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Nelson Mandela (1918 – 2013)
South African statesman

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EDITORIAL

112 Stem Cell Replacement Therapies in Parkinson's Disease
Li Zeng, Ling Ling Chan, Erle CH Lim, Eng King Tan

ORIGINAL ARTICLE

115 Validating a Standardised Approach in Administration of the Clinical Frailty Scale in Hospitalised Older Adults
Edward Chong, Jia Qian Chia, Felicia Law, Justin Chew, Mark Chan, Wee Shiong Lim

LETTERS TO THE EDITOR

125 Electronic Bicycles and Scooters: Convenience at the Expense of Danger?
Serene SN Goh, Xin Yi Leong, Jolene YX Cheng, Li Tserng Teo

129 First Percutaneous Tricuspid Valve Repair with MitraClip Device in Singapore
Khung Keong Yeo, Ningyan Wong, Ghee Chee Phua, Mohammed Rizwan Amanullah, Jie Sheng Foo, Louis LY Teo, See Hooi Ewe

133 *HLA-B*5701* Genotyping for Abacavir Prescription: Re-Examination of its Cost-Effectiveness in Singapore
Kang Shiong Goh, Ritika Kapoor, Cheng Chuan Lee, Khai Pang Leong, Carol YL Ng

Please see inside Contents for the full list of articles.

Free Papers

Editorial

Stem Cell Replacement Therapies in Parkinson's Disease — Li Zeng, Ling Ling Chan, Erle CH Lim, Eng King Tan — 112

Original Article

Validating a Standardised Approach in Administration of the Clinical Frailty Scale in Hospitalised Older Adults — Edward Chong, Jia Qian Chia, Felicia Law, Justin Chew, Mark Chan, Wee Shiong Lim — 115

Letters to the Editor

Electronic Bicycles and Scooters: Convenience at the Expense of Danger? — Serene SN Goh, Xin Yi Leong, Jolene YX Cheng, Li Tserng Teo — 125

First Percutaneous Tricuspid Valve Repair with MitraClip Device in Singapore — Khung Keong Yeo, Ningyan Wong, Ghee Chee Phua, Mohammed Rizwan Amanullah, Jie Sheng Foo, Louis LY Teo, See Hooi Ewe — 129

*HLA-B*5701* Genotyping for Abacavir Prescription: Re-Examination of its Cost-Effectiveness in Singapore — Kang Shiong Goh, Ritika Kapoor, Cheng Chuan Lee, Carol YL Ng, Khai Pang Leong — 133

Images in Medicine

Painful Purpuric Ulcers of the Legs: A Tell-Tale Sign of Systemic Disease? Sophie Carrie S Cai, Wai Leong Kok, Yen Loo Lim, Joyce SS Lee, Wei Sheng Chong 139

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Forthcoming Issues

Vol 48 No. 5, May 2019 – Free Papers
Vol 48 No. 6, June 2019 – Free Papers

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General Information

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Editorial

Stem Cell Replacement Therapies in Parkinson's Disease

Li Zeng, [1]*PhD*, Ling Ling Chan, [2]*MBBS, FRCR*, Erle CH Lim, [3,4]*MBBS, MMed*, Eng King Tan, [4,5,6]*MBBS, FRCP*

World Parkinson's Disease Day—which falls on 11 April—commemorates the birthday of the late physician and geologist, James Parkinson. All around the world, efforts are under way to increase public awareness of the condition first described by Parkinson over 200 years ago. Over the past 2 decades, Parkinson's disease (PD) is viewed as more a clinical syndrome than a single disease entity characterised by motor features of tremor, bradykinesia, rigidity and postural instability. The identification of several pathogenic genes and loci and the recognition of non-motor symptoms and prodromic features have redefined classification of PD and expanded the clinical spectrum of the disease.[1-6]

Despite advances made in the treatment of PD and various drugs that have since been added to the armamentarium, there is still no specific cure for the condition. Currently, available treatments focus primarily on relieving motor symptoms that result from degeneration of dopamine (DA) neurons in the substantia nigra. Thus, dopaminergic medicines are administrated to restore DA signalling. However, systemic administration of dopaminergic medicines are associated with adverse long-term side effects such as levodopa-induced dyskinesias. While deep brain stimulation is effective in select patients, it does not prevent progression of PD. Transplantation of DA-producing cells in brains of PD patients to replace degenerated DA cells has seen a resurgence in popularity due to successful generation of DA-producing cells via induced pleuripotent stem cells (iPSC) and advances in methodologies that enable the production of authentic midbrain DA neurons via embryonic stem cells (ESC).[7,8]

More than 3 decades ago, studies on transplantation of foetal ventral midbrain tissue in PD patients have shown that it provided long-term relief of motor symptoms in early-stage patients.[9] However, due to ethical concerns, limited availability and heterogeneity of tissues which may contain serotoninergic cells that led to troubling dyskinesias, this approach could not be adopted as routine clinical therapy.[10]

Recently, great strides have been made in cell transplantation in PD that leveraged on the significant advances made in stem cell research and in vitro midbrain dopaminergic (mDA) cell differentiation techniques.[11-13] Various sources of cells could now be used as starting materials to generate transplantable DA neurons or progenitors. Several human ESC lines are also available to provide unlimited renewable and bankable cells. Through these well established in vitro differentiation protocols, uniform authentic mDA cells can be generated, characterised, cryopreserved and distributed worldwide.[12,13]

One drawback of human ESC is immunogenicity of allografts. However, since the central nervous system is an immune-privileged site, the transplanted cells can survive for decades even after a short period of immunosuppressant has been applied. Another starting material that can be used to generate transplantable mDA cells is iPSC which is derived from somatic cells of patients.[7]

The advantage of using autografts is that it is less likely to suffer from immune rejection. However, there are some disadvantages. First, iPSC from patients may carry genetic risk factors that might make them less than ideal therapeutic materials. Second, the potential genomic instability and tumourigenic property of iPSC make extensive genetic testing—an extremely expensive approach—a necessity to guarantee the safety of transplanted cells. As such, use of induced neurons (iN) converted directly from somatic cells has been proposed. Like iPSC, however, iN has several intrinsic limitations that have led to a halt in its use. The limitations of iN include limited quantity that can be generated from somatic cells, safety concerns over the introduction of exogenous genes with viral vectors and highly variable quality of each batch of iN.[14,15]

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Prior to transplantation, several fundamental aspects must be addressed that include in vivo DA neuronal survival, identification of a transplantable stage during DA neuron differentiation and establishment of reliable and sensitive analytical methods capable of assessing the efficacy of transplantable DA neurons. In our previous work with PD rodent models, we showed that cells transplanted in the form of aggregates survived far better than single cells.[16] We also conducted systematic comparison analysis that identified optimal differentiation stages of DA cells most suitable for transplantation to achieve the best therapeutic effect. We investigated DA progenitors, immature DA neurons and DA neurons which were differentiated in vitro for 16, 25 and 35 days, respectively. Of these, neurons at day 25 were identified as most suitable for PD cell therapy while the other 2 cell types were less capable of producing functional recovery.[17]

These findings provide valuable guidelines to standardise the differentiation stage of transplantable cells used to treat PD. To better quantify the quality of transplantable DA neurons, one should perform a longitudinal assessment of the efficacy of transplanted mDA neurons using various neuroimaging modalities such as magnetic resonance imaging, magnetic resonance spectroscopy and positron emission tomography (PET) as well as behavioural measurement several months post-transplantation. It is possible that PET is able to better quantify the quality of transplantable mDA neurons using specific ligands before the cells can be used in clinical trials. It is therefore likely that molecular neuroimaging will play a major role in neurotransplantation research.

A major challenge in cell therapy in PD is identification of the discordance between satisfactory survival of transplanted cells and clinical improvement in some patients.[18] Certain confounders like ageing, disease progression, metabolic condition and mental health may affect axon sprouting and synaptic formation of grafted cells or postsynaptic efficacy of the host brain. These confounders may modulate the response to cell transplantation therapy. Identification of these confounders will greatly help clinicians to better stratify PD patients who are to be treated with cell transplantation.

Besides the therapeutic values of stem cell-derived cell transplantation, stem cell research also holds great promise by revolutionising the investigation of the aetiology of PD. Taking advantage of cutting-edge techniques such as human midbrain organoid generation and xeno-transplantation, it is now feasible to re-examine the aetiology of PD in a multiple organ, polygenetic and human cell-based context. Human midbrain organoids can be generated from either healthy subjects or somatic cells (with mutation) of PD patients and then transplanted into a cavity created in the retrosplenial cortex of rodents.[19] Intracerebral implantation in rodents supports long-term survival and vascularisation of implanted organoids.[20] Many neuroimmunological features in PD—including blood brain barrier penetration of circulated immune cells in conditions of infection, innate microglia and astrocyte activation and gut-brain axis interaction—can be studied in this xenotransplantation platform.[21,22] Additionally, the interaction between genetic and environmental factors in PD pathogenesis can be investigated using this novel platform.

Currently, several trials that test DA neuron transplantation in PD patients are ongoing. A clinical trial that uses GMP (good manufacturing practice) grade DA cells derived from stem cells to treat PD patients is being funded by TRANSEURO.[23] Likewise, NYSTEM is supporting Lorenz Studer and Viviane Tabar of Memorial Sloan Kettering in New York for their work in this area (https://www.mskcc.org/research-areas/programs-centers/newyork-state-stem-cell-science-consortia).[24] The first clinical transplantation trial using iPSC began in Japan in 2018 and to date 1 patient has undergone neurotransplantation.[25] In Australia, a clinical trial that uses parthenogenetic stem cells (from chemically-induced unfertilised oocytes) as starting materials has been initiated. Parthenogenetic stem cells are rather attractive since they have fewer ethical issues, a lower number of de novo mutations (compared to iPSC) and apparently low immunogenicity. A summary of the unpublished preliminary findings (available online at https://www.globenewswire.com/news-release/2018/11/05/1645106/0/en/International-Stem-Cell-Corporation-Announces-Positive-Top-Line-Preliminary-Results-from-Parkinson-s-Disease-Clinical-Trial.html) seems to suggest the absence of any major safety issues to date.

There is considerable excitement over the prospect that human stem cell-derived DA neuron transplantation may usher in a new era in PD therapy. However, a lot will depend on the outcomes of ongoing clinical trials and subsequent validation of their findings and results through randomised controlled trials. At this stage, it is too early to draw any definitive conclusions while we wait with cautious optimism.

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Original Article

Validating a Standardised Approach in Administration of the Clinical Frailty Scale in Hospitalised Older Adults

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Abstract

Introduction: We developed a Clinical Frailty Scale algorithm (CFS-A) to minimise inter-rater variability and to facilitate wider application across clinical settings. We compared the agreement, diagnostic performance and predictive utility of CFS-A against standard CFS. Materials and Methods: We retrospectively analysed data of 210 hospitalised older adults (mean age, 89.4 years). Two independent raters assessed frailty using CFS-A. Agreement between CFS-A raters and with previously completed CFS was determined using Cohen's Kappa. Area under receiver operator characteristic curves (AUC) for both measures were compared against the Frailty Index (FI). Independent associations between these measures and adverse outcomes were examined using logistic regression. Results: Frailty prevalence were 81% in CFS and 96% in CFS-A. Inter-rater agreement between CFS-A raters was excellent (kappa 0.90, *P* <0.001) and there was moderate agreement between CFS-A and standard CFS (kappa 0.42, *P* <0.001). We found no difference in AUC against FI between CFS (0.91; 95% CI, 0.86-0.95) and CFS-A (0.89; 95% CI, 0.84-0.95; *P* <0.001). Both CFS (OR, 3.59; 95% CI, 2.28-5.67; *P* <0.001) and CFS-A (OR, 4.31; 95% CI, 2.41-7.69; *P* <0.001) were good predictors of mortality at 12 months. Similarly, CFS (OR, 2.59; 95% CI, 1.81-3.69; *P* <0.001) and CFS-A (OR, 3.58; 95% CI, 2.13-6.02; *P* <0.001) were also good predictors of institutionalisation and/or mortality after adjusting for age, sex and illness severity. Conclusion: Our study corroborated the results on inter-rater reliability, diagnostic performance and predictive validity of CFS-A which has the potential for consistent and efficient administration of CFS in acute care settings.

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Key words: Assessment, Frailty, Geriatric, Inpatient, Risk

Introduction

Singapore is ageing at an exponential rate. Commensurate with the worldwide trend of population ageing, 13% of residents were aged 65 years and older in 2017 with a life expectancy of 83.1 years.[1] By 2030, the aged population is projected to constitute approximately 25% of its total population with the cost of providing care to older adults rising to US$49 billion (S$66 billion) annually and an average cost of US$37,427 for each older person.[1,2] Therefore, it is imperative that healthcare services across Singapore become frailty-ready to face and embrace the growing challenges of caring for older adults.[3]

Frailty—a modern geriatric giant—is defined as a state of reduced strength and physiological malfunctioning that increases a person's susceptibility to increased dependency, vulnerability and even death.[4,5] Its rising prevalence is leading to greater healthcare needs and costs that will impact on government, community and individuals.[6] From a public health perspective, frailty in a population is now increasingly used as an indicator of healthcare utilisation and successful ageing.[7] Hence, greater emphasis on identifying frailty is needed to facilitate early detection, intervention and appropriate resource allocation in hospitals and community.

