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"All civilization has from time to time become a thin crust over a volcano of revolution."

Havelock Ellis (1859 – 1939)
British psychologist

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Editorial

Psychiatric Neurostimulation in Singapore

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Psychiatric conditions are estimated to account globally for 21.2% of years lived with disability (YLD) and 7.1% of disability-adjusted-life-years (DALYs),[1] although the actual figure may be even higher.[2] In Singapore, 12% of the population will have at least one lifetime affective, anxiety or alcohol use disorder.[3] Treatment for psychiatric conditions is broadly divided into talking therapies, pharmacotherapies and neurostimulation. For more severe psychiatric conditions, the latter two therapies are often required. However, investment in psychiatric pharmacotherapies has diminished in recent years with most major pharmaceutical companies pulling out of or scaling back investment into psychiatric drug development.[4] Psychoactive drug development is now the preserve of small- and medium-sized companies.

The implication is that future advances in psychiatric treatment will depend increasingly on the development of neurostimulatory techniques. Neurostimulation is defined as modulation of the central or peripheral nervous system by electrical or magnetic impulses and has novel mechanisms distinct from the typical monoamine or dopamine pathways that the majority of psychiatric drugs are thought to function. The good news is that there have been rapid advances in the field of neurostimulation over the past 20 years that portends hope for psychiatric treatment advances. We will describe briefly the major psychiatric neurostimulation modalities currently available and on the horizon for Singapore.

Current Psychiatric Neurostimulation in Singapore

The oldest psychiatric treatment still in active use is electroconvulsive therapy (ECT).[5] ECT is essentially the induction of a brief medically controlled seizure by passing an electrical current through the brain. ECT is one of the most effective acute treatments for depression,[6] bipolar disorder,[7] treatment resistant schizophrenia,[8] catatonia and affective disorders with high suicidal risk.[9] This effectiveness is also evident in the child and adolescent population.[10] It is also effective in the treatment of neuroleptic malignant syndrome, Parkinson's disease, self-injurious behaviour in intellectual disability and catatonia in autism. It is a highly safe treatment with a mortality rate of less than 2 per 100,000 treatments[11] with the most common side effects being mild headache and muscle ache. The most worrying side effects of ECT are possible cognitive side effects like delirium, anterograde and retrograde amnesia which are more common with the older forms of ECT, like sine wave and high fixed dose bitemporal ECT.[12] Over the past 25 years, ECT techniques have moved from a "one-size-fits-all" approach to an individualised seizure titration method with different electrode placements (bitemporal, bifrontal, right unilateral),[13] dosages relative to individual seizure threshold and different electrical current parameters[14] to customise the efficacy versus side effect profile of various types of ECT to the individual patient's needs.

Our institution runs a large ECT service and we conduct more than 2000 ECT treatments a year for about 400 patients. We have recently revamped our ECT services to provide modern ECT with an 83% remission rate for patients with depression, an improvement on clinical global improvement (CGI) score from "severely ill" to "mildly ill" for patients with schizophrenia and most significantly of all, a 76% rate of cognitive improvement on the Brief ECT Cognitive Scale (BECS)[15] for our patients after just 3 sessions of ECT. The observed cognitive improvement after ECT underscores the pernicious effects of severe mental illness on our patient's cognition and the effectiveness of ECT in treating these psychiatric conditions.

Despite the strong evidence base for the efficacy of ECT, it remains an underused and highly stigmatised treatment due to the misconceptions of ECT from the media and the possible cognitive side effects of ECT. Partly in response to the difficulty of prescribing ECT, new neurostimulation techniques like repetitive transcranial magnetic stimulation (rTMS) have been developed in the past 2 decades and is

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now part of standard treatment for depression in many developed countries, including Singapore where the College of Psychiatrists endorses the use of rTMS in treatment-resistant depression.[16] Modern rTMS started when Anthony Barker and his colleagues in Sheffield developed a practical high performance rTMS machine that could deliver powerful and focal magnetic pulses to stimulate the brain. Since that seminal work, extensive research has demonstrated the efficacy of rTMS in the treatment of depression[17] and it has been United States FDA approved for use in treatment-resistant depression since 2008. There is also increasingly convincing data of its efficacy in treating auditory hallucinations in schizophrenia, anxiety and possibly addictive disorders. While rTMS is not as efficacious as ECT, it has much higher patient acceptability due to the lack of anaesthesia, benign side effect profile (typically a mild and transient headache) and high safety profile. There are also less exclusions to treatment compared to ECT, with the main two being a history of seizures or ferromagnetic material in the brain. At this time, rTMS therapy is available in the private sector and in our institution. Other public healthcare institutions are also in the process of setting up rTMS programmes.

The Future of Psychiatric Neurostimulation in Singapore

An exciting new neurostimulatory technique called transcranial direct current stimulation (tDCS) is also rapidly gathering evidence as a unique neurostimulatory modality for depression,[18] auditory hallucinations in schizophrenia and possibly cognitive disorders. As compared to ECT or rTMS, tDCS does not cause neuronal depolarisation and instead seems to cause a sustained change in resting neuronal stimulatory threshold and may have a pro-cognitive effect independent of its antidepressant effects. The side effect and safety profile is even more favourable than rTMS and it carries the promise of possible self-administration of treatment which would be a significant advantage over ECT and rTMS, both of which require the patient to travel to a treatment site. Researchers in Singapore General Hospital and National University Hospital are currently conducting trials in our local population and the results are highly anticipated by the local psychiatric community.

Non-ablative (e.g. deep brain stimulation, DBS) neurosurgeries for psychiatric conditions like obsessive compulsive disorders (OCD)[19] and depression[20] are tantalising future treatment options. Local neurosurgeons have been trained and conversant in using DBS in the treatment of OCD and depression and active discussions about offering this treatment modality are in progress to offer the most treatment-resistant patients a chance of improvement.

Techniques aside, a key future development will be the heartware (i.e. training future doctors and psychiatrists about current and future neurostimulation modalities), local research, development and implementation of neurostimulation programmes to give our patients access to the full menu of treatment options for psychiatric conditions. One key step will be the establishment of a Section for Neurostimulation under the College of Psychiatrists to establish local treatment standards, drive education and research as well as serve as an expert body for local psychiatric neurostimulation. The future will indeed be stimulating for neurostimulation in psychiatry.

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Original Article

Psychometric Properties of Alzheimer's Disease Assessment Scale-Cognitive Subscale for Mild Cognitive Impairment and Mild Alzheimer's Disease Patients in an Asian Context

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Abstract

Introduction: The purpose of the current study is to assess the psychometric properties of Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) on patients with mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) in a multicultural Asian context. Materials and Methods: Sixty-four mild AD patients (mean age ± SD; 72.24 ± 7.88 years), 80 MCI patients (66.44 ± 7.45 years) and 125 healthy controls (HCs) (61.81 ± 6.96 years) participated in the study. Participants underwent a clinical interview and serial neuropsychological testing. ADAS-Cog total and subtest scores were compared across the 3 groups. Receiver operating characteristics (ROC) analysis were performed and sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were calculated. Results: Patients with MCI attained significantly worse neuropsychological test scores than healthy controls but significantly better results than patients with mild AD on ADAS-Cog total score, subtest items, and the delayed recall item (P <0.001). The best cutoff score to differentiate between MCI and HC was ≥4 (sensitivity = 0.73, specificity = 0.69, PPV = 0.90, NPV = 0.40), while the best cutoff score to distinguish between MCI and mild AD was ≥12 (sensitivity = 0.86, specificity = 0.89, PPV = 0.99, NPV = 0.32). Evidence of internal consistency of the ADAS-Cog (Cronbach α = 0.85) as well as convergent validity with the Mini-Mental State Examination (MMSE) (ρ = -0.75) and Montreal Cognitive Assessment (MoCA) (ρ = -0.81) (both P <0.001) was also found. Conclusion: The ADAS-Cog which is widely used in clinical trials is applicable to the Asian cohort. It is useful in the detection of MCI and mild AD as well as in distinguishing these 2 conditions.

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Key words: Dementia, Neuropsychology, Psychometric validation

Introduction

The Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) is widely used in research settings to detect and follow-up cognitive deficits in persons suffering from Alzheimer's disease (AD), a neurodegenerative disorder associated with progressive, gradual decline in memory and cognition.[1] The ADAS-Cog is a psychometrically reliable and valid tool[1,2] that is commonly adopted as both a process and outcome measure in multinational AD pharmacological treatment trials and used in a plethora of settings including but not limited to the assessment of day-to-day functional status,[3,4] disease staging[5] and caregiver burden.[6] Although not equivalent to a comprehensive neuropsychological test battery, it provides a more complete assessment in comparison to other cognitive screening instruments.[7]

The extensive usage of the ADAS-Cog is reflected by several psychometric validation studies in diverse cultures and languages (e.g. Turkish version,[8] Slovak version,[9] Hong Kong version,[10] Brazil version[11]). Slight modifications were made to the original English version in an attempt to make the ADAS-Cog more culturally nuanced. For instance, the word 'ocean' in the word recall task was replaced by 'sea' because the latter word reflected higher imagery to Turkish people.[12]

ADAS-Cog 11 scale (total score ranges from 0 to 70)

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comprises 11 items measuring cognition: 3 trials of an immediate recall task comprising a 10-word list (average score), comprehension of commands, constructional praxis, object and finger naming, ideational praxis, orientation, 1 trial of a 12-word recognition task, word-finding difficulty, expressive language, language comprehension and recall of instructions. The ADAS-Cog 12 scale includes an additional 10-word delayed recall list administered 5 minutes after the immediate recall task (total score ranges from 0 to 80).[12] Impairment in these functions forms the constellation of core and peripheral cognitive symptoms in AD. Higher scores denote greater impairment and errors made by either commission or omission. In recent years, however, more attention has been paid to mild cognitive impairment (MCI), generally defined as a prodromal condition for AD[13] with an annual progression rate of 10% to 15% to dementia in tertiary referral clinic settings.[14]

A few studies have examined the clinical utility of the ADAS-Cog in predicting the conversion from MCI to dementia with proposed cutoff scores.[15-17] A baseline cutoff score of 9.5 on ADAS-Cog predicted good conversion rate (area under the curve (AUC) = 0.67; sensitivity value = 0.62; specificity value = 0.73) from amnestic MCI to AD 1 year later.[15] ADAS-Cog has also been demonstrated to be a promising tool to detect patients with MCI, using a cutoff score of 6 on total ADAS-Cog (sensitivity value = 0.73 and specificity value = 0.89).[16] The normative cutoff score on ADAS-Cog has also been determined to be ≥5 and the best ADAS-Cog cutoff score for dementia is ≥12 (AUC = 0.94; sensitivity value = 0.89; specificity value = 0.89).[18]

The normative data and cutoff scores of the ADAS-Cog derived from the sample characteristics of the above-mentioned studies, however, may not be representative of and generalisable to the sociodemographic realities in the Asian context.[19-21] In particular, there remains a knowledge gap with regards to the ADAS-Cog as a culturally appropriate and psychometrically valid tool in multicultural societies such as Singapore. For example, Monllau and colleagues (2007) determined the cutoff score for MCI based on a patient group with an average formal education of 13 years to be 5 based on normal subjects who had 10 to 21 years of education. These highly educated groups may not be reflective of the lower education level attained by the normal elderly in Singapore. Based on the Census of Population report in 2010, 65.6% of the elderly aged 55 years and above obtained less than 10 years of formal education.[19] A recent publication from the Singapore Longitudinal Ageing Study (SLAS) which enrolled healthy elderly Chinese from the local community highlighted the need for neuropsychological batteries to be tailored to less well-educated Asian elderly.[21,22]

The purpose of the current study is to therefore extend our understanding of the psychometric properties of the ADAS-Cog in the Asian context. We assessed the clinical utility of the ADAS-Cog to detect patients with MCI and mild AD in Singapore. We determined the optimal cutoff scores (including AUC, sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]), internal consistency, and convergent validity of the ADAS-Cog with other global cognition measures.

Materials and Methods

Power Analysis

Based on an a priori power analysis, it was determined that a sample size of at least 72 participants was required to observe a medium between-groups effect size (Cohen's f = 0.30) with a level of 0.05 and power of 0.80.[23]

Procedures

A total of 269 subjects, aged 50 years and above, were enrolled between 2010 and 2014 in this cross-sectional study. Patients attending a tertiary neurology institute based in Singapore who either fulfilled Petersen's criteria for MCI[24] or the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD[25] were invited for the study. Patients who fulfilled Petersen's criteria of MCI were also required to have a Clinical Dementia Rating (CDR) sum of boxes (SOB) score of 0.5 and patients meeting NINCDS-ADRDA criteria for AD were required to have CDR of 0.5 to 1 to ensure that only patients with mild AD were recruited.[26,27] Healthy controls were recruited from the community and were required to have a CDR of 0. Participants were excluded if they had major depression and serious systemic or metabolic abnormalities that could contribute to the cognitive deficits. The eligible participants underwent a battery of neuropsychological tests that included the ADAS-Cog. Locally-validated versions of the Mini-Mental State Examination (MMSE)[28,29] and Montreal Cognitive Assessment (MoCA)[30,31] were administered as global cognition measures and the Frontal Assessment Battery (FAB) was used to assess executive dysfunction.[32,33] All the tests were administered in either English or Mandarin by 3 experienced raters (NHZ, EE, and LL). The raters were experienced psychologists who have and were blinded to the clinical information. The Mandarin version of the tests was forward and backward translated by native bilinguals proficient in both languages and was locally validated by prior studies.[29,31,33] All raters assessed the MMSE, MOCA, ADAS-Cog, and FAB independently and were blinded to the clinical data. Inter-rater agreement for the ADAS-Cog among the 3 raters was excellent (κ = 0.86 – 1; mean = 0.99;

median = 1.00). Ethics approval was obtained from the SingHealth Centralised Institutional Review Board (CIRB). All participants provided voluntary informed consent.

ADAS-Cog Measures

The total and subtest scores on the ADAS-Cog were compared across the 3 diagnostic groups. Higher total score in ADAS-Cog reflects greater degree of cognitive deficit (scale range 0-70). The ADAS-Cog comprises 11 items and was administered according to the methodology described by Rosen and colleagues:

1. Word recall task (3 trials of immediate recall task of 10 high imagery words) (scale range = 0-10)
2. Commands (understand and carry out 1 to 5 steps commands) (scale range = 0-5)
3. Constructional praxis (duplication of 4 different geometric shapes) (scale range = 0-5)
4. Naming (naming of fingers and 4 low frequency, 4 medium frequency and 4 high frequency objects) (scale range = 0-5)
5. Ideational praxis (performing a familiar yet complex sequenced task) (scale range = 0-5)

Table 1. Mean, Standard Deviations and Median Scores across the 3 Diagnostic Groups on Key Sociodemographic, Clinical, and Cognitive Variables

	HCs (n = 125) M ± SD (Median)	**MCI (n = 80) M ± SD (Median)**	**Mild AD (n = 64) M ± SD (Median)**	**Overall *P* Value**
Age (years)	61.81 ± 6.96 (61)	66.44 ± 7.45 (67.01)	72.24 ± 7.88 (73.42)	<0.001
Education (years)	11.70 ± 3.13 (10)	10.88 ± 3.89 (10)	6.02 ± 5.21 (4)	<0.001
Gender, n (%)				
Males	39 (31.2%)	40 (50%)	40 (62.5%)	<0.001
Females	86 (68.8%)	40 (50%)	24 (37.5%)	
Race, n (%)				
Chinese	113 (90.4%)	71 (88.75%)	49 (76.56%)	0.024
Malay, Indian, Eurasian and Others	12 (9.6%)	9 (11.25%)	15 (23.44%)	
CDR-SOB (scale range 0 – 2)	0.08 ± 0.18 (0)	0.45 ± 0.20 (0.5)	1.00 ± 0.42 (1)	<0.001
GDS (scale range 0 – 15)	2.03 ± 2.58 (1)	2.12 ± 1.95 (2)	2.56 ± 2.46 (2)	0.049
MMSE (scale range 0 – 30)	29.13 ± 1.05 (29)	27.38 ± 2.11 (27)	22.32 ± 4.80 (23)	<0.001
MoCA (scale range 0 – 30)	28.41 ± 1.81 (29)	25.47 ± 3.65 (26)	19.22 ± 5.92 (20.5)	<0.001
FAB (scale range 0 – 18)	17.47 ± 0.76 (18)	15.92 ± 2.26 (17)	13.50 ± 4.13 (14.50)	<0.001
ADAS-Cog				
11-item total score	3.99 ± 2.68 (3)	8.63 ± 5.43 (7)	20.88 ± 10.07 (19)	<0.001
12-item total error	5.26 ± 3.73 (4)	11.76 ± 7.21 (10.5)	28.39 ± 11.89 (27)	<0.001
Memory				
Word recall	2.14 ± 1.19 (2)	3.28 ± 1.52 (3)	6.06 ± 2.04 (6)	<0.001
Word recognition	0.87 ± 1.30 (0)	1.66 ± 1.95 (1)	5.39 ± 3.59 (5)	<0.001
Remembering instructions	0.10 ± 0.32 (0)	0.40 ± 0.69 (0)	1.39 ± 1.47 (1)	<0.001
Orientation	0.04 ± 0.20 (0)	0.25 ± 0.46 (0)	2.16 ± 2.15 (1.5)	<0.001
Language				
Naming (fingers and objects)	0.37 ± 0.58 (0)	0.60 ± 0.74 (0)	1.08 ± 1.03 (1)	<0.001
Word-finding difficulty	0.10 ± 0.31 (0)	0.41 ± 0.72 (0)	0.84 ± 0.98 (1)	<0.001
Following oral commands	0.21 ± 0.48 (0)	0.66 ± 0.99 (0)	1.14 ± 1.13 (1)	<0.001
Expressive language	0.02 ± 0.15 (0)	0.23 ± 0.55 (0)	0.67 ± 0.91 (0)	<0.001
Comprehension	0.05 ± 0.22 (0)	0.51 ± 0.68 (0)	1.05 ± 0.99 (1)	<0.001
Praxis				
Constructional praxis	0.09 ± 0.28 (0)	0.56 ± 1.04 (0)	0.66 ± 0.70 (1)	<0.001
Ideational praxis	0.02 ± 0.13 (0)	0.06 ± 0.24 (0)	0.42 ± 0.75 (0)	<0.001
Delayed recall	1.26 ± 1.53 (1)	3.14 ± 2.42 (3)	7.52 ± 2.93 (9)	<0.001

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SOB: Clinical Dementia Rating-Sum of Boxes score; GDS: Geriatric Depression Scale; HC: Healthy control; MCI: Mild cognitive impairment, SD: Standard deviation

6. Orientation (assessment of temporal and geographic orientation) (scale range = 0-8)
7. Word recognition (discriminating words that had been presented from distractors) (scale range = 0-12)
8. Remembering instructions (of preceding recognition task) (scale range = 0-5)
9. Spoken language ability (assessment of patient's ability to communicate) (scale range = 0-5)
10. Word-finding difficulty (assessment of patient's ability to express himself with precise words) (scale range = 0-5)
11. Language comprehension (assessment of patient's ability to understand speech) (scale range = 0-5)

Items 1 to 7 were performance-based while items 8 to 11 were rater-based. The ADAS-Cog delayed recall item was administered in between Constructional Praxis and Naming subtest to prevent interference from the naming list. A 90-second time limit was given for the 10-word immediate and delayed recall (scale range = 0-10).

Data Analysis

The statistical analyses were conducted using SPSS (Statistical Package for Social Sciences, Version 20.0). Continuous scores which were not normally distributed as reflected by the Shapiro-Wilk tests ($P<0.05$) were analysed using non-parametric methods: the omnibus Kruskall-Wallis H test, a non-parametric equivalent of the one-way ANOVA test,[34] was used to compare statistical differences among the 3 groups, and non-parametric Mann-Whitney U test for between-groups comparisons. Age which was normally distributed was analysed using parametric methods: one-way analysis of variance (ANOVA) across groups and independent sample t-test was used for between-groups comparisons. Dichotomous variables such as gender (0 = male; 1 = female) were analysed using the χ^2 test. All statistical tests for significances were two-tailed at a probability level of 0.05. The best ADAS-Cog cutoff scores, defined as maximal sensitivity and specificity[35] to differentiate between MCI and HC as well as MCI and mild AD were determined using receiver operating characteristic (ROC) analysis.[36] Cohen's kappa was calculated to examine inter-rater agreement among the 3 trained raters (NHZ, EE, and LL) for a random sample of 30% of the tests.[37] The AUC, sensitivity, specificity, PPV, and NPV were also calculated for ADAS-Cog 11-item and 12-item scales, as well as a composite ADAS-Cog Episodic Memory subscale. Spearman's rank correlation coefficient was used to examine the convergent validity of ADAS-Cog with MMSE and MoCA.

Results

Participants

We compared 64 mild AD patients, 80 MCI patients and 125 HCs in terms of key sociodemographic, clinical, and cognitive variables (Tables 1 and 2). Age showed significant correlations with ADAS-Cog total score for both the 11-item (Pearson's r = 0.42, $P<0.001$) and 12-item (r = 0.45, $P<0.001$) scales. The effect remained when divided into age strata ($F(2, 148) = 36.44$, $P<0.001$). The mean age in years (± SD) for the HCs, MCIs and mild ADs were 61.81 ± 6.96, 66.44 ± 7.45 and 72.24 ± 7.88, respectively.

Table 2. *P* Values of Demographics and Cognitive Scores in Between-Groups Comparisons

	HC vs MCI	MCI vs Mild AD	HC vs Mild AD
Age (years)	0.00002	0.00006	0.00001
Education (years)	0.20162	0.00001	0.00001
Gender	0.00698	0.13361	0.00004
Race	0.70391	0.05118	0.01009
CDR-SOB	0.00001	0.00001	0.00001
GDS	0.15604	0.28654	0.01714
MMSE	0.00001	0.00001	0.00001
MoCA	0.00001	0.00001	0.00001
FAB	0.00001	0.00002	0.00001
ADAS-Cog			
11-item total error score	0.00001	0.00001	0.00001
12-item total error score	0.00001	0.00001	0.00001
Memory			
Word recall	0.00001	0.00001	0.00001
Word recognition	0.00178	0.00001	0.00001
Remembering instructions	0.00006	0.00001	0.00001
Orientation	0.00002	0.00001	0.00001
Language			
Naming objects/figures	0.02155	0.00434	0.00001
Word-finding difficulty	0.00037	0.00199	0.00001
Commands	0.00011	0.00354	0.00001
Language	0.00028	0.00018	0.00001
Comprehension	0.00001	0.00073	0.00001
Praxis			
Constructional praxis	0.00001	0.04625	0.00001
Ideational praxis	0.07443	0.00025	0.00001
Delayed recall	0.00001	0.00001	0.00001

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR-SOB: Clinical Dementia Rating Sum of Boxes score; FAB: Frontal Assessment Battery; MCI: Mild cognitive impairment; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination; GDS: Geriatric Depression Scale

There were also overall significant differences in education (H(2) = 46.76, P <0.00001), gender ($\chi^2(2) = 18.34$, P = 0.001) and race ($\chi^2(2) = 7.74$, P = 0.024). The healthy controls were similar in education level to the MCI patients (11.70 ± 3.13 vs 10.88 ± 3.89; U = 4377.00, P = 0.20162), but had significantly higher education compared to mild AD patients (11.70 ± 3.13 vs 6.02 ± 5.21; U = 1236.50, P = 0.00001). MCI patients in turn received longer years of formal education than mild AD patients (10.88 ± 3.89 vs 6.02 ± 5.21; U = 1236.00, P = 0.00001). The gender distribution was relatively similar between the MCI and mild AD group (percentage of males: 50.00 vs 62.50; $\chi^2(1) = 2.25$, P = 0.13361), but the ratio of males to females were lower when comparing HCs versus MCI (31.20 vs 50.00; $\chi^2(1) = 7.28$, P = 0.00698) and HC versus mild AD ($\chi^2(1) = 17.05$, P = 0.00004) patients. The race distribution was different between the mild AD and HCs wherein a higher proportion of non-Chinese were present in the former group ($\chi^2(1) = 6.62$, P = 0.01).

Functional status as measured by the CDR was also associated with ADAS-Cog 11-item (r = 0.67, P <0.001) and 12-item (r = 0.68, P <0.001) scales. The positive associations are illustrated by the boxplots in Figures 1a and 1b. On the other hand, depression as reflected by the Geriatric Depression Scale (GDS) correlated neither with the ADAS-Cog 11-item (r = 0.09, P = 0.152) nor the 12-item (r = 0.10, P = 0.113) total error scales.

Cognitive Scores

The total scores and individual subtest scores of ADAS-Cog were significantly different among the 3 diagnostic groups ($H(2) = 143.21$, P <0.001). The ADAS-Cog subtest scores of healthy controls were significantly different from MCI patients except on the ideational praxis subtest (0.02 ± 0.13 vs 0.23 ± 0.55; U = 4767.50, P = 0.07443). The ADAS-Cog scores of MCI patients were significantly different from mild AD patients on all subtests (all P <0.05).

