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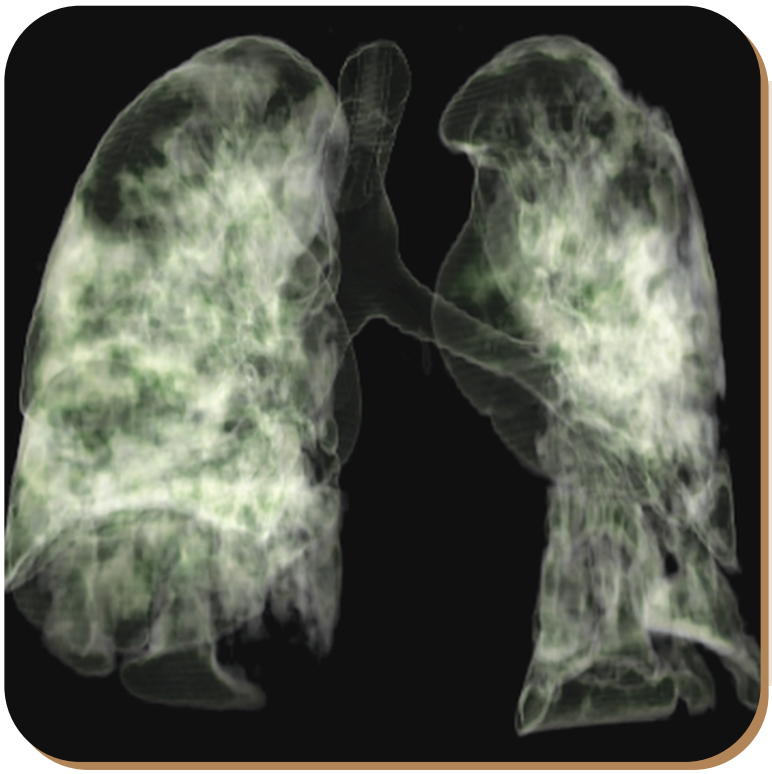

3D reformatted image showing extensive ground-glass and consolidation throughout the lungs of a COVID-19 ICU patient, with relatively increased lower lobe infiltration.

As the world battles the COVID-19 pandemic, we would like to acknowledge and thank all healthcare personnel in Singapore and worldwide for their dedication, valiant and tireless effort in providing the best care for the patients through these difficult times. Your sacrifices are not for naught and as the saying goes, there will be a rainbow at the end of the storm. Until then, let us soldier on and together we will defeat this invisible enemy.

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Department of Diagnostic Radiology, Tan Tock Seng Hospital and National Centre for Infectious Diseases

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Editorial

The Annals and the Medical Narrative of Singapore

Vernon MS Oh, [1,2]*MD, FRCP*, Raymond CS Seet, [1,3]*FRCP, FAMS*[*]

The start of the new decade has brought nothing short of chaos to health services from around the world. At hand, there is the global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first reported in Wuhan City in Hubei Province in Mainland China before it spread to Singapore and rest of the world.[1,2]

Initially, stringent containment measures and border controls in Singapore had curtailed the spread of COVID-19 to the local community. However, the country soon saw a second wave of COVID-19 infection after a spike in the number of confirmed cases was reported among returning residents—citizens and permanent residents—and visitors from the United States of America (USA), United Kingdom, Italy and other parts of Europe.[1,2] While there is still an atmosphere of relative calm in Singapore, the situation elsewhere has, unfortunately, been quite dire. Several major hospitals in the USA and Italy have declared that they had run out of mechanical ventilators and personal protective equipment after frontline health workers and hospitals were overwhelmed by the large numbers of symptomatic patients who were seeking treatment. Consequently, doctors were forced to make heartbreaking decisions to triage patients who arrived at hospitals into those who qualify for ventilatory support and those who do not by resorting to the use of crude age cut-offs because of lack of knowledge of the pathophysiology of COVID-19 and reliable biomarkers that can guide clinical management, as well as from growing scarcity of medical resources (both human and material).[1] The age cut-offs also seem to be getting lower as the crisis deepens.

In most countries, the psychological impact of COVID-19 is palpable as scenes of panic buying and paranoia filled the headlines in the news media, public spaces within hospitals are emptied out and once-busy streets and malls turned lifeless.[3] Singapore is not unaccustomed to the threat of epidemics. Important infectious disease episodes and events have been carefully chronicled through various articles published in the Annals of the Academy of Medicine, Singapore (the Annals), from the country's experience with the severe acute respiratory syndrome (SARS) outbreak[4] caused by the SARS coronavirus in 2003 and numerous outbreaks of infectious disease that struck us throughout our recorded existence as a nation.[4–7]

The Communicable Disease Centre (CDC), formerly Middleton Hospital, was founded in 1913 to manage infectious diseases in Singapore before it was succeeded by the National Centre for Infectious Diseases (NCID)[7] in 2019. In January 1979, the Annals reported on the threat of tuberculosis and malaria in Singapore.[4,5] This was followed by initial reports on the first molecular tool that was developed in Singapore to diagnose hepatitis B infection.[7] Indeed, progress in the delivery of health services in Singapore may be gleaned from the rich repository of articles published in the Annals that covered contemporaneous issues faced by Singapore including drug efficacy and safety,[8] drug abuse,[9] suicide,[10,11] diabetes mellitus,[12] hypertension[13] and many others.[14] At a time when teaching materials were limited and management updates were not easily accessed by most medical practitioners, senior physicians and academics often engaged the print platform provided by the Annals to update the local medical community on the latest information to inform the practice of medicine and surgery. With a repository of >6000 articles spanning >4 decades, the Annals has provided Singapore with an important account of issues that confronted us in the past.

More than ever, there is a need to continue this narrative as our health system is now being challenged on multiple fronts: ageing population, high prevalence of non-communicable diseases (such as diabetes mellitus, stroke, ischaemic heart disease and cancer) and rising costs of health services. As Singapore continues to earn

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international accolades for her delivery of affordable and consistent health services, there is a need for her medical community to continue to add to the evolving narrative on the transformation of health services through scholarly contributions.

The medical and research communities should take advantage of the rich disease phenotypes found in multiethnic Singapore and in the region that are ripe for detailed investigation. Some of these phenotypes include high prevalence of diabetes mellitus, younger age onset of stroke and other cardiovascular diseases, and ethnic differences in disease prevalence and outcomes.[12] The latter observations—considered "localised" issues—have not received much attention in international journals that understandably choose to focus on pressing issues pertinent to the geographic location of authors and journal publishers. The neglect of the importance of characterising our population well could lead to an over-reliance on overseas data to guide local health policies, treatment guidelines and foci of biomedical research.

The Annals needs your support to continue to evolve our health narrative. There is a rich source of data and materials that could have immediate health implications in Singapore and beyond. As the main publication of the Academy of Medicine, Singapore, the Annals was founded on the premise of promoting medical education and research excellence. The current COVID-19 pandemic has shown us clearly how quickly news travels, from a need to describe the clinical and genetic entity of the virus to the global scramble to develop a point-of-care diagnostic assay, new treatments, new vaccines and, crucially, the need for a medical journal that provides strong, independent peer review to validate pertinent new information. The Annals addresses these needs and aims to publish and disseminate the findings of research within a short handling time. As an indexed journal, the articles published in the Annals are accessible from most popular medical search engines (such as PubMed, Ovid and Web of Science) and from our very own website (www.annals.edu.sg). Our move to an online platform has meant that all accepted submissions to the Annals have international viewership and are freely downloadable. The Annals invites you to leverage on our platform to publicise your best science and research, and to help shape our medical narrative in Singapore and beyond.

On a personal note, to health workers (doctors, nurses, clinic staff, administrators, cleaners, porters, security officers, scientists, emergency/public services and academic publishing staff) and other unsung heroes, a sincere thank-you for your tireless work and enormous sacrifices fronting our response against COVID-19. Please keep well and stay safe!

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Editorial

The Novel Coronavirus (SARS-CoV-2) Pandemic

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began in early December in Wuhan, the 7th most populous city in Mainland China, and was reported to the World Health Organization (WHO) on 31 December 2019.[1] An outbreak of unknown aetiology was suspected because many early cases were linked to a large, live animal market that was misleadingly named Huanan Seafood Market, and the causative agent was identified as a novel coronavirus on 7 January 2020.[1,2] On 11 February 2020, the official names of the virus, SARS-CoV-2, and the disease, coronavirus disease 2019 (COVID-19), were announced by the International Committee on Taxonomy of Viruses and the WHO, respectively.[3]

On 23 January 2020, in view of the exponential increase in the number of cases in Wuhan and the spread of the virus to almost every province in Mainland China during the annual Spring Festival travel season—known as the largest human migration in the world—a quarantine of greater Wuhan was imposed.[4] Over the next 2 weeks, the quarantine order was extended to the rest of Hubei province and other mainland Chinese cities. At the time, these public health interventions were considered unprecedented in scale and geographical coverage.[5,6] Although these measures succeeded in reducing the considerable spread of SARS-CoV-2 to the rest of the world, it soon became clear to many that the virus had already spread far and wide beyond the Chinese Mainland.

Outside Mainland China, the first confirmed case of COVID-19 was a Wuhan resident who was diagnosed on 13 January 2020 in Bangkok, Thailand.[1] Other Asian countries reported cases in short order over the following 2 weeks.[1] As of 2 March 2020, 67 territories outside the Chinese Mainland had reported 8565 confirmed cases of COVID-19 and 132 fatalities, and widespread infection was reported in several Asian countries and in Iran and Italy.[7]

The Virus

A novel coronavirus was identified in the first patients in China. Its genetic sequence is closely related to bat betacoronaviruses (96% homology), while the 2003 SARS-CoV was found to be the most closely related (approximately 79% homology) among coronaviruses that are capable of infecting humans,.[2] Using published viral genomes (which number 119 at the time of writing), scientists at the open-source project, Nextstrain, have estimated that SARS-CoV-2 likely jumped into human hosts as a single introduction (or, less likely, a small number of introductions) between November and early December of 2019.[8] The secondary animal host responsible for the outbreak in Mainland China has yet to be identified.

In terms of human infections, SARS-CoV-2 is substantively different from SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV). Unlike SARS-CoV and MERS-CoV, SARS-CoV-2 is capable of causing sustained community transmission since an infected host can infect, on average, 2–3 uninfected individuals .[9] The estimated infection fatality rate (IFR)—used in place of case fatality ratio because it is generally believed that a significant number of infected individuals are not diagnosed—of SARS-CoV-2 is also much lower at 0.3–1.0%; in comparison, SARS-CoV had a case fatality rate of 9.6%.[10]

In the first few days of disease onset, the clinical presentation of SARS-CoV-2 is virtually indistinguishable from that of upper respiratory tract infections (URTI) before it progresses to severe and critical disease in just under 20% and 5%, respectively, of all diagnosed cases in a huge cohort of Chinese patients.[6] To date, there is no effective and definitive

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treatment for the virus, although a large number of clinical trials on multiple antiviral drugs and traditional Chinese medications have been launched, mostly in Mainland China.

In brief, SARS-CoV-2 has the transmissibility and lethality of a particularly virulent pandemic influenza virus that is matched only by the 1918 influenza virus which had an estimated case fatality rate of >1%.[11] Unlike influenza, however, SARS-CoV-2 predominantly causes relatively mild disease in infants and young children.[6]

SARS-CoV-2 in Singapore

In Singapore, the first case of COVID-19 was diagnosed on 23 January 2020 in a tourist from Wuhan. Health authorities in Singapore responded promptly by instituting, in rapid succession, a series of public health measures that included aggressive contact tracing, quarantine of contacts, issuance of travel advisories and restrictions, compulsory leave of absence for workers returning from Mainland China and ramping up case detection and infection prevention measures in clinics and hospitals.[12] Almost overnight, all clinics and hospitals had set up temperature and visitor screening facilities and had taken steps to ensure adequate supplies of surgical masks and personal protective equipment (PPE). The primary health sector was hit hardest since most family physician clinics were not equipped to handle an infectious disease outbreak.

Collectively, the measures succeeded in containing the spread of SARS-CoV-2 in the city-state, but they did not eliminate sustained transmission of the virus in the community. Consequently, the level of Disease Outbreak Response System Condition (DORSCON)—a colour-coded national framework that is used to map the disease situation in Singapore—was raised from Yellow to Orange since 7 February 2020, the second highest alert level, to indicate SARS-CoV-2 has not spread widely throughout the country and is contained.[13]

As of 2 March 2020, there were 106 confirmed cases of SARS-CoV-2 including a handful that were not linked to existing cases.[14] Most of them were isolated as inpatients in the newly-built National Centre for Infectious Diseases (NCID); however, to date all public hospitals have had to manage at least 1 confirmed and several suspected COVID-19 cases.

Unfortunately, NCID and the public hospitals were soon faced with the risk of being overwhelmed by the large number of patients that were sent them for screening by primary care physicians who did not want to miss a case of COVID-19, given that it was difficult to distinguish suspected COVID-19 cases from routine URTI and pneumonia, and particularly after local transmission of the virus had taken place and global epidemiology of the virus had changed. It also did not help that employers had begun to send their employees who returned from countries affected by SARS-CoV-2 to them for screening. The situation was only mitigated after the Ministry of Health, Singapore, activated the Public Health Preparedness Clinic (PHPC) scheme—established during the 2009 influenza pandemic—on 14 February 2020 to divert community patients with URTI to any of the 878 clinics that provide subsidised treatment and up to 5 days of medical leave. In particular, the longer duration of medical leave awarded to patients was helpful in reducing patient loads in public hospitals and NCID, since the implicit message to primary care physicians was that it was appropriate for them to miss a mild case of COVID-19.

Future Scenarios

Although the WHO did not declare SARS-CoV-2 as a pandemic on 28 February 2020 and had stressed that containment was still possible,[15] this view was not shared by many from around the world. In any case, it will become increasingly difficult for Singapore—a global hub for travel—to curb cross-border transmissions as SARS-CoV-2 spreads to more countries that, in turn, serve as foci for the spread of the virus. Current efforts at containment in Singapore have cost her economy and health services millions of dollars.[16] It will take months, if not weeks, before the SARS-CoV-2 pandemic is contained globally. Until then, the hope is for an effective vaccine to be developed and launched soon; however, it will take >1.5 years before the first batch of successful vaccines are introduced.

A key aim of containment and mitigation is to prevent existing health services from being overwhelmed by the outbreak of SARS-CoV-2 and its fallout, which was exactly what happened in Wuhan and it led to increased mortality and morbidity not just from COVID-19, but from other diseases as well. The projected IFR for COVID-19 is currently too high for any country to contemplate the possibility of allowing the virus to spread freely through its population just like other respiratory viruses and influenza pandemics in the past.[17] Public health interventions directed at social distancing, improving hygiene practices and countering "misinfodemics" remain a priority and could potentially reduce the spread of influenza and other respiratory viruses. For the general population, these interventions must be balanced against the need to live life normally as far as possible. For workers and students, a possible "new normal" could involve more telecommuting and online learning, respectively.

However, it is important to recognise that not every individual can be expected to do so since there are vulnerable and disadvantaged groups in our workforce and schools who require assistance—in the form of financial aid or subsidies—to use new media and technological tools and applications. As Singapore is a major hub for global professional services and a MICE (Meetings, Incentives, Conferences and Exhibitions) destination, novel ways must be found to convene small to large events to sustain her economic growth.

In clinics and hospitals, it is difficult to contemplate standing down from existing health and safety measures. SARS-CoV-2 can cause severe disease in young and healthy individuals, and critical illnesses and deaths had been reported in health workers in the Chinese Mainland that were attributed to nosocomial transmission.[6,9] Should the current situation deteriorate into a full-blown pandemic, 2 difficult interventions may need to be considered to ease the strain on health workers and facilities.

The first—and easier—intervention is to expand the capacity to conduct rapid diagnostic tests at the primary care level, either in the form of easy to use point-of-care tests by clinics or by a centralised laboratory. This is useful to identify early cases, empower primary care physicians and curb onward transmission.

The second, but more difficult, intervention is to re-evaluate and restructure delivery of health services for non-communicable diseases to minimise contact with health facilities beyond even an expansion of telemedicine and home care services. This will involve a move away from the current model of centralised health financing—where manpower, expertise and equipment are concentrated for efficiency—to a decentralised model. When that happens, it is likely to outlast the SARS-CoV-2 outbreak, but will nonetheless stand us in good stead for the future.

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Original Article

Rapid Progression to Acute Respiratory Distress Syndrome: Review of Current Understanding of Critical Illness from Coronavirus Disease 2019 (COVID-19) Infection

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Abstract

The outbreak of coronavirus disease 2019 (COVID-19) in December 2019 in the city of Wuhan in Mainland China has spread across the globe with >100,000 infected individuals and 3000 deaths reported in 93 countries as of 7 March 2020. We report a case of COVID-19 infection in a 64-year-old man who developed rapidly worsening respiratory failure and acute respiratory distress syndrome (ARDS) that required intubation. As the clinical spectrum of COVID-19 infection ranges from mild illness to ARDS with high mortality risk, there is need for research that identifies early markers of disease severity. Current evidence suggests that patients with advanced age, dyspnoea or pre-existing comorbidities should be monitored closely, especially at 1–2 weeks after symptom onset. It remains to be seen whether laboratory findings such as lymphopaenia or elevated lactate dehydrogenase may serve as early surrogates for critical illness or markers of disease recovery. Management of ARDS in COVID-19 patients remains supportive while we await results of drug trials. More studies are needed to understand the incidence and outcomes of ARDS and critical illness from COVID-19 infection which are important for critical care management of patients and resource planning.

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Key words: Intensive Care, Mortality, Pneumonia, Risk factors

Introduction

The outbreak of coronavirus disease 2019 (COVID-19)—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—was first reported on 31 December 2019 in the city of Wuhan in Mainland China.[1] On 30 January 2020, the World Health Organization (WHO) declared the outbreak a global health emergency; as of 7 March 2020, >100,000 individuals in 93 countries had been infected by the virus.[2] At this early stage of the outbreak, COVID-19 has already exceeded the total number of cases and deaths from Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS).[3]

On 23 January 2020, Singapore reported her first case of COVID-19 infection in a tourist from Wuhan.[4] On 4 February 2020, the country reported the first cluster of local transmission. By 7 March 2020, there were 130 COVID-19 cases and approximately 15% of them developed respiratory failure that required mechanical ventilation.[5]

In this report, we describe a patient who developed acute respiratory distress syndrome (ARDS) with rapid clinical deterioration. Unfortunately, not much is known

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about the clinical features and risk factors for ARDS and critical illness even as the number of COVID-19 cases continues to climb at an alarming rate throughout the world. However, recent published data suggested that advanced age and comorbidities such as cardiovascular disease may be associated with more severe disease.[6] In this review, we examine current understanding of critical illness from COVID-19 infection and explore areas where research is urgently needed.

Case Presentation

A 64-year-old Chinese man presented with a fall that was preceded by dizziness. He reported dyspnoea and fever that lasted 1 day and 1 week, respectively, and had no significant past medical history. Prior to presentation, he worked as a taxi driver and reported ferrying passengers who were tourists from Mainland China. He denied a history of recent travel or contact with individuals infected by COVID-19.

Clinically, he was alert and comfortable; his temperature was 39.0°C, oxygen saturation was 92% on room air and respiratory rate was 20 breaths/min. On examination, his lungs were clear to auscultation. Laboratory investigations revealed haemoglobin 14.1 g/dL, white blood cell count 4.6×10^9/L, lymphopaenia with lymphocyte count 0.23 $\times 10^9$/L (normal 1–3 $\times 10^9$/L) and platelet count 147 $\times 10^9$/L. C-reactive protein was elevated at 87.9 mg/L (normal 0.2–9.1 mg/L) and procalcitonin was 0.55 μg/L (normal <0.50 μg/L).

On admission, findings of liver and renal function tests and serum lactate were normal, but chest radiograph showed subtle ground-glass opacities in lower zones with minor interstitial changes at the right base and atelectasis in left lower zone. Consolidation or pleural effusion was absent (Fig. 1A). In view of his recent contact with tourists from Mainland China, he was immediately isolated in an airborne infection isolation room (AIIR). Throat swab on real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tested positive for SARS-CoV-2 and he was started on lopinavir/ritonavir (Kaletra) on day 2 of admission. Oxygen saturation was stable on 3 L/min flow of oxygen. Apart from a respiratory rate of 18–20 breaths/min, all vital signs were normal.

Within 48 hours of presentation, however, he deteriorated rapidly with severe hypoxemic respiratory failure that required high-flow oxygen supplementation with a face mask. Repeat chest radiograph showed rapid development of bilateral diffuse ground-glass opacities (Fig. 1B) and he was intubated and initiated on mechanical ventilation.

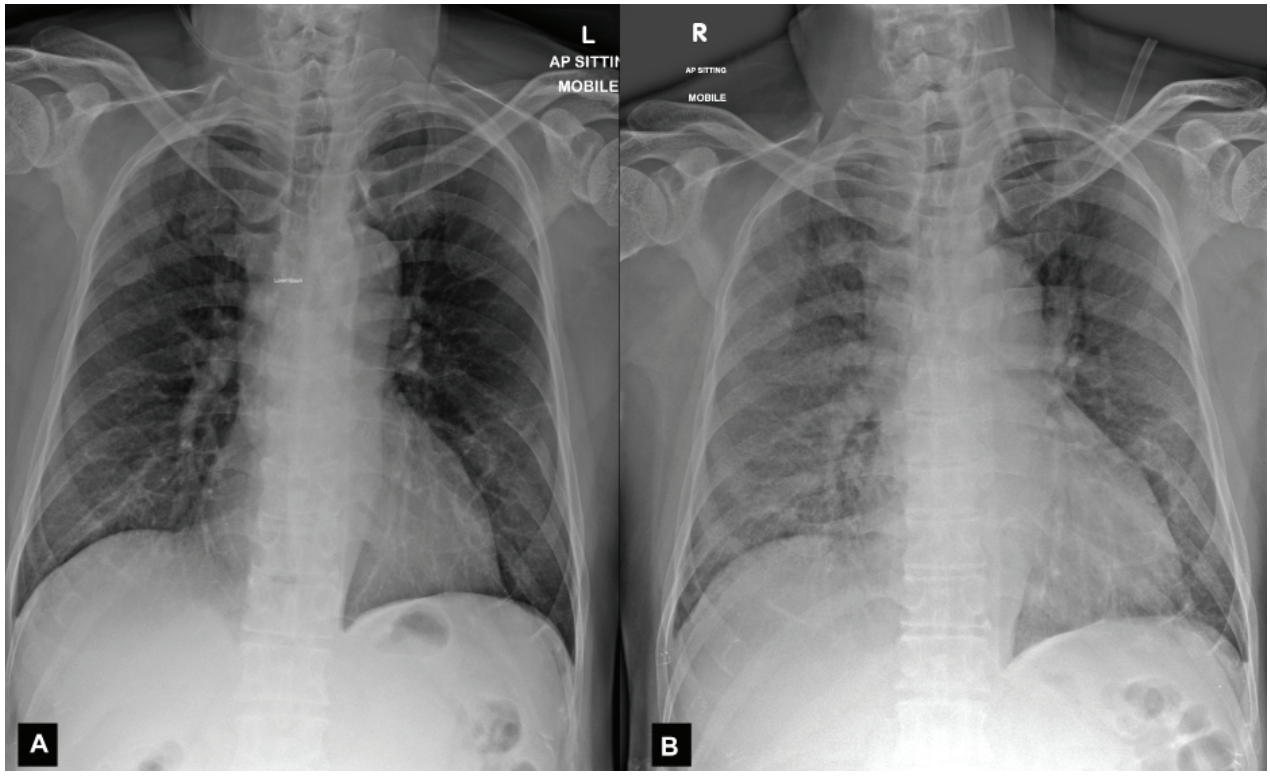

Fig. 1. A: On admission, chest radiograph showed minimal ground-glass opacities in lower zones with interstitial thickening in right base and atelectasis in left lower zone. No consolidation or pleural effusion was evident. B: On day 2, repeat chest radiograph showed rapid development of diffuse ground-glass opacities bilaterally. The patient was intubated on the same day.

