V or known IV drug use as predictors had sensitivity of 92.9% (95% CI, 64.2% to 99.6%), specificity of 51.1% (95% CI, 43.7% to 58.4%) and NPV of 99% (95% CI, 93.5% to 99.9%). **Conclusion:** In retrospective external validation, the Cham score performed better than in derivation with acceptable sensitivity and NPV. Simplified criteria (PSI class IV/V or known IV drug use), as yet not validated, had similar sensitivity and NPV but would avoid blood cultures in a higher proportion of patients.

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Key words: Blood culture, Emergency department, Pneumonia

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Introduction

Some guidelines currently promote the taking of blood cultures in patients admitted to hospital with non-hospital acquired pneumonia in order to identify pathogens and guide therapy.^{1,2} Previous studies have reported that the proportion of patients returning a true positive blood culture is between 2.1% and 9%.³⁻¹⁰ False positive cultures have been reported to occur in 2.5% to 3.7% of tests.^{3,7} This low rate of true positive results and significant false positive rate pose a serious challenge to their utility, both on clinical and cost-effectiveness grounds and debate challenging these guidelines is growing.^{7,11,12}

A selective approach has been suggested, with the ordering of cultures being reserved for patients with severe disease.⁵ Another approach, taken by Cham and colleagues,³ is the development of a score to assist in identifying patients

more likely to have a true positive culture. They conducted a case control study of emergency department (ED) patients diagnosed with community acquired pneumonia to identify factors independently associated with positive blood cultures. Using regression analysis, a predictive probability equation with minimum number of culture positive misclassification was developed. Based on the predictive model, a scoring system was devised, with scores predicting which patients would be likely to have a positive or negative blood culture upon presentation at the ED. That scoring system is shown in Table 1. The score ranges from -5 to +5 and a cut-off score ≤ -1 was chosen as the discriminator level. They reported an area under the receiver operating characteristic (ROC) curve of 0.64 (95% CI, 0.58 to 0.70). The model had a sensitivity of 82% and specificity was 38.2% for a positive blood culture.

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Table 1. The Cham Score and Modified Cham Score

Predictor	Cham Score	Modified Cham Score
PSI class V	3	3
PSI class IV	2	2
Prior antibiotic treatment	– 2	– 2
COPD	– 2	– 2
Smoker	1	1
Cough	– 1	– 1
Malay ethnicity	1	NA
Range	– 5 to +5	– 5 to +4

COPD: Chronic obstructive pulmonary disease; NA: Not applicable;
PSI: Pneumonia severity index

The aim of this study was to externally validate the Cham score for the prediction of bacteraemia in ED patients with non-hospital acquired pneumonia. We hypothesised that the score would have >95% negative predictive value for true positive blood culture.

Materials and Methods

This is a secondary analysis of a dataset collected to identify independent predictors of true positive blood cultures in ED patients with pneumonia.¹³ Participants were a convenience sample of 200 patients with an ED discharge diagnosis of non-hospital acquired pneumonia treated at the ED of a community teaching hospital in Melbourne, Australia between July 2008 and May 2009 and in whom at least one set of blood cultures was taken as part of their initial investigations. ED discharge diagnosis was made by the treating clinician with access to all the clinical and investigative data available at ED discharge. Taking of blood cultures was at the discretion of treating clinicians, however it would be usual practice to collect blood cultures in patients being admitted to hospital for treatment of pneumonia or who exhibit a fever >38°C. Patients were identified from an administrative database. Eligibility criteria included age over 18 years, having a blood culture taken within 6 hours of arrival in ED and availability of record for review. The study hospital has an adult census of 35,000 per year with an admission rate of approximately 35%.

Patients were identified from an administrative database covering the period 1 July 2008 to 30 June 2009. Data were collected by explicit medical records review (MP, SK) on to a specifically designed data form. Eligibility criteria included age over 18 years, having a blood culture taken within 6 hours of arrival in ED and availability of record for review. Data abstractors were trained in data collection from medical records and had predefined definitions for all data elements. As this is an unplanned secondary analysis,

data collectors were unaware of the specific hypothesis.

Data collected included demographics, past medical history of chronic obstructive pulmonary disease (COPD), smoking, immunosuppression, intravenous (IV) drug use or diabetes, antibiotic use prior to ED attendance, biochemistry, haematology and blood culture results, clinical features and ED disposition. Inter-rater reliability was tested on 10% of records. Inter-rater agreement of data collection was 100% for the items: age, gender, white cell count, serum sodium concentration and ED disposition.

During study development, an issue arose with a data element of the Cham score. Malay ethnicity was not clinically relevant in the study population, representing <1% of all patients. We elected to remove 'Malay ethnicity' from the score calculation but retained the score cut-off for recommended ordering of blood cultures (≥ -1). The modified score has a range of –5 to +4. Pneumonia severity index (PSI) and Cham score were calculated retrospectively.

The primary outcome of interest was the clinical performance (sensitivity, specificity, negative predictive value (NPV)) of the score with respect to true positive blood cultures. True positive was defined according to previously published standards.¹⁴ Secondary outcomes included the performance of the score in patients not known to be IV drug users, the predictive performance of PSI class IV/V or PSI class IV/V or IV drug use as predictors and the clinical impact of Cham score application on test ordering. We included the latter analysis because the parent study¹³ had shown a very strong association between IV drug use and positive blood culture (OR 16.7, 95% CI, 2.65 to 105) and this variable had not been collected in the Cham score derivation study.³

Data analysis was by sensitivity, specificity and negative predictive value analyses (with 95% confidence intervals) and ROC curve analysis. As this was a secondary analysis, sample size was not calculated a priori.

Results

Characteristics of the sample are shown in Table 2. There were 14 true positive blood cultures (7%, range, 4% to 11%). Organisms were *Streptococcus pneumoniae* (7), *Streptococcus pyogenes* (2), *Staphylococcus aureus* (2), *Escherichia coli* (1), *Candida albicans* (1) and *Corynebacterium jeikeium* (1).

The Cham score at the ≥ -1 cut-off had a sensitivity of 92.9% (13/14 true positives) (95% CI, 64.2% to 99.6%), specificity of 26.3% (95% CI, 20.3% to 33.4%) and NPV of 98% (87.0% to 99.9%). Area under the ROC curve was 0.71 (95% CI, 0.56 to 0.86) (Fig. 1). For patients not known to be IV drug users, the Cham score at the same cut-off had a sensitivity of 100% (10/10 true positives) (95% CI, 65.5% to 100%), specificity of 26.3% (95% CI, 20.1% to 33.3%)

Table 2. Characteristics of the Study Sample

Variable	Grouping	Number
Gender (male n, %)		118, 59%
Age in years (median, IQR)		72, 60 to 81
Residential care (n, %)		26, 13%
Duration of symptoms (n, %)	>2 days	124, 52%
	<2 days	75, 37.5%
	Unknown	1
Temperature (n, %)	35 to 38.5 °C	59, 29.5%
	<35 or >38.5 °C	141, 70.5%
Past history (n, %)	Diabetes	56, 28%
	COAD	59, 29.5%
	Immunosuppression	4, 2%
	IV drug use	7, 3.5%
	Antibiotics prior to ED	53, 26.5%
PSI group (n, %)	I	16, 8%
	II	47, 23.5%
	III	39, 19.5%
	IV	66, 33%
	V	32, 16%
Respiratory rate (median, IQR)		28, 22 to 32
Pulse rate (median, IQR)		112, 91 to 128
Oxygen saturation (n, %)	≥93%	115, 57.5%
	<93%	79, 39.5%
	Unknown	6, 3%
WCC (n, %)	<4	8, 4%
	4 to 11	80, 40%
	11 to 20	88, 44%
	>20	22, 11%
	Unknown	2, 1%
Final hospital diagnosis (n, %)	Pneumonia	178, 89%
	COAD/ Respiratory failure	16, 8%
	Sepsis	4, 2%
	Other	2, 1%

COAD: Chronic obstructive airways disease; IQR: Interquartile range; PSI: Pneumonia severity index; WCC: White cell count x 10⁹/litre

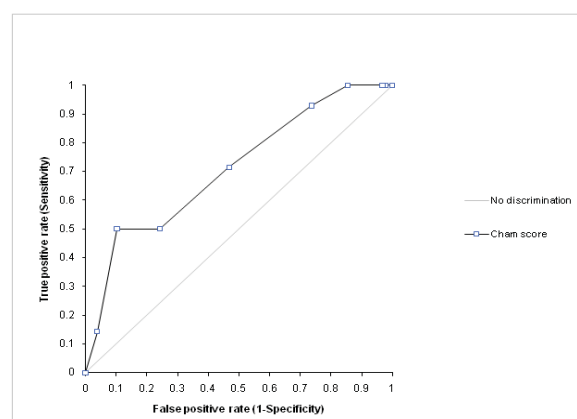


Fig. 1. Receiver operator characteristic curve for the Cham score as a predictor of positive blood culture.

and NPV of 100% (90.8% to 100%). Area under the ROC curve was 0.77 (95% CI, 0.63 to 0.92). Use of the Cham score to guide blood culture ordering would have avoided 50 tests (25%) in the overall cohort and 48 (24.9%) in the cohort not known to be IV drug users.

Using PSI class IV/V alone as a predictor of positive blood culture had a sensitivity of 71.4% (10/14 true positive) (95% CI, 42% to 90.4%), specificity of 52.7% (95% CI, 45.2% to 60%) and NPV of 96.1% (95% CI, 89.7% to 98.7%). Using PSI class IV/V or known IV drug use as predictors had sensitivity of 92.9% (13/14 true positives) (95% CI, 64.2% to 99.6%), specificity of 51.1% (95% CI, 43.7% to 58.4%) and NPV of 99% (95% CI, 93.5% to 99.9%). Application of this criterion would have avoided 96 tests (48%).

Discussion

Our results confirm that blood cultures for community acquired pneumonia have a low yield of true positives (7%). This is consistent with data from other centres showing bacteraemia rates of 2% to 9%.^{3,10} This low rate of positive results coupled with previously published data that results rarely impact therapy or outcome^{4,6,7,8,10} seriously challenge the practice of routine blood cultures for patients presenting with community acquired pneumonia and support calls for a more selective approach.

In this retrospective external validation, the Cham score had higher sensitivity than in derivation (92.9% vs 82%) but with lower specificity (26.3% vs 38%). The predictive performance was also better (area under the curve (AUC) 0.71 vs 0.64). We found that 25% of cultures might have been avoided if the rule had been applied, compared with 38% predicted in the derivation set. The score performed even better when the subset of patients known to be IV drug users were excluded. This likely reflects the impact of this

predictor on the finding of bacteraemia in our original study.

We also found that using the criteria PSI class IV/V or known IV drug use as predictors had similar sensitivity (92.9%), higher specificity (51.1%) and high NPV (99%). Application of these criteria is estimated to avoid 48% of tests. This approach would be simpler as it has fewer elements and no score to calculate. It has not however been prospectively validated.

One element of the Cham score was not relevant to the Australian context (Malay ethnicity) which impacted score calculation but does not appear to have had an adverse influence on score predictive performance. In our local context, we have shown that IV drug use is a powerful predictor of bacteraemia (OR 17.7).¹³ This was not identified as a predictor in Cham's original study, possibly due to a very low rate of IV drug use in Singapore. These data are a reminder that some predictors of bacteraemia may relate to local context and this should be taken into account in setting local practice guidelines.

This study has some limitations that should be considered when interpreting the results. This is a secondary analysis of an existing dataset that was not collected for the purpose to which it has been applied. Data on the inter-rater reliability of Cham score items was not collected as this was not the primary objective of the research. To do so retrospectively is not feasible within available resources. It utilises a convenience sample based on availability of medical records during the study period, so results should not be viewed as definitive. We have no reason to suspect any systematic bias in record availability. The data were collected by explicit medical record review so is subject to data omissions in the records accessed. Data were collected at a single site in Australia, so it may not be generalisable to other settings.

Conclusion

In retrospective external validation, the Cham score performed better than in derivation with acceptable sensitivity and NPV. Simplified criteria (PSI class IV/V or known IV drug use), as yet not validated, had similar sensitivity and NPV but would avoid blood cultures in a higher proportion of patients.

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A 10-Year Profile of Trauma Admissions Caused by Interpersonal Violence: A Major Trauma Centre's Experience

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Abstract

Introduction: This study aimed to characterise interpersonal violence victims admitted to a major trauma centre. **Materials and Methods:** A retrospective cohort study of interpersonal violence victims who were admitted to our centre from 1 January 2001 to 31 December 2010 was conducted. Data were obtained from our trauma registry. **Results:** Interpersonal violence victims constituted 444 (90.1% males and 9.9% females) out of a total of 8561 trauma admissions in the same time period. The average age was 36.6 years (range, 14 to 83 years). Majority were Chinese (53.4%) and Singaporeans (77.3%). The number of cases increased from 10 per year to 96 per year in the first 8 years, then decreased in the last 2 years (55 in year 2010). Time of injury was predominantly 0000 to 0559 hours (72.3%). Interpersonal violence mostly occurred in public spaces for both genders (88.7%). However, the number of females who were injured at home was significantly higher than males ($P = 0.000$). Blunt trauma (58.3%) was more common than penetrating trauma (41.7%). The average injury severity score (ISS) was 13.5 (range, 1 to 75); 34.9% of patients had major trauma (ISS >15). The average Glasgow coma scale (GCS) score was 13.5 (range, 3 to 15); 16.4% of patients had moderate-to-severe brain injury (GCS 3-8). Blunt trauma was significantly more likely to cause major trauma than penetrating trauma ($P = 0.003$). The sole case of firearm assault caused most morbi-mortality. Overall mortality was 4.5%. Major trauma (OR: 25.856; $P = 0.002$) and moderate-to-severe brain injury (OR: 7.495; $P = 0.000$) were independent risk factors of mortality. **Conclusion:** There has been no prior published data on interpersonal violence locally. This study is thus useful as preliminary data for future population-based studies. It also provides data for authorities to formulate preventive and intervention strategies.

