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"We're all in this human experience together, so let's try to be kind, gracious, and compassionate to each other."

Kailin Gow
American author

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Free Papers

Editorial

Tuberculosis in Singapore: Past and Future

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Tuberculosis—a curable and largely preventable disease—remains one of the top 10 global causes of death today. In 2017, the World Health Organization estimated that 23% of the world population had latent tuberculosis and 10 million people had developed active tuberculosis, of which just under half a million were new cases of multidrug-resistant tuberculosis that accounted for approximately 1.6 million deaths.[1]

In a historic high-level meeting held at the United Nations General Assembly on 26 September 2018, world leaders unanimously endorsed a political declaration that—among a host of other public health, clinical, research and financing actions—reaffirmed the resolve to end the global tuberculosis epidemic by 2030 and committed to treat 40 million people with tuberculosis by 2022.[2] Their actions particularly highlighted that tuberculosis is not just a medical disease, but it is also one with considerable historical, political and socioeconomic dimensions.[2]

History provides important lessons on the combined roles played by government and community in tuberculosis control in Singapore. The late prime minister, Lee Kuan Yew, used the disease as a metaphor for nation-building after the People's Action Party led by him registered a decisive victory in the 1963 general elections: "Unite the people, build a prosperous and an equal society, isolate the Communists, contain them, like the tuberculosis bacilli is contained, where you throw a hard crust around an infected wound and keep your patient healthy and he would live a good life".[3] After the Second World War, successive governments and the community made robust efforts to combat tuberculosis which substantially shaped the nation state and its society across the colonial and postcolonial periods.

The pivotal years of tuberculosis control in Singapore were in the 3 decades that followed the end of the Second World War when the disease rates declined sharply following a series of defining environmental, housing and medical reforms. These included compulsory notification, creation of a central registry of cases and comprehensive case-finding, multidrug treatment (usually as outpatients), mass chest radiograph screening, addressing patients' needs by almoners and nurses, an allowance scheme for patients undergoing treatment and the vaccination of infants and young children (Fig. 1).[4,5]

Policy-wise, tuberculosis control in Singapore was started by the British colonial government. In 1948, after widespread criticism, the British colonial government reluctantly made tuberculosis control an important part of its 10-year Medical Plan and converted Tan Tock Seng Hospital into a sanatorium.[6] A decade later, more reforms were instituted that included compulsory notification of the disease and the establishment of a central registry of cases maintained by the Tuberculosis Control Unit (TBCU), a newly formed agency under the purview of the Ministry of Health (MOH) which coordinated all aspects of tuberculosis control.

After 1959, the government built and improved on the colonial precedents, especially by using TBCU as a coordinating body. Its political commitment effectively elevated tuberculosis control to a national policy such as the conduct of mass chest radiograph screening of the local population according to district. The equally expansive urban renewal and public housing programmes undertaken by the Housing and Development Board and Urban Redevelopment Authority played a complementary role when they relocated the populace from congested and insanitary shophouses and villages to clean housing estates and new towns.[7]

There is also an important history of community involvement and participation. The formation of the Singapore Anti-Tuberculosis Association (SATA) in 1947 by businessmen, community leaders and doctors in response to colonial disinterest in combatting tuberculosis was a successful social movement that focussed on anti-tuberculosis work in the community. SATA worked with the government to implement initiatives such as mobile chest radiograph screening, public education and rehabilitation of tuberculosis survivors.[8] SATA also maintained an independent position on important issues that enriched the discussion on tuberculosis control in Singapore. While it usually supported government policy, it disagreed with the need for a centralised registry of tuberculosis cases and the

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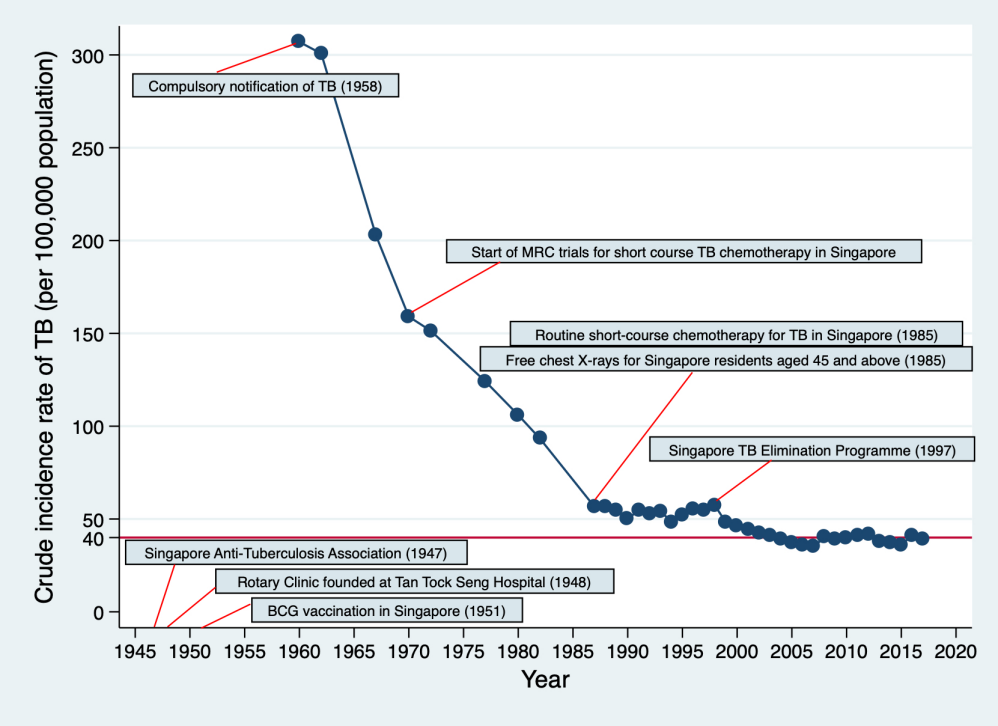

Fig. 1. Graph showing the incidence of tuberculosis in Singapore (1958-2017) and some of the key events in the attempt to control tuberculosis locally. Other than those described in the text, the Rotary Clinic was established in 1948 in Tan Tock Seng Hospital, and it was jointly funded by both the community and the government. The British Medical Research Council (MRC) had conducted a series of clinical trials on short-course chemotherapy for tuberculosis with Singapore being a key recruitment site from 1967 to 1985. BCG: Bacille Calmette-Guérin; TB: Tuberculosis.

proposal for compulsory Bacille Calmette-Guérin (BCG) vaccination, for example.[8]

Even after the country had witnessed a steep decline in the number of reported cases of tuberculosis from the 1960s that resulted in a de-emphasis on tuberculosis relative to other diseases, Singapore did not lose sight of the illness. Government officials, doctors and SATA remained concerned about the prevalence of tuberculosis cases among some social groups, particularly the elderly, as there were patients who did not complete their treatment. Both issues prompted MOH to launch the Singapore Tuberculosis Elimination Programme (STEP) in 1997.[4]

However, the incidence of tuberculosis in Singapore has stagnated since the mid-2000s despite the efforts of STEP and MOH (Fig. 1). This contrasts sharply with the global trend.[1] There were likely several contributing issues including an ageing local population and an expanding migrant worker population drawn from countries with a high incidence of tuberculosis.[9,10] The rollout of directly observed treatment, short course (DOTS) under STEP revealed just how difficult it was for the state to monitor and change patient behaviour even in a tightly regulated country like Singapore. Conversely, despite decades of intensive public health education (which has proven to be particularly successful in the campaign to clamp down on spitting in public, for example), exaggerated fears of infection have forged a persistent social stigma against tuberculosis that has deterred some sufferers from seeking help. This phenomenon has also been reported in other countries.[11]

The emergence of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis are 2 global trends that are unlikely to diminish in the short term. They will increasingly impact future tuberculosis control in Singapore since they require longer courses of drug therapy that carry greater risks of adverse side-effects and are more costly.[12]

Nonetheless, there are grounds for optimism in the long run. The recently concluded Phase 2b Controlled Trial of the new M72/AS01$_E$ tuberculosis vaccine in Africa demonstrated both safety and a protective efficacy of approximately 54% in an "according-to-protocol efficacy" cohort of 3283 participants, particularly in young adults.[13] Though still a long way from becoming a widely available commercial product, the result marked an important and significant step forward in the iterative process of developing an effective vaccine—generally one of the most cost-effective options to prevent infectious diseases—against tuberculosis that may potentially improve on the current BCG vaccine.

The development of new antituberculosis drugs and breakthroughs in other fields such as immunotherapy offer the distinct possibility of shorter course and potentially less toxic drug regimens in treating multidrug-resistant tuberculosis and drug-susceptible active and latent tuberculosis in the near future. Similarly, advances in tuberculosis diagnostics offer hope of earlier diagnosis and confirmation of tuberculosis which are important to prevent further spread of the disease.[14]

New and imaginative partnerships between the public and private sectors have also emerged worldwide, the most prominent of which is Zero TB Initiative. It was launched in 2016 by a coalition that includes Stop TB Partnership, Harvard Medical School, Advance Access & Delivery (a non-profit company) and Interactive Research and Development (an international non-governmental organisation now based in Singapore). This ambitious initiative aims to create "islands of tuberculosis elimination" by providing support to coalitions of local governments, businesses and society in urban areas to set up comprehensive tuberculosis control strategies that involve case-finding, treatment and prevention of new cases of tuberculosis (including via treatment of latent tuberculosis) at the household level.[15]

In addition to being an early adopter of interventions that showcase cost-effective tuberculosis control, Singapore must continually monitor and uncover high-risk groups to shorten the time to diagnosis and treatment and to minimise the risk of transmission. It is also important to address the issue of disease stigma. Singapore should have a public, ambitious target for tuberculosis control and this might help to generate or focus its resources like in Japan and other high-income countries.

The success of biomedical breakthroughs, initiatives by the public and private sectors and other innovative approaches to tuberculosis control is ultimately less important than the need for governments, businesses and communities to be collectively and continuously engaged in tuberculosis control. Such cooperation has, in the past, marked many of the advances made in reducing the burden of tuberculosis—including in postwar Singapore—and will remain equally crucial in the future.

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Original Article

Ethnic Differences and Trends in ST-Segment Elevation Myocardial Infarction Incidence and Mortality in a Multi-Ethnic Population

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Abstract

Introduction: This study aimed to compare the incidence and mortality of ST-segment elevation myocardial infarction (STEMI) across the 3 main ethnic groups in Singapore, determine if there is any improvement in trends over the years and postulate the reasons underlying the ethnic disparity. Materials and Methods: This study consisted of 16,983 consecutive STEMI patients who sought treatment from all public hospitals in Singapore from 2007 to 2014. Results: Compared to the Chinese (58 per 100,000 population in 2014), higher STEMI incidence rate was consistently observed in the Malays (114 per 100,000 population) and Indians (126 per 100,000 population). While the incidence rate for the Chinese and Indians remained relatively stable over the years, the incidence rate for the Malays rose slightly. Relative to the Indians (30-day and 1-year all-cause mortality at 9% and 13%, respectively, in 2014), higher 30-day and 1-year all-cause mortality rates were observed in the Chinese (15% and 21%) and Malays (13% and 18%). Besides the Malays having higher adjusted 1-year all-cause mortality, all other ethnic disparities in 30-day and 1-year mortality risk were attenuated after adjusting for demographics, comorbidities and primary percutaneous coronary intervention. Conclusion: It is important to continuously evaluate the effectiveness of existing programmes and practices as the aetiology of STEMI evolves with time, and to strike a balance between prevention and management efforts as well as between improving the outcome of "poorer" and "better" STEMI survivors with finite resources.

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Key words: Chinese, Indian, Malay, STEMI

Introduction

Ischaemic heart disease (IHD) is the world's leading cause of death and is responsible for more than 8 million deaths each year.[1] Mirroring global trends, IHD has been among the top 3 causes of death for Singapore residents in recent years.[2] With Singapore's ageing population, coupled with the high prevalence of cardiovascular (CV) risk factors in the community,[3] the incidence and mortality of acute myocardial infarction (AMI) are expected to rise in future. Hence, it is imperative to identify at-risk subpopulations so that targeted prevention and management programmes can be implemented to improve outcomes.

ST-segment elevation myocardial infarction (STEMI), a type of AMI, is one of the most acute and severe presentation of IHD. It contributes significantly to CV mortality and morbidity. While the risk of getting AMI is increased by smoking, physical inactivity, poor nutrition, obesity, high blood cholesterol, high blood pressure, diabetes and metabolic syndrome,[4] the risk of dying after AMI is affected by the frailty of patient, severity of AMI, time of first treatment and process of continuous management in the short- and long-term.[5,6,7] Prior studies have shown ethnic differences in patients diagnosed with AMI in terms of presentation, risk factors, coronary vessel

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diameters, prognoses and outcomes.[8,9,10,11,12,13] Specifically, South Asians were found to have high risk for mortality, complications and recurrent AMI. These studies were generally conducted in Caucasian-majority settings and South Asians were generally treated as a single group. Asia houses some 60% of the world's population and as a region, has the fastest population growth rate. It has been increasingly recognised that even among subtypes of Asians, ethnicity is emerging as an important determinant of acute coronary syndrome outcomes.[14]

Singapore is a small, densely populated multi-ethnic country in Asia with 3 main ethnic groups—Chinese, Malay and Indian. Besides having a universally accessible healthcare system, Singapore has a good infrastructure for disease surveillance. These characteristics make Singapore suitable as a natural population laboratory to study the interaction between ethnicity and diseases. As the risk profile of each ethnic group differs due to varying genetic composition, dietary preference and lifestyle behaviour, the type and prevalence of CV incidence and mortality risk factors in each ethnic group are expected to differ.

This study aimed to compare the incidence and mortality of STEMI across the 3 main ethnic groups in Singapore, determine if there is any improvement in trends over the years and postulate the reasons underlying the ethnic disparity.

Materials and Methods

Setting

Singapore is a highly urbanised island city-state located in Southeast Asia with a population of 5.6 million, a land area of 719.1 square kilometres and a population density of 7797 persons per square kilometres in 2016.[15] Singapore has a gross domestic product of 402,160 million dollars (at 2010 market prices) and a life expectancy of 82.9 years in 2016.[16] Singapore has a mixed healthcare system,[17] where the public healthcare system is funded through a system of compulsory savings, subsidies and price controls.[18] There are 5 public hospitals that are located geographically evenly in Singapore which provide around-the-clock emergency percutaneous coronary intervention (PCI).[19,20] The composition of the 3 main ethnic groups in Singapore in 2016 was: 74% Chinese, 13% Malays and 9% Indians.[15] Specifically, the Singapore population comprises primarily third- and fourth-generation migrants of Han Chinese, Malay (Austronesian) and Indian (South Asian) descent.

Data Sources

The study population was obtained from the Singapore Myocardial Infarction Registry (SMIR). The SMIR is a state-funded nationwide registry managed by the National Registry of Diseases Office.[21] It captures epidemiological data on AMI cases diagnosed in all public and private hospitals and a small number of out-of-hospital AMI deaths certified by medical practitioners. All public hospitals provide notification of AMI cases to the SMIR since 2007, while legislation mandated notification from all hospitals (including private hospitals) since 2012. About 98% of all AMI cases in Singapore are managed by the public hospitals. The SMIR receives AMI case notification from 1) Hospital Inpatient Discharge Summary, 2) cardiac biomarker lists from all hospitals, 3) Mediclaim lists, 4) Casemix and Subvention lists from the Ministry of Health, and 5) death lists from the Ministry of Home Affairs, based on International Classification of Diseases 9th (ICD-9) Clinical Modification code 410 and ICD-10 Australian Modification codes I21 and I22. A team of registry coordinators—who are trained nurses—would review each case to verify that it is indeed an AMI. Detailed patient data for each AMI case will then be captured from the electronic medical records and physical casenotes. The same data extraction method is applied to all hospitals. To ensure that the data captured are accurate and consistent, yearly internal audit is performed by the SMIR to ensure inter-rater reliability of at least 95%.

Case-level procedural data related to PCI were obtained from the Singapore Cardiac Databank, which captures data related to CV diseases and procedures delivered in the public hospitals.[22]

Aggregated data on the number of Singapore residents were obtained from the Singapore Department of Statistics, which releases mid-year resident population estimates annually.

Patient-level death data were obtained from the Death Registry under the purview of the Ministry of Home Affairs.

Study Population

All patients with STEMI in January 2007 to December 2014 were included. Only STEMI (rather than all AMI) were included in this study as STEMI often results from a primary CV event rather than secondary to another disease such as sepsis. A small number of patients (~2%) who presented to the private hospitals were excluded as data from the private hospitals were available only from 2012 onwards.

Outcomes of Interest

The outcomes of interest in this study are: STEMI incidence, 30-day mortality and 1-year mortality from all-cause, CV and non-CV deaths. All-cause death was selected as it encompasses the overall mortality and can be ascertained without adjudication. Mortality was further classified into CV and non-CV to differentiate whether the death is likely resultant of STEMI or other diseases. CV mortality was defined as death due primarily to a CV disease such as IHD, heart failure, arrhythmia, valvular heart disease, pericardial disease, myocarditis, pulmonary

hypertension or stroke.[23] The 30-day mortality was used to assess immediate outcome of STEMI, while 1-year mortality was for longer-term assessment. As the reporting of death is mandatory for all Singapore residents and the vital statuses of study population (patients with STEMI in January 2007 to December 2014) were matched until 30 April 2016 (a date that is beyond 1 year from the last AMI case included in this study), no patient was lost to follow-up for all mortality outcomes.

Ethics Approval

The Centralised Institutional Review Board of Singapore General Hospital (CIRB Reference: 2014/130/C) granted ethics approval with waiver of patient consent for this study, which utilised anonymised registry data.

Statistical Analysis

Differences in patients' demographics, comorbidities, procedural characteristics, medications and in-hospital events across the ethnic groups were compared using Kruskal-Wallis rank test for numeric variables and chi-square test for categorical variables.

Yearly STEMI incidence rates were plotted for the 3 ethnic groups to compare their trends over the years. Annual incidence rate was calculated by dividing the number of STEMI episodes by the number of Singapore residents in each year.