To minimise risk of viral transmission to health workers during intubation, a high-efficiency particulate air mechanical filter was used with bag-valve-mask interface and an emphasis on adequate preoxygenation and rapid sequence induction to minimise dispersion of respiratory droplets. After initial stabilisation, arterial blood gas showed partial pressure of oxygen (PaO_2) of 80 mmHg, fraction of inspired oxygen (FiO_2) of 0.7 and positive end-expiratory pressure (PEEP) of 10 cmH_2O that were consistent with moderate to severe ARDS (PaO_2/FiO_2 114).[7] Despite deep sedation, significant ventilator dyssynchrony was observed, and neuromuscular blockade was initiated to maintain lung protective ventilation.

During this period of paralysis, oxygenation improved. On day 2 of mechanical ventilation, he was supported with volume-controlled ventilation: tidal volume 350 mL (5.0 mL/kg predicted body weight), FiO_2 0.4, PEEP 10 cmH_2O and respiratory rate 30 breaths/min with a plateau pressure of 20 cmH_2O. Repeat arterial blood gas showed pH 7.31, partial pressure of carbon dioxide 51 mmHg and PaO_2 78 mmHg. He did not require prone ventilation.

On day 8, computed tomography (CT) of thorax revealed diffuse ground-glass opacities and consolidation in the dependent segments of both lungs (Fig. 2), findings that were consistent with ARDS. He was started on

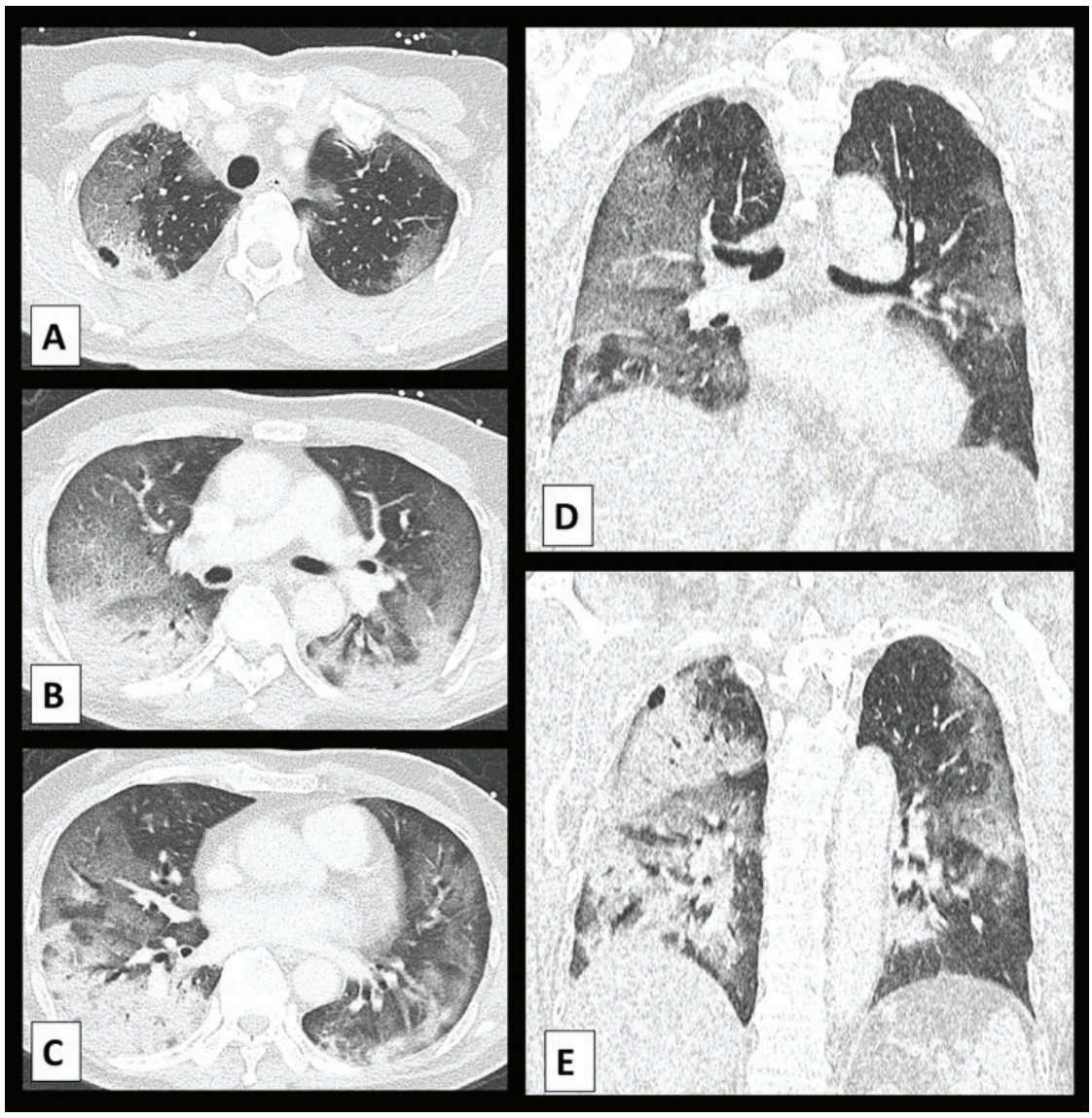

Fig. 2. Computed tomography (CT) of lung. A: Axial contrast-enhanced CT image showed ground-glass opacities that predominate in upper lobes with stark thin rim of subpleural sparing. B: Axial CT image showed mild, smooth intralobular septal thickening that gave the appearance of "crazy paving". C: Axial CT image showed consolidation in dependent segments of both lungs with an asymmetric distribution that involved predominantly the right lower lobe. D and E: Coronal CT images showed an incidental small, thin-walled subpleural cyst in right upper lobe that likely represents a pneumatocele. Neither intrathoracic lymphadenopathy nor pleural effusion was observed.

empirical broad-spectrum antibiotics, but these were discontinued after 8 days when all bacterial cultures returned negative. Despite withholding of sedative and analgesia agents, Glasgow Coma Scale remained depressed and full recovery was seen only after all sedatives were discontinued 4 days later. No metabolic disturbances were observed and brain CT was normal.

On day 10, his ventilatory requirements increased with a concurrent rise in purulent endotracheal tube (ETT) secretions and development of new left mid-zone consolidation on chest radiograph (Fig. 3). *Pseudomonas aeruginosa* was isolated from ETT aspirates. He completed 7 days of culture-directed antibiotics for ventilator-associated pneumonia. After 11 days of mechanical ventilation, he was successfully extubated on day 14.

During his stay in the Intensive Care Unit (ICU), RT-PCR for SARS-CoV-2 was performed on ETT and throat swab specimens on alternate days until the first negative culture was obtained on day 15 of admission, which was approximately 3 weeks after symptom onset. A day later, lymphopaenia resolved. Incidentally, he had diarrhoea during the first 2 days of admission before lopinavir/ritonavir was initiated and SARS-CoV-2 was detected in stool samples on RT-PCR; results of *Clostridium difficile* toxin assays were negative. The events and progress of his ICU stay are illustrated in Figure 4.

Discussion

In our patient, we described the clinical course of COVID-19 infection that developed rapidly into ARDS requiring intubation. This case highlighted the need to identify risk factors associated with critical illness so that at-risk patients can be promptly identified and closely monitored. It also prompts a discussion of our current understanding of critical illness from COVID-19 infection after the outbreak was declared a global pandemic by the WHO on 11 March 2020.[8]

Incidence of ARDS and Critical Illness

There is wide variability in the reported incidence of ARDS or critical illness from COVID-19 infection. As shown in Table 1, initial studies from hospitals in Wuhan city in Mainland China had reported an alarming incidence of ARDS (17–29%) and critical illness that required ICU admission (23–32%).[9-12] The reported incidence may be underestimated since most patients remained hospitalised in some of the studies.[10,11] Conversely, the reported incidence of critical illness in areas further away from the epicentre of the outbreak in Wuhan city appeared to be lower.

In their study of 1099 patients from 30 provinces in Mainland China, Guan et al reported an incidence of 3–5% for ARDS or admission to ICU.[13] In their study, most patients (94%) remained hospitalised at the time of writing, again suggesting that outcomes may be significantly underestimated. Consequently, their study is better described as a cross-sectional survey of hospitalised patients.[13] Differences in age and comorbidities may also account for these differences (Table 1).[14,15]

The true incidence of critical illness is difficult to determine due to differences in resources available for diagnostic testing, contact tracing and surveillance. In Zhejiang Province, individuals with respiratory symptoms or significant contact history with COVID-19

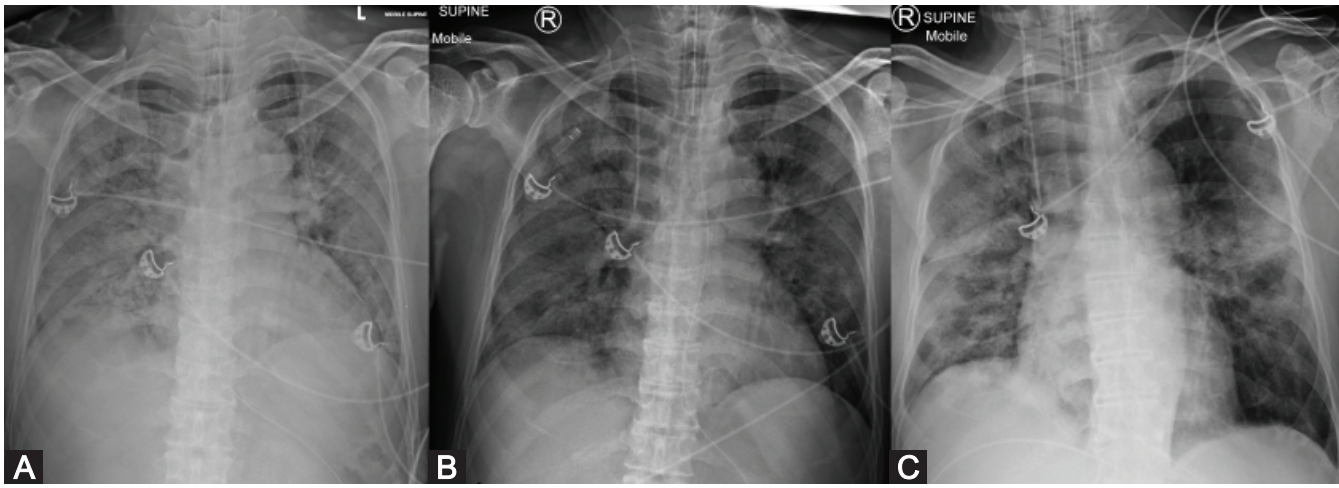

Fig. 3. A: Chest radiograph after endotracheal intubation. B: On day 4, chest radiograph showed mild improvement in extensive airspace opacification. C: On day 11, chest radiograph showed interval development of patchy consolidation in right lung and focal consolidation in left mid-zone. A nasogastric tube (A, B and C) and right internal jugular venous catheter (B and C) were inserted.

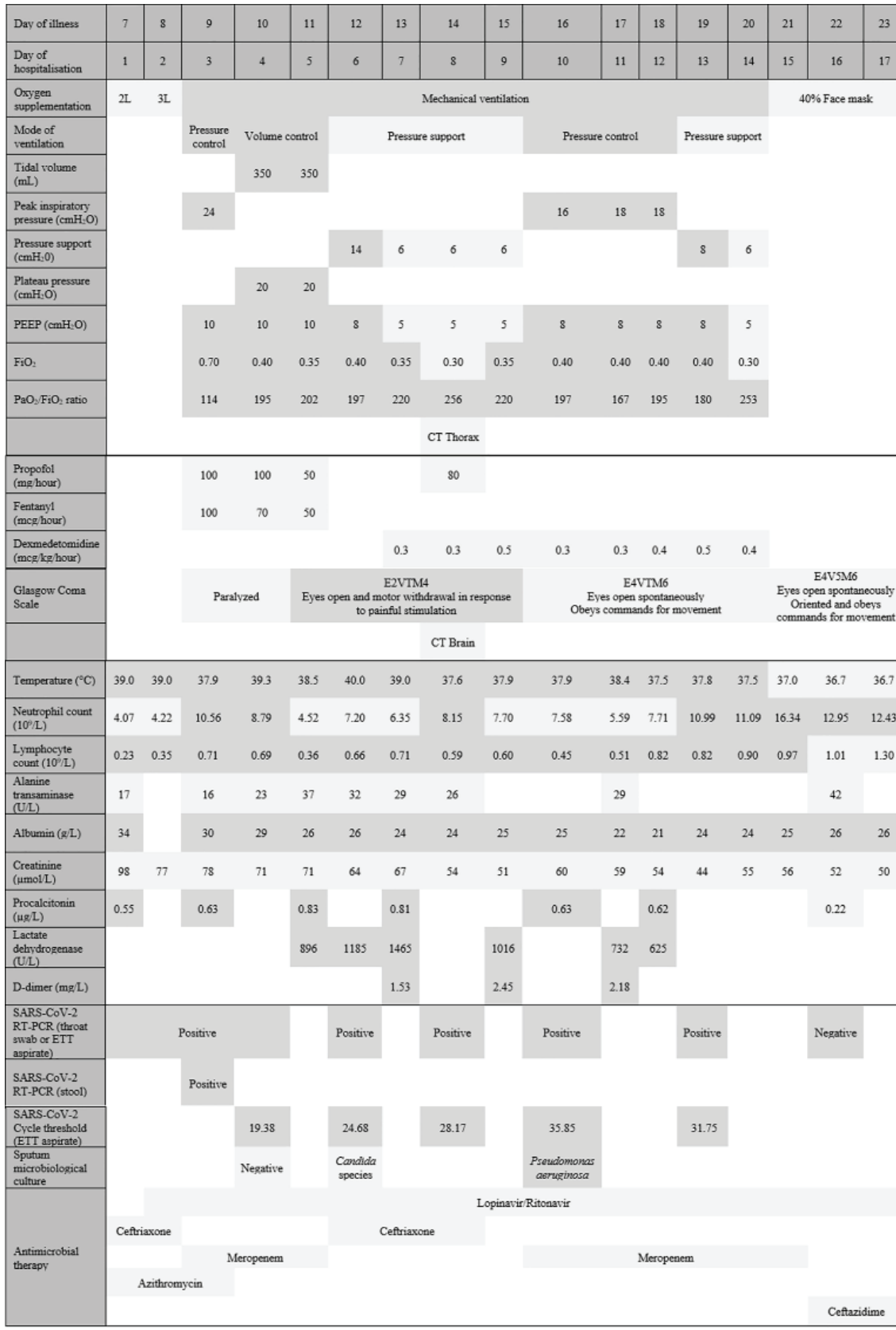

Fig. 4. Clinical course of patient on admission. COVID-19: Coronavirus disease 2019; CT: Computed tomography; ETT: Endotracheal tube; FiO_2: Fraction of inspired oxygen; PaO_2: Partial pressure of oxygen; PEEP: Positive end-expiratory pressure; RT-PCR: Reverse transcriptase-polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Table 1. Patient Outcomes from Coronavirus Disease 2019 Infection in Mainland China

Variable	Huang et al*	Chen et al†	Wang et al‡	Yang et al§	Xu et al‖	Wu et al¶	Guan et al#
Centre(s)	Jin Yin-Tan Hospital in Wuhan, Hubei Province	Jin Yin-Tan Hospital in Wuhan, Hubei Province	Zhongnan Hospital in Wuhan, Hubei Province	Jin Yin-Tan Hospital in Wuhan, Hubei Province	7 hospitals in Zhejiang Province	3 hospitals in Jiangsu Province	552 hospitals in 30 provinces
Hospitalisation/recruitment	16 Dec 2019 – 2 Jan 2020	1 – 20 Jan 2020	1 – 28 Jan 2020	24 Dec 2019 – 12 Jan 2020	10 – 26 Jan 2020	22 Jan – 14 Feb 2020	11 Dec 2019 – 29 Jan 2020
Final follow-up date	22 Jan 2020	25 Jan 2020	3 Feb 2020	9 Feb 2020	26 Jan 2020	14 Feb 2020	31 Jan 2020
Number of patients	41	99	138	201	62	80	1099
Median age in years (IQR)	49 (41 – 58)	56 (13)	56 (42 – 68)	NA	41 (32 – 52)	46 (31 – 62)	47 (35 – 58)
Comorbidity (%)							
Hypertension	15	NA	31	NA	8	NA	15
Diabetes mellitus	20	NA	10	NA	2	NA	7
Cardiovascular disease	15	40	15	NA	NA	NA	3
Cerebrovascular disease	NA	NA	5	NA	2	NA	1
Chronic respiratory disease	2	1	3	NA	2	1	1
Outcome (%)							
Admission to ICU	32	23	26	27	2	0	5
ARDS	29	17	20	17	2	0	3
Death	15	11	4	17	0	0	1
Hospitalised at time of writing	17	58	62	6	98	76	94

ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; IQR: Interquartile range; NA: Not available

*Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.

†Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.

‡Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalised patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;DOI:10.1001/jama.2020.1585.

§Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;DOI:10.1016/S2213-2600(20)30079-5.

‖Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;DOI:10.1136/bmj.m606.

¶Wu J, Liu J, Zhao X, Liu C, Wang W, Wang D, et al. Clinical characteristics of imported cases of COVID-19 in Jiangsu province: a multicenter descriptive study. Clin Infect Dis 2020;DOI:10.1093/cid/ciaa199.

#Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;DOI:10.1056/NEJMoa2002032.

patients were advised to visit hospitals and ARDS was only reported in 1 out of 62 hospitalised patients.[14] Nevertheless, it is clear that the clinical spectrum of COVID-19 infection ranges widely from asymptomatic individuals to those with a mild form of the illness to patients with critical illness and with high mortality risk.[6] Large multicentre studies from other countries with adequate follow-up to hospital discharge or death will shed more light on the incidence of critical illness that is crucial to resource planning of health services from around the world.

Critical Illness from COVID-19 Infection: Clinical Features and Risk Factors

In our patient, the observation of rapid clinical deterioration is concerning. With the wide spectrum of clinical severity observed in COVID-19 patients, it is necessary to identify patients who are at higher risk of critical illness. Unfortunately, the risk factors and clinical characteristics of ARDS from COVID-19 infection are still not fully known or understood. What appears to be a consistent finding, however, is that ARDS and critical illness mostly develop between 1–2 weeks after symptom onset.[9,11,12] Similar to findings from published studies (Table 2), our patient developed ARDS on day 9 after symptom onset.[9,11]

Like MERS-CoV[16] and SARS[17], patients with older age, comorbidities (such as cardiovascular and cerebrovascular diseases) and dyspnoea appeared to have worse outcomes.[9,11,12] Median age of ICU patients was 63–6 years compared to 46–51 years in non-ICU patients.[11,13] A similar finding for age was also seen between survivors and non-survivors.[9,18] While cough and fever were observed in most patients, dyspnoea was reported in about 30–50% of patients; based on studies from Wuhan city in Mainland China, approximately half of patients with dyspnoea required ICU admission.[9,11] Pre-existing chronic lung disease is also a concern. In the study by Guan et al, more than half of patients with chronic obstructive pulmonary disease and COVID-19 infection were admitted to ICU or required mechanical ventilation.[11]

The age of our patient (64 years old) and presence of dyspnoea were worrisome features. Additionally, initial blood tests revealed significant lymphopaenia which has been reported to be associated with critical illness.[9,11,18] Neutrophilia, hypoalbuminaemia and elevated levels of lactate dehydrogenase (LDH) and D-dimer were other markers of critical illness in COVID-19 infection that were seen in our patient.[9,11,18] These observations appear to be consistent with SARS, where multivariate analysis had identified elevated LDH and neutrophilia as markers that were associated with worse outcomes.[17] However, these markers are non-specific and are commonly found in critically ill patients.

For clinicians, an early surrogate of disease severity—ideally before the onset of critical illness—is useful. The issue of whether the degree of lymphopaenia or LDH elevation can be early markers of disease severity—or even a surrogate for disease recovery from COVID-19 infection—is still unclear. In their study of patients who were not critically ill, Young et al reported a decline in viral loads—based on RT-PCR cycle thresholds—after a peak was reached shortly after symptom onset.[19] This finding was also observed in our patient. However, it remains to be seen whether trends in viral loads can serve as a surrogate for disease recovery.

In our patient, chest CT showed extensive multilobar ground-glass changes with intralobular septal thickening and more confluent consolidation in the dependent portions of the lungs. Despite the peripheral location of the ground-glass changes, there were thin rims of subpleural sparing which—to the best of our knowledge—have not been reported previously. Nevertheless, ground-glass opacities with or without consolidation—with posterior and peripheral predominance—appear to be the most common finding in COVID-19 pneumonia,[20,21] MERS-CoV and SARS.[22,23] In our patient, lack of thoracic lymphadenopathy and pleural effusions are also consistent with reported findings of COVID-19 infection.[20,21]

Findings of normal chest images, however, do not rule out the development of severe illness. Guan et al reported that up to 23% and 12% of patients who required ICU admission had normal chest radiographs and CT images, respectively.[13] Despite the rapid deterioration observed in our patient, only subtle ground-glass and interstitial changes were seen in the initial chest radiograph. This observation is limited by the fact that it is based on a single case report. However, with more studies, we will hopefully be able to shed more light on the clinical course of patients who develop critical illness. Nevertheless, it is prudent for clinicians to closely monitor patients with advanced age, comorbidities or dyspnoea, especially at 1–2 weeks after symptom onset.

Interestingly, our patient remained in a semi-conscious state for almost 4 days without sedation and opioid therapy. No abnormalities were seen on brain CT and no significant metabolic disturbances could be found to explain the degree of unconsciousness. Subsequently, he regained full consciousness without any neurological deficit. Although septic encephalopathy is a likely diagnosis, it is also possible that this outcome could be attributed to the accumulation of fentanyl from

Table 2. Patient Outcomes from Coronavirus Disease 2019 Infection in Mainland China Who Required ICU Admission

Variable	Huang et al[*]	Chen et al[†]	Wang et al[‡]	Yang et al[§]	Guan et al[‖]
Centre(s)	Jin Yin-Tan Hospital in Wuhan, Hubei Province	Jin Yin-Tan Hospital in Wuhan, Hubei Province	Zhongnan Hospital in Wuhan, Hubei Province	Jin Yin-Tan Hospital in Wuhan, Hubei Province	552 hospitals in 30 provinces
Hospitalisation/recruitment	16 Dec 2019 – 2 Jan 2020	1 – 20 Jan 2020	1 – 28 Jan 2020	24 Dec 2019 – 12 Jan 2020	11 Dec 2019 – 29 Jan 2020
Final follow-up date	22 Jan 2020	25 Jan 2020	3 Feb 2020	9 Feb 2020	31 Jan 2020
Number of patients	13	23	36	52	67[¶]
Median age in years (IQR)	49 (41 – 61)	NA	66 (57 – 78)	60 (13)	63 (53 – 71)
Comorbidity (%)					
Hypertension	15	NA	58	NA	NA
Diabetes mellitus	8	NA	22	17	36
Cardiovascular disease	23	NA	25	NA	27
Cerebrovascular disease	NA	NA	17	14	6
Chronic respiratory disease	8	NA	8	8	10
Symptom onset to ARDS in days, median (IQR)	9 (8 – 14)	NA	8 (6 – 12)	NA	NA
Symptom onset to ICU admission in days, median (IQR)	11 (8 – 17)	NA	10 (6 – 12)	10 (7 – 13)	NA
ICU outcome (%)					
Nosocomial infection	31	NA	NA	14	NA
Shock	23	17	31	35	13
Renal replacement therapy	23	39	6	17	12
ARDS	85	74	75	67	40
Mechanical ventilation	15	17	47	71	37
ECMO	15	12	11	12	8
Death	38	48	17	62[#]	22
Hospitalised at end of study	8	NA	58	23	76
On mechanical ventilation at end of study	NA	NA	17	1	NA

ARDS: Acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; IQR: Interquartile range; NA: Not available

[*]Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.