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Key words: Demographics, Glasgow coma scale, Injury severity score, Mortality

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A 10-Year Profile of Trauma Admissions Caused by Interpersonal Violence: A Major Trauma Centre's Experience

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Abstract

Introduction: This study aimed to characterise interpersonal violence victims admitted to a major trauma centre. **Materials and Methods:** A retrospective cohort study of interpersonal violence victims who were admitted to our centre from 1 January 2001 to 31 December 2010 was conducted. Data were obtained from our trauma registry. **Results:** Interpersonal violence victims constituted 444 (90.1% males and 9.9% females) out of a total of 8561 trauma admissions in the same time period. The average age was 36.6 years (range, 14 to 83 years). Majority were Chinese (53.4%) and Singaporeans (77.3%). The number of cases increased from 10 per year to 96 per year in the first 8 years, then decreased in the last 2 years (55 in year 2010). Time of injury was predominantly 0000 to 0559 hours (72.3%). Interpersonal violence mostly occurred in public spaces for both genders (88.7%). However, the number of females who were injured at home was significantly higher than males ($P = 0.000$). Blunt trauma (58.3%) was more common than penetrating trauma (41.7%). The average injury severity score (ISS) was 13.5 (range, 1 to 75); 34.9% of patients had major trauma (ISS >15). The average Glasgow coma scale (GCS) score was 13.5 (range, 3 to 15); 16.4% of patients had moderate-to-severe brain injury (GCS 3-8). Blunt trauma was significantly more likely to cause major trauma than penetrating trauma ($P = 0.003$). The sole case of firearm assault caused most morbi-mortality. Overall mortality was 4.5%. Major trauma (OR: 25.856; $P = 0.002$) and moderate-to-severe brain injury (OR: 7.495; $P = 0.000$) were independent risk factors of mortality. **Conclusion:** There has been no prior published data on interpersonal violence locally. This study is thus useful as preliminary data for future population-based studies. It also provides data for authorities to formulate preventive and intervention strategies.

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Key words: Demographics, Glasgow coma scale, Injury severity score, Mortality

Introduction

The World Health Organization (WHO) has divided violence into 3 categories: interpersonal violence, self-directed violence, and collective violence. Violence is defined as “the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation.”¹ Interpersonal violence can be categorised into violence against family (victimisation of the elderly, children, spouse, siblings, parents, etc.), and violence against members of the community who may be acquaintances or strangers (workplace assault, rape, assaults, etc.).² Globally, it accounts for 10% of deaths, which translates to about half

a million deaths a year.³ In Singapore, about 5000 cases are recorded by the Singapore Police Force annually.⁴

Traditionally, police records and crime surveys serve as sources of information regarding interpersonal violence. Although they are good indications of the incidence of interpersonal violence, they are poor measures of the severity of the injuries sustained and the outcomes of the victims. In contrast, hospital data from trauma registries are good measures of harm and patient outcomes, because information about the violence can be prospectively acquired from the victims simultaneously with their management. Nonetheless, studies which use hospital data to characterise interpersonal violence tend to be region-specific due to differences in socio-politico-economic circumstances

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amongst regions.⁵⁻¹¹ There remains a lack of similar data specific to Singapore, which has made it difficult to develop evidence-based and appropriate intervention and prevention strategies. Hence, this paper attempts to characterise the epidemiology, circumstances and characteristics of injury, and outcomes of patients who were admitted to the Tan Tock Seng Hospital (TTSH) over a 10-year period from 1 January 2001 to 31 December 2010 with injuries caused by interpersonal violence.

Materials and Methods

Study Population

All interpersonal violence victims who had injury severity scores (ISS) of ≥ 9 and who were admitted to the TTSH High Dependency Unit or Intensive Care Unit from 1 January 2001 to 31 December 2010 were studied. A person is defined as a victim of interpersonal violence if his or her principal diagnosis was injury that was caused by another person, as designated by the International Classification of Disease (ICD) Tenth Revision Version for 2010, Chapter XX External Causes of Morbidity and Mortality, Assault codes (X85 to Y09).¹² A retrospective cohort study was performed.

Data Collection

Information regarding patient demographics, circumstances of injury, characteristics of injury, and outcomes were collected from the trauma registry, which is a prospectively maintained database managed by our centre's Trauma Service.

Definitions

The causes of injury were categorised by the ICD into: (i) Assault by sharp objects (X99), (ii) Assault by blunt objects (Y00), (iii) Assault by bodily force (Y04), (iv) Assault by firearms (X93, X94, X95), (v) Sexual assault by bodily force (Y05), (vi) Maltreatment, which includes,

but not limited to neglect, abandonment, torture, and abuse (Y06.0 – Y06.9, Y07.0 – Y07.9), and (vii) Other methods (all other codes between X85 and Y09).¹²

The pre-hospital time interval for patients who arrived via ambulance is defined as the elapsed time from the time of call for the ambulance to the time of arrival of the patient at our centre's Accident and Emergency (A&E) department. Major trauma was defined as an ISS of 16 and above.¹³ Severe, moderate and mild brain injuries were defined as Glasgow Coma Scale (GCS) scores of 3 to 8, 9 to 12, and 13 to 15 respectively.¹⁴

Data Analysis

The data were analysed using IBM SPSS Statistics for Windows, Version 19.0 (IBM, Chicago, IL). The means, standard deviations, ranges, and medians were reported for categorical variables where appropriate, and the numbers and individual percentages were reported for categorical variables. Normality of quantitative data was checked for using the Quantile-Quantile plot. Differences between groups were tested using the Pearson's chi-Squared Test, the Fisher's Exact Test, the Independent T-Test, and the One-way Analysis of Variance Test where appropriate. A multiple logistic regression analysis was performed to identify significant factors of mortality.

Results

Overall

Interpersonal violence victims constituted 444 (90.1% males; 9.9% females) out of a total of 8561 trauma admissions in the same time period. There was a steady increase in the number of interpersonal violence admissions from 10 cases in 2001 to a peak of 96 cases in 2008. This was followed by a decrease from 2008 to 2010 (55 cases in 2010) (Fig. 1). There was an average of 3 to 4 admissions every month. There was no seasonality in the distribution of admissions.

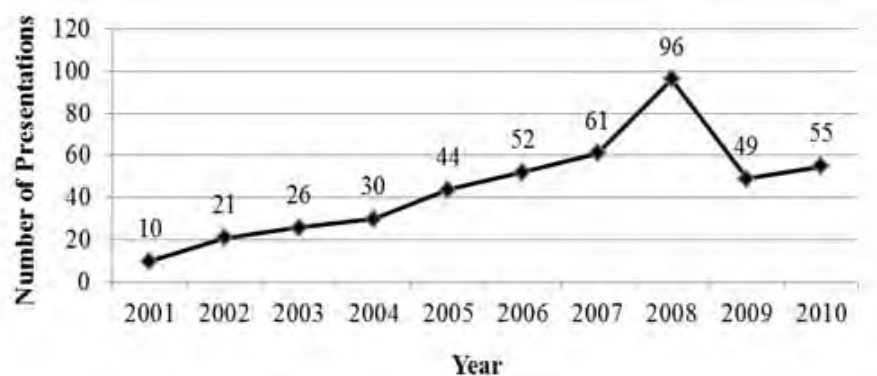


Fig. 1. Graph showing the number of interpersonal violence presentations in the years 2001 to 2010.

Demographics

There were 400 males (90.1%) and 44 females (9.9%). The average age was 36.6 years (median: 36.0 years; range, 14 to 83 years); 46.8% of the patients were between 20 and 39 years of age. The distribution of patients across all age groups for both genders was similar. The Chinese accounted for the majority of patients (53.4%), whereas Indians and Malays constituted 17.1% and 20.7% of the patient population respectively. The majority of the patients were Singaporeans (77.3%) (Table 1).

Table 1. Demographics of Patients

Demographics	Number (%)
Gender	
Male	400 (90.1)
Female	44 (9.9)
Age (years)	
0 to 19	46 (10.4)
20 to 39	208 (46.8)
40 to 59	163 (36.7)
60 to 79	25 (5.6)
80 to 100	2 (0.5)
Ethnic Group	
Chinese	237 (53.4)
Malay	92 (20.7)
Indian	76 (17.1)
Minority	39 (8.8)
Nationality	
Singaporean	343 (77.3)
Malaysian	19 (4.3)
Indian National	16 (3.6)
Chinese National	15 (3.4)
Others*	51 (11.5)

*Includes Thai, Bangladeshi, Nepalese, Burmese, Indonesian, Vietnamese, American, British and European

Table 2. Circumstances of Injury (Univariate Analysis)

	Male (%)	Female (%)	P value
Time (hours)			NS
0000 to 0559	293 (73.3)	28 (63.6)	
0600 to 1159	19 (4.8)	5 (11.4)	
1200 to 1759	24 (6.0)	2 (4.5)	
1800 to 2359	64 (16.0)	9 (20.5)	
Place of Occurrence			0.000
Public Area	373 (93.3)	28 (63.6)	
Home	14 (3.5)	15 (34.1)	
Institution*	13 (3.3)	1 (2.3)	

P values in bold are statistically significant.

*Includes workplaces, nursing home, and the Institute of Mental Health (IMH)

Time of Injury

The time of injury was predominantly from 0000 to 0559 hours (72.3%). There was no significant difference in the time of injury between the genders (Table 2).

Places Where the Interpersonal Violence Events Occurred

The most common place where interpersonal violence events occurred was public spaces (88.7%). This was common to both genders. However, the number of females who were injured at home (34.1%) was significantly higher compared to males (3.5%) ($P = 0.000$) (Table 2). The age of the female victims who were injured at home was 40.0 ± 14.8 years (range, 18 to 65 years). For these victims, injury was caused by the use of bodily force two-thirds of the time.

Mode of Arrival at the A&E Department

The majority of patients (338) arrived via ambulance (76.1%). One patient arrived via air transport (0.2%). The remaining 105 patients arrived via their own means (23.6%).

Pre-Hospital Time Interval

The average pre-hospital time interval for patients who arrived via ambulance was 36.0 ± 13.0 minutes (median: 36.0 minutes; range, 16.0 to 91.0 minutes). The pre-hospital time interval for the majority of the patients (312 patients, 70.3%) was up to 60.0 minutes.

Types of Trauma

Blunt trauma (58.3%) was more common than penetrating trauma (41.7%) (Table 3).

Causes of Injury

Assault by sharp objects was the most single most common cause of injury (48.6%). Only 1 case of firearm assault was reported (0.2%). No patient was injured by sexual assault by bodily force, or maltreatment. A variety of sharp and blunt objects used in the attacks was described. Sharp objects included knives, scissors, blades, and broken glass bottles. Blunt objects included beer mugs, bottles, hammers, hoes (changkols), crowbars, and golf clubs. For assault by bodily force, injury was caused almost entirely by the fist

Table 3. Types of Trauma

Type	Number (%)
Penetrating	185 (41.7)
Blunt	259 (58.3)

Table 4. Causes of Injury

Cause	Number (%)
Sharp Object*	216 (48.6)
Blunt Object†	133 (30.0)
Bodily Force	75 (16.9)
Firearm	1 (0.2)
Other Methods‡	19 (4.3)

*Includes knives, scissors, blades and broken glass bottles.

†Includes beer mugs, bottles, hammers, hoes (changkols), crowbars and golf clubs.

‡Mostly unspecified; 1 patient was reportedly dragged along the road by robbers who were on motorcycles.

blows and/or kicks, and 1 patient was pushed into the drain. Assault by other methods was mostly unspecified, except for 1 patient who was reportedly dragged along the road by robbers who were on motorcycles (Table 4).

Severity of Trauma

The overall average ISS was 13.5 (median: 10; range, 1 to 75). One hundred fifty-five patients had major trauma (34.9%), i.e. ISS of >15. The average ISS of patients with major trauma (22.3) was significantly higher than that of patients with non-major trauma (8.7) ($P = 0.000$). Blunt trauma was significantly more likely to result in major

Table 5. Severity of Trauma (Univariate Analysis)

	Male (%)	Female (%)	P value
Total	289 (65.1)	155 (34.9)	
Severity of Injury	8.7 ± 3.2	22.3 ± 7.4	0.000*
Gender			NS
Male	257 (64.3)	143 (35.8)	
Female	32 (72.7)	12 (27.3)	
Age	36.6 ± 13.8	36.8 ± 15.0	NS
Type of Trauma			0.003*
Penetrating	135 (73.0)	50 (27.0)	
Blunt	154 (59.5)	105 (40.5)	
Cause of Injury			0.003*
Sharp Object	157 (72.7)	59 (27.3)	
Blunt Object	81 (60.9)	52 (39.1)	
Bodily Force	44 (58.7)	31 (41.3)	
Firearm	0 (0.0)	1 (100.0)	
Other Methods	7 (36.8)	12 (63.2)	

*Statistically significant on univariate analysis.

trauma than penetrating trauma ($P = 0.003$). The cause of injury was significantly associated with the severity of trauma ($P = 0.003$). Although sharp objects was the most common cause of injury, they were the least likely to result in severe injuries. In contrast, the sole case of firearm assault resulted in major trauma (Table 5).