ADAS-Cog 11-item and 12-item Cutoff Scores

The best cutoff score to differentiate MCI and HC was ≥4 (AUC = 0.78 [95% confidence interval (CI), 0.71 to 0.84]; sensitivity = 0.73, specificity = 0.69, PPV = 0.90, NPV = 0.40), while the best cutoff score to distinguish between MCI and mild AD was ≥12 (AUC = 0.93 [95% CI, 0.80 to 0.95]; sensitivity = 0.86, specificity = 0.89, PPV = 0.99, NPV = 0.32). When the ADAS-Cog delayed recall subtest was added, the optimal cutoff score for ADAS-Cog 12-item scale to differentiate between MCI and HCs was ≥5 (AUC = 0.79 [95% CI, 0.72 to 0.85]; sensitivity = 0.90, specificity = 0.53, PPV = 0.88, NPV = 0.58), ≥21 to discriminate between MCI and mild AD (AUC = 0.88 [95% CI, 0.82 to 0.94]; sensitivity = 0.79, specificity = 0.89, PPV = 0.98, NPV = 0.37) and ≥21 to differentiate between HC and mild AD (AUC = 0.98 [95% CI, 0.96 to 0.99]; sensitivity = 0.73, specificity = 1.00, PPV = 0.88, NPV = 1.00). Adjusting for age and education did not improve AUC, sensitivity and specificity values for both ADAS-Cog 11-item and 12-item scales (see Table 3 for a summary as well as Figures 2 and 3 for ROC curves).

Table 3. Cutoff Scores of ADAS-Cog Measures and Associated Sensitivity, Specificity, PPV and NPV

	Cutoff	AUC	95% CI	Sensitivity	Specificity	PPV	NPV
ADAS-Cog 11 (scale range = 0 – 70)							
MCI vs HC (n = 205)	≥4	0.78	0.71 – 0.84	0.73	0.69	0.81	0.61
MCI vs mild AD (n = 145)	≥12	0.93	0.80 – 0.95	0.86	0.89	0.87	0.74
HC vs mild AD (n = 189)	≥14	0.97	0.94 – 0.99	0.81	1.00	0.91	1.00
ADAS-Cog 12 (scale range = 0 – 80)							
MCI vs HC (n = 205)	≥5	0.79	0.72 – 0.85	0.90	0.53	0.88	0.58
MCI vs mild AD (n = 145)	≥21	0.88	0.82 – 0.94	0.79	0.89	0.98	0.37
HC vs mild AD (n = 189)	≥21	0.98	0.96 – 0.99	0.73	1.00	0.88	1.00
ADAS-Cog Episodic Memory Composite Scale* (scale range = 0 – 32)							
MCI vs HC (n = 205)	≥6	0.73	0.66 – 0.80	0.61	0.73	0.86	0.41
MCI vs mild AD (n = 145)	≥14	0.87	0.81 – 0.93	0.76	0.85	0.97	0.35
HC vs mild AD (n = 189)	≥14	0.96	0.93 – 0.99	0.77	0.98	0.89	0.96

AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; AUC: Area under the curve; HC: Health control; MCI: Mild cognitive impairment; NPV: Negative predictive value; PPV: Positive predictive value

*Comprises of the ADAS-Cog 10-word immediate recall, 10-word delayed recall and word recognition.

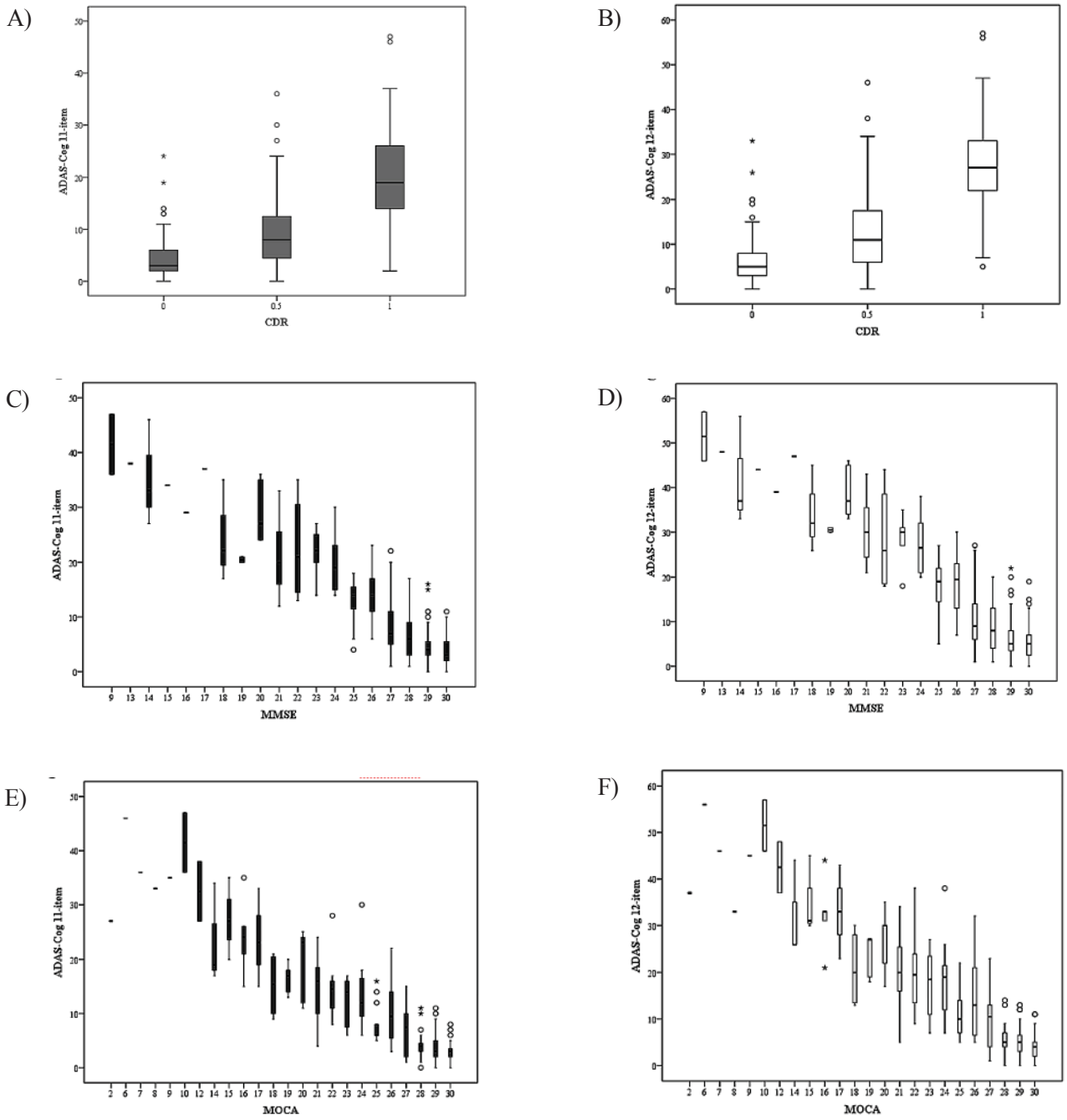

Fig. 1. Cross-sectional bloxplots. A) shows the ADAS-Cog 11-item total error score with the CDR staging; B) shows the ADAS-Cog 12-item total error score with the CDR staging; C) shows the ADAS-Cog 11-item total error score with the MMSE; D) shows the ADAS-Cog 12-item total error score with the MMSE; E) shows the ADAS-Cog 11-item total error score with the MoCA; and F) shows the ADAS-Cog 12-item total error score with the MoCA. ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment

ADAS-Cog 11-item and 12-item Convergent Validity with MMSE and MoCA

The ADAS-Cog 11-item total error score showed good convergence with global cognition measures of MMSE ($\rho(269) = -0.75$, $P < 0.001$) and MoCA ($\rho(269) = -0.81$, $P < 0.001$) with large effect sizes.[34] Relatively smaller significant and negative correlations were observed with the FAB ($\rho(269) = -0.67$, $P < 0.001$) (Table 4).

Comparatively, the ADAS-Cog 12-item error scores were inversely, and significantly related to the MMSE scores ($\rho(269) = -0.74$, $P < 0.001$) and MoCA scores ($\rho(269) = -0.81$, $P < 0.001$). Figures 1c to 1f illustrate the boxplots for the positive correlations between ADAS-Cog and the 2 global cognition measures.

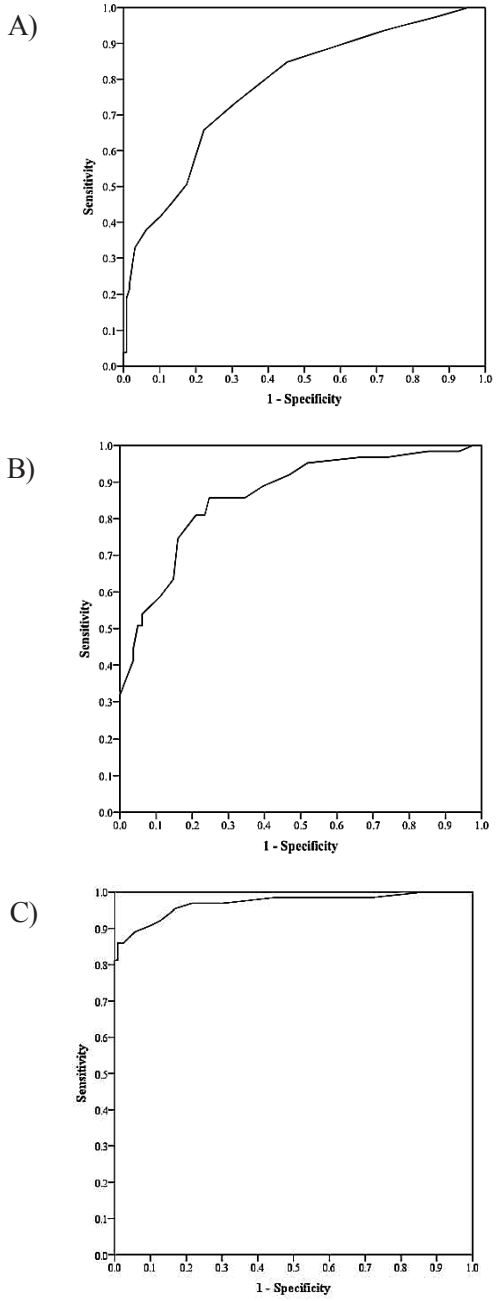

Fig. 2. ROC curves. A) shows the curve for differentiating between healthy controls and MCI patients for ADAS-Cog 11-items (n = 205); B) shows the curve for differentiating MCI from mild AD for ADAS-Cog 11-items (n = 145); and C) shows the curve for differentiating HC from mild AD for ADAS-Cog 11-items (n = 189). AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; HC: Healthy control; MCI: Mild cognitive impairment; ROC: Receiver operating characteristics

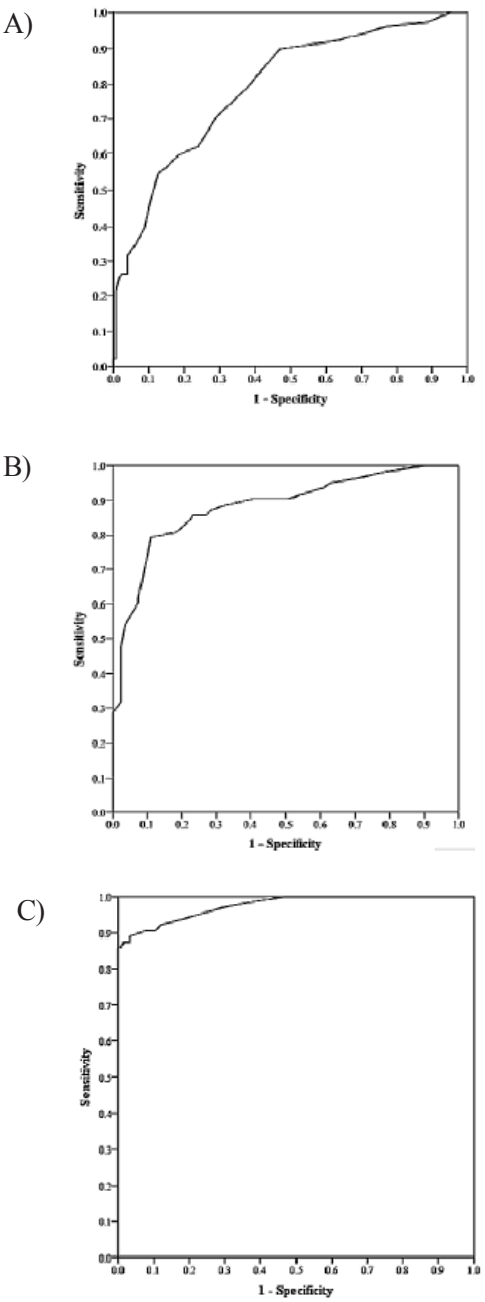

Fig. 3. ROC curves. A) shows a curve for differentiating between HCs and MCI patients for ADAS-Cog 12-items (n = 205); B) shows a curve for differentiating MCI from mild AD for ADAS-Cog 12-items (n = 145); and C) shows a curve for differentiating HCs from mild AD for ADAS-Cog 12-items (n = 189). AD: Alzheimer's disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; HC: Healthy control; MCI: Mild cognitive impairment; ROC: Receiver operating characteristics

Selective Subtest Items

Spearman's correlation was also used to analyse which subtest items are highly correlated to the total ADAS-Cog score. Most subtest items showed moderate to large correlations (ρ >0.36, all P <0.001) with total ADAS-Cog score. Items that showed modest correlation are Ideational Praxis, Naming, and Constructional Praxis (ρ = 0.36, ρ = 0.49 and ρ = 0.53 respectively). The 3 items that have the highest correlation with total ADAS-Cog score are Word Recall (ρ = 0.83), Word Recognition (ρ = 0.79) and 10-word Delayed Recall (ρ = 0.78). When these 3 subtest items were clustered as one and reanalysed, the correlation with the total ADAS-Cog score is very large (ρ = 0.91).

Table 4. Correlation between ADAS-Cog Total Error Score and Cognitive Measures

	ADAS-Cog 11 Item	
	ρ(269)	*P* Value
Overall ADAS-Cog and cognitive tests		
MMSE	-0.75	<0.001
MoCA	-0.81	<0.001
FAB	-0.67	<0.001
ADAS-Cog 11-item subtests and MMSE		
Recall	-0.69	<0.001
Commands	0.51	<0.001
Constructional praxis	-0.41	<0.001
Naming	-0.32	<0.001
Ideational praxis	-0.39	<0.001
Orientation	-0.62	<0.001
Recognition	-0.62	<0.001
Remembering instructions	-0.50	<0.001
Comprehension	-0.51	<0.001
Word-finding difficulty	-0.39	<0.001
Language	-0.42	<0.001
ADAS-Cog 11-item subtests and MoCA		
Recall	-0.74	<0.001
Commands	-0.50	<0.001
Constructional praxis	-0.50	<0.001
Naming	-0.33	<0.001
Ideational praxis	-0.35	<0.001
Orientation	-0.53	<0.001
Recognition	-0.62	<0.001
Remembering instructions	-0.53	<0.001
Comprehension	-0.60	<0.001
Word-finding difficulty	-0.46	<0.001
Language	-0.43	<0.001

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; FAB: Frontal Assessment Battery; MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Examination

ADAS-Cog Internal Consistency

The ADAS-Cog demonstrated excellent internal consistency for the total scale (11 items; Cronbach α = 0.85), total scale with delayed recall (12 items; α = 0.83), and for the 3 subtests showing the highest correlation with the ADAS-Cog total score (α = 0.78).

Given that the 3 subscales (Word Recall, Word Recognition, and 10-word Delayed Recall) demonstrated the largest correlation with the ADAS-Cog total score, we amalgamated the 3 subscale scores and labelled it to be the 'ADAS-Cog Episodic Memory' composite scale. Upon further analyses, ADAS-Cog Episodic Memory composite scale appears to differentiate between MCI and mild AD patients (cutoff score: ≥14, AUC = 0.87 (95% CI, 0.81 to 0.93); sensitivity = 0.76, specificity = 0.85, PPV = 0.97, NPV = 0.35) relatively better than between MCI and healthy controls (cutoff score: ≥6, AUC = 0.73 (95% CI, 0.66 to 0.80); sensitivity = 0.61, specificity = 0.73, PPV = 0.86, NPV = 0.41). The optimal cutoff score to distinguish between HC and mild AD was ≥14 (AUC = 0.97 (95% CI, 0.94 to 0.99); sensitivity = 0.81, specificity = 1.00, PPV = 0.91, NPV = 1.00).

Discussion

This study presents evidence that ADAS-Cog is a sensitive tool to differentiate between cognitively intact and MCI, and between MCI and mild AD in a multicultural and multilingual Asian context of Singapore. The psychometric reliability and validity of the ADAS-Cog to detect MCI and mild AD withstands despite being conceptualised, designed and validated in the west.

ADAS-Cog 11-item and 12-item normative scores and psychometric analyses (AUC, sensitivity, specificity, PPV, and NPV) for MCI and mild AD for the local population were presented. The best ADAS-Cog 11-item cutoff score to differentiate between MCI and HC was ≥4 (sensitivity = 0.73, specificity = 0.69, PPV = 0.90, NPV = 0.40), while the best cutoff score to distinguish between MCI and mild AD was ≥12 (sensitivity = 0.86, specificity = 0.89, PPV = 0.99, NPV = 0.32). The excellent sensitivity, specificity, and PPV values implies that the ADAS-Cog may be useful in cognitive research settings, clinical trials and busy clinical settings involving healthy elderly, subjects with MCI and mild AD in the Asian context.

Noteworthy is the fact that the cutoff score of ≥4 on the ADAS-Cog 11 differed from prior literature showing a cutoff score of ≥6. This may be explained by the fact that we found a mean score for ADAS-Cog 11 item of 3.99 ± 2.68 that was, on average, lower than the mean score of approximately 5.0 that was reported by Graham et al who used a purely Caucasian sample,[17] Liu et al who assessed a low-education population,[38] as well as the mean score of about 5.5 that was found by Zec et al[39] and 5.6 that was found by Graham et al[40] who both recruited North American samples. It is plausible that the large sample of 125 healthy controls may account for the lower average error score on the ADAS-Cog 11.

Additionally, our findings are consistent with previous local[19-21,27,29] and international validation studies[15-18] that have reported associations between key sociodemographic variables and ADAS-Cog total error score. Lower levels of education affected ADAS-Cog performance (r = -0.50, *P* <0.001).[38-40] Younger elderly participants generally

performed relatively better on the ADAS-Cog (r = 0.42, P <0.001)[6,38-42] and males demonstrated modestly superior performance (ρ = -0.33, P<0.001).[38] Self-reported depressive symptoms was higher in mild AD as compared to healthy controls but not MCI, suggesting that the neurodegenerative disease may exert a toll on the emotional well-being and quality of life of the patients albeit at the mild stage. In addition, the high proportion of non-Chinese in the mild AD patient group (23.44%) may imply that ethnic minorities are generally at-risk of cognitive impairment.

The ADAS-Cog items that presented with the lowest correlation with the ADAS-Cog total score include Ideational Praxis (ρ = 0.36) and Constructional Praxis (ρ = 0.53). These items measure apraxia; a person's impaired ability to conceptualise and carry out a familiar or learned complex task in a proper sequence despite neurologically intact motor function. According to DSM-V criteria, unusual non-amnestic presentations in major neurocognitive disorder (MCD) due to AD, such as apraxia, also exists but do not reflect the core symptom of MCD due to AD.[43] Languages disturbances, such as Aphasia, are also cognitive symptoms peripheral to the diagnosis of AD and are reflected by the modest correlation between subtest items that measure language and total ADAS-Cog 11-item scores (Naming: ρ = 0.49; Word Finding Difficulty: ρ = 0.57; Comprehension: ρ = 0.65; Spoken Language Ability: ρ = 0.54; Commands: ρ = 0.57).

This study also highlights that some subtest items in ADAS-Cog are highly correlated to its total score. A briefer version comprising of an amalgamation of subtests measuring episodic memory, specifically 10-word Immediate Recall, Word Recognition, and 10-word Delayed Recall therefore demonstrates usefulness in attending to patients with short attention span and difficulty focusing throughout the entire ADAS-Cog assessment. These 3 items evaluate the episodic memory and learning aspect of cognition, the key cognitive DSM-V criteria for MCD due to AD. As such, tests sensitive in detecting episodic memory impairment show good promise and should be recommended to facilitate the diagnosis of mild AD. Since ADAS-Cog assessment takes approximately 30-45 minutes to administer, a brief test with these 3 subtest items would be a preferred choice to be used in busy and time-constraint clinic settings and to avoid mental fatigue of the elderly patients.

While the literature generally showed an ADAS-Cog 11-item cutoff score of ≥6[18-21] our study revealed a recommended cutoff score of ≥4. This difference is likely a result of the mild nature of the dementia group in our study. The mean MMSE score in our patient group was 25.12 ± 4.36 which is reflective of the mild severity of dementia. The ADAS-Cog as a screening test will be more useful for the detection of mild dementia due to a lack of ceiling effect. Hence, we believe that the ADAS-Cog will be most useful for the detection of mild dementia wherein the traditional screening tests such as MMSE will suffer from a ceiling effect.

Given that the results showed that the 3 subtests of the ADAS-Cog Episodic Memory scale were better at differentiating between persons with mild AD as compared to persons with MCI, it is thus recommended that the composite scale be used to screen for mild AD instead of MCI, though larger studies with participants with MCI and mild AD are required to shed further light on this. Several strengths and limitations of the study deserve mention. One of the strengths of the study was the recruitment of patients attending a tertiary neurology clinic who met the diagnosis of mild AD or MCI based on published criteria, therefore enabling the ADAS-Cog instrument to be used as a screening tool in clinical practice. Validation studies of screening tools that are helpful for screening for cognitive impairment and dementia in the Asian context are scarce, and this study attempted to fill this knowledge gap. Limitations include the cross-sectional design of the data that precludes the examination of the predictive validity of the tool to prognosticate disease progress. In addition, given that the ADAS-Cog scale was administered in either English or Mandarin, it may not be applicable to elderly persons who do not converse in either of the 2 languages. The number of tests administered in English were 202 (75%) and in Mandarin 67 (25%). The mean (± SD) years of education for patients who took the test in English were 10.15 ± 3.94 and in Mandarin were 9.33 ± 6.40. As such, we do not think language proficiency resulted in score differences. In addition, given that the 3 diagnostic groups comprised of mainly elderly persons of Chinese ethnicity, ethnic minorities are under-represented in the study. Future studies will need to recruit more ethnic minorities to ensure a representative sample that is more reflective of a diverse multicultural population. Future prospective validation studies may also explicate the optimal cutoff scores at baseline for predicting conversion from the prodromal MCI stage to AD pathology in the multicultural and multilingual Asian context.

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Original Article

Disability in Singapore's Elderly Population

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Abstract

Introduction: Disability increases an individual's dependence and negatively impacts their physical, mental, and social functioning. The current study aims to establish the prevalence and risk factors of disability in Singapore's population. Materials and Methods: Data was extracted from the Well-being of the Singapore Elderly (WiSE) study. This cross-sectional study recruited participants aged 60 years and above (n = 2421) who were representative of Singapore's multiethnic population. We used the World Health Organization Disability Assessment Schedule (WHODAS) 2.0 to assess the severity of disability in our sample while establishing its associations and correlations with cognitive levels, sociodemographic variables, and chronic illness. Results: Cognitive deficits, old age, female gender, Malay and Indian ethnicity, lack of education, retired or homemaker status, presence of chronic illness (specifically stroke, heart problems, depression, and dementia) were found to be significantly associated with disability in Singapore's elderly population. As hypothesised, participants with deficits in cognition were more likely to indicate higher WHODAS scores. Conclusion: The findings highlighted specific factors associated with disability in this multiethnic population. The identification of these factors would lead the way to the development of appropriate interventions.