Yearly 30-day and 1-year all-cause, CV and non-CV mortality rates were plotted for the 3 ethnic groups to compare their trends over the years. Annual 30-day and 1-year mortality rates were calculated by dividing the number of STEMI patients who died within 30 days and 1 year, respectively, from the onset date of STEMI by the number of STEMI patients in each year. Kaplan-Meier curves were plotted for the 3 ethnic groups to compare their cumulative mortality rate within 30 days and 1 year after STEMI.

The relationship between ethnic group and mortality was examined using Cox regression. Demographics (age, gender), comorbidities (history of hypertension, history of diabetes, history of hyperlipidaemia, history of AMI/PCI/coronary artery bypass graft, smoking status, body mass index, heart failure on admission, serum creatinine on admission) and primary PCI were adjusted sequentially in multivariable Cox regression. These factors were selected based on their clinical and statistical significance to mortality. For CV mortality, competing risk from non-CV death was accounted in Cox regression. The reverse was applied to non-CV mortality.

The data used in this study were mostly completed and missing data were mostly missing at random. To maintain the data in its original form, missing data were dropped from analyses through case deletion without any imputation. Of the 16,983 consecutive patients in the univariable analyses, 13,500 (79%) were also in the multivariable analyses after dropping those with missing data. Sensitivity analysis done on the 13,500 patients that remained in the multivariable models found similar ethnic disparities in patients' characteristics.

All statistical analyses were done using STATA SE (version 13) software. All reported *P* values were two-sided and $P < 0.05$ was considered statistically significant.

Results

Study Population

Of the 16,983 consecutive patients in this study, 11,056 (65.1%) were Chinese, 3399 (20.0%) Malays and 2528 (14.9%) Indians. Table 1 shows the ethnic differences in demographics, comorbidities, procedural characteristics, medications and in-hospital events. Median age at STEMI was oldest for the Chinese (62 years) and they had the highest proportion of patients with history of hypertension (59.1%). Median serum creatinine on admission was highest for the Malays (96 μmol/L) and they had the highest proportion of patients who smoked (67.9%) and with high body mass index (73.2%). The Indians had the highest proportion of patients with history of diabetes (44.1%), hyperlipidaemia (51.3%) and AMI/PCI/coronary artery bypass graft (21.5%). The proportion of Indians who received primary PCI (70.1%) and pharmacotherapy was higher than the Chinese and Malays. Median door-to-balloon time was longest for the Indians (70 minutes), but median symptom-to-balloon time was longest for the Malays (195 minutes). While in-hospital arrhythmia was most common among the Chinese (28.7%), in-hospital acute renal failure was most common among the Malays (8.6%). The proportion of Chinese and Malays experiencing heart failure during hospitalisation were similar at 15%, but higher than the Indians (12.8%).

Incidence

STEMI incidence rate for the Malays and Indians were consistently higher than the Chinese from 2007 to 2014 (Fig. 1). While the incidence rate for the Chinese (62 and 58 per 100,000 population in 2007 and 2014, respectively) and Indians (122 and 126 per 100,000 population in 2007 and 2014, respectively) remained relatively stable over the years, the incidence rate for the Malays rose slightly from 97 per 100,000 population in 2007 to 114 per 100,000 population in 2014.

30-Day Mortality

All-cause and CV mortality rate for the Chinese (all-cause mortality 17%, CV mortality 14%) and Malays (all-cause

Table 1. Demographics, Comorbidities, Procedural Characteristics, Medications, In-Hospital Events and Mortality of the Study Population

	Chinese (n = 11,056)	Malays (n = 3399)	Indians (n = 2528)	*P* Value
Demographics				
Age in years, median (IQR)	62 (54 − 74)	58 (51 − 67)	56 (49 − 64)	<0.001
Male, n (%)	8549 (77.3)	2741 (80.6)	2037 (80.6)	<0.001
Comorbidities				
History of hypertension, n (%)	6466 (59.1)	1815 (54.0)	1324 (52.8)	<0.001
History of diabetes, n (%)	3131 (28.6)	1242 (37.0)	1108 (44.1)	<0.001
History of hyperlipidaemia, n (%)	5127 (46.9)	1522 (45.3)	1286 (51.3)	<0.001
History of AMI/PCI/CABG, n (%)	1526 (13.9)	575 (17.1)	541 (21.5)	<0.001
Current/former smoker, n (%)	5899 (55.1)	2238 (67.9)	1446 (58.5)	<0.001
Body mass index >23 kg/m^2, n (%)	5305 (60.0)	2028 (73.2)	1489 (69.4)	<0.001
Heart failure on admission, n (%)	2365 (21.6)	721 (21.4)	501 (19.9)	0.180
Serum creatinine on admission in μmol/L, median (IQR)	93 (77 − 118)	96 (80 − 121)	88 (74 − 104)	<0.001
Procedural Characteristics				
Reperfusion therapy, n (%)	6948 (62.8)	2233 (65.7)	1852 (73.3)	<0.001
Primary PCI, n (%)	6585 (59.6)	2140 (63.0)	1773 (70.1)	<0.001
Door-to-balloon in minutes, median (IQR)	68 (51 − 91)	67 (51 − 90)	70 (53 − 95)	0.001
Symptom-to-balloon in minutes, median (IQR)	188 (122 − 315)	195 (129 − 333)	189 (120 − 321)	0.028
Number of diseased vessels, n (%)				0.003
Normal or minor coronary artery disease	15 (0.3)	3 (0.2)	5 (0.4)	
Single-vessel disease	1907 (36.4)	632 (36.6)	573 (42.0)	
Double-vessel disease	1757 (33.5)	545 (31.5)	421 (30.8)	
Triple-vessel disease	1561 (29.8)	548 (31.7)	366 (26.8)	
Number of lesions intervened, n (%)				0.673
Single	5191 (95.0)	1705 (94.6)	1366 (95.2)	
Multiple	272 (5.0)	98 (5.4)	69 (4.8)	
Lesion intervened, n (%)				
Left main	117 (2.1)	38 (2.1)	22 (1.5)	0.337
Left anterior descending	2786 (51.0)	916 (50.8)	678 (47.3)	0.037
Left circumflex	627 (11.5)	205 (11.4)	244 (17.0)	<0.001
Right coronary artery	2225 (40.7)	755 (41.9)	569 (39.7)	0.437
Pre-PCI TIMI flow (%)				0.382
0	3481 (72.5)	1168 (71.4)	902 (71.3)	
I	314 (6.5)	129 (7.9)	85 (6.7)	
II	479 (10.0)	158 (9.7)	119 (9.4)	
III	531 (11.0)	180 (11.0)	160 (12.6)	
Post-TIMI flow >II and resolution of ST-segment elevation >50%, n (%)	5338 (97.8)	1761 (97.7)	1403 (97.9)	0.902
Use of stent, n (%)				
Bare metal stent	3461 (63.4)	1128 (62.6)	847 (59.0)	0.011
Drug eluting stent	1557 (28.5)	518 (28.7)	420 (29.3)	0.848
Bioresorbable vascular scaffold	66 (1.2)	30 (1.7)	15 (1.1)	0.228
Medications Given Within 24 hours from Onset				
Aspirin, n (%)	9860 (89.2)	3086 (90.8)	2342 (92.6)	<0.001
Beta blocker, n (%)	5393 (48.8)	1651 (48.6)	1391 (55.0)	<0.001
Other antiplatelets, n (%)	9839 (89.0)	3129 (92.1)	2389 (94.5)	<0.001

ACEI: Angiotensin converting enzyme inhibitor; AMI: Acute myocardial infarction; ARB: Angiotensin receptor blocker; CABG: Coronary artery bypass graft; CV: Cardiovascular; IQR: Interquartile range; PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarct

Table 1. Demographics, Comorbidities, Procedural Characteristics, Medications, In-Hospital Events and Mortality of the Study Population (Cont'd)

	Chinese (n = 11,056)	Malays (n = 3399)	Indians (n = 2528)	*P* Value
Medications Given at Discharge				
Aspirin, n (%)	8639 (93.0)	2719 (92.6)	2160 (94.9)	0.002
Beta blocker, n (%)	7938 (85.4)	2547 (86.8)	1985 (87.2)	0.035
ACEI/ARB, n (%)	6696 (72.1)	2084 (71.0)	1704 (74.9)	0.006
Lipid-lowering therapy/statin, n (%)	8842 (95.2)	2811 (95.8)	2203 (96.8)	0.003
Other antiplatelets, n (%)	8480 (91.3)	2756 (93.9)	2159 (94.9)	<0.001
Events During Hospitalisation				
Heart failure, n (%)	1668 (15.3)	511 (15.2)	322 (12.8)	0.007
Arrhythmia, n (%)	3141 (28.7)	901 (26.8)	592 (23.6)	<0.001
Complete heart block, n (%)	420 (3.8)	134 (4.0)	81 (3.2)	0.266
Acute renal failure, n (%)	796 (7.3)	290 (8.6)	148 (5.9)	<0.001
Stroke, n (%)	164 (1.5)	67 (2.0)	34 (1.4)	0.082
Left ventricular ejection fraction <50%, n (%)	6247 (66.2)	1995 (66.6)	1436 (63.7)	0.054
Mortality				
All-cause death within 30 days, n (%)	1848 (16.7)	490 (14.4)	253 (10.0)	<0.001
CV death within 30 days, n (%)	1557 (14.1)	431 (12.7)	229 (9.1)	<0.001
Non-CV death within 30 days, n (%)	291 (2.6)	59 (1.7)	24 (1.0)	<0.001
All-cause death within 1 year, n (%)	2454 (22.2)	674 (19.8)	352 (13.9)	<0.001
CV death within 1 year, n (%)	1876 (17.0)	543 (16.0)	287 (11.4)	<0.001
Non-CV death within 1 year, n (%)	578 (5.2)	131 (3.9)	65 (2.6)	<0.001

ACEI: Angiotensin converting enzyme inhibitor; AMI: Acute myocardial infarction; ARB: Angiotensin receptor blocker; CABG: Coronary artery bypass graft; CV: Cardiovascular; IQR: Interquartile range; PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarct

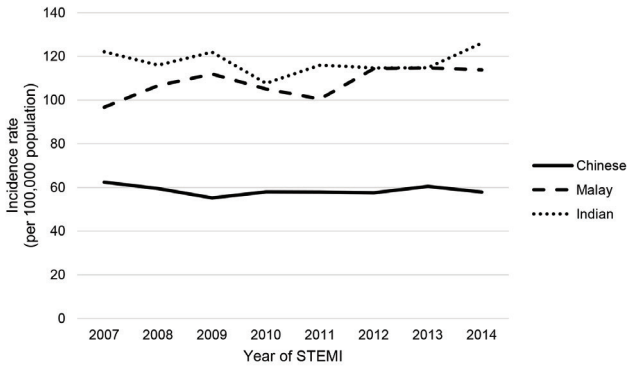

Fig. 1. Graph showing the incidence rate across the years. STEMI: ST-segment elevation myocardial infarction.

mortality 14%, CV mortality 13%) were consistently higher than the Indians (all-cause mortality 10%, CV mortality 9%) from 2007 to 2014, although the mortality rate did not show any clear upward or downward trend over the years for the 3 ethnic groups (Fig. 2). Cumulative mortality rate after STEMI was highest for the Chinese and lowest for the Indians (Fig. 3). The number of CV deaths was about 5-, 7- and 9-fold of non-CV deaths among the Chinese, Malays and Indians, respectively (Table 1). Compared to the Chinese, the unadjusted risk of all-cause death after STEMI was significantly lower for the Malays (hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.75-0.94) and Indians (HR 0.58, 95% CI 0.50-0.67) (Table 2). The lower unadjusted mortality risk among the Malays and Indians was also observed for CV deaths (Malays: HR 0.89, 95% CI 0.78-1.00; Indians: HR 0.63, 95% CI 0.54-0.74) and non-CV deaths (Malays: HR 0.64, 95% CI 0.47-0.86; Indians: HR 0.39, 95% CI 0.26-0.59). Notably, the mortality risks among the Malays exceeded the Chinese—albeit not significantly higher—after adjusting for demographics, comorbidities and primary PCI. For the Indians, their adjusted mortality risks were similar to the Chinese.

One-Year Mortality

All-cause and CV mortality rates for the Chinese (all-cause mortality 22%, CV mortality 17%) and Malays (all-cause mortality 20%, CV mortality 16%) were consistently higher than the Indians (all-cause mortality 14%, CV mortality 11%) from 2007 to 2014, although the mortality rate did not show any clear upward or downward trend over the years for the 3 ethnic groups (Fig. 2). Cumulative mortality rate after STEMI was highest for the Chinese and lowest for the Indians (Fig. 3). The number of CV deaths was more than non-CV deaths, but not more than 5-fold across the 3 ethnic groups (Table 1). Compared to the Chinese, the unadjusted risk of all-cause death after STEMI was significantly lower

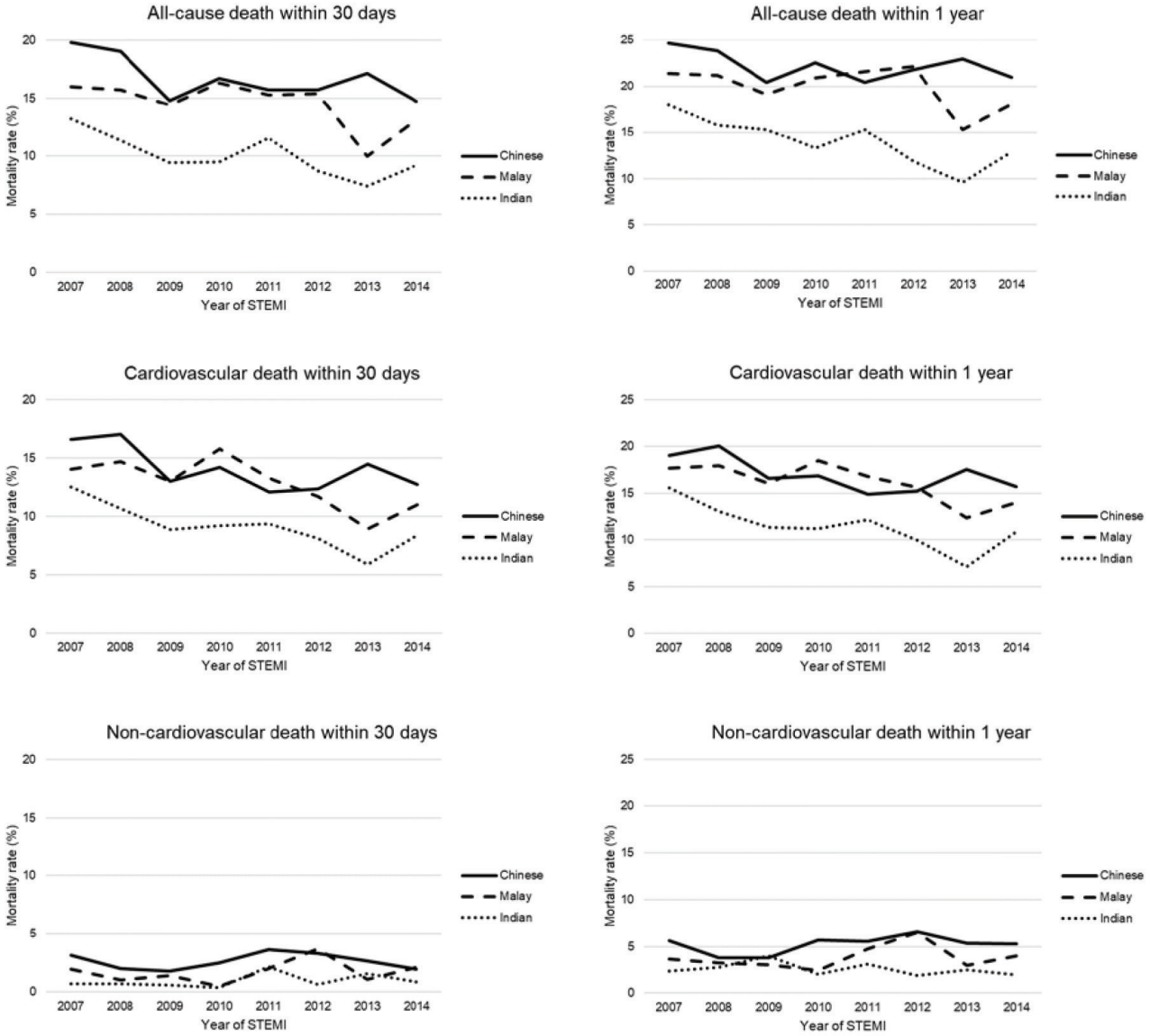

Fig. 2. Graphs showing the mortality rate across the years. STEMI: ST-segment elevation myocardial infarction.

for the Malays (HR 0.87, 95% CI 0.80-0.96) and Indians (HR 0.60, 95% CI 0.53-0.68) (Table 2). The lower unadjusted 1-year mortality risk among the Malays and Indians were also observed for CV deaths (Malays: HR 0.94, 95% CI 0.84-1.04; Indians: HR 0.66, 95% CI 0.57-0.75) and non-CV deaths (Malays: HR 0.72, 95% CI 0.60-0.88; Indians: HR 0.50, 95% CI 0.39-0.65). The 1-year all-cause and CV mortality risks for the Malays became significantly higher than the Chinese after adjusting for demographics, comorbidities and primary PCI, although the adjusted risk of non-CV death for the Malays was similar to the Chinese. For the Indians, their adjusted mortality risks were similar to the Chinese.