Table 6. Severity of Brain Injury (Univariate Analysis)

	Mild (%)	Moderate (%)	Severe (%)	P value
Total	371 (83.6)	24 (5.4)	49 (11.0)	
Severity of Injury	14.8 ± 0.4	10.4 ± 1.2	5.1 ± 2.1	0.000*
Gender				NS
Male	334 (83.5)	21 (5.3)	45 (11.3)	
Female	37 (84.1)	3 (6.8)	4 (9.1)	
Age (years)	36.3 ± 14.3	37.6 ± 12.0	38.8 ± 14.6	NS
Cause of Injury				0.000*
Sharp Object	188 (87.0)	7 (3.2)	21 (9.7)	
Blunt Object	103 (77.4)	11 (8.3)	19 (14.3)	
Bodily Force	69 (92.0)	4 (5.3)	2 (2.7)	
Firearm	0 (0.0)	0 (0.0)	1 (100.0)	
Other Methods	11 (57.9)	2 (10.5)	6 (31.6)	
Mode of Arrival				0.000*
Paramedic Transport	268 (79.1)	22 (6.5)	49 (14.5)	
Self	103 (98.1)	2 (1.9)	0 (0.0)	

*Statistically significant on univariate analysis.

Severity of Brain Injury

The overall average GCS score was 13.5 (median: 15; range, 3 to 15). Seventy-three patients had moderate-to-severe brain injury (16.4%), i.e. GCS 3-12. The average GCS score of patients with severe brain injury (5.1) was significantly lower than that of patients with moderate brain injury (10.4), and both were in turn significantly lower than that of patients with mild brain injury (14.8) ($P = 0.000$). The cause of injury was significantly associated with the severity of brain injury ($P = 0.000$). Bodily force produced the mildest brain injury. In contrast, the sole case of firearm assault resulted in severe brain injury. Patients who arrived via paramedic transport were significantly more likely to have moderate-to-severe brain injury ($P = 0.000$) (Table 6).

Mortality

The overall mortality rate was 4.5%. Six patients died in the A&E department. The other 14 patients were transferred to the other services before they eventually died from their injuries.

The gender, age, place of occurrence of interpersonal violence, type of trauma, and the pre-hospital time interval were not significantly associated with mortality in the univariate analysis. In contrast, the cause of injury, mode of arrival at the A&E department, severity of trauma, and the severity of brain injury were significantly associated with mortality in the univariate analysis.

Bodily force did not cause any mortality, whereas the sole case of firearm assault resulted in mortality. All of the patients who died had originally arrived at the A&E department via paramedic transport.

The average ISS of the 20 patients who died was 31.9 (median: 31; range, 16 to 75). The average ISS of the 6 patients who died in the A&E department was 39.0 (median: 34.5; range, 26 to 75). The average ISS of the 14 patients who eventually died in the other admitting services was 29.0 (median: 28.0; range, 14 to 43). The average ISS of the patients who died was higher than that of the 424 patients who survived, i.e. 12.6 (median: 10; range, 1 to 41).

The average GCS score of the 20 patients who died was 4.9 (median: 3; range, 3 to 14). The average GCS score of the 6 patients who died in the A&E department was 3.0 (median: 3.0; range, 3 to 3). The average GCS score of the 14 patients eventually died in the other admitting services was 5.7 (median: 3.5; range, 3 to 14). The average GCS score of the patients who died was lower than that of the remaining 424 patients who survived, i.e. 13.9 (median: 15.0; range, 3 to 15) (Table 7).

In the multiple logistic regression analysis, major trauma (OR: 25.856; $P = 0.002$) and moderate-to-severe brain injury (OR: 7.495; $P = 0.000$) were found to be independent risk factors of mortality (Table 8).

Table 7. Mortality (Univariate Analysis)

	Alive (%)	Dead (%)	P value
Total	424 (95.5)	20 (4.5)	
Gender			NS
Male	383 (95.8)	17 (4.3)	
Female	41 (93.2)	3 (6.8)	
Age (years)	36.5 ± 14.0	40.3 ± 17.1	NS
Place of Occurrence			NS
Home	28 (96.6)	1 (3.4)	
Outside Home	396 (95.4)	19 (4.6)	
Type of Trauma			NS
Penetrating	177 (95.7)	8 (4.3)	
Blunt	247 (95.4)	12 (4.6)	
Pre-Hospital Time Interval (min)			NS
	36.0 ± 11.0	40.0 ± 21.0	
Cause of Injury			0.000*
Sharp Object	208 (96.3)	8 (3.7)	
Blunt Object	125 (94.0)	8 (6.0)	
Bodily Force	75 (100.0)	0 (0.0)	
Firearm	0 (0.0)	1 (100.0)	
Other Methods	16 (84.2)	3 (15.8)	
Mode of Arrival			0.006*
Paramedic Transport	319 (94.1)	20 (5.9)	
Self	105 (100.0)	0 (0.0)	
Severity of Trauma			0.000*
Non-Major	288 (99.7)	1 (0.3)	
Major	136 (87.7)	19 (12.3)	
Severity of Brain Injury			0.000*
Mild	370 (99.7)	1 (0.3)	
Moderate-to-Severe	54 (74.0)	19 (26.0)	

*Statistically significant on univariate analysis.

Table 8. Multiple Logistic Regression Analysis of Factors which Influence Mortality

	Odds Ratio (95% CI)	P Value
Cause of Injury		NS
Firearm	1.148 (0.728, 1.811)†	
Non-Firearm (Reference)		
Mode of Arrival		NS
Paramedic Transport	1.257 (0.636, 1.819)†	
Self (Reference)		
Severity of Trauma		0.002*
Major	25.856 (3.203, 58.694)†	
Non-Major (Reference)		
Severity of Brain Injury		0.000*
Moderate-to-Severe	7.495 (3.374, 16.649)†	
Mild (Reference)		

*Statistically significant.

†Values in parentheses are the 2.5th and 97.5th of the 95% confidence intervals (i.e. 2.5% and 97.5%).

Discussion

Interpersonal violence remains relatively uncommon in Singapore. These 444 cases represent a very specific subset of the total of 8561 patients who were admitted to TTSH over the same time period for all forms of trauma, including vehicular accidents. This low prevalence can be accounted for by the strict laws in Singapore.

Nearly half of all victims (46.8%) were young, of age 20 to 39 years. This male predominance (90.1) may be attributed to the tendency for males to engage in violent behaviour or crime. This gender disproportion was also noted in other studies.^{5,7-11} It was also noted that there were no significant differences in the severity of trauma, severity of brain injury and mortality between the genders.

Victims were mainly young adults and not adolescents (average: 36.6 years). Adults may be more likely to spend a greater proportion of their time in public spaces where there are higher risks of confrontation and interpersonal violence. It may also suggest that teenage violence is a less common cause of interpersonal violence in the hospital catchment area.

The Indians (20.7%), Malays (17.1%) and minor ethnic groups (8.8%) experienced a disproportionately higher burden of interpersonal violence compared to the Chinese. This is not in keeping with the respective proportions of Malays, Indians, and minor ethnic groups, who represented 13.9%, 7.9% and 1.4% of the population in 2000, and 13.4%, 9.2%, and 3.3% of the population in 2010.¹⁵ Also, this study has demonstrated that the majority of the patients were actually Singaporeans (77.3%).

Interpersonal violence tended to happen between 1200 and 0600 hours in public spaces for both genders. Also, the number of females who were injured at home was disproportionately higher compared to males, which suggests that domestic violence is still a significant issue for females. These female victims represent a fairly wide age range from 18 to 65 years. Also, they tended to be injured by bodily force rather than sharp or blunt objects. The sub-analysis did not indicate disproportionate representation by any ethnic group for domestic violence. The reported rate in this study is likely to be an underestimation since it is well known that domestic violence victims often do not report to the authorities.¹⁶

Blunt trauma was more common, and was significantly more likely to cause major trauma than penetrating trauma. There was only 1 case of firearm assault in this study. Access to and use of firearms in Singapore is restricted to authorised members of the Police Force and the Armed Forces. Its use resulted in major trauma, severe brain injury, and mortality.

The pre-hospital time interval was 36.0 minutes for paramedic transport. This may not be fast enough depending

on the injury severity. Keeping this time interval short is crucial because the lapse of critical time denies patients of timely management. However, there was no association between the pre-hospital time interval and mortality.

In total, 34.9% and 16.4% of the patients had major trauma and severe brain injury respectively. Their respective severities were not influenced by gender and age. The overall mortality rate was 4.5%, which is relatively low. Unsurprisingly, major trauma (OR:25.856; $P = 0.002$) and moderate-to-severe brain injury (OR:7.495; $P = 0.000$) were independent risk factors of mortality.

From here, it can be seen that a trauma registry is an essential component of any efficient trauma management system. The information can be analysed, and the findings can provide data for policy makers to formulate violence prevention and intervention programmes. An example of this could be the identification of domestic violence in the catchment area for TTSH. Within their own homes, it is difficult for law enforcers to bring to task perpetrators of domestic violence. However, softer approaches in the form of promoting awareness, befriender services, or even refuge/shelter facilities can be considered.

The main limitation of this study is that it is specific to a single centre. The Singapore Police Force reports approximately 5000 cases of interpersonal violence in Singapore annually. Given that a major trauma centre like the TTSH admits only about 40 of such cases every year, it is obvious that the majority are probably not seriously injured and do not get admitted to the hospitals. Hence, we may conclude that hospital-based data does not add very much to what we know about the incidence and prevalence of interpersonal violence. However, it remains a good measure of harm and patient outcomes. In support of this, there are recommendations which state that data from both health care and law enforcement systems must be considered simultaneously to evaluate violence burden judiciously.¹⁷

The data reported is only representative of the areas served by the hospital. Some of the trends described like the over-representation of certain ethnic groups, a decrease in the admission rates in the last 2 years of the study, and the low incidence of teenage violence may not be extrapolated to the entire country. In fact, external factors may have accounted for these trends, such as the opening of the Khoo Teck Puat Hospital could have led to a diversion of trauma cases, resulting in the drop in admissions to our centre. Teenage violence could also have been diverted to the women and children hospital. Nonetheless, TTSH is located at the intersection of 2 major expressways in Singapore, and serves a large catchment area in the central portion of the island, making these data representative of a significant subpopulation of the country.

Another limitation of this study is that it could not consider victims of interpersonal violence who did not seek treatment, who were treated by private doctors or other medical personnel, and who deliberately concealed the associations of their injuries with interpersonal violence. This may be particularly so in women and young children. Singapore is also a place where there are still strong social pressures to keep violence behind closed doors, and where, unfortunately, non-consensual sexual intercourse within marriage is yet to be considered as illegal under most circumstances. Taken together, it is reasonable to assume a certain degree of underreporting of interpersonal violence. Nonetheless, this study is still a good characterisation of interpersonal violence where moderate to severe trauma is concerned.

Conclusion

This study provides factual health data of interpersonal violence victims treated at a major trauma centre. While attempts were made to draw certain conclusions from these data, we recognise the limitation of data from a single institution. However, this limitation does highlight the paucity of national data in this area. There has been no prior published data on interpersonal violence locally. The National Trauma Registry is currently still in the early years of establishment. It is hoped that a matured national registry will provide even more compelling data for policy makers to formulate and implement preventive measures.

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Ceftaroline—An Anti-MRSA Cephalosporin and Its Implications for Singapore

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Abstract

Introduction: Ceftaroline is a fifth-generation cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) that was recently launched in Singapore. It received approval from the United States (US) Food Drug Administration (FDA) and European Commission for the treatment of adult patients with community-acquired pneumonia (CAP) and complicated skin and soft tissue infections (cSSTI). This study aimed to review current published data and determine its clinical role, particularly in the local setting. **Materials and Methods:** A literature review on published articles in English on ceftaroline, focusing in particular on clinical trials and other clinical reports. Susceptibility testing was also performed on a limited sample of local MRSA and *Streptococcus pneumoniae* isolates. **Results:** Ceftaroline has an extensive spectrum of activity, including coverage of MRSA and multidrug-resistant *S. pneumoniae*. However, it has limited activity against non-fermenting Gram-negative bacteria and is susceptible to hydrolysis by extended spectrum beta-lactamases. It is only available for intravenous delivery, with a reconstituted stability of just 6 hours, rendering it unavailable for use for outpatient antibiotic therapy. Clinical trials demonstrate non-inferiority compared to first-line comparators in the treatment of CAP and cSSTI. Published case reports/series suggest a potential greater role in the treatment of MRSA bacteremia and endocarditis. No resistance was found among local archived MRSA and *S. pneumoniae* isolates. **Conclusion:** We believe ceftaroline will occupy primarily niche roles for culture-directed treatment of various infections—in particular those caused by MRSA—until further clinical trial data become available. A variety of factors render it less useful or appealing for empirical treatment of CAP or healthcare-associated infections.