Various frailty tools have been developed and validated to screen and assess frailty.[5] While this has improved frailty identification, it has also led to great variability in frailty classification and heterogeneity in predictive abilities.[5,8] For example, kappa coefficients ranged from 0.3 to 0.58 for agreement between 2 widely used seminal approaches of frailty index (FI)[9] and Fried's physical phenotype.[10]

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The harmonisation of frailty assessment is especially salient in acute settings since hospitalised older adults have a high prevalence of frailty, are vulnerable to adverse outcomes and consume a disproportionately large amount of healthcare resources.[11] A recent local study of hospitalised older adults similarly reported that while frailty tools have good predictive outcomes, they are not equivalent in terms of frailty prevalence estimates, diagnostic performance (against the FI) and predictive validity for different outcomes.[12] This underscores the importance of developing a global tool which provides a common language for frailty identification and grading of severity that is akin to the Clinical Dementia Rating in dementia evaluation. The latter has found widespread utility as a severity-ranking global assessment scale in many studies of Asian populations.[13]

Against this backdrop, the Clinical Frailty Scale (CFS) is attractive as a global synthesis assessment tool that allows frailty to be defined and graded using simple clinical descriptors which are available from routine clinical assessment.[14] CFS is a well validated measure for frailty that has been shown to predict adverse outcomes in older adults.[5,15,16] The 9-point scale allows classification across the frailty continuum that ranges from 1 (very fit) to 9 (terminally ill). A score of 5 to 8 is considered frail. Each CFS category has a brief description and visual depiction to aid the classification of frailty. CFS requires some clinical judgement in its scoring and trained assessors are needed for accurate classification.[5] Although 1 study reported CFS predicted adverse health outcomes when administered by junior medical staff,[15] studies that specifically examined the reliability and diagnostic performance of CFS in real-world settings are sparse. Various algorithm-based approaches have been developed to simplify the evaluation of CFS for research purposes and they ranged from telephonic administration to multinational survey analyses.[15-18] However, to our knowledge, there is no standardised approach to aid rapid administration of CFS in busy clinical settings. This provides the impetus to develop a standardised algorithmic approach to ensure accurate and consistent scoring of CFS. The algorithm simplifies the process by making the key nodal decision points explicit and it minimises arbitrary and tentative synthetic assessment and scoring of CFS.

This study compares the agreement, diagnostic performance and predictive utility of CFS algorithm (CFS-A) against the standard approach of completing a detailed assessment, or comprehensive geriatric assessment (CGA), prior to rating an individual's CFS score[14] in older adults admitted to an acute hospital. We aim to establish the usefulness of CFS-A as a tool that provides accurate and consistent identification of frailty in a feasible manner and its potential for wider administration across acute care settings and by non-physicians.

Materials and Methods

Study Design and Eligibility Criteria

Our earlier study had increased our understanding of the diagnostic and predictive performance of 3 frailty measures (Tilburg Frailty Indicator,[19] FRAIL[20] and CFS) against the "gold-standard" FI. For this study, we proceeded to examine the usefulness of CFS-A by using the database of collected variables.

A total of 210 older adults who were consecutively admitted to the Department of Geriatric Medicine at Tan Tock Seng Hospital in Singapore in 2015 were examined. We collected data on patient demographics, comorbidities and severity of illness using the modified Charlson's comorbidity index (CCI) and modified severity of illness index, respectively.[21,22] Each subject was scored on CFS by an independent rater based on clinical information. As stipulated by the exclusion criteria, individuals with CFS 9 were excluded from the study. Further details of the study methods, including how frailty assessment was performed using FI, were described previously.[12]

Informed consent was obtained from the patient or from a legally acceptable representative (in individuals who lack capacity to provide consent). Ethics approval was obtained from the Domain Specific Review Board of the National Healthcare Group of Singapore.

Frailty Assessment Using a Standardised Approach

We developed a standardised algorithmic approach to aid assessors to perform rapid frailty screen (see Appendix 1). It includes the following information: 1) brief description of CFS, 2) definition of premorbid frailty status, 3) step-by-step guide to score CFS-A, 4) original descriptors of CFS, and 5) list of basic and instrumental activities of daily living (ADL).

Two independent raters were assigned to score CFS-A. They were asked to retrospectively score each patient's premorbid frailty status using CFS-A based on information from the database. The variables included: 1) demographics (age and gender), 2) CCI, 3) self-reported symptoms of fatigue or difficulties in ambulation, 4) premorbid basic and instrumental ADLs, and 5) self-reported change in general health, increasing breathlessness or significant weight loss. Both assessors were blinded to each other's scores as well as original CFS scores in our previous study.[12]

Due to limited information available to the assessors from the database, it was decided that it would be challenging for them to distinguish between CFS stages 1 to 3 and stages 7 to 8 without access to relevant information about each patient's overall fitness and anticipated clinical outcomes and prognoses. Therefore, we combined CFS stages 1 to 3 and 7 to 8 in the final rating which resulted in 5 frailty categories: robust (CFS 1 to 3), vulnerable (CFS 4), mildly frail (CFS

5), moderately frail (CFS 6) and severely frail (CFS 7 to 8). Discordant CFS ratings were resolved through discussion between the 2 assessors and any further disagreement was adjudicated by a third independent assessor.

Outcome Measures

We compared inter-rater agreement of CFS-A and agreement with prior clinically-rated CFS ratings ("standard CFS"). Next, we compared the diagnostic performance of CFS-A and standard CFS against the "gold standard", our locally validated 37-item FI. Details of the FI were described previously.[12] Finally, we compared the predictive performance of standard CFS and CFS-A against the outcomes of hospital stay, mortality, institutionalisation and functional decline (defined as incremental Katz ADL[23] dependency at discharge compared to premorbid) up to 12 months post-enrolment. To accommodate the larger number of moderately frail (CFS 6) patients in our study population of hospitalised older adults, we selected a cutoff score of CFS 5 or less for group 1 versus CFS 6 or more for group 2. This provides a more meaningful clinical comparison between established degrees of frailty in patients who are not frail or are mildly frail in acute care settings.

Statistical Analyses

Data was gathered using standardised forms which were then entered into an electronic database. We expressed continuous variables as mean ± standard deviation (SD) or median (interquartile range). Categorical variables were expressed as counts and percentages. Area under receiver operator characteristic curves (AUC) for CFS and CFS-A were compared against FI to determine their diagnostic performance in identifying frailty. A CFS score of 5 or more and FI ratio of 0.25 or more were used as cutoff scores for frailty diagnosis. Cohen's kappa and Gwet's agreement coefficient were used to measure agreement between CFS-A raters and between CFS and CFS-A.

We then analysed outcomes at 3 different time points: initial hospitalisation, 6 months and 12 months post-enrolment. For specific outcomes of interest, we performed univariate analyses for a comparison between group 1 (CFS 1 to 5) and group 2 (CFS 6 to 8), chi-square test for categorical variables (mortality, institutionalisation and functional decline) and Mann-Whitney U-test for non-parametric data (length of hospitalisation). For analysis of outcomes of institutionalisation and functional decline, a participant who died during the specified period was counted as a case according to the statistical method used in our earlier study.[14] We also performed logistic regression analysis—adjusted for a priori defined covariates of age, sex and severity of illness—to investigate the independent association between moderate-severe frailty and adverse outcomes of interest.

Statistical analysis was performed using SPSS version 19.0 (SPSS, Chicago, IL) and STATA version 12.0 (Stata Corp, College Station, TX) assuming a two-sided test at 5% level of significance.

Results

Of the 210 participants,[12] 4 were lost to follow-up leaving a total of 206 patients for follow-up analyses. Their mean age was 89.4 ± 4.6 years and there was a preponderance of females (69.5%) and Chinese (81.4%). Frailty prevalence estimates for CFS and CFS-A were 81.0% (robust, 10.0%; vulnerable, 9%; mildly frail, 23.3%; moderately frail, 30.5%; and severely frail, 27.1%) and 95.7% (robust, 1.9%; vulnerable, 2.4%; mildly frail, 28.6%; moderately frail, 50.5%; and severely frail, 27.1%), respectively. Median CFS score for both measures was 6.

Age, sex and ethnicity were similar for both groups on either measure. We observed significantly higher severity of illness, functional dependency, dementia and delirium in group 2 (CFS 6 to 8) on both measures (Table 1). Comorbidities were significantly higher in group 2 than in group 1 (CCI, 3.0 vs 2.0; P <0.001) when measured using CFS.

In our earlier study,[12] there was good inter-rater reliability of CFS between 2 blinded independent assessors on 20 consecutive participants from our cohort (kappa, 0.78; P <0.001). For this study, the inter-rater reliability of CFS-A between the 2 blinded independent assessors was excellent (kappa, 0.90; P <0.001; Gwet's AC1 0.93; 95% confidence interval [CI], 0.89-0.97). There were only 11 (5.2%) cases where initial CFS-A scored by both independent raters were discordant. Of these, 10 had a CFS-A discordance of 1 point. They comprised 5 cases between CFS 5 to 6, 2 cases between CFS 4 to 5, another 2 between CFS 1 to 3 and 4 and 1 between CFS 6 to 7. The 2-point discordance in the remaining case was between CFS 4 to 6. In contrast, inter-measurement reliability between CFS and CFS-A was only moderate (kappa, 0.42; P <0.001; Gwet's AC1 0.48; 95% CI, 0.40-0.57).

AUC for CFS and CFS-A against the gold standard FI for diagnosis of frailty were 0.91 (95% CI, 0.86-0.95; P <0.001) and 0.89 (95% CI, 0.84-0.93; P <0.001), respectively. There was no significant difference between CFS and CFS-A (P = 0.56) on receiver operating characteristic contrast (Fig. 1).

Table 2 shows CFS and CFS-A were significantly associated with mortality at initial hospitalisation (0.0% vs 6.6%, P = 0.013 and 0.0% vs 5.7%, P = 0.044, respectively) and up to 12 months (7.9% vs 41.3%, P <0.001 and 7.2% vs 36.9%, P <0.001, respectively). Both CFS and CFS-A were also significantly associated with institutionalisation and/or mortality up to 12 months (12.8% vs 47.5%, P <0.001 and 10.6% vs 43.6%, P <0.001, respectively).

Table 1. Baseline Characteristics of CFS and CFS-A Participants

	CFS			CFS-A		
	Group 1 (CFS 1 to 5) n = 89	Group 2 (CFS 6 to 8) n = 121	*P* Value	Group 1 (CFS 1 to 5) n = 69	Group 2 (CFS 6 to 8) n = 141	*P* Value
Demographics						
Age (mean ± SD)	88.7 ± 3.8	89.9 ± 5.1	0.588	88.4 ± 4.1	89.9 ± 4.8	0.658
Male gender (%)	31 (34.8)	33 (27.3)	0.240	24 (34.8)	40 (28.4)	0.343
Chinese ethnicity (%)	75 (84.3)	96 (79.3)	0.705	62 (89.9)	109 (77.3)	0.101
Median CCI (IQR)	2.0 (1.0 – 3.0)	3.0 (2.0 – 4.0)	0.027	2.0 (1.0 – 3.0)	3.0 (2.0 – 4.0)	0.015
SII						
Level 1 (%)	3 (3.4)	0 (0.0)	0.026	2 (2.9)	1 (0.7)	0.026
Level 2 (%)	71 (79.8)	87 (71.9)		58 (84.1)	100 (70.9)	
Level 3 (%)	15 (16.9)	34 (28.1)		9 (13.0)	40 (28.4)	
Median Katz ADL (IQR)	6.0 (5.0 – 6.0)	0.0 (0.0 – 1.0)	<0.001	6.0 (6.0 – 6.0)	1.0 (1.0 – 3.0)	<0.001
Cognitive function						
Median AMT (IQR)	7.0 (5.0 – 8.0)	0.0 (0.0 – 4.0)	<0.001	6.0 (4.0 – 8.5)	1.0 (0.0 – 6.0)	<0.001
Dementia (%)	16 (18.0)	78 (64.5)	<0.001	12 (17.4)	82 (58.2)	<0.001
Delirium on admission (%)	7 (7.9)	35 (28.9)	<0.001	6 (8.7)	36 (25.5)	0.004
Admitting diagnosis						
Sepsis (%)	45 (50.6)	75 (62.0)	0.027	36 (52.2)	84 (59.6)	0.051
Fall/syncope/seizure (%)	14 (15.7)	15 (12.4)		12 (17.4)	17 (12.1)	
Delirium/dementia (%)	2 (2.2)	8 (6.6)		1 (1.4)	9 (6.4)	
Other medical (%)	27 (30.3)	18 (14.9)		20 (29.0)	25 (17.7)	
Surgical (%)	1 (1.1)	5 (4.1)		0 (0.0)	6 (2.9)	

ADL: Activities of daily living; AMT: Abbreviated mental test; CCI: Charlson's comorbidity index; CFS: Chronic frailty scale; CFS-A: Chronic frailty scale algorithm; IQR: Interquartile range; SD: Standard deviation; SII: Severity of illness index

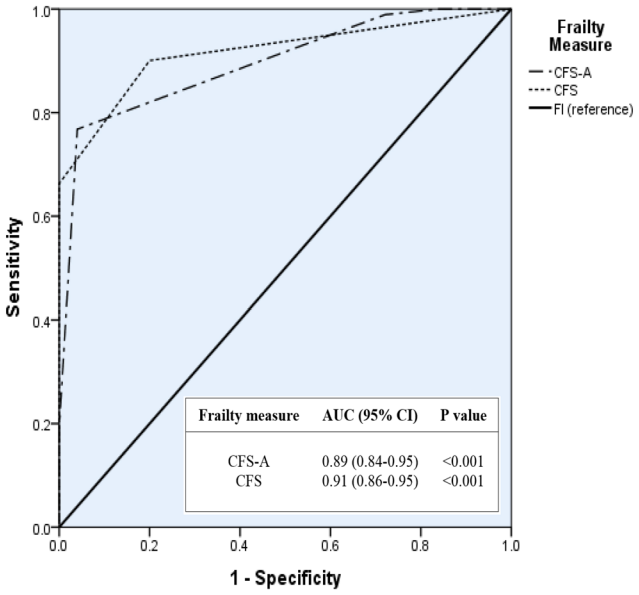

Fig. 1. Graph showing the AUC for CFS and CFS-A against FI in diagnosis of frailty. AUC: Area under receiver operating characteristic curves; CFS: Clinical frailty scale; CFS-A: Clinical frailty scale algorithm; CI: Confidence interval; FI: Frailty index. Receiver operating characteristic curve contrast: CFS-A vs CFS, $P = 0.522$. Inter-rater reliability: kappa, 0.903; $P < 0.001$; Gwet's AC1, 0.93; 95% CI, 0.89-0.97. Inter-measurement reliability (CFS-A and CFS): kappa, 0.422, $P < 0.001$; Gwet's AC1, 0.48; 95% CI, 0.40-0.57.