Discussion

Ethnic disparity in STEMI incidence rate was observed in the general population as well as in 30-day and 1-year mortality rates among STEMI patients. Higher STEMI incidence rate was consistently observed in Malays and Indians. While the incidence rate for Chinese and Indians remained relatively stable over the years, the incidence rate for Malays rose slightly. Higher 30-day and 1-year mortality rates were observed in Chinese and Malays for all-cause and CV deaths, but not non-CV deaths. Cumulative mortality rate within 30 days and 1 year after STEMI was highest for the Chinese and lowest for the Indians. Of the deaths within 30 days after STEMI, Indians had the highest

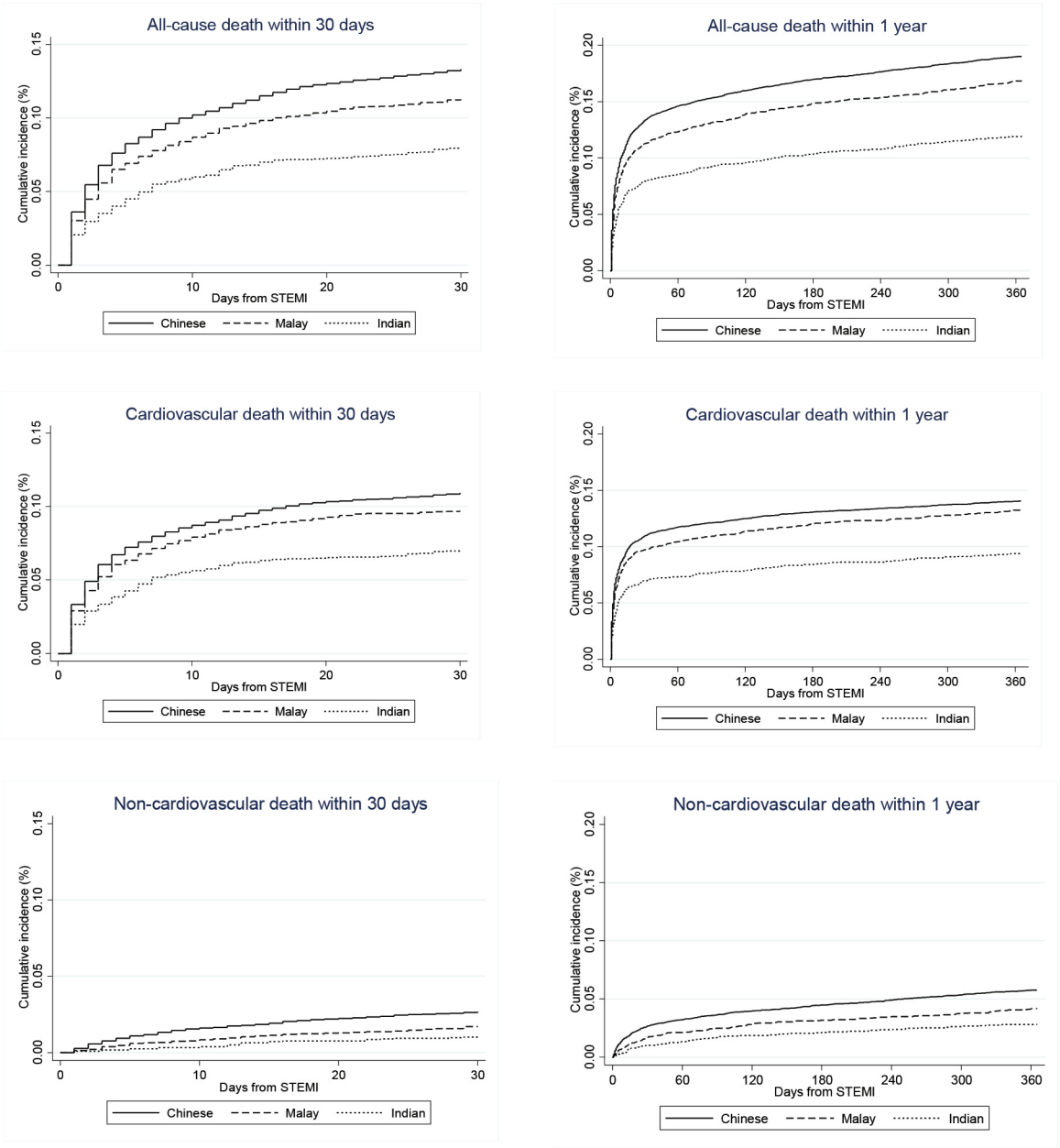

Fig. 3. Graphs showing the cumulative mortality rate after ST-segment elevation myocardial infarction (STEMI).

proportion of CV deaths. Besides Malays having higher adjusted 1-year all-cause and CV mortality risk, all other ethnic disparities in 30-day and 1-year mortality risk were attenuated after adjusting for demographics, comorbidities and primary PCI.

The findings in this study corroborated with that from existing literature. In a similar study by Mak et al, higher AMI incidence was observed among Malays and Indians from 1991 to 1999.[24] The 28-day and 1-year age-adjusted mortality rates were lowest for Indians and highest for Malays. The study, however, did not adjust for other factors besides age and gender. In a more recent study by Gao et al, ethnic disparities were found to be wider in 30-day and 10-year CV mortality than non-CV mortality in patients with AMI from 2000 to 2005.[25] Our study complements theirs with the inclusion of analyses on incidence and intermediate 1-year mortality.

Incidence

The National Health Surveys and National Nutrition Surveys done by the Ministry of Health and Health Promotion Board, respectively, found that the Malays had the highest prevalence of hypertension, hyperlipidaemia, smoking, obesity, physical inactivity and low consumption

Table 2. Hazard Ratios (95% Confidence Interval) for Mortality

	Chinese (n = 11,056)	Malays (n = 3399)	Indians (n = 2528)
All-cause death within 30 days			
Model 1	1.00	0.84 (0.75 − 0.94)	0.58 (0.50 − 0.67)
Model 2	1.00	1.16 (1.04 − 1.31)	0.89 (0.76 − 1.03)
Model 3	1.00	1.06 (0.90 − 1.23)	0.92 (0.76 − 1.12)
Model 4	1.00	1.03 (0.88 − 1.21)	0.97 (0.80 − 1.18)
CV death within 30 days			
Model 1	1.00	0.89 (0.78 − 1.00)	0.63 (0.54 − 0.74)
Model 2	1.00	1.22 (1.08 − 1.38)	0.96 (0.81 − 1.12)
Model 3	1.00	1.10 (0.92 − 1.31)	0.97 (0.79 − 1.20)
Model 4	1.00	1.08 (0.91 − 1.29)	1.01 (0.82 − 1.24)
Non-CV death within 30 days			
Model 1	1.00	0.64 (0.47 − 0.86)	0.39 (0.26 − 0.59)
Model 2	1.00	0.91 (0.68 − 1.23)	0.61 (0.40 − 0.93)
Model 3	1.00	0.93 (0.64 − 1.36)	0.73 (0.44 − 1.21)
Model 4	1.00	0.88 (0.61 − 1.29)	0.82 (0.50 − 1.35)
All-cause death within 1 year			
Model 1	1.00	0.87 (0.80 − 0.96)	0.60 (0.53 − 0.68)
Model 2	1.00	1.24 (1.13 − 1.36)	0.94 (0.83 − 1.06)
Model 3	1.00	1.16 (1.03 − 1.31)	0.92 (0.79 − 1.08)
Model 4	1.00	1.14 (1.01 − 1.28)	0.98 (0.84 − 1.14)
CV death within 1 year			
Model 1	1.00	0.94 (0.84 − 1.04)	0.66 (0.57 − 0.75)
Model 2	1.00	1.30 (1.17 − 1.44)	0.99 (0.87 − 1.14)
Model 3	1.00	1.19 (1.03 − 1.38)	0.99 (0.83 − 1.18)
Model 4	1.00	1.18 (1.02 − 1.36)	1.03 (0.87 − 1.23)
Non-CV death within 1 year			
Model 1	1.00	0.72 (0.60 − 0.88)	0.50 (0.39 − 0.65)
Model 2	1.00	1.06 (0.87 − 1.29)	0.81 (0.62 − 1.05)
Model 3	1.00	1.11 (0.88 − 1.40)	0.76 (0.56 − 1.04)
Model 4	1.00	1.07 (0.85 − 1.35)	0.82 (0.60 − 1.13)

CV: Cardiovascular
Chinese is the reference group.
Model 1 consists of: ethnic group.
Model 2 consists of: variable in Model 1, demographics (age, gender).
Model 3 consists of: variables in Model 2, comorbidities (history of hypertension, history of diabetes, history of hyperlipidaemia, history of acute myocardial infarction/percutaneous coronary intervention/ coronary artery bypass graft, smoking status, body mass index, heart failure on admission, serum creatinine on admission).
Model 4 consists of: variables in Model 3, primary PCI.

of fruits and vegetables which are common risk factors of STEMI.[3,4,26] Their prevalence of diabetes, hypertension, smoking, obesity, physical inactivity and low consumption of fruits and vegetables increased over the years.[3,26] Malays were also least likely to go for regular health screening for hypertension, diabetes and hyperlipidaemia.[3] Although the prevalence of hypertension and hyperlipidaemia among Indians were lower than the Chinese, the prevalence of diabetes among Indians was higher than the Chinese.[3] Furthermore, Indians have ethnic-specific risk for coronary artery disease.[27,28] The high prevalence of STEMI risk factors among Malays and the combination of STEMI risk factors in the backdrop of genetic predisposition to heart diseases among Indians are likely reasons for their higher STEMI incidence rate relative to the Chinese.

Thirty-Day Mortality

Unadjusted all-cause and CV mortality among Chinese was evidently higher, but there was no significant ethnic difference in mortality risk after adjusting for demographics, comorbidities and primary PCI. This suggests that the ethnic differences in all-cause and CV mortality could be

largely explained by their differences in demographics, comorbidities and primary PCI. Older age at STEMI, accompanied by hypertension and other comorbidities (not restricted to those captured in this study), predisposed the Chinese to higher mortality risk.[29] These factors could have also led to the lower proportion of Chinese receiving treatment (primary PCI with pharmacotherapy) recommended by the American Heart Association[30] and European Society of Cardiology.[31]

One-Year Mortality

Unadjusted all-cause and CV mortality among the Chinese was evidently higher. The mortality risk was significantly higher among Malays, but not significantly lower among Indians after adjusting for demographics, comorbidities and primary PCI.

The lower unadjusted mortality risk among Malays than the Chinese could be due to Malays having lower prevalence of mortality risk factors in terms of quantity and/or impact. However, after adjusting for demographics, comorbidities and primary PCI, Malays could have fared worse among the mortality risk factors (not restricted to those captured in this study) that were not adjusted in the models, thereby pushing up their adjusted mortality risk to be higher than the Chinese. Although the proportion of Malays who underwent primary PCI was higher than the Chinese, the median symptom-to-balloon time for Malays was longer than the Chinese. Longer symptom-to-balloon time could potentially compromise the benefit of primary PCI.[32,33] Moreover, despite significantly higher proportion of Malays having triple-vessel disease, the proportion of them having multiple lesions intervened was not significantly higher. Incomplete revascularisation of non-culprit lesions in non-infarct-related artery could have also contributed to the higher adjusted mortality risk among Malays.[34]

Higher rates of primary PCI and pharmacotherapy are associated with lower rates of in-hospital event, which could have conferred lower unadjusted mortality risk among Indians.[29] The higher rates of primary PCI and pharmacotherapy among Indians also implied that they might be physically fitter at the onset of STEMI, rendering them eligible for primary PCI and pharmacotherapy.

Implications

The findings in this study revealed different risk profiles across the 3 ethnic groups. For the Chinese, the high mortality rate was largely attributed to their older age at STEMI with accompanying comorbidities that impeded their treatment options. More could be done to reduce treatment-risk paradox in the hope of narrowing the ethnic gap, although the trend of Chinese having the highest mortality rate is expected to persist in future.

For the Malays, the high STEMI incidence and mortality rate were largely due to their high prevalence of STEMI and mortality risk factors. More intensive prevention and management programmes are warranted to improve the health status of Malays before and after STEMI. For example, the smoking cessation programme organised by the Health Promotion Board has a special Ramadan edition with intensive targeted outreach to Malay smokers during their fasting month. In addition, chronic disease screening and health workshops that equip participants with practical ways of keeping active and eating wisely are also offered at no charge to religious institutions such as mosques. This makes early detection and management of chronic diseases—which is crucial in preventing STEMI—more accessible for the ethnic groups. Efforts to improve the survival of STEMI patients are ongoing. Besides having primary PCI as the main modality of reperfusion therapy, more strategically located acute and community hospitals have been built. Twelve-lead electrocardiogram machines that allow wireless transmission of data en-route to hospital and mechanical cardiopulmonary resuscitation devices that deliver consistent and quality chest compressions have been installed in all public emergency ambulances.[35] However, these population-based management efforts are not ethnic-specific. Mirroring the ethnic-specific prevention programmes that are already in place in the community, more risk stratification and targeted management programmes, which take into account socio-cultural sensitivities could be implemented in the clinical setting as well.

For the Indians, although their mortality rate was low, most of their deaths within 30 days after STEMI was CV-related and might be preventable with closer monitoring to ensure adequate medical compliance and cardiac rehabilitation.

Strengths and Limitations

As the study population is an unselected pool of STEMI patients with data that were consistently captured across all hospitals and close to complete coverage of all AMI cases, the findings in this study are representative of the entire STEMI cohort in Singapore. However, this study also has its limitations.

Firstly, there is some ambiguity in the classification of ethnicity for the offspring of inter-ethnic marriages. Ethnicity is currently classified based on the race that a person most identified with (socially) as reflected in the unique identity card that every Singapore resident holds, rather than his/her (biologically) dominant genetic makeup. There is no official national statistic on the number of people of mixed-ethnicity, but using the number of inter-ethnic marriages in Singapore as a proxy, about 1 in 5 people are estimated to be of mixed-ethnicity.[15] The impact of mixed-ethnicity on our findings remains to be answered and

it would be interesting for future studies to focus on this group of people and investigate how their disease patterns vary from people of pure-ethnicity. Secondly, as the study population is limited to only STEMI patients without any control, a more in-depth analysis on the association between STEMI incidence and its risk factors could not be done. Nonetheless, triangulation of our findings with existing national surveys had been done in an attempt to explain the incidence trends. Thirdly, postdischarge factors related to mortality such as medication compliance and cardiac rehabilitation—which are not available at population-level—could not be accounted in this study. Fourthly, as there is time lag between behavioural change and STEMI development, it is not feasible to evaluate the impact of existing ethnic-specific prevention programmes at this juncture. If proven to be successful, such programmes can pave the path for tailored lifestyle intervention programmes to be extended to more religious institutions as a viable scale-up plan in future.

Conclusion

Ethnic differences in STEMI incidence and mortality persist in the contemporary cohort despite the implementation of ethnic-specific prevention programmes, improvement in prehospital facilities and rise in usage of primary PCI and pharmacotherapy in recent years. It will be useful to continuously evaluate the effectiveness of existing programmes and practices as the aetiology of STEMI evolves with time. It is also crucial to strike a balance between prevention and management efforts, as well as between improving the outcome of "poorer" and "better" STEMI survivors with finite resources.

Acknowledgement

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Original Article

The Singapore Heart Failure Risk Score: Prediction of Survival in Southeast Asian Patients

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Abstract

Introduction: Numerous heart failure risk scores have been developed but there is none for Asians. We aimed to develop a risk calculator, the Singapore Heart Failure Risk Score, to predict 1- and 2-year survival in Southeast Asian patients hospitalised for heart failure. Materials and Methods: Consecutive patients admitted for heart failure were identified from the Singapore Cardiac Databank Heart Failure registry. The follow-up was 2 to 4 years and mortality was obtained from national registries. Results: The derivation (2008-2009) and 2 validation cohorts (2008-2009, 2013) included 1392, 729 and 804 patients, respectively. Ten variables were ultimately included in the risk model: age, prior myocardial infarction, prior stroke, atrial fibrillation, peripheral vascular disease, systolic blood pressure, QRS duration, ejection fraction and creatinine and sodium levels. In the derivation cohort, predicted 1- and 2-year survival was 79.1% and 68.1% compared to actual 1- and 2-year survival of 78.2% and 67.9%. There was good agreement between the predicted and observed mortality rates (Hosmer-Lemeshow statistic = 14.36, *P* = 0.073). C-statistics for 2-year mortality in the derivation and validation cohorts were 0.73 (95% CI, 0.70-0.75) and 0.68 (95% CI, 0.64-0.72), respectively. Conclusion: We provided a risk score based on readily available clinical characteristics to predict 1- and 2-year survival in Southeast Asian patients hospitalised for heart failure via a simple online risk calculator, the Singapore Heart Failure Risk Score.

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Key words: Asia, Heart failure, Mortality

Introduction

Heart failure is a growing public health problem with a significant disease burden worldwide.[1,2] Given the substantial uncertainty associated with disease outcomes,[3] risk scores play an important role in prognosticating survival and aiding the clinician to identify and counsel at-risk patients.

Mortality outcomes in heart failure have been shown to be affected by ethnicity.[4-6] In Western cohorts, mortality among African American heart failure patients was found to be higher than in whites. In Asian patients with heart failure, there have been greater adverse outcomes in Malays compared to the Chinese.[4,5] Asian cohorts present and fare differently from their Western counterparts. In the Acute Decompensated Heart Failure Registry (ADHERE), patients from the Asia Pacific presented much younger than those from America and had more severe clinical features with higher rates of mechanical ventilation and in-hospital mortality.[7-9] To date, the vast majority of risk scores were designed and validated in Western populations. None of them were validated in Asian patients. In a recently published risk score incorporating 40,000 patients from 30 studies, only 1 study was from Asia.[10]

Reviews of existing risk scores have highlighted their potential limitations. The predictive accuracy of earlier models, such as the Heart Failure Survival Score (HFSS),

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have been shown to be suboptimal.[11] Some models look primarily at in-hospital mortality.[12-16] Yet others incorporate subjective variables that may compromise prognostic utility[17-19] or more complex variables—peak oxygen consumption (pVO_2) or other measurements obtained through invasive cardiac procedures[20-23]—which may not be readily available in clinical practice.

Our aim was to develop a simple online risk calculator to predict 1- and 2-year survival in Southeast Asian heart failure patients based on readily available clinical and laboratory parameters.

Materials and Methods

Study Population

Singapore is a multi-ethnic Southeast Asian city-state with a population of 5.31 million people (74% Chinese, 13% Malay and 9% Indian).[24] Tertiary healthcare in Singapore is provided predominantly by a network of public hospitals that account for about 80% of all hospital admissions.[25] The Singapore Cardiac Databank (SCDB) is the national registry that collects data on cardiovascular diseases.[18,19] Information from all heart failure admissions to all the public hospitals in Singapore are prospectively collected as part of the SCDB Heart Failure (SCDB-HF) registry. The SCDB-HF registry commenced on 1 January 2008 and collates data on demographics, comorbidities, medical history, clinical characteristics, initial evaluations, laboratory and imaging results and treatment and discharge outcomes. All consecutive patients ≥21 years and admitted with the DRG code 252 (Heart Failure) are included in the registry. Trained coordinators use a standardised case report form to collect data which is then entered into an electronic database following internal and external validation. Registry participation does not alter any treatment or medical care and is not linked to specific therapy or medication. Ethical approval for this study was obtained from the institutional review board.