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Key words: Antimicrobial agent, Bacteremia, Pharmacodynamics, Pharmacokinetics, Vancomycin hetero-resistant *Staphylococcus aureus*

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Ceftaroline—An Anti-MRSA Cephalosporin and Its Implications for Singapore

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Abstract

Introduction: Ceftaroline is a fifth-generation cephalosporin with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) that was recently launched in Singapore. It received approval from the United States (US) Food Drug Administration (FDA) and European Commission for the treatment of adult patients with community-acquired pneumonia (CAP) and complicated skin and soft tissue infections (cSSTI). This study aimed to review current published data and determine its clinical role, particularly in the local setting. **Materials and Methods:** A literature review on published articles in English on ceftaroline, focusing in particular on clinical trials and other clinical reports. Susceptibility testing was also performed on a limited sample of local MRSA and *Streptococcus pneumoniae* isolates. **Results:** Ceftaroline has an extensive spectrum of activity, including coverage of MRSA and multidrug-resistant *S. pneumoniae*. However, it has limited activity against non-fermenting Gram-negative bacteria and is susceptible to hydrolysis by extended spectrum beta-lactamases. It is only available for intravenous delivery, with a reconstituted stability of just 6 hours, rendering it unavailable for use for outpatient antibiotic therapy. Clinical trials demonstrate non-inferiority compared to first-line comparators in the treatment of CAP and cSSTI. Published case reports/series suggest a potential greater role in the treatment of MRSA bacteremia and endocarditis. No resistance was found among local archived MRSA and *S. pneumoniae* isolates. **Conclusion:** We believe ceftaroline will occupy primarily niche roles for culture-directed treatment of various infections—in particular those caused by MRSA—until further clinical trial data become available. A variety of factors render it less useful or appealing for empirical treatment of CAP or healthcare-associated infections.

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Introduction

Ceftaroline fosamil (TAK-599 or PPI-0903)—the prodrug of the active metabolite, ceftaroline—was launched in Singapore in March 2013 under the tradename Zinforo® by AstraZeneca. It is designated as a member of a new subclass of cephalosporins with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) by the Clinical Laboratory Standards Institute (CLSI) of the USA.¹ Ceftaroline has also been described in the medical literature as a ‘fifth-generation’ cephalosporin.² Ceftaroline was approved by the United States (US) Food and Drug Administration (FDA) in October 2010³ and the European Commission in August 2012⁴ for the treatment of adult patients with community-acquired pneumonia (CAP) and complicated skin and soft tissue infections (cSSTI). The Health Sciences

Authority approved it for the same indications in Singapore in November 2012.⁵

This article will provide an overview of ceftaroline, including its mechanism of action, spectrum of activity, pharmacokinetics and pharmacodynamics, clinical efficacy, case reports on its use in other types of infections, as well as its clinical limitations and potential use in the Singapore healthcare setting.

Chemical Structure and Mechanism of Action

The structure of ceftaroline fosamil is shown in Figure 1. As with other beta-lactam antibiotics, ceftaroline’s anti-bacterial activity results from the binding of the drug to

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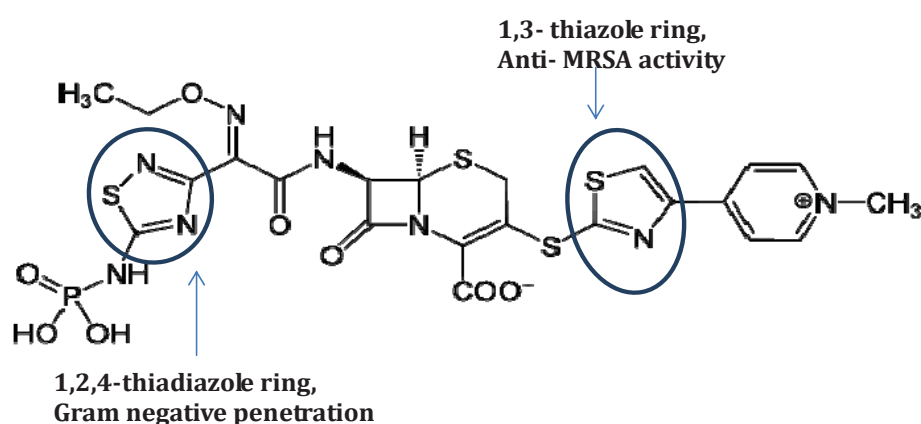


Fig. 1. Chemical structure of ceftaroline fosamil. (Adapted from Wikipedia - <https://en.wikipedia.org/wiki/File:Ceftarolinefosamil.svg>.)

penicillin-binding proteins (PBPs), thereby interfering with bacterial cell wall synthesis. MRSA is resistant to almost all beta-lactam antibiotics because of the presence of the *mecA* gene encoding a modified PBP 2a with poor binding affinity for these drugs.⁶ Ceftaroline binds to PBPs 1-4 and also equally strongly to PBP 2a in MRSA – the latter believed to be due to the addition of a 1,3-thiazole ring at the 3' position of the cephem ring (Fig. 1).^{7,8} It is also able to bind to the

PBPs that confer beta-lactam resistance in *Streptococcus pneumoniae* (i.e. PBP 2b, PBP 2x, etc.), and thus is also active against multidrug-resistant pneumococci.^{8,9}

The retention of the 1,2,4-thiadiazole ring (Fig. 1) permits penetration past the Gram-negative cell wall, with activity against the majority of Enterobacteriaceae and other Gram-negative bacteria.¹⁰ However, the coverage is variable, as further described below.

Table 1. Spectrum of Activity of Ceftaroline, Including MIC₉₀ Results Against Specific Organisms Where Available^{11,12}

Organism (number of isolates)	MIC 90s (mcg/mL) of Ceftaroline
Gram positive	
<i>Staphylococcus aureus</i>	
MSSA (348)	0.25
MRSA (92)	1
VISA (20)	1
VRSA (10)	0.5
Coagulase-negative staphylococci	
Methicillin susceptible (201)	0.12
Methicillin resistant (299)	0.5
<i>Enterococcus faecalis</i>	
Vancomycin susceptible (157)	4
Vancomycin resistant (25)	4
<i>Enterococcus faecium</i> (157)	>16
<i>Streptococcus pyogenes</i>	
Erythromycin susceptible (91)	<0.008
Erythromycin resistant (10)	<0.015
<i>Streptococcus agalactiae</i>	
Erythromycin susceptible (59)	0.015
Erythromycin resistant (42)	0.015
<i>Streptococcus pneumoniae</i>	
Penicillin sensitive (202)	0.015
Penicillin intermediate (103)	0.06
Penicillin resistant (296)	0.12

Table 1. Spectrum of Activity of Ceftaroline, Including MIC₉₀ Results Against Specific Organisms Where Available^{11,12} (Con't)

Organism (number of isolates)	MIC 90s (mcg/mL) of Ceftaroline
Gram negative	
Enterobacteriaceae	
Ceftazidime susceptible (833)	1
Ceftazidime resistant (220)	>16
<i>Citrobacter freundii</i>	
Ceftazidime susceptible (50)	0.25
Ceftazidime resistant (33)	>16
<i>Enterobacter cloacae</i>	
Ceftazidime susceptible (50)	1
Ceftazidime resistant (35)	>16
<i>Escherichia coli</i>	
Ceftazidime Susceptible (345)	0.5
Ceftazidime resistant (63)	>16
<i>Klebsiella pneumoniae</i>	
Ceftazidime susceptible (210)	0.25
Ceftazidime susceptible (66)	>16
<i>Proteus mirabilis</i> (58)	4
<i>Providencia</i> species (27)	>16
<i>Serratia marcescens</i> (59)	16
Acinetobacter species	
Imipenem susceptible (47)	16
Imipenem resistant (16)	>16
<i>Pseudomonas aeruginosa</i> (20)	>32

Spectrum of Activity

The list of organisms against which ceftaroline has demonstrated *in vitro* activity is shown in Table 1 along with the MIC₉₀'s (the minimum concentration of the drug wherein 90% of the tested isolates were inhibited) where available.^{11,12} It is in general active against all *S. aureus* isolates, including those isolates that are non-susceptible to vancomycin, linezolid and/or daptomycin.¹⁰⁻¹³ The European Committee on Antimicrobial Susceptibility Testing (EUCAST)¹⁴ and CLSI recommended breakpoint for *S. aureus* is currently 1 mcg/mL. It is also active against *Streptococcus pyogenes* and *Streptococcus agalactiae*, with all tested isolates inhibited by concentrations of ≤ 0.015 µg/mL.¹¹ All *Streptococcus pneumoniae* isolates, regardless of phenotype, were inhibited at concentration levels below the EUCAST and CLSI recommended breakpoint of 0.25 µg/mL and 0.5 µg/mL respectively.

We had performed ceftaroline susceptibility testing on 40 well-characterised MRSA isolates (Table 2)¹⁵⁻¹⁷ and 40 well-characterised *S. pneumoniae* isolates (Table 3)¹⁸ via both Etest and microbroth dilution. The results mirrored international findings,¹⁰⁻¹³ where both organisms were susceptible to ceftaroline despite the presence of resistance to other commonly-used antibiotics. The Etest MIC₉₀ for local MRSA and *S. pneumoniae* was 1.0 µg/mL and 0.125 µg/mL respectively, with slightly higher MICs seen for healthcare-associated MRSA clones and penicillin-resistant *S. pneumoniae* isolates.

Ceftaroline is active against ampicillin-susceptible *Enterococcus faecalis* (even vancomycin-resistant isolates) and ampicillin-susceptible *Enterococcus faecium* *in vitro*,¹⁰ but there is little clinical experience to support these results at present, and neither CLSI nor EUCAST have issued recommended breakpoints against these organisms.

Ceftaroline has variable activity against many Gram-negative Enterobacteriaceae (Table 1).^{10,11} Like the majority of cephalosporins, the drug is susceptible to inactivation by extended-spectrum beta-lactamases and *ampC* beta-lactamases, hence it is potentially inactive against organisms that produce such enzymes.¹⁰ It also has limited activity against non-fermenting Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, with MIC₉₀ of >16 µg/mL for such organisms.^{10,11}

Ceftaroline possesses anti-anaerobic activity similar to that of amoxicillin-clavulanate against Gram-positive anaerobes and 4- to 8-fold greater activity than that of ceftriaxone.¹⁹ It has limited activity against Gram-negative anaerobes, particularly members of the *Bacteroides fragilis* group, but is active against most beta-lactamase-negative anaerobes, including *Actinomyces* spp., *Propionibacterium* spp., *Eubacterium* spp., *Clostridium perfringens*, *Clostridium ramosum*, and *Clostridium innocuum*.¹⁹

The drug has no activity against atypical organisms and mycobacteria. In summary, ceftaroline demonstrates potent activity against Gram-positive organisms but only moderate activity against Gram-negative organisms *in vitro*.

Pharmacokinetics

Ceftaroline fosamil is a prodrug that undergoes rapid dephosphorylation in the bloodstream to the active compound after infusion.²⁰ The volume of distribution is 28.3 L (0.37 L/kg; range, 0.31 to 0.45 L/kg), representing distribution into the total body water compartment. The drug does not significantly bind to serum proteins ($<20\%$ protein-bound), and undergoes further conversion by hydrolysis of its beta-lactam ring to form an inactive, open-ring metabolite (ceftaroline M-1). The average half-life of ceftaroline and ceftaroline M-1 is 2.6 hours and 4.5 hours respectively. The CYP450 system does not appear to be a significant metabolic pathway for ceftaroline, which implies that this drug has a low potential for drug-drug interactions.²⁰

Approximately 50% of the dose of ceftaroline is excreted as active drug in the urine. In patients with mild renal impairment (creatinine clearance [CrCl] of 50 to 80 mL/min), the area under the curve (AUC) was 25% higher and the half-life 14% longer. In patients with moderate renal impairment (CrCl 30 to 50 mL/min), the AUC was 50% higher. Because of these characteristics, ceftaroline should be used with caution in patients with moderate to severe renal impairment, and dosing adjustments according to renal function are advised.⁸ The dosing recommendation for intravenous dosing is as follows, depending on the CrCl:^{20,21}

- >50 mL/min: no adjustment (600 mg every 12 hours).
- 30 to 50 mL/min: 400 mg every 12 hours.
- 15 to 30 mL/min: 300 mg every 12 hours.
- <15 mL/min and patients on dialysis: 200 mg every 12 hours.

Pharmacodynamics

As with other beta-lactams, ceftaroline exhibits time-dependent killing. The amount of time that the serum concentration remains above the MIC represents the main pharmacodynamic predictor of efficacy.