[†]Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.

[‡]Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalised patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;DOI:10.1001/jama.2020.1585.

[§]Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;DOI:10.1016/S2213-2600(20)30079-5.

[‖]Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;DOI:10.1056/NEJMoa2002032.

[¶]Composite outcome of death, ICU admission or mechanical ventilation.

[#]28-day ICU mortality.

inhibition of cytochrome P450 by ritonavir, which is another important consideration for intensivists in their management of such patients.[24]

Outcomes and Mortality of Critical Illness from COVID-19 Infection

Critical illness from COVID-19 infection is associated with high mortality risk even though its estimated case fatality rate of 3.4%[2] is significantly lower than MERS-CoV (34.4%)[3] and SARS (11%).[25] In Jin Yin-Tan Hospital in Wuhan city, mortality rate of ICU patients was reported to range between 38–62% and >10% of patients required extracorporeal membrane oxygenation (ECMO).[9,10,12] Yang et al reported a 28-day mortality rate of 62% in patients who required ICU care; in patients who developed ARDS, the mortality rate was 74%.[12] In-hospital mortality rate was likely to be higher since most survivors were still hospitalised, 3 patients were on mechanical ventilation and 1 patient was on ECMO.[12] Indeed, the mortality rates that were being reported were alarming since they were higher than that commonly seen in severe ARDS attributed to other causes and conditions.[26]

It is possible, however, that the quality of health services was severely compromised and resulted in poorer outcomes in Wuhan city after health workers there were overwhelmed by the exponential increase in the number of COVID-19 patients. A recent publication by Xie et al reported severe shortages in ventilators and only about 25% of patients who died had received invasive mechanical intubation.[27] Additionally, most patients were supported with high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) and received systemic corticosteroids.[9,12] It is unclear whether delayed intubation or systemic corticosteroids might have adversely affected the outcomes in some patients.[28] As was the case with our patient, up to a third of critically ill patients developed nosocomial or secondary bacterial infections and intensivists who manage such patients must remain vigilant since early administration of antibiotics may potentially improve outcomes.[9,12] Finally, data is still lacking on duration of mechanical ventilation or ECMO in survivors since such information is important for critical care management and resource planning.

Clinical Management of Critical Illness from COVID-19 Infection

In the absence of studies on ARDS induced by COVID-19 infection, principles of clinical management of patients should be consistent with established guidelines for ARDS. The WHO has published similar guidelines for severe respiratory infections from COVID-19 infection.[29] In our patient, we adopted lung protective ventilation, conservative fluid strategy and neuromuscular blockade to manage moderate to severe ARDS. Neuromuscular blockade was initiated after significant ventilator dyssynchrony was seen despite deep sedation.

Since there was a lack of clear benefit with the use of HFNC in acute respiratory failure and high failure rates were observed with the use of NIV in MERS-CoV,[30] the management of our patient was therefore guided by the principles of conventional oxygen therapy and early intubation. The presumed benefit of lopinavir/ritonavir was extrapolated from the management of SARS patients.[31,32] Remdesivir—a broad-spectrum pro-drug that inhibits RNA-dependent RNA-polymerase activity—has shown promise in in vitro studies and is currently under evaluation in a randomised, controlled clinical trial (NCT04257656).[33]

To date, no antiviral therapy has proven effective against COVID-19 infection. In our patient, corticosteroids were not administered since there was a lack of evidence to support their efficacy;[34] The use of corticosteroids is associated with worse outcomes or delayed viral clearance in SARS and MERS-CoV patients.[35,36] Finally, infection control and prevention is a key component of ICU management.[37] The emphasis is on use of appropriate personal protective equipment and practice of standard contact and airborne precautions with eye protection by health workers. Known or suspected COVID-19 patients should be isolated in AIIR and measures to minimise aerosolisation or dispersion of respiratory droplets by patients should be stringently practised.[38]

Interestingly, our patient had diarrhoea and SARS-CoV-2 was detected in his stool samples. A small study of 8 patients by Young et al also reported that the stools of 4 of them tested positive for SARS-CoV-2 on RT-PCR.[19] These findings suggest that viral transmission through the faecal-oral route may be a concern in patients with COVID-19 infection.[39]

Conclusion

The wide clinical spectrum of COVID-19 infection ranges from individuals who are asymptomatic to those who present with critical illness and with high mortality risk. Since there is a likelihood that patients will deteriorate rapidly, more studies are needed to identify early predictive markers of the more severe form of the disease. In the absence of a clear, dysregulated host response to infection, abnormal laboratory findings such as lymphopaenia or elevated LDH may potentially serve as early surrogate markers for the development of

critical illness. While we await results of studies that can shed more light on definitive treatment options, management of ARDS induced by COVID-19 infection is mainly supportive and does not differ from that caused by other conditions other than a need to adhere strictly to established infection control measures.

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Original Article

Elevated Serum Interleukin-18 Level is Correlated with Vascular Access Dysfunction in Patients on Maintenance Haemodialysis

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Abstract

Introduction: We evaluated the impact of serum interleukin-18 (IL-18) level on short-term vascular access (VA) function in chronic haemodialysis (HD) patients. Materials and Methods: Samples were collected from 80 clinically stable patients (58.8% were men) with a mean age of 60.9 years (standard deviation 11.7 years) who were undergoing maintenance HD and were followed up for 1 year. Multivariate logistic regression was used to analyse data on demographics, biochemical parameters and serum IL-18 level to predict VA dysfunction events. The cut-off for IL-18 was derived from the highest score obtained on Youden index. Survival data was analysed using Cox proportional hazards regression analysis and Kaplan-Meier method. Results: Patients were classified as having either low IL-18 (<199.3 pg/mL) or high IL-18 (≥199.3 pg/mL). Multivariate logistic regression showed that serum IL-18 level was independently correlated with VA dysfunction events; patients with high IL-18 had a higher risk of VA dysfunction events than those with low IL-18 (odds ratio 9.47, 95% confidence interval 1.75–51.31, *P* = 0.009). In patients with high IL-18, Kaplan-Meier survival analysis found that incidence of VA dysfunction was significantly higher than patients with low IL-18 (*P* = 0.047). After adjustment for age, gender, inflammation (C-reactive protein) and calcium-phosphorus metabolism, decreased serum albumin and increased serum IL-18 levels were found to be independent prognostic predictors of VA dysfunction. Conclusion: HD patients with high IL-18 level tend to have worse rates of VA dysfunction. In HD outpatients, IL-18 is an independent risk factor for short-term VA dysfunction.

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Key words: Access survival, Cytokines, Short-term

Introduction

Renal replacement therapy (RRT) is a long-term, life-sustaining intervention in patients with end-stage renal disease (ESRD) and most of them are on haemodialysis (HD).[1] Although various dialysis treatments have improved the prognosis in HD patients,[2] the establishment and maintenance of appropriate vascular access (VA) and reduction in incidence of VA dysfunction are important factors that can impact on their long-term prognoses.[3]

In the last few decades, extensive application of autologous arteriovenous fistula (AVF) and innovations in VA—including arteriovenous graft (AVG) and tunnelled cuffed catheter (TCC)—have improved prognosis in HD patients. However, 9–16% of HD patients still experience insufficient dialysis that is attributed to VA dysfunction and complications of the access point.[4] Therefore, it is crucial to understand the pathogenesis of VA dysfunction, identify possible risk factors and provide early intervention.

Currently, it is believed that systemic abnormalities in ESRD patients—such as uraemic toxins, systemic inflammation, endothelial dysfunction, lipid abnormalities, hyperparathyroidism,

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hyperphosphataemia and hypercalcaemia—can easily remodel and narrow the vascular wall of mature AVF.[5–7] In ESRD patients, some studies have found that the levels of cytokines—such as interleukin-6 (IL-6), transforming growth factor beta (TGF-beta) and tumour necrosis factor alpha (TNF-alpha)—are significantly higher than those in the general population. Elevated levels of cytokines may be linked to the development of neointimal hyperplasia (NIH) and progression of VA dysfunction; however, their pathogeneses remain unclear.[8,9]

Interleukin-18 (IL-18) is a member of the interleukin-1 superfamily and can induce an immune response and inflammatory reaction.[10,11] In patients with chronic kidney disease (CKD) and those who were on continuous ambulatory peritoneal dialysis (CAPD), studies have found evidence of chronic inflammation and increased levels of serum IL-18.[12] Formanowicz et al[13] have reported that IL-18 level can predict cardiovascular mortality in patients with CKD. Recently, Wang et al[14] found that serum IL-18 level is an independent risk factor for major adverse cardiovascular events in HD patients.

Other studies have reported a correlation between elevated IL-18 levels and increased hospitalisation in HD patients.[15] In their observational study, Liu et al[16] found that IL-18 level was an independent risk factor for all-cause mortality in patients on maintenance dialysis but no correlation was found with cardiovascular function. However, it is unclear whether IL-18 contributes to the development and progression of VA dysfunction, and if it can be used as an early predictor of VA dysfunction in patients on maintenance dialysis.

Consequently, we conducted a 1-year prospective, observational study to examine the correlation between serum IL-18 level and VA function in patients who were attending our outpatient HD centre. The primary outcome of interest was incidence of VA dysfunction, and a preliminary evaluation of risk factors for VA dysfunction in patients on maintenance HD was performed.

Materials and Methods

The study commenced on 1 June 2017 and included 80 mainland Chinese patients who had been undergoing regular dialysis—4 hours per session—thrice a week for at least 1 month in our HD centre. All of them were followed up for 1 year until 31 May 2018. Information on their medical history, primary diagnosis and complications were collected. To ensure that all patients met the criteria for adequate dialysis, they were evaluated according to the guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI).[17] The study was approved by the Institutional Review Board (IRB No.: KY2016-394) of our centre and all patients provided written consent.

The definition of VA dysfunction is based on the consensus statement on VA to HD published by the Chinese Hospital Association[18] which stipulates the presence of any of the following signs and symptoms: 1) flow rate <600 mL/min and <500 mL/min for internal fistula graft and autologous internal fistula, respectively; 2) static pressure ratio of venous end of internal fistula graft or autologous internal fistula >0.5, or static pressure ratio of arterial end of internal fistula graft >0.75; 3) acute thrombosis; and 4) sufficient dialysis cannot be achieved when arterial pressure is <250 mmHg or venous pressure is >250 mmHg in the event that catheter blood flow is <200 mL/min or blood pump flow is <200 mL/min.

VA dysfunction event is defined as: 1) percutaneous angioplasty or surgery to treat AVF vascular stenosis; 2) Fogarty catheter thrombectomy, surgical thrombectomy or internal fistula reconstruction to treat AVF thrombosis; and 3) balloon dilatation and stent implantation to treat AVG stenosis.

Demographic and dialysis-related data were collected including age, gender, primary disease, dialysis age, systolic blood pressure (SBP) and diastolic blood pressure (DBP) before dialysis and interval dialysis weight gain (IDWG). IDWG was derived by subtracting body weight before dialysis from body weight after previous dialysis and then dividing the result over body weight after previous dialysis.

In the middle of the week, fasting and resting venous blood was drawn from patients prior to dialysis. The blood samples were centrifuged at 12,000 × g at 4ºC for 15 minutes to separate the serum from supernatant, and were stored at −80ºC. Findings of biochemical parameters included haemoglobin (Hb), white blood cell (WBC), platelet (PLT), creatinine, albumin (Alb), total cholesterol (CHO), low-density lipoprotein cholesterol (LDL), B-type natriuretic peptide (BNP), C-reactive protein (CRP), intact parathyroid hormone (iPTH), blood calcium (Ca) and blood phosphorus (P). To evaluate adequacy of dialysis, urea Kt/V was used.[17]

Serum IL-18 was determined with enzyme-linked immunosorbent assay (Human IL-18 ELISA Kit, MyBioSource, San Diego, CA, USA). The cut-off for IL-18 was derived from the highest score obtained on Youden index.[19] Patients were classified as having either low (<199.3 pg/mL) or high (≥199.3 pg/mL) IL-18.

Statistical analyses were performed with Stata Statistical Software, Release 14 (StataCorp LP, College Station, TX, USA). Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range; categorical variables were expressed as counts and percentages. Student's t-test or Mann-Whitney U test (non-normal distribution) was performed to compare differences among continuous variables; to compare categorical variables, chi-square test or Fisher's Exact test was used. Univariate or multifactorial logistic regression was used to analyse correlations between biochemical markers and dialysis-related data with VA dysfunction. Kaplan-Meier method and logarithmic rank test were used to compare adverse VA events between the 2 groups. Univariate and multivariate Cox regression analyses were used to examine risk factors for VA dysfunction. A value of P <0.05 was considered statistically significant.

Results

There were 47 (58.8%) male and 33 (41.2%) female patients in the study. Their mean age was 60.93 years (SD 11.70 years, range 32–89 years). Median duration of dialysis was 3.14 years. Aetiologies of ESRD included chronic glomerulonephritis (n = 32, 40%), hypertensive nephropathy (n = 20, 25%), diabetic nephropathy (n = 9, 11.25%), polycystic kidney disease (n = 7, 8.75%) and other causes (n = 12, 15%). VA types included AVF (n = 64, 80%), AVG (n = 3, 3.75%) and TCC (n = 13, 16.25%).

There were 30 and 50 patients in the high and low IL-18 groups, respectively. In both groups, no differences were found in age, gender, dialysis age, diabetes-to-hypertension ratio, mean IDWG, SBP and DBP before dialysis (P >0.05). Likewise, no differences were seen in results of biochemical parameters between the 2 groups (P >0.05) including creatinine, BNP, CRP, iPTH, calcium-phosphorus product, Hb, WBC, PLT, CHO and LDL.

Serum albumin level was lower in the high IL-18 (41.6 g/L) group than low IL-18 (43.4 g/L) group (P = 0.003). During the study, 11 (13.75%) patients experienced VA dysfunction and required surgical intervention; 2 patients experienced VA events within half a year after access was established and the remainder had late-stage VA dysfunction. As shown in Table 1, although the incidence of VA dysfunction was higher in the high IL-18 group, the difference between the 2 groups (23.3% vs 8%) was not statistically significant (P = 0.973).

After adjustments for age, gender, dialysis age, iPTH, calcium-phosphorus product, CRP and albumin, multivariate logistic regression found that only IL-18 level was independently correlated with VA dysfunction events (Table 2). The high IL-18 group had a higher risk of VA dysfunction events than the low IL-18 group (odds ratio 9.47, 95% confidence interval 1.75–51.31, P = 0.009). Kaplan-Meier survival analysis (Fig. 1) showed that VA dysfunction in the high IL-18 group was significantly higher than low IL-18 group (P = 0.047).

Findings of multivariate Cox proportional hazards regression model revealed that decreased serum albumin level and increased serum IL-18 level were independent prognostic predictors of VA dysfunction events (Table 3). This predictive effect was still statistically significant even after adjustments were made for age, gender, inflammation (CRP) and calcium-phosphorus metabolism (calcium-phosphorus product). Additionally, a significant correlation between serum IL-18 level and reduced albumin level for VA dysfunction events was not found (P = 0.27). Findings from receiver operating characteristic curve analysis showed that when IL-18 and albumin levels were used with age and gender, short-term (within 1 year) risk of VA dysfunction can be predicted in HD patients (Fig. 2).

Discussion

This prospective cohort study demonstrated that elevated serum IL-18 level is correlated with VA dysfunction in patients on maintenance HD, and that it is also an independent risk factor for short-term VA dysfunction in them. Patients with high serum IL-18 concentration also had higher incidence of VA dysfunction. Additionally, the combination of albumin, IL-18, age and gender can be a better predictor of short-term risk of VA dysfunction in HD patients.

VA is the lifeline of HD patients,[5] and VA dysfunction is a major cause of insufficient dialysis that affects their long-term prognosis.[4] Due to its high patency rate, lower rate of complications and lower cost, AVF is recommended as the preferred access for HD by NKF-KDOQI.[20] This was clearly seen in our patients where 80% of them used AVF. In the 11 patients who experienced VA dysfunction, 4 (36.4%) of them had AVF, 5 (45.5%) had TCC and 2 (18.1%) had AVG. The issue of lowering the incidence of VA dysfunction, especially in HD patients with short- and long-term AVF dysfunction, continues to pose a huge challenge to dialysis physicians.

Table 1. Demographic and Clinical Characteristics of Haemodialysis Patients

Variable	Aggregate (n = 80)	IL-18 <199.3 pg/mL (n = 50)	IL-18 ≥199.3 pg/mL (n = 30)	*P* Value
Mean age in years (SD)	60.9 (11.7)	60.3 (11.9)	62.0 (11.5)	0.731
Male gender (%)	47 (58.8)	32 (64.0)	15 (50.0)	0.109
Median dialysis age in years (IQR)	3.14 (2.25 – 6.75)	2.85 (2.15 – 6.23)	4.03 (2.42 – 7.42)	0.201
Diabetes mellitus (%)	9 (11.25)	6 (12)	3 (10)	0.392
Hypertension (%)	20 (25)	12 (24)	8 (26.7)	0.605
Mean IDWG, % (SD)	3.3 (1.2)	3.3 (1.2)	3.4 (1.2)	0.612
Median Kt/V (IQR)	1.36 (1.16 – 1.5)	1.37 (1.15 – 1.55)	1.30 (1.18 – 1.46)	0.538
Mean SBP, mmHg (SD)	142.1 (15.6)	143.8 (14.6)	139.4 (16.9)	0.122
Mean DBP, mmHg (SD)	79.8 (9.4)	80.7 (8.4)	78.3 (0.9)	0.154
Mean creatinine, μmol/L (SD)	1009.6 (250.2)	1014.8 (258.8)	1001 (239.1)	0.809
Median BNP, pg/mL (IQR)	2658 (1429 – 5084)	2978.5 (1362 – 5473)	1962 (1497 – 3712)	0.290
Median albumin, g/L (IQR)	42.2 (39.8 – 44.0)	43.4 (41.1 – 48.7)	41.6 (39.2 – 43.1)	0.003
Median C-reactive protein, mg/L (IQR)	2.9 (0.91 – 5.4)	2.6 (0.88 – 7.2)	3.0 (0.94 – 4.67)	0.992
Median iPTH, pg/mL (IQR)	385 (180.2 – 639.6)	353.2 (180.2 – 596.9)	390 (182.6 – 639.6)	0.936
Mean Ca × P, mg^2/dL^2 (SD)	57.4 (16.8)	59.5 (15.8)	53.9 (18.2)	0.083
Median haemoglobin, g/L (IQR)	105.5 (95.5 – 113)	107 (97 – 115)	104 (94 – 113)	0.423
Median WBC count, × 10^9/L (IQR)	6.03 (5.24 – 7.36)	6.03 (5.41 – 7.48)	6.04 (5.18 – 7.24)	0.901
Median platelet count, ×10^9/L (IQR)	168 (138 – 211)	170 (139 – 212)	166 (136 – 211)	0.885
Median cholesterol, mmol/L (IQR)	4.2 (3.6 – 4.9)	4.1 (3.7 – 4.7)	4.6 (3.5 – 5.1)	0.604
Median LDL, mmol/L (IQR)	2.3 (1.9 – 2.8)	2.3 (1.9 – 2.7)	2.6 (1.8 – 3.3)	0.271
Vascular access dysfunction (%)	11 (13.75)	4 (8)	7 (23.3)	0.973

BNP: B-type natriuretic peptide; Ca × P: Calcium-phosphorus product; DBP: Diastolic blood pressure; IDWG: Interval dialysis weight gain; iPTH: Immunoreactive parathyroid hormone; IL-18: Interleukin-18; IQR: Interquartile range; LDL: Low-density lipoprotein; SBP: Systolic blood pressure; SD: Standard deviation; WBC: White blood cell

The development and progression of AVF dysfunction is complex. In ESRD patients, some studies found that they often experienced systemic microinflammation of factors such as IL-6, interleukin-8 and TNF-alpha which contribute to the development of AVF dysplasia.[21] In uraemia, elevation of IL-6, TGF-beta and TNF-alpha also renders the vascular wall of mature AVF easy to remodel and narrow, and has been linked to the development of NIH and advanced AVF dysfunction.[8,9] However, the specific mechanisms that contribute to these adverse events have not been elucidated.

IL-18 is produced by an inactive 24-kDa precursor, preIL-18, that generates an 18-kDa protein with an endoprotease IL-1-beta-converting enzyme. IL-18 promotes maturation of T cells and natural killer cells, as well as synthesis of cytokines and increased cytotoxicity.[22] IL-18 and its receptor are expressed in endothelial cells, vascular smooth muscle cells and macrophages.[23] Several studies have found that IL-18 is an important prognostic biomarker for atherosclerosis.[24–6] In a multifactorial analysis that controlled for age and gender, a significant correlation was found between IL-18 and carotid intima-media thickness that was independent of traditional risk factors for atherosclerosis.[27] It is postulated that IL-18 may contribute to the development of vascular diseases by inducing expression of IL-1-beta, TNF-alpha and NF-kappaB, inhibition of antiapoptosis factors (such as Bcl-2 and Bcl-XL), upregulation of expression of pro-apoptosis factors (such as Fas, Fas-L and Bcl-XS) and interference with mitogen-activated protein

Table 2. Logistic Regression Analysis of Vascular Access Dysfunction According to Baseline Prognostic Markers

Parameter	Beta Coefficient	Standard Error	Odds Ratio (95% CI)	*P* Value
Univariate logistic regression				
Age	0.029	0.029	1.030 (0.974 – 1.089)	0.307
Male gender	1.300	3.004	3.671 (0.738 – 18.254)	0.112
Dialysis age	-0.007	0.085	0.918 (0.765 – 1.101)	0.356
Diabetes mellitus	-0.271	0.850	0.763 (0.086 – 6.771)	0.808
Hypertension	-0.463	0.522	0.630 (0.124 – 3.193)	0.577
IDWG	0.001	0.269	1.001 (0.591 – 1.696)	0.996
Systolic blood pressure	-0.007	0.021	0.994 (0.954 – 1.035)	0.753
Diastolic blood pressure	0.003	0.035	1.003 (0.937 – 1.073)	0.938
Albumin	-0.129	0.075	0.880 (0.744 – 1.039)	0.131
Haemoglobin	-0.013	0.021	0.987 (0.947 – 1.029)	0.543
iPTH	-0.001	0.001	0.999 (0.997 – 1.001)	0.269
Calcium-phosphorus product	-0.006	0.020	0.994 (0.957 – 1.034)	0.775
C-reactive protein	0.013	0.018	1.103 (0.977 – 1.049)	0.486
Interleukin-18	1.253	2.369	3.500 (0.929 – 13.188)	0.064
Multivariate logistic regression				
Age	0.029	0.038	1.030 (0.958 – 1.107)	0.429
Male gender	1.819	5.876	6.167 (0.953 – 39.910)	0.056
Dialysis age	-0.074	0.096	0.929 (0.759 – 1.137)	0.474
Albumin	-0.198	0.097	0.820 (0.650 – 1.035)	0.095
iPTH	-0.001	0.002	0.999 (0.996 – 1.002)	0.507
Calcium-phosphorus product	0.024	0.032	1.024 (0.964 – 1.088)	0.441
C-reactive protein	0.008	0.024	1.008 (0.962 – 1.056)	0.750
Interleukin-18	2.248	8.164	9.471 (1.748 – 51.307)	0.009

CI: Confidence interval; IDWG: Interval dialysis weight gain; iPTH: Immunoreactive parathyroid hormone

kinase-dependent signalling pathways. IL-18 may also promote proliferation and migration of vascular smooth muscle cells.[28,29]

While some studies had detected increased levels of serum IL-18 in CKD patients and those on CAPD,[12] others found a correlation between elevated IL-18 and poor prognosis in HD patients including increased hospitalisation.[15] Our study found that elevated IL-18 was significantly correlated with VA dysfunction and this finding persisted even after adjustment had been made for age, gender, blood pressure, diabetes, dialysis age, ultrafiltration volume, anaemia, infection, secondary hyperparathyroidism, nutrition status and blood lipid level. These findings were also similar to those found for the correlation between IL-18 and atherosclerosis.