Only CFS-A was significantly associated with functional decline and/or mortality at 6 months (37.9% vs 57.9%, $P = 0.007$) and 12 months (39.4% vs 55.7%, $P = 0.029$). CFS-A was also significantly associated with increased length of hospitalisation (7 days vs 10 days, $P = 0.025$) but not CFS (8 days vs 10 days, $P = 0.051$).

AUC analysis was used to investigate whether group 2 (CFS 6 to 8) patients were at greater risk of adverse outcomes (Table 3). CFS (AUC, 0.78; 95% CI, 0.72-0.85; $P < 0.001$) and CFS-A (AUC, 0.73; 95% CI, 0.66-0.81; $P < 0.001$) performed well in predicting mortality. The same observation was seen in institutionalisation and/or mortality at 12 months post-hospitalisation for CFS (AUC, 0.75; 95% CI, 0.68-0.81; $P < 0.001$) and CFS-A (AUC, 0.71; 95% CI, 0.64-0.79; $P < 0.001$). However, both performed poorly at predicting functional decline and/or mortality (Fig. 2).

We performed logistic regression analyses after adjusting a priori for age, sex and severity of illness (Table 4). CFS (OR, 3.59; 95% CI, 2.28-5.67; $P < 0.001$) and CFS-A (OR, 4.31; 95% CI, 2.41-7.69; $P < 0.001$) were found to predict mortality at 12 months post-hospitalisation. Over the same period, CFS (OR, 2.59; 95% CI, 1.81-3.69; $P < 0.001$) and CFS-A (OR, 3.59; 95% CI, 2.13-6.02; $P < 0.001$) also

Table 2. Adverse Outcomes between CFS and CFS-A at Initial Hospitalisation and 6-Month and 12-Month Follow-Up

Frailty Measure	Mortality			Institutionalisation and/or Mortality			Functional Decline and/or Mortality		
	Initial Hospitalisation	6 Months	12 Months	Initial Hospitalisation	6 Months	12 Months	Initial Hospitalisation	6 Months	12 Months
CFS									
Group 1 (CFS 1 to 5)	0/89 (0.0%)*	4/89 (4.5%)†	7/89 (7.9%)†	2/89 (2.2%)*	7/86 (8.1%)†	11/86 (12.8%)†	29/89 (32.6%)	42/86 (48.8%)	41/86 (47.7%)
Group 2 (CFS 6 to 8)	8/121 (6.6%)*	38/121 (31.4%)†	50/121 (41.3%)†	11/121 (9.1%)*	44/120 (36.7%)†	57/120 (47.5%)†	37/121 (30.6%)	64/120 (53.3%)	63/120 (52.5%)
Unadjusted OR (95% CI)	–	9.73 (3.33 – 28.5)	8.25 (3.52 – 19.35)	4.25 (0.94 – 20.14)	6.53 (2.77 – 15.4)	6.17 (2.98 – 12.8)	0.91 (0.51 – 1.64)	1.19 (0.69 – 2.08)	1.21 (0.68 – 2.11)
CFS-A									
Group 1 (CFS 1 to 5)	0/69 (0.0%)*	3/69 (4.3%)†	5/69 (7.2%)†	0/69 (0.0%)*	4/66 (6.1%)†	7/66 (10.6%)†	22/69 (31.9%)	25/66 (37.9%)*	26/66 (39.4%)*
Group 2 (CFS 6 to 8)	8/141 (5.7%)*	39/141 (27.7%)†	52/141 (36.9%)†	13/141 (9.2%)*	47/140 (33.6%)†	61/140 (43.6%)†	44/141 (31.2%)	81/140 (57.9%)*	78/140 (55.7%)*
Unadjusted OR (95% CI)	–	8.41 (2.48 – 28.33)	7.48 (2.83 – 19.80)	–	7.83 (2.69 – 22.84)	6.51 (2.78 – 15.25)	0.97 (0.52 – 1.80)	2.25 (1.24 – 4.10)	1.94 (10.7 – 3.51)

CFS: Clinical frailty scale; CFS-A: Clinical frailty scale algorithm; CI: Confidence interval; OR: Odds ratio
Four patients were lost to follow-up and excluded from 6-month and 12-month analyses.
*P <0.05 (between group 1 and group 2).
†P <0.001 (between group 1 and group 2).

Table 3. Comparison of AUC in Predicting Adverse Outcomes between CFS and CFS-A at Initial Hospitalisation and 6-Month and 12-Month Follow-Up

Frailty Measure	Initial Hospitalisation	6 Months	12 Months
	AUC (95% CI)	AUC (95% CI)	AUC (95% CI)
Mortality			
CFS	0.77 (0.65 – 0.88)*	0.77 (0.70 – 0.85)†	0.78 (0.72 – 0.85)†
CFS-A	0.72 (0.57 – 0.86)*	0.73 (0.65 – 0.81)†	0.73 (0.66 – 0.81)†
Institutionalisation and/or mortality			
CFS	0.63 (0.49 – 0.78)	0.74 (0.66 – 0.81)†	0.75 (0.68 – 0.81)†
CFS-A	0.67 (0.56 – 0.78)*	0.72 (0.64 – 0.80)†	0.71 (0.64 – 0.79)†
Functional decline and/or mortality			
CFS	0.49 (0.40 – 0.57)	0.53 (0.46 – 0.61)	0.58 (0.50 – 0.66)*
CFS-A	0.45 (0.37 – 0.52)	0.56 (0.48 – 0.64)	0.59 (0.52 – 0.67)*

AUC: Area under receiver operating characteristic curves; CFS: Clinical frailty scale; CFS-A: Clinical frailty scale algorithm; CI: Confidence interval
Four patients were lost to follow-up and excluded from 6-month and 12-month analyses. Composite outcomes of institutionalisation and/or mortality and functional decline and/or mortality were used as mortality and assumed to lead to either outcome. All receiver operating characteristic curve (ROC) contrasts were not significant (see Figure 2 for ROC diagrams).
*P <0.05.
†P <0.001.

predicted institutionalisation and/or mortality. CFS-A, but not CFS, significantly predicted functional decline and/or mortality (OR, 1.65; 95% CI, 1.13-2.40; P = 0.01) at 12 months post-hospitalisation.

Discussion

A recent study which used a large English inpatient database reported that frailty accounted for almost one-half of all hospitalisation days even when only one-fifth of patients were frail.[11] This highlights the pressing need to incorporate systematic and early identification of frailty in acute care settings to facilitate appropriate patient-centred care plans for this at-risk group.[24] Disconcertingly, a recent scoping review of frailty studies in acute care reported that two-thirds of studies identified participants as frail without measuring frailty and there was great variability in tools used.[25] Of note, CFS is increasingly used in acute settings to identify frailty and to grade its severity to help formulate care plans and improve shared decision-making.[26-28] Our study adds to the body of evidence by corroborating inter-rater reliability, diagnostic performance and predictive validity of CFS-A.

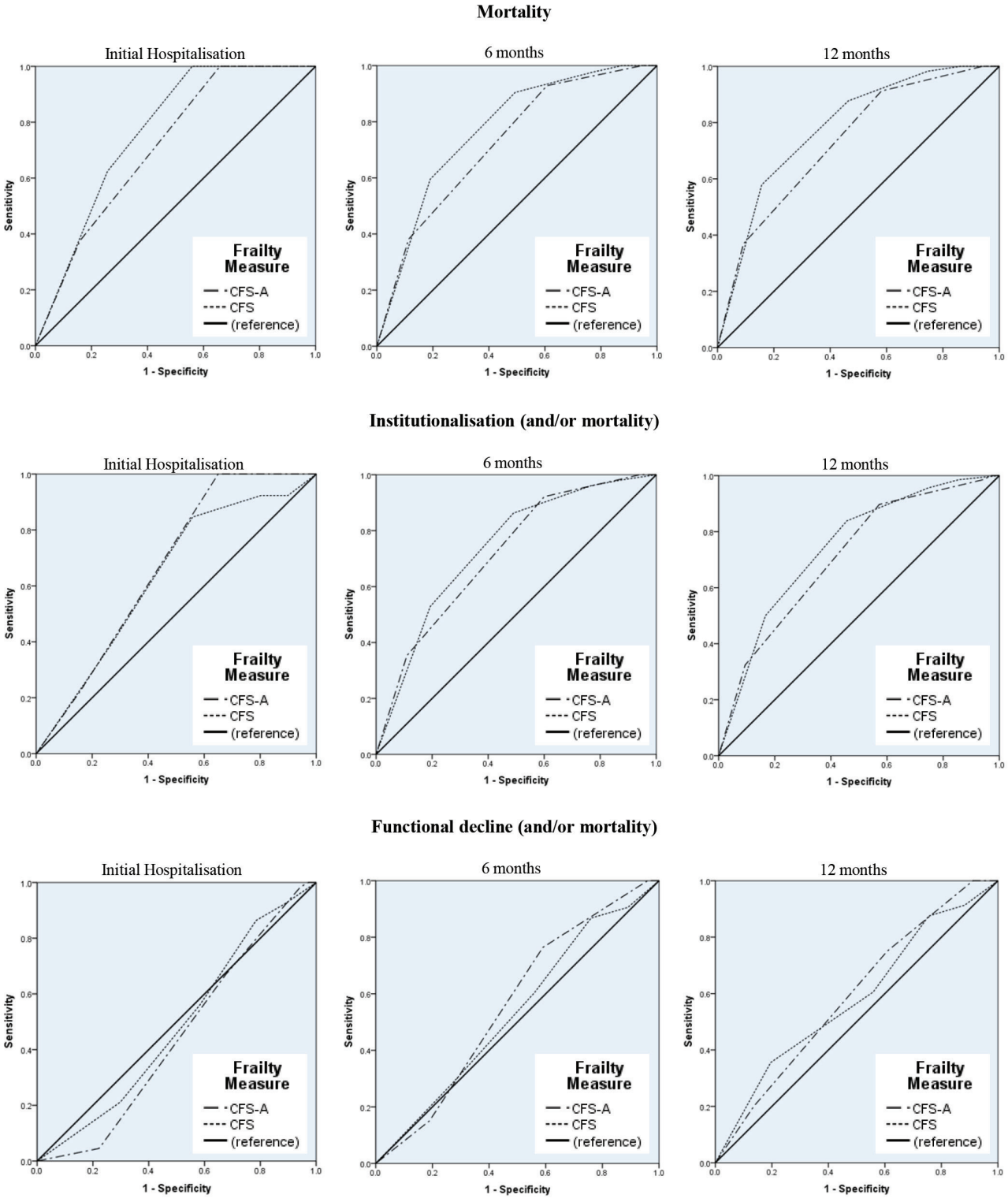

Fig. 2. Graphs showing the AUC for CFA and CFS-A in predicting adverse outcomes at initial hospitalisation and 6-month and 12-month follow-up. AUC: Area under receiver operating characteristic curves; CFS: Clinical frailty scale; CFS-A: Clinical frailty scale algorithm.