A minimal post-antibiotic effect ranging from 1.9 hours to 7.2 hours for *S. pneumoniae*, *Escherichia coli* and *S. aureus* was demonstrated in murine thigh and lung infection models.²² Ceftaroline was found to be bacteriostatic for staphylococci and Gram-negative bacilli when free drug concentration exceeded the MIC for 30% and 40% of the dosing interval respectively. However, bactericidal activity for staphylococci and Gram-negative bacilli with ceftaroline occurred when percentage time $>MIC$ was 50% and 60%, respectively.^{22,23}

Table 2. Ceftaroline and Vancomycin Susceptibility Testing Results for Local MRSA Isolates¹⁵⁻¹⁷

Isolate	Year	MLST ^a	Vancomycin MIC (Etest), µg/mL	hVISA/ VISA ^b	Ceftaroline MIC (Etest), µg/mL	Ceftaroline MIC (Microbroth), µg/mL
1	2003	239	4	VISA	0.75	1.024
2	2005	239	0.75	-	1.0	1.024
3	2008	239	1	-	1.0	1.024
4	2006	239	1.5	-	0.75	1.024
5	2001	239	2	hVISA	1.0	1.024
6	2005	239	4	VISA	0.5	0.512
7	2009	239	3	VISA	0.75	1.024
8	2000	239	3	VISA	0.75	1.024
9	2007	239	2	hVISA	1.0	1.024
10	2005	239	2	-	0.75	1.024
11	2005	239	2	-	0.75	1.024
12	2006	239	2	-	1.0	1.024
13	2006	239	2	-	1.0	1.024
14	2008	239	2	-	1.0	1.024
15	2008	239	2	-	0.75	1.024
16	2009	239	2	-	1.0	1.024
17	2009	239	2	-	0.38	0.512
18	2010	239	2	-	1.0	1.024
19	2010	239	2	-	0.75	1.024
20	2010	239	2	-	1.0	1.024
21	2006	22	2	hVISA	0.75	0.512
22	2009	22	2	hVISA	0.75	1.024
23	2009	22	3	VISA	0.75	0.512
24	2005	22	0.75	-	1.0	1.024
25	2007	22	0.75	-	0.5	0.512
26	2004	22	1	-	0.75	1.024
27	2003	22	0.75	-	0.75	0.512
28	2007	22	1	-	0.75	0.512
29	2010	22	0.75	-	0.75	0.512
30	2010	22	0.5	-	0.75	0.512
31	2005	30	1	-	0.5	0.512
32	2007	30	0.75	-	0.75	0.512
33	2005	30	0.75	-	0.5	0.512
34	2005	30	0.75	-	0.75	0.512
35	2008	30	0.75	-	0.5	0.512
36	2003	80	1.5	-	0.38	0.512
37	2005	8	0.75	-	0.5	0.512
38	2004	59	1	-	0.38	0.512
39	2007	59	1	-	0.38	0.512
40	2005	398	1.5	-	0.38	0.512

^aMLST: Multilocus sequence type. ST239 and ST22 are healthcare-associated MRSA; all others are community-associated MRSA except ST398, which is a livestock-associated MRSA.

^bhVISA: Heterogeneous vancomycin-intermediate *S. aureus*; VISA: Vancomycin-intermediate *S. aureus*.

Table 3. Ceftaroline, Penicillin and Ceftriaxone Susceptibility Testing Results for Local *Streptococcus Pneumoniae* Isolates¹⁸

Isolate	Year	Sero-type	Penicillin MIC (Etest), µg/mL	Ceftriaxone MIC (Etest), µg/mL	Ceftaroline MIC (Etest), µg/mL	Ceftaroline MIC (Microbroth), µg/mL
1	2000	19F	1.5	0.75	0.125	0.128
2	2000	14	0.016	0.016	0.008	0.008
3	2000	20	0.016	0.023	0.012	0.008
4	2000	8	0.016	0.008	0.008	0.008
5	2000	9A/L	0.016	0.012	0.012	0.008
6	2000	12F	0.016	0.006	0.008	0.008
7	2000	8	0.016	0.012	0.012	0.008
8	2000	3	0.016	0.012	0.008	0.004
9	2001	14	0.75	0.38	0.125	0.128
10	2001	14	2	0.5	0.125	0.128
11	2001	7C	2	0.5	0.094	0.128
12	2001	NT ^a	0.016	0.06	0.008	0.004
13	2001	1	0.016	0.008	0.012	0.008
14	2001	20	0.016	0.016	0.008	0.008
15	2002	14	0.75	0.5	0.125	0.128
16	2002	1	1	0.138	0.094	0.064
17	2003	33F	1	0.5	0.125	0.256
18	2003	19F	1.5	0.5	0.19	0.256
19	2004	23F	2	1	0.125	0.128
20	2004	19F	2	1	0.125	0.128
21	2004	14	0.016	0.032	0.008	0.008
22	2004	33F	0.016	0.016	0.008	0.008
23	2004	6B	0.016	0.06	0.008	0.008
24	2005	3	0.016	0.016	0.008	0.004
25	2005	14	0.75	0.38	0.094	0.128
26	2005	6B	1	0.5	0.064	0.064
27	2005	14	1	0.12	0.094	0.129
28	2005	23F	2	1	0.125	0.128
29	2005	8	0.012	0.012	0.012	0.008
30	2005	NT ^a	0.016	0.016	0.012	0.008
31	2005	18C	0.016	0.008	0.008	0.008
32	2005	23F	0.016	0.016	0.006	0.008
33	2005	10A	0.016	0.016	0.008	0.004
34	2006	19F	1	0.5	0.094	0.128
35	2006	14	1.5	0.5	0.094	0.128
36	2010	6B	2	1	0.19	0.128
37	2007	19A	1	0.25	0.047	0.032
38	2007	23F	1	0.5	0.094	0.128
39	2007	23F	2	1	0.19	0.256
40	2007	19F	2	1	0.125	0.128

^aNT: Non-typeable

Clinical Efficacy

The efficacy and safety of ceftaroline was assessed in 4 large phase 3 programmes of randomised, double-blind, clinical trials for CAP and cSSTI, and these are summarised in Table 4.²⁴⁻²⁹

The FOCUS 1 and 2^{24,25} (ceFtarOline Community-acquired pneUmonia trial vS ceftriaxone in hospitalised patients) trials were the 2 pivotal trials used for registration with FDA for the indication of CAP. Similarly, the CANVAS 1 and 2^{27,28} (CeftAroliNe Versus VAncomycin in Skin and Skin Structure Infections) trials were the 2 registration trials used for the indication of cSSTI.

The FOCUS programme was prospectively designed to pool results from both FOCUS 1 and 2 for integrated analysis as the 2 trials were similar to each other.²⁶ The primary objective was to determine non-inferiority in the clinical cure rates of ceftaroline compared with ceftriaxone in the clinically evaluable (CE) and modified intention-to-treat efficacy (MITTE) populations at the test-of-cure visit. The cure rates in both CE and MITTE populations met the non-inferiority criteria (lower limit of the 95% confidence interval being ≥ -10) but could not be considered superior to the comparator drugs in view of the design of the trials (Table 4).²⁶

In the CANVAS studies, ceftaroline monotherapy was compared with vancomycin plus aztreonam in cSSTI. Similar to the FOCUS programmes, the 2 trials were designed to allow pooling of results for a larger database of pathogens and safety information.²⁹ The primary objective of each trial was also to determine non-inferiority of the clinical cure rate achieved with ceftaroline compared to vancomycin plus aztreonam combination therapy in the CE and MITTE patient populations. This was achieved. In a subgroup analysis, the clinical cure rates in microbiologically evaluable patients with MRSA were 93.45% and 94.3% in the ceftaroline and comparator arms respectively, but no confidence interval was reported.²⁹

In summary, for the indications of CAP and cSSTI, therapy with ceftaroline was observed to be non-inferior to the comparator agents at both a standard test of cure assessment time (8 to 15 days after discontinuation of study drug) and an early assessment time point (day 3 or 4 of study). The recommended duration of therapy is 5 to 7 days and 5 to 14 days for CAP and cSSTI respectively.

Safety and Tolerability

Ceftaroline was generally well tolerated in the licensing trials, with an adverse event profile similar to the comparator agents—ceftriaxone and vancomycin plus aztreonam.^{24,25,27,28} The most common adverse events reported in clinical trials were diarrhoea, nausea and headache and these are summarised in Table 4.²⁴⁻²⁹

Use of Ceftaroline for Other Indications

Currently, there is no clinical trial data available for use of ceftaroline out of its approved indications for CAP and cSSTI. A search on the clinical trials website (<http://clinicaltrials.gov/>) revealed 2 other studies on urinary tract infections and MRSA bacteremia respectively, but the results are not yet available. Nonetheless, there are numerous case reports/series on the use of ceftaroline for other infections, especially endocarditis. We have summarised these reports in Table 5.³⁰⁻³⁴

The anti-MRSA activity of ceftaroline has been exhibited in both in vitro and animal studies, including rabbit endocarditis models.^{35,36}

In order to mitigate its vulnerability to extended-spectrum beta-lactamase-producing Enterobacteriaceae, ceftaroline has also been tested in combination with avibactam (formerly known as NXL104), a novel non-beta-lactam beta-lactamase inhibitor.³⁷⁻³⁹ Avibactam permanently inactivates extended-spectrum beta-lactamases and *ampC* enzymes by forming a stable and irreversible covalent bond within their active sites.⁴⁰ The combination of ceftaroline and avibactam has demonstrated in vitro potency against extended-spectrum beta-lactamase- and *ampC*-producing Enterobacteriaceae, but not against *P. aeruginosa* or *Acinetobacter baumannii*.³⁷⁻³⁹ It is currently being evaluated in Phase 2 studies of complicated urinary tract and intra-abdominal infections by AstraZenica/Forest.⁴¹

Clinical Limitations and Potential Usage of Ceftaroline (Especially Local Context)

Ceftaroline has only been rigorously tested on specific populations of patients with CAP and cSSTI in randomised controlled clinical trials,²⁴⁻²⁹ and its clinical efficacy on other types of infections and also within CAP and cSSTI subpopulations remain uncertain. Much of its presumptive efficacy—as evidenced by the case reports and series (Table 5)³⁰⁻³⁴—has been extrapolated based on in vitro susceptibility testing and by its nature as a cephalosporin, where, as a class of antibiotics, extensive experience has been accumulated.

For the indication of CAP, the results from the FOCUS trials support the efficacy and safety of the drug in inpatients with CAP who are managed in a non-intensive care unit (ICU) setting, but its efficacy in other populations is not clear. Based on the exclusion criteria, data are lacking in patients that are immunosuppressed, require ICU admission, or have risk factors for other hospital-acquired infections. Importantly, ceftaroline demonstrated clinical efficacy for the treatment of multidrug-resistant *S. pneumoniae*, but larger studies are needed to confirm these findings. In the local and regional setting, where pneumonia caused by *Burkholderia pseudomallei* is a concern particularly in severely ill patients where early appropriate antibiotic

Table 4. Summary of Licensing Trials for Ceftaroline²⁴⁻²⁹

FOCUS 1 and 2 ²⁴⁻²⁶		CANVAS 1 and 2 ²⁷⁻²⁹		
Drugs	Ceftaroline	Ceftriaxone	Ceftaroline	Vancomycin plus Aztreonam
Indication	Community-acquired pneumonia		Complicated skin and soft tissue infection	
Type of Trials	Phase III multicenter, randomised, double-blind		Phase III multicenter, randomised, double-blind	
Study design	To demonstrate non-inferiority of comparator		To demonstrate non-inferiorityof comparators	
Number of patients randomised	1240		1396	
Key exclusions	Patients - Admitted to the intensive care unit - On dialysis - With risk factors for an MRSA Infection (as ceftriaxone is not effective against this organism)		Patients with - Suspected <i>Pseudomonas aeruginosa</i> or anaerobic infection - Decubitus ulcer, diabetic foot ulcer, ulcer associated with peripheral vascular disease accompanied by osteomyelitis - Extensive burns	
Doses	600 mg IV every 12 hours	1g IV every 24 hours	600 mg IV every 12 hours	Vancomycin 1g IV every 12 hours plus aztreonam 1g IV every 8 hours
Clinical cure rates				
a) In clinically evaluable populations	387/459 (84.3%)	349/449 (77.7%)	559/610 (91.6%)	549/592 (92.7%)
	95% CI, 1.6 to 11.8		95% CI, – 4.2 to 2.0	
b) In modified intent-to-treat efficacy populations	479/580 (82.6%)	439/573 (76.6%)	595/693 (85.9%)	586/685 (85.5%)
	95% CI, 1.4 to 10.7		95% CI, – 3.4 to 4	
c) In microbiologically evaluable populations	131/154 (85.1%)	111/147 (75.5%)	434/468 (92.7%)	421/446 (94.4%)
	95% CI, 0.7 to 18.8		95% CI, – 4.9 to 1.6	
d) In community-acquired pneumonia caused by <i>Streptococcus pneumoniae</i>	59/69 (85.5%)	48/70 (68.8%)		
	No 95% CI reported			
e) In multidrug-resistant <i>S. pneumoniae</i> pneumonia	4/4 (100%)	2/9 (22%)		
f) In microbiologically evaluable patients with MRSA cSSTI			142/152 (93.4%)	115/122 (94.3%)
	No CI reported			
g) In MRSA bacteremia			6/7 (85.7%)	2/2 (100%)
	95% CI, – 53.5 to 58.4			
Treatment emergent adverse events				
a) Nausea (%)	2.3	2.3	5.9	5.1
b) Headache (%)	3.4	1.5	5.2	4.5
c) Rash (%)	NA	NA	3.2	2.5
d) Diarrhoea (%)	4.2	2.6	4.9	3.8
e) <i>Clostridium-difficile</i> associated diarrhoea	0	0	2 cases	1 case

CI: Confidence interval; NA: Not available

Table 5. Summary of Case Reports of Ceftaroline Used in Indications Other Than CAP And cSSTI³⁰⁻³⁴

Author of case reports	No. of patients	Type of Infection	Failed prior therapy (if any)	Indication for Ceftaroline	Highest dose of ceftaroline used	Clinical outcome ^{a, b}
Ho et al ³⁰	6	Persistent MRSA bacteremia • 2 endocarditis • 1 uveitis and endophthalmitis • 1 UTI • 1 uveitis and ethmoid osteomyelitis • 1 prostatitis and septic thrombophlebitis	Vancomycin and/or daptomycin	Salvage	600 mg 8H	5 achieved clinical cure; 6 achieved microbiological cure; 1 death
Lin et al ³¹	10	• 4 MRSA bacteremia with probable endocarditis • 1 MRSA bacteremia with probable endocarditis and septic arthritis • 2 MRSA pneumonia • 1 MRSA bacteremia with septic arthritis • 2 osteomyelitis	Vancomycin and/or daptomycin	Salvage and/or add on therapy to daptomycin	600 mg 8H (or lower for patients with impaired renal function)	6 achieved clinical cure; 7 achieved microbiological cure; 3 deaths
Rose et al ³²	1	Persistent MRSA bacteremia, septic shock and development of reduced daptomycin susceptibility	Daptomycin	Add on therapy to daptomycin	200 mg bd (adjusted for ESRF)	Achieved microbiological cure and discharged to hospice
Jongsma et al ³³	1	Persistent MRSA bacteremia and daptomycin-non-susceptible <i>Staphylococcus aureus</i> infective endocarditis and osteomyelitis	Daptomycin and vancomycin	Salvage	600 mg bd	Clinical and microbiological cure
Sakoulas G et al ³⁴	1	Recurrent case of left-sided endocarditis caused by high-level aminoglycoside-resistant <i>Enterococcus faecalis</i>	Ampicillin and ceftriaxone, followed by ampicillin and daptomycin	Add on therapy to daptomycin for synergy (ampicillin was discontinued)	600 mg 8H	Clinical and microbiological cure

^aClinical cure was defined as resolution of all signs and symptoms of infection or improvement such that no further antimicrobial therapy was necessary.