Consecutive patients admitted with heart failure to 2 institutions in the SCDB-HF registry from 1 January 2008 to 31 December 2009 were included in the study. Both institutions are representative of Singapore hospitals that see a large number of public hospital admissions since they accounted for about 40% of admissions in the SCDB-HF registry. Repeat admissions and patients who were foreigners (due to inadequate follow-up) were excluded. The derivation cohort was derived from the first institution and an initial validation cohort was provided by the second institution (validation cohort 1). A second validation cohort was obtained from patients in the SCDB-HF registry who were admitted to the second institution between 1 January 2013 and 31 December 2013 (validation cohort 2).

Outcomes

The primary outcome measure was all-cause mortality. In Singapore, all mortality data are maintained by the National Registry of Diseases Office (NRDO). All study patients were followed up for 2 to 4 years. Mortality data and cause of death were obtained from the NRDO.

Statistical Analysis

The baseline characteristics of study patients were summarised as frequencies and percentages for categorical variables and as mean ± standard deviation (SD) for continuous variables. The demographic, clinical and laboratory variables available from the registry are listed in Table 1. Univariate analysis was performed on all these

Table 1. Demographics and Clinical Characteristics of Study Population

	Derivation Cohort (n = 1392)	Validation Cohort 1 (n = 729)	Validation Cohort 2 (n = 804)
Demographics			
Mean age (SD)	68.2 (12.4)	71.4 (11.6)	70.9 (13.5)
Male (%)	789 (56.7)	317 (43.5)	406 (50.5)
Race (%)			
Chinese	976 (70.1)	530 (72.7)	589 (73.3)
Indian	162 (11.6)	88 (12.1)	74 (9.2)
Malay	223 (16.0)	103 (14.1)	122 (15.2)
Others	31 (2.2)	8 (1.1)	19 (2.4)
Clinical characteristics (%)			
Prior coronary artery disease	515 (37.0)	453 (62.1)	381 (47.4)
Prior myocardial infarction	435 (31.3)	171 (23.5)	146 (18.2)
Atrial fibrillation	409 (29.4)	149 (20.4)	183 (22.8)
Diabetes mellitus	707 (50.8)	391 (53.6)	398 (49.5)
Hypertension	986 (70.8)	577 (79.1)	603 (75.0)
Hyperlipidaemia	894 (64.2)	418 (57.3)	447 (55.6)
Stroke	207 (14.9)	136 (18.7)	108 (13.4)
Peripheral vascular disease	82 (5.9)	61 (8.4)	55 (6.8)
COPD	165 (11.9)	105 (14.4)	84 (10.4)
Ever smoker	583 (41.9)	212 (29.1)	225 (28.0)
Implantable cardioverter-defibrillator	89 (6.4)	5 (0.7)	8 (1.0)
Left ventricular ejection fraction			
≥50%	464 (33.3)	381 (52.3)	446 (55.5)
30% – 49%	417 (30.0)	190 (26.1)	225 (28.0)
<30%	511 (36.7)	158 (21.7)	133 (16.5)
Systolic blood pressure (SD) (mmHg)	137.0 (30.1)	141.9 (29.8)	141.4 (28.3)
Diastolic blood pressure (SD) (mmHg)	76.5 (18.2)	73.6 (18.0)	73.8 (15.5)

ACE: Angiotensin-converting-enzyme; COPD: Chronic obstructive pulmonary disease; NT proBNP: N-terminal pro b-type natriuretic peptide; SD: Standard deviation
*There were 312 patients with missing data.

Table 1. Demographics and Clinical Characteristics of Study Population (Cont'd)

	Derivation Cohort (n = 1392)	Validation Cohort 1 (n = 729)	Validation Cohort 2 (n = 804)
Heart rate (SD)	88.9 (23.4)	85.1 (19.9)	87.1 (20.3)
QRS duration (SD)	103.3 (25.6)	97.0 (23.1)	97.1 (21.1)
NT proBNP (SD) (pg/mL)*	9737.3 (13202.7)	9869.8 (15635.9)	10529.6 (16022.9)
Creatinine (SD) (μmol/L)	128.8 (79.9)	155.1 (138.4)	170.9 (172.9)
Sodium (SD) (mmol/L)	136.2 (8.0)	135.9 (5.0)	134.9 (5.4)
Potassium (SD) (mmol/L)	4.4 (3.8)	4.2 (0.8)	4.3 (0.8)
Haemoglobin (SD) (g/dL)	12.5 (4.0)	11.6 (2.2)	11.4 (2.4)
Discharge medications (%)			
ACE inhibitor (ACEI)	753 (54.1)	297 (40.7)	216 (26.9)
Angiotensin receptor blocker (ARB)	279 (20.0)	150 (20.6)	184 (22.9)
ACEI/ARB	1016 (73.0)	429 (58.8)	390 (48.5)
Beta-blocker	890 (63.9)	359 (49.2)	490 (60.9)
Spironolactone/ aldosterone antagonist	274 (19.7)	78 (10.7)	86 (10.7)
Nitrate	741 (53.2)	272 (37.3)	182 (22.6)
Diuretic	1210 (86.9)	553 (75.9)	485 (60.3)
Digoxin	406 (29.2)	83 (11.4)	76 (9.5)
Aspirin	759 (54.5)	313 (42.9)	428 (53.2)
Clopidogrel	233 (16.7)	63 (8.6)	428 (53.2)
Warfarin	249 (17.9)	46 (6.3)	71 (8.8)
Statins	1006 (72.3)	426 (58.4)	459 (57.1)

ACE: Angiotensin-converting-enzyme COPD: Chronic obstructive pulmonary disease; NT proBNP: N-terminal pro b-type natriuretic peptide; SD: Standard deviation
*There were 312 patients with missing data.

variables for the derivation cohort to identify predictors of mortality. The significant variables on univariate analysis are shown in Table 2. Following univariate analysis, stepwise Cox multiple regression analysis was performed on the significant univariate variables to obtain the candidate variables for the Singapore Heart Failure Risk Score (SHFRS). The significance level for entry and retention in the model was P <0.05. After multivariable analysis, the significant candidate variables in the selection pool were prior myocardial infarction (MI), atrial fibrillation (AF), hyperlipidaemia, stroke, diabetes mellitus, peripheral vascular disease (PVD) and left ventricular ejection fraction (LVEF). The continuous candidate variables were age, systolic blood pressure (SBP), diastolic blood pressure (DBP), QRS duration, sodium, creatinine and haemoglobin. LVEF was analysed in 3 categories (≥50%, 30-49% and ≤30%) as collected by the registry.

In the derivation cohort, survival at time t was estimated by the fitted equation

$$\hat{S}(t|\boldsymbol{X}\hat{\boldsymbol{\beta}}) = [\hat{S}_0(t)]^{exp\{\sum_{i=1}^{p}\hat{\beta}_i X_i\}}, \quad 0 < t \leq 2 \qquad (1)$$

where time is expressed in years, $\hat{S}_0(t)$ is the baseline survival function—purely a function of time—and $\hat{l} = \sum_{i=1}^{p}\hat{\beta}_i X_i$ is the estimated linear predictor which is a linear combination of the independent predictor variables $X_1, X_2, \ldots, X_p$ and the corresponding parameter estimates $\hat{\beta}_1, \hat{\beta}_2, \ldots, \hat{\beta}_p$.

Based on the derivation data and use of the selected independent variables, the fitted linear predictor was

$$\hat{l} = 0.023 \cdot Age + 0.437 \cdot Prior\ MI + 0.221 \cdot AF + 0.245 \cdot Stroke - 0.009 \cdot SBP + 0.004 \cdot QRS - 0.007 \cdot Sodium + 0.003 \cdot Creatinine + 0.456 \cdot PVD + 0.118 \cdot LVEF_1 + 0.301 \cdot LVEF_2$$

The categorical variables—prior MI, AF, stroke, PVD, $LVEF_1$ (EF 30-49%) and $LVEF_2$ (EF <30%)—were coded as 1 for "yes" and 0 for "no".

An equation that approximated the estimated baseline survival function was obtained in the following manner: 1) coordinates $[t_i, \hat{S}_0(t_i)]$ $i = 1, \ldots, n$ were obtained as output from the Cox regression analysis (SAS PROC PHREG) and then transformed into $x_t = ln(t)$, $y_t = ln(-ln(\hat{S}_0(t))$ using Weibull coordinates; 2) a fifth-degree polynomial, $y = P_0^5(x)$, was fitted to the (x_i, y_i) coordinate pairs over the range of the observed data; 3) $\hat{S}_0(t)$ was approximated as $\check{S}_0(t) = exp\{-exp(y_t)\}$. The derived survival predictor equation is restricted to 0 <t ≤2 and is expressed as

$$\check{S}(t|\boldsymbol{X}\hat{\boldsymbol{\beta}}) = [\check{S}_0(t)]^{exp\{\sum_{i=1}^{p}\hat{\beta}_i X_i\}}, \quad 0 < t \leq 2 \qquad (2)$$

Derived from the derivation cohort, equation 2 was then prospectively applied to each patient in the validation cohorts to provide individual estimates of survival at 1 and 2 years. In both cohorts, predicted survival was compared against actual survival. Using the predictive model, mean survival for each cohort was compared to actual mean survival. Model discriminant ability was assessed by the 1-year and 2-year receiver operating characteristics (ROC) area under the curve (AUC) for both data sets. A similar model was analysed that included medication data in addition to demographic, clinical and laboratory variables. The interaction between ejection fraction (EF) and individual predictors with the overall model for outcomes was also tested. The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) risk score10 was also validated in the derivation cohort.

All significance tests were two-sided and conducted at P <0.05. All analyses were performed using SAS© software

Table 2. Significant Univariate and Multivariate Predictors of Mortality in the Derivation Cohort

	Univariate Hazard Ratio (95% CI)	*P* Value	Multivariate Hazard Ratio (95% CI)*	*P* Value
Age	1.021 (1.014 – 1.028)	<0.001	1.024 (1.016 – 1.032)	<0.001
Implantable cardioverter-defibrillator	0.664 (0.457 – 0.965)	0.032		
Prior myocardial infarction	1.664 (1.412 – 1.961)	<0.001	1.548 (1.295 – 1.850)	<0.001
Atrial fibrillation	1.199 (1.011 – 1.422)	0.037	1.248 (1.032 – 1.508)	0.022
Hyperlipidaemia	1.209 (1.019 – 1.435)	0.030		
Stroke	1.502 (1.223 – 1.844)	<0.001	1.278 (1.027 – 1.589)	0.028
Diabetes mellitus	1.240 (1.056 – 1.456)	0.009		
Peripheral vascular disease	2.114 (1.609 – 2.779)	<0.001	1.578 (1.188 – 2.096)	0.002
Left ventricular ejection fraction				
≥50% (ref)	-	-	-	-
30% – 49%	1.234 (1.002 – 1.520)	0.048	1.125 (0.899 – 1.408)	0.303
<30%	1.409 (1.161 – 1.711)	0.001	1.351 (1.077 – 1.694)	0.009
Systolic blood pressure (mmHg)	0.992 (0.989 – 0.995)	<0.001	0.991 (0.988 – 0.994)	<0.001
Diastolic blood pressure (mmHg)	0.984 (0.979 – 0.989)	<0.001		
QRS duration (ms)	1.007 (1.004 – 1.010)	<0.001	1.004 (1.001 – 1.007)	0.019
NT proBNP (pg/mL)†	1.000 (1.000 – 1.000)	<0.001		
Sodium (mmol/L)	0.990 (0.984 – 0.997)	0.003	0.993 (0.986 – 0.999)	0.030
Creatinine (μmol/L)	1.003 (1.002 – 1.003)	<0.001	1.003 (1.002 – 1.004)	<0.001
Haemoglobin (g/dL)	0.922 (0.883 – 0.962)	<0.001		
ACE inhibitor/angiotensin receptor blocker	0.699 (0.589 – 0.831)	<0.001		
Nitrate	1.240 (1.054 – 1.458)	0.009		
Beta-blocker	0.791 (0.672 – 0.932)	0.005		
Warfarin	0.715 (0.571 – 0.897)	0.004		
Aspirin	0.848 (0.723 – 0.996)	0.044		

ACE: Angiotensin-converting-enzyme; NT proBNP: N-terminal pro b-type natriuretic peptide; ref: Reference
*Excludes NT proBNP and medications.
†There were 312 patients with missing data.

version 9.3 (SAS Institute, Cary, NC) and SPSS software version 22.0 (SPSS Inc., Chicago, IL). The SHFRS calculator can be accessed online via the homepage of Duke-NUS Medical School (https://webapps.duke-nus.edu.sg/tools/SHFRiskScore) (shown in Figure 1).

Results

A total of 1392 patients were included in the derivation cohort, 729 patients in validation cohort 1 and 804 patients in validation cohort 2. The demographics and clinical characteristics of the patients are described in Table 1.

Predictors of Mortality

The overall 2-year mortality was 32.1% (n = 447), 35.9% (n = 262) and 34.8% (n = 280) in the derivation and validation cohorts, respectively. The univariate and multivariate predictors of mortality in the derivation cohort are shown in Table 2. The findings of the multivariable analysis showed that older age (HR 1.024, 95% CI, 1.016-1.032, *P* <0.001), prior MI (HR 1.548, 95% CI, 1.295-1.850, *P* <0.001), AF (HR 1.248, 95% CI, 1.032-1.508, *P* = 0.022), prior stroke (HR 1.278, 95% CI, 1.027-1.589, *P* = 0.028), PVD (HR 1.578, 95% CI, 1.188-2.096, *P* = 0.002), lower EF (HR 1.351, 95% CI, 1.077-1.694, *P* = 0.009, EF ≥50% vs <30%), longer QRS duration (HR 1.004, 95% CI, 1.001-1.007, *P* = 0.019) and higher creatinine levels (HR 1.003, 95% CI, 1.002-1.004, *P* <0.001) were associated with significantly increased mortality. Higher SBP (HR 0.991, 95% CI, 0.988-0.994, *P* <0.001) and higher sodium levels (HR 0.993, 95% CI, 0.986-0.999, *P* = 0.03) were associated with decreased mortality. Ethnicity was not a significant predictor of mortality.

We tested the interaction between EF and individual predictors with the overall model for outcomes. With the

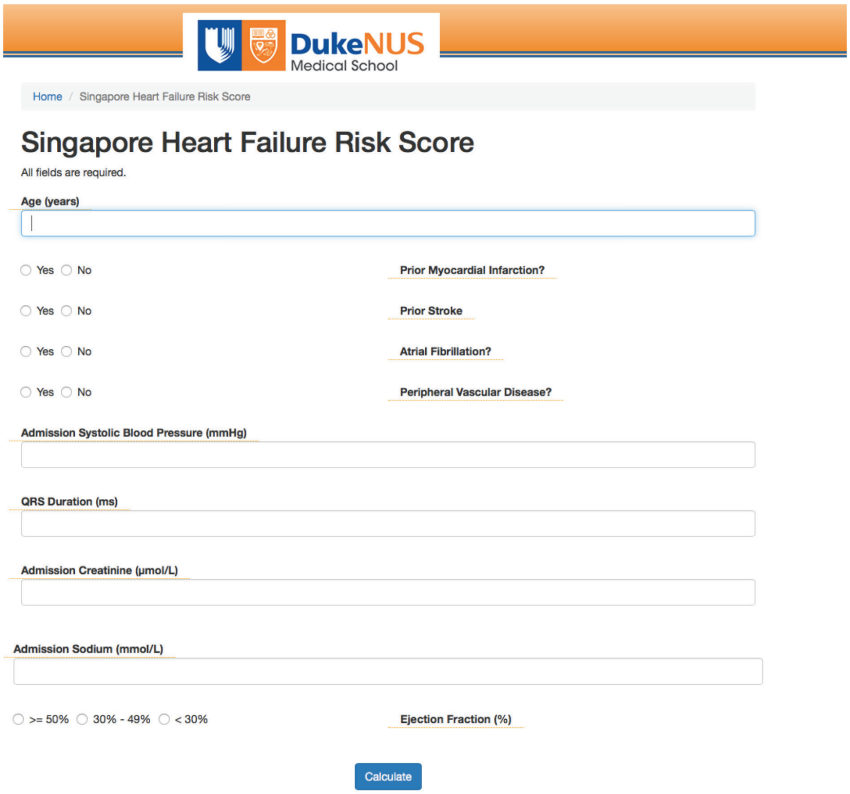

Fig. 1. The Singapore Heart Failure Risk Score (SHFRS) calculator found on the homepage of Duke-NUS Medical School. Reprinted with permission from Duke-NUS Medical School.

exception of PVD (its inclusion did not change the variables in the model), there was no significant interaction with the remaining 8 clinical predictors. Thus, a combined risk score for heart failure was proposed.

Performance of Model in Derivation and Validation Cohorts

The overall model performed well. In the derivation cohort, the predicted 1- and 2-year survival was 79.1% and 68.1%, respectively, compared to the actual 1- and 2-year survival of 78.2% and 67.9%, respectively. There was a good match between predicted and observed mortality rates (Hosmer-Lemeshow statistic = 14.36, $P = 0.073$ for 2-year survival). In validation cohort 1, the predicted 1- and 2-year survival was 78.8% and 67.9%, respectively, compared to the actual 1- and 2-year survival of 75.2% and 64.1%, respectively. There was a good match between predicted and observed mortality rates (Hosmer-Lemeshow statistic = 8.35, $P = 0.400$ for 2-year survival). In validation cohort 2, the predicted 1- and 2-year survival was 78.2% and 67.7%, respectively, compared to actual 1- and 2-year survival of 75.7% and 65.2%, respectively. There was good agreement between the predicted and observed mortality rates (Hosmer-Lemeshow statistic = 6.33, $P = 0.610$). C-statistics for 2-year mortality in the derivation cohort, validation cohort 1 and validation cohort 2 were 0.726 (95% CI, 0.697-0.754), 0.681 (95% CI, 0.640-0.722) and 0.648 (95% CI, 0.606-0.690), respectively (Fig. 2 and Table 3).