Table 4. Comparison between CFS and CFS-A in Predicting Adverse Outcomes

Frailty Measure	Initial Hospitalisation	6 Months	12 Months
	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Mortality			
CFS	3.74 (1.15 – 12.10)*	3.19 (1.98 – 5.17)†	3.59 (2.28 – 5.67)†
CFS-A	3.39 (1.05 – 10.97)*	3.76 (2.08 – 6.82)†	4.31 (2.41 – 7.69)†
Institutionalisation and/or mortality			
CFS	1.57 (0.88 – 2.81)	2.45 (1.67 – 3.60)†	2.59 (1.81 –3.69)†
CFS-A	2.70 (1.10 – 6.64)*	3.63 (2.09 – 6.32)†	3.58 (2.13 – 6.02)†
Functional decline and/or mortality			
CFS	1.02 (0.79 – 1.29)	1.09 (0.87 – 1.36)	1.25 (0.99 – 1.57)
CFS-A	0.86 (0.59 – 1.24)	1.35 (0.94 – 1.93)	1.65 (1.13 – 2.40)*

CFS: Clinical frailty scale; CFS-A: Clinical frailty scale algorithm; CI: Confidence interval; OR: Odds ratio
Adjusted for age, gender and severity of illness. Four patients were lost to follow-up and excluded from 6-month and 12-month analyses.
*P <0.05.
†P <0.001.

The initial study of the 7-point CFS showed an intra-class correlation coefficient (ICC) of 0.97 (P <0.001) between 2 measures at different times.[14] Subsequent studies have demonstrated high inter-rater reliability when CFS was administered by clinicians (kappa, 0.76; 95% CI, 0.68-0.84; n = 104),[29] nurses (ICC, 0.97; 95% CI, 0.94-0.98; n = 30)[30] and even when administered telephonically (kappa, 0.69; P = 0.002; first 20 ratings).[16] However, there is still a paucity of data on the accuracy of CFS scoring by different clinicians in a busy acute care setting. Although previous studies have shown that CFS is quick and easy to use, no large-scale study has compared the accuracy of these scores against those scored following a CGA. Recently, a small study reported a Cohen's kappa coefficient of 0.64 when CFS scores were compared between an interview-based CFS and a chart review data score.[31] In our study, we demonstrated greater inter-rater agreement when CFS is scored by expert clinicians using a standardised algorithmic approach (CFS-A). We will, however, need to evaluate if these results can be replicated by other non-expert healthcare professionals.

The excellent inter-rater agreement attests to the inter-rater reliability of CFS-A. This is attributed to the standardised and systematic algorithmic approach to frailty identification via 6 key questions of the patient's health status that reduces assessor variability which can be caused by different interpretations of each CFS category descriptors. In our study, the independent raters found that CFS-A was easy to use and were generally able to assign CFS scores within 1 to 2 minutes. Hence, by providing a user-friendly and systematic approach to frailty identification and severity grading, there is potential for scalability to other acute non-ward-based care settings such as the emergency department, intensive care units and evaluation by non-physicians. The finding of lower agreement with standard CFS may pertain more to the limitations of retrospective scoring of CFS-A that used database variables and it would require further evaluation in real-world comparative studies.

Our findings also suggest that frailty is highly prevalent in the acutely ill hospitalised oldest-old (>80 years). This corroborates the findings of previous studies that reported increasing age as a strong predictor of frailty.[32,33] In contrast to CFS, the higher detection rate of frailty by CFS-A was likely due to the fact that it was designed to detect the slightest impairment in physical functioning. In CFS-A, the loss of at least 1 basic ADL suggests moderate frailty (CFS 6) and the loss of all basic ADLs would suggest severe to very severe frailty (CFS 7 or 8).

Similar to previous studies, frailty measured by CFS was found to be an independent predictor of adverse health outcomes following acute hospitalisation.[12,15,27,34] However, CFS-A appears to better predict mortality, institutionalisation and length of hospital stay in individuals with moderate to severe frailty compared to those who are robust to mildly frail. One plausible explanation for this observation is that CFS-A can better discriminate between mild (CFS 5) and greater severity of frailty (CFS 6 and above) since it takes into account the basic ADLs of an individual. In previous studies, the loss of independence in personal care is strongly associated with poorer health outcomes.[35-38] Thus, the ability of CFS-A to clearly distinguish between these 2 pivotal categories may explain partly why it is a better predictor of adverse health outcomes than standard CFS.

A recent commentary has emphasised the need for more comprehensive and coordinated inclusion of frailty into clinical management protocols and models of care.[39]

It is therefore important that CFS assessments—when performed rapidly and in the absence of a CGA—are done accurately. This is because information generated from CFS (frailty identification and severity grading) has potential to help formulate individualised care plans and improve shared decision-making in acute care settings. For instance, specific interventions may be designed to prevent iatrogenic disability[40] in prefrail and mildly frail older adults while conversations about advance care planning should be initiated with those who have severe frailty. However, it is also important to recognise that interventions should go beyond targeted individuals to include redesigning hospital infrastructure, remodelling care processes and bringing together multiple stakeholders in the community, healthcare sector, academia, and policymaking to create a frailty-ready healthcare system.[3,39]

Our study had a number of limitations. First, CFS was originally designed as a global synthetic tool that is best scored following CGA by a trained assessor.[5,15] As such, the reductionist approach of an algorithm may result in the loss of some finesse of global judgement in CFS scoring. This consideration may be especially salient in complex cases. Nevertheless, both measures provide comparable diagnostic and predictive performances. This suggests that either approach can be used effectively. However, CFS-A offers more rapid administration and a possibility of lower inter-rater variability.

Second, the retrospective nature of scoring CFS-A based on database variables from our earlier study—and the fact that we needed to reduce the number of CFS categories to 5 instead of 9—may have reduced variability between raters and potentially overestimated CFS-A's inter-rater agreement. Third, both scores were completed by expert clinicians in geriatric medicine and it is unclear whether the high level of agreement can be replicated by other healthcare workers.

Fourth, our study is limited to acutely ill hospitalised oldest-old patients. As such, we cannot generalise the finding of the reliability and diagnostic performance of CFS-A to younger and more robust populations. Finally, 4 participants were lost to follow-up and were excluded from follow-up analyses. Nonetheless, this low dropout rate had no material impact on the results of our study and we were able to determine their mortality status from local hospital electronic medical records.

Conclusion

In conclusion, our study supports the effectiveness of the use of a standardised approach to assess frailty in acutely ill hospitalised older adults. CFS-A shows potential for consistent and efficient administration of CFS across various acute care settings. Moving forward, we aim to conduct a prospective study to validate CFS-A in community-dwelling individuals to be administered by various healthcare workers with the hope to encourage its wider use beyond acute hospital care.

Acknowledgement

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Appendix

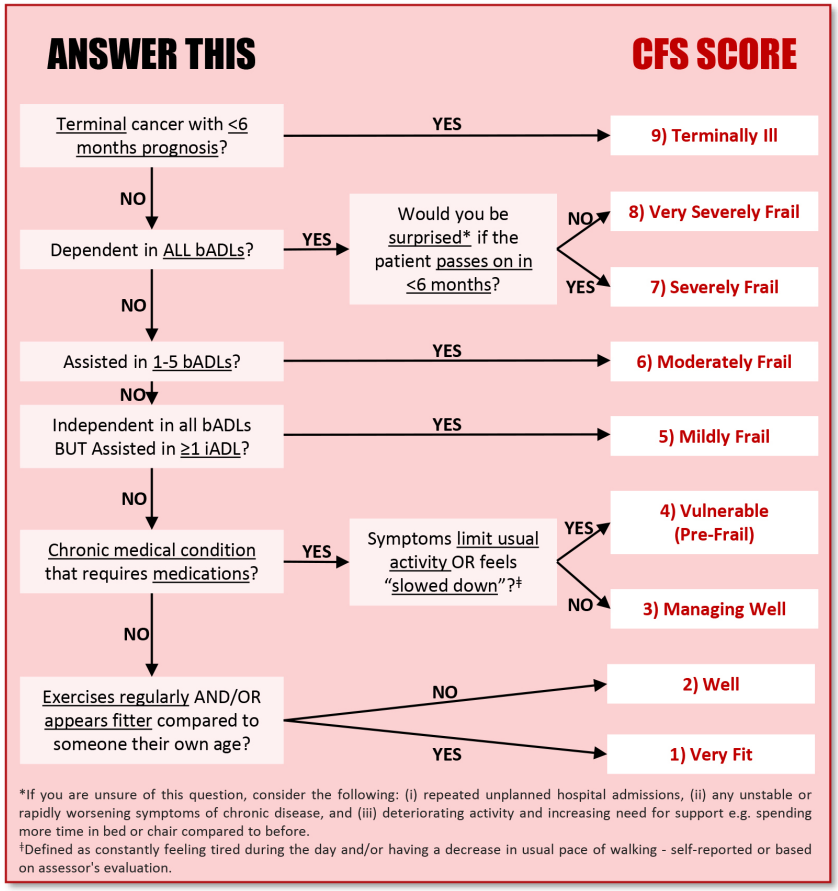
GUIDE TO SCORING

CLINICAL FRAILTY SCALE

The Clinical Frailty Scale (CFS) is a 9-point clinical assessment tool designed to assist healthcare professionals in evaluating a person's frailty status across various clinical settings.
It serves to assist clinicians in identifying frailty, risk stratification, and guide clinical management.

IDENTIFYING PREMORBID FRAILTY STATUS

1. When hospitalized, it is important to identify a patient's **premorbid frailty status.**
2. Premorbid frailty status should be a reflection of the patient's overall health **at least 2 weeks prior** to their acute illness and/or functional decline.



*If you are unsure of this question, consider the following: (i) repeated unplanned hospital admissions, (ii) any unstable or rapidly worsening symptoms of chronic disease, and (iii) deteriorating activity and increasing need for support e.g. spending more time in bed or chair compared to before.
‡Defined as constantly feeling tired during the day and/or having a decrease in usual pace of walking - self-reported or based on assessor's evaluation.

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CFS CATEGORIES

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3 Managing Well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order iADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).

8 Very Severely Frail – Completely dependent, approaching end of life. Typically, they could not recover even from a minor illness.

9 Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Basic ADL (DE²ATH)

Dressing
Eating (feeding self)
Evacuation (bladder/bowel)
Ambulation (walking/transfer)
Toileting
Hygiene (bathing)

Instrumental ADL (SHAFT²)

Shopping
Housekeeping
Accounting
Food preparation
Transportation
Takes own medications

Guide to Scoring Clinical Frailty Scale. Version 2.0 (13th April 2018) Produced by the Department of Geriatric Medicine, Tan Tock Seng Hospital

Electronic Bicycles and Scooters: Convenience at the Expense of Danger?

Dear Editor,

Electronic bicycles and scooters—or personal mobility devices (PMDs)—are becoming popular means of commute given their convenience, low cost and ease in obtaining regulatory approval. They have also been successfully marketed as a fun and environment-friendly way to travel. However, the recent surge in PMD-related accidents is cause for concern. Singapore has witnessed a threefold increase in PMD-related accidents between 2016 (n = 46) and 2017 (n = 128).[1] In the first half of 2017, there were 4 mortalities and up to 90 injuries reported.[2] In an effort to regulate the sale and usage of PMDs in the country, the Singapore government passed the Active Mobility Act in January 2017 (Fig. 1).[3-5] Since May 2018, the Land Transport Authority (LTA) has been regulating the use of PMDs under the Act.[4,5]

In light of the spike in PMD-related accidents, our study aimed to examine the prevalence, patterns and severity of injuries related to the use of PMDs in our institute. A secondary objective was to identify trends that could potentially improve current safety regulations.

Materials and Methods

A retrospective review of patients admitted to Tan Tock Seng Hospital for PMD-related accidents between January 2014 and November 2017 was conducted. We included patients with tiers 1 and 2 injuries defined as having an injury severity score (ISS) of at least 9. We excluded

Fig. 1. Safety regulations governing the sale and use of PMDs under the Active Mobility Act (infographics by authors). PAB: Power-assisted bicycle; PMA: Personal mobility aid; PMD: Personal mobility device.

patients below 16 years old since they were transferred to the nearest paediatric hospital after stabilisation. Patient demographics, injury profile and helmet use were obtained from electronic medical records. Data on surgeries, length of stay, mortality and hospital bills were collected.

Results

A total of 22 PMD-related accidents with ISS of at least 9 were seen in our centre. Over the years, we observed an increasing trend of accidents with significant injuries. There were 6 accidents in 2015, 7 in 2016 and 9 in 2017 (Fig. 2). The mean age of patients was 48.8 ± 19.3 years (range, 16-73 years). Most were males (82%) and Chinese (63.6%), followed by Malays (18.2%), Indians (13.6%) and others.

Mean ISS score was 17.7 ± 10.0. It was highest in 2017 at 23.4. The most common PMD-related injuries involved the head and neck region followed by extremities (Fig. 3). There were 3 deaths in this study.

Nine injuries occurred on the roads and involved other vehicles. Mean ISS score was higher for PMD accidents that occurred on roads and involved other vehicles (19.1 vs 11.8, $P = 0.195$). Two of the 3 deaths occurred on roads ($P = 0.476$). Only 4 patients had donned helmets. ISS score in patients without helmets was higher than in patients with helmets (18.7 vs 13.5, $P = 0.365$). All 3 deaths occurred in patients without helmets (Fig. 4).

A total of 8 (32%) patients required surgery. The most common surgeries performed were related to bony fractures of extremities and spine followed by soft tissue debridement and repair. Mean hospital stay was 4 days (range, 1 to 16 days) and annual average hospital bill ranged from $2700 to $4300 (Table 1).