^bMicrobiological cure was defined as negative cultures after antimicrobial therapy.

UTI: Urinary Tract Infection

coverage may be critical, it is less easy to delineate a niche for ceftaroline, especially as the cost of the drug is high compared to standard CAP therapy. Existing in vitro susceptibility testing data on 30 isolates suggest that the *B. pseudomallei* ceftaroline MIC is equivalent to ceftazidime MIC,⁴² but the dose required to attain the pharmacodynamic breakpoint (extrapolated to be 5 to 6 grams daily) is far higher than is currently recommended for CAP or that which has been tested in early human studies to date.

For the indication of cSSTI, its anti-MRSA activity increases the options for clinicians who may be able to use ceftaroline as a single agent for the treatment of mixed Gram-negative and Gram-positive (with MRSA) infections. However, ceftaroline does not have good in vitro activity against several important nosocomial Gram-negative pathogens such as *P. aeruginosa*. Thus it may not be an adequate substitute for currently used antibiotics such as ceftazidime, cefepime or piperacillin/tazobactam for the

empiric treatment of nosocomial cSSTI, or as empirical treatment for any nosocomial infection locally. Ceftaroline will likely not become the first-line therapy for nosocomial cSSTI in the near future but is otherwise a viable alternative in the right setting, i.e. culture-directed therapy where only MRSA and susceptible Gram-negative bacteria are cultured out, and/or where vancomycin is not appropriate or has failed therapy.

Although not currently recommended as a treatment for MRSA bacteremia, this is the area where ceftaroline has the greatest potential to improve on current therapy. Other than daptomycin, beta-lactam antibiotics have generally proven superior to other classes of antibiotics for the treatment of *S. aureus* bacteremia and endocarditis.⁴³ Early data from case reports are promising, but a formal clinical trial is required to ascertain the role of ceftaroline for *S. aureus* (including MRSA) bacteremia. As this point in time, we would recommend that ceftaroline should only be prescribed

for patients with severe systemic MRSA infections who have already failed vancomycin and/or daptomycin therapy. More frequent dosing intervals (IV 600 mg 8H) is recommended based on pharmacodynamics parameters and the experiences reported in existing case reports.³⁰⁻³⁴

In terms of drug delivery, ceftaroline has to be provided via the intravenous route twice (or thrice) daily for patients with normal renal function. It therefore offers no advantage in terms of administration when compared with alternative agents, particularly for CAP (levofloxacin or moxifloxacin can be orally administered, whereas ceftriaxone can be administered intravenously once a day). Once reconstituted, the drug is only stable for 6 hours at room temperature (or 24 hours at 2 to 8 degrees Celsius).³ Thus it has no role in terms of outpatient antibiotic therapy (OPAT).

Because ceftaroline has just been launched in Singapore and has not been included in any public hospital's drug formulary, local experience is limited and largely restricted to patients with disseminated MRSA infections who have failed more conventional therapy such as vancomycin and daptomycin. Anecdotally, success rates have been variable.

Conclusion

In summary, ceftaroline is the first cephalosporin to be approved for the treatment of MRSA infections with an efficacy profile similar to its comparators in the treatment of CAP and cSSTI. Its strength lies in this enhanced Gram-positive coverage. More research is necessary to determine its role in other severe systemic MRSA infections such as bacteremia and osteomyelitis. While its spectrum of activity is extensive in comparison to earlier-generation cephalosporins, inadequate coverage of non-fermenting Gram-negative bacteria such as *P. aeruginosa* and *A. baumannii*, and its vulnerability to extended-spectrum beta-lactamases produced by a significant proportion of local nosocomial Enterobacteriaceae restrict its usefulness as an antimicrobial agent for empirical treatment of healthcare-associated infections. In the local context, the high drug costs, uncertainty about coverage of *B. pseudomallei* and low rates of community-associated MRSA pneumonia⁴⁴ render it less appealing as empirical therapy for moderate-to-severe CAP. We anticipate that ceftaroline will occupy primarily niche roles for culture-directed treatment of various infections—in particular those caused by MRSA—until further clinical trial data become available.

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Does Experience Meet Expectations Among General Surgical Trainees in Australia and New Zealand?

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Introduction

One of the key aspects to become a skilful surgeon is to acquire the technical competence in performing the various operations safely. Several changes in the general surgical (GS) training curriculum in the United States have highlighted concerns regarding the experience of final year GS residents.¹⁻⁴ This study was undertaken to determine if the experiences of the GS trainees under the supervision of the Royal Australasian College of Surgeons (RACS) coincides with their expectations and those of their training supervisors.

Materials and Methods

General surgery is one of the 9 surgical specialties supervised by the RACS. The surgical education and training (SET) programme comprises 5 years of supervised training (SET-1 to SET-5). The adequacy of the training is monitored with regular accreditation of the hospitals by RACS and review of the trainees' logbooks.

For this study, all the GS trainees of the RACS were contacted via email in 2010 to complete an online questionnaire. Participation was voluntary and blinded. A list of 15 surgical skills (Table 1) was compiled after consultation with the Board in GS as to what were considered core surgical skills that should be mastered upon completion of the SET programmes.

The trainees were asked to describe the expected number of cases that they consider should be completed at the end of their training and the actual number of cases that they have performed. Questions on the percentage of skills that the trainees are expected to perform independently without mentor intervention (mentor being scrubbed) and the actual number of cases that they could complete independently were also asked. All the training supervisors in the GS specialty of the RACS were also contacted and asked similar questions regarding their expectations of trainees' competencies. The study protocol was reviewed and

Table 1. List of 15 Surgical Skills Expected of the Trainees upon Completion of the General Surgery Training Programme

1.	Assessment of shock
2.	Assessment of the acute abdomen
3.	NGT insertion
4.	Skin closure
5.	Chest drain insertion
6.	Insertion of hasson cannula
7.	Open/close abdomen
8.	Open inguinal hernia repair
9.	Open appendectomy
10.	Laparoscopic appendectomy
11.	Mastectomy
12.	Open cholecystectomy
13.	Laparoscopic cholecystectomy
14.	Hemicolectomy
15.	Colonoscopy

NGT: Nasogastric tube

approved by our Institutional Ethics Committee. Statistical analysis was carried out using the Mann Whitney U and Wilcoxon test (SPSS program (Chicago, Illinois, USA)).

Results

A total of 159 of 478 (33.3%) GS SET trainees and 42 of 187 (22.2%) SET supervisors completed the survey. Apart from colonoscopy which the supervisors expected a higher number of cases ($P = 0.025$), there were no significant differences in the numbers expected to be performed between the trainees and supervisors in the other skills (Table 2).

Among the senior trainees (SET 4-5), open cholecystectomy was the only procedure which they did not achieve the caseload expected by the supervisors ($P = 0.001$) (Table 3).

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Table 2. Median Numbers of General Surgical Skills Expected for Competency and Actually Performed at SET 4-5 Level

Surgical Skills	Expected			Actual
	SET Supervisor	Trainees	SET 4-5	SET 4-5
Number in group	42	159	52	52
Shock	21 – 50	21 – 50	21 – 50	101 – 150
Acute abdomen	51 – 100	51 – 100	51 – 100	>300
NGT	12 – 20	6 – 11	6 – 11	21 – 50
Skin closure	21 – 50	21 – 50	21 – 50	>300
Chest drain	12 – 20	12 – 20	6 – 11	21 – 50
Hasson cannula	21 – 50	21 – 50	21 – 50	>300
Open/close abdomen	21 – 50	21 – 50	21 – 50	151 – 200
Open inguinal hernia	21 – 50	21 – 50	21 – 50	101 – 150
Open appendectomy	21 – 50	21 – 50	21 – 50	51 – 100
Laparoscopic appendectomy	21 – 50	21 – 50	21 – 50	101 – 150
Mastectomy	21 – 50	21 – 50	12 – 20	21 – 50
Open cholecystectomy	21 – 50	21 – 50	21 – 50	12 – 20
Laparoscopic cholecystectomy	51 – 100	51 – 100	51 – 100	101 – 150
Hemicolectomy	51 – 100	51 – 100	21 – 50	51 – 100
Colonoscopy	101 – 150	51 – 100	51 – 100	151 – 200

NGT: Nasogastric tube

Table 3. Univariate Analysis of Median Numbers of General Surgical Skills Expected for Competency and Actually Performed at SET4-5 Level (*P* values)

Surgical Skills	Expected by Supervisors vs Expected by Trainees	Expected by Supervisors vs Expected by SET 4-5	Expected by Supervisors vs Actually Performed by SET 4-5	Expected by SET 4-5 vs Actually Performed by SET 4-5
Type of Analysis Performed	Mann Whitney U	Mann Whitney U	Mann Whitney U	Wilcoxon
Shock	0.840	0.781	0.001	0.001
Acute abdomen	0.534	0.665	0.001	0.001
NGT	0.105	0.112	0.006	0.001
Skin closure	0.501	0.784	0.001	0.001
Chest drain	0.064	0.032	0.006	0.001
Hasson cannula	0.507	0.588	0.001	0.001
Open/Close abdomen	0.929	0.901	0.001	0.001
Open Inguinal hernia	0.997	0.528	0.001	0.005
Open appendectomy	0.520	0.311	0.004	0.001
Laparoscopic appendectomy	0.919	0.545	0.001	0.001
Mastectomy	0.974	0.105	0.799	0.098
Open cholecystectomy	0.332	0.079	0.001	0.002
Laparoscopic cholecystectomy	0.879	0.526	0.001	0.001
Hemicolectomy	0.700	0.641	0.223	0.337
Colonoscopy	0.025	0.019	0.277	0.002

NGT: Nasogastric tube

Table 4. Median Percentages of General Surgical Skills Expected to be Performed Without Mentor Intervention and Actually Performed at SET 4-5 Level

Surgical Skills	Expected		Actual	
	SET Supervisor	Trainees	SET 4-5	SET 4-5
Number in Group	42	159	52	52
Shock	71 – 80	81 – 90	81 – 90	81 – 90
Acute Abdomen	91 – 100	91 – 100	91 – 100	91 – 100
NGT	91 – 100	91 – 100	91 – 100	91 – 100
Skin Closure	91 – 100	91 – 100	91 – 100	91 – 100
Chest Drain	91 – 100	91 – 100	91 – 100	91 – 100
Hasson Cannula	91 – 100	91 – 100	91 – 100	91 – 100
Open/Close Abdomen	91 – 100	91 – 100	91 – 100	81 – 90
Open Inguinal Hernia	91 – 100	91 – 100	91 – 100	81 – 90
Open Appendectomy	91 – 100	91 – 100	91 – 100	91 – 100
Laparoscopic Appendectomy	91 – 100	91 – 100	91 – 100	91 – 100
Mastectomy	71 – 80	71 – 80	71 – 80	21 – 30
Open Cholecystectomy	61 – 70	61 – 70	61 – 70	1 – 10
Laparoscopic Cholecystectomy	81 – 90	81 – 90	71 – 80	71 – 80
Hemicolectomy	71 – 80	61 – 70	61 – 70	41 – 50
Colonoscopy	81 – 90	81 – 90	81 – 90	81 – 90

NGT: Nastrogastric tube

Table 5. Univariate Analysis of Median Percentages of General Surgical Skills Expected to be Performed Without Mentor Intervention and Actually Performed at SET4-5 level (*P* values)

Surgical Skills	Expected by Supervisors vs Expected by Trainees	Expected by Supervisors vs Expected by SET 4-5	Expected by supervisors vs Actually Performed by SET 4-5	Expected by SET 4-5 vs Actually Performed by SET 4-5
Type of Analysis Performed	Mann Whitney U	Mann Whitney U	Mann Whitney U	Wilcoxon
Shock	0.303	0.524	0.907	0.185
Acute Abdomen	0.853	0.908	0.896	0.351
NGT	0.496	0.803	0.292	0.063
Skin Closure	0.155	0.085	0.530	0.207
Chest Drain	0.673	0.595	0.642	0.464
Hasson Cannula	0.286	0.341	0.137	0.596
Open/Close Abdomen	0.126	0.042	0.002	0.211
Open Inguinal Hernia	0.419	0.404	0.043	0.098
Open Appendectomy	0.274	0.586	0.203	0.131
Laparoscopic Appendectomy	0.911	0.951	0.823	0.442
Mastectomy	0.831	0.903	0.001	0.001
Open Cholecystectomy	0.765	0.354	0.002	0.001
Laparoscopic Cholecystectomy	0.526	0.361	0.116	0.376
Hemicolectomy	0.146	0.377	0.003	0.003
Colonoscopy	0.394	0.750	0.372	0.355

NGT: Nastrogastric tube

The SET 4-5 trainees actually performed more cases in 12 of 15 (80%) listed skills than expected by the supervisors.