When medication data was included in the analysis, no improvement in the predictive accuracy of the model was seen. The C-statistics for 2-year mortality in the derivation cohort and validation cohort 1 were 0.723 (95% CI, 0.694-0.752) and 0.686 (95% CI, 0.646-0.727), respectively.

We compared the performance of our model against the MAGGIC risk score in the derivation cohort. The C-statistic for 1-year mortality in our model was 0.731 (95% CI, 0.699-0.764) against 0.620 (95% CI, 0.583-0.658) for the MAGGIC risk score.

Discussion

We report a new risk model, the SHFRS, that accurately predicted 1- and 2-year survival in patients hospitalised with heart failure. The SHFRS uses readily available clinical and laboratory variables on heart failure patients in Southeast Asia. It accurately predicted 1- and 2-year survival in these patients with AUC values of 0.731 and 0.726, respectively. These findings are comparable to the Seattle Heart Failure Model (SHFM) which had a 1-year AUC of 0.729 in the derivation cohort and an AUC of 0.679 in one of its validation cohorts.[11] Our score prognosticates longer-term mortality and expands on previous models such as the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) which looked primarily at inpatient mortality.[12-16]

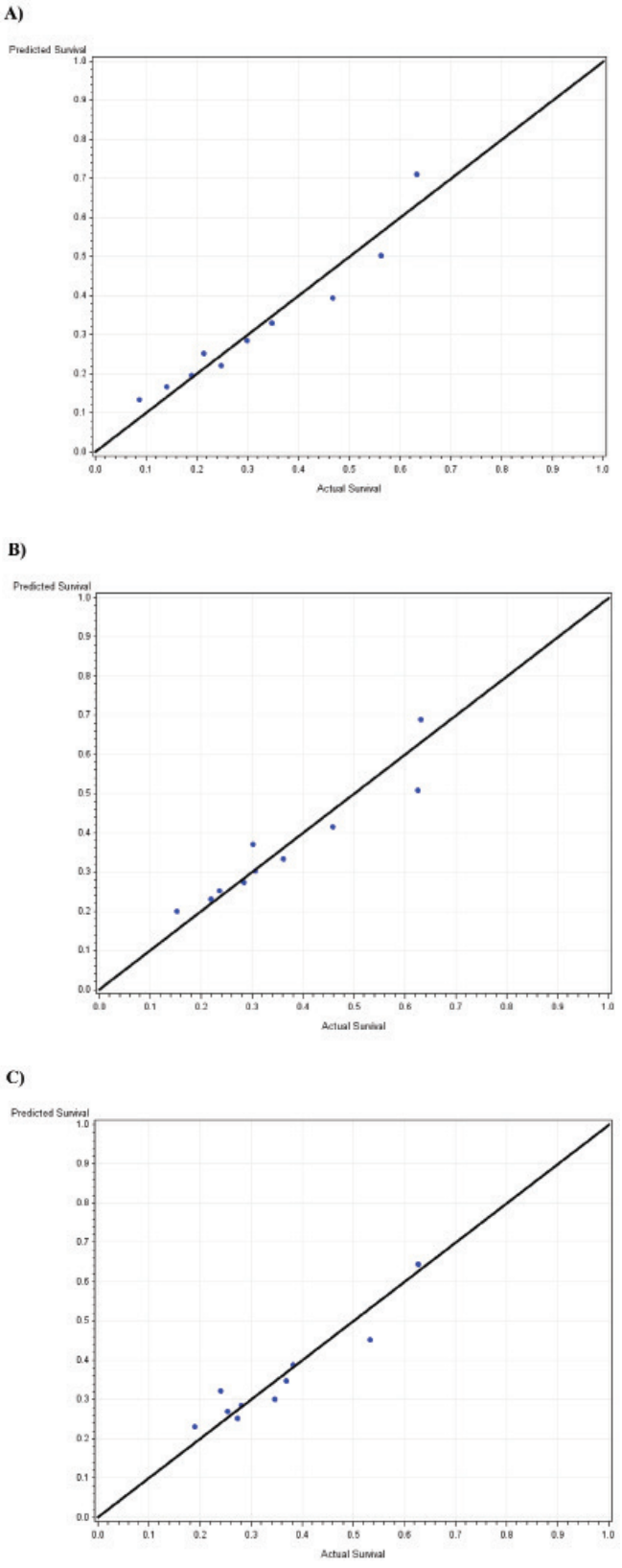

Fig. 2. Predicted vs actual 2-year survival in A) derivation cohort, B) validation cohort 1 and C) validation cohort 2.

Table 3. Survival in the Derivation and Validation Cohorts

	Derivation Cohort (n = 1392)	Validation Cohort 1 (n = 729)	Validation Cohort 2 (n = 804)
Death (n)	601	353	386
1-year survival (95% CI)			
Actual	0.782 (0.760 – 0.804)	0.752 (0.720 – 0.783)	0.757 (0.728 – 0.787)
Predicted	0.791 (0.785 – 0.798)	0.788 (0.778 – 0.798)	0.782 (0.771 – 0.794)
2-year survival (95% CI)			
Actual	0.679 (0.655 – 0.704)	0.641 (0.606 – 0.676)	0.652 (0.619 – 0.685)
Predicted	0.681 (0.673 – 0.690)	0.679 (0.667 – 0.692)	0.677 (0.663 – 0.690)
1-year AUC (95% CI)	0.731 (0.699 – 0.764)	0.670 (0.623 – 0.716)	0.630 (0.583 – 0.677)
2-year AUC (95% CI)	0.726 (0.697 – 0.754)	0.681 (0.640 – 0.722)	0.648 (0.606 – 0.690)

AUC: Area under the curve; CI: Confidence interval

Most risk scores were derived and validated in Western patients. To date, none has been validated in Asian patients. Among the 30 studies used for the risk model by the MAGGIC investigators, only 1 study originated from Asia (Japan).[10] Ethnic differences in heart failure outcomes have previously been demonstrated. African American patients had higher mortality than white patients in the Studies of Left Ventricular Dysfunction (SOLVD).[6] In the Multi-Ethnic Study of Atherosclerosis (MESA),[26] African Americans had the highest incidence of heart failure followed by Hispanics and whites. One local study found that mortality in elderly Malay heart failure patients was 3.5 times higher than their Chinese and Indian counterparts.[4] This finding was similar to that of all-comers in a smaller study by Lee and colleagues.[5] In this study, ethnicity did not impact mortality after careful multivariable adjustment was made for baseline differences. Our study did not focus exclusively on the elderly and had a much larger cohort than Lee and colleagues. Our findings are similar to another local study[27] which did not find any ethnic differences in patients with reduced EF. We also did not report any significant ethnic differences in mortality in Asian patients with preserved EF in a previous study.[28] Although no significant differences were found among the Chinese, Indians and Malays, SHFRS nonetheless provides the first risk score that was developed for Asians.

Asian heart failure cohorts have been shown to present and fare differently from Western cohorts. In the Acute Decompensated Heart Failure Registry (ADHERE), patients from the Asia Pacific presented at younger ages (67

years vs 75 years) than those from America and had more severe clinical features, longer hospital stay, higher rates of mechanical ventilation and higher in-hospital mortality.[7-9] In particular, Southeast Asian patients in the ADHERE-Asia Pacific registry presented even younger at 54 years.[29]

The SHFRS comprises 10 readily available clinical and objective parameters. It contrasts with more complex models such as SHFM and CHARM (Candesartan in Heart Failure – Assessment of Mortality and Morbidity) which require a total of 24 variables each.[11,19] The variables in our model were also objective and did not include subjective factors found in other models such as the New York Heart Association (NYHA) Functional Classification.[10,17-19] The NYHA model may vary over different time points and studies have found significant differences in physician-rated and patient-rated classifications[30] as well as significant inter-observer assessment of NYHA class.[31] The clinical parameters used in the SHFRS are readily available to the clinician and do not require further exercise test or any invasive cardiac test like in the HFSS[20] and other risk models,[21-23] thereby improving its ease of use.

Gorodeski and associates reported that pVO_2 improved discrimination beyond the SHFM but it did not significantly improve reclassification of risk.[32] Aaronson and colleagues observed that there was no added benefit in including Pulmonary Capillary Wedge Pressure in risk models.[20] In comparison, the MUerte Súbita en Insuficiencia Cardiaca (MUSIC) risk score—which also used 10 objective clinical variables—was based on a cohort of less than 1000 patients without a validation group.[3] It required both troponin and N-terminal pro b-type natriuretic peptide (NT proBNP) levels and 24-hour Holter monitor results which may not be readily available to all heart failure patients. Several of the published risk models also require manual calculation.[3,13,20,23,33-35] We compared the SHFRS to the MAGGIC model in our derivation cohort and it was shown that SHFRS performed better (C-statistic of 0.731 vs 0.620). The availability of the SHFRS as an online calculator also ensures its easy access. It allows scores to be easily applied in clinical practice for risk stratification and in prognostication to guide patient management.

The clinical variables selected by the stepwise multivariable analysis were all supported by a strong body of evidence. In many previous studies, age,[2,12,16,17,19,33,34,36,37] prior MI,[37] prior stroke,[12] prior PVD,[38] lower EF,[16,17,19] AF,[39] longer QRS duration,[40,41] lower SBP,[12,16,17,42-44] lower haemoglobin[45,46] and lower sodium levels[2,12,13,16,36,44,47] have all been shown to be independent predictors of increased mortality. Higher creatinine levels[2,13,16,17,36,37,42] have also previously been shown to be a significant risk factor for mortality in heart failure patients. Creatinine levels have been included in our score as a surrogate for renal function. This is especially pertinent since impaired renal function is commonly associated with heart failure and patients with cardio-renal syndrome often have a poorer prognosis.[48-50] In contrast, SHFM[11] and MAGGIC[10] did not include any markers of renal function to aid prognostication.

Medications were excluded from our risk model for several important reasons. First, the beneficial effects of medications in the treatment of patients with preserved EF have not been established.[28,51-55] The inclusion of medications may affect the predictive accuracy of the model in patients with preserved EF. Second, differences in the dosage of medications administered affect mortality and morbidity outcomes.[56,57] Very often, exact dosing is not readily available. To account for the potential impact of medications, a separate analysis that included the effects of medications was performed. The result did not show any significant change in the predictive accuracy of the model. The exclusion of medications is commonly found in many risk scores.[3,11-13,15,20,23,33,35,36,58]

The strengths of our study include a large cohort size, the ease of use of the SHFRS and its ability to provide accurate and reliable mortality estimates. It is also the first heart failure risk score developed in Southeast Asia. It has the potential to provide the clinician with a means to better risk-stratify heart failure patients in order to guide management and to allocate resources more equitably. This helps to identify high-risk heart failure patients who may need more intensive therapy and follow-up. Additionally, the SHFRS may provide valuable prognostic information in the conversation with the patient and family regarding possible end-of-life care.

Limitations

Our study has several limitations. Similar to other registry studies, bias may have arisen from missing data but this was kept to a minimum (<3%) for all data fields except NT proBNP. Due to about 15% of missing data, NT proBNP was excluded from our model. We were unable to compare the performance of some of the existing risk models in our cohort due to differences in the variables collected by the various registries. Second, our cohort was based on hospitalised patients with a DRG code of 252. Patients in the outpatient setting may have different outcomes and the restriction of the DRG code may give rise to the possibility of misclassification. Third, our study included mainly Chinese, Indian and Malay ethnicities and will need to be validated in similar Asian cohorts, other Asian ethnicities and Western cohorts. Fourth, the exact EF was not available in the registry as such data was coded into the above categories. Within limitations, the categories provide good differentiation among patients with preserved, impaired and severely impaired EFs. Last, with constant

improvements in heart failure management,[59,60] the SHFRS will need to be validated in future patient cohorts.

Conclusion

We provide a risk score based on readily available clinical characteristics to predict 1- and 2-year survival in Southeast Asian patients hospitalised for heart failure. This was done using a simple online risk calculator.

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Commentary

Peer Support in Mental Health: A Growing Movement in Singapore

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Peer Support in Healthcare Services

Peer support is a growing global phenomenon in healthcare services. Peers for Progress, an international peer support association based in the University of North Carolina, currently oversees 320 peer support programmes in 6 continents. It defined peer support as "(linking) people living with a chronic condition such as diabetes. People with a common illness are able to share knowledge and experiences—including some that many health workers do not have".[1] Service users engaged in peer support work include breast cancer survivors[2] to young persons with diabetes[3] to people who have experienced a mental health crisis.[4] A reason for the growth of peer support in healthcare services is embedded in the definition of peer support—it enhances existing services by encouraging peers to share their knowledge and experiences with other healthcare staff and providers. Recovery from mental illness is a complex process[5,6] that often includes wellness in physical and mental health, social functioning and personal identity.[7]

Even as mental health professionals attend to the health and functioning of their patients, they could use more support in terms of rebuilding their patients' personal identities in the aftermath of a mental illness. Peer support therefore helps to enhance mental healthcare services when peer support specialists (PSS) are engaged to assist their peers to rebuild their identities after a mental health crisis. It can introduce a systemic shift in the delivery of mental healthcare services with a greater focus on all aspects of recovery. Much effort has therefore been made to establish peer support as a vocation in mental healthcare. Unlike peer support in other fields that relies mostly on volunteers, peer support in mental healthcare is gaining recognition as a profession in Singapore and overseas.[8]

Peer Support in Mental Health

Peer support is a relatively new field in modern mental health services. It traces its roots to 18th century Paris when Philippe Pinel and Jean Baptiste Pussin pioneered a new form of treatment to help mental patients in the Bicentre Hospital.[9] Their humanised approach included hiring workers who were recovering patients of the hospital. Harry Sullivan employed a similar strategy when he hired patients who had recovered from psychotic episodes in his inpatient unit in the 1920s. In 1935, Bill Wilson and his psychiatrist, Bob Smith, founded Alcoholics Anonymous in Akron, Ohio as a peer support group to help recovering alcoholics stay sober.[10,11]

Modern peer support originated from the psychiatric survivors movement in 1970s America after former patients organised themselves into a group to lobby collectively for reforms in mental healthcare and to advocate for fair treatment towards individuals with mental illness.[12] Over time, it evolved into a recovery movement, and peer support has become a part of the mental health system in the United States since the 1990s. It has also spread to other parts of the world like Australia, Hong Kong and the United Kingdom.

Peer Support Services in Singapore

In Singapore, peer movement formed organically after several individuals who had survived a mental health crisis published memoirs of their experiences with mental illness.[13-16] In 2009, the Early Psychosis Intervention Programme (EPIP)—which was established in 2001[17]—began to pay PSS for the support rendered.[18] In 2011, the Singapore Association for Mental Health (SAMH) and Singapore Anglican Community Services partnered the Agency for Integrated Care and invited trainers from the United States to introduce recovery-oriented services and peer support as a vocation to the country. In 2012, SAMH became the first organisation to conduct the peer specialist certification course. In 2013, the first full-time PSS was hired by SAMH.[19]

In 2014, the first PSS was hired by IMH for its Occupational Therapy Department and this was followed by similar hires for its Case Management Unit. The work of the PSS in IMH differed from one department to the next. Since the Case Management Unit serves only the outpatients of the hospital, the job of the PSS primarily involves the provision of one-to-one support sessions for these patients. As EPIP serves both inpatients and outpatients in the hospital, PSS

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are also expected to engage inpatients on an individual basis or through group work. They also empower their peers to contribute in services by providing them training and engagement. While the details of their job scope may vary in IMH, peer support still constitutes the core of the work of PSS. When PSS intentionally share their lived experience of their own illness, they instill hope in their peers.

In an effort to introduce peer support to the local social service sector, the National Council of Social Services (NCSS) and IMH launched the inaugural Certified Peer Specialist (CPS) course at the Social Service Institute in February 2017. A total of 23 peers graduated from the first intake and the third run of the programme was completed in September 2018. NCSS also worked with Workforce Singapore to offer a Work Trial Apprenticeship Scheme that matches CPS graduates to participating social service organisations to work as apprentices.[20] In July 2018, NCSS supported the establishment of a peer-managed social service organisation called Resilience Collective. It is tasked to pilot recovery colleges[21] in Singapore to empower persons in recovery through education, peer support and stigma reduction. It is viewed as a symbolic move because it is the first organisation in Singapore that is run by peers to serve their peers in the mental health community.

Challenges in Local Peer Support Services

Within a few years, Singapore has established peer support training with help from its Western counterparts and has trained a pool of individuals in recovery to provide peer support in mental health. Although the local peer movement has grown greatly, it still faces challenges and obstacles.

From the beginning, the implementation of peer support services was met with resistance from the public as there were concerns over the readiness of peers to handle the demands and pressures of the workplace and even the possibility of an illness relapsing due to work stress. Although the public meant well, such concerns nevertheless expose the underlying prejudices they have against individuals with mental illness in the workplace.[22]

Philosophical differences over the career longevity of PSS have also since surfaced. Some have advocated the development of a career path for PSS since it may be maladaptive for such individuals to continue to work in the peer role indefinitely. Others argued that the vocation can be a stepping stone into a different profession in the mental health sector. They believed that the constant use of a lived experience of an illness can limit one's growth and impede their progression up the career ladder. The authors propose that lived experiences can still evolve as PSS continue their journey in recovery. Nevertheless, career progression can also help to hone the leadership skills of PSS and efforts can be made to help them have a career.

Peer support is a nascent field in Singapore. There is a pressing need to adapt and develop the sector to ensure the longevity of the movement in the country. Although the principles of peer support have remained unchanged throughout the world, they should be adapted to meet the needs of a local culture and its system in order to be effective. IMH has therefore set up a PSS unit under its Allied Health Department to train and develop PSS. Efforts are underway to define a clear reporting structure, job scope, continuous learning and development, and mapping competencies to create a career path for PSS.

There is a myriad of opinions on the job design of PSS in mental healthcare. Some believe that PSS who have full-time roles in a medical setting will bring about best recovery in patients. Others have argued their preference to integrate the peer function into existing healthcare positions to create peer healthcare attendant roles. There is worry that the efficacy of peer support in recovery may be diluted when peers are subsumed into conventional healthcare roles. This is because peer support is built upon the premise of hope and recovery with an intentional use of lived experiences and is therefore different from other mental healthcare roles. The authors envision that when PSS become more entrenched and accepted in the mental health sector, it will provide more clarity on how peer support vocations can fit into the job categories in the healthcare sector.