Discussion

PMD-related accidents highlight a significant public health issue. Their rising incidence could be explained by the rapid adoption of PMDs over the years and the recent introduction of safety regulations mandated by the government.[6] It was also aggravated by a lack of public awareness of the perils of PMDs and regulations enshrined in the Active Mobility Act. Besides a spike in the number of PMD-related accidents, there was also a rise in the severity of injuries (higher ISS score) and mortality.[7]

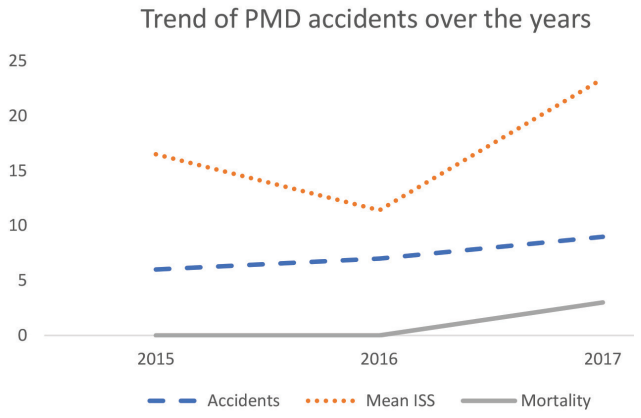

Fig. 2. Growing trend of PMD-related accidents, ISS and mortality. ISS: Injury severity score; PMD: Personal mobility device.

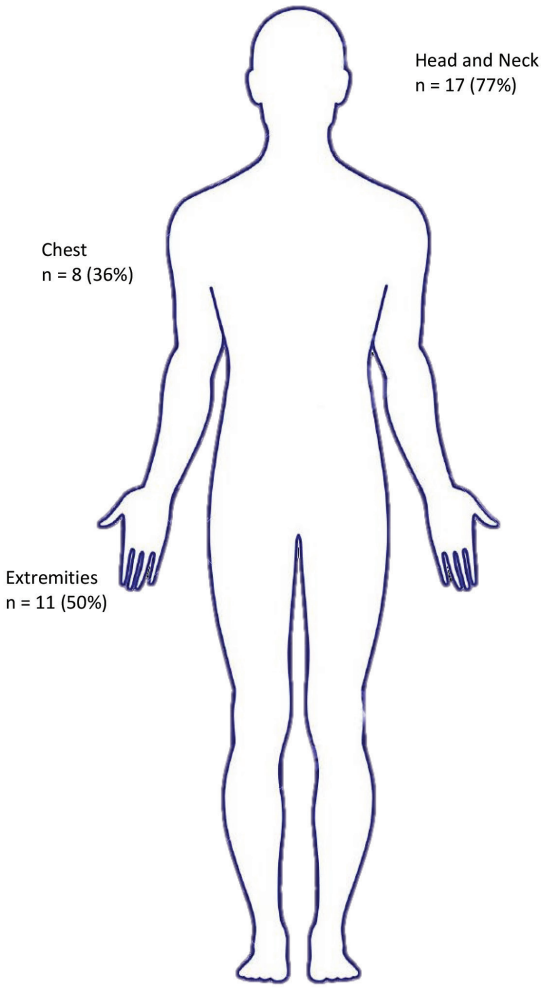

Fig. 3. Injury profile of users of personal mobility devices.

In our study, riders who suffered injuries tended to be males in their 40s. This observation was corroborated by similar findings in current literature (Table 2).[8-10] The impact of injuries in this age group is more than just health-related morbidities. They also include the loss of productive years, long-term cost of caregiving and opportunity cost to the economy. Although mean inpatient stay ranged from 2 to 5 days, it did not include the period of rehabilitation required to achieve functional recovery. The adjusted average hospital bill size also ranged from $2600 to $4300 for each patient.

The most common injuries were seen in the head and neck region. This is a common finding in the literature.[8-10]

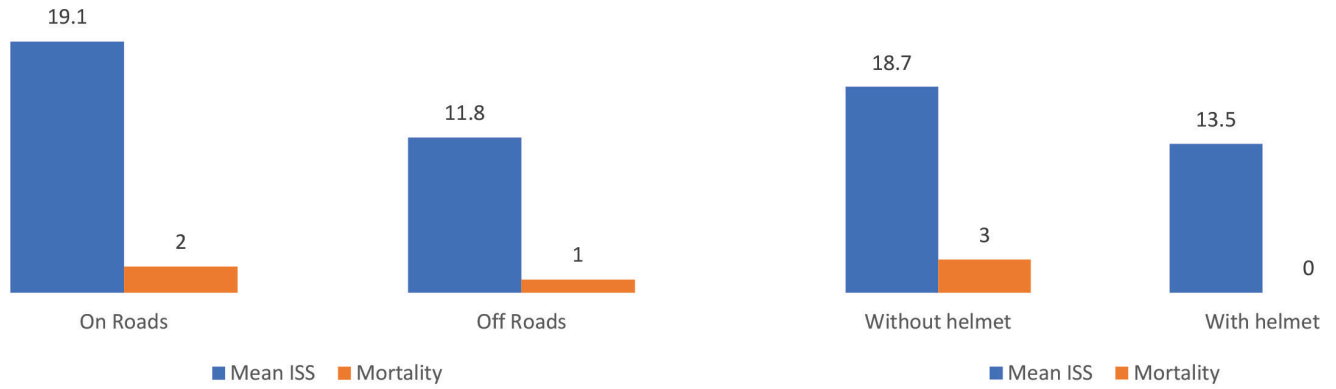

Fig. 4. Association between accidents that occurred on roads and helmet use with ISS/mortality rates. ISS: Injury severity score.

Table 1. Length of Hospital Stay and Hospital Bill Size between 2015 and 2017

	2015	2016	2017
Mean hospital stay (days)	4.8	5.9	2.1
Annual hospital bill ($)	21,306.60*	29,504.50	24,612.50
Average hospital bill ($)	4261.30	4214.90	2734.70
Adjusted average for 2014 healthcare cost ($)†	4265.80	4174.50	2642.60

*Excludes a patient with a medical bill of $22,500 in 2015.
†Adjusted to 2014 dollars based on healthcare division of consumer price index (www.singstat.gov.sg).

In our study, all 3 mortalities were riders who had sustained fatal head and neck injuries and did not wear helmets. The failure to don helmets is one of the most common reasons that has been attributed to the rise in PMD-related injuries in China.[11] It is therefore important that there are preventive measures in place to ameliorate head and neck injuries related to PMD accidents. The authors feel that helmet use should be enforced.

One observation from our study was that injuries sustained on roads where PMDs were not allowed were more severe than those that were. The 3 mortalities in our study occurred on roads where PMDs had collided with other vehicles. As such, public awareness on road safety and designated pathways where PMDs are allowed should be raised. Much value can be gained from improving traffic infrastructure by building more designated paths for PMDs since shared paths between pedestrians and PMDs may still risk injuries to pedestrians due to the faster travel speed—albeit strict (<25 km/h)—of PMDs.

In our study, mean ISS score of 17.7 was higher than that reported in studies from China, Israel and Switzerland (Table 2). Although this result may be attributed to the selection

Table 2. Summary of Literature on PMD-Related Injuries

First Author	Year	Country	PMD Type	Age Group	Mean ISS Score	Most Common Injury	No Helmet Use	Surgery Required	In-Hospital Mortality
Zhou	2017	China	Electric bicycles (n = 482)	41 – 60	10	1) Head 2) Extremities 3) Trunk	–	34.9%	6.26%
Siman-Tov	2016	Israel	Electric bicycles, electric scooters (n = 795)	<14	1 – 14	1) Head 2) Face and neck	–	–	0.37% (n = 3)
Weber	2014	Switzerland	Electric bicycles (n = 504)	40 – 65	–	–	43.8%	–	0.4% (n = 2)
Papoutsi	2014	Switzerland	Electric bicycles (n = 23)	21 – 62	8.48	1) Head 2) Face and neck 3) Extremities	25%	–	–

ISS: Injury severity score; PMD: Personal mobility device

of only tiers 1 and 2 injuries in our study, the severity of injuries continues to highlight the perils faced by users of PMDs in this country. Mortality (13.6%) was also much higher in our study compared to the study by Papoutsi and associates who used a comparable sample size and did not report any mortality in their study.[10] The number of patients (36.4%) who required surgery for PMD-related accidents in our study were similar to the study by Zhou and colleagues.[8]

The limitations of our study include the small number of PMD-related accidents seen in a single institute. However, it is the first study in Singapore to highlight the prevalence of severe PMD-related injuries, injury patterns and mortality. Future studies will include a collaborative nationwide study of PMD-related accidents and factors that influence safe riding practices. It is also important to compare the incidence and severity of PMD-related accidents before and after the implementation of the Active Mobility Act.

Conclusion

Accidents involving electronic bicycles and scooters are a rising national health, economic and social problem. To truly enjoy the cost efficiency and convenience offered by PMDs, public awareness should be heightened on its potential perils and legislation should be tightened to ensure safety regulations are adhered to. Donning of helmets should be considered to ameliorate serious head and neck injuries in PMD-related accidents.

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First Percutaneous Tricuspid Valve Repair with MitraClip Device in Singapore

Dear Editor,

Treatment of patients who have severe mitral regurgitation (MR) and tricuspid regurgitation (TR) is surgical repair or replacement. However, it becomes a therapeutic challenge in patients who are at prohibitive surgical risk. In such patients, percutaneous edge-to-edge repair of mitral valve with the MitraClip system (Abbott Vascular, Santa Clara, CA, USA) has demonstrated its clinical efficacy and safety. For the tricuspid valve, various percutaneous techniques are emerging rapidly.[1] We report a patient in cardiogenic shock from severe MR and TR who underwent percutaneous repair of both valves using the MitraClip system. This is the first successful percutaneous intervention of the tricuspid valve in Singapore.

Case Presentation

A 68-year-old lady was transferred to our institution for further management of refractory heart failure from severe MR and TR. She had a history of primary biliary cirrhosis and underwent a living donor liver transplant in 2014, stage 3 chronic kidney disease, atrial fibrillation, moderate-to-severe functional MR and severe TR. She was initially admitted to 2 other institutions before transferring to our centre. Her hospital stay was stormy and prolonged (close to 3 months) with repeated intensive care unit (ICU) admissions for heart failure that required inotropes and mechanical ventilation as well as hospital-acquired pneumonia. In addition, her kidney function took a toll and required dialysis.

During our evaluation, she was in cardiogenic shock and was inotropic-dependent for 2 weeks. Echocardiography showed severe functional MR (Fig. 1A) from a dilated mitral annulus of 3.5 cm; tenting of mitral valve with restricted posterior leaflet motion; and massive functional TR (Figs. 2A-B) from a dilated tricuspid annulus of 4.5 cm with a central broad jet arising from incomplete coaptation between the anterior-septal leaflets and anterior-posterior leaflets. Using three-dimensional (3D) transoesophageal echocardiography (TEE) volumetric dataset, 3D-derived effective regurgi-tant orifice area (EROA) for TR was 1.09 cm^2 which would conventionally be classified as severe,[2] but would be considered massive based on a new TR severity grading scheme proposed by Hahn and Zamorano.[3] Her left ventricle (LV) was dilated (LV end-diastolic diameter, 6.2 cm; indexed by BSA 3.6 cm/m^2) with LV ejection fraction of 40%. Her right ventricle (RV) was also dilated (RV inlet diameter, 6.5 cm) with impaired systolic function (tricuspid annular plane systolic excursion, 1.3 cm; RV fractional area change, 16%). Additionally, there was flattening of interventricular septum during diastole indicative of significant RV volume overload. Coronary angiography showed minor coronary artery disease. She was evaluated by cardiac surgeons who deemed her too frail and high risk for open heart surgery (EuroSCORE II and STS scores for mortality were 25.9% and 56.6%, respectively).[4,5] After a heart team discussion, she was subsequently offered off-label use of the percutaneous MitraClip device to treat both severe MR and TR. Our aim was to stabilise her haemodynamic status and prevent further ICU admissions for heart failure.

The procedure was performed by a multidisciplinary team comprising interventional cardiologists, echocardiologists, a cardiac anaesthesiologist, nurses and a radiographer. The patient was placed under general anaesthesia and mechanically ventilated during the procedure. Our plan was to first treat the mitral valve and then the tricuspid valve. Vascular access was obtained through the right femoral vein. Transseptal puncture was performed under TEE guidance. A single MitraClip was deployed at the A2/P2 segment where the predominant MR jet was (Fig. 1B). This reduced the overall MR grade from 4+ to 2+ (Fig. 1C). The mean pressure gradient was 3 mmHg and the 3D mitral valve area was 2.9 cm^2.

The steerable guide catheter (SGC) was withdrawn across the interatrial septum into the right atrium and positioned above the tricuspid valve leaflets. The clip delivery system was inserted with the blue line rotated 90 degrees anti-clockwise (miskey) and exited the SGC straddled. Using TEE and fluoroscopic guidance, the SGC was turned clockwise while the "A" knob was slowly turned to steer the clip towards the tricuspid valve. Using the tricuspid valve inflow-outflow view with X-plane, the clip was advanced across the tricuspid valve annulus and positioned at the coaptation between the anterior and septal leaflets.