Independence of Trainees

The SET 4-5 trainees were able to complete 8 of 15 (53%) skills independently at the same levels expected by the supervisors (Tables 4 and 5). The 5 skills they were not able to perform independently at levels expected by supervisors included opening and closing the abdomen ($P = 0.002$), open inguinal hernia ($P = 0.043$), mastectomy ($P = 0.001$), open cholecystectomy ($P = 0.002$) and hemicolectomy ($P = 0.003$).

Discussion

In this study, the trainees and supervisors largely agreed on the expected number of cases that are required of each trainee to perform at the end of their training. What is more worrying is that senior trainees were unable to fulfil their expected caseload in 5 of the procedures independently. For opening and closing of abdomen and open inguinal hernia, the numbers of cases performed, with and without mentor intervention, were considerably different. The underlying reason is likely multifactorial. These may include operative time constraints, and assistance provided by the mentor in parts of the procedure.⁵⁻⁸

Perhaps even more concerning was the lower numbers being achieved for mastectomy, hemicolectomy and especially open cholecystectomy. This is likely due to the continual expansion of fellowship programs (Breast, colorectal and upper gastrointestinal) in Australia and New Zealand. This trend was also noted in the United States with more than 80% of the general surgical residents opting for further training in various fellowship programmes.⁹⁻¹² Although the presence of the fellows does not necessarily imply that the cases of the residents would drop, the fellows or the attending consultant may remained scrubbed longer and intervene earlier during the operations. This trend will likely create a vicious cycle whereby the cases that were previously deemed to be mastered by the senior trainees will only be performed during the fellowship years. It is imperative that the training board needs to be proactive and be explicit in determining which core skill must be taught and mastered in general surgery.

Teaching the next generation of surgeons can no longer be one-dimensional; the continual advancement in technology should be gradually embraced. Although simulation does not create the same environment and experience as in the operative theatre, there is no doubt that tools such as endoscopy models and laparoscopic modules can help shorten the learning curve of trainee.¹³⁻¹⁶ Moreover, mastering simpler procedures would also aid the subsequent

acquisition of the expertise necessary for a more challenging operation. The concept of skill transference would be applicable in the various laparoscopic procedures and types of bowel anastomoses.

While a response rate of 33.3% among trainees could be viewed as disappointing and a significant limitation of our study, this is the first time that such an endeavour has been achieved in the GS fraternity within the RACS. Our study highlights that regular feedback between the trainees and supervisors is essential to ensure the transparency of the programme. The surgical experience of each trainee should not be the only factor to determine for competency. Knowledge, decision-making, and pre- and post-operative management skills are also vital to ensure that the outcomes of the patients are not jeopardised. The impact of the fellowship programmes on the general surgical trainees can no longer be underestimated.

Conclusion

The experiences of the general surgical trainees concur well with their own expectations, as well as that of their supervisors. A multitude of factors are likely accountable for the lower number of independent operative experience in certain procedures encountered by the trainees.

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Evolving Practice Patterns in Treatment of Major Retinal Diseases in Singapore

Dear Editor,

Neovascular (“wet”) age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vein occlusion (RVO) are amongst the most common causes of blindness.¹⁻³

Traditionally, these conditions were treated with thermal laser photocoagulation, however, the advent of anti-vascular endothelial growth factor (VEGF) has revolutionised the treatment of these diseases.^{1,4,5} These anti-VEGF agents (ranibizumab and bevacizumab) aim to stop retinal angiogenesis and reduce macular oedema. Numerous trials have evaluated the efficacy of these treatments in western populations, however, there are no clear guidelines for anti-VEGF use in Asian countries where the pattern of retinal disease is different.

This study surveyed the current practice patterns of ophthalmologists in Singapore with regards to the use of anti-VEGF and established therapies for the management of 3 major retinal disease: AMD, DME and central retinal vein occlusion (CRVO).

Materials and Methods

A questionnaire was sent to all accredited ophthalmologists in Singapore. The survey included 32 questions on anti-VEGF treatment, follow-up and investigations of AMD, polypoidal choroidal vasculopathy (PCV), DME and CRVO.

Results

Seventy-seven responses (40%) were received. DME was considered ‘treatable’ by majority (81.0%), followed by CRVO (67.0%) and wet AMD (59.0%). Anti-VEGF monotherapy was the most common initial treatment for wet AMD, while combination therapy consisting of anti-VEGF and photodynamic therapy was the most common initial treatment for PCV. The estimated mean annual number of injections was 5.25 for ranibizumab and 5.75 for bevacizumab. Laser without anti-VEGF therapy was the most common treatment for DME (55%) and CRVO (46%).

Discussion

In our survey, we found that most non-retinal specialists referred wet AMD cases to their retinal colleagues. This was

likely due to the growing complexity behind the diagnosis and treatment of AMD. In contrast, many non-retinal specialists prefer to continue treating DME and CRVO. Responses reflected an increased level of familiarity to DME and CRVO compared to AMD and the overall perception of the condition being ‘treatable’ was also rated as highest for DME, followed by CRVO, and wet AMD (Fig. 1).

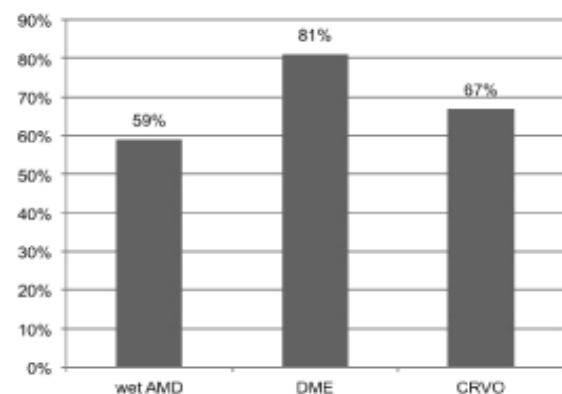


Fig. 1. Chart showing the percentage of responses indicating conditions perceived as ‘treatable’ by clinicians (n = 77).

Our survey demonstrated that despite the established superior visual outcome with anti-VEGF therapy,⁶ laser monotherapy remains the most commonly used treatment for DME. We suspect that factors such as financial constraints, intensive follow-up, and visual outcome affect the choice of treatment modality. In such cases, clinicians must explain these factors carefully to patients, and together, agree at a preferred treatment regime. Our survey showed a similar spread of preferred treatment modalities in CRVO reflecting the multitude of opinions, and treatment options for treating this condition. In the case of AMD, majority of respondents indicated anti-VEGF monotherapy was their treatment of choice. Most respondents indicated they would initiate their treatment with 3-monthly injections and a pro re nata regime afterwards.

Overall, bevacizumab and ranibizumab use appeared to be divided roughly in a 7 to 3 ratio. Similar trends were noted in the American Preferences and Trends survey.⁷ However, there remains a large variation in terms of monitoring and retreatment. The estimated number of retreatments within the first year was <6 in our survey (Fig. 2). This retreatment number suggested that the monthly dosing of anti-VEGF used in the pivotal MARINA, ANCHOR and CATT trials^{5,8,9} was rarely adopted in practice. This was consistent with data described in the US Medicare analysis (2006 to 2008) showing the mean number of injections to be only 4.3 within the first year, and discontinuation rate of 53.6% within 1 year. The reasons for discontinuity were found to be multifactorial and avoidable, including lack of understanding and mismatch in expectations. Therefore, efforts to improve patient education are important to achieve optimal treatment outcome.

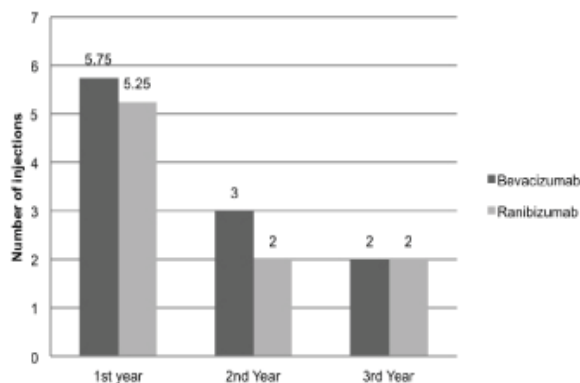


Fig. 2. Chart showing the estimated number of injections received by AMD patients up to year 3.

Responses regarding treatment of PCV reflected the unfamiliarity to this condition. In our survey, the proportion of PCV among wet AMD cases was estimated to be 30% to 50% consistent with most Asian populations.¹⁰ The optimal treatment for PCV remains unclear, although the EVEREST trial reported superior angiographic (but not visual acuity) outcome with PDT and PDT combined with ranibizumab over ranibizumab monotherapy. Despite the sound rationale behind combining the vaso-occlusive effect of PDT with the anti-angiogenic effects of anti-VEGF therapy, potential deleterious effects such as damage to choroidal vasculature remains a concern. A recent consensus paper from Singapore recommends combination therapy as initial treatment for subfoveal PCV.¹¹ This highlights that for PCV, further research is needed to study the optimal treatment regime.

Conclusion

In conclusion, our survey shows the trends and evolving practice patterns of clinicians in Singapore in the management of major retinal disease. Despite the myriad of recent randomised controlled trials which have demonstrated the safety and efficacy of these new treatments, the variation in current practice patterns likely reflects the lack of consensus for optimal strategies. In such an environment, frequent update of the latest information and audit of local data are important to ensure practice patterns evolve in the right direction. Particular attention should also be paid during the informed consent process to ensure that all relevant information has been explained to the patient before arriving at a consensus for the treatment regime.

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Residual Perfluorocarbon Liquid (PFCL) in Human Eyes

Dear Editor,

The use of perfluorocarbon liquid (PFCL) has changed the surgical approach to retinal detachment, as its high density allows unfolding and stabilisation of the retina while displacing the subretinal fluid anteriorly.¹ However, this same high density, together with the low viscosity, are causes of retinal toxicity and emulsion if PFCL is left into the vitreous cavity.² PFCL removal is commonly obtained by air-fluid exchange. We noticed that, after an appropriate interval of 10 minutes, small epiretinal droplets could be detected at the posterior pole. The purpose of this study was to investigate the nature of this fluid.

Materials and Methods

Study Subjects

We conducted a prospective, non-comparative, case series involving 8 eyes affected by rhegmatogenous retinal detachment of 8 consecutive patients treated with pars plana vitrectomy with intra-operative use of PFCL.

Surgical Techniques

Perfluorodecalin (F-Decalin, Fluoron GmbH, Ulm, Germany) was used to assist surgical vitrectomy procedures and stabilise the retina. During vitrectomy, the vitreous base was thoroughly trimmed. Air-fluid exchange was then performed with humidified air. The PFCL was completely removed with active 25 gauge flute needles. The last drops of fluid were removed with passive aspiration on the optic disc, waiting until the retinal surface appeared dry. Ten minutes after the air-fluid exchange, a residual amount of epiretinal fluid was detected on the posterior pole, aspirated with a new flute needle and sent for analysis.

Fluid Samples

Three samples were collected for each patient: (A) a sample of pure PFCL from the original vial; (B) a sample of PFCL removed from the eye at the time of air-fluid exchange; and (C) the residual epiretinal fluid. Low viscosity silicone oil was added to each sample to avoid evaporation. The heavy micro-bubbles of fluid were taken from the bottom of the tube using 5 μ L microsyringe and were injected into gas-chromatographic system.

Results

In all 8 eyes, the data obtained from the 3 chromatograms confirm the presence of residual perfluorodecalin even after its careful removal by air-fluid exchange. In particular, we observed 2 peaks related to the 2 isomers cis- and trans- in the perfluorodecalin area ranging from 15 minutes to 18 minutes (Fig. 1). The perfect overlap of retention times of the 2 isomeric forms cis- and trans- of the samples examined confirms that the residual fluid is perfluorodecalin (Fig. 1).