A common question on peer support is the perceived lack of its effectiveness in Singapore. While the overseas success of peer support is acknowledged, there is doubt that it has been replicated in this country. This poses a dilemma for the planning and delivery of local peer support services. Before any data or evidence can be furnished to demonstrate its usefulness, peer support must be implemented first (perhaps with a leap of faith) and then evaluated for its efficacy in the local context. Since the theoretical framework of recovery and peer support is fundamentally different from other medical interventions such as pharmacotherapy and psychotherapy, one must think out of the box to effectively evaluate the efficacy of local peer support services.

Finally, peer movement in Singapore is largely driven by mental health professionals. A more probing mind may wonder if it is truly a peer movement since most of the initiatives were undertaken by this group of healthcare professionals. This observation has implications on the significance of the movement. For a long time, people with mental illness were deprived of a voice. To help them regain their voice, the local peer movement must tread carefully between authentic peer involvement and tokenistic peer involvement. The concept of coproduction is a trendy one and it is easy to invoke it in proposals and presentations. However, the practice of coproduction in real life will require peer leaders to rise to the occasion and

for professionals to relinquish some of their power. This translates into a need for more dialogue between PSS and mental health professionals and they must move from a "us versus them" mentality to a collaborative paradigm working from a common set of shared beliefs and values. It is only when this power differential is levelled out that the peer movement could perhaps scale new and greater heights.

Conclusion

There are many hurdles to overcome in the journey to recovery from mental illness. Peer support provides a helpful means for patients to scale these obstacles. As we move in tandem with the mental health community worldwide, the stage is set for peer support and recovery to grow further in Singapore.

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Letter to the Editor

Empiric Meropenem-based versus Ceftazidime-based Therapy for Severe Community-Acquired Pneumonia in a Retrospective Cohort Study

Dear Editor,

Optimal antibiotic regimen is unknown for severe community-acquired pneumonia (SCAP) which has mortality rates of up to 67% locally.[1] Recommended empiric regimens from the West cannot be extrapolated to our region where melioidosis is endemic[2] and *Streptococcus pneumoniae* penicillin resistance is common.[3] Unfortunately, studies that compare optimal antibiotic regimens for SCAP in Southeast Asia are lacking.

Considering local epidemiology, our hospital's guidelines recommended ceftazidime as empiric therapy for SCAP due to its activity against *Burkholderia pseudomallei*. To complement its poorer activity against *S. pneumoniae,*[4] levofloxacin or moxifloxacin was added for pneumococcal and atypical coverage. However, physicians could deviate from the guidelines and use meropenem with a macrolide instead. Anecdotally, we observed higher mortality rates in patients on empiric ceftazidime-based regimen. Hence, this retrospective study was conducted with a primary objective of comparing 30-day all-cause mortality between the 2 regimens.

Materials and Methods

We conducted a single-centre, retrospective cohort study in Singapore General Hospital from January 2011 to April 2015. This study was approved by Singhealth Centralised Institutional Review Board (IRB No. 2010/114/E) and consent to participate in it was waived in view of the retrospective nature of the study. Patients were screened using pharmacy antibiotic consumption records. They were included if they were adults (≥21 years old) and initiated with ceftazidime or meropenem for SCAP within 48 hours of hospitalisation. Community-acquired pneumonia (CAP) was determined based on radiological findings and/or presence of clinical signs and symptoms within 48 hours of hospitalisation.[5-7] SCAP was defined as requiring admission to the intensive care unit (ICU) and mechanical ventilation within 48 hours of hospitalisation.[5] The exclusion criteria were: 1) hospital or long-term care facility admission for at least 2 days within the last 90 days or exposure to healthcare risk factors (haemodialysis, receipt of intravenous drug therapy or wound care) within the last 30 days; 2) interstitial lung disease or bronchiectasis; 3) recent organ transplant within the last 6 months; 4) active malignancy with neutropaenia; and 5) changes in antibiotics within 48 hours of initiation or receipt of antibiotics other than ceftazidime, meropenem, macrolides, fluoroquinolones and doxycycline during the first 48 hours.

Relevant demographic, clinical, laboratory and microbiology data were collected using electronic medical records. Primary cause of death was determined from primary physicians' documentation in the medical records.

The primary outcome was all-cause mortality within 30 days of CAP onset. Secondary outcomes included CAP-attributable mortality, clinical response at end of antibiotic therapy, duration of ICU and hospital stay and 30-day readmission from date of discharge. Clinical recovery and clinical improvement were defined as resolution and partial resolution of presenting signs and symptoms of pneumonia, respectively. Clinical failure was defined as persistence or worsening of these signs and/or symptoms during treatment.

Statistical analyses were performed using IBM® SPSS® Statistics version 23 (IBM Corporation, Armonk, NY). Pearson chi-square or Fisher's Exact tests were used for nominal data. Independent samples T-test was used for normal continuous data while Mann-Whitney U test was used for non-normal data. Univariate analysis was performed using Kaplan-Meier survival analysis with log-rank test. Multivariate Cox regression analysis was used to adjust for potential confounders. All statistical tests were performed at 95% two-sided confidence level.

Results

A total of 100 patients were included (59 ceftazidime, 41 meropenem). A flowchart on the patient screening process is shown in Figure 1. Patient demographics and microbiology results are summarised in Tables 1 and 2. More patients in the meropenem group (n = 29, 71%) were admitted in the last 2 years of the study period (2014 to 2015) compared to the ceftazidime group (n = 17, 29%), thereby reflecting the change in prescribing trends in our institution.

Few patients had positive bacterial cultures and most were sensitive to narrower spectrum antibiotics, including ceftazidime and fluoroquinolones, with only 1 case of extended spectrum beta-lactamase producing *K. pneumonia* in the meropenem group. The meropenem group had significantly more positive respiratory cultures (n = 13,

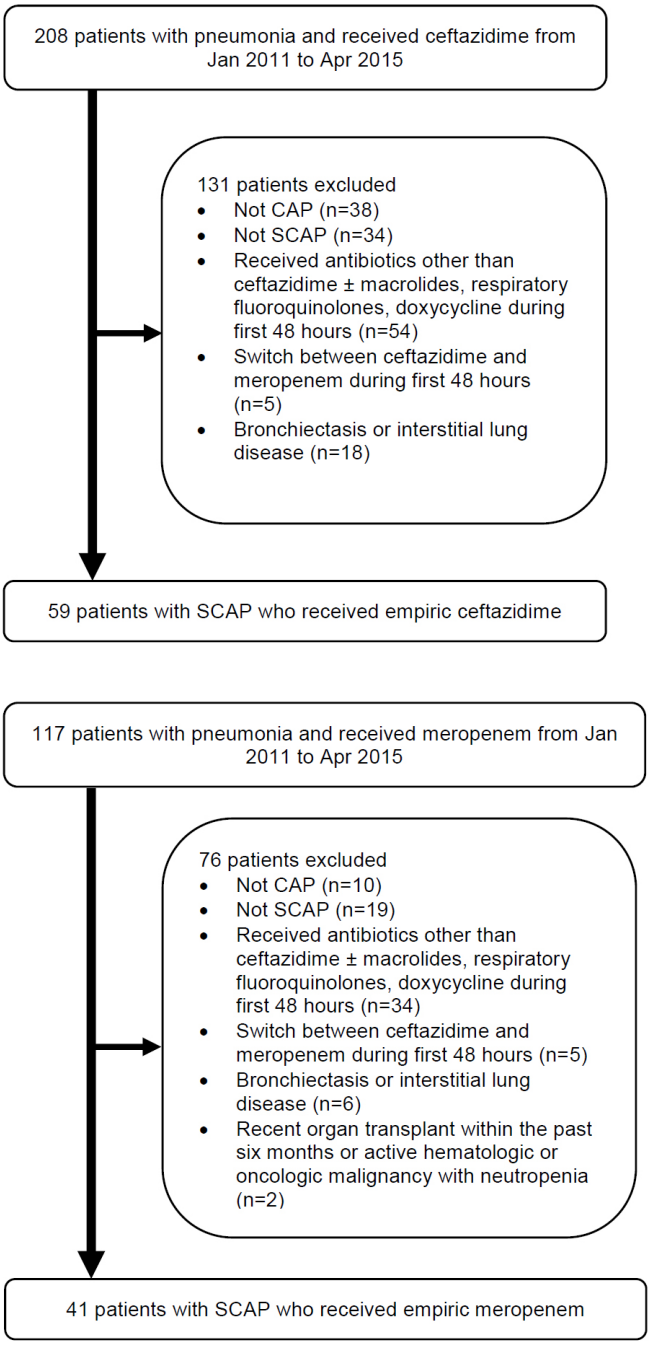

Fig. 1. Flowchart of patient selection process. CAP: Community-acquired pneumonia; SCAP: Severe community-acquired pneumonia.

32%) compared to the ceftazidime group (n = 4, 7%; P = 0.001). It also had more cases of documented bacteraemia (n = 14, 34% vs n = 8, 14%, respectively; P = 0.015).

All doses were appropriately titrated based on renal function. Median doses were 4 g/day in the ceftazidime group and 3 g/day in meropenem subjects. More patients presented with acute renal failure in the ceftazidime group

Table 1. Patient Baseline Characteristics

Baseline Characteristics	Ceftazidime (n = 59)	Meropenem (n = 41)	*P* Value
Median age (IQR)	64 (56 – 75)	62 (54 – 74)	0.375
Male (%)	33 (56%)	30 (73%)	0.079
Race (%)			0.964
Chinese	37 (63)	26 (63)	
Indian	5 (9)	3 (7)	
Malay	14 (24)	9 (22)	
Others	3 (5)	3 (7)	
Charlson Comorbidity Index (IQR)	5 (3 – 6)	5 (3 – 7)	0.367
Comorbidities (%)			
Diabetes mellitus	26 (44)	16 (39)	0.615
Ischaemic heart disease	17 (29)	8 (18)	0.291
Heart failure	6 (10)	4 (10)	1.000
Chronic kidney disease	8 (14)	7 (17)	0.628
Liver cirrhosis	0	2 (5)	0.166
Malignancy	5 (9)	9 (22)	0.056
Pulmonary disease*	7 (12)	4 (10)	1.000
Obesity†	6 (10)	2 (5)	0.466
Immuno-compromised state‡	2 (3)	3 (7)	0.398
APACHE II score (IQR)	20 (17 – 28)	22 (18 – 28)	0.582
CURB-65 score (IQR)	2 (1 – 4)	3 (2 – 4)	0.277
Pneumonia Severity Index (IQR)	4 (4 – 4)	4 (4 – 4)	0.658
Positive respiratory culture (%)	4 (7)	13 (32)	0.001
Endotracheal tube aspirate	4 (100)	13 (100)	
Broncho-alveolar lavage	0	1 (8)	
Documented bacteraemia (%)	8 (14)	14 (34)	0.015
Viral PCR test performed (%)§	32 (54)	24 (59)	
Positive respiratory virus infection	13 (41)	7 (29)	0.376

IQR: Interquartile range; NA: Not applicable; PCR: Polymerase chain reaction

*Pulmonary diseases include asthma and chronic obstructive pulmonary disease.

†Obesity is defined as body mass index of at least 30 kg/m^2.

‡Immunocompromised state is defined as presence of acquired immune deficiency syndrome or receipt of any immunosuppressive agent (such as methotrexate and tacrolimus) or prednisolone ≥20 mg/day for at least 2 weeks (or equivalent). The ceftazidime group had 1 patient with acquired immune deficiency syndrome and 1 patient with rheumatoid arthritis on methotrexate while the meropenem group had 2 patients on chronic systemic steroid therapy.

§The respiratory virus multiplex polymerase chain reaction test kit was used to detect the following: respiratory syncytial virus, influenza A and B, parainfluenza 1 to 3, metapneumovirus, rhinovirus, human coronavirus OC43 and 229E and adenovirus. Among those with positive respiratory virus infection, influenza was the most common in the meropenem group (n = 4). Rhinovirus was the most common in the ceftazidime group (n = 5) followed by influenza (n = 4).

‖Mortality cases were excluded.

Table 1. Patient Baseline Characteristics (Cont'd)

Baseline Characteristics	Ceftazidime (n = 59)	Meropenem (n = 41)	*P* Value
Average daily dose (IQR)	4 g (3 – 6 g)	3 g (2 – 3 g)	NA
Concurrent antibiotic used (%)			<0.001
None	1 (2)	0	
Moxifloxacin	49 (83)	7 (17)	
Levofloxacin	3 (5)	2 (5)	
Azithromycin	4 (7)	30 (73)	
Doxycycline	2 (3)	2 (5)	
Duration of therapy (IQR)‖	3 (2 – 4)	3 (2 – 4)	0.954

IQR: Interquartile range; NA: Not applicable; PCR: Polymerase chain reaction
*Pulmonary diseases include asthma and chronic obstructive pulmonary disease.
†Obesity is defined as body mass index of at least 30 kg/m^2.
‡Immunocompromised state is defined as presence of acquired immune deficiency syndrome or receipt of any immunosuppressive agent (such as methotrexate and tacrolimus) or prednisolone ≥20 mg/day for at least 2 weeks (or equivalent). The ceftazidime group had 1 patient with acquired immune deficiency syndrome and 1 patient with rheumatoid arthritis on methotrexate while the meropenem group had 2 patients on chronic systemic steroid therapy.
§The respiratory virus multiplex polymerase chain reaction test kit was used to detect the following: respiratory syncytial virus, influenza A and B, parainfluenza 1 to 3, metapneumovirus, rhinovirus, human coronavirus OC43 and 229E and adenovirus. Among those with positive respiratory virus infection, influenza was the most common in the meropenem group (n = 4). Rhinovirus was the most common in the ceftazidime group (n = 5) followed by influenza (n = 4).
‖Mortality cases were excluded.

Table 2. Bacterial Cultures Isolated from Patients' Respiratory or Blood Specimens

Culture Site and Bacteria Isolated	Ceftazidime (n = 59)	Meropenem (n = 41)
Respiratory tract (%)	4 (7)	13 (32)
Streptococcus pneumoniae	2 (3)	
Beta-haemolytic *Streptococcus*	1 (2)	2 (5)
Haemophilus influenzae	1 (2)	1 (2)
Moraxella catarrhalis		1 (2)
Klebsiella pneumoniae		5 (12)
Pseudomonas aeruginosa		2 (5)
Methicillin-sensitive *Staphylococcus aureus*		1 (2)
Mycobacterium tuberculosis	2 (3)	2 (5)
Mycobacterium avium complex		1 (2)
Blood (%)	8 (14)	14 (34)
Klebsiella pneumoniae		6 (15)
Klebsiella species	3 (5)	1 (2)
Streptococcus pneumoniae	2 (3)	3 (7)
Streptococcus intermedius	1 (2)	
Beta-haemolytic *Streptococcus*		2 (5)
Haemophilus influenzae		1 (2)
Burkholderia pseudomallei	1 (2)	
Rhodococcus species	1 (2)	
Pseudomonas aeruginosa		1 (2)
Concordant blood and respiratory cultures (%)		
Klebsiella pneumoniae		5 (12)
Streptococcus pneumoniae	2 (3)	
Beta-haemolytic *Streptococcus*		2 (5)
Haemophilus influenzae		1 (2)
Pseudomonas aeruginosa		1 (2)
Discordant blood and respiratory cultures (%)		
S. pneumoniae (blood), *P. aeruginosa* and *M. avium complex* (sputum)	2 (3)*	1 (2)

*Only 2 patients in ceftazidime group have blood cultures that were unlikely to be respiratory pathogens (*Rhodococcus* species and *Streptococcus intermedius*). Respiratory cultures for both patients were negative.
Note: In the ceftazidime group, there were 2 cases of concurrent pulmonary tuberculosis and 1 case of acquired immune deficiency syndrome with concurrent *Pneumocystis jiroveci* pneumonia and *Rhodococcus sp.* bacteraemia. In the meropenem group, there were 3 patients with concurrent pulmonary mycobacterium infection.

(n = 40, 68%) compared to the meropenem group (n = 24, 59%; *P* = 0.435). Hence, more patients in the ceftazidime group did not receive the recommended dose of 6 g/day. After excluding mortality cases, median duration of empiric ceftazidime or meropenem therapy was 3 days in both groups before modifications were made to antibiotic therapy.

Median time to all-cause mortality was significantly shorter in the ceftazidime group (7 days from CAP onset) than in meropenem group (>30 days, *P* = 0.002) as shown in Figure 2. It also had significantly greater 30-day all-cause mortality (n = 37, 63% vs n = 12, 29%, respectively; *P* = 0.001). After adjusting for the confounder (immunocompromised state) in the multivariate Cox regression analysis, patients on ceftazidime were thrice more likely to die earlier than those on meropenem (HR = 2.9; 95% CI, 1.5%-5.7%; Table 3).

CAP-attributable mortality was not significantly different between both groups (Table 3, Fig. 3). After adjusting for the confounder (documented bacteraemia with the same pathogen isolated from respiratory site), patients on ceftazidime were thrice more likely to die earlier from CAP compared to patients on meropenem (HR = 2.9; 95% CI, 1.2%-7.0%; Table 3). We also noted that more patients on the ceftazidime-based regimen (n = 11) died from cardiovascular cause compared to meropenem patients (n = 0), 7 of whom died within 72 hours.