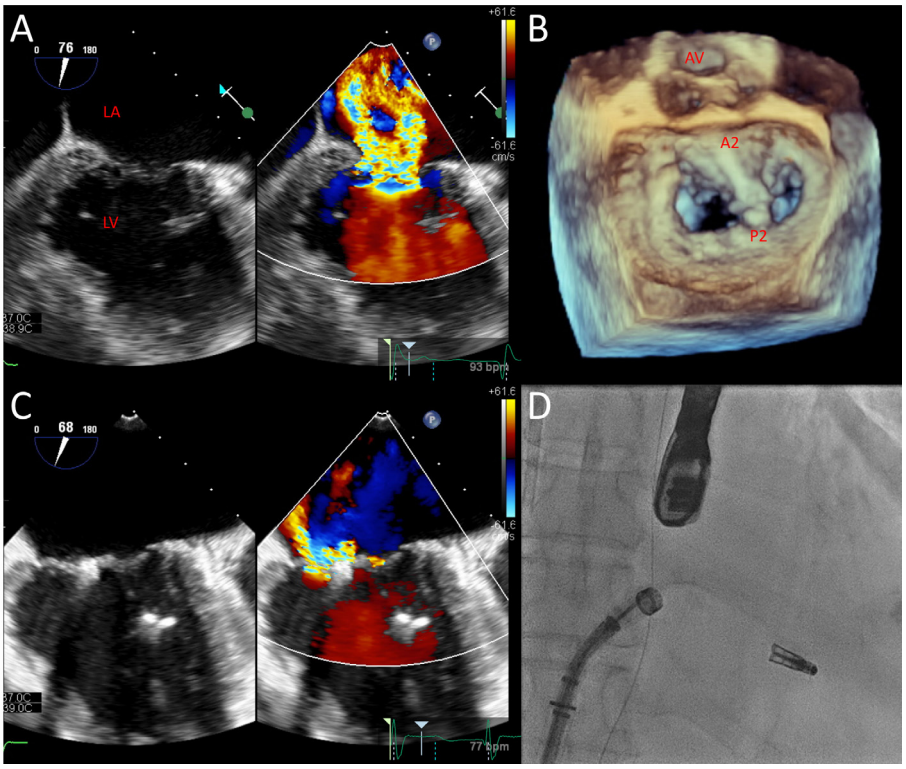

Fig. 1. A: Preprocedural transoesophageal echocardiogram in the intercommissural view shows 4+ functional mitral regurgitation with a central jet. B: Three-dimensional view of the mitral valve (surgical view from left atrium) shows deployment of single MitraClip to the A2/P2 segment. C: Reduction of overall mitral regurgitation grade to 2+. D: Fluoroscopic view of deployed MitraClip. AV: Aortic valve; LA: Left atrium; LV: Left ventricle

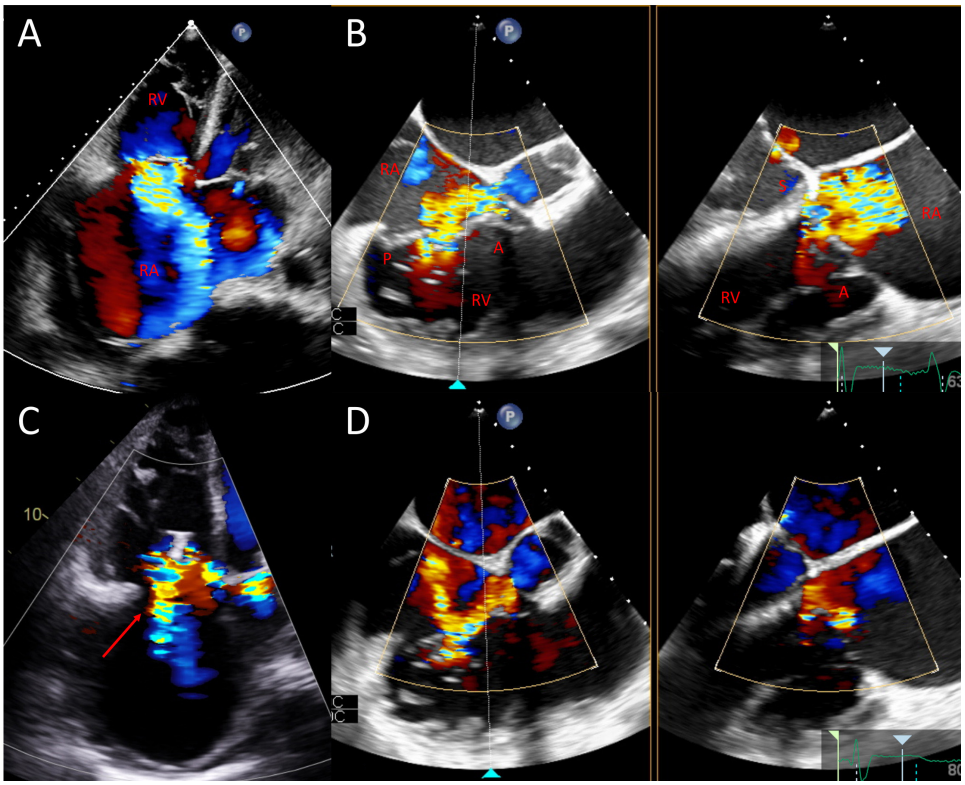

Fig. 2. Preprocedural massive tricuspid regurgitation in (A) transthoracic apical 4-chamber and (B) transoesophageal tricuspid valve inflow-outflow view with X-plane. C and D: Clip was deployed between the anterior and septal leaflets with reduction in tricuspid regurgitation (red arrow). A: Anterior tricuspid leaflet; P: Posterior tricuspid leaflet; RA: Right atrium; RV: Right ventricle; S: Septal tricuspid leaflet

We applied manual compressive pressure over the anterior precordium to enhance tricuspid leaflets approximation during grasping of tricuspid leaflets. Anterior and septal leaflet grasp was imaged with adequate tissue seen within the clip before deployment (Figs. 3A-C). TR severity was reduced from massive to moderate (Figs. 2C-D). The 3D-derived EROA for TR was reduced from 1.09 cm^2 to 0.59 cm^2 at the end of the procedure (46% reduction). Final mean trans-tricuspid valve gradient was 1 mmHg.

Postprocedural care was uneventful and she was successfully weaned off inotropic support. She underwent a period of rehabilitation and was discharged home.

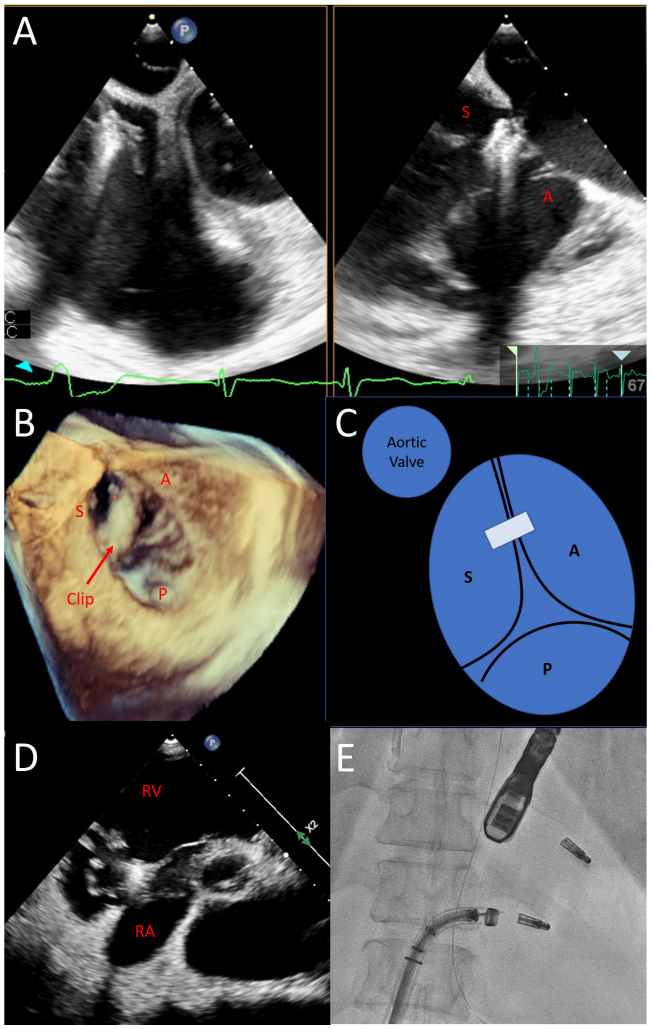

Fig. 3. A: Grasping of anterior and septal leaflets was imaged with adequate tissue seen within the clip before deployment. B: Three-dimensional view (surgical view from right atrium) of clip deployment. C: Schematic diagram of clip deployment. D: Modified short axis view on transthoracic echocardiogram shows stable deployment of clip between anterior and septal leaflets. E: Final fluoroscopic view shows deployment of clips in mitral (superior) and tricuspid (inferior) valves. A: Anterior tricuspid leaflet; P: Posterior tricuspid leaflet; RA: Right atrium; RV: Right ventricle; S: Septal tricuspid leaflet

Discussion

The past decade has seen rapid advancement in structural heart interventions that have expanded treatment options for patients with aortic, mitral, pulmonary and even tricuspid valve disease. Severe TR has been shown to be associated with significant mortality and morbidity.[6,7] Thus far, treatment options for severe TR are limited. Medical management is restricted mostly to the use of diuretics which provides symptomatic relief but does not prevent disease progression. Surgical repair or replacement is reserved for patients with severe TR undergoing left-sided valve surgery and those with isolated TR who are symptomatic despite optimal medical therapy.[8,9] However, the benefit of isolated surgery on prognosis is not clear and perioperative mortality is high.

Additionally, the prognostic impact of surgical tricuspid valve repair in patients with concomitant functional TR undergoing left-sided open heart surgery is also not clear.[10] Currently, multiple percutaneous techniques to address TR have been developed to address this unmet need.[1] The most widely used is edge-to-edge repair technique using the MitraClip system and its safety and feasibility have been demonstrated in several overseas studies.[11-13] Favourable short-term outcomes (6 months and 30 days) have been seen in reduction of TR severity and improvement in functional status even as we await results from larger studies with longer-term outcomes.[12,13]

Our case is the first successful percutaneous intervention of the tricuspid valve in Singapore using the MitraClip system. It paves the way for future transcatheter therapies in tricuspid valve repair. The tricuspid valve is no longer the "forgotten valve" and patients with severe TR who are not candidates for open valve surgery could now be treated with the use of catheter-based techniques.

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*HLA-B*5701* Genotyping for Abacavir Prescription: Re-Examination of its Cost-Effectiveness in Singapore

Dear Editor,

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) that is used to control disease progression of human immunodeficiency viruses (HIV). It reduces the morbidity and mortality of HIV infections.[1] A serious side effect of abacavir is hypersensitivity reaction (HSR) which usually begins within 6 weeks of starting treatment and manifests as fever, malaise, nausea, vomiting and rashes. In severe cases, it results in multiple organ system failure.[2]

Patients with *HLA-B*5701* polymorphism are more likely to develop HSR.[3] Studies from several countries have demonstrated the efficacy of screening for this polymorphism prior to abacavir prescription.[4,5] A large-scale clinical trial has provided strong evidence to order *HLA-B*5701* genotyping prior to abacavir prescription and to avoid this drug in patients who carry the polymorphism.[6]

We need to assess the cost-effectiveness of screening tests such as *HLA-B*5701* genotyping even when they are shown to be clinically useful.[7] An assessment of the cost-effectiveness of *HLA-B*5701* genotyping before abacavir prescription was carried out in the local context.[8] The parameters used to assess the economic costs of the test include the additional cost of genotyping, prescription of expensive alternative antiretroviral therapy drugs in allele-positive patients, the burden of additional expenses and the loss of health that may be incurred after no such test was carried out. The report concluded that *HLA-B*5701* genotyping was not cost-effective in Singapore except for a specific subgroup of newly diagnosed Indian patients with early-stage HIV in whom tenofovir was contraindicated.

Since the publication of the results of that study, new information on *HLA-B*5701* genotyping has become available that includes the actual price of the test in Singapore, genotype frequency in a real cohort of patients and the actual costs of managing adverse reactions based on physicians' input. We attempted to ascertain whether refinement of data in the cost-effectiveness model would change the conclusions. To ensure consistency with our previous work, we retained the TreeAge model and same data where no new information was available.[8]

Materials and Methods

Our institutional review board verified that ethics review was not needed for this study. Patient data from Tan Tock Seng Hospital (TTSH) was anonymised. In TTSH, most infectious disease physicians order *HLA-B*5701* genotyping when they prescribe abacavir. The Clinical Immunology Laboratory in TTSH has been offering the test since 2015. Information on ethnicity and *HLA-B*5701* status of patients was provided by the laboratory without identifiers. The genotype frequency of Chinese (n = 758), Malay (n = 164) and Indian (n = 53) patients was 0.26%, 2.44% and 15.10%, respectively.