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Introduction

The World Health Organization (WHO) endorses a balanced approach to defining disability which incorporates equal weight to the medical and the social aspects that influence the term.[1] Thus, disability is a multi-dimensional concept which encompasses impairment as well as the social or environmental barriers that limit the individual's participation in society[1,2] and independence.[3] Individuals with disability experience elements of impairment, activity limitations, and participation restrictions.[2] Longer life expectancies enhance risk of disability in elderly population due to declining health and vulnerability to chronic illness.[3,4] Worldwide, the prevalence of moderate and severe disability in persons over the age of 60 years is estimated to be 46.1%.[1]

Two-thirds of the elderly population with disability have a comorbid chronic illness.[5] Most cases of disability are predicted by dementia,[5,6] stroke,[5] limb impairment,[5,7] arthritis,[5,8] depression, eyesight problems,[5,7] and gastrointestinal impairments.[5] Previous population-based studies in elderly samples have also identified associations between disability and symptoms of mild cognitive impairment (MCI)[8,9] or lacking of educational background.[3,9,10] Developed cognitive ability or a "cognitive reserve" was found to be protective against MCI and its associated disability.[11,12]

WHO defines an aged society as one whose population has 14% residents over the age of 65,[13] thus it is predicted that Singapore will fall into this category within the next 5 years.[13] Studies on Singapore's ageing population indicate that in 2005, 1 in every 12 residents was over the age of

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65 years and by 2030, this will increase to 1 in every 5 residents who would be over the age of 65.[14] Previous literature suggests that disability is prevalent among elderly Singaporeans.[13,15] On assessing the activities of daily living (ADL) as a measure of disability, a recent report suggests that 6% of men over the age of 65 years reported 1 or more limitations in performing their daily activities, compared to 16% of older women who reported limitations.[13]

The aim of this study was to establish the prevalence and correlates of disability in a cross-sectional epidemiological study conducted on older adults i.e. those aged 60 years and above in Singapore. We explored associations of disability with regards to sociodemographic variables, cognitive ability, and diagnosis of chronic illnesses. Research in this field clarifies markers of disability and provides policymakers and clinicians with the necessary information to establish strategies which will enhance quality of life in elderly populations. Data for this study was extracted from the Well-being of the Singapore Elderly (WiSE) study – a population-based study to establish the prevalence of dementia among the elderly in Singapore.[16]

Materials and Methods

Sample

The WiSE study[16] adopted the 10/66 Dementia Research Group protocols[17,18,19] to establish the prevalence of dementia in Singapore's elderly resident population. This cross-sectional study was conducted on Singapore citizens or permanent residents aged 60 years or above who were living in Singapore at the time of the survey. Participants in this age group were randomly selected from an administrative database. Respondents were approached in their homes as well as day care centres, nursing homes, and institutions. This study used a nationally representative sample which encompassed the 3 main ethnic groups in Singapore: Chinese, Malay, and Indians; 10/66 questionnaires were available in English, Chinese and Tamil while our research team translated the instruments into Malay. The questionnaires were also transcribed into 3 major dialects: Hokkien, Cantonese, and Teochew. Choice of administered language was based on the participant's preferences.

An informant, selected for each participant, was a "person who knew the older person best"; and were most commonly co-residents, family members, or caregivers of the participant.[20] A Computer Assisted Personal Interviewing (CAPI) mode was used for real-time data collection in the field. Sample sizes were estimated to be n = 2500 based on the previously estimated prevalence rate of 5.2% of dementia in Singapore's population.[16,21] There were a total of 2565 respondents which yielded a response rate of 65.6%. Within this sample, only 2421 respondents were able to complete cognitive tests and provide a suitable caregiver for informant reports. The sample consisted of Chinese (38.5%), Malay (30.1%), Indian (30.1%), and Others (1.4%).

The WiSE study was approved by the institutional ethics review boards (National Healthcare Group Domain Specific Review Board [DSRB] and the SingHealth Centralised Institutional Review Board [CIRB]). Written informed consent was obtained from all participants; in the event that the respondent was unable to understand or give consent, consent was obtained from a legally acceptable representative. Details of the WiSE study are described in an earlier article by Subramanian et al.[16]

Main Instruments

World Health Organization Disability Assessment Schedule (WHODAS) 2.0

The World Health Organization Disability Assessment Schedule (WHODAS) 2.0 was established as an international and cross-cultural method to comprehend severity of disability levels in patients.[22] WHODAS was developed by the International Classification of Functioning, Disability, and Health (ICF) to identify symptoms of disorders that hindered everyday living. Disability levels measured by this assessment have good test-retest reliability with validation in 16 languages in 14 countries.[23] WHODAS measures functioning based on 6 domains: cognition, mobility, self-care, getting along, life activities, and participations.[22] Items were measured and computed using a specific scale: "None" (0), "Mild" (1), "Moderate" (2), "Severe" (3), and "Extreme" (4). Items in each domain were summed and weighted, then all 6 weighted scores were converted into a summary score ranging from 0-100 (where 0 = no disability; 100 = full disability).

Community Screening Instrument for Dementia (CSI-D)

The Community Screening Instrument for Dementia (CSI-D) questionnaire is used to measure cognition and can be administered to both non-literate and literate populations.[20] CSI-D scores incorporate elements of memory, orientation, naming and language expression, and comprehension.[24] CSI-D establishes a cognitive score (COGSCORE) based on an item-weighted total score from each participant's cognitive test.[18,25,26]

CSI-D Informant Interview (RELSCORE)18,27

The CSI-D Informant Interview (RELSCORE) is an informant-based interview used to trace cognitive and functional decline in participants by enquiring about the participant's general health and daily functioning. RELSCOREs were measured by interviews and reports

by "informants" or individuals who knew the participant best.[27] Informant scores range from 0-16 (where 0 = no impairment, 16 = complete functional impairment) and have been used in various sites and populations.[20,28]

Sociodemographic Questionnaire

The Sociodemographic Questionnaire included questions on age, gender, ethnicity, marital status, education, employment status, social support, and personal/family income. Participants were asked if they had been diagnosed with any chronic illnesses: hypertension, high blood pressure, any type of heart trouble, stroke, serious head injury, diabetes, tuberculosis, depression, dementia, arthritis, eye sight problems, hearing difficulty, persistent cough, difficulty breathing, stomach problems, faints, paralysis, and skin disorders. For difficult terms and complex medical terms such as transient ischaemic attack, the question asked: "Have you ever developed sudden weakness of a limb, loss of speech, or partial blindness which got better quickly, in less than one day? Doctors sometimes call these transient ischaemic attacks." With regard to chronic illness, results that either showed significance or a trend towards significance (P <0.05) are represented. The study used the 10/66 algorithm to diagnose dementia. For this particular study, cognition, as measured by the CSI-D COGSCOREs and RELSCOREs, was correlated with domains integrated within the WHODAS 2.0 measure.[22]

Statistical Analysis

Survey data analysis of 10/66 protocols were completed on Statistical Analysis Software (SAS) Version 9.3. Data were weighted to encompass findings that appropriately signify Singapore's elderly population. Mean scores were compared of n = 2421 responses on cognitive tests (COGSCORE) and informant reports (RELSCORE) versus levels of disability (WHODAS). Descriptive statistics were used to compare differences in mean WHODAS scores among various sociodemographic subgroups: gender, age groups, ethnicity, marital status, education, and employment status. Other sociodemographic and risk factors pertinent to disability like education levels, physical and mental health, and comorbid chronic illness were also explored. Multiple linear regressions were used in order to form predictors based on effects of COGSCORE and RELSCORE on WHODAS scores. We used 5 models to explore effects of COGSCOREs/RELSCOREs on WHODAS scores: 1) effects of only COGSCOREs/RELSCOREs with no adjustments, 2) after adjusting for sociodemographic variables, 3) after adjusting for sociodemographic variables and presence of any chronic illness, 4) after adjusting for sociodemographic variables, and presence of either hypertension, heart problems, stroke, diabetes, or transient ischaemic attack, 5) after adjusting for sociodemographic variables, and presence of either hypertension, heart problems, stroke, diabetes, transient ischaemic attack, depression, or dementia. Each model used R-squares and root mean square error (RMSE) tests for fit statistics. Significant variables were identified by P values (<0.05) with a 95% confidence interval indicating effects on WHODAS scores.

Results

The WiSE study collected data from 2421 sets of residents and informants in Singapore. The mean age of respondents was 72.7 years. The proportion of males to females was 43% to 57%, respectively. The sample's ethnic distribution was 38.5% Chinese (n = 931), 30.1% Malay (n = 728), 30.1% Indian (n = 728) with an additional component of 1.4% Other ethnicities (n = 34) (Table 1). As indicated in Table 2, the average disability for the entire sample as measured by WHODAS 2.0 was 11.2 (± 0.47). The average COGSCORE was 28.1 (± 0.12) while the average RELSCORE was 1.6 (± 0.08).

Comparison of Mean WHODAS Scores among Sociodemographic Groups

Table 1 indicates the mean WHODAS scores among various sociodemographic groups. Participants aged 85 years or more had a mean WHODAS of 44.0 (± 2.1). This was followed by those in the age group of 75 to 84 with average WHODAS scores of 19.6 (± 1.3), and age group of 60 to 74 attaining the least severe WHODAS scores of 6.5 (± 0.05). Females had significantly higher disability levels compared to males, WHODAS scores of 13.0 (± 0.65) and 8.8 (± 0.75), respectively. Malay and Indian participants had higher levels of disability compared to Chinese and those belonging to Other ethnicity group. The mean WHODAS score of widowed participants were significantly higher (21.7 ± 1.2) compared to married/ cohabitating (8.1 ± 0.57) or never married (7.6 ± 2.0) participants.

Disability measured by WHODAS 2.0 was associated with educational levels. Participants with no educational background had a mean WHODAS score of 21.0 (± 1.5); while those with some background without completing primary education had WHODAS scores of 12.3 (± 1.0). Results consistently indicated that as educational level increased, mean WHODAS scores decreased (Table 1). Participants who were homemakers (average WHODAS score of 14.6 ± 1.0) or retired (15.4 ± 0.94) had significantly higher WHODAS scores than participants who were employed (3.1 ± 0.33) and unemployed (3.8 ± 2.2) (Table 1).

Table 1. Sociodemographic Characteristics and Mean WHODAS Score

Variable	Sample			WHODAS Score	
	Unweighted (n)	Unweighted (%)	Weighted (%)	Mean	SE
Overall	2421	100	100	11.2	0.47
Age group					
60 – 74	1403	58.0	74.8	6.5	0.05
75 – 84	633	26.2	19.4	19.6	1.3
85+	385	15.9	5.7	44.0	2.1
Gender					
Men	1039	42.9	43.0	8.8	0.75
Women	1382	57.1	57.0	13.0	0.65
Ethnicity					
Chinese	931	38.5	82.6	10.9	0.56
Malay	728	30.1	9.8	13.8	0.78
Indian	728	30.1	6.1	13.1	0.70
Others	34	1.4	1.5	7.7	1.8
Marital status					
Never married	108	4.5	6.8	7.6	2.0
Married/cohabiting	1419	58.7	65.4	8.1	0.57
Widowed	798	33.0	22.8	21.7	1.2
Divorced/separated	94	3.9	5.0	8.5	2.4
Education					
None	502	20.9	17.1	21.0	1.5
Some, but did not complete primary	579	24.1	23.8	12.3	1.0
Completed primary	597	24.8	24.1	9.5	1.0
Completed secondary	488	20.3	22.5	7.0	0.9
Completed tertiary	241	10.0	12.5	6.1	1.3
Employment status					
Paid work (part- and full-time)	632	26.4	32.9	3.1	0.33
Unemployed	30	1.3	1.4	3.8	2.2
Homemaker	782	32.7	27.2	14.6	1.0
Retired	947	39.6	38.5	15.4	0.94

SE: Standard error; WHODAS: World Health Organization Disability Assessment Schedule

Table 2. Comparison of Cognitive Ability, Informant Reports, and Disability Score of Sample Population

Variable	Label	n	Mean	Standard Error	95% CI for Mean		Minimum Score	Maximum Score
COGSCORE	Cognitive ability	2421	28.1	0.1	27.8	28.3	0.0 (full impairment)	32.2 (no impairment)
RELSCORE	Informant report	2421	1.6	0.1	1.4	1.8	0.0 (no impairment)	30.0 (full impairment)
WHODAS-12	Levels of disability	2421	11.2	0.5	10.3	12.2	0.0 (no disability)	100.0 (full disability)

COGSCORE: CSI-D cognitive test; RELSCORE: CSI-D informant interview; WHODAS: World Health Organization Disability Assessment Schedule

Correlates of Cognition, Sociodemographic Factors, and Chronic Illness on Disability

Analyses of data from regressions were compared based on 5 sets of models. The first model in Table 3 indicated that participants with deficits in cognition (low COGSCORE, β = 2.9) were more likely to have higher levels of disability (high WHODAS score). Model 2, adjusting for sociodemographic variables, found that those aged 60 to 74 years (β = -11.76) and 75 to 84 years (β = -7.45) were less likely to have higher WHODAS scores compared to those aged 85 years and older. Males (β = -1.7) were less likely than females to express high levels of disability. Participants who were widowed (β = 3.5) were more likely to have higher WHODAS scores versus those who were never married (Table 3). Those who were retired (β = 2.6) and homemakers (β = 2.3) were more likely to have higher WHODAS scores compared to those who were working part- and full-time.

Participants with comorbid diagnosis of a chronic illness (β = 2.8) were more likely to have higher WHODAS scores. Chronic illnesses that were significantly associated with disability were heart problems (β = 4.12), stroke (β = 10.4), and transient ischaemic attack (β = 6.7) (Model 4, Table 3). In Model 5, depression (β = 4.25) and dementia (β = 14.6) were strongly associated with disability. Despite adjusting for sociodemographic factors and chronic illnesses in all 5 models, COGSCORE consistently had significant effects on WHODAS scores indicating that participants with deficits in cognitive ability had greater levels of disability (Table 3).

Correlates of Informant Reports, Sociodemographic Factors and Chronic Illness on Disability

In Model 1 of Table 4, impairment indicated by RELSCOREs or informant reports (β = 3.8) were associated with higher levels of disability. Consistent with COGSCOREs, participants aged 85 years or more had greater disability as compared to those aged 60 to 74 (β = 15.70) and 75 to 84 (β = 10.78). Participants with no education (β = 4.95) were more likely to indicate higher levels of disability as compared to those with tertiary education. RELSCOREs of participants who were retired (β = 4.19) and had homemaker status (β = 3.41) were more likely to indicate higher disability as compared to participants with full- or part-time paid work (Model 2, Table 4).

Model 5 using RELSCOREs found that depression (β = 3.12) and dementia (β = 19.29) were also significant predictors of disability. Similar to COGSCOREs, RELSCOREs in all 5 models was significantly associated with higher WHODAS scores despite adjusting for various factors (Table 4).

Discussion

This study aimed to establish risk factors and the extent of disability in Singapore's elderly population. With a mean WHODAS score of 11.2, Singapore's elderly population falls within the range of 8.0 to 16.5 that was reported from previous 10/66 studies in the urbanised centres of Cuba, Dominican Republic, Peru, Venezuela, Mexico, China, and India.[5] Our results suggest that disability is associated with older age, female gender, Malay or Indian ethnicity, being widowed, poor educational background, being retired or a homemaker, deficits in cognitive ability and comorbidity with at least 1 chronic illness (physical and/or mental).

As expected, age was positively correlated with severity in disability scores, with participants aged 85 years and above reporting higher levels of disability compared to those in the age groups of 60 to 74 and 75 to 84 years. These results were consistent with WHO findings stating that within those with some type of disability, 20% were older than 70 years and 50% were older than 85 years.[3] In examining disability scores between genders, our results suggest that females are more likely than males to have higher WHODAS scores. In line with this, a report by the International Longevity Centre found 29% of elderly females as compared to 8% of elderly males in Singapore report at least 1 limitation in executing their daily activities.[13] Likewise, another study that used 10/66 protocols measuring cognition in Latin America, India, and China found that men had higher cognitive ability (based on COGSCOREs) compared to women.[24] In Singapore, 71% of elderly females were diagnosed with cognitive impairment as compared to 29% of elderly males.[13] Gender differences in disability could potentially be due to the fact that in Singapore, females have a longer life expectancy and thus may be susceptible to chronic diseases and disability as compared to men.[3,8]

Our results indicate that disability scores of Indians and Malay participants were significantly higher than that of Chinese participants. A study by Ng et al,[8] consistent with our results on ethnic differences in disability, suggests that the higher prevalence of health-related factors such as chronic medical illness could result in Malays having higher levels of functional disability compared to the Chinese. Their study suggests that Indians also had higher levels of functional disability compared to the Chinese, but this association remains persistent despite adjusting for both sociodemographic and health-related variables.[8] Though our study is consistent with previous literature stating that Indians have higher levels of disability compared to the Chinese, the reason behind this finding is yet to be determined. Another study pertaining to Singapore's ethnic differences suggested that Indians and Malays have significantly lower health-related quality of life (incorporating both physical and mental health conditions) as compared to the Chinese.[29] Ethnic

Table 3. Associations between COGSCORE, Sociodemographic Factors, and Chronic Illness on WHODAS 2.0 Scores

Variable	Model 1			Model 2			Model 3			Model 4			Model 5		
	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value
COGSCORE	-2.99	(-3.18, -2.79)	<0.0001*	-2.69	(-2.95, -2.44)	<0.0001*	-2.69	(-2.94, -2.44)	<0.0001*	-2.49	(-2.74, -2.25)	<0.0001*	-1.88	(-2.16, -1.59)	<0.0001*
Age groups															
60 – 74				-11.76	(-15.64, -7.88)	<0.0001*	-11.81	(-15.66, -7.96)	<0.0001*	-12.15	(-15.83, -8.47)	<0.0001*	-9.71	(-13.35, -6.07)	<0.0001*
75 – 84				-7.45	(-11.36, -3.54)	0.00*	-7.73	(-11.63, -3.84)	0.00*	-8.23	(-11.97, -4.49)	<0.0001*	-6.73	(-10.34, -3.12)	0.00*
85+				REF			REF			REF			REF		
Gender															
Males				-1.70	(-3.35, -0.05)	0.04*	-2.02	(-3.68, -0.37)	0.02*	-2.62	(-4.27, -0.97)	0.00*	-2.22	(-3.81, -0.63)	0.01*
Females				REF			REF			REF			REF		
Ethnicity															
Others				1.46	(-2.12, 5.05)	0.42	1.36	(-2.24, 4.97)	0.46	-1.10	(-5.24, 3.04)	0.6	-0.49	(-4.60, 3.62)	0.82
Indian				2.99	(1.57, 4.41)	<0.0001*	2.80	(1.38, 4.22)	0.00*	2.19	(0.79, 3.58)	0.00*	2.36	(0.97, 3.75)	0.00*
Malay				2.66	(1.11, 4.20)	0.00*	2.73	(1.20, 4.26)	0.00*	2.96	(1.50, 4.42)	<0.0001*	3.26	(1.83, 4.68)	<0.0001*
Chinese				REF			REF			REF			REF		
Marital status															
Divorced/ separated				3.03	(-0.02, 6.08)	0.05	3.06	(-0.03, 6.15)	0.05	2.50	(-0.68, 5.68)	0.12	1.80	(-1.40, 5.00)	0.27
Widowed				3.53	(0.73, 6.34)	0.01*	3.22	(0.42, 6.02)	0.02*	2.92	(0.29, 5.55)	0.03*	1.79	(-0.78, 4.36)	0.17
Married				2.41	(0.04, 4.77)	0.05	2.29	(-0.07, 4.64)	0.06	2.07	(-0.11, 4.25)	0.06	1.22	(-0.93, 3.38)	0.26
Never married				REF			REF			REF			REF		
Educational background															
No education				-2.42	(-5.28, 0.43)	0.1	-2.59	(-5.42, 0.24)	0.07	-2.67	(-5.23, -0.10)	0.04*	-1.72	(-4.25, 0.81)	0.18
Some but did not complete primary education				-2.45	(-4.66, -0.24)	0.03*	-2.47	(-4.68, -0.26)	0.03*	-2.43	(-4.50, -0.36)	0.02*	-1.65	(-3.73, 0.43)	0.12

COGSCORE: CSI-D cognitive test; WHODAS: World Health Organization Disability Assessment Schedule

*Significant variables were identified by *P* values (<0.05) with a 95% confidence interval.

Note: Beta coefficient was derived from multiple linear regression analysis.

Table 3. Associations between COGSCORE, Sociodemographic Factors, and Chronic Illness on WHODAS 2.0 Scores (Con't)

Variable	Model 1			Model 2			Model 3			Model 4			Model 5		
	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value
Completed primary education				-1.20	(-3.30, 0.91)	0.27	-1.16	(-3.25, 0.93)	0.28	-1.34	(-3.30, 0.62)	0.18	-1.31	(-3.25, 0.64)	0.19
Completed secondary education				0.14	(-1.84, 2.11)	0.89	0.18	(-1.78, 2.14)	0.86	-0.11	(-1.97, 1.74)	0.9	-0.39	(-2.20, 1.42)	0.67
Completed tertiary education				REF			REF			REF			REF		
Employment status															
Retired				2.62	(1.11, 4.13)	0.00*	2.21	(0.69, 3.73)	0.00*	1.54	(0.03, 3.04)	0.05	1.29	(-0.19, 2.78)	0.09
Homemaker				2.35	(0.43, 4.27)	0.02*	2.01	(0.08, 3.94)	0.04*	1.42	(-0.47, 3.31)	0.14	1.02	(-0.73, 2.77)	0.25
Unemployed				0.79	(-2.18, 3.75)	0.6	0.55	(-2.36, 3.46)	0.71	1.17	(-1.99, 4.34)	0.47	1.28	(-2.08, 4.63)	0.46
Paid work				REF			REF			REF			REF		
Diagnosis of any chronic illness															
Yes							2.83	(1.49, 4.16)	<0.0001*						
No							REF								
Hypertension															
Yes										1.03	(-0.22, 2.28)	0.1	1.16	(-0.03, 2.35)	0.06
No										REF			REF		
Heart problems															
Yes										4.12	(1.87, 6.37)	0.00*	3.67	(1.51, 5.83)	0.00*
No										REF			REF		
Stroke															
Yes										10.42	(6.19, 14.66)	<0.0001*	10.00	(6.06, 13.94)	<0.0001*
No										REF			REF		
Diabetes															
Yes										1.39	(-0.27, 3.05)	0.1	1.59	(-0.01, 3.18)	0.05
No										REF			REF		

COGSCORE: CSI-D cognitive test; WHODAS: World Health Organization Disability Assessment Schedule

*Significant variables were identified by *P* values (<0.05) with a 95% confidence interval.

Note: Beta coefficient was derived from multiple linear regression analysis.

Table 3. Associations between COGSCORE, Sociodemographic Factors, and Chronic Illness on WHODAS 2.0 Scores (Con't)

Variable	Model 1			Model 2			Model 3			Model 4			Model 5		
	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value
Transient ischaemic attack															
Yes										6.69	(1.86, 11.53)	0.01*	6.28	(1.17, 11.39)	0.02*
No										REF			REF		
Depression															
Yes													4.25	(1.47, 7.02)	0.00*
No													REF		
Dementia															
Yes													14.60	(9.62, 19.57)	<0.0001*
No													REF		

COGSCORE: CSI-D cognitive test; WHODAS: World Health Organization Disability Assessment Schedule

*Significant variables were identified by *P* values (<0.05) with a 95% confidence interval.

Note: Beta coefficient was derived from multiple linear regression analysis.

Table 4. Associations between RELSCORE, Sociodemographic Factors, and Chronic Illness on WHODAS 2.0 Scores

Variable	Model 1			Model 2			Model 3			Model 4			Model 5		
	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value
RELSCORE	3.80	(3.48, 4.12)	<0.0001*	3.17	(2.83, 3.50)	<0.0001*	3.16	(2.83, 3.49)	<0.0001*	2.87	(2.56, 3.18)	<0.0001*	1.83	(1.46, 2.19)	<0.0001*
Age groups															
60 – 74				-15.70	(-19.73, -11.68)	<0.0001*	-15.79	(-19.80, -11.78)	<0.0001*	-16.00	(-19.73, 12. 27)	<0.0001*	-12.12	(-15.98, -8.27)	<0.0001*
75 – 84				-10.78	(-14.77, -6.80)	<0.0001*	-11.04	(-15.01, -7.07)	<0.0001*	-11.31	(-15.03, -7.58)	<0.0001*	-8.73	(-12.44, -5.03)	<0.0001*
85+				REF			REF			REF			REF		
Gender															
Male				-0.37	(-2.30, 1.55)	0.7036	-0.62	(-2.57, 1.32)	0.5298	-1.45	(-3.30, 0.41)	0.1274	-1.40	(-3.12, 0.31)	0.108
Female				REF			REF			REF			REF		
Ethnicity															
Others				-0.13	(-3.80, 3.52)	0.9432	-0.21	(-3.91, 3.49)	0.91	-2.67	(-7.16, 1.83)	0.2445	-1.40	(-5.78, 2.98)	0.5308
Indian				3.25	(1.76, 4.74)	<0.0001*	3.11	(1.60, 4.61)	<0.0001*	2.84	(1.30, 4.37)	0.0003*	2.94	(1.44, 4.43)	0.0001*
Malay				3.35	(1.74, 4.96)	<0.0001*	3.41	(1.82, 5.00)	<0.0001*	3.86	(2.37, 5.36)	<0.0001*	3.88	(2.42, 5.34)	<0.0001*
Chinese				REF			REF			REF			REF		
Marital status															
Divorced/ separated				0.27	(-4.48, 5.03)	0.91	0.30	(-4.52, 5.12)	0.9037	-0.06	(-4.75, 4.64)	0.9806	0.15	(-4.20, 4.50)	0.9465
Widowed				0.12	(-3.58, 3.82)	0.948	-0.12	(-3.83, 3.60)	0.9514	-0.04	(-3.70, 3.62)	0.9825	-0.27	(-3.63, 3.10)	0.8754
Married				-1.95	(-5.33, 1.42)	0.2561	-2.04	(-5.46, 1.37)	0.2407	-1.77	(-5.15, 1.61)	0.3046	-1.53	(-4.58, 1.52)	0.3252
Never married				REF			REF			REF			REF		
Educational background															
No education				4.95	(1.62, 8.28)	0.0036*	4.82	(1.49, 8.16)	0.0046*	4.09	(1.12, 7.07)	0.007*	3.01	(0.09, 5.93)	0.0432*
Some but did not complete primary education				1.81	(-1.06, 4.68)	0.2162	1.80	(-1.08, 4.67)	0.2198	1.16	(-1.31, 3.63)	0.358	0.86	(-1.56, 3.27)	0.4844

RELSCORE: CSI-D informant interview; WHODAS: World Health Organization Disability Assessment Schedule

*Significant variables were identified by *P* values (<0.05) with a 95% confidence interval.