Significantly more patients on meropenem had clinical recovery (n = 24, 59%) compared to ceftazidime patients (n = 17, 29%; *P* = 0.003). A total of 28 (68%) patients had antibiotic de-escalation after a median of 3 days

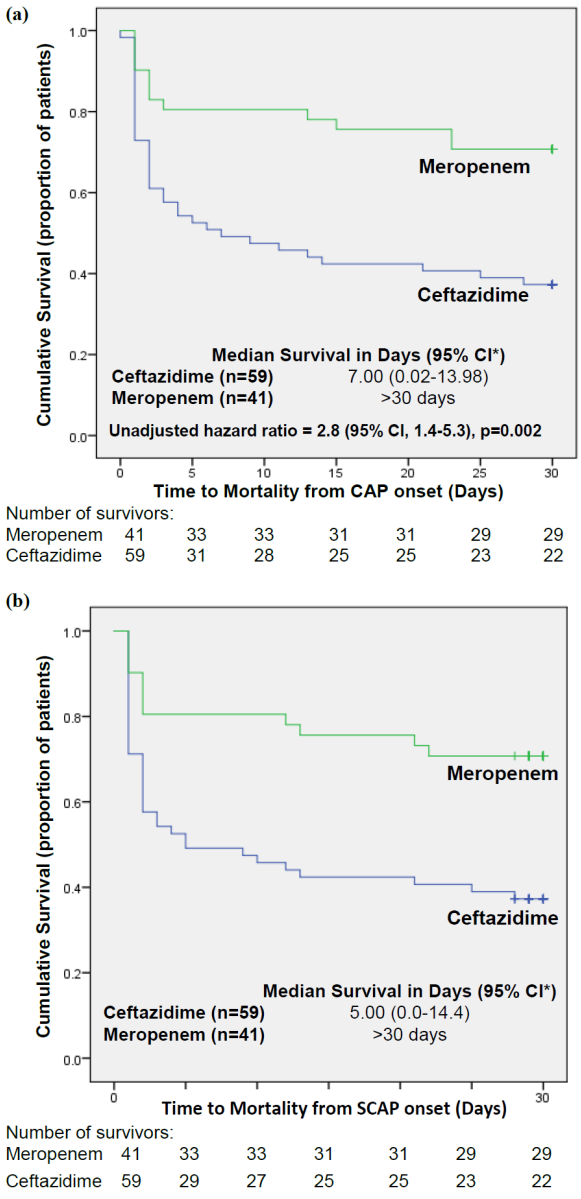

Fig. 2. Kaplan-Meier survival curve with all-cause mortality as outcome measure. A: Median time to all-cause mortality from onset of CAP was significantly shorter in the ceftazidime group (7 days) versus the meropenem group (median was not reached). B: Median time to all-cause mortality from onset of SCAP was significantly shorter in the ceftazidime group (5 days) versus the meropenem group (median >30 days as more than 50% of patients were still alive beyond 30 days). CAP: Community-acquired pneumonia; CI: Confidence interval; SCAP: Severe community-acquired pneumonia.

(interquartile range, 1-4 days). They were de-escalated to ceftriaxone (n = 8, 20%), ceftazidime with fluoroquinolones (n = 6, 15%), fluoroquinolone monotherapy (n = 5, 12%), co-amoxiclav (n = 3, 7%) and piperacillin-tazobactam (n = 3, 7%). In contrast, 13 (22%) patients in the ceftazidime group had antibiotic escalation to a carbapenem after a median of 2 days (interquartile range, 1-4 days). There was no significant difference between both groups in length of ICU and hospital stays and 30-day readmission.

Table 3. Clinical Outcomes and Results of Multivariate Analysis

Clinical Outcomes	Ceftazidime (n = 59)	Meropenem (n = 41)	*P* Value
30-day all-cause mortality (%)*	37 (63)	12 (29)	0.001
30-day CAP-attributable mortality	20 (34)	9 (22)	0.195
Clinical response (%)			0.007
Failure	35 (59)	12 (29)	0.003
Improvement	7 (12)	5 (12)	1.000
Recovery	17 (29)	24 (59)	0.003
Change in empiric antibiotic therapy (%)			<0.001
None	27 (46)	13 (32)	0.158
Escalation	13 (22)	0	0.001
De-escalation	19 (32)	28 (68)	<0.001
Length of hospital stay in days (IQR)†	8 (6 – 22)	14 (7 –31)	0.435
Duration of ICU stay in days (IQR)†	3 (2 – 7)	4 (2 – 8)	0.356
30-day readmission (%)†	3 (14)	4 (14)	1.000
Multivariate Analysis	**Hazards Ratio**	**95% Confidence Interval**	***P* Value**
All-cause mortality as outcome measure (demographic factors)			
Ceftazidime use	2.931	1.514 – 5.673	0.001
Immunocompromised state	3.139	1.106 – 8.914	0.032
CAP-attributable mortality as outcome measure (demographic factors)			
Ceftazidime use	2.935	1.229 – 7.010	0.015
Documented bacteraemia (same pathogen isolated from respiratory site)	3.139	1.324 – 7.442	0.009

CAP: Community-acquired pneumonia; ICU: Intensive care unit; IQR: Interquartile range

*In the ceftazidime group, other documented causes of death included cardiovascular causes (n = 11), pulmonary tuberculosis (n = 1), severe H1N1 infection (n = 1), acquired immune deficiency syndrome (n = 1), toxin ingestion (n = 1), pancreatitis (n = 1) and liver failure (n = 1). In the meropenem group, other causes of death included injury from fall (n = 1), stroke (n = 1) and invasive pulmonary aspergillosis in a non-immunocompromised host (n = 1).

†Mortality cases were excluded.

Note: Other potential confounders that were found not to be significant included age, gender, race, Charlson Comorbidity Index, APACHE II score, CURB-65 score, Pneumonia Severity Index, positive respiratory culture, documented viral respiratory tract infection, diabetes mellitus, congestive heart failure, chronic kidney disease, liver cirrhosis, malignancy, pulmonary disease, obesity, immunocompromised state, concurrent fluoroquinolone use and concurrent macrolide use.

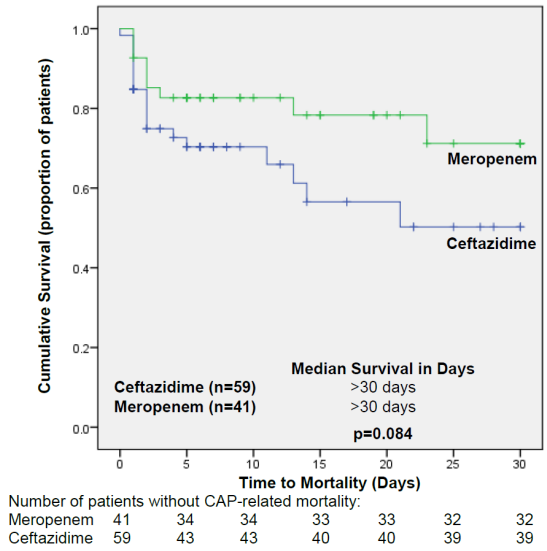

Fig. 3. Kaplan-Meier survival curve with CAP-attributable mortality as outcome measure. There was no statistically significant difference in median time to CAP-attributable mortality in both ceftazidime and meropenem groups. However, the ceftazidime group showed earlier CAP-attributable mortality. CAP: Community-acquired pneumonia.

Discussion

This is the first study that compared outcomes between 2 beta-lactam regimens in adult patients with SCAP in a region where melioidosis may be common. Our study suggests that ceftazidime-based regimen was significantly associated with early all-cause and CAP-attributable mortality (after adjustment for confounders) and greater clinical failure compared to meropenem-based regimen. This difference could be due to a few reasons. First, the inoculum effect is more commonly observed in cephalosporins compared to carbapenems.[8] The inoculum effect is a phenomenon in which higher minimum inhibitory concentrations are observed when the initial bacterial burden is high. This effect may be more significant in severe pneumonia where high bacterial burden is expected. Second, the immunomodulatory effects from macrolides could have contributed to better outcomes in meropenem-based regimens.[9] However, in our multivariate analysis, concurrent macrolide use was ruled out as confounder. Further studies are required to confirm the clinical significance of these contributing factors.

We also observed more early cardiovascular-related deaths in the ceftazidime group. CAP has been associated with cardiovascular complications, which contributes up to 60% increased risk in short-term mortality.[10] The systemic inflammatory response to pneumonia and hypoxemia could have led to endothelial dysfunction, myocardial injury, arrhythmias and heart failure.[11] Hence, lower efficacy of the ceftazidime-based regimen could potentially have resulted in greater incidence of cardiovascular complications and earlier mortality. Other plausible reasons for this observation could be cardiotoxicity risk from concurrent fluoroquinolone use and a greater number of patients with underlying ischaemic heart disease in the ceftazidime group. However, similar to fluoroquinolones, macrolides are known to have QTc-prolonging effects that carry the risks of cardiac arrhythmias and sudden cardiac deaths.[12-15] Unfortunately, there are no head-to-head comparison studies that can confirm which of the 2 classes of antibiotics carry greater cardiotoxicity risk. In our analysis, neither agents increased the risk of overall mortality and were ruled out as confounders. A complex interplay of various factors (underlying cardiac comorbidities and risk factors, severity of sepsis, concurrent use of macrolides or fluoroquinolones) could have contributed to this observation. Hence, further studies are required to confirm these findings.

One result of our study is that it may encourage more empiric carbapenem use, thereby leading to concerns over carbapenem abuse. However, we need to emphasise that in our study, patients on meropenem-based regimens were promptly de-escalated after a median of 3 days. To avoid carbapenem overuse, antimicrobial stewardship is necessary to ensure prompt antibiotic de-escalation as soon as patients have achieved adequate clinical response after 3 days.

A major limitation of this study is its retrospective design. It was a challenge to retrospectively determine the cause of death, especially when multiple factors were involved. As such, we had to rely on primary physicians' documentation of the cause of death. Second, our study had only 1 confirmed case of melioidosis which is against the trend observed in earlier studies. Nevertheless, empiric melioidosis cover is still important given that melioidosis can be endemic, especially during the monsoon season in our region.[1,2,15] Third, there may still be confounders that are unaccounted for. For example, the identification of causative pathogens in pneumonia is a challenging task due to its low yield of positive cultures. The reported rate of positive blood cultures in patients with CAP in Australia and Singapore was only around 7% to 8%.[16,17] It is therefore a difficult task to establish whether the difference in pathogens could be a contributing factor. We were also unable to evaluate whether certain cardiovascular comorbidities (such as pre-existing arrhythmias) could have contributed to more cardiovascular-related deaths, especially with concurrent macrolide or quinolone use. Finally, as more patients in the meropenem group were admitted in the last 2 years of the study period, we were not able to rule out the contribution of improvements in ICU care to better patient outcomes in these patients. A randomised, controlled trial will help to address the limitations of this study.

Conclusion

Empiric meropenem-based regimen appeared to be associated with lower mortality than ceftazidime-based regimen in SCAP. More studies are needed to establish optimal antibiotic regimen for SCAP in regions where empiric melioidosis cover may be required.

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A Review of Four Cases of Leptospirosis Presenting for Acute Care to a Tertiary Paediatric Hospital in Singapore

Dear Editor,

Leptospirosis is a widespread and potentially fatal zoonosis that is endemic in many tropical regions.[1] Small mammals are the most important reservoirs. Humans commonly become infected through direct contact with an infected animal or through contact via soil or water contaminated with urine from an infected animal. Leptospirosis ranges in severity from a mild, influenza-like illness to a severe infection characterised by multiorgan dysfunction. The combination of jaundice and renal failure is known as Weil's disease. The incubation period is 2 to 30 days and illness usually occurs 5 to14 days after exposure.[2] Based on the World Health Organization's laboratory criteria of leptospirosis, a probable diagnosis can be made when a positive result is obtained from a rapid screening test such as IgM enzyme-linked immunosorbent assay (ELISA), latex agglutination test, lateral flow or dipstick. A confirmatory diagnosis can be made based on any of the following: isolation from blood or other clinical materials through culture of pathogenic Leptospira, a positive polymerase chain reaction (PCR) result using a validated method (primarily for blood and serum in the early stages of infection) or a fourfold or greater rise in titre or seroconversion in microscopic agglutination test (MAT) on paired samples obtained at least 2 weeks apart.[3]

On 28 September 2016, leptospirosis was added to the list of notifiable infectious diseases in Singapore. A total of 53 human leptospirosis cases were notified in 2017.[4] In the first 48 weeks of 2018, 39 cases of leptospirosis were notified compared to 48 cases over the same period in 2017.[5]

In Singapore, a lower incidence of leptospirosis was observed in children compared to adults. According to data published by the Ministry of Health, the risk factors associated with leptospirosis included being male and aged between 15 and 34 years.[6] The annual incidence of leptospirosis cases reported in Singapore for the age group 5 to14 years were 0.8, 0.4 and 0.8 per 100,000 residents in 2013, 2014 and 2015, respectively. No case of leptospirosis was reported in the age group 0 to 4 years. Comparatively, the annual incidence of leptospirosis cases reported in the age group 15 to 24 years were 1.5, 1.6 and 0.8 per 100,000 residents in 2013, 2014 and 2015, respectively. In 2016, the incidence of reported leptospirosis cases in the age groups 0 to 14 years, 15 to 24 years and 25 to 34 years were 0, 0.9 and 0.2 per 100,000 residents, respectively.[7]

Under the requirements of Singapore's Communicable Diseases Live and Enhanced Surveillance (CDLENS) system, leptospirosis is notifiable within 24 hours when there is clinical suspicion or positive laboratory results have been obtained from any of the following tests: isolation of *Leptospira* from blood or cerebral spinal fluid or urine, PCR, serology (4 times or greater increase in *Leptospira* agglutination titre between acute-phase and convalescent-phase serum specimens) or immunoglobulin M (IgM).[8]

This study is a retrospective review of patients diagnosed with probable leptospirosis in a tertiary paediatric hospital in Singapore. They were identified from an electronic database of all patients referred to its Infectious Diseases Service. The diagnosis of leptospirosis was made by antibody detection (*Leptospira* IgM). The aim of this case series is to better characterise the clinical profiles of paediatric patients with probable leptospirosis and to provide a detailed description of severe leptospirosis in children. The study was approved by the Institutional Review Board and approval was also obtained for waiver of consent.

Case 1

A 15-year-old Pakistani girl presented on 17 November 2011 for fever, vomitting and abdominal pain. She had travelled to Malaysia from 30 October 2011 to 4 November 2011 where she did white water rafting and drank unboiled river water. She was hypotensive at 90/50 mmHg and tachycardic. Her physical examination was unremarkable. Her laboratory tests revealed leukocytosis, hyperbilirubinaemia, elevated creatine kinase-muscle/brain (CK-MB) and troponin I. She was admitted to the intensive care unit for septic shock and required fluid boluses and dopamine infusion. She did not require ventilatory support. There were concerns of intra-abdominal sepsis in view of vomitting and abdominal pain. She was treated with intravenous ceftriaxone and metronidazole. Her electrocardiogram was normal and echocardiogram showed good contractility. Tests for influenza, dengue, typhoid, group A streptococcus, melioidosis and blood cultures were negative. Her chest radiograph revealed bilateral pneumonia with pleural effusions. Her *Leptospira* IgM returned positive on 25 November and *Mycoplasma pneumoniae* total antibody titre was 160. She was discharged well and completed a 10-day course of ceftriaxone and clarithromycin (for presumptive mycoplasma infection).

Case 2

A 3-year-old girl who resides in Indonesia presented on 30 December 2013 for fever, diarrhoea, vomitting and abdominal pain. She had been admitted to a hospital in Indonesia 12 days earlier. Initial physical examination was normal other than a maculopapular rash on her trunk and limbs. She was initially treated for enteric fever with intravenous ceftriaxone. Laboratory tests revealed elevated C-reactive protein and erythrocyte sedimentation rate. On 2 January 2014, she developed right lower limb swelling. Tests for respiratory viruses, dengue, chikungunya, typhoid, melioidosis, rickettsia, bartonella, group A streptococcus, malaria and blood cultures were negative. Tuberculin skin test was negative. Magnetic resonance imaging of her right thigh showed right tibial shaft osteomyelitis. In view of sightings of rats at her home in Indonesia, *Leptospira* IgM was sent. She completed a week of intravenous ceftriaxone and was discharged with oral cephalexin for a total of 6 weeks for treatment of osteomyelitis. Her *Leptospira* IgM returned positive after she was discharged.

Case 3

A 10-year-old girl travelled to Australia, Indonesia and Malaysia in August 2015 and presented on 16 September 2015 for fever, chest pain and vomitting. There was report of sightings of rats during her travels. She was hypotensive and tachycardic with cool peripheries. Her laboratory tests revealed elevated transaminases, elevated serum creatinine, raised cardiac enzymes (CK-MB/troponin I), raised C-reactive protein and raised erythrocyte sedimentation rate. Her echocardiogram showed poor contractility. She was admitted to the intensive care unit and treated for acute myocarditis. She developed ventricular tachycardia and subsequently bradycardia with complete heart block. She was started on extracorporeal membrane oxygenation from 17 to 28 September 2015. She also developed acute kidney injury that required renal replacement therapy, ventilator-associated pneumonia and left lower limb deep vein thrombosis. Tests for adenovirus, enterovirus, rickettsia, legionella, toxoplasma were negative. Galactomannan antigen testing for bronchoalveolar lavage (BAL) fluid was positive and *Candida parapsilosis* complex was detected in the BAL fluid. *Leptospira* IgM was done on 25 September 2015 and came back positive on 30 September 2015. She was empirically treated with intravenous piperacillin-tazobactam, vancomycin, meropenem, voriconazole and 2 doses of intravenous immunoglobulin (on 19 and 20 September 2015). She received 9 days of meropenem in view of her critically ill state and subsequently switched to ceftriaxone for 5 days after she improved. Prior to discharge, her echocardiogram showed normal biventricular function. She was discharged well on 15 October 2015.

Case 4

A 14-year-old boy attended an outdoor school camp from 1 to 3 July 2017 and presented on 26 July with fever, abdominal pain, nausea and jaundice after he had contact with murky water. He had scleral icterus and hepatosplenomegaly. His laboratory results revealed conjugated hyperbilirubinaemia with elevated transaminases, pyuria and haematuria. He was treated for acute infective hepatitis. Tests for hepatitis A, B and C, Epstein-Barr virus, cytomegalovirus, adenovirus, influenza, enterovirus, melioidosis, dengue and rickettsia were negative. On his second day of admission, he developed sudden onset of chest pain with no haemodynamic instability. Electrocardiogram showed ST elevation in leads V4-6 and ST depression in V1. Cardiac enzymes were raised and echocardiogram showed mildly decreased left ventricular systolic function indicating myocardial injury. He was transferred to the intensive care unit and commenced on milrinone. He was treated empirically with intravenous piperacillin-tazobactam. His fever persisted and he developed bilateral conjunctivitis. There were concerns of a possible diagnosis of atypical Kawasaki disease. *Leptospira* IgM done on 27 July 2017 was negative, but when repeated on 3 August, it returned positive. His cardiac enzymes improved, fever resolved and he completed a week of oral doxycycline upon discharge.