Patients were segmented according to early- and late-stage disease. Similar to the earlier study, late-stage HIV infection is defined as CD4 count <200/μL.[9] Each group was further divided based on tenofovir contraindications into 2 groups: 1) patients who contraindicated to tenofovir and were prescribed abacavir, and 2) patients who could be prescribed both abacavir and tenofovir. In the latter, 4 strategies were examined: 1) abacavir was assigned as first-line (without genotyping) treatment with tenofovir as second-line therapy; 2) abacavir was assigned as first-line (with genotyping) treatment with tenofovir as second-line therapy; 3) tenofovir was assigned as first-line treatment with abacavir as second-line (without genotyping) therapy; and 4) tenofovir was assigned as first-line treatment with abacavir as second-line (with genotyping) therapy. In patients whom tenofovir was contraindicated, 2 strategies were investigated: 1) abacavir was assigned as first-line treatment without genotyping, and 2) abacavir was assigned as first-line treatment with genotyping.

Zidovudine was assigned as next-in-line treatment followed by last-line therapy in both patient groups. All 3 NRTI, abacavir, tenofovir and zidovudine were used with lamivudine. The last line of treatment comprised personalised combination of stavudine, lamivudine, emtricitabine, atazanavir, lopinavir and ritonavir.

The treatment costs and cost structures shown in Table 1 were retrieved from the homepage of TTSH and after consultation with infectious disease physicians. Although we mirrored the cost calculations in the study by Kapoor and associates,[8] we have revised the cost structure to better reflect contemporary clinical practice.

The costs of treating side effects of abacavir, tenofovir and zidovudine were calculated using 2 categories of data: 1) public versus private fees for consultations and tests, and 2) inpatient treatment versus outpatient treatment. We have

Table 1. Cost Structures of Inpatient and Outpatient Treatments with Antiretroviral Drugs

Cost Structure	No. of Consultations	Bed Rest Duration (Week)	No. of Full Blood Count Tests	No. of Renal Panel Tests	No. of Liver Panel Tests	No. of Urine and PCR Tests	No. of Blood Transfusions
Outpatient cost of treating side effects of:							
Abacavir	3	–	3	3	3	–	–
Tenofovir	3	–	3	3	3	3	–
Zidovudine	3	–	3	3	3	–	–
Inpatient cost of treating side effects of:							
Abacavir	–	1	7	7	7	–	–
Tenofovir	–	1	7	7	7	2	–
Zidovudine	–	1	7	7	7	–	1

PCR: Polymerase chain reaction

Each treatment strategy takes into account multiple factors including the number of consultation sessions or duration of bed rest and important biochemical tests.

assumed that the outpatient group received 3 consultations and 3 sets of tests—full blood count, liver and renal panel tests—and the inpatient group was hospitalised for 1 week and received 7 sets of tests. Patients on tenofovir were at risk of renal impairment and they were monitored with urinalysis and protein-creatinine ratio determination while those on zidovudine may have required blood transfusions because of anaemia.

For costs that could not be calculated, we relied on data from the study by Kapoor and associates (Table 2),[6,10-15] especially those that pertained to the treatment of abacavir HSR and abacavir-induced fatalities based on studies done in the United States.[10] All financial costs are shown in US currency based on an exchange rate of S$1.26 to US$1.00 which was the rate used by Kapoor and associates in their study.[8]

Like the earlier study, the cost-effectiveness of *HLA-B*5701* screening was performed in early- and late-stage HIV patients independently in the 3 ethnic groups. Although a threshold of US$50,000 for each quality-adjusted life year (QALY) was used to maintain consistency with our earlier study, we were aware that this benchmark is not without controversy. The Patient Protection and Affordable Care Act (PPACA) of the United States has prohibited the use of thresholds[16] and the quantum of US$50,000/QALY has also been questioned.[17] Costs and QALY have not been discounted and were consistent with the methodology used in the earlier study.

Results

Incremental cost-effectiveness ratio (ICER)—defined as difference in costs between 2 interventions divided by the difference in outcomes for each intervention[14]—was used to compare cost savings enjoyed by early- and late-stage HIV patients under each strategy. Regardless of treatment strategy, Tables 3 and 4 showed that abacavir as first-line therapy without genotyping in all early-stage HIV patients in the 3 ethnic groups was the cheapest and most cost-effective treatment, irrespective of contraindication to tenofovir.

In late-stage HIV patients who could be prescribed abacavir and tenofovir, regardless of treatment strategy abacavir as first-line therapy without genotyping remained the cheapest and the most cost-effective treatment in the Chinese. However, for Malays and Indians, abacavir as first-line therapy with genotyping was the cheapest and most cost-effective strategy. Compared to subjects with abacavir without genotyping, their counterparts who underwent genotyping before abacavir enjoyed lower cost and this made it the dominant therapy in this group of patients.

Discussion

Using updated data, we reviewed the cost-benefit ratio of *HLA-B*5701* genotyping before abacavir prescription. Genotyping was not cost-effective prior to abacavir use in early-stage HIV patients in all ethnicities. However, genotyping of late-stage Malay and Indian HIV patients was cost-effective. This finding differs from the conclusion of the study by Kapoor and associates[8] which showed that genotyping was not cost-effective in all patients except for newly diagnosed, early-stage HIV Indian patients who contraindicated to tenofovir. The main reason for different ICER in the Chinese, Malays and Indians could be attributed to the different prevalence of *HLA-B*5701* gene in the 3 ethnicities. The *HLA-B*5701* gene frequencies

Table 2. Variable Values for Base Case and Corresponding Value Ranges for Sensitivity Analysis in Cost-Effectiveness Modelling

Variable	Base Value	Sensitivity Analysis Range	Source
Cost (US$)			
Mean monthly cost of ABC + lamivudine	92	46 – 184	Tan Tock Seng Hospital
Mean monthly cost of tenofovir + lamivudine	319	160 – 638	Tan Tock Seng Hospital
Mean monthly cost of AZT + lamivudine	372	186 – 744	Tan Tock Seng Hospital
Mean monthly cost of EFV	85	42 – 170	Tan Tock Seng Hospital
Mean monthly cost of hypothetical drug	740	370 – 1480	Tan Tock Seng Hospital
Three clinician consultations due to side effects	210	–	Tan Tock Seng Hospital
*HLA-B*5701* genetic test	110	55 – 220	Tan Tock Seng Hospital
Treatment of ABC-HSR cases	1983	959 – 3836	Tan Tock Seng Hospital
Treatment of intolerable side effects of ABC	1918	959 – 3836	Tan Tock Seng Hospital
Fatal ABC-HSR cases	31,600	15,800 – 63,200	Schackman, et al[*]
Treatment of intolerable side effects of tenofovir	3499	1750 – 7000	Tan Tock Seng Hospital
Treatment of intolerable side effects of AZT	3490	1745 – 6980	Tan Tock Seng Hospital
Routine renal panel and urine analyses	47	–	Tan Tock Seng Hospital
Probabilities			
Mild ABC-HSR cases	0.585	–	Eron, et al[†]
Severe non-fatal ABC-HSR cases	0.408	–	Tan Tock Seng Hospital
Intolerable side effects of tenofovir (%)	7	3 – 15	Tan Tock Seng Hospital
Intolerable side effects of ABC (%)	1	0 – 5	Tan Tock Seng Hospital
Intolerable side effects of AZT (%)	1	0 – 5	Tan Tock Seng Hospital
HSR mortality in ABC-HSR cases (%)	0.03	0 – 0.06	Tan Tock Seng Hospital
*HLA-B*5701* genotyping (%)			
Gene frequency in Chinese	0.26	–	Tan Tock Seng Hospital
Gene frequency in Malays	2.44	–	Tan Tock Seng Hospital
Gene frequency in Indians	15.10	–	Tan Tock Seng Hospital
Positive predictive value in suspected cases	61.20	10 – 90	Mallal, et al[‡]
Negative predictive value in suspected cases	95.50	93.3 – 96.7	Mallal, et al[‡]
Quality of life score			
Early-stage HIV cases	0.781	0.616 – 0.946	Kauf, et al[§]
Late-stage HIV/AIDS cases	0.746	0.572 – 0.92	Kauf, et al[§]
Quality of life decrease due to side effects			
Mild HSR	0.08 (for 3 days)	0.08 (for 1 – 7 days)	Dodek, et al[‖]
Severe HSR	0.15 (for 7 days)	0.15 (for 3 – 15 days)	Pepper, et al[¶]
Fatal HSR	0.36 (for 15 days)	0.36 (for 7 – 30 days)	Freedberg, et al[#]
Mean decrease in ABC-HSR cases (except fatal cases)	0.12 (for 5 days)	0.12 (for 3 – 10 days)	–
Tenofovir side effects	0.15 (for 7 days)	0.15 (for 3 – 15 days)	Similar to severe HSR
Zidovudine side effects	0.15 (for 7 days)	0.15 (for 3 – 15 days)	Similar to severe HSR
Abacavir side effects (except HSR)	0.72	(0.36 – 1.44)	Ratio of mild to severe cases = 1:1

ABC: Abacavir; AIDS: Acquired immunodeficiency syndrome; AZT: Zidovudine; EFV: Efavirenz; HIV: Human immunodeficiency viruses; HSR: Hypersensitivity reaction

[*]Schackman BR, Gebo KA, Walensky RP, Losina E, Muccio T, Sax PE, et al. The lifetime cost of current human immunodeficiency virus care in the United States. Med Care 2006;44:990-7.

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Table 3. Cost-Effectiveness of Treatment Strategies in Newly Diagnosed Early- and Late-Stage HIV Patients on Abacavir and Tenofovir

Treatment Strategy	Cost (US$)	Change in Cost	QALY	Change in QALY	ICER (US$/QALY)
Early-stage					
Chinese					
ABC as first-line without genetic screen	68,661	–	23.25458	–	–
ABC as first-line with genetic test	68,853	192	23.25459	0.000013	14,323,794
TDF as first-line (genetic test before ABC)	142,878	74,025	23.25477	0.00018	412,147,302
TDF as first-line	142,958	79	23.25477	-1E – 06	Dominated
Malays					
ABC as first-line without genetic screen	69,743	–	23.25447	–	–
ABC as first-line with genetic test	70,621	878	23.25459	0.000126	6,985,711
TDF as first-line (genetic test before ABC)	143,026	72,405	23.25477	0.000176	412,134,575
TDF as first-line (no genetic test before ABC)	143046	21	23.25476	-0.00001	Dominated
Indians					
ABC as first-line without genetic screen	76,024	–	23.25384	–	–
ABC as first-line with genetic test	80,887	4863	23.25462	0.000778	6,251,947
TDF as first-line (no genetic test before ABC)	143,561	62,675	23.25472	0.000098	637,809,573
TDF as first-line (genetic test before ABC)	143,883	321	23.25477	0.000055	5,865,668
Late-stage					
Chinese					
ABC as first-line without genetic screen	22,954	–	7.459795	–	–
ABC as first-line with genetic test	23,090	136	7.459801	0.000006	23,154,854
TDF as first-line (no genetic test before ABC)	47,794	24,705	7.459782	-1.8E – 05	Dominated
TDF as first-line (genetic test before ABC)	47,804	24,715	7.459783	-1.8E – 05	Dominated
Malays					
ABC as first-line with genetic screen	23,090	–	7.459801	–	–
ABC as first-line without genetic test	23,329	240	7.459746	-5.5E – 05	Dominated
TDF as first-line (genetic test before ABC)	47,804	24,715	7.459783	-1.8E – 05	Dominated
TDF as first-line (no genetic test before ABC)	47,824	24,735	7.459779	-2.2E – 05	Dominated
Indians					
ABC as first-line with genetic screen	23,090	–	7.459801	–	–
ABC as first-line without genetic test	25,509	2420	7.45946	-0.00034	Dominated
TDF as first-line (genetic test before ABC)	47,804	24,715	7.459783	-1.8E – 05	Dominated
TDF as first-line (no genetic test before ABC)	47,999	24,909	7.45976	-0.00004	Dominated

ABC: Abacavir; HIV: Human immunodeficiency viruses; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year; TDF: Tenofovir
The term "dominated" was used to supplant actual negative cost-effectiveness ratio values. These are values in which the alternative strategy in question was more costly and produced fewer QALY.

reported by Kapoor and associates for the Chinese (1.10%), Malays (1.80%) and Indians (6.30%) were different from the findings of this study.

While screening of *HLA-B*5701* was shown to be cost-effective in countries such as the United States[10] and the United Kingdom,[18] differences in cost structures and population genetics mean that such conclusions could not cross national boundaries. Our study also suggests that the conclusions provided by pharmaco-economic analyses will vary across time because of the accumulation of new data and fluctuating test costs and drug prices.