Note: Beta coefficient was derived from multiple linear regression analysis.

Table 4. Associations between RELSCORE, Sociodemographic Factors, and Chronic Illness on WHODAS 2.0 Scores (Con't)

Variable	Model 1			Model 2			Model 3			Model 4			Model 5		
	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value
Completed primary education				0.59	(-2.02, 3.19)	0.6592	0.61	(-1.99, 3.22)	0.6442	0.23	(-2.11, 2.58)	0.8452	-0.27	(-2.52, 1.98)	0.8118
Completed secondary education				0.19	(-2.38, 2.76)	0.8857	0.22	(-2.36, 2.80)	0.8656	-0.14	(-2.47, 2.20)	0.9072	-0.50	(-2.67, 1.67)	0.6507
Completed tertiary education				REF			REF			REF			REF		
Employment status															
Retired				4.19	(2.36, 6.00)	<0.0001*	3.88	(2.04, 5.71)	<0.0001*	2.86	(1.14, 4.58)	0.0011*	2.25	(0.64, 3.86)	0.0063
Homemaker				3.41	(1.19, 5.62)	0.0026*	3.15	(0.91, 5.39)	0.0058*	2.35	(0.25, 4.46)	0.0285*	1.66	(-0.22, 3.53)	0.0833
Unemployed				-0.04	(-3.62, 3.54)	0.9819	-0.23	(-3.80, 3.34)	0.9017	0.75	(-3.04, 4.55)	0.6969	0.98	(-2.86, 4.82)	0.6176
Paid work				REF			REF			REF			REF		
Diagnosis of any chronic illness															
Yes							2.17	(0.69, 3.66)	0.0042*						
No							REF								
Hypertension															
Yes										0.20	(-1.19, 1.58)	0.7826	0.60	(-0.68, 1.87)	0.3571
No										REF			REF		
Heart problems															
Yes										2.41	(-0.25, 5.07)	0.0757	2.34	(-0.09, 4.77)	0.0592
No										REF			REF		
Stroke															
Yes										14.79	(9.89, 19.69)	<0.0001*	13.02	(8.64, 17.41)	<0.0001*
No										REF			REF		
Diabetes															
Yes										0.38	(-1.40, 2.15)	0.6764	0.93	(-0.74, 2.60)	0.2733
No										REF			REF		

RELSCORE: CSI-D informant interview; WHODAS: World Health Organization Disability Assessment Schedule

*Significant variables were identified by *P* values (<0.05) with a 95% confidence interval.

Note: Beta coefficient was derived from multiple linear regression analysis.

Table 4. Associations between RELSCORE, Sociodemographic Factors, and Chronic Illness on WHODAS 2.0 Scores (Con't)

Variable	Model 1			Model 2			Model 3			Model 4			Model 5		
	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value	β	(95% CI)	*P* Value
Transient ischaemic attack															
Yes										11.34	(3.47, 19.22)	0.0048*	9.73	(2.19, 17.28)	0.0115
No										REF			REF		
Depression															
Yes													3.12	(0.34, 5.90)	0.028*
No													REF		
Dementia															
Yes													19.29	(13.37, 25.22)	<0.0001*
No													REF		

RELSCORE: CSI-D informant interview; WHODAS: World Health Organization Disability Assessment Schedule

*Significant variables were identified by *P* values (<0.05) with a 95% confidence interval.

Note: Beta coefficient was derived from multiple linear regression analysis.

differences in health-related quality of life may be explained by studies indicating that Malays and Indians have lower plasma folate concentrations compared to Chinese.[30] This contributes to cognitive impairment, behavioural disorders, weakness, fatigue, and shortness of breath.[31] This and other such dietary or cultural factors may be responsible for the observed differences.

We found that higher educational backgrounds act as a protective measure against disability. Previous studies have linked a lack of educational background to deficits in cognitive abilities which lead to disability in elderly populations.[2,8,9,24,26,32] Dotchin et al (2014), for instance, found a lack of educational background in an elderly Tanzanian population to be an accurate predictor of cognitive impairment and dementia which in turn predicted disability.[9] Links between education, cognition, and disability could be explained by the cognitive reserve theory which posits that brain networks formed from intellectual experiences related to education or occupation avert incidence of dementia and thus disability by increasing cognition.[11] Consistent with previous literature,[8,12] low educational background and cognitive impairment were found to be strongly associated with disability in the current study.

Significantly, association of low COGSCOREs with WHODAS scores in all 5 models indicate that impaired cognition strongly influences disability. Studies suggest that deficits in various domains of cognition (attention, memory, language, and visuo-spatial performances) directly reduce an individual's ability to perform everyday tasks; thereby, impacting disability and increasing dependence in elderly populations.[33,34,35]

Presence of any chronic illness was strongly associated with disability in this elderly population. Other studies have also found that comorbid physical illnesses such as heart problems, stroke[5,7,36,37] and transient ischaemic attacks were significantly correlated with disability. As in other studies, depression was associated with higher levels of disability.[5,33,36-38] Depression is one of the most important causes for disability worldwide[39] as untreated depression has been reported to increase disability by making the individual vulnerable to cognitive decline, [33] personal suffering and additional health risks.[40] Similar to our study, numerous other studies suggest associated risk factors between dementia and disability.[5,6-8,10,12,36,37]

Strengths and Limitations of the Study

As most participants were recruited from their homes, information from residents of nursing homes is somewhat limited in this study. Another limitation in terms of recruitment was that some participants were not able to provide a suitable informant; hence they were excluded from the analyses. The cross-sectional design of the study did not permit us to determine any causal relationships. The strengths of the study include a large sample with a good response rate which makes it representative of the elderly population in Singapore. The study was also a single phase study that ensured that detailed data was collected from all individuals.

Conclusion

This study has identified a number of putative risk factors of disability among the elderly in this particular population. With a rapidly ageing population, it is crucial to further elucidate the relative contributions of these risk factors so that the appropriate strategies and interventions can be implemented. These might include screening for depression among the elderly, better management of chronic medical illnesses, and encouraging activities that could increase and preserve cognition.

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Original Article

Enteric Fever in a Tertiary Paediatric Hospital: A Retrospective Six-Year Review

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Abstract

Introduction: Enteric fever is a multisystemic infection which largely affects children. This study aimed to analyse the epidemiology, clinical presentation, treatment and outcome of paediatric enteric fever in Singapore. Materials and Methods: A retrospective review of children diagnosed with enteric fever in a tertiary paediatric hospital in Singapore was conducted from January 2006 to January 2012. Patients with positive blood cultures for *Salmonella typhi* or *paratyphi* were identified from the microbiology laboratory information system. Data was extracted from their case records. Results: Of 50 enteric fever cases, 86% were due to *Salmonella typhi*, with 16.3% being multidrug resistant (MDR) strains. Sixty-two percent of *S. typhi* isolates were of decreased ciprofloxacin susceptibility (DCS). Five cases were both MDR and DCS. The remaining 14% were *Salmonella paratyphi A*. There were only 3 indigenous cases. Ninety-four percent had travelled to typhoid-endemic countries, 70.2% to the Indian subcontinent and the rest to Indonesia and Malaysia. All patients infected with MDR strains had travelled to the Indian subcontinent. Anaemia was a significant finding in children with typhoid, as compared to paratyphoid fever ($P = 0.04$). Although all children were previously well, 14% suffered severe complications including shock, pericardial effusion and enterocolitis. None had typhoid vaccination prior to their travel to developing countries. Conclusion: Enteric fever is largely an imported disease in Singapore and has contributed to significant morbidity in children. The use of typhoid vaccine, as well as education on food and water hygiene to children travelling to developing countries, needs to be emphasised.

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Key words: Children, Fever, Paratyphoid, Typhoid

Introduction

Enteric fever refers collectively to typhoid and paratyphoid fever. It is a potentially fatal multisystemic infection caused by bloodstream invasion with the bacteria *Salmonella enterica* serotype *typhi* (*S. typhi*) or *Salmonella enterica* serotype *paratyphi* (*S. paratyphi*).[1,2]

Transmission occurs via the faecal-oral route through contact with food handled by infected individuals or from ingestion of sewage-contaminated water or shellfish.[3] As such, enteric fever is endemic in areas with low socioeconomic indices where sanitary conditions are suboptimal.[4] Globally, the estimated total number of enteric fever episodes in 2010 was 13.5 million, with a large majority concentrated in Asia, Africa, Latin America and the Caribbean. The median enteric fever incidence rate per 100,000 was <0.1 in Europe and 0.3 in North America, compared to 394.2 and 724.6 in South Asia and Sub-Saharan Africa, respectively.[5]

Enteric fever is largely a disease affecting the young.[6,7] The incidence peaks in school-age children aged 5 to 19 years.[8] The incubation period is typically 8 to 14 days and the illness begins with fever associated with constitutional and abdominal symptoms.[9] Approximately 20% of patients develop a rash known as "rose spots" due to bacterial emboli

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in the dermis.[10,11] If left untreated, the disease progresses to involve multiple systems and may even lead to death.[12,13] Both typhoid and paratyphoid fever share similar clinical features, although paratyphoid fever usually follows a more benign course. Crump et al estimated that without effective treatment, enteric fever had a case fatality rate of 10% to 30%.[4] This number was reduced to 1% to 4% in those receiving appropriate therapy.

This is a retrospective review of children diagnosed with enteric fever in a tertiary paediatric hospital in Singapore, over a 6-year period from January 2006 to January 2012. The aim of this study was to describe the epidemiology, clinical presentation, treatment and outcome of paediatric enteric fever in Singapore, and thus, review the current standard of care.

Materials and Methods

We conducted a search of our microbiology laboratory information system for positive blood cultures for *S. typhi* or *S. paratyphi* among children less than 17 years of age admitted to our hospital for treatment between 1 January 2006 and 31 January 2012. Data was then extracted from their case records.

Imported cases were defined as those with a travel history to a typhoid-endemic country within the preceding 3 months before the onset of illness. We reported the nationality of the study cases, as a significant proportion of them were found to be foreigners or tourists. Fever was defined as an axillary or tympanic temperature more than or equal to 38˚C. The finding of Faget's sign described sphygmothermic dissociation, or fever associated with relative bradycardia.[14]

We analysed blood culture, stool culture, and Widal and Weil-Felix serology results in our patients, in addition to relevant haematological and biochemical laboratory parameters. Blood results analysed were those taken on admission to the hospital. In our institution, antibiotic susceptibility testing to ampicillin, sulfamethoxazole/trimethoprim and ceftriaxone was routinely performed for all cases of blood culture-positive enteric fever. Our laboratory has ceased antibiotic susceptibility testing to chloramphenicol. Multidrug resistant (MDR) typhoid fever was defined as infection with a strain of *S. typhi* resistant to both traditional first-line antibiotics of ampicillin and sulfamethoxazole/trimethoprim.[15,16] Additionally, isolates were screened for decreased ciprofloxacin susceptibility (minimum inhibitory concentration [MIC] ≥0.125 mg/L) based on resistance to nalidixic acid.[17]

Widal and Weil-Felix serology was interpreted as significant if O and H antigen titres were more than 1/320.[18,19] Anaemia was defined as a haemoglobin value more than 2 standard deviations (SD) below the mean for the reference population.[20] Normal values for platelets, leucocytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and liver transaminases were defined based on the standard reference ranges employed by our laboratory.[21]

Outcome was assessed in terms of time to fever defervescence, disease complications, need for intensive care, length of hospital stay and mortality. Time to fever defervescence was defined as the number of days for fever to lyse completely for at least 24 hours, after starting therapeutic doses of culture-sensitive intravenous antibiotics.[22]

Statistical analysis was performed using the SPSS statistical software programme, version 20 (IBM Corporation, Armonk, NY, USA). Chi-square and Fisher's exact tests were used for categorical data, while Mann-Whitney U and SPSS independent samples median tests were used for continuous data. *P* values <0.05 were considered statistically significant. This study was approved by the SingHealth Institutional Review Board and approval was obtained for waiver of consent.

Results

A total of 43 cases of typhoid and 7 cases of paratyphoid fever were identified over this 6-year period. All paratyphoid cases involved *S. paratyphi A*. The median age of patients was 7.8 years. Males accounted for 60% of cases. Ninety-four percent of cases were imported. Three cases were indigenous, with all 3 being citizens or permanent residents without any contact history with a known infected person, nor any returning traveller from a typhoid-endemic country (Table 1).

All 50 cases presented with fever, with a median duration of 9.0 days (interquartile range [IQR]: 6.0 to 11.3 days). Table 1 lists the significant clinical findings. There were no cases of typhoid encephalopathy and none had the characteristic rose spots described in classic typhoid fever. Forty-eight percent were tachycardic on arrival to the children's emergency department. Of these, 87.5% had tachycardia in proportion to the degree of fever.[23] Three had tachycardia in association with hypotension, all of whom were infected with *S. typhi*. None of the affected children demonstrated relative bradycardia (Faget's sign).

Of the 43 typhoid fever cases, 14% were infected with MDR strains. Sixty-two percent of isolates tested were found to have decreased ciprofloxacin susceptibility (DCS). Five cases were both MDR and DCS, and these patients were found to have had recent travel to India or Pakistan. While there were no MDR *S. paratyphi A* strains, 60% of isolates tested were DCS. All strains were sensitive to ceftriaxone (Table 2).

Anaemia was present in the majority (74%) of children, with a median lowest haemoglobin level of 11.1 g/dL.

Table 1. Population Characteristics and Clinical Signs at Presentation

	Enteric Fever (n = 50)
Age in years	
Median	7.8
Interquartile range	(5.1 – 11.5)
Males, n (%)	30 (60.0)
Nationality, n (%)	
Singaporean	29 (58.0)
Indian	10 (20.0)
Indonesian	7 (14.0)
Bangladeshi	2 (4.0)
Nepalese	1 (2.0)
Pakistani	1 (2.0)
Positive travel history, n (%)	47 (94.0)
Country of travel	
India	29 (61.6)
Indonesia	13 (27.7)
Bangladesh	2 (4.1)
Nepal	1 (2.2)
Pakistan	1 (2.2)
Malaysia	1 (2.2)
Symptoms	
Headache	10 (20.0)
Lethargy	8 (16.0)
Anorexia/weight loss	18 (36.0)
Myalgia	4 (8.0)
Abdominal pain or discomfort	27 (54.0)
Vomiting	29 (58.0)
Diarrhoea	32 (64.0)
Constipation	2 (4.0)
Signs	
Tachycardia	24 (48.0)
Hypotension	3 (6.0)
Abdominal distension	6 (12.0)
Abdominal tenderness	20 (40.0)
Hepatomegaly	16 (32.0)
Splenomegaly	2 (4.0)

Table 2. Antibiotic Resistance and Other Investigations for Enteric Fever

	***S. typhi* (n = 43)**	***S. paratyphi* A (n = 7)**
Antibiotic resistance, n (%)		
Ampicillin	6 (14.0)	0
Sulfamethoxazole/trimethoprim	7 (16.3)	0
Ceftriaxone	0	0
MDR*	6 (14.0)	0
DCS†	18/29 (62.1)	3/5 (60.0)
MDR and DCS	5/29 (17.2)	0
Stool culture‡, n	43	7
Positive, n (%)	18 (41.9)	0
Serological (Widal and Weil-Felix test), n	37	6
Significant titres, n (%)		
O antigen titre >1/320	21 (48.8)	2 (28.6)
H antigen titre >1/320	31 (72.1)	5 (71.4)

DCS: Decreased ciprofloxacin susceptibility; MDR: Multi-drug resistant
*Ampicillin and sulfamethoxazole/trimethoprim resistance.
†Minimum inhibitory concentration (MIC) ≥0.125 mg/L.
‡Results for stool cultures taken before initiation of antibiotic treatment.

Patients with typhoid fever had lower haemoglobin levels than those with paratyphoid fever (P = 0.04). However, thrombocytopaenia and leucopaenia occurred in only 10% and 14% of patients, respectively, of which all were typhoid fever (Table 3). Although full blood count readings were done on all 50 patients, not all had inflammatory markers or liver function tests. Among the patients who did have values for ESR and CRP, all were raised, with median highest readings of 45 mm/hr (IQR: 21.5 to 70 mm/hr) and 94.8 mg/L (IQR: 53.4 to 173.8 mg/L) respectively. Raised liver transaminases were a feature in the majority (69.7%) of patients, with median highest alanine transaminase levels at 71.5 U/L (IQR: 40.3 to 100.8 U/L) and median highest aspartate transaminase levels at 85.5 U/L (IQR: 54.6 to 127.3 U/L).

All study cases received intravenous (IV) ceftriaxone once culture results were confirmed, at a median duration of 7 days (IQR: 5 to 10 days). The dosages of IV ceftriaxone ranged from 50 to 100 mg/kg/day. This was followed by a course of oral antibiotics, of which 82.5% were prescribed sulfamethoxazole/trimethoprim at dosages of between 8 to 12 mg/kg/day (trimethoprim) in 2 divided doses. The rest received azithromycin at 10 mg/kg/day (10%), ceftibuten at 10 mg/kg/day (7.5%), amoxicillin at 50 mg/kg/day (2.5%) or cefuroxime at 30 mg/kg/day (2.5%). The median duration of total antibiotics received (IV and oral) was 14 days (IQR: 14 to 16 days).

The median value for time to fever defervescence from initiation of appropriate antibiotic treatment was 5 days (IQR: 3 to 7 days). We observed that the time to fever defervescence did not differ significantly among children with typhoid or paratyphoid fever.

Depending on the clinical presentation and progress, some patients underwent imaging studies during their hospital stay. About half (48%) had ultrasound scans of the abdomen performed, while 8 (16%) underwent computed tomography (CT) scans of the abdomen. Indications for performing

Table 3. Haematological Parameters and Outcomes of Enteric Fever

	***S. typhi* (n = 43)**	***S. paratyphi A* (n = 7)**	***P* Value**
Haematological indices			
Anaemia: n, %	34 (79.1)	3 (42.9)	0.04
Lowest Hb (g/dL): median (IQR)	10.7 (10.0 – 12.0)	12.7 (12.0 – 13.7)	0.004
Thrombocytopaenia: n, %	5 (11.6)	-	-
Leucopaenia: n, %	7 (16.3)	-	-
Leucocytosis: n, %	2 (4.7)	-	-
Duration of treatment (days)	14	17	0.796
Median, IQR	(14 – 15)	(10 – 20)	
Time to fever defervescence (days)	5	5	0.642
Median, IQR	(3 – 7)	(3 – 5)	
Length of hospital stay (days)	8	10	0.516
Median, IQR	(7 – 9)	(6 – 11)	
Complicated cases (n)	6	1	0.895
Complications			
Ascites	3	1	
Enterocolitis	2	1	
Haemodynamic shock*	2	-	
Pleural/pericardial effusion	2	-	
Ileus	1	-	
Pyelonephritis	1	-	
Relapse (n)	1	0	0.655

IQR: Interquartile range; *S.*: *Salmonella enterica*

*Acute circulatory failure with hypotension.

the above studies included significant abdominal pain or distension, persistent fever, and uncertainty regarding the initial clinical diagnosis. Of the 7 patients with complications, only 1 was infected with paratyphoid fever. Table 3 lists the significant complications noted. The finding of pleural effusion was detected on abdominal ultrasound, while the pericardial effusion was seen on a 2-dimensional (2D) echocardiogram. Both did not require drainage. Urine culture performed for the child with pyelonephritis did not yield significant growth.

Repeat blood cultures to document clearance of infection were not routinely done. Criteria for discharge were mainly resolution of fever and stable clinical status. The median duration of hospital stay was 8 days (IQR: 7 to 10 days). In our study, there was no significant difference between the duration of hospital stay for typhoid versus paratyphoid fever.

Discharged patients were planned for follow-up in the outpatient clinic for a period of between 3 to 6 months. However, only 14% returned for follow-up. One child infected with a drug-susceptible strain of *S. typhi* was re-admitted for a relapse despite being discharged on resolution of initial fever. He had completed 5 days of IV ceftriaxone at a dose of 100 mg/kg/day followed by 7 days of oral sulfamethoxazole/trimethoprim at a dose of 8 mg/kg/day (trimethoprim). He presented to the children's emergency department a month later in view of recurrent fever. A repeat blood culture yielded *S. typhi* with the same sensitivity as previously documented. Abdominal ultrasound showed mild hepatosplenomegaly; no further work-up was done as he was otherwise well. He received an additional 7 days of IV ceftriaxone at 100 mg/kg/day followed by 7 days of oral sulfamethoxazole/trimethoprim at 8 mg/kg/day (trimethoprim). In this case, there was documented clearance on repeat blood and stool cultures after the relapse.

None of the children required intensive care and there were no cases of mortality from enteric fever in our study. On examination of their immunisation records, none were vaccinated against typhoid fever.

Discussion

Although enteric fever is more common in children, few studies focusing on the paediatric population have been done in Singapore. Singapore is a developed city-state where enteric fever is non-endemic. It is however, located in Southeast Asia, where enteric fever rates are among

the highest in the world.[24] A previous epidemiological study of enteric fever in Singapore by Ty et al (1990 to 2009) reported the incidence of indigenous enteric fever in Singapore as 0.26 per 100,000 in 2009.[25,26] This was comparable to that of Europe and North America. However, the disease burden was still significant as more than 90% of cases were imported.

In our study, we found that 94% of paediatric enteric fever cases were imported, mainly from India and Indonesia. Only 3 cases did not have any significant travel or contact history. These results are comparable to the findings by Ty et al, whereby the majority of cases were imported from India and Indonesia. A separate study of 121 patients in Singapore infected with *S. typhi* demonstrated that 17.4% were MDR strains.[27] The study reported that all patients from whom these strains were isolated had a history of recent travel to the Indian subcontinent. In our study, MDR *S. typhi* was detected in 14% of paediatric patients. Interestingly, all these patients had also recently travelled to India, Bangladesh or Pakistan. This echoes the conclusion that MDR typhoid fever in Singapore is mainly imported from countries in the Indian subcontinent.

Until the mid-1980s, ampicillin, chloramphenicol or sulfamethoxazole/trimethoprim was the standard treatment for enteric fever.[28] Due to the emergence of MDR strains, ciprofloxacin was recommended as an alternative antibiotic in 1990.[29,30] However, nalidixic acid-resistant strains with DCS started to emerge in the literature in 1992, and these were found to be associated with treatment failure.[31,32] In our study, DCS was observed in a majority of *S. typhi* isolates tested; however, all strains were sensitive to ceftriaxone.

In our institution, the recommended first-line empirical antibiotic for suspected enteric fever is IV ceftriaxone at a dose of 80 to 100 mg/kg/day. A similar regimen of initial IV ceftriaxone therapy followed by oral therapy once there is adequate clinical response is also recommended by the Department of Health and Human Services of Victoria, Australia.[33] Although this is a recommendation for the adult population, we have adapted it for use in our institution. To date, this has been our practice for years and our study has demonstrated only 1 case of relapse (2%) in this 6-year period.

In terms of clinical presentation, persistent fever was a feature in all our paediatric cases despite some patients having been pretreated with oral antibiotics from primary care physicians. Abdominal symptoms and signs were also seen in 92% of patients. Thus, enteric fever should be considered as a differential diagnosis in children with unexplained or prolonged fever, in association with any abdominal complaints, especially in the presence of positive travel history.

Typical haematological and biochemical manifestations reported in enteric fever include pancytopaenia, raised acute inflammatory markers[34,35] and raised liver transaminases.[36] Our study has demonstrated that anaemia is a significant feature of paediatric enteric fever, particularly in cases of *S. typhi* infection. In addition, raised inflammatory markers were seen in all patients who had these tests done. The majority had isolated raised liver transaminases as well. Although non-specific, when analysed as a whole together with the relevant clinical presentation, these findings may aid in a decision to treat empirically for enteric fever while awaiting confirmatory cultures.