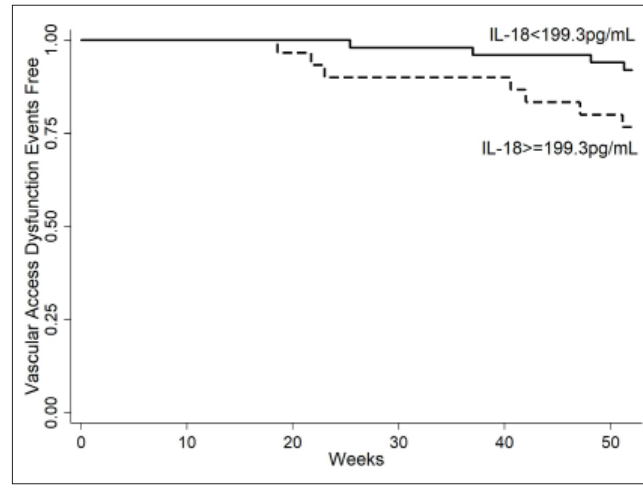


Fig. 1. Kaplan-Meier survival analysis showed that haemodialysis patients with high IL-18 (≥199.3 pg/mL) level had more vascular access dysfunction events (P = 0.047).

Table 3. Multivariate Cox Regression Analysis of Vascular Access Dysfunction in Haemodialysis Patients

Covariate	Model 1		Model 2		Model 3		Model 4		Model 5	
	Hazards Ratio (95% CI)	*P* Value	Hazards Ratio (95% CI)	*P* Value	Hazards Ratio (95% CI)	*P* Value	Hazards Ratio (95% CI)	*P* Value	Hazards Ratio (95% CI)	*P* Value
Age	1.020 (0.97 – 1.07)	0.78					1.009 (0.97 – 1.05)	0.702	1.007 (0.96 – 1.05)	0.776
Male gender	4.004 (0.86 – 18.71)	0.078			3.883 (0.83 – 18.21)	0.085	3.700 (0.78 – 17.58)	0.1	3.766 (0.78 – 18.13)	0.098
IL-18	3.694 (1.07 – 12.79)	0.039	5.834 (1.63 – 20.83)	0.007	5.939 (1.71 – 20.66)	0.005	5.740 (1.63 – 20.22)	0.007	5.654 (1.51 – 21.1)	0.01
Albumin			0.827 (0.71 – 0.97)	0.017	0.811 (0.68 – 0.97)	0.022	0.817 (0.68 – 0.98)	0.03	0.817 (0.68 – 0.99)	0.036
CRP									1.004 (0.97 – 1.04)	0.795
Ca × P									0.997 (0.96 – 1.04)	0.883

Ca × P: Calcium-phosphorus product; CI: Confidence interval; CRP: C-reactive protein; IL-18: Interleukin-18

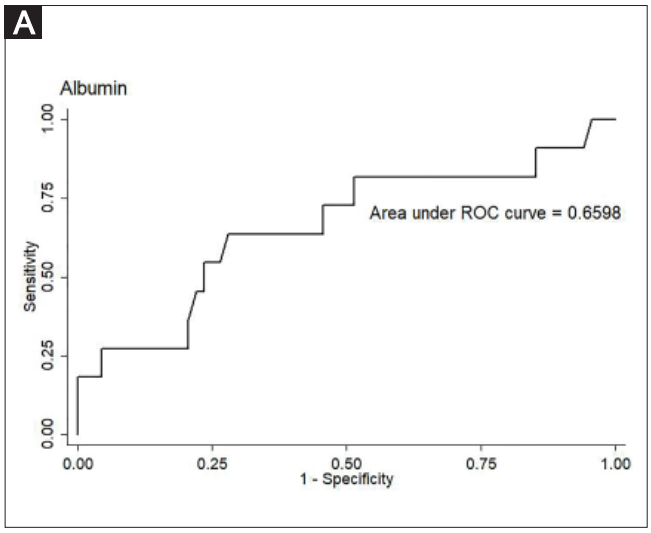
Our finding that elevated IL-18 and decreased albumin levels are independent risk factors for VA dysfunction, and that the combination of IL-18, albumin, age and gender can better predict risk of short-term VA dysfunction in HD patients, suggests that the causes of VA dysfunction are attributed to multiple factors.

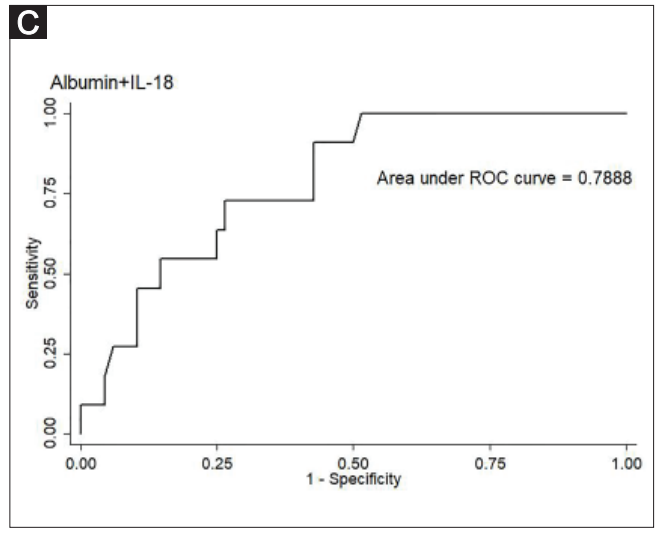
Late AVF dysfunction is closely correlated with NIH, and the contribution of IL-18 to AVF dysfunction requires further study. It is possible that IL-18 may have a role in the activation of the signal pathways described earlier, or it is involved in some causative mechanisms that are specific to ESRD patients.

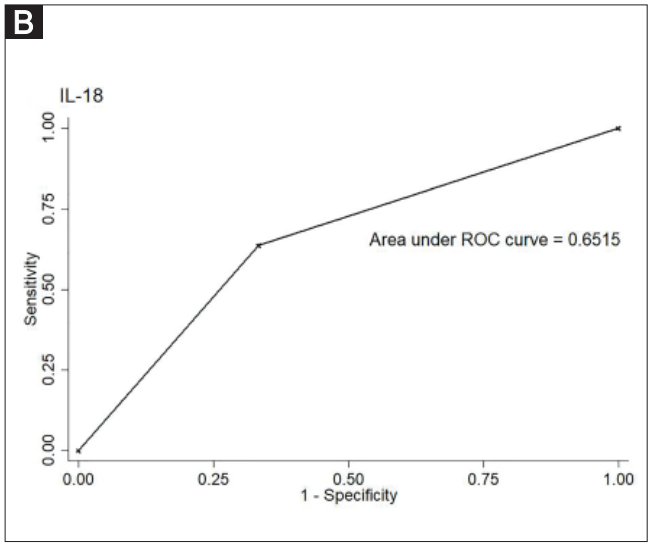
Some of the limitations of our study included small sample size and short follow-up period. Consequently, our finding of a correlation between serum IL-18 level and VA dysfunction—and whether this correlation persists after a longer period of observation—may not be extrapolated to a larger HD population unless it is validated by further research. Also, the lack of regular ultrasound data on VA meant that our study recorded only adverse events that were related to access function in cases that required surgical intervention. Consequently, our results may be skewed. Finally, our study excluded IL-18 levels of healthy individuals from analysis.

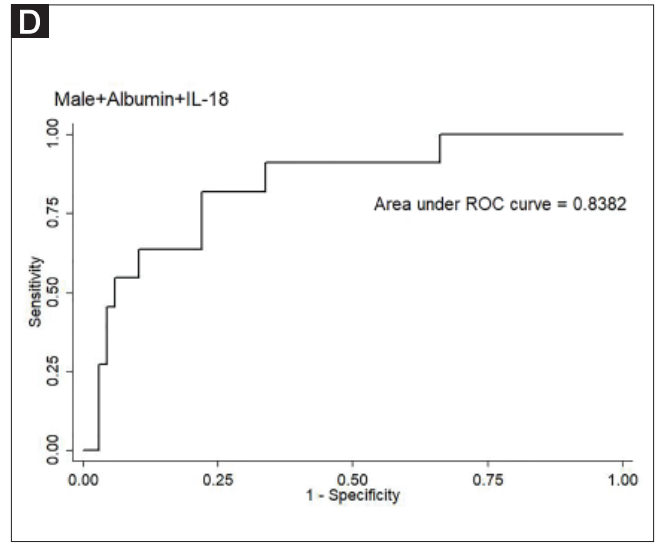
Conclusion

This study has shown that serum IL-18 level is closely correlated with VA function in HD patients, and that elevated IL-18 can be used as an independent risk factor for short-term, adverse VA-related events in outpatients on HD. IL-18 can be used with serum albumin, age and gender to predict likelihood of such events in HD patients. Future cohort studies could involve larger sample sizes to validate our finding on the correlation between IL-18 and VA function. Further research is needed to elucidate how IL-18 contributes to VA dysfunction and new interventions that can improve access function and prognosis in HD patients.









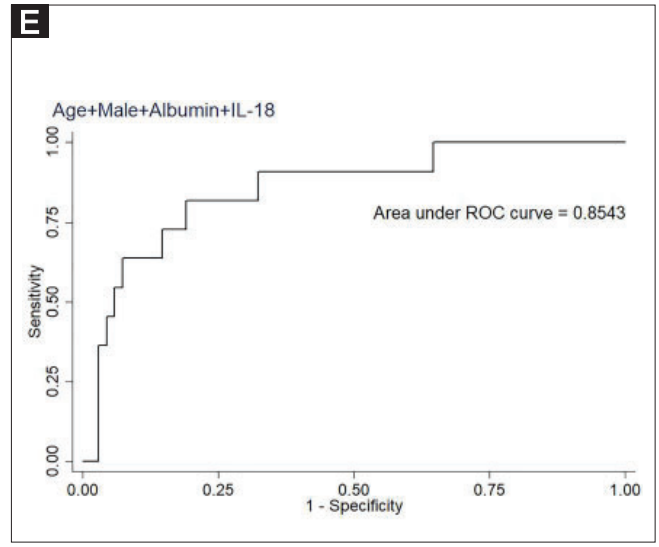


Fig. 2. Receiver operating characteristic (ROC) curve analysis of biochemical parameters in predicting vascular access dysfunction in haemodialysis patients. A: Serum albumin. B: Serum IL-18. C: Serum IL-18 with serum albumin. D: Serum IL-18 with serum albumin and gender. E: Serum IL-18 with serum albumin, gender and age. IL-18: Interleukin-18

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Original Article

Mortality and Neurological Outcomes in Out-of-Hospital Cardiac Arrest Patients With and Without Targeted Temperature Management in a Multiethnic Asian Population

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Abstract

Introduction: The use of targeted temperature management (TTM) is increasing although adoption is still variable. We describe our 6-year experience and compare the mortality and neurological outcomes of out-of-hospital cardiac arrest (OHCA) patients with and without the use of TTM in a multiethnic Asian population. Materials and Methods: We performed a retrospective observational study at a tertiary academic medical centre. OHCA survivors admitted to our hospital between April 2010–December 2016 were included. Outcomes of interest were 30-day mortality postresuscitation, Cerebral Performance Category (CPC) and Overall Performance Category (OPC) scores. Results: A total of 121 of 261 patients (46.3%) underwent TTM. TTM patients were younger (TTM 60.0 years old vs no TTM 63.7 years old, *P* = 0.047). There was no difference in the initial arrest rhythm of shockable origin between the 2 groups (*P* = 0.289). There was suggestion of lower 30-day mortality (TTM 24.3% vs no TTM 31.4%, *P* = 0.214), higher and good CPC/OPC scores (TTM 19.0% vs no TTM 15.7%, *P* = 0.514) with TTM although this did not reach statistical significance. On multivariable logistic regression analysis, TTM was not associated with 30-day mortality (*P* = 0.07). However, older age, initial non-shockable rhythm and increased duration from arrest to return of spontaneous circulation were associated with increased mortality. Malay ethnicity was associated with a poorer CPC/OPC score. Conclusion: Adoption and outcomes of TTM postresuscitation is variable and there is still a need to optimise management of the identified predictors of survival and good neurological outcomes while TTM is being used.

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Key words: Heart attack, Neurological function, Neuroprotection, Therapeutic hypothermia

Introduction

Targeted temperature management (TTM) is an established but evolving modality for treating out-of-hospital cardiac arrest (OHCA) patients. There have been significant advances in the management of OHCA patients and prevention of sudden cardiac death, but much is still unknown.[1,2] Two landmark clinical studies performed in Europe and Australia demonstrated that the initiation of TTM improved mortality and neurological outcomes.[3,4] Since then, the International Liaison Committee on Resuscitation and the American Heart Association have recommended the use of TTM after cardiac arrest as soon as possible after return of spontaneous circulation (ROSC).[5] They further released an advisory statement regarding TTM in 2015 recommending it for adults with OHCA who have an initial shockable or non-shockable rhythm but remain unresponsive after ROSC and TTM for at least 24 hours.[6]

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Almost 2 decades on and despite the recommendations, there are still areas of controversy. In many centres, adoption is still based on individual clinician and institutional discretion. There are unresolved issues of optimal targeted temperature, haemodynamic and neurological monitoring methods, and the treatment of fever among various other issues.[7] Guidelines were developed based on studies of Caucasian populations, and the landmark studies recruited only patients with OHCA and ventricular fibrillation. In Asia, experience with the use of TTM is still developing and is variable.[8,9] Most of the larger published Asian studies involved countries with ethnically homogenous populations (The Korea Hypothermia Network Registry from Korea[10] and the J-PULSE-HYPO study registry from Japan).[11] In other parts of Asia, there are single-centre studies from Thailand[12,13] and Taiwan,[14] which again consist of ethnically homogenous populations. A pilot study from our own group in Singapore[15] in 2014 showed that a therapeutic hypothermia protocol could be safely implemented, but consisted of a small sample size of TTM patients (n = 25). Furthermore, ethnic differences have also been shown to affect neurological outcomes in studies performed in the United States of America (USA). In particular, the non-White ethnic groups were demonstrated to have poorer neurological outcomes after cardiac arrest.[16,17] A local study of a paediatric population with in-hospital cardiac arrests did not show any ethnic differences, although the sample size was small.[18] Whether ethnicity is a factor affecting neurological outcomes in OHCA in our local context is not known.

As such, the primary aim of this study was to describe the use of TTM on OHCA patients admitted to a tertiary academic medical centre serving a multiethnic adult Asian population over a 6-year period. The outcomes of interest were 30-day mortality, good cerebral performance category (CPC) and overall performance category (OPC) scores. We aimed to identify predictors of improved 30-day mortality and CPC/OPC scores.

Materials and Methods

This was a retrospective observational study using Singapore data from the Pan-Asian Resuscitation Outcomes Study (PAROS)[19] and our institution's electronic medical records. PAROS is a collaborative research network that collects data prospectively and aims to improve outcomes of prehospital and emergency care in the Asia-Pacific region.

Data was collected on all OHCA patients who presented to the Singapore General Hospital Emergency Department and survived to admission between April 2010–December 2016. The inclusion criteria for TTM were as follows (although discretion was given to the attending clinician as to whether to eventually initiate TTM): 1) OHCA patients with all-presenting rhythms and sustained ROSC after cardiac arrest for >30 minutes, 2) patients who were comatose (with a Glasgow Coma Score of ≤8) or who were unresponsive postresuscitation, and 3) patients who were haemodynamically stable with systolic blood pressure (BP) >90 mmHg (with or without inotropic support). The exclusion criteria included OHCA patients deemed unsuitable for further active intervention, those who regained consciousness, patients with persistent hypotension despite fluid and/or vasopressor support, those with a positive pregnancy test in females <50 years old and trauma patients. Patient characteristics collected include demographics (age, gender, race and comorbidities), arrest details (location, time, witness, bystander cardiopulmonary resuscitation [CPR]), first presenting rhythm, time of ROSC, aetiology (cardiac vs non-cardiac) and post-ROSC interventions (percutaneous coronary intervention [PCI], coronary artery bypass graft, implantable cardioverter-defibrillator use). Prehospital data was obtained from the PAROS registry. The time of arrest was estimated and based on the time the patient was found unresponsive/unconscious with no pulse and no/abnormal breathing by relatives or a bystander. The time of ROSC was taken as the first ROSC confirmed by a palpable pulse and electrocardiogram in the emergency department. The main primary outcomes measured at 30 days postresuscitation were mortality, discharge status, CPC and OPC scores.[20] A good CPC score was defined as having a score of 1 or 2 according to the Glasgow-Pittsburg Outcome Categories. Neurological status was assessed by attending physician either upon discharge or at the 30 days postarrest. Mortality was assessed within 30 days of cardiac arrest. This would be documented in the inpatient discharge summary notes and extracted accordingly in the case record form by a clinical research coordinator.

Patients received standard intensive care as per the treating physician. Sedation was started with intravenous midazolam (0.02–0.08 mg/kg over 1–2 minutes, initially). Doses were uptitrated to achieve sedation as BP tolerated. Paralysis was induced with atracurium (0.4–0.5 mg/kg intravenous bolus, initially) and titrated as required. The target temperature was 34°C. The emergency department would initiate cooling with cold saline infusion and surface icepacks until the cooling device was commenced in the intensive care unit. Ice packs were subsequently replaced by a wearable cooling suit in July 2015 as standard-of-care treatment for eligible patients.[21] Core temperature was monitored via rectal or oesophageal temperature probe. The target temperature of 34°C was maintained for 24 hours followed by passive rewarming to 36.5°C by setting the cooling unit accordingly. The aim was to increase temperature by 1°C every 4 hours and achieve rewarming over at least 12 hours. The patient would be warmed no

faster than 1°C in 4 hours over a period of 8 hours. A detailed protocol can be found in the Appendix.

Data management was carried out using the REDCap data entry platform.[22] All data analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, New York, USA). For categorical data, frequency tables, together with 95% confidence interval (CI) were reported. Continuous variables were reported using mean, and where appropriate the 95% CI and median with interquartile range were reported. Those with *P* values <0.2 were included for consideration to develop a multivariable logistic regression model. The significance level was set at 0.05.

The study protocol was approved by SingHealth Centralised Institutional Review Board with waiver of informed consent.

Results

There were 1171 OHCA patients who presented to our emergency department from April 2010–December 2016, and 262 survived to admission (Fig. 1). Of the 262, 1 was excluded due to incomplete documentation of relevant TTM variables. Out of 261 that were included in this study, 121 (46.4%) underwent TTM and 140 (53.6%) either did not undergo TTM or were ineligible for TTM.

Table 1 shows the baseline characteristics of OHCA patients, grouped by whether they underwent TTM. The mean age of those who underwent TTM was about 3 years younger than those who had not (60.0 years old vs 63.7 years old, $P = 0.047$). Significant differences between these 2 groups were age, race, incidence of stroke, year of arrest, presence of witness to the arrest and the person who performed initial CPR. Among patients who did not undergo TTM, survival to discharge was 24.3%—compared to 31.4% in those who underwent TTM—although not statistically significant ($P = 0.200$). There was also no significant difference in good neurological outcome (CPC 1–2) between patients who underwent TTM and those without (19.0% vs 15.7%, $P = 0.514$). The 6-year trend of TTM use in our population is shown in Figure 2.

In the multivariable logistic regression analysis (Table 2), TTM was not associated with 30-day mortality ($P = 0.07$). However, 3 variables were found to be significantly associated. These were increased age (odds ratio [OR] 1.04, 95% CI 1.02–1.07), longer time between arrest and first ROSC (OR 1.06, 95% CI 1.04–1.09) and an initial non-shockable arrest rhythm (OR 6.62, 95% CI 3.16–14.54). Positive predictor of good neurological outcome was presence of prehospital defibrillation (OR 3.82, 95% CI 1.28–12.53). Negative predictors for good neurological outcome were age, duration between time of arrest and first ROSC, Malay ethnicity (with Chinese as the reference group, adjusted OR 0.10, 95% CI 0.01–0.65, $P = 0.0319$) and first CPR initiated by emergency medical services (EMS)/private ambulance (Table 3).