Discussion

To our knowledge, this is the first paediatric case series of leptospirosis in Singapore and the first to provide a detailed description of severe leptospirosis in children in Singapore. Table 1 summarises the clinical and laboratory data of the patients in our series. There were 2 prior publications on leptospirosis from Singapore but they were not relevant to our study.[9,10]

In our series, the diagnosis of probable leptospirosis was made by IgM ELISA (SERION ELISA classic *Leptospira* IgM, catalogue No. ESR125M; SERION RF-Absorbent, catalogue No. Z200) performed according to manufacturer's instructions. Results were reported as negative, indeterminate or positive. The serological gold standard test is microscopic agglutination test (MAT) which is difficult to perform. As such, *Leptospira* IgM ELISA is commonly performed in clinical laboratories for early diagnosis.[11]

Leptospirosis is one of the most important differential diagnoses associated with febrile illness in returned travellers. In our series, 3 of 4 cases had recent travel to Southeast Asian countries. This is consistent with reports from Japan that all imported cases of travel-related leptospirosis contracted the infection in Southeast Asian countries.[12] All our cases reported recreational activities in fresh water or contact with rats within the expected incubation period (2-30 days) for leptospirosis.

Table 1. Summary of Patients' Clinical Information and Treatment

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Date of admission	17 November 2011	30 December 2013	16 September 2015	26 July 2017
Age (years)	15	3	10	14
Gender	Female	Female	Female	Male
Ethnicity	Pakistani	Chinese	Arab-Indian	Chinese
Travel location	Malaysia	Indonesia	Australia, Indonesia, Malaysia	None
Exposure	White water rafting	Rats	Rats	Outdoor camp, swam in ponds
Interval between travel/exposure and presentation (days)	13	12	16	23
Fever duration (days)	2	14	2	6
Abdominal pain duration (days)	12	3	0	5
Vomitting (days)	2	14	1	0
Chest pain (days)	0	0	1	1
Rash	No	Maculopapular	No	No
Jaundice	No	No	No	Yes
Other signs	Hypotension	Right lower limb swelling	Hypotension	Conjunctival injection, hepatosplenomegaly
WBC on admission/peak, 10^9/L	11.93/17.8	12.84/12.84	12.61/22.94	9.43/11.27
Platelets on admission/nadir, 10^9/L	375	200	260	235
	295	200	71	235
CRP peak, mg/L	60.5	52.8	321.3	157.8
Pro-calcitonin peak, µg/L	-	-	5	0.55
ESR peak*	25 mm/50 min	110 mm/hr	18 mm/hr	68 mm/hr
Bilirubin peak (total/direct), µmol/L	25/4	6/4	132/92	197/144
AST/ALT peak, U/L	31/27	21/12	305/147	109/212
Kidney dysfunction (serum creatinine peak), µmol	No	No	Yes (367)	No
Creatine kinase peak, U/L	168	68	20,634	359
Cardiac dysfunction (peak troponin-I, range)†	Yes (0.31 ng/mL, ≤0.1 ng/mL)	No	Yes (44,274 ng/L, ≤10 ng/L)	Yes (12,642 ng/L, ≤10 ng/L)
Other investigations	CXR pulmonary infiltrates, pleural effusion	MRI: Osteomyelitis of right tibial shaft	Microscopic haematuria, ECG: ventricular tachycardia, heart block	US: hepatomegaly
Interventions				
Inotropes	Yes	No	Yes	Yes
Ventilation	No	No	Yes	No
Dialysis	No	No	Yes	No
ECMO	No	No	Yes	No
Length of hospital stay (days)	11	9	29	12
Antibiotic therapy and duration	Ceftriaxone 10 days, clarithromycin 10 days	Ceftriaxone 7 days, cephalexin 42 days	Piperacillin-tazobactam 5 days, meropenem 9 days, ceftriaxone 5 days	Piperacillin-tazobactam 5 days, doxycycline 7 days

ALT: Alanine transaminase; AST: Aspartate transaminase; CRP: C-reactive protein; CXR: Chest radiograph; ECG: Electrocardiogram; ECMO: Extracorporeal membrane oxygenation; ESR: Erythrocyte sedimentation; MRI: Magnetic resonance imaging; US: Ultrasound; WBC: White blood count
*ESR was reported in mm/50 min (range 0-20 mm/50 min) before it switched to mm/hr (range 3-15 mm/hr) from August 2013.
†Troponin-I was reported in ng/mL (range ≤0.1 ng/mL) before it switched to high-sensitive troponin-I in ng/L (range ≤10 ng/L) from December 2014.

The clinical features of leptospirosis are non-specific and its signs and symptoms are similar to many other infectious diseases including influenza, malaria, dengue fever and typhoid fever. Conjunctival injection is a characteristic and relatively specific manifestation that can distinguish leptospirosis from other infectious diseases.[13,14] Though rare, leptospirosis has been reported to present as acute acalculous cholecystitis and pancreatitis.[15] In our series, only 1 case was reported to have conjunctival injection. The most common symptoms in our series were fever, abdominal pain and vomitting.

In our series, 3 of 4 patients had myocardial injury or myocarditis. Myocarditis and myocardial failure have been reported in severe cases of leptospirosis. However, its frequency of occurrence, exact pathophysiological basis and contribution to morbidity and mortality are not well understood. Cardiac involvement—demonstrated electrocardiographically or clinically—tends to predict poor outcome.[16]

In view of the varied presentation of leptospirosis, particularly fever with conjunctival suffusion, Kawasaki disease is an important differential. Kawasaki disease has been reported in patients with leptospirosis.[17] Leptospirosis is believed to produce milder symptoms in children with lower rates of classic signs and symptoms of Weil's disease.[18] Among children, adolescents and adults with severe leptospirosis, there is a higher need of dialysis in adults suggesting severe acute kidney injury and milder renal disease in children.[19] In our series, 3 cases required admission to the intensive care unit and inotropic support with one needing extracorporeal membrane oxygenation and dialysis. This highlights the severity of the cases in our series. There were no fatalities in our patients.

Severe cases of leptospirosis should be treated with high doses of intravenous penicillin. Third-generation cephalosporins, such as ceftriaxone and cefotaxime, and quinolone antibiotics are also effective. Oral antibiotics such as amoxycillin, ampicillin, doxycycline or erythromycin can be considered in less severe cases.[20] Antibiotic treatment for leptospirosis is shown to decrease the duration of clinical illness by 2 to 4 days. The selection of penicillin, doxycycline or cephalosporin does not seem to impact mortality or duration of fever.[21] In all 4 cases, there was initial clinical suspicion of leptospirosis. However, as the presentations were non-specific and in view of the clinical severity, empirical antibiotics (ceftriaxone and piperacillin-tazobactam) were started while awaiting confirmatory laboratory results.

In conclusion, a diagnosis of leptospirosis must be considered in children who present with a febrile illness, especially in returned travellers, and where there is a history of recreational activity in fresh water or contact with rats. The presentations are varied and non-specific and can overlap with many infections as well as Kawasaki disease. This series also highlights the severity of paediatric leptospirosis as 3 of 4 cases required admission to the intensive care unit with cardiac involvement. A high index of suspicion is therefore needed to institute early treatment and to reduce morbidity and mortality.

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A Rare but Disabling Stroke

A 59-year-old woman presented with recurrent vomitting, problem with speech and swallowing difficulty for 2 days with sudden onset of bilateral upper and lower limb weakness. She did not have dizziness, vertigo, headache or neck pain. There was no recent history of head and neck trauma. She had an ischaemic stroke in 2016 with weakness in the left face, left upper limb and left lower limb. She was diagnosed with lacunar stroke but had full neurological recovery. She had a history of hypertension and diabetes mellitus with poor glycaemic control.

On examination, she was fully conscious but had dysphonia, absent gag reflex and weak tongue movement. Her bilateral upper limb power was 3/5 proximally and 4/5 distally while her bilateral lower limb power was 1/5 proximally and 2/5 distally. Tone was normal bilaterally. She had bilateral extensor plantar reflexes with no sensory loss, ophthalmoplegia or facial asymmetry.

What subtype of stroke did this patient have and what was the anatomical variant present in magnetic resonance angiography (Fig. 1)?

A. Lateral medullary infarct with hypoplastic left vertebral artery
B. Lateral medullary infarct with hypoplastic right vertebral artery
C. Medial medullary infarct with hypoplastic left vertebral artery
D. Right medial medullary infarct with hypoplastic right vertebral artery
E. Bilateral medial medullary infarct with hypoplastic right vertebral artery

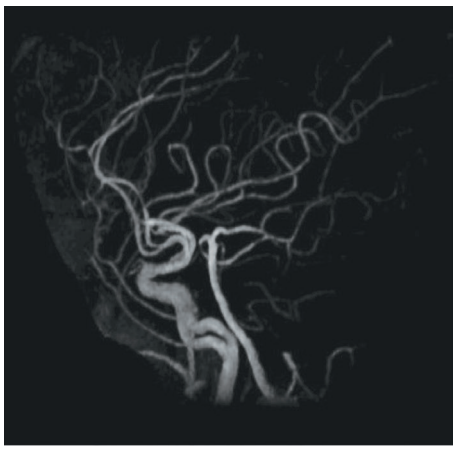

Fig. 1. Magnetic resonance angiography of artery.

Discussion

Option E is correct because brain magnetic resonance image (MRI) showed bilateral medial medullary infarct. Additionally, magnetic resonance angiography showed hypoplastic right vertebral artery that terminated as posterior inferior cerebellar artery (PICA).

Options A and B are incorrect because brain MRI showed medial medullary infarct and not lateral medullary infarct. Option C is also incorrect because the patient had hypoplastic right vertebral artery and not hypoplastic left vertebral artery. Option D is incorrect since the patient had bilateral medial medullary infarct but no right medial medullary infarct.

Medial medullary infarct (MMI) comprises the clinical triad of contralateral hemiparesis, contralateral loss of deep sensation and ipsilateral lingual palsy (Dejerine's triad).[1,2] It is a rare subtype of stroke with an incidence of 0.5% to 1.5%.[1,2] Bilateral MMI is even rarer.[1,2]

Patients with bilateral MMI usually present with acute onset of quadriparesis or quadriplegia, bulbar palsy, lingual palsy and bilateral sensory loss with or without respiratory failure.[3] In patients with lateral medullary syndrome, they present with ipsilateral Horner's syndrome, ipsilateral facial sensory loss and contralateral hemisensory loss. This patient did not have dizziness, vertigo, headache, neck pain or trauma to the neck and head which suggested arterial dissection. With a diversity of clinical symptoms, diagnosis is often delayed and patients are often treated for other more common diseases.

With advancements in brain neuroimaging techniques such as MRI, bilateral MMI can be diagnosed earlier and more easily. In acute bilateral MMI, MRI shows a characteristic "heart-shaped appearance" in the ventral medulla (Fig. 2).[3] The probable stroke mechanism in this patient was occlusion of perforators (from vertebral artery or basilar artery) or atherosclerosis of vertebral artery. Another possible stroke mechanism described in the literature is anterior spinal artery occlusion.[3] The patient had bilateral MMI but not unilateral MMI because the anatomical variation of hypoplastic right vertebral artery terminated as PICA. It was not occlusion because the right vertebral artery can be visualised but it was small with a diameter of ≤2 mm. Additionally, the larger left vertebral artery was the dominant artery.

Answer: E

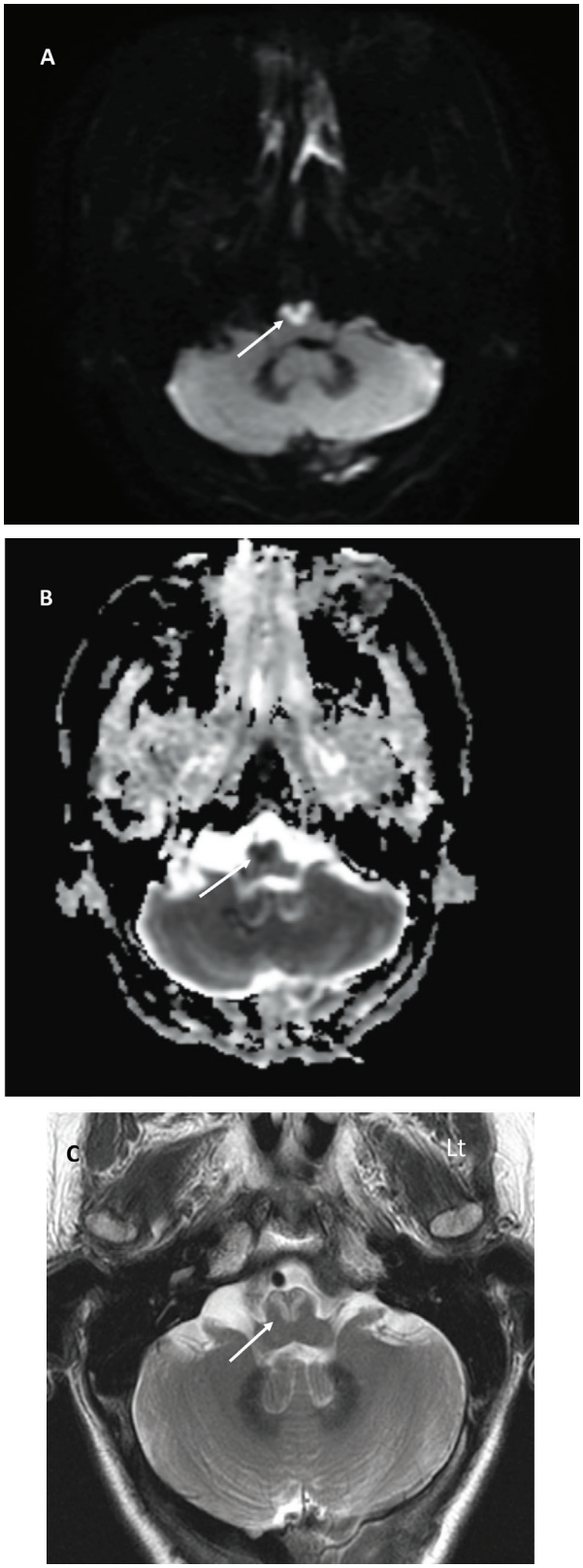

Fig. 2. A) MRI of heart-shaped appearance (arrow) in ventral medulla in diffusion-weighted image; B) Apparent diffusion coefficient sequence; and C) T2-weighted sequence. MRI: Magnetic resonance image.

PICA termination of vertebral artery (PICA-VA) happens when the vertebral artery does not communicate directly with the basilar artery and ends in PICA instead (Fig. 3).[4] PICA-VA is a variant of vertebral artery hypoplasia and is present in 2% of population.[4] In a recent study, the prevalence of PICA-VA in patients with posterior circulation stroke was shown to be significantly higher than normal individuals.[4] Sarah and colleagues reported a patient who had aplasia of left vertebral artery and left PICA that originated from the right vertebral artery and crossed the midline and supplied the contralateral side of the cerebellar hemisphere.[5] Figure 4 illustrates the arteries and PICA-VA.

Patients with bilateral MMI have a poor prognosis and high in-hospital mortality.[2] Most of them are dependent on follow-up.[3] Knowledge of stroke presenting with features

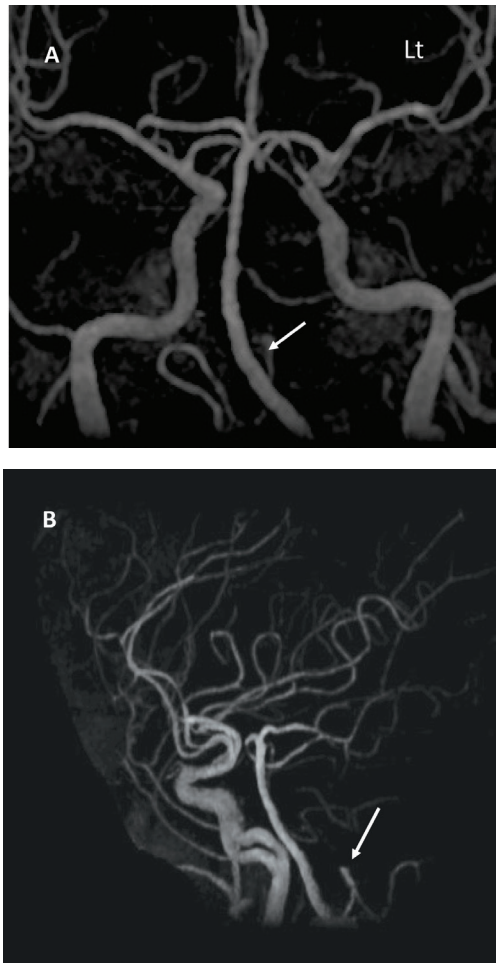

Fig. 3. A) Right PICA (white arrow) seen in brain MRI and B) MRA. MRA: Magnetic resonance angiography; MRI: Magnetic resonance image; PICA: Posterior inferior cerebellar artery.

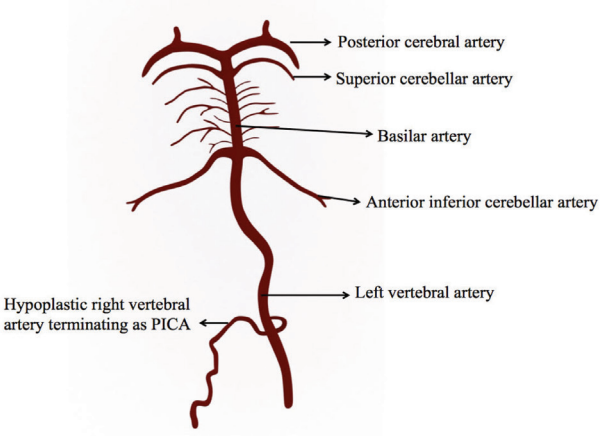

Fig. 4. PICA termination of vertebral artery. PICA: Posterior inferior cerebellar artery.

such as MMI is associated with early health-seeking practice.[6] In conclusion, there should be a high index of suspicion in patients with bilateral MMI presenting with quadriparesis and bulbar palsy since this condition is treatable and morbidity or mortality can be avoided.

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