Despite inpatient treatment with appropriate antibiotics at recommended doses, our study has shown that morbidity is substantial as significant complications arose among the affected paediatric population. Thus, it is important that primary disease prevention in the form of immunisation is emphasised. In our analysis, none of the 47 affected patients who travelled to typhoid-endemic countries received immunisation against typhoid fever.[37] This occurred despite the World Health Organisation (WHO) specifically recommending typhoid fever vaccination for those travelling to destinations where the risk of typhoid fever is high.[38] Of the 2 typhoid vaccines with demonstrated safety and efficacy available on the market, the injectable vaccine is licensed for individuals aged above 2 years, with a protective efficacy 1.5 years after vaccination of about 72%.

A review of 580 cases of vaccine-preventable diseases among returned international travellers by the GeoSentinel Surveillance Network (1997 to 2007) reported that confirmed or probable enteric fever was the most common disease acquired.[39] Yet immunisation against typhoid disease was not routinely practised for individuals who travelled to typhoid-endemic countries. These findings are likely contributed by the fact that a significant number of travellers may have been visiting friends and/or relatives in these countries which they consider to be their home, and would not have visited travel clinics. Therefore, while primary prevention in the form of typhoid vaccination for travellers to typhoid-endemic countries needs to be strongly emphasised,[40] education on food and water hygiene should not be neglected.

To date, this is the first study on paediatric enteric fever in Singapore. Our study was purely observational in nature, and one limitation was that we only included patients with blood culture positivity in our analysis, potentially missing culture negative cases treated for possible enteric fever.

Conclusion

Although Singapore has low rates of indigenous enteric fever, additional imported cases contributed to an average of

10 cases of paediatric enteric fever per year in our hospital. Through advocating for routine vaccination of children above 2 years prior to travel to typhoid-endemic areas as well as emphasising on the education of food and water hygiene, we hope to reduce the prevalence of imported enteric fever in Singapore.

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Original Article

Evaluation of Efficacy of Chloroquine for *Plasmodium Vivax* Infection Using Parasite Clearance Times: A 10-Year Study and Systematic Review

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Abstract

Introduction: Chloroquine, in combination with primaquine, is used as the firstline treatment for uncomplicated *P. vivax* malaria in Thailand. In view of the declining efficacy of chloroquine in many *P. vivax* endemic areas, the possibility of emergence of chloroquine-resistant *P. vivax* in Thailand is a concern. The aim of this study was to assess the trends in therapeutic efficacy of chloroquine and primaquine for the treatment of uncomplicated *P. vivax* malaria and to assess the utility of parasite clearance times as a measure of efficacy. Materials and Methods: This study consisted of: 1) review of medical records of patients who were hospitalised for a period during their treatment for uncomplicated *P. vivax* malaria at the Hospital for Tropical Diseases, Bangkok, Thailand between 2004 and 2013. Treatment consisted of chloroquine (1500 mg base administered over 3 days) or chloroquine (as before) plus primaquine (15 to 30 mg base/daily for 14 days from day 2); and 2) systematic review of the literature in English to assess current standards in the reporting of parasite clearance times. Results: The 28-day cure rate was 99.1%. The range of median parasite clearance time over the 10-year period was 46 to 59 hours, and there was statistical evidence for an increasing trend in parasite clearance times between 2009 and 2013. Heterogeneity was noted among previous chloroquine efficacy studies in the measurement and reporting of parasite clearance. Conclusion: The treatment of *P. vivax* infection with a combination of chloroquine and primaquine has remained efficacious in Thailand. Increasing rates of parasite clearance in a population over time may be a useful early warning mechanism for the emergence of chloroquine resistance. The utility of monitoring time-trends in parasite clearance to detect resistance may be enhanced if parasite clearance measurements are standardised.

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Key words: *Vivax* malaria, Parasite clearance rates, Chloroquine resistance, Time-trends

Introduction

Malaria is a major public health problem, causing an estimated 655,000 deaths worldwide in 2010.[1] It is a protozoan disease which occurs throughout the tropical regions of the world and is caused by the genus *Plasmodium* and is transmitted by *Anopheles* mosquitoes. Five species of the genus *Plasmodium* cause all malarial infections in human beings: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*.[1] *P. vivax* is currently endemic in about 50 countries. It is estimated that 2.6 billion people worldwide live at risk of infection by *P. vivax*, of whom between 72 and 390 million are estimated to become infected each year.[2] For many centuries, vivax malaria has been referred to as "benign tertian fever" because of its fever periodicity and because it was considered to be rarely severe or fatal.[3] However, case reports have shown that *P. vivax* infection may cause severe complications and may occasionally be associated with fatal outcomes. Complications of vivax malaria reported in the literature include severe anaemia and thrombocytopaenia, acute respiratory distress syndrome, acute renal failure, and splenic rupture.[4,5] *P. vivax* infection during pregnancy is associated with maternal anaemia, low birth weight, and increased risk of miscarriage.[6] Infections in young children may be associated with malnutrition and may have adverse consequences for education and development.[7] Thus, the disease may cause substantial morbidity and socioeconomic disruption in endemic regions.

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Since *P. vivax* may exist in a dormant form in the liver as hypnozoites which may reactivate to cause relapses of infection weeks to months after the initial attack, treatment of *P. vivax* ideally involves the administration of a schizonticidal drug such as chloroquine in combination with a hypnozoiticidal agent. The only licensed hypnozoiticidal agent currently available is primaquine.[2,8] The goal of treatment of malaria is to cure the infection rapidly and reliably, and early diagnosis and effective treatment significantly lowers the risk of progression to severe disease and the morbidity and costs associated with treatment failure.[7] The combination of chloroquine and primaquine is highly effective against both the acute illness and in prevention of relapses in the treatment of chloroquine-sensitive *P. vivax* infections.[7] However, the efficacy of chloroquine against *P. vivax* varies in different countries. In Papua New Guinea and parts of Indonesia, treatment failure rates greater than 20% have been recorded, and there have been reports of lower level resistance to *P. vivax* in various countries, including Cambodia, Ethiopia, Madagascar and in South America.[7,9]

Resistance to antimalarial drugs is a major impediment to the effective treatment and control of malaria. It is therefore important to implement effective surveillance systems to detect emerging resistance of *P. vivax* against chloroquine. In view of the declining efficacy of chloroquine in many *P. vivax* endemic areas, the possibility of the emergence of chloroquine-resistant *P. vivax* in Thailand is a concern. Previous studies have generally shown that chloroquine is effective for the treatment of *P. vivax* malaria in Thailand,[9] but there have been no studies demonstrating the trends in treatment efficacy over time. Variation in reporting of parasite clearance was also noted in a preliminary review of the literature.

This study has 2 components: a clinical study and a systematic review. The primary objectives of the clinical component were to investigate the trends in parasite clearance time (PCT) in patients treated for uncomplicated *P. vivax* malaria with chloroquine and primaquine at the Hospital for Tropical Diseases, Bangkok, Thailand between 2004 and 2013, and to determine the proportion of treatment failures in each year of the study period. The secondary objective was to assess trends in fever clearance time (FCT) over the 10-year period. The objective of the systematic review was to assess standards in the scientific literature for the measurement, reporting and interpretation of PCTs in the treatment of uncomplicated *P. vivax* malaria with chloroquine.

Materials and Methods

Clinical Study

The study population consisted of patients diagnosed with uncomplicated *P. vivax* malaria from 2004 to 2013 and who were treated with chloroquine only or chloroquine in combination with primaquine. Data were obtained from medical records of these patients. The inclusion criteria were: i) age ≥15 years at time of diagnosis, ii) mono-infection with *P. vivax* diagnosed by microscopy, and iii) completion of 28-day follow-up period. The exclusion criteria were: i) mixed infection diagnosed by microscopy (i.e. *P. vivax* and another *Plasmodium* species), ii) severe malaria (based on the World Health Organisation (WHO) criteria for severe malaria[10]), and iii) *P. vivax* in pregnancy.

Patients diagnosed with *P. vivax* malaria were admitted to hospital and treated with chloroquine 1500 mg base in divided doses over 3 days, either as monotherapy or in combination with primaquine which was started on day 2. Most patients were administered a primaquine regimen of 15 to 30 mg base/day for 14 days; a few patients with G6PD deficiency received an alternative regimen of 45 mg base/week for 8 weeks. Treatment administered in the hospital was supervised. Patients were monitored for clinical and parasitological responses, and were discharged if they were clinically well and blood smears were negative. Temperature was obtained from the oral site and was measured 4 hourly. At the time of discharge from hospital, patients were advised to complete the course of primaquine treatment, and were scheduled for follow-up visits on days 7, 14 and 28. At each visit, patients were examined clinically and thin and thick blood smears were obtained to check for parasitaemia.

Thick and thin blood films were prepared from a capillary blood sample using Giemsa's stain, and examined under a light microscope at 1000X magnification. Microscopic examination was performed every 12 hours until blood smears were negative for parasites. The number of parasites were counted for every 200 white blood cells and for every 1000 red blood cells in the thick and thin blood film respectively.

Treatment failure was defined according to WHO guidelines.[10] The categories of treatment failure include i) early treatment failure (ETF), ii) late clinical failure (LCF), iii) late parasitological failure (LPF), and iv) adequate clinical and parasitological response (ACPR) (Table 1). PCT was defined as the time interval (in hours) from the start of treatment until the first negative blood smear for parasites, and remained negative for the subsequent 24 hours. FCT was defined as the time (in hours) from the start of treatment until the oral temperature decreased to <37.5°C and remained so for at least 48 hours. Time 0 was defined as the time treatment was initiated. Day 0 represented the first 24 hours after treatment was started.

Table 1. WHO Classification of Treatment Outcomes*

Early treatment failure (ETF)	a) Danger signs or severe malaria on day 1, 2 or 3 in the presence of parasitaemia; or b) Parasitaemia on day 2 higher than on day 0, irrespective of axillary temperature; or c) Parasitaemia on day 3 with axillary temperature ≥37.5°C; or d) Parasitaemia on day 3 ≥25% of count on day 0.
Late clinical failure (LCF)	a) Danger signs or severe malaria in the presence of parasitaemia on any day between day 4 and day 28 in patients who did not previously meet any of the criteria of early treatment failure; or b) Presence of parasitaemia on any day between day 4 and day 28 with axillary temperature ≥37.5°C in patients who did not previously meet any of the criteria of early treatment failure.
Late parasitological failure (LPF)	The presence of parasitaemia on any day between day 7 and day 28 and axillary temperature <37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.
Adequate clinical and parasitological response (ACPR)	The absence of parasitaemia on day 28, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure.

*Source: Methods of surveillance of antimalarial drug efficacy. World Health Organisation 2009.

Data were entered from medical records onto a standard template. SPSS version 15.0 was used for data management and analysis. Data were summarised using mean or median values for continuous data, and percentages for categorical data. Continuous data were assessed for normality by Shapiro-Wilk test and by inspection of frequency distribution plots. Differences in mean or median values between each time interval for each variable were assessed using ANOVA or the Kruskal-Wallis test. General linear modelling was used to assess for differences and trends in PCT and FCT. The a priori level of statistical significance was taken as <0.05. In posthoc analyses of significant results, the Type 1 error was adjusted using the Bonferroni approach. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

Systematic Review

A database of antimalarial clinical efficacy trials, consisting of 1157 studies published between 1960 and 2013, is available online at the Worldwide Antimalarial Resistance Network (WWARN).[11] We filtered this database for all studies on *P. vivax*. We also searched MEDLINE, Scopus, and Web of Science databases using the search terms 'Vivax' in combination with each of the search terms 'Efficacy', 'Resistance', 'Clearance' 'Chloroquine', and 'Primaquine', for studies published between 1 January 2013 and 30 July 2015. The reference lists of some publications were also screened for relevant studies. The inclusion criterion was any single-arm or comparative clinical study published in English that assessed the in-vivo efficacy of chloroquine alone or chloroquine in combination with primaquine for the treatment of *P. vivax* mono-infection. This included studies on *P. vivax* relapses and in-vitro studies which also presented results of the schizonticidal phase of treatment. Exclusion criteria included: i) study participants with mixed *Plasmodium* infections, ii) study participants who were treated with chloroquine in combination with another antimalarial drug other than primaquine, iii) studies of patients with *Plasmodium* infections in which the clinical data were not presented separately for each *Plasmodium* species, and iv) studies that limited the study population to pregnant women or children <15 years of age. Information extracted from these studies included the date of publication, study site, study duration, treatment regimen, inclusion criteria, sample size, follow-up period, technique of microscopy, timing of microscopic examination, time for resolution of parasitaemia, and the treatment success rate. The data were directly extracted from the full-length articles to a standard template containing all the relevant variables and outcomes. EndNote X7 was used to manage, deduplicate and screen article references for eligibility.

Results

Clinical Study

This study included data from 335 patients who were diagnosed with uncomplicated *P. vivax* malaria during the period 2004 to 2013, all of whom completed 28-days of follow-up. A total of 332 patients were treated with a combination of chloroquine and primaquine and 3 patients were treated with chloroquine only. There were 21 patients who defaulted follow-up before the 28-day period (5 patients in 2009, 11 patients in 2010 and 5 patients in 2011) and were excluded from the data analysis. There were relatively few eligible patients in 2004, 2005, and 2007 (11, 8 and 11 patients respectively); therefore, the data from years 2004 to 2007 were combined and analysed as one group. The majority of patients were Myanmar nationals (68.9%). Other nationalities/ethnic groups represented in the study included Karen (10.8%), Thai (10.3%), Mon (4.3%), Laos (3.4%) and Cambodia (2.3%).

Table 2 shows baseline characteristics of the study population. Information on G6PD status was not available

Table 2. Baseline Characteristics of Study Population

	2004 – 2007	2008	2009	2010	2011	2012	2013
Number of patients, n	64	46	30	46	53	45	51
Age (years)*	22 (15 – 50)	23 (15 – 45)	23 (15 – 45)	25.5 (16 – 55)	24.5 (14 – 60)	27 (16 – 76)	23 (15 – 64)
Male gender (%)	62.5	100	100	95.7	100	82.2	90.3
Height (cm)*	161 (139 – 182)	161 (151 – 174)	163 (149 – 172)	164 (153 – 176)	163 (142 – 181)	162 (141 – 176)	163 (135 – 178)
Weight (kg)*	52.0 (35 – 85)	53.0 (38 – 82)	51.5 (37 – 71)	52.8 (44 – 71)	55.0 (43 – 70)	54.0 (40 – 90)	55.6 (43 – 94)
Body surface area (m^2)†	1.54 (0.15)	1.56 (0.11)	1.54 (0.12)	1.57 (0.09)	1.58 (0.10)	1.59 (0.17)	1.62 (0.16)
G6PD deficiency‡	1/64 (1.6)	8/46 (17.4)	4/30(13.3)	2/45 (4.4)	4/52 (7.7)	5/39 (12.8)	3/49 (6.1)
Other medical history‡	0	0	0	1 (2.2)	2 (3.8)	3 (6.7)	1 (2.0)
Concurrent antibiotic treatment‡	6 (9.4)	1 (2.2)	2 (6.7)	3 (6.5)	3 (5.7)	0	1 (2.0)
Haemoglobin (g/dL)*	12.6 (6.3 – 17.3)	12.9 (11.2 – 17.4)	13.4 (6.8 – 15.8)	12.8 (8.0 – 15.3)	13.0 (8.1 – 17.5)	12.2 (6.5 – 16.7)	13.0 (8.2 – 15.9)
Total white cell count ($/mm^3$)*	6.5 (2.1 – 13.7)	6.3 (3.2 – 10.8)	6.0 (2.3 – 17.5)	6.3 (2.6 – 10.0)	6.1 (2.6 – 10.9)	6.5 (3.1 – 10.9)	5.3 (3.0 – 10.2)
Platelet count ($/mm^3$)*	158 (25 – 568)	85 (26 – 198)	110 (30 – 267)	105 (17 – 459)	101 (12.5 – 516)	124 (33 – 542)	88 (35 – 320)

*Data represent median values (range).

†Body surface area (BSA) was calculated using Dubois formula (BSA = $height^{0.725}$ x $weight^{0.425}$ x 0.007184). Data represent mean values (standard deviation).

‡Data represent number of patients (%).

in 11 patients. Height measurements and information on nationality were missing in 6 and 3 patient records, respectively. For the other variables, the data were either complete or there was 1 missing data point over the 10-year period. Normality testing showed that most of the variables, except temperature on day 0 and body surface area, had a non-normal distribution. The median age for each time interval was between 22 to 27 years. Overall, males comprised 87.5% of patients. Most patients were otherwise healthy; only 7 patients were noted to have underlying medical conditions.

The temperature and parasitaemia levels before initiation of treatment and the temperature and parasitological responses to treatment are shown at Tables 3 and 4 respectively. The range of median PCT was between 46 and 59 hours and the range of median FCT was between 14 and 28 hours. The FCT was ≥100 hours in 8 patients, including 2 patients with FCT ≥200 hours. Co-infection was present in 3 patients (2 patients with dengue and 1 with enteric fever), including both patients with a FCT ≥200 hours, and 1 patient with a FCT of 126 hours.

Sixteen patients were also treated with antibiotics for intercurrent illnesses during the admission period. Antibiotics that were used included ceftriaxone (2 patients), amoxicillin (5 patients), cloxacillin (4 patients), metronidazole (2 patients), ciprofloxacin (1 patient), ofloxacin (1 patient), and azithromycin (1 patient). The median PCT of patients on antibiotics was 55.5 hours

Table 3. Temperature and Parasitaemia Levels before Initiation of Treatment

	2004 – 2007	2008	2009	2010	2011	2012	2013
Number of patients, n	64	46	30	46	53	45	51
Mean temperature on D0 (°C) (standard deviation)	38.5 (1.0)	38.6 (1.1)	38.2 (0.9)	38.2 (0.8)	38.5 (1.0)	38.5 (0.9)	38.4 (1.0)
Geometric mean asexual parasitaemia on D0 (/μL) [range]	7922 [150 – 115000]	6334 [98 – 58320]	7719 [162 – 101640]	6187 [129 – 55080]	11481 [132 – 90800]	7747 [150 – 70980]	5860 [150 – 38290]
Presence of gametocytes on D0, number (%)	16 (25.0)	22 (47.8)	9 (30.0)	20 (43.5)	19 (35.8)	15 (33.3)	10 (19.6)
Geometric mean gametocytaemia on D0 (/μL) [range]	16.79 [0 – 297]	53.49 [0 – 756]	50.3 [0 – 570]	46.0 [0 – 360]	53.0 [0 – 1068]	45.0 [0 – 788]	51.0 [0 – 488]

D0: Day 0

Table 4. Temperature and Parasitological Responses to Treatment

	2004 – 2007	2008	2009	2010	2011	2012	2013
Number of patients with asexual parasitaemia (%)							
Day 0	64 (100)	46 (100)	30 (100)	46 (100)	53 (100)	45 (100)	51 (100)
Day 1	60 (93.8)	41 (89.1)	23 (76.7)	36 (78.3)	41 (77.4)	37 (82.2)	43 (84.3)
Day 2	28 (43.8)	13 (28.3)	6 (20.0)	8 (17.4)	23 (43.4)	17 (37.8)	23 (45.1)
Day 3	6 (9.4)	1 (2.2)	0	1 (2.2)	4 (7.5)	1 (2.2)	6 (11.8)
Day 4	2 (3.1)	1 (2.2)	0	0	1 (1.9)	0	1 (2.0)
Day 5	0	0	0	0	0	0	0
Number of patients with gametocytaemia (%)							
Day 0	16 (25.0)	22 (47.8)	9 (30)	20 (43.5)	19 (35.8)	15 (33.3)	10 (19.6)
Day 1	3 (4.7)	6 (13.0)	2 (6.7)	5 (10.9)	7 (13.2)	5 (11.1)	4 (7.8)
Day 2	0	1 (2.2)	0	1 (2.2)	1 (1.9)	1 (2.2)	1 (2.0)
Day 3	0	0	0	0	0	0	0
Median parasite clearance time (hours) [range]	58.0 [30 – 123]	57.0 [33 – 118]	46.0 [21 – 82]	51.5 [27 – 100]	59.0 [22 – 135]	57.0 [12 – 172]	53.0 [24 – 160]
Median fever clearance time (hours) [range]	28 [0 – 126]	14 [0 – 52]	18 [0 – 36]	22 [0 – 264]	26 [0 – 144]	24 [0 – 72]	28 [0 – 200]

(range: 33 to 133 hours), which was similar to the median PCT of 56 hours (range: 12 to 172 hours) of the entire study population. The median FCT of patients on antibiotics and of the study population was 30 hours (range: 0 to 264 hours) and 24 hours (range: 0 to 264 hours) respectively. There was no significant difference in median PCT of patients who received 15 mg base of primaquine per day (n = 182) compared to those who received 30 mg base per day (n = 145) ($P = 0.122$).

In the univariate analysis, the differences in median PCT between each time interval were marginally non-significant ($P = 0.051$). The differences in median FCT values were not statistically significant ($P = 0.067$). Among the baseline demographic and clinical data, the differences in median platelet counts were statistically significant (χ^2: 18.81, $P = 0.004$). Posthoc pairwise comparisons showed that the difference in the median platelet count between 2004 to 2007 and 2008 and between 2004 to 2007 and 2013 were significant ($P = 0.001$). There were no significant differences between time intervals in age, weight, height, body surface area, haemoglobin, haematocrit, white blood cell count, temperature on day 0, asexual parasitaemia on day 0 and gametocytaemia on day 0.

The influence of potential confounding variables on PCT and FCT values was assessed by ANCOVA testing. In view of the non-normal distributions of PCT and FCT, outliers were identified using the outlier labelling rule and removed from the dataset for the purpose of this analysis. In these modified datasets, 6 subjects with PCT >130 hours (1 in 2011, 4 in 2012, and 1 in 2013) and 8 subjects with FCT >90 hours (4 in 2004 to 2007, 2 in 2010, 1 in 2011 and 1 in 2013) were excluded from the PCT and FCT analysis, respectively. In both analyses, the year of diagnosis was entered as the factor variable, and age, body surface area, haemoglobin, white blood cell count, platelet count, asexual parasitaemia on day 0 and gametocytaemia on day 0 were entered as covariates. In the analysis of FCT, temperature on day 0 was entered as an additional covariate. The differences in adjusted mean PCT values between year of diagnosis were statistically significant ($F = 4.047$, $P = 0.001$, partial eta-squared = 0.073). Posthoc comparisons showed significant differences in adjusted mean PCT values between 2004 to 2007 and 2009 ($P < 0.001$), and between 2009 and 2013 ($P = 0.001$). The differences in adjusted mean values of FCT between time intervals were not significant ($F = 1.778$, $P = 0.103$, partial eta-squared = 0.034).

The plots of adjusted mean values of PCT and FCT appear to show a decreasing trend in PCT and FCT between 2004 and 2009, and an increasing trend from 2009 onwards (Figs. 1 and 2). To further assess the possibility of a linear time-trend in PCT and FCT, we also fitted linear regression models on the modified datasets using PCT and FCT as the response variable. The independent variables in both models included the year of diagnosis, gender, and the covariates used in the ANCOVA analysis. When the analyses were limited to data from 2009 and subsequent years only, there was a statistically significant linear relationship between PCT and year of diagnosis ($\beta = 2.340$, $P = 0.013$, adjusted

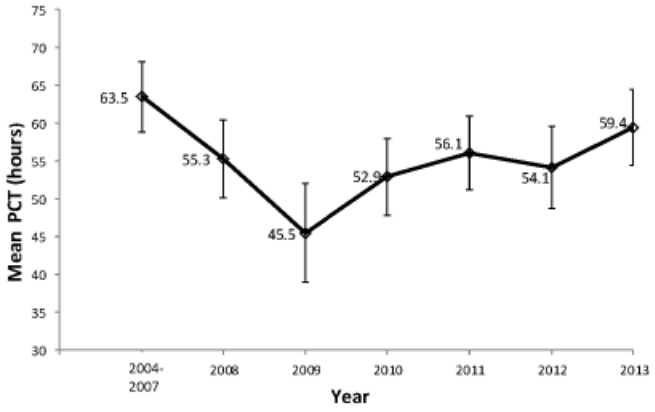

Fig. 1. Graph showing time-trends in adjusted mean parasite clearance time. PCT: Parasite clearance time. Data labels represent the adjusted mean PCT values for each time interval. Vertical bars represent the confidence interval for each adjusted mean value.