Discussion

The key findings from our paper are as follows: 1) patients who underwent TTM were younger and fewer had a past history of stroke, 2) while there was a suggestion of improved survival to discharge and better CPC/OPC scores in the TTM group, this did not reach statistical

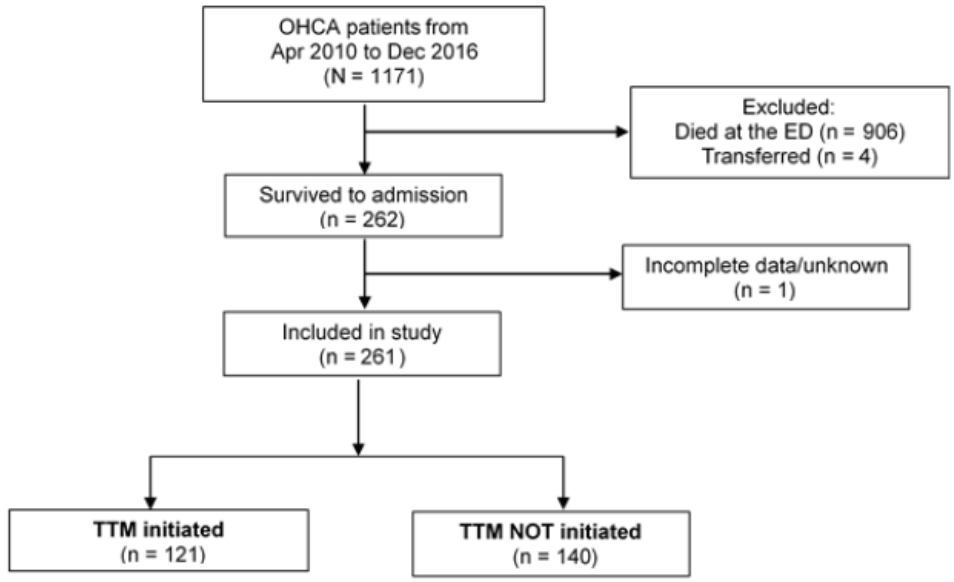

Fig. 1. Flow chart of out-of-hospital cardiac arrest patients included in the study. ED: Emergency department; OHCA: Out-of-hospital cardiac arrest; TTM: Targeted temperature management

Table 1. Baseline Characteristics of Out-of-Hospital Cardiac Arrest Patients With and Without Targeted Temperature Management

Characteristic, n (%)	TTM (n = 121)	Non-TTM (n = 140)	*P* Value
Mean age in years (IQR)	60.0 (48 – 72)	63.7 (55 – 76)	0.047
Race			0.009
Chinese	92 (76.0)	88 (62.9)	
Malay	12 (9.9)	12 (8.6)	
Indian	11 (9.1)	16 (11.4)	
Eurasian	2 (1.7)	1 (0.7)	
Others	4 (3.3)	23 (16.4)	
Gender, male	92 (76.0)	96 (68.6)	0.214
Premorbidities			
No medical history	24 (19.8)	19 (13.6)	0.185
Unknown medical history	4 (3.3)	7 (5.0)	0.552
Heart disease	45 (37.2)	62 (44.3)	0.258
Diabetes	28 (23.1)	42 (30.0)	0.262
Cancer	8 (6.6)	11 (7.9)	0.813
Hypertension	61 (50.4)	66 (47.1)	0.621
Renal disease	13 (10.7)	20 (14.3)	0.457
Respiratory disease	24 (19.8)	21 (15.0)	0.327
Hyperlipidaemia	42 (34.7)	50 (35.7)	0.897
Stroke	7 (5.8)	19 (13.6)	0.040
Mean estimated time in minutes between cardiac arrest and first sustained ROSC (IQR)	48 (32 – 64)	46 (31 – 61)	0.656
Year of incidence			0.002
2010	5 (4.1)	20 (14.3)	
2011	13 (10.7)	24 (17.1)	
2012	12 (9.9)	23 (16.4)	
2013	15 (12.4)	16 (11.4)	
2014	32 (26.4)	21 (15.0)	
2015	15 (12.4)	19 (13.6)	
2016	19 (24.0)	17 (12.1)	
Arrest witnessed by			0.001
Not witnessed	17 (14.0)	43 (30.7)	
Emergency medical services/private ambulance	12 (9.9)	20 (14.3)	
Bystander	92 (76.0)	77 (55.0)	
Initial cardiopulmonary resuscitation performed by			0.029
Not performed	4 (3.3)	8 (5.7)	
Emergency medical services/private ambulance	54 (44.6)	79 (56.4)	
Bystander	59 (48.8)	53 (37.9)	
Hospital staff	4 (3.3)	0 (0)	
Cardiac cause of arrest	85 (70.2)	85 (60.7)	0.063
Initial rhythm			0.289
Shockable	34 (28.1)	48 (34.3)	
Non-shockable	87 (71.9)	92 (65.7)	

IQR: Interquartile range; ROSC: Return of spontaneous circulation; TTM: Targeted temperature management

Table 1. Baseline Characteristics of Out-of-Hospital Cardiac Arrest Patients With and Without Targeted Temperature Management (Cont'd)

Characteristic, n (%)	TTM (n = 121)	Non-TTM (n = 140)	*P* Value
Prehospital defibrillation	52 (43.0)	54 (38.6)	0.528
Emergency percutaneous coronary intervention/stent performed	34 (28.1)	29 (20.7)	0.192
Coronary artery bypass grafting performed	1 (0.8%)	0 (0)	0.464
Outcomes			
Survived to discharge	38 (31.4)	34 (24.3)	0.214
Mortality	83 (68.6)	106 (75.7)	0.214
Good Cerebral Performance Category score (1 – 2)	23 (19.0)	22 (15.7)	0.514

IQR: Interquartile range; ROSC: Return of spontaneous circulation; TTM: Targeted temperature management

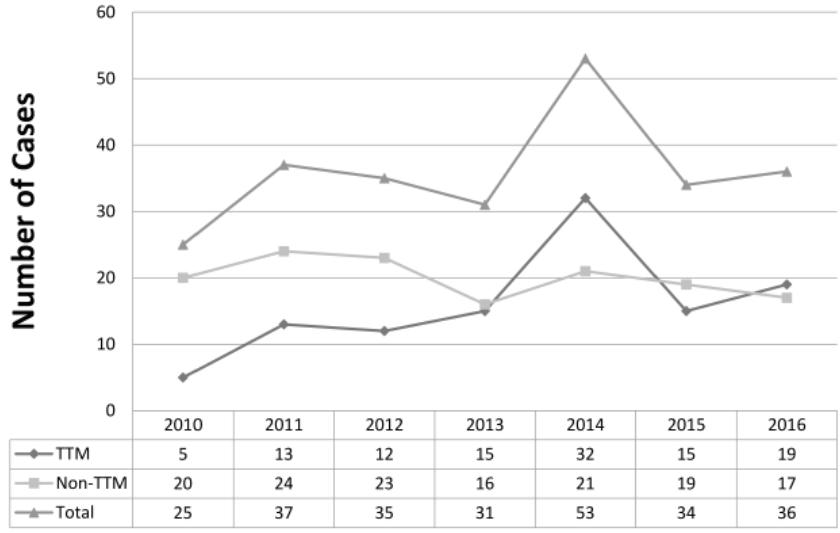

Fig. 2. Trend of targeted temperature management (TTM) over the 6 years of the study.

Table 2. Multivariable Analysis of Predictors of Mortality

Variable	Number of Survivals	Number of Deaths	Odds Ratio (95% CI)	*P* Value
Mean age	61	178	1.04 (1.02 – 1.07)	0.0005
Time between arrest and ROSC (downtime)	61	178	1.06 (1.04 – 1.09)	<0.0001
First arrest rhythm				
Shockable	37	39	Reference	
Non-shockable	24	139	6.62 (3.16 – 14.54)	<0.0001

CI: Confidence interval; ROSC: Return of spontaneous circulation

significance, 3) an older age, a longer time from cardiac arrest to ROSC and presence of a non-shockable initial rhythm were predictors of mortality after adjustment, 4) a positive predictor of good neurological outcome was the use of prehospital defibrillation, and 5) Malay ethnicity as compared to Chinese ethnicity as the reference was associated with a poorer neurological outcome.

We compared the characteristics between our study population and previously published TTM populations in developed Asia (South Korea and Japan), a centre in developing Asia and a registry based in the USA.[10,11,13,23] The age across the populations was similar (about 60 years old) and there was a male predominance. Our TTM population had a higher proportion of patients who had witnessed arrest, but they were less likely to have an initial documented shockable rhythm. The difference in practices observed may be due to geographical size, provision of EMS services and individual hospital practices and would be of

Table 3. Multivariable Analysis of Neurological Outcome (CPC)

Variable	Poor CPC Score (3 – 4)	Good CPC Score (1 – 2)	Odds Ratio (95% CI)	*P* Value
Mean age	216	45	0.95 (0.92 – 0.98)	0.0049
Time between arrest and ROSC (downtime)	203	36	0.90 (0.86 – 0.93)	<0.0001
Race				
Chinese	150	30	Reference	
Malay	21	3	0.10 (0.01 – 0.65)	0.0319
Indian	24	3	-	0.9924
Others	21	9	1.89 (0.50 – 7.24)	0.3460
Who initiated CPR				
No CPR initiated	6	6	Reference	
Emergency medical services/private ambulance	120	13	0.07 (0.01 – 0.66)	0.0237
Bystander	87	25	0.19 (0.01 – 2.00)	0.1762
Hospital staff	3	1	0.13 (0.00 – 2.66)	0.2025
Any prehospital defibrillation				
No	140	15	Reference	
Yes	76	30	3.821(1.28 – 12.53)	0.0196

CI: Confidence interval; CPC: Cerebral performance category; CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation

interest in further studies. This is because while guidelines are developed mainly from Caucasian populations,[24] these need to be suitably applied in an Asian[7] or local context.

We identified predictors of mortality and good CPC/OPC scores in our population. Modifiable factors identified include time between arrest and ROSC, diabetes, hypertension, initial CPR performed by EMS/private ambulance, prehospital defibrillation and PCI/placement of stent. Better education of the public can reduce the incidence and severity of chronic diseases such as diabetes and hypertension. As prehospital defibrillation and CPR performed by EMS/private ambulance are of significance in reducing mortality, possible measures to increase these may be to educate lay people on where to find and use automated external defibrillators and to regularly ensure our paramedics are up-to-date with their CPR skills.[25] These findings as a whole strongly support a focus on basic life support measures through community and prehospital intervention to increase prompt and effective CPR and automated external defibrillator use, which have far greater effect on outcomes.[25–27]

Although there was some suggestion that TTM improved mortality and CPC in our study population, there was insufficient power to demonstrate statistical significance. We postulate that TTM may not have been complete in many patients and complications may not have been accounted for. The next step in this study will be to analyse specific TTM factors such as duration of TTM, temperature used, presence of overcooling and complications from TTM which can theoretically cause TTM to be less effective than it should have been. This is especially so in light of developments in TTM, such as a randomised-controlled trial (RCT) in 2013 by Nielsen et al showing that there were similar favourable outcomes in patients who underwent regimens of TTM set to 33°C and 36°C.[28] Another example is also evidence that time to target temperature plays a role in outcomes.[29] Precautions must be taken because TTM can be associated with complications such as sepsis and renal failure.[30] Clinicians taking care of such patients need to be well versed in managing patients with medical complexity beyond the cardiac issue itself. This parallels the trend of subspecialty training in cardiac intensive care.[31] It can be postulated that benefits of TTM are realised in non-trial populations. As the finer technical details of TTM are investigated,[32] clinician familiarity in treating TTM patients improves and more refined patient selection is achieved. As such, ongoing registries will continue to play an important role in informing care of OHCA patients.[19,33] Having knowledge of these factors can thus aid us to utilise TTM to greatly benefit our patients.

Ethnicity has previously been reported to be a factor in affecting outcomes of patients undergoing TTM. A study by Jacobs et al in a single tertiary care hospital in the USA demonstrated that despite a strict TTM protocol, non-white patients were associated with poorer outcomes as compared to white patients, despite adjusting for possible confounders.[34] This echoes a previous study performed by Agarwal et al which demonstrated that Hispanic ethnicity was associated with a poorer 1-year neurological outcome.[35] Chen et al studied an in-hospital cardiac arrest population and found that black survivors had a lower absolute rate of long-term survival after discharge from hospital, although

they could not rule out effects of postdischarge care.[16] Ethnic differences in our local context have been shown to affect disease outcomes, such as in diabetes control.[17] Our study consisted of a multiethnic Asian population. Based on the above studies, we would possibly have expected a difference in neurological outcomes. In our study (with Chinese as the reference group), Malays were less likely to have a good neurological outcome on multivariable analysis (adjusted OR 0.10, 95% CI 0.01–0.65, $P = 0.0319$) although this was not observed in Indians and other ethnicities. This finding deserves further investigation in future studies to understand whether it is an ethnic-specific or systems-specific factor that is resulting in this observed disparity.

A final discussion point would be that the protocols used in our study—in comparison to the 2 TTM trials mentioned—were different. In our study, TTM was initiated in the emergency department via external cooling and then initiation of internal cooling within 30 minutes. In the trial by the Hypothermia after Cardiac Arrest Study Group, temperature management was performed via an external cooling blanket[3] and temperature was maintained between 32–34°C for 24 hours before rewarming. In the study by Bernard et al, cooling was initiated prehospital by paramedics via applying cold packs externally and continued in the emergency department.[4] The total cooling period was 12 hours at 33°C in this study and thereafter they were rewarmed. In our study, our patients did not have prehospital cooling and instead of using external cooling alone, internal cooling was also performed. The target temperature in our study was also 34°C. As there was heterogeneity in the initiation of cooling, the methods used to cool, the target temperature, the duration of cooling and the study population characteristics, it is therefore not surprising that we observed a non-significant neurological benefit although there was a trend towards this. Our paramedics are currently not trained to initiate TTM in the field, although this could be for further discussion with the relevant authorities to improve prehospital care.[36,37] We believe that further RCTs, with a standardised protocol, would highlight further the external validity of the trials in different populations and health systems.

Strengths and Limitations

To the best of our knowledge, this study is the largest reported population of OHCA patients in a multiethnic Asian population. We were able to collect mortality and neurological outcome data over a 6-year period with a high percentage of data available for analysis (99.6%, 261/262). However, we do acknowledge that this was a single-centre study that may limit generalisation. As this was a retrospective study, and because PAROS did not capture the reasons why patients were not included for TTM, we cannot conclusively describe why certain patients who met the inclusion criteria were not started on TTM. We did not have information on time of TTM induction, duration of TTM, target temperature achieved, cooling methods for each group or complications experienced. Also, we could only demonstrate association and not causation in this observational study. Multicentre collaborative efforts to study TTM and well designed RCTs can be the focus of future efforts.

Conclusion

Adoption and outcomes of TTM postresuscitation varies and there is still a need to optimise management of the identified predictors of survival and good neurological outcomes while TTM is being used. Further longitudinal studies on TTM use in Asian populations are warranted.

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Conflict of Interest

Marcus EH Ong has a licensing agreement and patent filing (Application no: 13/047,348) with Zoll Medical Corporation for a study titled 'Method of predicting acute cardiopulmonary events and survivability of a patient'. He is also a Scientific Advisor for Global Healthcare SG, a commercial entity that manufactures cooling devices.

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Appendix

TTM Protocol

Induction Phase:

• The Emergency Department will initiate cooling with cold saline infusion 2 L over 2 hours and ice packs on patient's axilla and groin until the cooling device is started in the CCU/MICU.
• Reach target temperature rapidly.
• Insert a temperature sensing foley catheter or rectal temperature probe or oesophageal temperature probe to monitor core temp.
• Record temp every 30 min until rewarming is complete (temperature data should be downloaded if possible or at least every 15 minutes during induction phase).
• Obtain a Glasgow Coma Score prior to giving paralytics.
• Sedate and paralyse to avoid shivering.
• Time to reach target temperature.
• The lowest temperature ever reached.

Sedation Protocol:

• IV Midazolam initial dose 0.02-0.08 mg/kg over 1-2 min, then 0.04 mg/kg/hr titrate up to 0.2 mg/kg/hr to achieve sedation, and if blood pressure tolerates.

Paralytic Protocol:

• Atracurium 0.4-0.5 mg/kg I.V. bolus then 5-10 mg/kg/min and titrate as needed
• CCU/MICU to place patient on Heat, Moisture, Exchange (HME) unit during cooling rather than heated wire circuit (ventilator).
• Initiate cooling device according to manufacturers' protocol.
• Set the target temperature on the cooling unit to 34^{o}C.
• Ice packs to axilla and groin can be removed at this point.
• Once patient temperature of 34^{o}C is achieved (will take about 3-8 hrs), keep target temperature at 34^{o}C.

Maintenance Phase:

• Target MAP >80 mmHg to maintain cerebral perfusion.
• Administer vasopressors through central venous access; as per physician's discretion.
• If hypertensive, short acting vasodilators such as Nitroglycerine may be used.
• Keep CVP 10-15 mmHg or PCOP >12 mmHg using Normal Saline or Lactated Ringers (CVP or PCOP monitoring not mandatory) per doctor's order.
• Use Low Molecular Weight heparin (LMWH), *Enoxaparine* at a dose of 40 mg once daily, if no contraindications.
• Lacrilube to both eyes quarter hour while receiving paralytics.
• Skin care to avoid cold-related injury.

• Frequent suctioning and pulmonary toilet.
• Nursing interventions to avoid complications of immobility (DVT, UTI, skin breakdown).
• Follow mixed venous saturation (Sv02) when available per doctor's orders rather than cardiac index since the O^2 extraction ratio will be very low due to a markedly decreased metabolic demand from hypothermia and paralytics. Avoid dobutamine or other arrhythmogenic inotropes if $Sv0^2$ is close to 70%.
• Stress Ulcer Prophylaxis: Famotidine 20 mg IV q 12 hr, or Famotidine 20 mg NGT q 12 hr per doctor's order.
• EEG monitoring is recommended to detect seizures in the paralysed patient.
• Manage status epilepticus with antiepileptic medication according to standard procedure.
• Any cardiac arrhythmias should be treated with standard anti-arrhythmia protocols.
• Potential laboratory abnormalities associated with hypothermia:

Potential Lab Abnormalities Treatment
Increased amylase → No intervention unless persistent after rewarming.
Increased LFT's → No intervention unless persistent after rewarming.
Increased serum glucose → Follow insulin protocol.
Decreased K+, Mg, Phosp, Ca → Correct as needed.
Increased lactate → Optimise oxygen delivery.
Metabolic acidosis → Optimise oxygen delivery.
Thrombocytopaenia → Correct if <30k, or to >50k if active bleeding.
Leukopaenia → No intervention unless persistent after rewarming.
• If the patient needs to go for cardiac catheterisation, the cooling device should accompany the patient. The patient may be unplugged from the device enroute, but cooling should be reinstituted on arrival at the catheterisation lab.
• In the event of cardiac arrest requiring defibrillation or cardioversion, it is suggested that the lower energy setting be initially employed, with escalating energy settings as necessary.

Rewarming Phase:
• After 24 hours at 34°C, rewarm passively to 36.5°C by setting the cooling unit accordingly. Aim to increase temperature by 1°C every 4 hours, and achieve rewarming over at least 12 h. Warm no faster than 1°C in 4 hours.
• If experiencing difficulty rewarming as above, use heated ventilator air to provide core rewarming.
• Discontinue all potassium in IVF during rewarming per doctor's order. Cases of severe hyperkalemia have been reported on rewarming. Represents a transcellular shift rather than true K+ depletion.

Documentation
• Temperature every 1 hour or more frequently.
• V/S every 1 hour or more frequently.
• Glasgow Coma scores on initiation and every 4 hours.
• Skin evaluation and care given every 2 hours or more frequent.
• Time of initiation and completion of cooling and reaching target temperature.
• Patient's response to procedure.
• All completed data will then be collected and sent to the research team for data management.
• At the end of rewarming, after target warm temperature achieved, to inform trial coordinator to perform data download from the machine data log.
• Temperature variation.
• Other cooling or warming methods used to reach and/or maintain target.

Original Article

Temporal Trends and Patient Characteristics Associated With Drug Utilisation After First-Ever Stroke: Insights From Chronic Disease Registry Data in Singapore

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Abstract

Introduction: Data on drug utilisation among stroke patients of Asian ethnicities are lacking. The objectives of the study were to examine the temporal trends and patient characteristics associated with prescription of thrombolytic, antithrombotic and statin medications among patients with first-ever stroke. Materials and Methods: First-ever ischaemic and haemorrhagic stroke patients admitted to 2 Singapore tertiary hospitals between 2010–2014 were included. Data were extracted from the National Healthcare Group Chronic Disease Management System. Association between drug utilisation and admission year, as well as characteristics associated with drug use, were explored using multivariable logistic regression. Results: There was an increasing trend in the combined use of all 3 guideline medications in ischaemic stroke patients (P <0.001)—specifically thrombolytic agents (P <0.001), oral antithrombotics (P = 0.002) and statins (P = 0.003) at discharge. Among antithrombotics, the use of clopidogrel (P <0.001) and aspirin-clopidogrel (P <0.001) had increased, whereas prescription of dipyridamole (P <0.001) and aspirin-dipyridamole (P <0.001) had declined. For statins, the increase in atorvastatin prescription (P <0.001) was accompanied by decreasing use of simvastatin (P <0.001). Age, ethnicity and certain comorbidities (hyperlipidaemia, atrial fibrillation and chronic kidney disease) were associated with the combined use of all 3 guideline medications (P <0.05). In haemorrhagic stroke, prescription of statins at discharge were comparatively lower. Conclusion: This study reveals changes in prescription behaviour over time in a multiethnic Asian population with first-ever stroke. Patient characteristics including younger age, Malay ethnicity and certain comorbidities (i.e. hyperlipidaemia, atrial fibrillation) were associated with the combined use of all 3 guideline medications among ischaemic stroke patients.

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Key words: Antithrombotics, Asian, Statins, Thrombolytic agents

Introduction

Medical professional organisations such as the American Heart Association (AHA), American Stroke Association (ASA) and American College of Cardiology (ACC), have published evidence-based clinical practice guidelines recommending pharmacotherapy to improve stroke outcomes.[1–5] Three medication classes, namely thrombolytic agents, antithrombotics and statins, are generally recommended for ischaemic stroke,[1–3] but not for haemorrhagic stroke unless specifically indicated for other comorbidities.[4,5]

Despite publication of these guidelines, limited data are available on physician and patient adherence to these practice recommendations.[6] Previous studies have indicated a wide heterogeneity in medication use and adherence in different populations[7–10] and it is unclear whether international recommendations are closely adhered to among Asians. Furthermore, sparse data are available on the drug prescription patterns among physicians caring for stroke patients in Singapore. One local study had found that most ischaemic stroke patients with atrial fibrillation (AF) were not on appropriate anticoagulation, indicating likely

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under-utilisation.[11] Hence, this study aimed to examine the temporal trends in prescription of thrombolytic agents, antithrombotics and statins during hospitalisation or at discharge among first-ever stroke patients admitted to 2 tertiary hospitals between 2010–2014, and to explore patient characteristics associated with drug utilisation.

Materials and Methods

Data Source and Study Population

Data were extracted from the National Healthcare Group (NHG) Chronic Disease Management System (CDMS). NHG is one of the public healthcare clusters in Singapore, providing both acute and primary care services through its network of clinics, hospitals and national specialty centres. CDMS is an enterprise-wide registry containing clinical and administrative information.[12] We used data from 2 tertiary hospitals in the NHG cluster, including one which houses the national specialty centre for neurosciences. The study protocol was approved by the NHG Domain Specific Review Board (reference number: 2015/01222) which waived the need for written informed consent.

Patients with first-ever ischaemic or haemorrhagic (intracerebral or subarachnoid) stroke aged ≥18 years old who were admitted between 1 January 2010–31 December 2014 were included for analysis. Patients with transient ischaemic attack or unclear stroke cause were excluded. The International Classification of Diseases (ICD) diagnosis codes were used for case inclusion (Supplementary Tables 1 and 2) and exclusion (Supplementary Tables 3 and 4). Patients with first-ever stroke did not have any ICD codes for stroke identified in the NHG CDMS before 2010. In addition, we excluded patients who were not Singapore citizens or permanent residents, had hospital transfers, with unknown discharge status or with missing medication data.

Drugs of Interest

Drugs of interest included thrombolytic agents during hospitalisation, antithrombotics (antiplatelets, oral and parenteral anticoagulants) within 3 days of hospital admission, as well as oral antithrombotics (antiplatelets and anticoagulants) and statins at discharge (Supplementary Table 5). Medications prescribed (ever used) during hospitalisation or at discharge were identified based on the dispensed status and date of record relative to the discharge date of each patient.

Demographic and Clinical Characteristics of Interest

Apart from drug use, demographic and clinical data collected include sex, age, ethnicity, year of admission (for first-ever stroke), cardiovascular comorbidities, intensive care unit admission and hospital length of stay (LOS). These were decided based on variables commonly reported in existing literature, as well as data availability in the NHG CDMS.

Statistical Analysis

Categorical variables were presented as n (%), while non-normally distributed continuous variables as median (interquartile range, IQR). In-hospital drug utilisation was analysed in the whole study cohort. Drug utilisation analyses of medications prescribed at discharge were conducted in a subcohort of patients discharged alive from non-rehabilitation departments. Patients discharged from rehabilitation departments were excluded, as some may have been transferred directly to inpatient rehabilitation wards within the same hospital or to affiliated community hospitals, hence resulting in missing drug records at discharge from acute care.

Association between drug utilisation and admission year were examined using the Cochran-Armitage test for trend and multivariable logistic regression adjusted for baseline characteristics including sex, age, ethnicity, cardiovascular comorbidities and hospital ward class (proxy for socioeconomic status). Patients admitted into Class A and Class B1 wards were considered private patients (receiving no to little government subsidy), whereas those in Class B2 and Class C wards were considered subsidised patients (receiving higher levels of government subsidy).[13] ICD diagnosis codes and prescription of medications (e.g. statins, antidiabetic drugs) were used to determine comorbid conditions.

Patient characteristics associated with drug utilisation were also explored using multivariable logistic regression, adjusting for admission year to control for the effect of temporal changes in drug utilisation. Intensive care unit (ICU) admission and hospital LOS were used as proxies for stroke severity. Univariable analyses were performed to identify variables based on $P < 0.10$. Selected variables were subsequently included in multivariable analyses and dropped via backward elimination if they did not achieve statistical significance of $P < 0.05$.

Adjusted odds ratios (aORs) and corresponding 95% confidence intervals (CIs) were reported. Independent variables were dropped if collinearity was detected during regression. All statistical analyses were conducted using Stata 13.0 (StataCorp LP, College Station, Texas, United States [US]).

Results

Characteristics and Outcomes of Study Population

Of the 4935 first-ever stroke patients in the whole study cohort, 69.1% had ischaemic stroke and 30.9% had haemorrhagic stroke (Fig. 1). The subcohort comprised

Fig. 1. Flow diagram of patient inclusion and exclusion.