The study has a few limitations. Specific data was derived from published literature cited in the study by Kapoor and associates that were not necessarily specific to Singapore and when we did not have new information. This included quality of life values. Since we used the same model structure

Table 4. Cost-Effectiveness of Treatment Strategies in Newly Diagnosed Early- and Late-Stage HIV Patients Contraindicated to Tenofovir

Treatment Strategy	Cost (US$)	Incremental Costs	QALY	Incremental QALY	ICER (US$/QALY)
Early-stage					
Chinese					
No genetic test	69,557	–	23.25459	–	–
*HLA-B*5701* test	69,764	208	23.2546	0.000014	15,305,250
Malays					
No genetic test	70,834	–	23.25448	–	–
*HLA-B*5701* test	71,861	1026	23.25461	0.000127	8,061,323
Indians					
No genetic test	78,255	–	23.25387	–	–
*HLA-B*5701* test	84,036	5781	23.25465	0.000788	7,336,974
Late-stage					
Chinese					
No genetic test	23,245	–	7.459805	–	–
*HLA-B*5701* test	23,386	141	7.459811	0.000006	23,361,205
Malays					
*HLA-B*5701* test	23,386	–	7.459811	–	–
No genetic test	23,684	298	7.459758	0.000053	Dominated
Indians					
No genetic test	26,234	2848	7.459484	-0.000326	Dominated
*HLA-B*5701* test	23,386	–	7.459811	–	–

HIV: Human immunodeficiency viruses; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year
The term "dominated" was used to supplant actual negative cost-effectiveness ratio values in which the alternative strategy in question was more costly and produced fewer QALY.

as the earlier study, we experienced the same limitations highlighted in the earlier paper including absence of scenarios of drug resistance, toxicity or co-infections and assumption of constancy in the quality of life throughout a HIV patient's life.[8]

Conclusion

HSR and side effects of abacavir impose a need for rigorous monitoring of HIV patients on highly active antiretroviral therapy. This study attempts to reflect actual clinical practice to accurately assess the cost-effectiveness of genotyping. Based on our findings, we recommend genotyping late-stage Malay and Indian patients irrespective of whether they contraindicated to tenofovir. While we are aware that some clinicians adopt the conservative approach of screening patients of all ethnicities, we believe that this study emphasises the need to subject genetics-based screening tests to continual analysis of cost-effectiveness. This study is useful in informing the "Community Blueprint to End HIV Transmission in Singapore" which constitutes part of the national strategy to eliminate HIV infection in Singapore.[19]

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Painful Purpuric Ulcers of the Legs: A Tell-Tale Sign of Systemic Disease?

A 71-year-old Chinese man presented with acute, painful and progressive purpuric patches with haemorrhagic bullae on the lower limbs. These lesions ulcerated and were very slow to heal with eschar formation (Fig. 1). His past medical history included hypertension. He denied any new medications, contactants or illicit drug use. A skin punch biopsy was taken from the foot lesion (Fig. 2). What is your diagnosis?

A. Pyoderma gangrenosum
B. Cholesterol crystal embolism
C. Cutaneous polyarteritis nodosa
D. Cryoglobulinaemia with occlusive vasculopathy secondary to multiple myeloma
E. Angioimmunoblastic T-cell lymphoma

Findings and Diagnosis

The images (Figs. 1A-B) show purpuric patches with necrotic centre over both feet along with a few overlying bullae on initial presentation. Despite optimal wound care, these progressed to slow-healing ulcers with thick eschar formation at day 30 (Fig. 1C) compared to day 10 of admission (Fig. 1D).

Investigations revealed normochromic, normocytic anaemia (Hb, 10.7 g/dL; normal, 14-18 g/dL) and markedly raised erythrocyte sedimentation rate at 105 mm/hr (1-10 mm/hr). Skin biopsy for histology showed epidermal necrosis and the superficial and deep vessels were thrombosed and occluded by hyaline deposits with paucity of inflammatory infiltrate which was consistent with occlusive vasculopathy (Fig. 2). Screening for thrombotic disorders, autoimmune diseases and infective causes including human immunodeficiency viruses, hepatitis B and C were unremarkable.

Subsequently, rouleaux formation was noted in the complete blood count. Thereafter, elevations were noted in serum creatinine of 108 µmol/L (CrCl, ~51 mL/min) and serum calcium of 2.72 mmol/L (2.15-2.58 mmol/L,

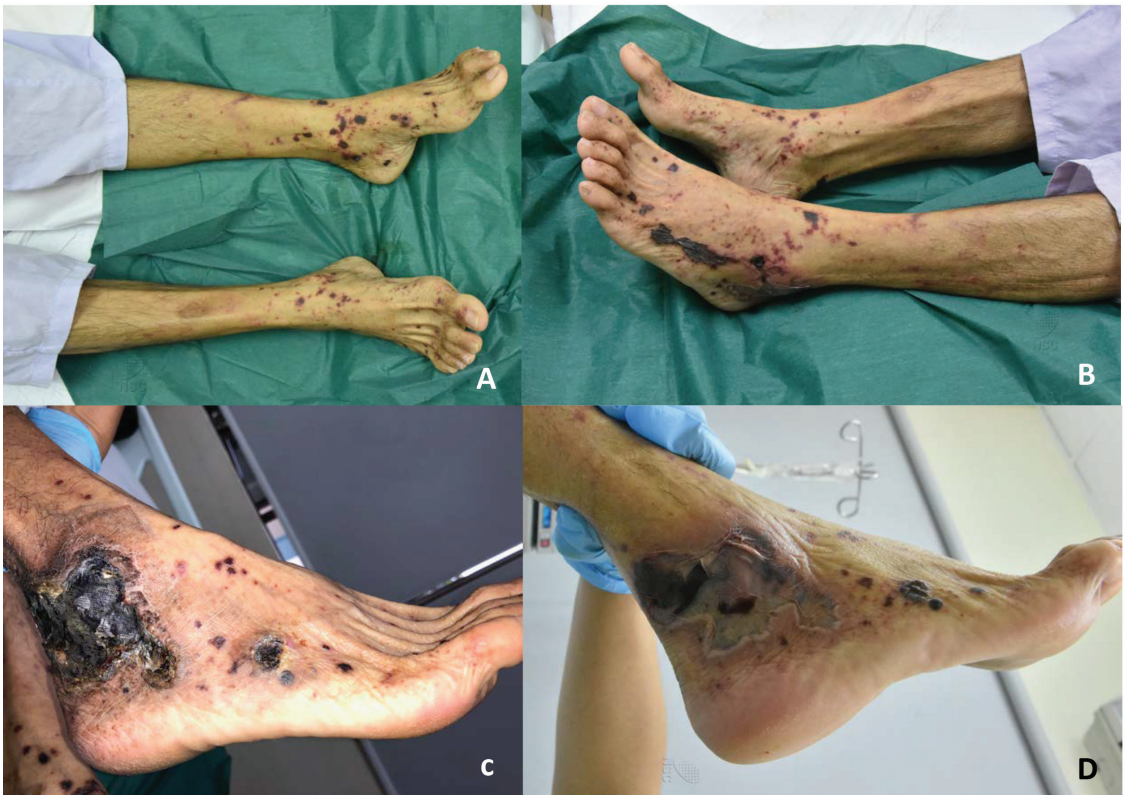

Fig. 1. A: Top view of purpuric patches with necrotic centre over both feet with a few overlying bullae. B: Lateral view of purpuric patches. C: Slow-healing ulcers on the right foot with thick eschar formation at day 30. D: Ulcers at day 10 of admission.

Answer: D

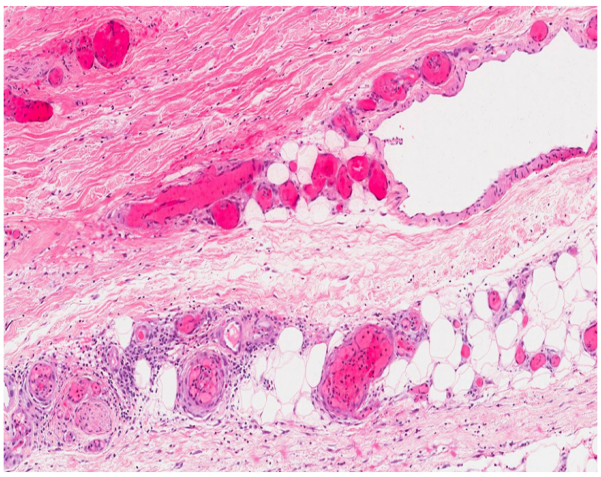

Fig. 2. Histopathology of occlusive vasculopathy shows superficial and deep vessels are thrombosed and occluded by hyaline deposits with paucity of inflammatory infiltrate (haematoxylin and eosin stain, original magnification ×100).

adjusted). Total protein was raised at 109 g/L (65-82 g/L) with hypoalbuminaemia at 22 g/L (38-48 g/L). Multiple myeloma was thus suspected. Serum protein electrophoresis showed an M-spike of 6 g/dL (0.7-1.6 g/dL) with a monoclonal gammopathy of IgG kappa in immunofixation electrophoresis. Serum IgG was markedly elevated at 62.7 g/L (8.5-19.5 g/L) while other immunoglobulins were suppressed.

There were no lytic bone lesions on skeletal survey. Biopsy of the bone marrow confirmed a plasma cell dyscrasia with increased plasma cells of 66% which was consistent with multiple myeloma. Cryoglobulin test was also positive. A diagnosis of type I cryoglobulinaemia with occlusive vasculopathy secondary to multiple myeloma was made. Patient was started on chemotherapy of lenalidomide and dexamethasone with improvement of the skin lesions.

Discussion

Multiple myeloma is characterised by a clonal proliferation of plasma cells that produce a monoclonal immunoglobulin. These plasma cells infiltrate into bone and organs leading to anaemia, hypercalcaemia, renal failure, bone pain, weight loss and neuropathy. Rarely, skin lesions in multiple myeloma patients may develop secondary to associated disorders such as cryoglobulinaemia. The prevalence of clinically significant cryoglobulinaemia is approximately 1 in 100,000.[1] Type 1 cryoglobulinaemia (10-15% of patients) results from cold precipitable monoclonal immunologlobulins that increase blood viscosity and lead to occlusion of vessels. It is associated with an underlying plasma cell dyscrasia or lymphoproliferative disorder.

Skin involvement is characterised by the cardinal sign of cold occlusion—that is, purpura (often retiform) and necrosis—leading to ulceration and even gangrene in severe cases. Other cutaneous findings include Raynaud's phenomenon, acrocyanosis and livedo reticularis. Histologically, skin lesions demonstrate occlusive vasculopathy with bland eosinophilic hyaline thrombi within blood vessels in the dermis and minimal inflammatory infiltrate.[2]

The above skin features can occur in other instances. They can be distinguished based on clinical history and investigations. Cholesterol crystal embolism is iatrogenic in the majority of cases (with angioplasty being the most common event that triggers it) and manifests as a classic triad of livedo reticularis, renal failure and eosinophilia.[3] Skin biopsy would reveal cholesterol clefts in the lumina of small arteries and arterioles. History of recent vascular surgery should raise suspicion of this cause.

As a form of vasculitis of the small- and medium-sized arteries of the dermis and subcutis, cutaneous polyarteritis nodosa usually presents as painful nodules, livedo reticularis and ulcers of the legs. Bullae, cutaneous necrosis and digital gangrene occur less frequently.[4] Characteristic leukocytoclastic vasculitis with fibrinoid necrosis in the dermal vessels confirms the diagnosis. Possible infectious triggers include hepatitis B and C, streptococcal infection and tuberculosis.

Pyoderma gangrenosum is an ulcerative neutrophilic dermatosis that often presents as violaceous papules or nodules that result in ulcers with undermined edges and is associated with inflammatory bowel disease, arthritis and myelogenous leukaemia.[5] It usually remains a clinical diagnosis of exclusion with non-specific histological findings that may include a necrotic or ulcerated epidermis and a diffuse infiltrate of neutrophils, lymphocytes and histiocytes in the dermis, sometimes with vasculitis.

Angioimmunoblastic T-cell lymphoma is an aggressive peripheral T-cell lymphoma characterised by fever, weight loss, night sweats, general lymphadenopathy, hepatosplenomegaly and polyclonal hypergammaglobulinaemia. Skin manifestations include maculopapular eruption (most common), erythroderma, nodules, palpable purpura and urticarial plaques.[6] Histologically, a dense superficial and deep infiltrate of atypical lymphoid cells is seen on skin biopsy.

Treatment for cutaneous occlusive vasculopathy is targeted at the underlying aetiology. In this case, the pathogenesis is likely related to the monoclonal cryoglobulins produced by the overproliferating plasma cells of multiple myeloma—precipitating as hyaline thrombi—which occlude the dermal blood vessels and result in acral ischaemia and necrosis.[7] Hence, management and prognosis should be tailored to control plasma cell lymphoproliferative disorder. Indeed, clinical improvement in cutaneous lesions has been reported 6 to 8 weeks after chemotherapy is started for multiple myeloma.[2,8] Plasmapheresis may also be used to quickly control severe cryoglobulinaemia symptoms at onset.[2,8]

Conclusion

Our patient had cutaneous lesions comprising painful, progressive purpuric patches that became slow-healing ulcers with eschar formation. Differential diagnoses of thrombotic disorders, autoimmune or vasculitic diseases, infection and malignancy were considered. Ultimately, investigations revealed an underlying multiple myeloma and associated type 1 cryoglobulinaemia. The learning point here is that cutaneous occlusive vasculopathy may manifest as an early sign of underlying haematologic malignancy such as multiple myeloma with cryoglobulinaemia. As such, a malignancy screen should be performed. A high index of suspicion is required and clues to the association include slow healing or progressive necrotic ulcers despite optimal standard treatment, or abnormal laboratory markers such as raised serum protein, erythrocyte sedimentation rate, creatinine, hypercalcaemia and/or anaemia. Prompt recognition and treatment of the underlying multiple myeloma will help prevent disease progression.

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