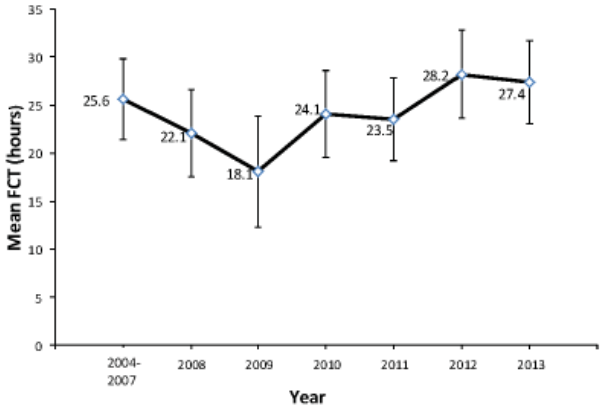

Fig. 2. Graph showing time-trends in adjusted mean fever clearance time. FCT: Fever clearance time. Data labels represent the adjusted mean FCT values for each time interval. Vertical bars represent the confidence interval for each adjusted mean value.

$R^2 = 0.164$), but no linear relationship between FCT and year of diagnosis ($\beta = 1.440$, $P = 0.072$, adjusted $R^2 = 0.312$).

A total of 332 patients (99.1%) showed an ACPR. There were 3 patients who had parasitaemia on day 3 together with temperature ≥37.5˚C (1 case each in 2004 to 2007, 2011 and 2013); thus, these patients met the WHO criteria for early treatment failure. All 3 patients received primaquine in addition to chloroquine. There were 16 other patients with parasitaemia on day 3, and 5 patients with parasitaemia on day 4; however, these patients were afebrile at that time and therefore did not meet the criteria for early treatment failure or late clinical failure. All patients with parasitaemia on and beyond day 3 responded well clinically and did not receive any additional treatment.

Systematic Review

Through review of study abstracts, 152 articles were selected for full-text retrieval (Fig. 3). Seven full-text articles were not available. Among 104 studies that met the inclusion criteria, a point estimate of parasite clearance was presented in hours in 26 studies, and in days in 6 studies. In 44 studies, there were other descriptions of parasite clearance, e.g. the proportion of patients who had cleared parasitaemia or failed to clear parasitaemia by a particular day. In 2 of the 26 studies which expressed PCT in hours, chloroquine was administered as a single dose of 300 mg or 450 mg,[12] and a weekly dose of 300 mg for 8 weeks.[13] In the other 24 studies, a standard regimen of chloroquine was administered in divided doses over 48 to 72 hours at a total dose of ≥1500 mg base or a total dose of 25 mg base/kg bodyweight. Table 5 shows some study parameters and results from these 24 studies.[14-37] There was variation in study design, including the sample size, parasite density on enrolment, primaquine regimen and the technique and timing of microscopy. Primaquine was administered concurrently with chloroquine in 4 studies,[18,21,29,34] and was commenced on completion of chloroquine or later in the follow-up period in 12 studies.[15-17,19-20,22,26,28,30-33] Parasite counts were initially obtained 6-hourly in 4 studies,[20,24,29,34] and 8-hourly in 4 studies.[27-28,35-36] In the remaining studies, parasite counts were obtained every 12 hours or less frequently. Both thick and thin films were used to assess for parasitaemia in 15 studies.[15-22,25-26,29,30,33-34,36] In 4 studies, thick blood films only were used,[27,32,35,37] and in 5 studies, the technique of microscopy was not specified.[14,23-24,28,31] In studies which defined PCT, the beginning of the interval was most commonly defined as the time from initiation of treatment.[15-16,18-20,22,25,27,31,35] The endpoint of the interval was defined as the time for blood films to become negative or to fall below the level of microscopic detection, and 4 studies also specified that blood films should remain negative for at least 24 hours.[19,22,27,31] Among these 24 studies, the mean and median values of PCT varied from 36.7 to 70 hours and 20 to 32 hours respectively. Eighteen of these 24 studies also reported a mean or median FCT in hours.[14-16,18-20,22,24,27,29-37]

There was similar heterogeneity in studies that reported other measures of parasite clearance. Overall, 73% (76/104) of studies provided some measure of parasite clearance; however, with the exception of a few studies that used parasite clearance measurements to assess the relative efficacies of different antimalarial regimens or treatment groups,[15-16,20,22] these measurements were not used to interpret the efficacy of the treatment regimen. The 28-day cure rate was the primary measure of efficacy. We did not identify any studies that assessed time-trends in parasite clearance.

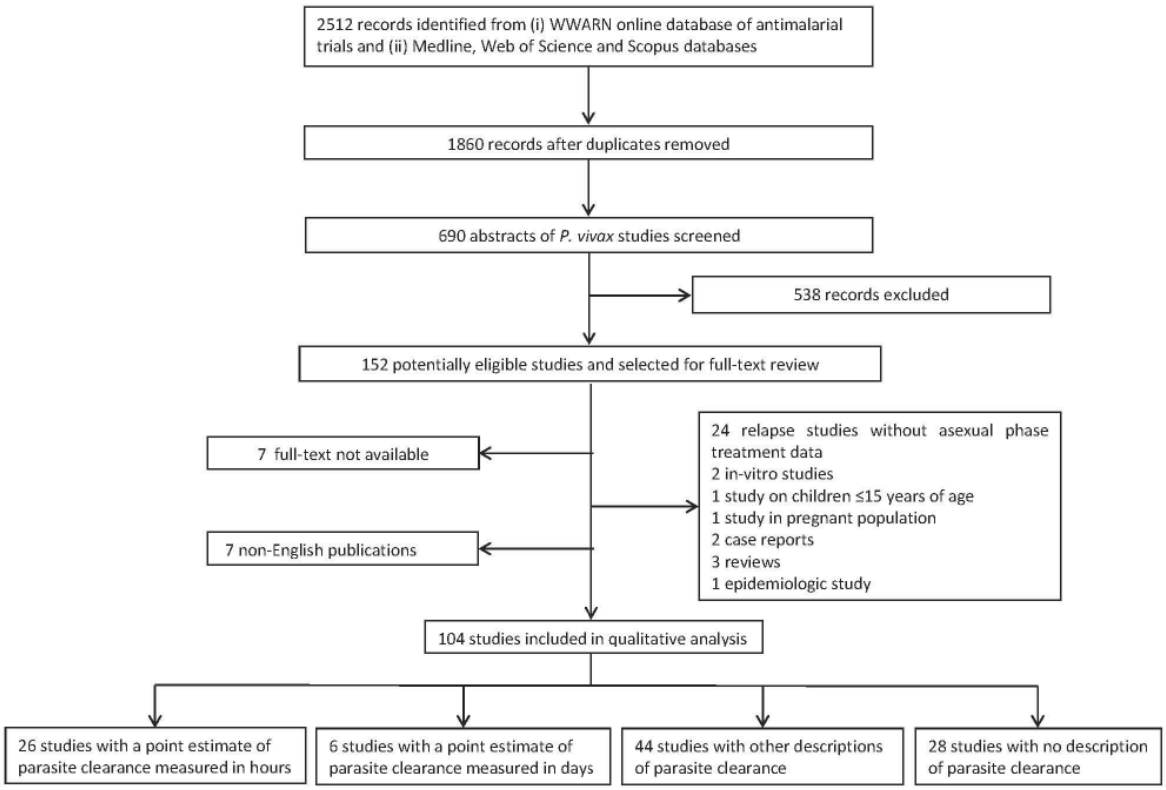

Fig. 3. Chart showing the systematic review search strategy and results.

Discussion

Of the total 335 patients, 332 (99.1%) showed an ACPR. Thus, the treatment of *P. vivax* infection with a combination of chloroquine and primaquine has remained efficacious over the study period. These findings are consistent with other studies on the in-vivo efficacy of chloroquine for treatment of *P. vivax* infection in Thailand.[19,29-31,34,38-40] There were 16 patients on antibiotics concurrently with antimalarial treatment but, with the exception of azithromycin, these antibiotics are not known to have any antimalarial effects and would not have influenced the rate of parasite clearance. The range of median PCT in our study was 46 to 59 hours. Previous studies of chloroquine treatment for *P. vivax* have recorded PCT values ranging from 20 to 70 hours. However, there was heterogeneity among these studies in study parameters which may influence the rate of parasite clearance, and significant variation in the reporting of parasite clearance. In view of this heterogeneity, we did not consider it meaningful to perform a meta-analysis of PCT from previously published studies. Since almost all patients in our study showed an adequate clinical and parasitological response, the PCT values obtained in this study may provide a reasonably valid interval estimate of the expected median PCT values in a population where *P. vivax* retains susceptibility to chloroquine.

The most commonly used measure of parasite clearance in the literature is the cumulative proportion of patients who are aparasitaemic or who have failed to clear parasitaemia by a particular day. This information is also provided in Table 3 which shows that for each time interval, >96% of patients were aparasitaemic at the end of day 4, and all patients were aparasitaemic by day 5. However, this provides little information about the initial changes in parasitaemia, and in some patients, especially those with high initial parasitaemia, low numbers of parasites may persist for several days.[41]

There are some potential limitations to this study. First, the quality of information collected was reliant on the accuracy and completeness of information in patients' medical records. Second, there were only 11, 8 and 11 eligible patients in 2004, 2005 and 2007 respectively. In order to avoid any possible biases resulting from the small number of patients, the data from 2004 to 2007 were combined and analysed as a single group. Since the primary aim of this study was to assess trends in PCT and therapeutic efficacy over a 10-year period, combining the data from the earlier years would likely not have distorted the conclusions of the study. Third, information on adverse events to drug treatment was not available from the medical records. There were records of symptoms experienced by patients during hospital

Table 5. Data from Studies that Reported Parasite Clearance as a Point Estimate in Hours

Study	Treatment Groups*	Sample Size†	Initial Parasitaemia‡ (/µL Blood)	Microscopy	Parasite Clearance Time		
					Mean/Median Value	Point Estimate (Hours)	Interval Estimate (Hours)
Dixon (1985)[14]	CQ only	11	<100,000	12 hourly	Mean	48	SD: 20
	CQ + PQ	14				50	SD: 19
Pukrittayakamee (1994)[15]	CQ +PQ	30	NS	12 hourly	Mean	62	SD: 22
Pukrittayakamee (1994)[16]	CQ only	30	NS	12 hourly	Mean	55 – 60§	-
	CQ + PQ	25				55 – 60§	-
Tan-ariya (1995)[17]	CQ + PQ	57	Any level	Once daily	Mean	48	SD: 15
Fryauff (1997)[18]	CQ + PQ	27	0.001% – 0.1%	NS	Mean	53	R: 24 – 120
Looareesuwan (1999)[19]	CQ only	445	NS	12 hourly	Mean	61.3	SD: 20.2
	CQ + PQ	441				59.1	SD: 17.1
Pukrittayakamee (2000)[20]	CQ only	30	NS	6 hourly	Mean	65	SD: 18
	CQ + PQ	30				64	SD: 22
Villalobos-Salcedo (2000)[21]	CQ + PQ	39	>100	Once daily	Mean	56.2	SD: 20.1
	CQ + short PQ regimen	40				59.0	SD: 20.4
Buchachart (2001)[22]	CQ + PQ (G6PD +ve)	342	NS	12 hourly	Mean	59.4	SD: 17.5
	CQ + PQ (G6PD –ve)	22				59.8	SD: 15.0
Soto (2001)[23]	CQ only	28	500 – 25,000	12 hourly	Mean	70	NR
Congpuong 2002)[24]	CQ + PQ	26	NS	6 hourly	Mean	49	R: 18 – 72
Fryauff (2002)[25]	CQ only	62	NS	Once daily	Mean	36.7	95% CI: +/-5.6
Hamedi (2002)[26]	CQ + PQ	40	2000 – 35,000	Once daily	Mean	67.2	SD: 22.5
Phan (2002)[27]	CQ + PQ	113	Any level	8 hourly	Median	24	R: 8 – 64
Dunne (2005)[28]	CQ + PQ	102	≤100,000	8 hourly	Median	20	NR
Tasanor (2006)[29]	CQ + PQ	31	1000 – 22000	6 hourly	Median	30	95% CI: 12 – 48
Krudsood (2006)[30]	CQ + PQ	71	Any level	12 hourly	Mean	43.68	SD: 17.29
Krudsood (2007)[31]	CQ + PQ	51	Any level	12 hourly	Mean	55.8	R: 23 – 106
Nateghpour (2007)[32]	CQ +PQ	195	250 – 100,000	Once daily	Mean	63.5	SD: 15.84
Yeshiwondim (2010)[33]	CQ only	145	≥250	Once daily	Mean	48.34	SD: 17.68
	CQ + PQ	145				50.67	SD: 15.70
Muhamad (2011)[34]	CQ + PQ	130	1000 – 100,000	6 hourly	Median	24	95% CI: 12 – 40
Poravuth (2011)[35]	CQ only	228	≥250/µL	8 hourly	Median	32	R: 7.5 – 63.9
Liu (2013)[36]	CQ + PQ	128	400 – 100,000	8 hourly	Mean	37.4	SD: 11.9
Liu (2014)[37]	CQ only	750	50 – 120,000	12 hourly	NR	38.1	± 12.6 hours

CI: Confidence interval; CQ: Chloroquine, NS: Not specified; NR: Not recorded; PQ: Primaquine; R: Range; SD: Standard deviation
*In all studies, chloroquine was administered as a total dose of 25 mg base/kg or a total dose of ≥1500 mg base over 2 – 3 days.
†In studies that compared a chloroquine regimen with a non-chloroquine regimen, sample size refers to size of the chloroquine treatment arm.
‡Parasite density enrolment criterion.
§Data were presented in graphical form.

admission, but it was not possible to ascertain whether these symptoms were drug-related or a consequence of the malarial infection. However, there were no occurrences of severe drug reactions which required discontinuation of treatment or switching to an alternative drug regimen. Fourth, information on PCT and treatment outcomes was not available for 21 patients who did not complete 28 days of follow-up (11 patients in 2010, and 5 patients in each of the years 2009 and 2011). A sensitivity analysis showed that the ACPR would decrease to 86%, 81% and 90% for 2009, 2010 and 2011 respectively, had all dropouts been included in the analysis and assuming all of them had failed

treatment. Fifth, oral temperature measurements were obtained in this study, whereas WHO criteria for treatment failure are based on axillary temperature measurements. However, axillary temperatures are generally lower than oral temperatures by approximately 1˚C.[42] Thus, the use of oral temperature instead of axillary temperature would not have increased the number of treatment failures or altered the study conclusions. Lastly, the recommended dose of primaquine for radical cure of vivax malaria is 0.5 mg base/kg bodyweight per day for tropical strain infections.[43] Thus, a dose of 30 mg base per day would have been inadequate for patients whose bodyweight was greater than 60 kg. All 3 patients who met the criteria for early treatment failure had a bodyweight of less than 60 kg.

The results from the regression analysis suggest that the covariates accounted for a relatively small proportion of the total variation in PCT and FCT. Therefore, there may be other variables not accounted for in this analysis that may influence the rates of parasite and fever clearance. We observed a statistically significant increase in PCT between 2009 and 2013. In our analyses, we applied the conventional value of 0.05 as a cutoff point for statistical significance, which does not necessarily imply clinical relevance. In order to use parasite clearance as a marker to guide policy, it would be necessary to develop guidelines for determining clinically significant values of parasite clearance rates and changes in these rates over time.

The reporting of the systematic review adhered to the recommendations of the PRISMA statement.[44] Seven full-text articles that were not available and 7 foreign language publications were excluded from the list of eligible studies. We retrospectively reviewed these studies to assess the possibility of selection bias. Of the 7 unavailable full-text articles, the abstracts were also not available for 5 studies. These studies were published prior to 1980.[45-49] The other 2 studies evaluated the efficacy of chloroquine and other antimalarials for treatment of *P. vivax* and other *Plasmodium* species.[50-51] These abstracts did not make any reference to parasite clearance. We also obtained the English language abstracts and a limited translation of the foreign language publications which comprised 7 chloroquine efficacy studies. Chloroquine was administered in a single dose of 600 mg in one study.[52] In the other studies which utilised a standard regimen of chloroquine, parasite clearance was expressed as the cumulative proportion of patients who were aparasitaemic by a particular day of treatment.[53-58] As the main focus of the review was to assess standards in measurement and reporting of parasite clearance in the scientific literature, we do not consider publication bias to be a significant concern in our review.

WHO has published guidelines on methods for surveillance of antimalarial drug efficacy.[10] These recommend establishing sentinel sites where data can be collected and which represent all the epidemiologic strata in the country. There are a number of potential difficulties in conducting and interpreting results from these studies. Each study is a single-arm or randomised clinical trial, and WHO recommends that all firstline and secondline medicines be evaluated at least once every 24 months at all sites.[59] Thus, these studies require adequate and ongoing preparation, financial support and human resources. Due to the prospective nature of the study and the need to achieve an adequate sample size, there is a lag period between the commencement of the study and availability of results. Thus, the results of the study may not represent the actual situation regarding drug resistance at a given time. In countries where the area of malaria transmission is very large, it may be necessary to establish a large number of sentinel sites in order for information collected to be representative of the disease in the entire region or country. This may not be practical due to resource constraints.

There are a few factors that may affect the reproducibility, accuracy and interpretation of parasite clearance measurements. These include i) Diagnostic protocols, i.e., the type of blood films obtained, and the frequency with which parasite counts are obtained. Thick blood films give counts approximately 30% lower than the corresponding thin film.[41,60] Increasing the frequency of microscopic examinations will improve the precision of parasite clearance estimates; ii) Concurrent use of chloroquine and primaquine. Since primaquine has blood schizonticidal activity against *P. vivax* at therapeutic doses,[16,61] administration of primaquine early in the disease course may accelerate PCT; iii) Interindividual variability in parasite clearance. This may be due to differences between individuals in splenic function and other host defences, and levels of acquired immunity;[41] iv) Initial parasitaemia. It is possible that patients with high parasite counts prior to treatment will take longer to clear their parasitaemia compared to patients with low initial counts; and v) Variation in estimation of parasitaemia between different laboratory personnel, especially between microscopists with different levels of skills and experience.

Previous studies have explored the correlation between parasite clearance and treatment response in individuals,[62,63] but in view of inherent variability in parasite clearance and the potential random and systematic errors in parasite clearance measurements, it may be difficult to interpret the significance of PCT in any particular individual. However, it is likely that the average PCT among all infected individuals treated with a particular drug regimen will remain fairly constant over time if that drug regimen remains efficacious, a sufficient number of patients are evaluated at each time interval, and the baseline demographic and clinical

characteristics of patients at each time interval are similar. An increasing population trend in parasite clearance rates over time, even amongst individuals who achieve an adequate clinical and parasitological cure, may provide early warning of drug resistance. Thus, time-trends in population rates of parasite clearance may be useful as a sentinel surveillance mechanism to detect emerging resistance of *P. vivax* to chloroquine, as random and systematic errors in parasite clearance measurements are expected to be approximately similar over different time periods. If increasing trends in PCT values are noted, clinical trials and in-vitro studies could be performed in the region of interest to determine if drug resistance exists and to characterise the level and nature of resistance.

An advantage of parasite clearance as a surrogate marker for resistance is that it is not confounded by relapse or reinfection.[7] Parasite clearance measurements can also be obtained as part of routine clinical practice and therefore do not incur any additional costs and other resources required to conduct a formal clinical trial. The parasite clearance estimator is an online tool developed to estimate parasite clearance rates in the treatment of falciparum malaria with artemisinin derivatives.[11] A similar tool validated for the treatment of *P. vivax* with chloroquine may help to provide robust estimates of PCT and facilitate routine monitoring of chloroquine efficacy. Information on parasite clearance could be transmitted to a central agency and pooled from different health centres across a region, allowing for real-time monitoring of trends in parasite clearance in that region, and also for comparisons between different geographical locations. However, estimation of parasite clearance is critically dependent on the ready availability of trained microscopists, and in resource-limited settings, manpower constraints may preclude highly precise measurements. Thus, measurement of PCT in hours may be relatively easy to obtain in hospitalised patients but less so in outpatient settings in endemic regions.

Temperature measurements are routinely obtained as part of clinical management of patients, and fever clearance is a useful indicator for monitoring the clinical progress in individual patients. However, measurement of fever clearance may be confounded by a number of factors including the frequency of temperature monitoring, the ambient temperature, use of antipyretics or cold compresses, use of intravenous fluids, cutoff temperature for definition of fever, site of temperature measurement, wrongly calibrated thermometers and interindividual variability in temperature. In addition, fever may be prolonged in patients for reasons other than malaria infection, such as co-infection or drug reactions. For these reasons, trends in fever clearance rates are unlikely to be helpful as a tool to monitor the efficacy of or the development of resistance to chloroquine or other drugs used to treat *P. vivax* malaria.

The use of alternative drugs to treat *P. vivax* infection would obviate the need to monitor for emerging resistance of *P. vivax* to chloroquine. Douglas et al (2010)[2] have reviewed the use of artemisinin combination therapies (ACTs) for the treatment of both *P. vivax* and *P. falciparum* infections. The advantages of this approach are that various ACTs are effective against chloroquine-resistant strains of *P. vivax*, and a unified treatment strategy would not depend on correct identification of malaria species.[2] However, ACTs are more expensive than chloroquine,[43] and the widespread use of ACTs for all malaria infections may also accelerate the development of resistance to ACTs in all malaria species. This may reduce the efficacy of ACTs in the treatment of severe malaria, with a resultant increase in the morbidity and mortality from malaria infections. Thus, chloroquine is still a viable and useful firstline treatment for chloroquine-sensitive *P. vivax* infections, and ongoing surveillance for emerging resistance to chloroquine would continue to be an important component of malaria control programmes.

Conclusion

The combination of chloroquine and primaquine has remained effective for the treatment of uncomplicated *P. vivax* malaria in Thailand over the period 2004 to 2013. There was some evidence for an increase in PCT between 2009 and 2013, which may warrant further evaluation for developing resistance. Relying on clinical efficacy studies alone to monitor drug resistance may result in a significant time-lag before resistance is detected, and monitoring trends in average population PCT over time may therefore be a useful sentinel surveillance mechanism to detect emerging resistance of *P. vivax* to chloroquine. Heterogeneity was observed among prior studies in study parameters which may influence the rate of parasite clearance. In order for PCT to be a useful marker for drug resistance, it would be necessary to standardise various aspects of measurement including the precise definition of PCT, the type of blood films used for assessment of parasitaemia, and the frequency of microscopy. If consensus guidelines on methodology, reporting, analysis and interpretation of parasite clearance rates and trends are developed and adopted by the scientific community worldwide, then cross-country comparisons of PCT may also be possible, thereby allowing for effective monitoring of emerging resistance globally.

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Commentary

Thirty Years of Bone Marrow Transplantation in the Singapore General Hospital

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"For patients transplanted for end-stage leukemia, it became apparent that a plateau was developing on the Kaplan-Meier plot of survival so that it became possible to use the term 'cure' for these patients".

Edward Donnall Thomas, Nobel Lecture,1990

The first adult haematopoietic stem cell (HSC) transplant (HSCT) in Singapore was performed in July 1985 at the Singapore General Hospital (SGH). A patient with relapsed acute lymphoblastic leukaemia received conditioning with total body irradiation (TBI) followed by infusion of bone marrow from his human leukocyte antigen (HLA)-matched brother. This commentary briefly recounts the major milestones in our HSCT programme which evolved with advances in the field as new scientific knowledge and novel technologies became available.

Conditioning therapy before HSC infusion aims to eradicate tumour cells and immunological memory, create "space" within the marrow niche, and in allogeneic HSCT, reduce the risk of graft rejection. The first conditioning regimen, as used by Edward Donnall Thomas in the 1960s consisted of TBI 10 Gy delivered in a single fraction.[1] This takes advantage of the extreme sensitivity of haematopoietic cells to radiation and the ability of TBI to penetrate "sanctuary" sites. However, despite myeloablative doses of TBI, relapses continued to occur and there were substantial problems with "non-target" organ toxicity when TBI was delivered in this way. Concurrently, there was general acknowledgment of the marked sensitivity of normal tissues to fractionation of TBI dose and rate of delivery and these eventually led to important modifications to initial myeloablative conditioning regimens. The first was the addition of chemotherapy to TBI and development of chemotherapy-only regimens with cyclophosphamide and busulfan, which is especially toxic to non-dividing early myeloid precursors.[2] The second was fractionation of TBI to deliver equivalent doses with lower toxicity.[3]

For many years, conventional myeloablation remained the only available preparative regimen, built upon the delivery of high-doses of ablative chemo-radiotherapy/chemotherapy before rescue of recipient haemopoiesis with either autologous or allogeneic HSCs depending on the disease. Whereas antitumour effects are solely from cytotoxic chemotherapy in autologous transplants, allogeneic HSCs may also have beneficial immune reactivity against tumour/leukaemia, the so-called graft-versus-leukaemia (GvL) effect.[4,5] This formed the basis for the development of regimens that relied less on ablative intensity and more on GvL for its antitumour effects. Non-myeloablative (NM) regimens act to immunosuppress the recipient permitting engraftment of allogeneic HSCs while reduced intensity conditioning (RIC) regimens employ variable chemotherapy intensities with varying cytotoxic effects, not amounting to conventional myeloablation. We performed our first NM transplant in 1990 using immunoablative-dose cyclophosphamide with antithymocyte globulin for a patient with severe aplastic anaemia. The improved toxicity profile and tolerability of RIC and NM preparative regimens meant that older patients with comorbidities which previously excluded them from transplantation became eligible for HSCT. This contributed significantly to the rise in our transplant activity from the 1990s (Fig. 1).