3469 patients, of whom 74.5% had ischaemic stroke and 25.5% had haemorrhagic stroke.

The majority of ischaemic stroke patients were male, aged ≥65 years old, of Chinese ethnicity, admitted to subsidised wards, and with hypertension and hyperlipidaemia (Table 1). Inpatient all-cause mortality averaged 10.1% over the 5-year period. ICU admission and median hospital LOS were 14.9% and 9 (IQR: 4–21) days in the whole cohort, and 9.6% and 8 (IQR: 4–17) days in the subcohort, respectively.

Unlike ischaemic stroke patients, the majority of haemorrhagic stroke patients were aged <65 years old, with inpatient all-cause mortality averaging 22.8% (Table 1). ICU admission and median hospital LOS were 62.4% and 15 (IQR: 6–35) days in the whole cohort, and 49.7% and 16 (IQR: 8–31) days in the subcohort, respectively.

Temporal Trends of Drug Utilisation in Ischaemic Stroke

An increasing trend in the combined use of all 3 guideline medications (in-hospital thrombolytic therapy, as well as antithrombotics and statins at discharge) was observed (P <0.001) (Fig. 2A and Table 2). Compared with 2010, there was a 1.9-fold increase (95% CI: 1.23–2.89) in 2014. This increasing trend was similarly observed for use of thrombolytic agents (P <0.001) (Fig. 2B and Table 2). Conversely, prescription of early antithrombotics (within 3 days of admission) was lower in 2014 (aOR = 0.71, 95% CI: 0.55–0.91) compared with 2010.

Most patients received oral antithrombotics (83.7%) at discharge, predominantly antiplatelets (73.9%) (Fig. 2C and Table 2). There was an increasing trend in the prescription of oral antithrombotics (P = 0.002). Compared with 2010, there was a 1.3-fold (95% CI: 1.01–1.80) and 1.6-fold (95% CI: 1.17–2.12) increase in use of antiplatelets in 2013 and 2014, respectively. Use of oral anticoagulants showed an increasing trend (P = 0.009), particularly for AF patients in 2014 (aOR = 2.54, 95% CI: 1.44–4.46) compared with 2010. Oral anticoagulation use in non-AF patients was low, averaging 5.4%.

Aspirin and clopidogrel were the most prescribed antiplatelets at discharge (Fig. 3A). Use of aspirin remained relatively stable from 2010–2014 (P = 0.510), while prescription of clopidogrel and aspirin-clopidogrel combination increased (P <0.001) (Figs. 3A, 3B and Table 2). Combined aspirin-clopidogrel use in 2013 and 2014

Table 1. Characteristics and Outcomes of Study Population, Stratified By Stroke Type

	Ischaemic Stroke		Haemorrhagic Stroke*	
	Cohort (n = 3410)	Subcohort† (n = 2586)	Cohort (n = 1525)	Subcohort† (n = 883)
Characteristic				
Male, n (%)	1951 (57.2)	1490 (57.6)	810 (53.1)	447 (50.6)
Median age (IQR)	69 (59 – 79)	69 (59 – 79)	61 (52 – 72)	61 (52 – 72)
Age group, n (%)				
18 – 64	1350 (39.6)	1039 (40.2)	902 (59.1)	517 (58.6)
65 – 74	828 (24.3)	598 (23.1)	330 (21.6)	199 (22.5)
75 – 84	824 (24.2)	633 (24.5)	209 (13.7)	123 (13.9)
≥85	408 (12.0)	316 (12.2)	84 (5.5)	44 (5.0)
Ethnic group, n (%)				
Chinese	2614 (76.7)	1949 (75.4)	1219 (79.9)	692 (78.4)
Malay	417 (12.2)	327 (12.6)	179 (11.7)	110 (12.5)
Indian	207 (6.1)	164 (6.3)	59 (3.9)	38 (4.3)
Others	172 (5.0)	146 (5.6)	68 (4.5)	43 (4.9)
Hospital ward class, n (%)‡				
Private (Class A and Class B1)	124 (3.6)	104 (4.0)	59 (3.9)	43 (4.9)
Subsidised (Class B2 and Class C)	3286 (96.4)	2482 (96.0)	1466 (96.1)	840 (95.1)
Year of admission, n (%)				
2010	824 (24.2)	638 (24.7)	381 (25.0)	209 (23.7)
2011	659 (19.3)	489 (18.9)	275 (18.0)	159 (18.0)
2012	686 (20.1)	516 (20.0)	296 (19.4)	173 (19.6)
2013	638 (18.7)	481 (18.6)	276 (18.1)	161 (18.2)
2014	603 (17.7)	462 (17.9)	297 (19.5)	181 (20.5)
Cardiovascular comorbidities, n (%)				
Hypertension	2600 (76.2)	1950 (75.4)	1080 (70.8)	644 (72.9)
Hyperlipidaemia	3237 (94.9)	2484 (96.1)	852 (55.9)	525 (59.5)
Diabetes mellitus	1571 (46.1)	1155 (44.7)	362 (23.7)	233 (26.4)
Atrial fibrillation	873 (25.6)	608 (23.5)	104 (6.8)	63 (7.1)
Coronary heart disease	815 (23.9)	593 (22.9)	176 (11.5)	100 (11.3)
Heart failure	411 (12.1)	295 (11.4)	76 (5.0)	40 (4.5)
Chronic kidney disease	1050 (30.8)	790 (30.5)	282 (18.5)	167 (18.9)
Number of cardiovascular comorbidities, n (%)§				
≤3	2146 (62.9)	1662 (64.3)	1286 (84.3)	733 (83.0)
>3	1264 (37.1)	924 (35.7)	239 (15.7)	150 (17.0)
Outcome				
Inpatient all-cause mortality, n (%)	346 (10.1)	0 (0.0)	348 (22.8)	0 (0.0)
Admitted to ICU, n (%)	508 (14.9)	248 (9.6)	951 (62.4)	439 (49.7)
Median ICU LOS (days) (IQR)	2 (1 – 5)	2 (1 – 5)	3 (2 – 7)	3 (2 – 7)
Median hospital LOS (days) (IQR)	9 (4 – 21)	8 (4 – 17)	15 (6 – 35)	16 (8 – 31)
Hospital LOS >8 days, n (%)	1786 (52.4)	1193 (46.1)	1014 (66.5)	651 (73.7)
Hospital LOS >16 days, n (%)	1114 (32.7)	670 (25.9)	723 (47.4)	430 (48.7)

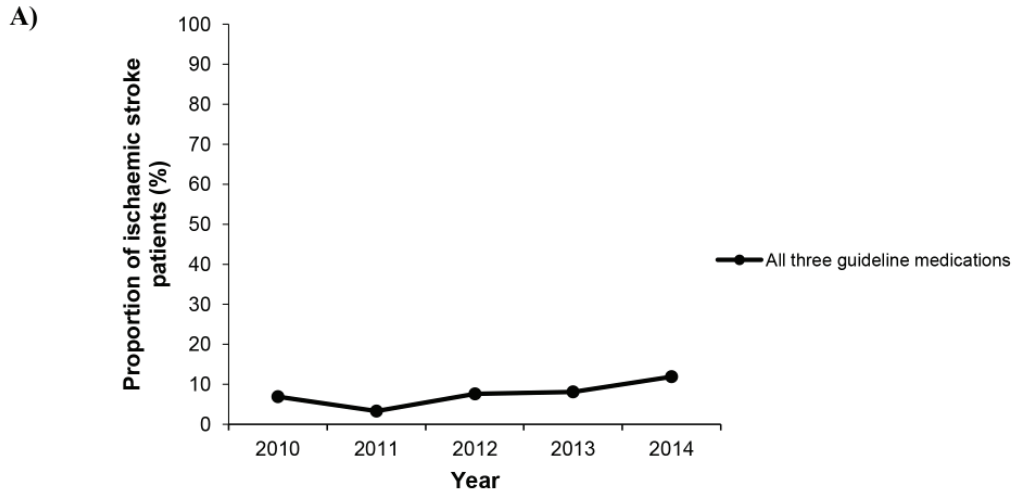
ICU: Intensive care unit; IQR: Interquartile range; LOS: Length of stay

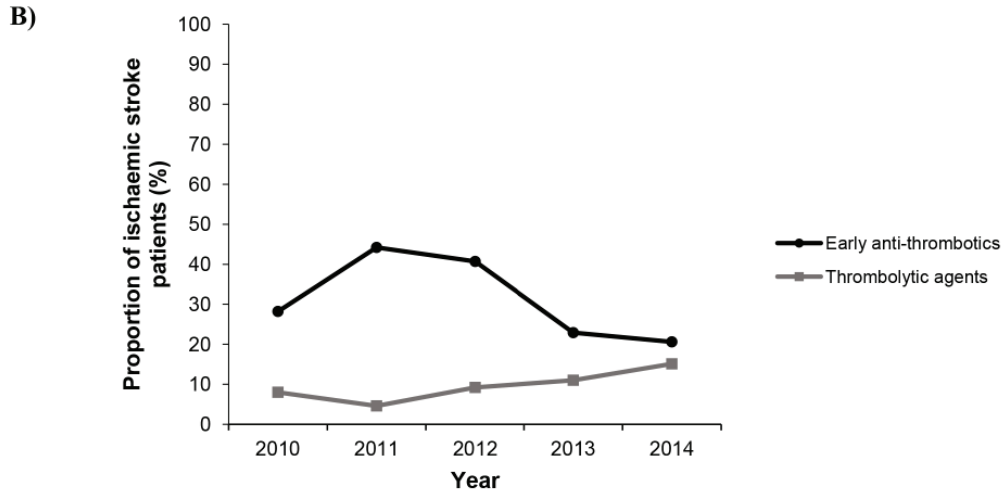
*Includes intracerebral haemorrhage and subarachnoid haemorrhage.

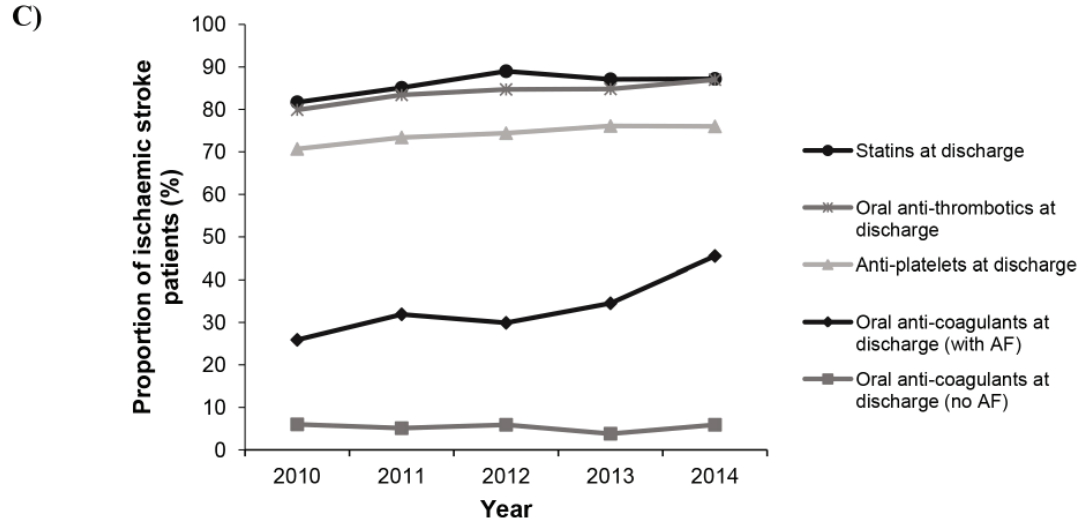
†Restricted to patients discharged alive from non-rehabilitation departments.

‡Patients admitted into class A and class B1 wards are considered private patients; those in class B2 and class C wards are considered subsidised patients (Source: Ministry of Health, Singapore. Hospital Services. 2018. Available at: https://www.moh.gov.sg/our-healthcare-system/healthcare-services-and-facilities/hospital-services. Accessed on 17 June 2019).

§Based on cardiovascular comorbidities, namely hypertension, hyperlipidaemia, diabetes mellitus, atrial fibrillation, coronary heart disease, heart failure and chronic kidney disease.


A)
Proportion of ischaemic stroke patients (%)
100
90
80
70
60
50
40
30
20
10
0
2010
2011
2012
2013
2014
Year
All three guideline medications


B)
Proportion of ischaemic stroke patients (%)
100
90
80
70
60
50
40
30
20
10
0
2010
2011
2012
2013
2014
Year
Early anti-thrombotics
Thrombolytic agents


C)
Proportion of ischaemic stroke patients (%)
100
90
80
70
60
50
40
30
20
10
0
2010
2011
2012
2013
2014
Year
Statins at discharge
Oral anti-thrombotics at discharge
Anti-platelets at discharge
Oral anti-coagulants at discharge (with AF)
Oral anti-coagulants at discharge (no AF)

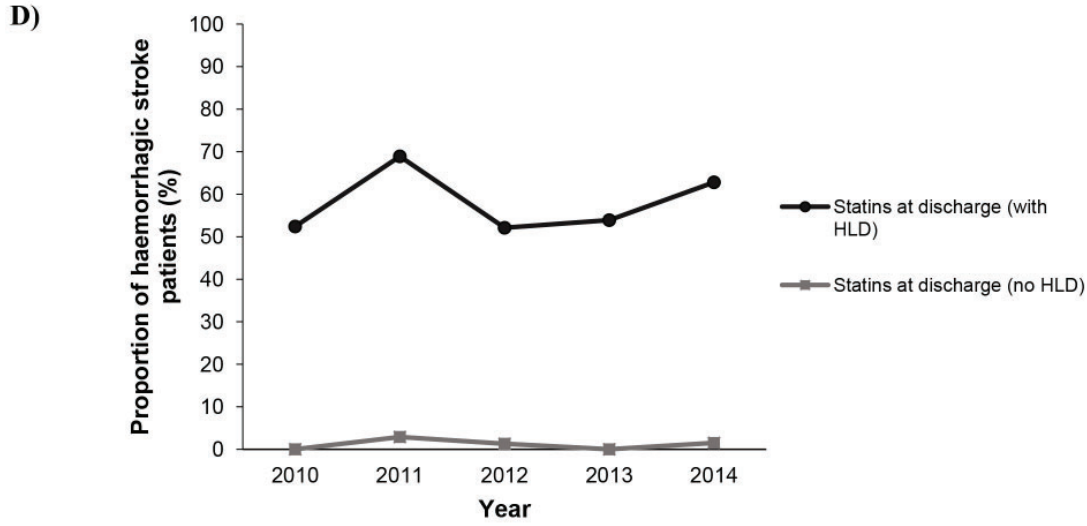


Fig. 2. Drug utilisation trends. A: Use of all 3 guideline medications (in-hospital thrombolytic agents, as well as antithrombotics and statins at discharge) in ischaemic stroke. B: In-hospital drug use in ischaemic stroke. C: Drugs prescribed at discharge in ischaemic stroke. D: Statins prescribed at discharge in haemorrhagic stroke. AF: Atrial fibrillation, HLD: Hyperlipidaemia

were 3.0-fold (95% CI: 1.66–5.28) and 5.3-fold (95% CI: 3.08–9.16) of 2010, respectively. Specifically, prescription of this dual antiplatelet combination after July 2013 was 2.9-fold (95% CI: 2.06–4.04) of the period before. Use of dipyridamole and aspirin-dipyridamole combination showed decreasing trends (P <0.001), while ticlopidine and clopidogrel-dipyridamole combination were almost negligible (Figs. 3A, 3B and Table 2).

Warfarin was the most prescribed oral anticoagulant at discharge (Fig. 3C), averaging 10.2% (P = 0.738) (Table 2). Use of the direct oral anticoagulants (DOACs), namely dabigatran, rivaroxaban and apixaban started in 2011, 2013 and 2014, respectively. In 2014, 10.8%, 2.6%, 2.4% and 0.6% of patients were prescribed warfarin, apixaban, rivaroxaban and dabigatran, respectively.

There was an increasing trend in the prescription of statins at discharge (P = 0.003) (Fig. 2C and Table 2). Simvastatin and atorvastatin were the most prescribed statins, with use averaging 68.4% and 19.8%, respectively (Fig. 4 and Table 2). Simvastatin utilisation declined from 76.6% in 2010 to 37.4% in 2014 (P <0.001), with prescription lower in 2013 (aOR = 0.60, 95% CI: 0.45–0.80) and 2014 (aOR = 0.17, 95% CI: 0.12–0.22), compared with 2010. Conversely, an increasing trend in atorvastatin prescription was observed from 4.2% in 2010 to 51.1% in 2014 (P <0.001). Utilisation of lovastatin and rosuvastatin were comparatively much lower, averaging 2.0% and 0.7%, respectively.

Predictors of Drug Utilisation in Ischaemic Stroke

Patients <85 years old, of Malay ethnicity, with hyperlipidaemia or AF, but without chronic kidney disease (CKD), were more likely to receive all 3 guideline medications (Table 3). Patients <75 years old, with AF or coronary heart disease (CHD), but without CKD, were more likely to be administered thrombolytic agents. Patients <65 years old, of Indian ethnicity, with hyperlipidaemia, but without hypertension or AF, were more likely to be prescribed early antithrombotics. Patients <75 years old, with hyperlipidaemia, without AF, without ICU admission or with shorter hospital LOS (≤8 days), were more likely to receive antiplatelets at discharge. Patients <65 years old, with AF or CHD, but without diabetes mellitus, were more likely to be prescribed oral anticoagulants at discharge. When restricted to only AF patients, age <75 years old, no diabetes mellitus and shorter hospital LOS (≤8 days) were predictors for oral anticoagulation use. Patients <85 years old, with hyperlipidaemia, without ICU admission or with shorter hospital LOS (≤8 days) were more likely to receive statins at discharge.

Temporal Trends of Statin Utilisation in Haemorrhagic Stroke

Prescription of statins at discharge averaged 34.8% (Fig. 2D and Table 2). A total of 57.7% of patients with hyperlipidaemia received statins.

Predictors of Statin Utilisation in Haemorrhagic Stroke

Patients with hyperlipidaemia, CHD or without ICU admission, were more likely to be prescribed statin therapy at discharge (Table 3). When restricted to those with hyperlipidaemia, CHD and without ICU admission remained as significant predictors.

Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for Drug Utilisation in Relation to Year of First-Ever Stroke Admission

Drug Use	2010 – 2014		n (%);‡ Adjusted OR (95% CI)§					*P* Value for Trend
	Overall n*	n (%)†	2010	2011	2012	2013	2014	
Ischaemic stroke								
All 3 guideline medications¶	2586	193 (7.5)	44 (6.9); Ref.	16 (3.3); 0.46 (0.25 – 0.83)#	39 (7.6); 1.08 (0.68 – 1.70)	39 (8.1); 1.20 (0.76 – 1.90)	55 (11.9); 1.89 (1.23 – 2.89)#	<0.001#
In-hospital drug utilisation								
Thrombolytic therapy	3410	320 (9.4)	66 (8.0); Ref.	30 (4.6); 0.55 (0.35 – 0.86)#	63 (9.2); 1.17 (0.81 – 1.69)	70 (11.0); 1.45 (1.01 – 2.08)#	91 (15.1); 2.09 (1.48 – 2.94)#	<0.001#
Early antithrombotic therapy**	3410	1072 (31.4)	232 (28.2); Ref.	291 (44.2); 2.15 (1.73 – 2.69)#	279 (40.7); 1.88 (1.51 – 2.35)#	146 (22.9); 0.80 (0.62 – 1.02)	124 (20.6); 0.71 (0.55 – 0.91)#	<0.001#
Drug utilisation at discharge¶								
Oral antithrombotic therapy	2586	2165 (83.7)	510 (79.9); Ref.	408 (83.4); 1.34 (0.96 – 1.85)	437 (84.7); 1.41 (1.02 – 1.95)#	408 (84.8); 1.39 (1.00 – 1.94)	402 (87.0); 1.94 (1.36 – 2.76)#	0.002#
Antiplatelet therapy	2586	1911 (73.9)	451 (70.7); Ref.	359 (73.4); 1.20 (0.91 – 1.60)	384 (74.4); 1.27 (0.95 – 1.68)	366 (76.1); 1.35 (1.01 – 1.80)#	351 (76.0); 1.57 (1.17 – 2.12)#	0.023#
Aspirin	2586	1386 (53.6)	329 (51.6); Ref.	252 (51.5); 1.04 (0.81 – 1.33)	298 (57.8); 1.33 (1.03 – 1.70)#	273 (56.8); 1.29 (1.00 – 1.66)	234 (50.6); 1.10 (0.85 – 1.42)	0.510
Clopidogrel	2586	683 (26.4)	139 (21.8); Ref.	131 (26.8); 1.32 (0.99 – 1.75)	105 (20.3); 0.96 (0.71 – 1.29)	131 (27.2); 1.32 (0.99 – 1.76)	177 (38.3); 2.29 (1.74 – 3.02)#	<0.001#
Dipyridamole	2586	152 (5.9)	70 (11.0); Ref.	36 (7.4); 0.62 (0.40 – 0.95)#	23 (4.5); 0.37 (0.23 – 0.60)#	12 (2.5); 0.20 (0.11 – 0.38)#	11 (2.4); 0.19 (0.10 – 0.36)#	<0.001#
Ticlopidine	2586	2 (0.1)	1 (0.2); NA	1 (0.2); NA	0 (0.0); NA	0 (0.0); NA	0 (0.0); NA	0.180

AF: Atrial fibrillation; CI: Confidence interval; OR: Odds ratio; Ref: Reference; NA: Not applicable

*Number of included patients between 2010–2014.

†Number and proportion (based on overall n) of patients who received the drug between 2010–2014.

‡Number and proportion of patients who received the drug in each year.

§Odds ratios were adjusted for sex, age, ethnicity, hospital ward class, hypertension, hyperlipidaemia, diabetes mellitus, atrial fibrillation, coronary heart disease, heart failure and chronic kidney disease, unless omitted due to collinearity. Regression was not performed if there were <5 patients prescribed with drug for any year.

‖All 3 guideline medications refer to in-hospital administration of thrombolytic agents, as well as prescription of antithrombotics and statins at discharge for ischaemic stroke.

¶Analyses restricted to patients discharged alive from non-rehabilitation departments.

#*P* <0.05.

**Early antithrombotic therapy includes oral antiplatelets, oral anticoagulants, heparin and low-molecular weight heparins prescribed within 3 days of admission.

††Cochran-Armitage test for trend was not performed as there was <2 years of drug use data.

Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for Drug Utilisation in Relation to Year of First-Ever Stroke Admission (Cont'd)

Drug Use	2010 – 2014		n (%);‡ Adjusted OR (95% CI)§					*P* Value for Trend
	Overall n*	n (%)†	2010	2011	2012	2013	2014	
Antiplatelet combinations								
Single antiplatelet	2586	1600 (61.9)	364 (57.1); Ref.	298 (60.9); 1.22 (0.95 – 1.56)	342 (66.3); 1.52 (1.18 – 1.96)#	316 (65.7); 1.46 (1.13 – 1.89)#	280 (60.6); 1.31 (1.01 – 1.69)#	0.040#
Dual antiplatelets	2586	310 (12.0)	86 (13.5); Ref.	61 (12.5); 0.90 (0.63 – 1.29)	42 (8.1); 0.58 (0.39 – 0.87)#	50 (10.4); 0.73 (0.50 – 1.07)	71 (15.4); 1.16 (0.82 – 1.65)	0.928
Aspirin and clopidogrel	2586	158 (6.1)	19 (3.0); Ref.	22 (4.5); 1.57 (0.83 – 2.96)	19 (3.7); 1.37 (0.71 – 2.64)	38 (7.9); 2.96 (1.66 – 5.28)#	60 (13.0); 5.31 (3.08 – 9.16)#	<0.001#
Aspirin and dipyridamole	2586	146 (5.6)	67 (10.5); Ref.	34 (7.0); 0.61 (0.39 – 0.94)#	22 (4.3); 0.37 (0.22 – 0.61)#	12 (2.5); 0.21 (0.11 – 0.39)#	11 (2.4); 0.20 (0.10 – 0.38)#	<0.001#
Clopidogrel and dipyridamole	2586	3 (0.1)	0 (0.0); NA	2 (0.4); NA	1 (0.2); NA	0 (0.0); NA	0 (0.0); NA	0.524
Oral anticoagulant therapy	2586	309 (11.9)	65 (10.2); Ref.	55 (11.2); 1.11 (0.73 – 1.69)	61 (11.8); 1.13 (0.75 – 1.70)	52 (10.8); 1.01 (0.66 – 1.55)	76 (16.5); 1.69 (1.14 – 2.51)#	0.009#
Warfarin	2586	263 (10.2)	65 (10.2); Ref.	53 (10.8); 1.08 (0.71 – 1.64)	56 (10.9); 1.03 (0.68 – 1.56)	39 (8.1); 0.70 (0.45 – 1.10)	50 (10.8); 0.95 (0.62 – 1.45)	0.738
Rivaroxaban	2586	19 (0.7)	0 (0.0); NA	0 (0.0); NA	0 (0.0); NA	8 (1.7); NA	11 (2.4); NA	<0.001#
Dabigatran	2586	16 (0.6)	0 (0.0); NA	2 (0.4); NA	6 (1.2); NA	5 (1.0); NA	3 (0.6); NA	0.050
Apixaban	2586	12 (0.5)	0 (0.0); NA	0 (0.0); NA	0 (0.0); NA	0 (0.0); NA	12 (2.6); NA	NA††

AF: Atrial fibrillation; CI: Confidence interval; OR: Odds ratio; Ref: Reference; NA: Not applicable

*Number of included patients between 2010–2014.

†Number and proportion (based on overall n) of patients who received the drug between 2010–2014.

‡Number and proportion of patients who received the drug in each year.

§Odds ratios were adjusted for sex, age, ethnicity, hospital ward class, hypertension, hyperlipidaemia, diabetes mellitus, atrial fibrillation, coronary heart disease, heart failure and chronic kidney disease, unless omitted due to collinearity. Regression was not performed if there were <5 patients prescribed with drug for any year.

‖All 3 guideline medications refer to in-hospital administration of thrombolytic agents, as well as prescription of antithrombotics and statins at discharge for ischaemic stroke.

¶Analyses restricted to patients discharged alive from non-rehabilitation departments.

#*P* <0.05.

**Early antithrombotic therapy includes oral antiplatelets, oral anticoagulants, heparin and low-molecular weight heparins prescribed within 3 days of admission.

††Cochran-Armitage test for trend was not performed as there was <2 years of drug use data.

Table 2. Adjusted Odds Ratios and 95% Confidence Intervals for Drug Utilisation in Relation to Year of First-Ever Stroke Admission (Cont'd)

Drug Use	2010 – 2014		n (%);‡ Adjusted OR (95% CI)§					*P* Value for Trend
	Overall n*	n (%)†	2010	2011	2012	2013	2014	
Oral anticoagulant therapy (restricted to AF patients	608	203 (33.4)	35 (25.9); Ref.	36 (31.9); 1.30 (0.72 – 2.35)	38 (29.9); 1.17 (0.66 – 2.08)	38 (34.5); 1.27 (0.71 – 2.29)	56 (45.5); 2.54 (1.44 – 4.46)#	0.002#
Oral anticoagulant therapy (restricted to non-AF patients)	1978	106 (5.4)	30 (6.0); Ref.	19 (5.1); 0.90 (0.49 – 1.66)	23 (5.9); 1.13 (0.63 – 2.02)	14 (3.8); 0.72 (0.37 – 1.40)	20 (5.9); 1.11 (0.61 – 2.04)	0.618
Statin therapy	2586	2218 (85.8)	521 (81.7); Ref.	416 (85.1); 1.28 (0.91 – 1.82)	459 (89.0); 1.76 (1.22 – 2.53)#	419 (87.1); 1.45 (1.01 – 2.07)#	403 (87.2); 1.95 (1.33 – 2.86)#	0.003#
Simvastatin	2586	1768 (68.4)	489 (76.6); Ref.	372 (76.1); 0.92 (0.68 – 1.24)	404 (78.3); 1.02 (0.75 – 1.37)	330 (68.6); 0.60 (0.45 – 0.80)#	173 (37.4); 0.17 (0.12 – 0.22)#	<0.001#
Atorvastatin	2586	512 (19.8)	27 (4.2); Ref.	65 (13.3); 3.65 (2.28 – 5.84)#	70 (13.6); 3.63 (2.28 – 5.78)#	114 (23.7); 7.35 (4.72 – 11.46)#	236 (51.1); 26.35 (17.08 – 40.67)#	<0.001#
Lovastatin	2586	52 (2.0)	18 (2.8); Ref.	13 (2.7); 0.90 (0.43 – 1.86)	9 (1.7); 0.60 (0.27 – 1.37)	7 (1.5); 0.46 (0.19 – 1.12)	5 (1.1); 0.34 (0.12 – 0.92)#	0.016#
Rosuvastatin	2586	18 (0.7)	3 (0.5); NA	2 (0.4); NA	4 (0.8); NA	4 (0.8); NA	5 (1.1); NA	0.161
Haemorrhagic stroke								
Drug utilisation at discharge¶								
Statin therapy	883	307 (34.8)	65 (31.1); Ref.	64 (40.3); 2.40 (1.34 – 4.29)#	51 (29.5); 1.06 (0.62 – 1.84)	55 (34.2); 0.98 (0.57 – 1.69)	72 (39.8); 1.69 (0.99 – 2.90)	0.249
Statin therapy (restricted to hyperlipidaemia patients)	525	303 (57.7)	65 (52.4); Ref.	62 (68.9); 2.24 (1.24 – 4.05)#	50 (52.1); 1.03 (0.59 – 1.80)	55 (53.9); 0.98 (0.56 – 1.70)	71 (62.8); 1.63 (0.94 – 2.82)	0.518
Statin therapy (restricted to non-hyperlipidaemia patients)	358	4 (1.1)	0 (0.0); NA	2 (2.9); NA	1 (1.3); NA	0 (0.0); NA	1 (1.5); NA	0.863

AF: Atrial fibrillation; CI: Confidence interval; OR: Odds ratio; Ref: Reference; NA: Not applicable

*Number of included patients between 2010–2014.

†Number and proportion (based on overall n) of patients who received the drug between 2010–2014.

‡Number and proportion of patients who received the drug in each year.

§Odds ratios were adjusted for sex, age, ethnicity, hospital ward class, hypertension, hyperlipidaemia, diabetes mellitus, atrial fibrillation, coronary heart disease, heart failure and chronic kidney disease, unless omitted due to collinearity. Regression was not performed if there were <5 patients prescribed with drug for any year.

‖All 3 guideline medications refer to in-hospital administration of thrombolytic agents, as well as prescription of antithrombotics and statins at discharge for ischaemic stroke.

¶Analyses restricted to patients discharged alive from non-rehabilitation departments.

#*P* <0.05.

**Early antithrombotic therapy includes oral antiplatelets, oral anticoagulants, heparin and low-molecular weight heparins prescribed within 3 days of admission.

††Cochran-Armitage test for trend was not performed as there was <2 years of drug use data.

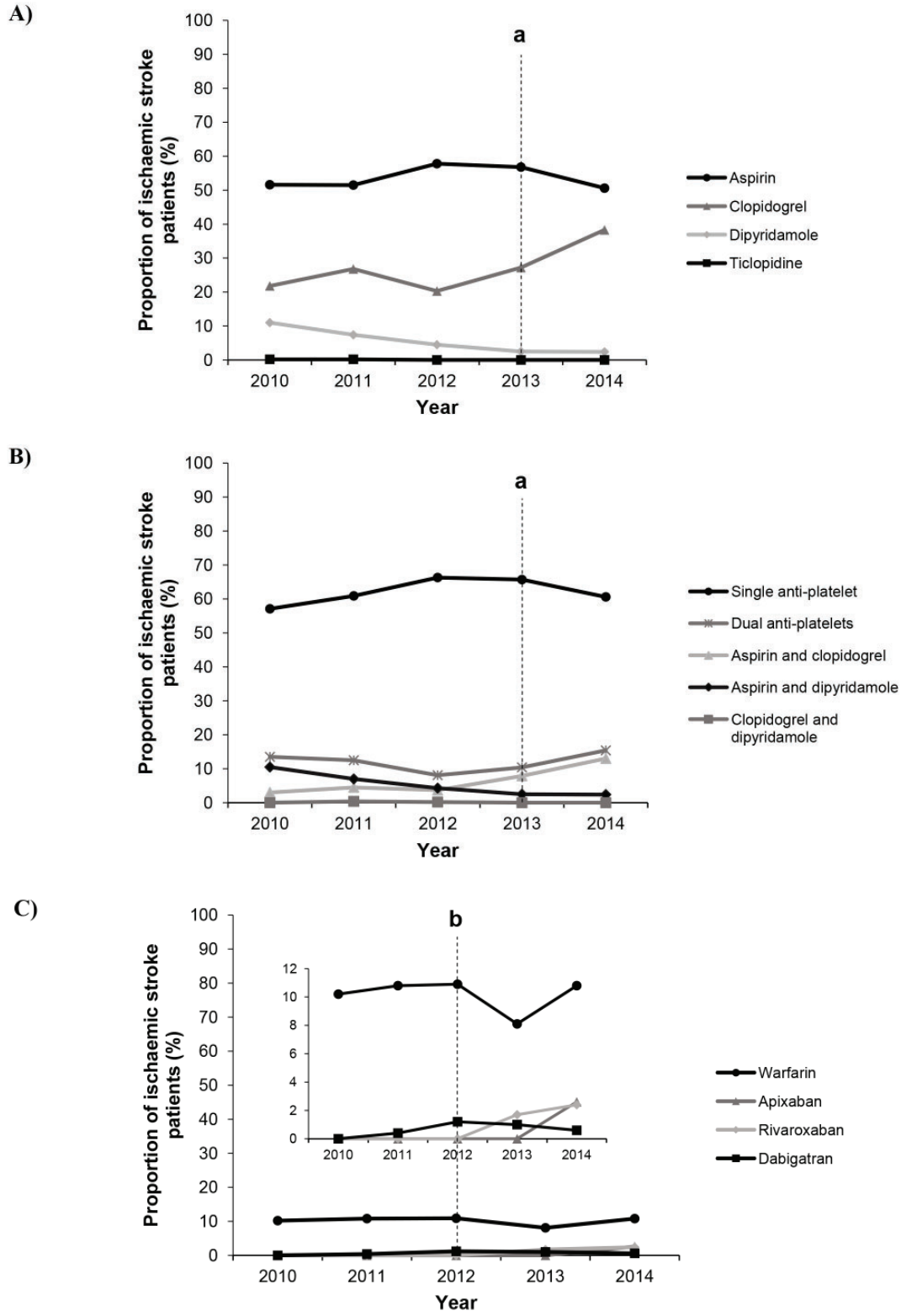


Fig. 3. Antithrombotic utilisation trends at discharge in ischaemic stroke. A: Specific antiplatelets. B: Selected antiplatelet combinations. C: Specific anticoagulants. The inset in C is presented on a different scale. Line "a" in graphs A and B points to the year in which results from the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial was published (i.e. July 2013), showing that the early use of aspirin and clopidogrel combination was superior to aspirin alone for reducing risk of stroke (Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369:11–9). Line "b" in graph C points to the year in which dabigatran, apixaban and rivaroxaban were added into the American Heart Association/American Stroke Association guidelines for prevention of stroke in patients with non-valvular atrial fibrillation (i.e. 2012) (Furie KL, Goldstein LB, Albers GW, Khatri P, Neyens R, Turakhia MP, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2012;43:3442–53).

Table 3. Predictors of Drug Utilisation Using Multivariable Logistic Regression

Drug Use	Overall n*	n (%)†	Predictor‡	Adjusted OR (95% CI)§
Ischaemic stroke				
All 3 guideline medications[l]	2586	193 (7.5)	Age group	
			18 – 64	Ref.
			65 – 74	0.87 (0.59 – 1.27)
			75 – 84	0.67 (0.44 – 1.01)
			≥85	0.32 (0.16 – 0.63)
			Ethnic group	
			Chinese	Ref.
			Malay	1.79 (1.21 – 2.64)
			Indian	1.19 (0.64 – 2.24)
			Others	1.10 (0.57 – 2.12)
			With hyperlipidaemia	4.72 (1.14 – 19.56)
			With atrial fibrillation	2.54 (1.82 – 3.57)
			With chronic kidney disease	0.60 (0.41 – 0.86)
Administration of thrombolytic agent	3410	320 (9.4)	Age group	
			18 – 64	Ref.
			65 – 74	0.93 (0.70 – 1.25)
			75 – 84	0.67 (0.49 – 0.93)
			≥85	0.38 (0.23 – 0.63)
			With atrial fibrillation	2.19 (1.69 – 2.84)
			With coronary heart disease	1.47 (1.12 – 1.94)
			With chronic kidney disease	0.61 (0.45 – 0.81)
Early antithrombotic therapy (within 3 days of admission)	3410	1072 (31.4)	Age group	
			18 – 64	Ref.
			65 – 74	0.81 (0.67 – 0.98)
			75 – 84	0.66 (0.54 – 0.81)
			≥85	0.49 (0.37 – 0.65)
			Ethnic group	
			Chinese	Ref.
			Malay	1.22 (0.97 – 1.53)
			Indian	1.40 (1.04 – 1.90)
			Others	1.28 (0.91 – 1.79)
			With hypertension	0.71 (0.59 – 0.84)
			With hyperlipidaemia	2.56 (1.65 – 3.97)
			With atrial fibrillation	0.76 (0.63 – 0.92)
Antiplatelet therapy at discharge	2586	1911 (73.9)	Age group	
			18 – 64	Ref.
			65 – 74	0.87 (0.67 – 1.13)
			75 – 84	0.77 (0.59 – 0.99)
			≥85	0.65 (0.47 – 0.89)

CI: Confidence interval; ICU: Intensive care unit; OR: Odds ratio; Ref: reference

*Number of patients included in model.

†Number and proportion (based on overall n) of patients who received the drug.

‡Unless otherwise stated, reference group comprised of patients who did not have the comorbidity or were not admitted to ICU.

§Odds ratios were adjusted for all covariates listed in the table, as well as year of admission to control for the effect of temporal changes in drug utilisation.

[l]All 3 guideline medications refer to in-hospital administration of thrombolytic agents, as well as prescription of antithrombotics and statins at discharge for ischaemic stroke.

Table 3. Predictors of Drug Utilisation Using Multivariable Logistic Regression (Cont'd)

Drug Use	Overall n*	n (%)†	Predictor‡	Adjusted OR (95% CI)§
			With hyperlipidaemia	4.10 (2.65 – 6.33)
			With atrial fibrillation	0.24 (0.20 – 0.30)
			With ICU admission	0.60 (0.44 – 0.81)
			Length of hospitalisation	
			≤8 days	Ref.
			>8 days	0.44 (0.36 – 0.54)
Ischaemic stroke				
Oral anticoagulant therapy at discharge	2586	309 (11.9)	Age group	
			18 – 64	Ref.
			65 – 74	0.61 (0.43 – 0.87)
			75 – 84	0.39 (0.27 – 0.56)
			≥85	0.13 (0.07 – 0.22)
			With diabetes mellitus	0.58 (0.44 – 0.77)
			With atrial fibrillation	12.35 (9.18 – 16.61)
			With coronary heart disease	1.58 (1.17 – 2.14)
Oral anticoagulant therapy at discharge (restricted to patients with atrial fibrillation)	608	203 (33.4)	Age group	
			18 – 64	Ref.
			65 – 74	0.82 (0.49 – 1.36)
			75 – 84	0.47 (0.28 – 0.77)
			≥85	0.14 (0.07 – 0.29)
			With diabetes mellitus	0.51 (0.35 – 0.75)
			Length of hospitalisation	
			≤8 days	Ref.
			>8 days	0.45 (0.31 – 0.66)
Statin therapy at discharge	2586	2218 (85.8)	Age group	
			18 – 64	Ref.
			65 – 74	0.86 (0.61 – 1.21)
			75 – 84	0.75 (0.54 – 1.04)
			≥85	0.39 (0.27 – 0.56)
			With hyperlipidaemia	27.32 (16.47 – 45.32)
			With ICU admission	0.53 (0.38 – 0.76)
			Length of hospitalisation	
			≤8 days	Ref.
			>8 days	0.32 (0.25 – 0.43)
Haemorrhagic stroke				
Statin therapy at discharge	883	307 (34.8)	With hyperlipidaemia	112.85 (41.21 – 309.02)
			With coronary heart disease	2.42 (1.46 – 4.01)
			With ICU admission	0.68 (0.47 – 0.96)
Statin therapy at discharge (restricted to patients with hyperlipidaemia)	525	303 (57.7)	With coronary heart disease	2.44 (1.47 – 4.06)
			With ICU admission	0.68 (0.47 – 0.97)

CI: Confidence interval; ICU: Intensive care unit; OR: Odds ratio; Ref: reference

*Number of patients included in model.

†Number and proportion (based on overall n) of patients who received the drug.

‡Unless otherwise stated, reference group comprised of patients who did not have the comorbidity or were not admitted to ICU.

§Odds ratios were adjusted for all covariates listed in the table, as well as year of admission to control for the effect of temporal changes in drug utilisation.

[l]All 3 guideline medications refer to in-hospital administration of thrombolytic agents, as well as prescription of antithrombotics and statins at discharge for ischaemic stroke.

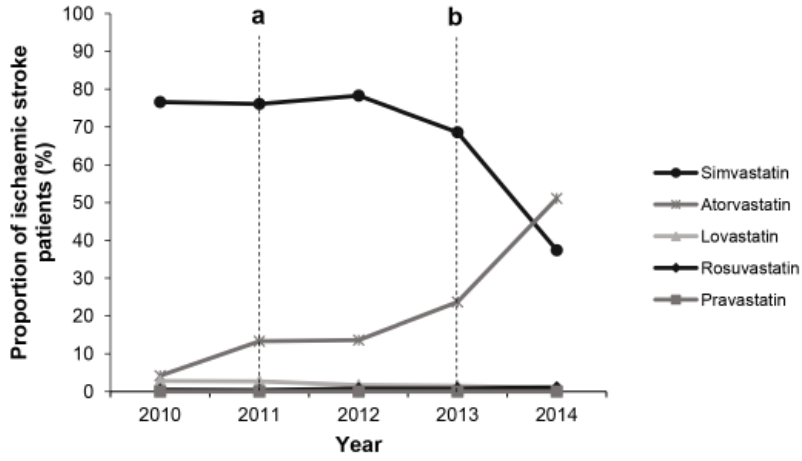


Fig. 4. Trends in specific statin prescribed at discharge for ischaemic stroke patients. Line "a" indicates the year in which the treatment goal for low-density lipoprotein-C was modified from <2.6 mmol/L to a reduction of at least 50% or <1.8 mmol/L in the American Heart Association/American Stroke Association guidelines (i.e. 2011) (Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke 2008;39:1647–52; Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:227–76). Patent for atorvastatin (Lipitor®) also expired in 2011 (Loch A, Bewersdorf JP, Kofink D, Ismail D, Abidin IZ, Veriah RS. Generic atorvastatin is as effective as the brand-name drug (LIPITOR®) in lowering cholesterol levels: a cross-sectional retrospective cohort study. BMC Res Notes 2017;10:291). Line "b" indicates the year in which guidelines from the American College of Cardiology/American Heart Association were published (i.e. 2013) on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults (including stroke), encouraging use of high-intensity statin therapy (Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S1–45).

Discussion

This study examined temporal trends and patient characteristics associated with drug utilisation among first-ever stroke patients admitted to 2 Singapore tertiary hospitals from 2010–2014. The increased use of all 3 guideline medications in ischaemic stroke was driven by increasing in-hospital use of thrombolytic agents, prescription of oral antithrombotics and statins at discharge. Younger patients, of Malay ethnicity, with hyperlipidaemia or AF but without CKD, were more likely to receive all 3 guideline medications. Among the antithrombotics, clopidogrel and combined aspirin-clopidogrel use had increased. For statins, the increase in atorvastatin prescription was accompanied by decreasing use of simvastatin. In haemorrhagic stroke, prescription of statins at discharge was expectedly lower than in ischaemic stroke.

Alteplase, a recombinant tissue plasminogen activator (rtPA), has been approved for treatment of acute ischaemic stroke since 1996.[2,14] As the benefit of thrombolysis diminishes over time, it was initially recommended within 3 hours of stroke-onset.[15] Delayed hospital arrival could reduce the number of eligible patients for thrombolysis.[16] The European Cooperative Acute Stroke Study (ECASS)-3 (published in 2008) provided evidence that intravenous rtPA could be safely administered to selected patients 3–4.5 hours after stroke.[17] An advisory was subsequently published by AHA/ASA, expanding the time window for thrombolytic therapy in 2009.[18] The observed increased utilisation of rtPA in our study was encouraging and could be attributed to both national and local efforts promoting its use. Guidelines from the Ministry of Health, Singapore were published in 2013, recommending treatment within 4.5 hours poststroke in centres with appropriate facilities and expertise.[19] Reorganisation of hospital acute stroke services, implementation of drug protocols and identification of ischaemic stroke patients quickly in the emergency department could have resulted in more patients meeting the therapeutic time window.

The cumulative risk of stroke recurrence is high and antiplatelets are the cornerstone of secondary ischaemic stroke prevention.[20] Prior to 2014, the AHA/ASA guidelines recommended aspirin, aspirin-dipyridamole combination and clopidogrel as options for initial therapy, while use of aspirin-clopidogrel combination was discouraged due to increased risk of haemorrhage.[21] In our study, we observed increased prescription of aspirin-clopidogrel combination in 2013 and 2014 over 2010, coinciding with publication of the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial in July 2013. The CHANCE trial included Chinese patients with minor ischaemic stroke or transient ischaemic attack, and showed that treatment with aspirin-clopidogrel combination for 21 days, followed by clopidogrel alone for a total of 90 days, was superior to aspirin alone in reducing stroke

recurrence.[22] While the AHA/ASA updated the guidelines only in the subsequent year to incorporate findings from the trial,[1] prescription of the drug combination had increased ahead of guideline changes. Increasing use of clopidogrel could also be attributed to expiration of its patent in 2012.[23]

Anticoagulants have better efficacy than antiplatelets for prevention of cardioembolic stroke due to AF.[24,25] Although we observed an increasing trend for prescription of oral anticoagulants for AF patients, the average use of 33.4% was lower than other Western countries such as Australia (57.4%)[26] and the US (91.1%).[27] Concerns over bleeding complications including haemorrhagic conversion may explain the lower utilisation of oral anticoagulants in our ischaemic stroke population, as some evidence has suggested that risk of bleeding is higher for Asians than non-Asians.[28,29] For many years, warfarin was the only oral anticoagulant available. Other approved DOACs were subsequently added to the AHA/ASA guidelines in 2012.[30] These newer agents have several advantages over warfarin, including reduced risk of intracranial haemorrhage, need for monitoring and potential for drug-drug or drug-food interactions.[31] However, higher costs of DOACs relative to warfarin could hinder utilisation in clinical practice. Between 2010–2014, warfarin was the predominant anticoagulant prescribed. With granting of government subsidies, and costs of DOACs to patients reduced,[32] there were subsequent greater utilisation of DOACs. Despite apixaban being the latest DOAC to be approved, its use had overtaken rivaroxaban and dabigatran in 2014. Practical considerations may have favoured the prescribing of apixaban over other DOACs. Dabigatran capsules cannot be broken, making it unsuitable for patients on enteral tube feeding that requires crushing or dissolution of medications.[33] Dabigatran also interacts with acid suppressants,[34] which may often be prescribed concomitantly with antithrombotics for gastric protection.[35] While randomised trials had reported that DOACs were non-inferior to warfarin in reducing stroke risk, apixaban was the only DOAC associated with a significantly lower rate of major bleeding.[36]

In 2011, the treatment goal for low-density lipoprotein-C (LDL-C) was modified from <2.6 mmol/L to a reduction of at least 50% or <1.8 mmol/L in the AHA/ASA guidelines.[21,37] Subsequently in 2013 and 2014, guidelines were revised to recommend statins to all patients with stroke secondary to atherosclerosis, encouraging use of high-intensity therapies which can potentially lower LDL-C by ≥50%.[1,3] Atorvastatin (40–80 mg/day) and rosuvastatin (20–40 mg/day) are considered high-intensity therapies, while simvastatin, lovastatin and pravastatin are considered low- to moderate-intensity therapies at their recommended doses.[3] In our study, there was an increasing trend in prescription of atorvastatin, while the inverse was observed for simvastatin. Based on the guideline changes,[1,3,21,37] prescription of higher potency statins is expected to rise. Although atorvastatin prescription had increased from 4.2% in 2010 to 51.1% in 2014, utilisation of rosuvastatin remained low. This preferential prescription of atorvastatin could be explained by the coincidental patent expiration for atorvastatin (Lipitor®) in 2011 that allowed generics to enter the market.[38] Conversely, the patent for rosuvastatin (Crestor®) remained in force during the study period.[39] Future studies could examine change in rosuvastatin use, after its patent expiration in 2016.[39] The reduced utilisation of simvastatin may also be due to safety alerts from the US Food and Drug Administration in 2011[40] and Health Sciences Authority of Singapore in 2012[41] to avoid use of the highest approved dose of simvastatin (80 mg) due to greater risk of myopathy, prompting physicians to switch to prescribing other statins.