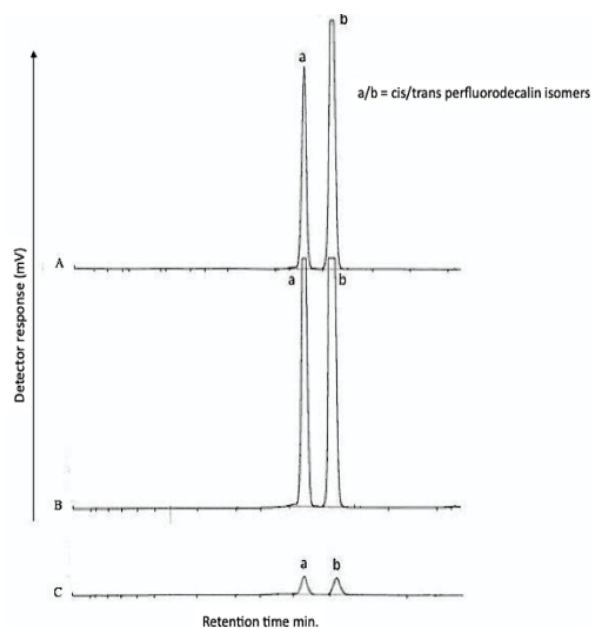


Fig. 1. The quantitative analysis with gas-chromatography confirms that the sample of residual fluid, 10 minutes after careful air-fluid exchange, is perfluorodecalin. The bottom part of the graph shows the 3 chromatograms: (A) a sample of pure PFCL from the original vial; (B) a sample of PFCL removed from the eye at the time of air-fluid exchange; and (C) the residual epiretinal fluid. The 2 peaks correspond to the 2 isomers of cis- and trans- perfluorodecalin.

Discussion

The fully fluorinated compounds with high specific gravity are associated (if left in the vitreous cavity) with damage of the photoreceptor outer segments and outer plexiform layer.³ The risk of ocular toxicity persists even if a small amount of PFCL remains in the vitreous cavity postoperatively despite intraoperative removal.⁴

Recently, we reported histological evidence of proliferative “vitreoretinopathy reaction” to the PFCL used to assist surgery and that was carefully removed afterwards. The swollen retinal pigment epithelial cells contained tamponade agent and the histological characteristics were compatible with a foreign body response to the PFCL used during the surgery.⁵

This made us willing to investigate whether the common surgical technique for removal of PFCL (air-fluid exchange) did really warrant the complete removal of PFCL from the vitreous cavity. A 10-minute long interval after the air-fluid exchange (during which careful inspection of the peripheral retina can be performed treating the retinal tears) led to the discovery of progressive accumulation of tiny droplets of unknown fluid on the vitreo-retinal interface at the posterior pole.

Chromatographic analysis of such fluid showed perfect overlap of retention times with the 2 isomeric forms of perfluorodecalin originally injected into the eye, confirming that the residual fluid is PFCL. To the best of our knowledge, this is the first report showing that the widely accepted technique of air-fluid exchange might not be sufficient to warrant a complete removal of PFCL from the vitreous cavity.

There are relevant clinical implications to this finding, both in terms of potential retinal toxicity but also in respect to intraocular emulsification of long-standing vitreal substitutes.

Friberg et al reported that PFCL and silicone oil interact physically and that PFCL can dissolve in small amounts of oil into solution over time.⁶ This interaction is particularly relevant for high-density silicone oil, as the close chemical relationship of the 2 substances makes them more prone to emulsion and inflammation.⁷ We advise to spend time at the end of the surgery, under air infusion, to clear the PFCL from the vitreous cavity. Stained PFCLs could also be helpful to facilitate appropriate visualisation and removal.

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Ganser Symptoms in a Chinese Speaking Corticobasal Syndrome (CBS) Patient

Dear Editor,

Ganser syndrome was first described by Sigbert Ganser in 1897, characterised by approximate answers to real questions, dulling of consciousness, hysterical neurological changes and hallucinations.¹⁻³ Ganser syndrome was mainly considered as a psychiatric illness, based on the theory that Ganser syndrome represents a means of coping with stress in those who are intellectually compromised through a dissociative or factitious reaction.³ However, Ganser syndrome also has been described in varieties of organic brain diseases, such as traumatic brain injury, alcoholism with Korsakoff's psychosis, neurosyphilis,³ and most recently, frontotemporal dementia.⁴ Neuropsychological characteristics of Ganser symptoms in organic brain syndromes have been described as inconsistent performance plus multiple verbal and visuospatial approximate answers, and suggested that the seemingly deliberate selection of incorrect responses may occur in the early stages of an organic dementia.⁴ It has been hypothesised that frontal-temporal lobe dysfunction may contribute to the picture of Ganser syndrome by leading to the malingering impulse.⁴ However, a precise or clear brain behaviour correlation of Ganser syndrome is still yet to be defined.

In this case, we describe a case of young onset parkinsonism that is suggestive of corticobasal syndrome (CBS), who developed gradual cognitive symptoms and neuropsychological assessment that are consistent with a Ganser episode. This case illustrates again the neuropsychological characteristic in Ganser symptoms in organic brain disease, which is still rare in literature, and reemphasises the potential association with a wide range of neurodegenerative diseases. It also poses a new question in the role of basal ganglia in producing Ganser episode due to its significant contribution to frontal-subcortical network connection.

Case Report

A Chinese Singaporean lady presented with gradual onset of gait instability and difficulty using her right hand since the age of 52. There were no visual hallucinations or fluctuation of consciousness. She was assessed by a neurologist at age of 53 and diagnosed as parkinsonism. She failed to respond to trial of levodopa. Other treatments such

as sulpiride were not given to the patient. A follow-up of 3 years showed gradual worsening of right hemiparkinsonism. She was referred to neurobehavioural clinic at the age of 56 due to developing neuropsychiatric symptoms over 1-year period. She became forgetful, easily distractible during conversation, was unable to handle finances, showed a change in personality, was easily agitated and irritable. She also reported depressive symptoms. She had no past psychiatric history or any significant family history suggestive of neurodegenerative conditions.

Physical examination showed significant right sided rigidity and bradykinesia. No gaze palsy was noted. Her gait was unsteady, shuffling with poor postural balance. There was also astereognosis of right upper extremity. Magnetic resonance imaging (MRI) of the brain at age of 54 showed no space occupying lesion, infarcts or focal brain atrophy. Fluorodeoxyglucose-positron emission tomography (FDG-PET) of the brain showed no metabolism abnormality.

Neuropsychological examination showed mini-mental state examination (MMSE) of 12/30, she reported date and year missed by 1, recalled 2 items of the same semantic category ('red' instead of 'blue', 'teacher' instead of 'cook'), took paper in her left hand instead of right, read '升起右手' (raise up right hand) instead of '举起双手' (raise up both hand); she wrote a sentence with reverse Chinese words sequence (Fig. 1). She also drew 2 non-intersecting triangles rather than pentagons and a square when asked to draw a circle. But when asked to recall the drawing at a later stage, she was able to redraw it as a circle rather than a square.

On mental calculation task, she answered '11' for $5 + 8$, '10' for $17 - 5$, '32' for 7×4 , and '5' for $18 \div 3$. She generated 7 animals for animal verbal fluency test. During 15-items modified Boston naming test, she only named correctly 8 items, by calling 'big flower' for the tree, 'horse' for camel, and 'single bed' for bench. She scored 11 out of 18 for frontal assessment battery (FAB) test. On clock drawing test, she filled in the numbers with repeatedly wrong sequence and drew the pointer at location suggestive of '55 after 10' (Fig. 2). She was also perseverative on both multiple loop and m's and n's alternating programmes drawing tests (Fig. 3).

She was diagnosed as Corticobasal Syndrome according to Mayo criteria (insidious onset and progressive course,

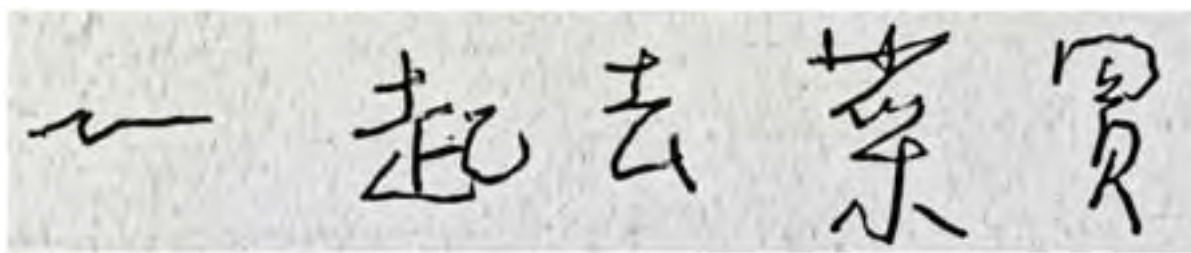


Fig. 1. Patient responded as “一起去菜買” instead of “一起去買菜” (translated as: let’s go to buy vegetables together) in sentence writing.

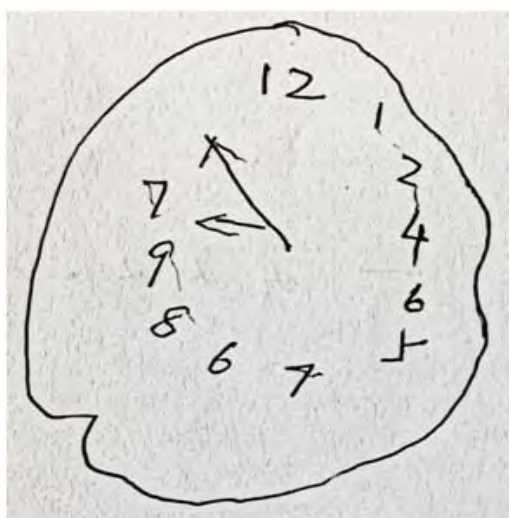


Fig. 2. Numbers were filled repeatedly in wrong sequence and needle pointer was drawn at location suggestive of “55 after 10”.

Discussion

This patient showed neuropsychological profile that is characteristic of Ganser symptoms. The “approximate” or “near miss” answers encompass verbal, arithmetic, as well as visuospatial domains.

Her pattern of language response was distinct to previous case report in alphabetic language.⁶ Her alexia was characterised by ‘lexical’ paraphasia in Chinese language. Chinese language is an ideographical language, with significant amount of words is formed by a monosyllabic morpheme, which carries its own semantic. Our patient has a tendency of using a different Chinese word with same semantic category during her reading task. For example, she used ‘升’ (read as ‘sheng’), rather than ‘舉’ (read as ‘ju’), 2 phonological and morphemically distinct words that share the same meaning, and ‘右’ (right), rather than ‘雙’ (both), which both signify quantity. As for agraphia, distinct from previous case report in alphabetic language in which the patient responded by using grapheme-phoneme conversion (GPC) route as the patient never learned the irregular words before,⁶ our patient responded by reversing the sequence of the words. This further supports the notion that Chinese language is a language that doesn’t support GPC route.

Despite significant responses during her neuropsychological test that were “approximate” thus making it difficult to interpret its significance, some evidence does suggest the element of dysexecutive syndrome in her response,

no identifiable cause, cortical dysfunction, extrapyramidal dysfunction and variable degrees of cognitive dysfunction).⁵ Other differential diagnosis such as parkinsonian dementia, reactional psychiatric disease due to parkinson’s disease, dementia of Lewy body and progressive supranuclear palsy were considered but excluded in view of intact gaze, failure to respond to levodopa, no visual hallucination and no consciousness fluctuation.

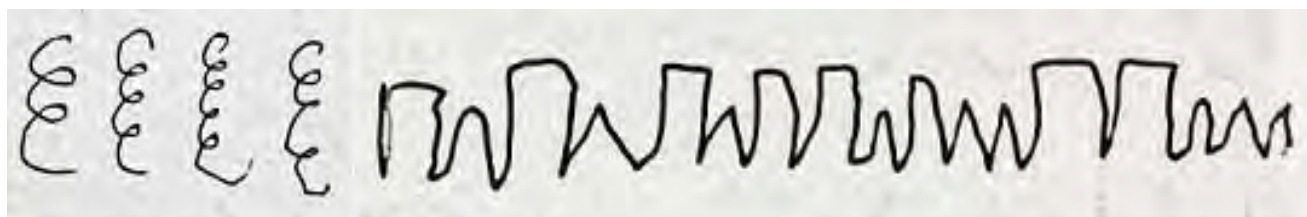


Fig. 3. Patient was perseverative on both multiple loop and m’s and n’s alternating programme drawing tests.

which is consistent with neuropsychological profile seen in parkinsonism diseases.⁷ The above findings suggest a potential link between frontal executive function and Ganser episode in an organic brain condition. Basal ganglia, an important neuroanatomical structure that participates in the frontal-subcortical network pathway, was shown to produce wide range of neuropsychiatric presentations when lesioned.⁸ From our knowledge, this is the first case to describe Ganser symptoms in parkinsonian disorder. This case raises an important question with regards to the role of basal ganglia in producing Ganser episode and provides an important insight of frontal-subcortical executive dysfunction in terms of brain behaviour correlation in Ganser, echoing previous reports of functional abnormality seen in FDG-PET scan in Ganser symptoms involving frontal, temporal lobe and caudate nucleus.^{4,6} Apart from frontal and temporal lobe, previous lesioned brain case reports also suggested involvement of parietal lobe and bipallidal structures in producing Ganser syndrome.⁹⁻¹² The exact mechanisms of cortical involvement in Ganser syndrome are still unknown, cerebral repression in a large cerebral network inducing functional hypoactivation was postulated in the previous study.⁶

Conclusion

In summary, this case illustrates neuropsychological characteristic seen in a corticobasal syndrome and highlights the pattern of Chinese verbal response encountered. Future study should look further into the role of basal ganglia and frontal executive function to better define brain behaviour correlation of Ganser symptoms.

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