The rise in the number of HSCTs performed also coincided with the increasing use of peripheral blood (PB) rather than bone marrow as the source of HSCs. Key to the development of peripheral blood stem cell harvesting (PBSCH) was

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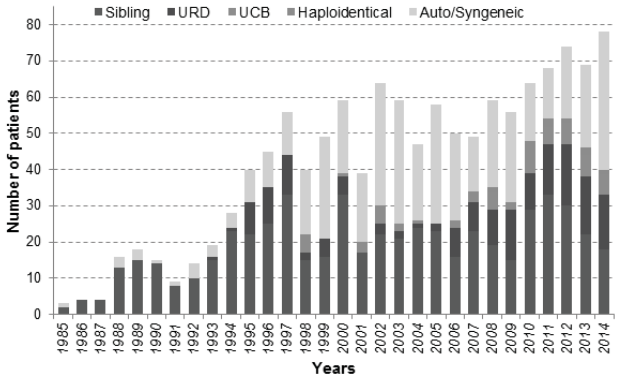

Fig. 1. Graph showing the number and types of transplants per year in Singapore General Hospital.

the observation in mice, of HSCs circulating from areas shielded from irradiation to radio-ablated marrow, followed by cross-circulation studies in primates demonstrating the ability of these circulating HSCs to recapitulate the entire haematopoietic system.[6,7] Together with improved leukapheresis and cryopreservation techniques, the first PBSCH that resulted in successful engraftment was carried out in London in 1981 for a patient with chronic myeloid leukaemia.[8] Mainstream application of PBSCH coincided with the use of G-CSF as a means of temporarily expanding PB CD34+ HSCs. The major advantages over bone marrow HSCs include a higher HSC cell dose, more rapid engraftment, lowered graft rejection rate, and easier HSC collection. The first autologous and allogeneic PBSC transplants performed in SGH were in 1990 and 1995, respectively. Worldwide, PBSCs are used much more frequently than bone marrow and in SGH, it accounts for 96.6% of all transplants done in the last 10 years.

One of the vital steps that propelled HSCT into the "modern era" was the characterisation of the HLA system. Prior to this, most transplants had resulted in graft failure or lethal graft-versus-host disease (GvHD). Standard practice currently dictates that HLA-typing is performed at the HLA-A, -B, -C, and -DRB1 loci except with cord blood when HLA-C is not needed for selection of a suitable donor. The best donor is a full "8/8" HLA-matched sibling donor followed by a fully-matched unrelated donor (URD) or "7/8" HLA-matched sibling or URD. The chance of a sibling of same parentage being fully HLA-matched is 25%. In the last decade, about 58% of our allogeneic transplants used a sibling donor, 29% URD, 11% cord blood, and 2% haploidentical donor.

Our first URD transplant was performed in 1994 for a patient with advanced myelodysplastic syndrome. The patient succumbed within 100 days of transplant from severe sepsis. A year later, we successfully carried out an URD transplant for a patient with thalassaemia major and he remains well and on follow-up today. Refinements in HLA-typing and improved immunosuppressive and preparative regimens (among others) have translated to an increase in URD transplant survival approaching that of matched sibling transplants.[9]

The 1990s also saw the adoption of alternative sources of HSCs. The first umbilical cord blood (UCB) transplant we performed was in 1998. UCB transplantation is an option for patients who are unable to find a suitable sibling or URD or who for medical reasons, require a transplant urgently. In this regard, UCB remains an important source of readily available "off-the-shelf" cryopreserved HSCs which have been screened for infectious diseases and which require less stringent HLA-matching (≥4/6 HLA-matching for HLA-A, -B, -DRB1). Survival outcomes after UCB transplants in adults are still inferior compared to adult donor transplants and relates to several factors including poorer platelet recovery, delayed immune reconstitution from thymopoietic failure and late memory T-cell skewing, higher rates of graft failure and longer time-to-engraftment (and therefore longer period of neutropaenia).[10,11] The latter is dependent on the interplay between the degree of HLA match and the total nucleated cell (TNC) dose with higher doses potentially able to overcome greater HLA disparity.[12] To this end, research into cord blood expansion strategies aim to overcome the discrepancy between available TNC dose per UCB unit and that required by an adult recipient. In 2013, our first transplant combining an unmanipulated UCB unit with an ex vivo expanded unit co-cultured with mesenchymal stem cells and an "in-house" cocktail was performed (NCT01624701).

Another alternative donor source is the haploidentical (half-matched) donor. Almost all patients would have a related donor (parent) identical for 1 HLA haplotype and mismatched at HLA-A, -B, -C or -DR of the unshared haplotype. For many years, the central problem with haploidentical transplants was controlling the potent alloreactivity of host T-cells (graft rejection) and donor T-cells which lead to hyperacute GvHD. However, using cyclosphosphamide (CY) at immunoablative doses on days 3 and 4 after HSC infusion (post-transplant CY) has diminished the aforementioned problems by promoting tolerance in host and donor T-cells.[13] The major mechanisms for the induction of tolerance by CY are the destruction of antigen-stimulated, proliferating T-cells in PB and intrathymic clonal deletion of reactive T-cells associated with establishment of mixed chimerism. Even though CY is administered after donor HSC infusion, engraftment consistently occurs because HSCs contain high levels of aldehyde dehydrogenase which render them insensitive to

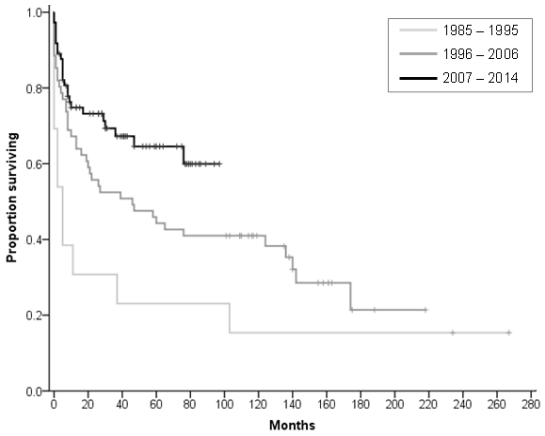

Fig. 2. Chart showing the survival of transplant recipients over 3 decades in Singapore General Hospital.

CY toxicity. Post-transplant CY forms the basis for the T-cell depleting strategy in our current haploidentical transplant protocol, which we first used in 2011.

Apart from refinements in conditioning regimens, harvesting techniques and donor accessibility, improvements in immunosuppressive therapy, antimicrobial agents, infrastructure, and overall medical care have resulted in a significant improvement in survival over 3 decades (Fig. 2). Accordingly, transplant-related mortality has also decreased through the years from 31.7% in the first 10 years to 17.9% in the last decade, consistent with results from other international transplant centres.[14] Although haematological malignancies and marrow failure remain the most frequent indications for adult HSCT, patients with autoimmune diseases like systemic lupus erythematosus and scleroderma as well as neurological conditions like multiple sclerosis who have failed standard immunosuppressive therapy have also benefited from autologous HSC transplantation. Putative mechanisms of action include thymic reprocessing and expansion of regulatory T-cells.

The service that began in 1985 is today, a large multidisciplinary programme comprising an internationally accredited HSC collection facility and processing laboratory, and the clinical programme itself. Over the years, SGH has become a referral centre for HSC transplantation in the region. The number of patients transplanted has steadily increased, surpassing a thousand patients in 2011 and providing a chance for survival in excess of 50%. Yet, there is a continuous need for us to improve on current patient outcomes. Post-HSCT relapse remains a major barrier to long-term survival. To this end, efforts into manipulating the graft to try shift the balance of alloreactivity in favour of graft-versus-tumour and engineering immune cells that preferentially kill tumour have already begun. These, together with refinements in overall medical care may bring us further in the pursuit of the "cure" we embarked upon many years ago.

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Letter to the Editor

Multiple Pathological Fractures Secondary to Endocrinopathy from Thalassaemia

Dear Editor,

Thalassaemia is a genetic haemoglobinopathy secondary to a defect in globin chain production. Morbidity from thalassaemia can arise from the deleterious effects of ineffective erythropoiesis or the complications associated with multiple transfusions. Osseous complications can occur in patients with thalassaemia. The ineffective erythropoiesis leads to marrow expansion with a thinning of the cortices.[1] In addition, endocrinopathy from transfusion-related complications can worsen bone density.[2] These factors predispose patients with thalassaemia to a higher risk of fracture.

Osseous complications in thalassaemia have been documented previously. Data from the Thalassemia Clinical Research Network of North America showed that fractures occurred in 36% of their patients with thalassaemia, with 8.9% of the patients reporting 3 or more lifetime fractures.[3] However, there is a paucity of literature on multiple pathological fractures occurring in a patient with beta thalassaemia major. We describe a patient with transfusion-dependent beta thalassaemia major complicated by hypogonadism secondary to transfusion haemachromatosis. The patient suffered multiple pathological fractures from minor trauma. This case report serves to highlight the features of multiple pathological fractures secondary to endocrinopathy from thalassaemia.

Case Report

The patient is a 38-year-old Chinese male with a known medical history of transfusion-dependent beta thalassaemia major. He was diagnosed with beta thalassaemia in childhood and underwent a splenectomy at the age of 16 years in an attempt to reduce haemolysis. He received blood transfusions twice a month to maintain a baseline haemoglobin level of 8 g/dL. In view of his transfusion-dependent thalassaemia, he was started on iron chelation therapy with desferoxamine (subcutaneous desferrioxamine 1500 mg, 5 times per week and oral deferiprone 1000 mg, 3 times a day). The ferritin levels remained stable at 6000.3 ug/L and 5833.4 ug/L at 25 and 30 years of age, respectively.

The patient first presented to our institution in 2001 with a left humerus supracondylar fracture after self-skidding whilst riding a motorcycle. Plate osteosynthesis was performed and the fracture went on to unite without complication. In 2006, the patient fell onto the right side from a standing position and suffered a right intertrochanteric fracture. A dynamic hip screw fixation was performed and the fracture united in 10 months. At the age of 32 years (2008), despite the iron chelation therapy, the patient developed endocrinopathies due to iron overload. He developed diabetes mellitus, hypothyroidism, hypoparathyroidism and hypogonadism. The biochemical investigations revealed a free T4 of 9.4 pmol/L, testosterone level of 2 nmol/L and a sex hormone binding globulin (SHBG) level of 183 nmol/L. The patient's renal and liver panel was within normal range, as were the levels of calcium, vitamin D and parathyroid hormone. The patient was started on oral hypoglycaemic therapy, thyroid replacement therapy (thyroxine 50 mcg) and testosterone replacement therapy (intramuscular testosterone cipionate 150 mg monthly). The patient's osteoporosis worsened after the development of endocrinopathies. Dual-energy x-ray absorptiometry (DEXA) bone mineral densitometry (BMD) of the proximal femur worsened from a Z score of -2.9 (in 2009) to -3.9 (in 2013). Despite worsening osteoporosis, the patient declined bisphosphonate therapy.

After the development of his endocrinopathies, the patient suffered several fragility fractures from trivial trauma (Table 1). At the age of 32 years, the patient fell from a standing position and suffered a right tibia and fibula fracture. The patient was treated with a cast. Unfortunately, a fall from a standing position later in the same year led to a right femoral periprosthetic fracture. The fracture occurred just distal to the previous dynamic hip screw. Removal of the right dynamic hip screw and intramedullary nailing of the right femur was performed. The right femur fracture united after 8 months.

At the age of 36 years, the patient fell again from a standing position and suffered a left proximal humerus fracture. He was treated non-surgically and the fracture united in 3 months. However, the patient was involved in a road traffic accident 2 months later and suffered a left humeral midshaft fracture. This was also treated non-surgically. At the age of 37 years, the patient fell from a standing position and suffered bilateral tibia and fibula fractures. These fractures were treated with plate osteosynthesis.

Table 1. Fracture History

No.	Age at Injury (Years)	Fracture Characteristics	Mechanism of Injury	Management
1	25	Left elbow supracondylar fracture	Road traffic accident (Motorcyclist self-skidded)	Plate osteosynthesis
2	30	Right femur intertrochanteric fracture	Fall from a standing position	Dynamic hip screw
3	32	Right tibia and fibula shaft fracture*	Fall from a standing position	Non-surgical treatment
4	32	Right femur periprosthetic fracture*	Fall from a standing position	Intramedullary nailing
5	36	Left proximal humerus shaft fracture*	Fall from a standing position	Non-surgical treatment
6	36	Left humerus midshaft fracture*	Road traffic accident (driver at 40 km/hr)	Non-surgical treatment
7	37	Right tibia fracture*	Fall from a standing position	Plate osteosynthesis
8	37	Left tibia fracture*	Fall from a standing position	Plate osteosynthesis
9	37	Left humerus midshaft fracture*	Fall from a standing position	Non-surgical treatment
10	37	Right tibia periprosthetic fracture*	No known mechanism	Intramedullary nailing
11	37	L2 compression fracture*	No known mechanism	Non-surgical treatment
12	38	Left femur subtrochanteric fracture*	Fall from bed	Intramedullary nailing
13	38	Right humeral shaft fracture*	Pressure from the blood pressure monitoring cuff	Intramedullary nailing

*Occurred after the development of hypogonadism.

Three months later, the patient complained of pain over the right tibia and left humerus, with no history of trauma or fall. It was then noted on radiographs that there was a new right tibia periprosthetic fracture (Fig. 1) as well as a left humerus periprosthetic fracture (Fig. 2). This was the third fracture to occur in his left humerus in just under 1 year. An intramedullary nail was inserted into the right tibia. The left humerus was treated non-surgically. The left humerus and right tibia united after 7 months. The patient subsequently complained of low back pain with no history of trauma or fall. Radiographs revealed a L2 compression fracture. This was treated non-surgically.

The patient presented to us once more in 2014 with a left comminuted subtrochanteric fracture after a fall off his bed (Fig. 3). Surgical fixation with an intramedullary nail was performed. On postoperative day 3, the patient complained of right humerus pain after a routine blood pressure measurement. X-rays revealed a right pathological humeral shaft fracture (Fig. 4). Intramedullary nailing was performed for the right humeral fracture.

Unfortunately, the patient developed an unrelated perforated pyloric ulcer during the twentieth postoperative and demised.

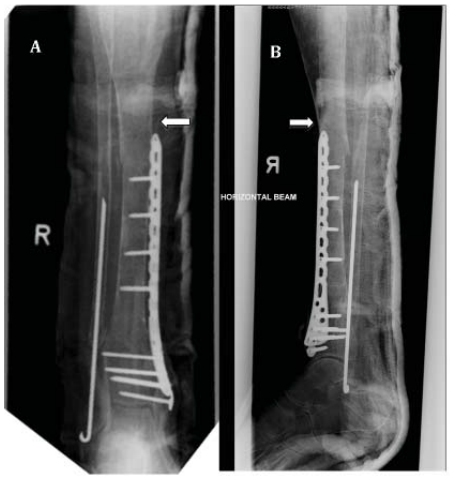

Fig. 1. Anteroposterior (A) and lateral (B) x-ray of the right tibia and fibula. There is a new periprosthetic fracture at the proximal aspect of the tibial plate (indicated by the arrow).

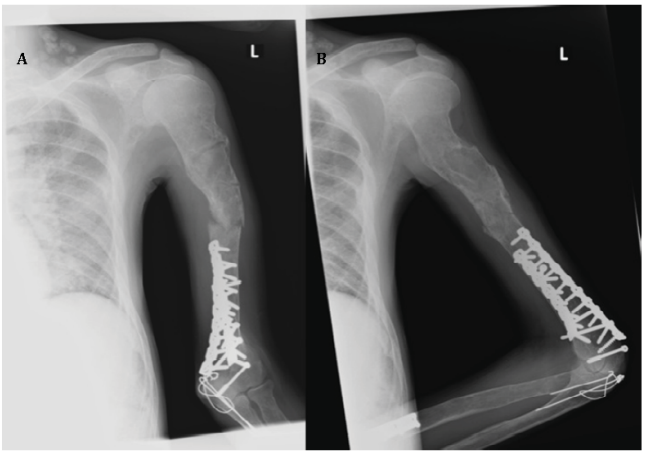

Fig. 2. Anteroposterior (A) and lateral (B) x-ray of the left humerus. Healing proximal and midshaft fractures of the left humerus are noted with a new periprosthetic fracture of the humeral shaft.

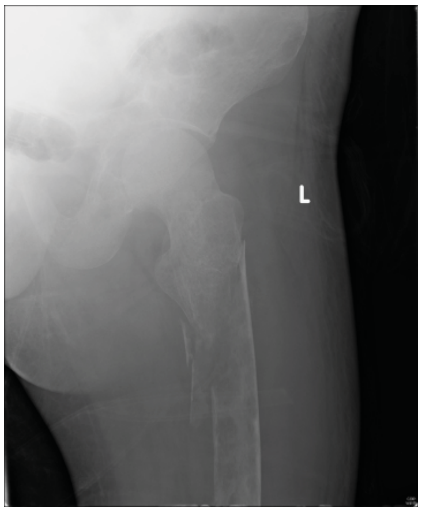

Fig. 3. Anteroposterior x-ray of the left subtrochanteric fracture. Comminuted subtrochanteric fracture is noted on the background of osteoporotic bone and thinned cortices.

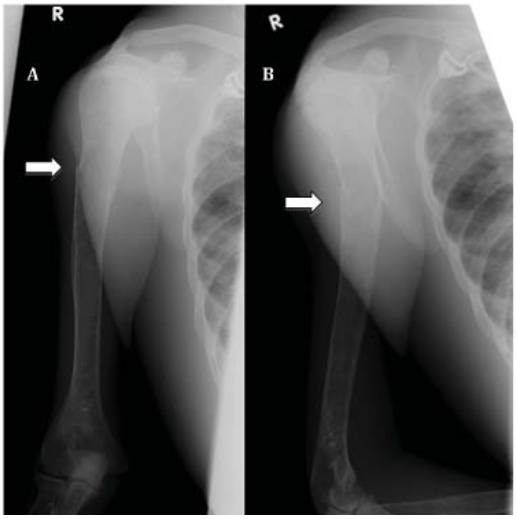

Fig. 4. Anteroposterior (A) and lateral (B) x-ray of the right humerus. A minimally displaced pathological fracture of the humeral shaft (indicated by the arrow) is noted on the background of osteoporosis.

Discussion

Osseous deformity, bone pain and fractures are some of the common osseous complications associated with thalassaemia.[3] The ineffective erythropoiesis stimulates bone marrow expansion by up to 30 to 40 times, leading to a thinning of the cortices.[4] Bone marrow expansion in bones such as the facial bones and long bones of the extremities can lead to the classical "chipmunk facies" appearance. Thalassaemia is associated with a low bone mineral density. It is postulated that an increased bone turnover in thalassaemia does not allow for positive bone accrual and attainment of optimal peak bone mass.[3] Polymorphism of the collagen type Ia1 (*COLIA 1*) gene has been associated with reduced BMD in postmenopausal osteoporosis.[5] Interestingly, polymorphism of *COLIA1* gene has also been noted in up to 30% of thalassaemic patients. This may contribute to the development of osteoporosis in thalassaemic patients. Other factors that may contribute to the development of osteoporosis include endocrinopathies, osteoblast toxicity from iron overload or bone toxicity from desferoxamine usage.[2]

Regular transfusion was introduced in the 1960s in an attempt to maintain a normal haemoglobin level.[6] Iron overload from multiple transfusions is a known complication. The body has no natural means of iron extraction and iron accumulation can occur in regions such as the myocardium, liver and endocrine glands. Iron chelation therapy with desferoxamine is widely used to assist in the excretion of chelated iron complexes from the body.[7]

Endocrinopathy is a known complication in patients with transfusion-dependent thalassaemia.[8] The anterior pituitary gland is sensitive to iron overload, and this can lead to a hypothalamic-pituitary axis dysfunction resulting in hypogonadism.[8] Common endocrinopathies include thyroid dysfunction, hypogonadism, diabetes and dyslipidaemias. In adult-onset hypogonadism, there is a profound effect on the BMD, which may worsen the osteoporosis. Male patients with thalassaemia, endocrine dysfunction and fracture history are at particular risk for future fracture.[9]

Hypogonadism can have a profound effect on the fracture risk of a thalassaemic patient. Androgens have a proliferative effect on osteoblasts and an inhibitory effect on osteoclasts. In hypogonadism, the diminished levels of androgens lead to a lowered BMD. In our patient, he suffered 2 fractures prior to the development of hypogonadism, with 1 fracture a result of minor trauma. There was an increased incidence of pathological fractures after the development of hypogonadism. He suffered a further 11 fractures after developing hypogonadism, of which 10 were due to minor trauma. In particular, a humeral fracture occurred from the use of an inflated blood pressure cuff. Notably, many of the fractures occurred from a low energy mechanism, with multiple fractures occurring in the same bone. The increase in pathological fractures after the development of hypogonadism reinforces the fact that hypogonadism is a strong independent predictor of fragility fractures in patients with thalassaemia. Patients with transfusion-dependent thalassaemia should be assessed regularly for hypogonadism. Alendronate therapy has been shown to increase the bone mineral density in thalassaemia-induced osteoporosis.[10] Patients should be counselled for an increased risk of pathological fracture after the development of hypogonadism.

Patients with transfusion-dependent beta thalassaemia major complicated by hypogonadism are at a high lifetime risk of fracture due to worsening and profound osteoporosis.[3,9] Such patients may suffer multiple pathological fractures from seemingly trivial trauma. These patients should be counselled appropriately for a high risk of fracture and their activities should also be modified to reduce risk. Surgical considerations in these patients include the use of locking plates and intramedullary devices where possible, due to the poor bone quality and propensity for implant failure.

Patients with transfusion-dependent beta thalassaemia major complicated by endocrinopathy tend to present later in adulthood. This is due to the delayed onset of endocrinopathy secondary to iron overload from multiple transfusions. As such, physicians should be aware of this clinical entity and conduct regular screening for the development of endocrinopathies in transfusion-dependent beta thalassaemia patients. If endocrinopathies develop, treatment should be started to prevent worsening osteoporosis.

Conclusion

Thalassaemia is a common haemoglobinopathy. Patients with transfusion-dependent thalassaemia should be placed on iron chelation therapy and monitored closely for development of endocrinopathies. Multiple pathological fractures can occur in transfusion-dependent thalassaemia complicated by hypogonadism. These patients should be counselled on the risks of multiple pathological fractures.

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Comparison of Outcomes of Transcatheter and Surgical Procedure in Perimembranous Ventricular Septal Defect Patients with Tricuspid Regurgitation

Dear Editor,

Surgery has long been considered as an optimal treatment strategy to treat ventricular septal defect (VSD) complicated with moderate or severe tricuspid regurgitation (TR).[1-3] Effects of non-surgical intervention, such as interventional closure, are not well-established yet.[4-7] This study aimed to compare the effects of TR and clinical outcomes in VSD patients, treated either with transcatheter closure procedure or surgery procedure. We hypothesised that transcatheter closure procedure was non-inferior to surgical procedure.

Materials and Methods

This study was a prospective, randomised, single-centre study in China. Overall, 43 patients with VSD and moderate or severe TR were prospectively recruited from January 2009 to February 2011. Inclusion criteria for surgery or transcatheter closure treatments were: 1) age >3 years old or weight >10 kg; 2) a perimembranous VSD with diameter of greater than 3 mm and less than 14 mm by transthoracic echocardiography; 3) the defect located at 9 - 11 o'clock positions counterclockwise in the short axis parasternal view; 4) complicated with moderate or severe TR; 5) a distance greater than 2 mm from the perimembranous VSD to the aortic valve and 3 mm from the perimembraneous VSD to the tricuspid valve (TV); 6) left to right shunt; and 7) pulmonary pressure <40 mmHg estimated by colour Doppler echocardiography. All patients had standard echocardiography examinations before and after the procedures.

Transcathether Closure Procedure

Right and left heart catheterisation, as well as ascending aortography was routinely performed to exclude aortic valve prolapse and regurgitation. Left ventriculography and echocardiography allowed the proper selection of the Shanghai pmVSD occluder (LEPU Medical Technology Co, Ltd, Beijing, China) (Fig. 1A). The established delivery cable was used to send the occluder into the left chamber along the long sheath. Based on x-ray examination, the occluder was released to the left chamber side. The occluder was then drawn back to allow the attachment of its left chamber side to the VSD. To fix the delivery cable, the long sheath was drawn back to the right chamber and the right chamber side of the plugging device was opened. The occluder was stabilised by exerting an appropriate force. Left ventriculography was performed again to observe the plugging effect of VSD and to evaluate whether the occluder affected the aortic valve (Figs. 1B and 1C).

Surgical Operation Procedure

Operations for VSDs were performed through a midline sternotomy incision. Bicaval cannulation with cannulation of the superior vena cava enabled the exposure of the defects through the right atrium. An oblique incision anterior to the terminal sulcus and parallel to the atrioventricular groove was made from the appendage inferiorly toward the inferior vena cava. Two stay sutures were placed on the posterior margin of the incision, by taking care to avoid the sinus

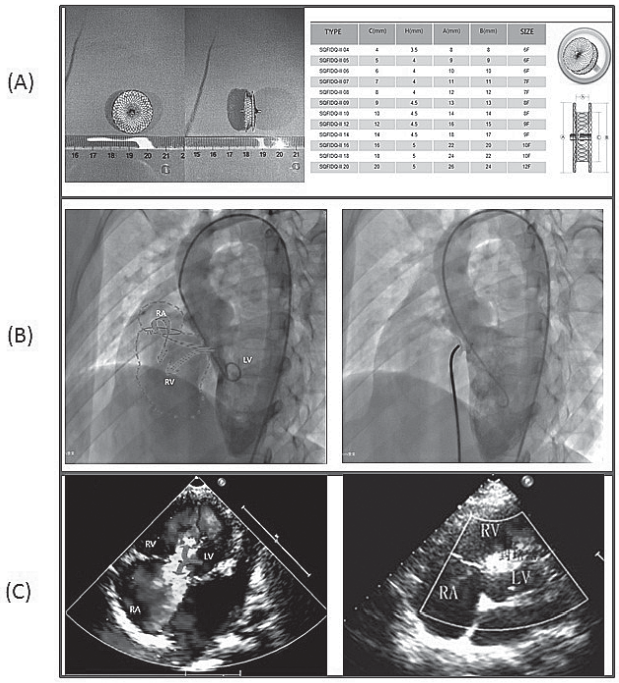

Fig. 1. A is an image of a perimembranous ventricular septal defect (VSD) occluder (Shanghai Shape Memory Alloy Co. Ltd). B shows ventriculographic images before and after an interventional closure procedure. C shows Doppler echocardiographic images before and after an interventional closure procedure.

Table 1. Patients' Characteristics and Clinical Data of VSD Patients with Tricuspid Regurgitation

Clinical Data	Surgery Group (n = 22)	Interventional Group (n = 21)	*P* Value†
Age (y)	16 ± 8	16 ± 9	0.80
Male, n (%)	13 (59)	12 (60)	0.50
Body weight (kg)	36 ± 10	38 ± 11	0.90
Body mass index (kg/m^2)	21 ± 1	21 ± 2	0.50
Echocardiography before procedure			
VSD diameter (mm)	7.4 ± 2.5	6.7 ± 1.9	0.50
Diameter of LV (cm)	4.9 ± 0.6	5.0 ± 0.5	0.90
Indexed diameter of LV* (cm/kg)	0.14 ± 0.03	0.14 ± 0.03	0.50
Moderate tricuspid regurgitation, n (%)	16 (73)	17 (81)	0.40
Severe tricuspid regurgitation, n (%)	6 (27)	4 (19)	0.40

LV: Left ventricle; VSD: Ventricular septal defect
*Ratio of diameter of LV and body weight.
†*P* <0.05 indicates a statistically significant difference.

node. The TV ring was exposed by everting the anterior margin of the atriotomy. Dacron patch was used to sew up the VSD directly or to repair the defect, respectively. A tricuspid water-thrashing test was then conducted to observe TR. Tricuspid valvuloplasty was performed if severe TR was present.

Results

All 43 patients were treated, of which 22 had surgical treatment and 21 had transcatheter treatment. Baseline clinical data are summarised in Table 1. Before operation, there were no statistical differences between the surgery group and interventional closure group in baseline conditions (*P* values >0.05). In the surgery group, the success rate was 100% without severe complications occurrence. There was 1 secondary complication involving low residual shunt, but it did not require treatment. In the interventional closure group, the success rate was 100%. There was 1 secondary complication, which involved mild aortic regurgitation but did not require special treatment. The postoperative follow-up was 3 to 12 months (i.e. mean duration follow-up of 10 months). The survival rate was 100%, and no complications occurred.

Table 2 summarised the data after closure operation. There was a significantly decreased length, area, volume, flow rate and differential pressure after both surgery and transcatheter closure groups. After closure operation, no statistical difference was found in the degrees of TR between the 2 groups. Second, in comparison with the surgical group, the transcatheter closure group had lower white blood cell (WBC), creatine kinase (CK-MB), cardiac troponin I (cTnI), myoglobin (MYO), and drug score. The interventional closure group had less operation time (39.8 ± 12.8 vs 63.6 ± 9.3 minutes, *P* <0.0001), but higher operation cost (2.3 ± 0.3 vs 1.9 ± 0.1 ×1000 ¥, *P* <0.0001), and comparable hospital stay and complications (*P* >0.05).

Discussion

Our study showed that interventional closure procedure was technically feasible to close the perimembraneous VSDs and then eliminated the occurrence of TR comparing to surgical closure procedure. Interventional closure procedure better protected myocardium and reduced myocardial injury and the operation time. Furthermore, compared with the surgical closure procedure, interventional closure procedure had the following advantages. First, the interventional closure group had shorter operation times. Second, the interventional closure group required smaller amounts of vasoactive drugs, had lower occurrence of postoperative inflammatory reactions, and showed lower incidence of myocardial injury. Third, there was no statistical difference in complication after operation than the surgical closure group.

Advantages of Transcatheter Closure of Perimembranous VSD Using Symmetrical Occluder

Compared with the asymmetric Amplatzer occluder, the symmetric Shanghai Shape Memory pmVSD occluder in this study (Lepu Medical Technology Co., Ltd., Beijing, China) (Fig. 1), had demonstrated to reduce the risk of atrioventricular block and residual shunt[4,8,9] due to: 1) its easier deployment, 2) reduction of pressure from occlude to interventricular septum, thus reducing damage of conduction system, and 3) occluder fringe of less than 2 mm so that the

Table 2. Patients' Tricuspid Regurgitation Features Before and After Operation, and Myocardial Injury Indices and Hospital Stay in Surgery Group and Interventional Closure Group

	Surgery Group (n = 22)		Interventional Group (n = 21)	
	Preoperative	**Postoperative**	**Preoperative**	**Postoperative**
Tricuspid regurgitation features using echocardiography				
Length (cm)	3.39 ± 0.80	0.51 ± 0.32*	3.26 ± 0.84	0.57 ± 0.22*
Area (cm^2)	3.66 ± 1.09	0.43 ± 0.27*	3.25 ± 0.89	0.56 ± 0.17*
Volume (mL)	3.47 ± 1.08	0.29 ± 0.20*	3.10 ± 0.89	0.40 ± 0.15*
Flow rate (m/s)	2.45 ± 0.42	0.65 ± 0.40*	2.48 ± 0.45	0.57 ± 0.27*
Differential pressure (mmHg)	24.00 ± 8.37	2.31 ± 1.89*	25.50 ± 8.13	1.60 ± 1.27*
Myocardial injury indices and hospital stay after operation				
WBC ($\times 10^9$/L)	16.0 ± 3.0		10.2 ± 2.7*	
CRP (mg/L)	90.8 ± 81.4		25.8 ± 17.5*	
CK-MB (ng/mL)	10.3 ± 5.1		3.4 ± 1.3*	
cTnI (ng/mL)	7.5 ± 5.8		1.5 ± 0.6*	
MYO (ng/mL)	879.2 ± 547.4		129.2 ± 35.3*	
Drug score	7.5 ± 3.6		5.5 ± 2.4*	
Operation time (minutes)	63.6 ± 9.3		39.8 ± 12.8*	
Operation cost (× ¥1000)	1.9 ± 0.1		2.3 ± 0.3*	
Hospital stay (days)	7.6 ± 0.8		7.7 ± 0.9	
Complications (n)	1		1	

CK-MB: Creatine kinase-MB; cTnI: Cardiac troponin I; CRP: C-reactive protein; MYO: Myoglobin; WBC: White blood cell
*Indicates a statistically significant, $P < 0.05$.

occluder does not contact the aortic valve, thus avoiding any damage to the aorta.

Interventional Closure Procedure May Cause Some Complications

In our study, we found 1 case with slight aortic valve regurgitation postoperation. This finding indicated that VSD closure operation could cause aortic valve regurgitation, similar to other reports.[9] However, this aortic regurgitation was minimal and did not require treatment. Another common complication was tricuspid damage.[10] However, in our study, no tricuspid damage related to interventional treatment was observed. Conduction block and other severe arrhythmias after VSD closure are of big concern to cardiologists because the defect is adjacent to the conduction tissues. In this study, no case of severe atrioventricular block occurrence was observed in the intervention group.

In this study, the cost of intervention was higher than surgery. The higher costs were from the occluder (i.e. about 13,000 yuan, approximately USD 2093.60) and a remote electrocardiogram (ECG) monitoring for 6 to 7 days in hospital. In terms of the number of days in hospitalisation, both groups had similar duration (i.e. about 7 days). This was because the patients in the catheter intervention group needed to be monitored for 6 to 7 days to detect possible arrhythmia, based on consensus from our intervention experts.

Conclusion

We have demonstrated that the TR outcomes and clinical outcomes of interventional closure procedure in patients with VSD complicated with moderate or severe TR were not inferior to surgical treatment.

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Clinical Outcome in Patients with Negative Rigid Oesophagoscopy for Suspected Foreign Body Ingestion

Dear Editor,

Foreign body (FB) ingestion, fishbones in particular, is commonly encountered in the emergency setting in Singapore.[1,2] While most are removed in the clinic, small percentages with oesophageal FBs require removal under general anaesthesia. Prompt removal avoids potential lethal complications like mediastinitis and aorto-oesophageal fistula.[3-6]

While imaging modalities like computed tomography (CT) have been instrumental in selecting patients for rigid oesophagoscopy, false-positive results are still evident, translating to unnecessary rigid oesophagoscopy. However, the prevalence and reasons of negative rigid oesophagoscopy are not well-reported.

This study aims to address the prevalence and reasons of negative rigid oesophagoscopy and evaluate the clinical outcomes of these patients.

Materials and Methods

Retrospective chart review was performed for patients with negative rigid oesophagoscopy following suspected FB ingestion over a 12-year period (1998 to 2010). This study was approved by the Institutional Review Board (IRB). Patients with negative rigid oesophagoscopy were classified into 3 categories—spontaneous passage of the FB, false-positive radiographic findings and migrated FB.

False-positive radiographic findings were defined by the presence of abnormal features on imaging which led to rigid oesophagoscopy. These patients had persistent findings on repeated imaging after negative rigid oesophagoscopy despite symptom resolution.

Spontaneous passage of FB included patients who had initial positive findings on imaging, which were no longer present on repeated imaging; or those with persistent symptoms despite negative imaging. These patients typically had resolution of their symptoms.

Migrated FB was defined by the migration of the FB out of the aerodigestive tract lumen confirmed by surgical exploration and retrieval. The classification of each case was independently reviewed by the resident and verified with both senior authors.

Clinical Evaluation of Patients with Suspected FB Ingestion

Patients with suspected FB ingestion underwent complete examination of the oropharynx and hypopharynx at the emergency department. Patients with negative findings were assessed with a lateral neck x-ray. Those with negative x-rays who were still symptomatic underwent non-contrasted CT of the neck and thorax. This was our preferred imaging protocol given its reported high sensitivity and specificity of 100% and 73% to 100% respectively.[7-9] Patients with suspicious imaging were consented for rigid oesophagoscopy under general anaesthesia.

Clinical Outcomes

Symptom resolution, complications and mortality secondary to intervention or FB ingestion were recorded. Data analysis was performed using SPSS version 21 (SPSS, Chicago, IL, USA); the ANOVA test and the chi-square test were used to compare the variables between patient groups. *P* value of less than 0.05 was considered significant.

Results

A total of 723 patients underwent rigid oesophagoscopy for FB ingestion and 88 (12.1%) had negative rigid oesophagoscopy. Table 1 summarises the demographics of negative rigid oesophagoscopy patients.

Table 1. Characteristics of Patient Population with Negative Rigid Oesophagoscopy

	Patients with Negative Rigid Oesophagoscopy
Age range (mean)	18 – 90 (46.5)
Gender (%)	
Male	37 (42.0)
Female	51 (58.0)
Ethnicity (%)	
Chinese	70 (79.5)
Malay	9 (10.2)
Indian	3 (3.4)
Others	6 (6.8)

Table 2. Characteristics of Patients from the 3 Cohorts

	Reasons for Negative Rigid Oesophagoscopy		
	Passed FB	**Migrated**	**False-Positive**
n (% of negative rigid oesophagoscopy)	75 (85.2)	2 (2.3)	11 (12.5)
Age (mean)	18 – 90 (46.1)	56 – 80 (68.0)	22 – 75 (43.8) $P = 0.181$
Gender (%)*			
Male	32 (42.7)	1 (50.0)	5 (45.0)
Female	43 (57.3)	1 (50.0)	6 (54.0) $P = 0.998$
Clinical indication for rigid oesophagoscopy (%)*			
X-ray	51 (68.0)	0	4 (16.0)
CT scan	11 (18.0)	2 (100.0)	7 (28.0)
Barium swallow	2 (3.2)	0	0
Clinical symptoms	11 (14.8)	0	0

CT: Computerised tomography; FB: Foreign body
*Percentages in parentheses correspond to percent of patients for each reason.

A total of 85.2% (75/88) of patients had spontaneous passage of their FB, 12.5% (11/88) had false-positive radiological findings, and 2 had migrated FBs. The group characteristics are summarised in Table 2. All patients were reviewed postoperatively following negative rigid oesophagoscopy and no mortality was identified.

Clinical Outcomes

Spontaneous FB Passage

Seventy-five patients (85.2%) had spontaneous symptom resolution. Five had mucosal injuries on rigid oesophagoscopy requiring nasogastric tube feeding for 5 days and prolonged hospitalisation (9.25 days). All were able to resume oral feeding on discharge.

False-Positive Radiological Findings

Eleven patients had persistent abnormal radiological findings. After a review of the repeat images taken after negative rigid oesophagoscopy, 8 (72.7%) had persistent abnormal calcifications along the aerodigestive tract. Three of these anomalies were visible on lateral neck radiographs, and 5 on CT.

Anomalies on repeat x-rays following negative rigid oesophagoscopy included 2 patients with calcifications along the posterior border of the cricoid and 1 with calcifications anterior to C7 vertebrae. Two patients were asymptomatic following negative rigid oesophagoscopy and declined CT. The last patient had persistent mild symptoms and underwent a repeat CT, which did not identify any possible FB.

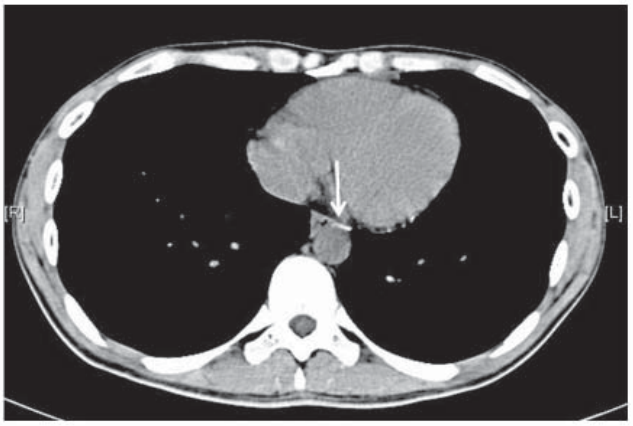

Fig. 1. Calcification in the aortopulmonary window. The arrow indicates the area of area false-positive foreign body.

Five patients had persistent calcifications on repeat CT; 2 had calcifications in the C5-6 region, which were attributed to dystrophic calcification while 3 had calcifications in the region of the aortopulmonary window (Fig. 1). Two of the later 3 patients underwent thoracic exploration and no FBs were identified. Both patients made an uneventful recovery with no postoperative complications. They did however require longer hospitalisation stay (mean of 10 days).

The remaining patient declined thoracic exploration. He was monitored and symptoms gradually subsided after 6 days. He remained asymptomatic and declined further CT at 1-month follow-up.

The other 3 patients had persistent abnormal imaging, namely soft tissue swelling or possible extra-luminal air suspicious of perforation. They were admitted for intravenous antibiotics and were discharged following resolution of their symptoms. All remained asymptomatic on their 1-month review upon discharge.

Migrated FB Group

Two patients were found to have FB migration on CT. Both underwent neck exploration and removal of FB from the trachea-esophageal groove, adjacent to the cervical esophagus. They required prolonged hospitalisation and nasogastric tube feeding for 5 days, but both were discharged well and none had vocal cord palsy postoperatively.

Discussion

The paucity of studies on negative rigid oesophagoscopy questions the reasons for and clinical outcomes of these

patients. This study aims to evaluate factors to identify situations where close observation may suffice without compromising patient safety.

Our data demonstrated that negative rigid oesophagoscopy were mostly secondary to spontaneous passage of the FB. This could be due to muscle paralysis during general anaesthesia or elevation of the laryngeal complex during intubation. Relaxation of pharyngeal or oesophageal musculature could result in passage of FB into the stomach. In fact, oesophageal relaxation using agents like glucagon have been used as adjuncts in patients with food bolus impaction.[10] Laryngeal elevation during intubation may also disimpact FBs, thus accounting for spontaneous passage of FB.

However, we acknowledge that some patients may have already disimpacted their FB prior to anaesthesia. As such, active review prior to induction may minimise unnecessary oesophagoscopy.

False-positive radiological findings constituted 12.1% of negative rigid oesophagoscopy. These findings were largely due to aberrant calcifications of the laryngeal framework. Cricoid calcifications on lateral neck x-rays are known to be mistakenly classified as FBs.[11-13] In our study, 4 negative rigid oesophagoscopy patients had abnormal findings on x-ray; 75% were secondary to aberrant calcifications in the laryngeal complex. Clinical correlation with suspected radiological finding is essential to minimise unnecessary intervention.

False-positive findings on CT are especially problematic in the aortopulmonary window. In our series, 2 patients underwent unnecessary thoracic exploration, highlighting the difficulty in distinguishing migrated FBs versus aortopulmonary window calcifications in lymph nodes. In retrospect, a period of close monitoring may be warranted rather than a reflex approach towards exploration. While there are no guidelines pertaining to duration of observation, our practice is to review the symptoms over a 48-hour period to determine if patients should undergo further investigations or procedures.

Migration of FB is uncommon.[14,15] Both our cases presented early, approximately 1 day following ingestion. This is unusual, as FB migration is thought to occur after protracted impaction. The sharpness of the bone could lead to early migration in these cases. A transcervical approach to the tracheo-oesophageal groove was successful in the removal of the migrated FBs. In these cases, the risk to the recurrent laryngeal nerve should be discussed with patients prior to surgery.

While it is impossible to eliminate all negative rigid oesophagoscopys, this study reports the possible reasons and highlights pitfalls where over-dependence on radiological findings may result in unnecessary interventions.

Conclusion

The prevalence of negative rigid oesophagoscopy in patients with suspected FB is low. While spontaneous passage of impacted FBs accounts for most of these cases, abnormal calcified shadows on imaging can result in unnecessary intervention, especially for calcifications seen in the aortopulmonary window.

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Progressive Weakness, Cognitive Dysfunction and Seizures

A 45-year-old man developed recurrent partial seizures with secondary generalisation. Four years earlier, he had first presented with diplopia from left abducens palsy and right hemiparesthesia, followed by left hemiparesis 1 month later. His magnetic resonance imaging (MRI) brain scan done then is shown in Figure 1. His MRI cervical spine with contrast was unremarkable for any cord lesion. The erythrocyte sedimentation rate, anti-nuclear antibody, anti-double-stranded deoxyribonucleic acid, anti-extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies, anti-cardiolipin antibodies, lupus anticoagulant test, and cerebrospinal fluid (CSF) analysis were unremarkable. He was treated with pulsed steroids and an immunomodulatory agent, but was lost to follow-up.

On re-evaluation during the current admission for seizures, his neurological function had been deteriorating progressively over the past 4 years. He had severe cognitive deficits (Mini-Mental State Examination 2/28), cerebellar dysarthria, and generalised pyramidal weakness with spasticity. Repeat MRI brain scan is shown in Figure 2. Serum calcium, vitamin B12, lactate, pyruvate, caeruloplasmin, rheumatoid factor, anti-thyroid peroxidase antibodies, anti-glutamic acid decarboxylase antibodies, anti-gliadin IgA and IgG antibodies, human immunodeficiency virus and syphilis serologies, and very long chain fatty acid levels were unremarkable. Ophthalmological examination excluded retinal vasculitic lesions or inflammation; pathergy test was negative. Repeat CSF analysis was positive for oligoclonal bands. Computed tomography thorax showed no evidence of pulmonary sarcoidosis. He was treated with but did not respond to further courses of pulsed steroids.

What is the most likely diagnosis?

A. Sjögren's syndrome
B. Multiple sclerosis
C. Cerebral lupus
D. CADASIL
E. Neurosarcoidosis

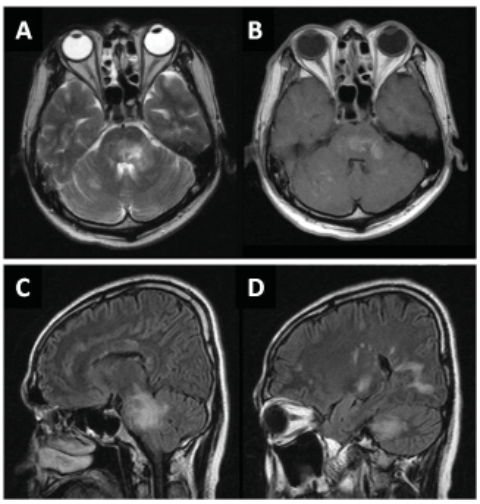

Fig. 1. Axial T2-weighted (A), T1-weighted post-contrast (B) and sagittal FLAIR (C, D) MRI images showing multifocal areas of T2 and FLAIR hyperintensities in both infra- and supra-tentorial regions, including the pons, bilateral subcortical, periventricular deep white matter and corpus callosum, with some of these areas demonstrating enhancement.

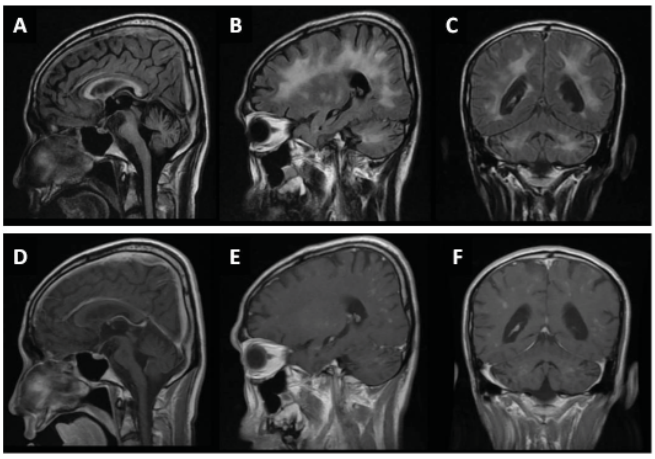

Fig. 2. Sagittal (A, B) and coronal (C) FLAIR, and sagittal (D, E) and coronal (F) T1-weighted post-contrast MRI images showing progression of T2 and FLAIR hyperintensities in the cerebral and cerebellar white matter and cortically, with multifocal patchy enhancement, as well as cerebral and cerebellar atrophy.

Answer: B

Discussion

The patient's progressive neurological dysfunction over 4 years without relapses, combined with the MRI brain lesions disseminated in time and space (in typical periventricular, juxtacortical and infratentorial regions), the presence of CSF oligoclonal bands, and an extensively unremarkable work-up for other autoimmune, infectious and metabolic diseases, is consistent with a diagnosis of primary-progressive multiple sclerosis (PPMS).[1] The lack of response to steroids and immunomodulatory therapy further supports the diagnosis of PPMS.[2,3]

Although multiple sclerosis (MS) is a predominantly white matter disease, seizures have been reported to occur in about 2% of MS patients, approximately 2.5 to 5 times higher than in the general population.[4] Seizures can occur throughout the disease course, and are sometimes the first symptomatic manifestation of MS. Seizures have been observed in relapsing-remitting and progressive MS. The aetiology of seizures is thought to be from cortical or juxtacortical lesions with or without inflammation.[4-8]

Studies suggest that partial seizures are more common in MS patients, accounting for more than 60% of seizures, and secondary generalisation frequently occurs.[5,6] Data on the prognosis is conflicting, although most studies report good seizure control on standard anti-epileptic regimens.[5] A few studies have noted an increased incidence of status epilepticus amongst MS patients, ranging from 17.6% to 38.4%, compared to 2% to 10% in the general population of epilepsy patients.[4]

Hence, MS should be considered as a differential diagnosis in patients presenting with seizures, with the relevant clinico-radiological features. The initiation of standard anti-epileptic drugs should be considered even after the first seizure in MS patients.

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