Our results showed significant associations between ethnicity and drug utilisation in ischaemic stroke. Compared with Chinese, Malays were more likely to receive all 3 guideline medications, while Indians were more likely to receive early antithrombotics. Previous studies conducted in the US had also reported ethnicity to be a significant predictor for drug use in stroke.[7,42–45] Access to specialised medical facilities, socioeconomic status, time to hospital arrival, stroke severity and drug contraindications, could differ by ethnicity and hence explain for the observed differences in drug utilisation.[7,42–45] In addition, based on the General Household Survey 2015 in Singapore, Malay residents aged ≥65 years old (69.8%) were more likely to live with their children and less likely to live alone, compared with Chinese (60.6%) and Indians (60.8%).[46] The higher level of caregiver support in the Malays could be another possible reason why they were more likely to receive all 3 guideline medications. A prospective study will be more suitable to evaluate how ethnicity and social factors influence drug utilisation, as such information on caregiver support and family structure are not routinely captured in the NHG CDMS.

In our study, ICU admission and longer hospital LOS reduced the likelihood for prescription of antiplatelets and statins at discharge. An earlier stroke study had reported that ICU admission was significantly associated with increased 30-day and 1-year mortality, while longer LOS increased death risk within 1 year.[47] Patients who had ICU admission or longer LOS may have poorer prognosis after hospital discharge. Hence, these patients could be considered by physicians as less likely to benefit from use of secondary stroke preventive medications.

The study's limitations include the reliance of our findings on the completeness of data in the NHG CDMS. We were unable to perform more in-depth analyses as information on drug doses and duration were not available. Data on

some variables which may influence drug utilisation such as education level, stroke severity, poststroke functional independence and cognition were also not captured. Physicians may consider these factors when prescribing drugs, as they impact the patient's ability to manage medications after hospital discharge.[26] In addition, some surgical procedures, such as decompressive surgery of large infarcts, may delay early prescription of antithrombotics in ischaemic stroke; however, this information was not captured in NHG CDMS. In our study, while we used hospital ward class as a proxy for patients' socioeconomic status, this may not be an accurate reflection as ward class may be influenced by personal preferences, insurance coverage and employment benefits. Furthermore, while we used ICU admission and hospital LOS as proxies for stroke severity, other unmeasured confounders could have affected the regression results. As we excluded patients who died or were discharged from rehabilitation departments, patients included in our study may have milder stroke or different distribution of risk factors. Future studies could also examine the use of antihypertensive therapy which could be beneficial for haemorrhagic stroke patients.

Conclusion

Among first-ever stroke patients admitted to 2 tertiary hospitals in Singapore between 2010–2014, the observed temporal trends in medication prescribing could be explained by guideline changes, publication of new evidence and availability of generic drugs. In ischaemic stroke, the increased combined utilisation of all 3 guideline medications was due to increased prescription of thrombolytic therapy, oral antithrombotics and statins. There was a trend for a switch from low-intensity statins to atorvastatin, and from single antiplatelet to dual antiplatelet combination during the acute stroke hospitalisation. Similarly, anticoagulation use had increased—specifically prescription of the DOACs among AF patients. Patient characteristics associated with use of all 3 guideline medications included age, ethnicity and certain comorbidities (hyperlipidaemia, AF and CKD). Prescription of statins in haemorrhagic stroke were expectedly lower, as they are not routinely recommended except for patients with comorbidities such as hyperlipidaemia and CHD. Additional information such as stroke severity should be included in future research examining predictors of drug utilisation.

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Supplementary Table 1. International Classification of Diseases 9th Revision Clinical Modification Codes Used for Case Identification

Code	Description
430	Subarachnoid haemorrhage
431	Intracerebral haemorrhage
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
434.01	Cerebral thrombosis with cerebral infarction
434.11	Cerebral embolism with cerebral infarction
434.91	Cerebral artery occlusion, unspecified with cerebral infarction
437.1	Other generalised ischaemic cerebrovascular disease

Supplementary Table 2. International Classification of Diseases 10th Revision Australian Modification Codes Used for Case Identification

Code	Description
I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation
I60.1	Subarachnoid haemorrhage from middle cerebral artery
I60.2	Subarachnoid haemorrhage from anterior communicating artery
I60.3	Subarachnoid haemorrhage from posterior communicating artery
I60.4	Subarachnoid haemorrhage from basilar artery
I60.5	Subarachnoid haemorrhage from vertebral artery
I60.6	Subarachnoid haemorrhage from other intracranial arteries
I60.7	Subarachnoid haemorrhage from intracranial artery, unspecified
I60.8	Other subarachnoid haemorrhage
I60.9	Subarachnoid haemorrhage, unspecified
I61.0	Intracerebral haemorrhage in hemisphere, subcortical
I61.1	Intracerebral haemorrhage in hemisphere, cortical
I61.2	Intracerebral haemorrhage in hemisphere, unspecified
I61.3	Intracerebral haemorrhage in brain stem
I61.4	Intracerebral haemorrhage in cerebellum
I61.5	Intracerebral haemorrhage, intraventricular
I61.8	Other intracerebral haemorrhage
I61.9	Intracerebral haemorrhage, unspecified
I63.0	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	Cerebral infarction due to embolism of precerebral arteries
I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, non-pyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I66.0	Occlusion and stenosis of middle cerebral artery
I66.2	Occlusion and stenosis of posterior cerebral artery
I66.3	Occlusion and stenosis of cerebellar arteries
I66.8	Occlusion and stenosis of other cerebral artery
I66.9	Occlusion and stenosis of unspecified cerebral artery

Supplementary Table 3. International Classification of Diseases 9th Revision Clinical Modification Codes Used for Case Exclusion

Code	Description
436	Acute, but ill-defined, cerebrovascular disease
437	Other and ill-defined cerebrovascular disease
437.5	Moyamoya disease
437.6	Non-pyogenic thrombosis of intracranial venous sinus
437.8	Other ill-defined cerebrovascular disease
437.9	Unspecified cerebrovascular disease

Supplementary Table 4. International Classification of Diseases 10th Revision Australian Modification Codes Used for Case Exclusion

Code	Description
I62.1	Non-traumatic extradural haemorrhage
I64	Stroke, not specified as haemorrhage or infarction
I67.5	Moyamoya disease
I67.6	Non-pyogenic thrombosis of intracranial venous system
I67.8	Other specified cerebrovascular diseases
I67.9	Cerebrovascular disease, unspecified

Supplementary Table 5. Drug Classes and Specific Drugs Included in Study

Drug Class	Specific Drug
Thrombolytic agents	Alteplase
Antiplatelets	Aspirin
	Clopidogrel
	Dipyridamole
	Ticlopidine
Oral anticoagulants	Apixaban
	Dabigatran
	Rivaroxaban
	Warfarin
Parenteral anticoagulants	Heparin
	Enoxaparin
	Nadroparin
Statins	Atorvastatin
	Lovastatin
	Pravastatin
	Rosuvastatin
	Simvastatin

Commentary

Mental Health Strategies to Combat the Psychological Impact of Coronavirus Disease 2019 (COVID-19) Beyond Paranoia and Panic

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On 30 January 2020, the World Health Organization (WHO) declared the outbreak of coronavirus disease 2019 (COVID-19) an international public health emergency after the number of cases soared across 34 regions in Mainland China and surpassed that of severe acute respiratory syndrome (SARS) in 2003. The virus was believed to have originated from a wholesale seafood market in the city of Wuhan in the province of Hubei towards the end of December 2019. Shortly after, the number of cases increased exponentially in Wuhan and nearby cities and provinces before spreading throughout the world.

Located approximately 3432 km from the epicentre of Wuhan, Singapore is a densely populated city-state of 5.7 million who saw 1,592,612 international visitors in 2019; of these, 380,933 were visitors from Mainland China.[1] After a tourist from Wuhan was identified as the first case of COVID-19 infection on 23 January 2020 in Singapore, the country responded decisively by initiating a series of public health measures to contain the outbreak that included travel advisories, restriction of entry into the country by individuals who had travelled to Mainland China in the preceding 2 weeks, mandatory quarantine for contact cases and rigorous contact tracing of individuals linked to confirmed COVID-19 cases.

On 7 February 2020, Singapore raised the Disease Outbreak Response System Condition (DORSCON) —a colour-coded framework that maps the current disease situation in the country—from Yellow to Orange after there was confirmatory evidence of community transmission of the virus involving several confirmed COVID-19 patients who were not linked to any existing cases and had no travel history to China. At the Orange level, the outbreak is deemed to have moderate to high impact on the health of the public. The last time it was raised to Orange was during the H1N1 flu pandemic in 2009, and would also have been the case during the SARS outbreak in 2003 had it been in place.

After DORSCON was raised to Orange, it triggered off—on the same day—widespread panic buying of food items and toiletries across the country, leading many stores to run out of supplies at short notice. This phenomenon was attributed to the intentions of locals who wanted to stock up on groceries after they feared exposure to heightened viral transmission. Additionally, the Ministerial Task Force that was convened to manage the COVID-19 outbreak had suggested the country needed to be psychologically prepared for the fallout from the current outbreak to be worse than the 2003 SARS crisis. The magnitude of fear and uncertainty among the public was so excessive that it prompted the Prime Minister of Singapore to address the public and reassure them that the country has adequate food supplies, while at the same time urging calm and prudence with their purchases. The response of locals to the pandemic, which has been likened to mass hysteria and paranoia, has led many to question their mental health and resilience.

More than a month into the current pandemic, 77,816 people from around the world have been infected as of 22 February 2020, of which 21,147 have recovered from the illness and 2360 have died.[2] Outside Mainland China, 32 countries and territories were affected, with Singapore ranked third as having the most number of confirmed COVID-19 cases after South Korea and Japan. Of the 86 cases that were tested positive for the virus with real-time reverse transcriptase-polymerase chain reaction, 47 patients had recovered and been discharged.[3]

In an infectious disease outbreak, the mounting fear that is aroused in individuals is a common phenomenon and can lead to erratic behaviour in them. It can afflict anyone irrespective of gender and sociodemographic status. This is true of COVID-19, especially when there is still much speculation surrounding its mode of transmission and the disease is spreading at an unparalleled rate with no definitive treatment in sight. In the early days of the COVID-19 outbreak in Mainland China, a survey

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found that 53.8% of respondents rated the psychological impact of the outbreak as moderate or severe, 16.5% reported moderate to severe depressive symptoms, 28.8% reported moderate to severe anxiety symptoms, and 8.1% reported moderate to severe stress levels.[4] Compared to the SARS outbreak 17 years ago, the fear among the public was even more palpable as increased air travel and entrenched global connectedness made the spread of COVID-19 appeared much more rampant. Extensive coverage of the pandemic by the mass media also influences the physical and psychological response of the public to the infectious disease threat, which may amplify their apprehension even when it is used to encourage them to take precautionary and preventive measures to protect themselves from the virus.[5,6]

Research has demonstrated the wide and profound psychological impact outbreaks can have on people. For individuals without mental illness, an outbreak can induce psychiatric symptoms; in those with pre-existing mental illnesses, their conditions could be aggravated and cause distress to their caregivers. Regardless of exposure, individuals may experience fear and anxiety of falling ill or dying, helplessness or blame those who are ill, which can potentially trigger off a mental breakdown.[7] Significant psychiatric morbidities have been found to vary from anxiety, depression, panic attacks, somatic symptoms and post-traumatic stress disorder (PTSD) to delirium, psychosis and even suicidality,[7–9] and have been associated with younger age and increased self-blame.[10]

In those who are grieving the sudden and traumatic loss of loved ones from the current outbreak, an inability to gain closure can lead to anger and resentment.[11] In patients and those who are quarantined, they may experience guilt, shame or stigma. Studies have reported high prevalence of psychological distress in those who undergo a longer period of quarantine, and it is also associated with increased PTSD prevalence that is correlated with depressive symptoms.[12] In the community, there is distrust of others in terms of disease spread and the capability of the authorities and health services to contain the outbreak. With cessation of community services and collapse of work industries that impact adversely on the economy, many individuals incur financial losses and run the risk of unemployment, further intensifying the negative emotions experienced by them.[13]

At the international level, communities that have been affected by the outbreak may be targeted for blame and stigma by other countries over fear of infection and this may impede cross-national trade and fuel further unrest. Since emotions can be amplified by pre-existing depressive and anxiety disorders and lead to increased rumination on contracting the virus, the behaviour and social interactions of individuals with others can be profoundly remodelled.

Psychological responses are associated with particular health-seeking behaviours. In a community survey of uninfected individuals during the SARS crisis in Hong Kong, it was found that those with a moderate level of anxiety and stronger perception of risk of contracting SARS were more likely to take comprehensive, precautionary measures to protect themselves from the virus.[14] Nonetheless, the feelings of helplessness and anxiety can often motivate individuals to resort to the use of unproven methods and remedies that may prove detrimental to their health.

Medical responders—including first responders such as paramedics and ambulance personnel—and healthcare workers (HCWs) have been found to display heightened stress and become emotionally affected and traumatised, and they also experience higher levels of anxiety and depression.[15] This is understandable since the anxiety and fear of becoming infected is higher from greater risk of increased exposure. There is also fear of infecting their loved ones and children. The delicate balance between the call of professional duty, altruism and fear for oneself and others often causes conflict and dissonance in many HCWs.[16]

Studies have shown that HCWs who work in emergency departments, intensive care units and isolation wards have a greater risk of developing adverse psychiatric outcomes than those from other job departments. This could be attributed to their direct exposure to infected patients and the demanding nature of their work.[17] A study from Singapore reported that doctors and those who were single were at a higher risk of developing psychiatric symptoms than nurses and those who were married.[18] A systematic review of the impact a disaster can have on the mental health of HCWs has identified common risk factors for the development of psychological morbidities that include lack of social support and communication, maladaptive coping and lack of training.[17]

During pandemics, the focus of public health authorities and the mass media is on biological and physical repercussions of the outbreak than on mental health issues. However, with a growing number of reports on the increasing mental health burden caused by the COVID-19 outbreak, there have been more calls for measures to enhance mental health support for the public. On 27 January 2020, the National Health Commission in Mainland China issued the first comprehensive guidelines on emergency psychological crisis intervention in individuals who were affected

by COVID-19;[19] the emphasis was on delivery of mental health support services to patients and HCW by multidisciplinary teams that consisted of mental health professionals.

In Singapore, psychological defence is one of 5 pillars in her Total Defence strategy to maintain faith and trust between the population and her government during a national crisis and to shore up resilience. Throughout this pandemic, the government and its health authority, the Ministry of Health, have kept the public abreast on the progress of the outbreak with regular news broadcasts and announcements on social media. These include daily updates such as the number of new and current infections, patients who are in critical condition or have been discharged and preventive measures. Social media channels have also been set up by the state to curb the spread of false information and "fake news". Regular dialogue with Cabinet Ministers and infectious diseases physicians is aired to clear doubts.

Before the current pandemic, Singapore has an established network of mental health services to meet the mental health needs of her population. They range from psychiatric clinics in all public hospitals and some polyclinics to private psychiatric and psychotherapy clinics and family service centres. Nevertheless, there are no national guidelines to support the mental health of the nation during the COVID-19 outbreak. To strengthen the mental health strategy of the country, 6 critical areas are identified that involve psychiatrists in specific roles. The following discussion will also help incumbent governments, hospitals and communities overseas to manage mass hysteria and paranoia that follows an outbreak and after viral transmission has occurred in the community.

Identification of High-Risk Groups

Health authorities must identify vulnerable groups in the community who are at high risk of psychological morbidities and target them for early psychological interventions. Additionally, foreigners who have been quarantined or isolated in hospitals are at increased risk of psychiatric episodes since they have been deprived of social support and face the risk of being repatriated back to their countries of origin. Consequently, they will benefit from practical and emotional support. Although there is a proliferation of medical studies on COVID-19, very few have examined the psychological impact the disease has on individuals.

In their study of 1210 Chinese residents in the 2 weeks that followed the outbreak of COVID-19 in Mainland China, Wang et al found that women reported higher levels of anxiety, depression and stress.[4] Their finding corroborated previous epidemiological studies that found women have an elevated risk of depression[20] which could be attributed to their unique biology and socioeconomic factors.[21] Although Wang et al also highlighted that students suffered greater psychological distress, this finding could be attributed to the closure of schools in Mainland China for an indefinite period and might not be generalisable to Singapore.

Nevertheless, should the situation in Singapore deteriorate and necessitate the closure of schools, the mental well-being of students in the country would merit study. Consequently, it is important that psychiatrists and public health experts undertake local epidemiological research so that their findings can provide a basis to introduce appropriate and targeted interventions.

Improved Screening of Psychiatric Morbidities

The finite number of mental health professionals in the country has made it essential that all physicians, particularly family and Emergency Department physicians, proactively screen patients for psychological issues when the latter visit them. The study by Wang et al had found that patients who presented with physical symptoms such as chills, coryza, cough, dizziness, myalgia and sore throat, those who rated their own health as poor and had a history of chronic illnesses were correlated with higher levels of anxiety, depression and stress that were attributed to the psychological impact of the outbreak.[4] This is understandable since the symptoms of COVID-19 are non-specific and difficult to distinguish from other viral illnesses.[22]

In the early stages of the disease, little is known about the characteristics of the virus in terms of its mode of transmission, virulence and transmissibility. This lack of understanding has fuelled further anxiety and uncertainty. It is therefore necessary to screen individuals for any history of psychiatric disorders and whether they have young children. This is because the psychological health of parents may be affected when they become fearful of the risk of infecting their own children.

To aid them in evaluating the mental state of their patients and those who are under quarantine, health professionals can consider the use of standard instruments such as the Impact of Event Scale-Revised that was used during public health crises in Singapore in the past.[10,23] They can also leverage on smartphone technology to do so.[24] Physicians can make use of the opportunity to provide patients with resources on psychological support and, when needed, refer them to psychiatrists for further evaluation and management.

Mode and Content of Psychological Intervention

In their efforts to curb the spread of COVID-19 that may result from face-to-face contact and therapy, several hospitals have launched online psychotherapy to manage psychiatric patients on video conferencing platforms such as Zoom. To address the needs of the general population during this pandemic, it is worthwhile to contemplate the introduction of online or smartphone-based psychoeducation on the outbreak to promote mental wellness and psychological interventions such as cognitive behavioural therapy (CBT) and mindfulness-based cognitive therapy (MBCT).

In patients who exaggerate the risk of contracting and dying from COVID-19, CBT may challenge their cognitive biases. Although behavioural therapy can help them to combat anxiety with the use of relaxation techniques and prevent depression onset by altering the schedule of their routine activities, CBT can mitigate maladaptive coping behaviours such as avoidance, antagonistic confrontation and self-blame by enhancing their ability to manage stress. Maladaptive coping behaviours are associated with worse psychological outcomes.[10,25]

MBCT, which focuses on the use of various mindfulness meditation practices to cultivate non-judgemental awareness in the present, have been found to be particularly helpful in alleviating stress in people with physical conditions.[26] When it is hosted on virtual platforms, MBCT can benefit patients who are infected and nursed in isolation rooms as well as those who are quarantined at home with no access to mental health professionals. Online platforms could also be a means for individuals to provide peer support to each other and to share their challenges and resolutions during the outbreak to foster comradeship and resilience in them.

More Support for Frontline Health Workers

It is important to safeguard the morale and mental health of HCWs since they can impact the outcome and success of delivery of health services.[27] Health facilities may consider shorter work hours, regular rest periods and rotating shifts for staff who work in high-risk jobs. It has been found that support from colleagues and supervisors and clear communication of directives and precautionary measures can reduce psychiatric symptoms.[18] Confidence in infection control measures may also mitigate and facilitate adaptive stress response.[28] Consequently, it is imperative to provide staff with adequate training on infection control. Hospital directives and protocols on COVID-19 should be clear, precise and disseminated to all staff.

Preventive measures must be put in place to ensure that HCWs do not become infected with the virus while at work. When they are infected, such incidents should be treated as work-related injuries. Their superiors can make a conscious effort to support staff and to set up a peer support system. It is vital to identify staff who suffers from work exhaustion or psychological distress so that timely intervention can be provided to them, and they should be encouraged to report their condition or mental state without fear of being blamed for doing so.

Accurate Dissemination of Health and Related Information to the Public

To minimise the detrimental impact of "fake news" that is so rampant in the social media, the government and health authorities must relay to the public timely and accurate evidence-based information on the pandemic through traditional and new media. Practical tips on how the public should react during the outbreak—such as the practice of good hygiene and donning of surgical mask—and manage fear and uncertainty of the virus—through positive reframing, stress management and relaxation techniques—can be disseminated to the public through video clips and cartoons that can be easily understood by them. Higher levels of satisfaction with existing health information have been found to correlate with lower psychological distress in individuals.

Accurate and updated information on the number of recovered cases, treatment (such as medicine or vaccine) and mode of transmission as well as regualr updates on the number of infected cases and localities (such as real-time or virtual map) are associated with lower stress and anxiety, respectively.[4] When individuals have access to adequate information and have sufficient trust in the government and health authorities to manage COVID-19, this could potentially reduce their anxiety and perceived vulnerability to the virus.[29] With growing confidence in the measures introduced by the authorities, there is better adherence to precautionary and preventive measures that will encourage the wider community to work together to combat the outbreak.

The government, community leaders and health facilities also play a vital role to maintain racial harmony to prevent discrimination and stigma that accompany an outbreak.[30] In the current pandemic, there are reports of xenophobic attacks against individuals of Asian descent that included refusals to be seated next to them on public transport, refused entry to restaurants, verbal attacks on social media and even physical assaults. In response, the WHO and the Centers for Disease Control in the United States have issued official statements and pamphlets that condemned such actions and behaviours.

Hopefully, with continued education on COVID-19 and constant reiteration to the public that viruses have no respect for borders, their fear of the unknown and magnitude of discrimination against other ethnicities can be curtailed.

Integration of Hospital and Community Resources

In Singapore, community psychiatric partners such as the Social Service Agencies (SSA) form an important first line to provide counselling to members of the public who need it during the current outbreak. In doing so, it strengthens mental resilience in the community and reduces the likelihood of psychiatric morbidities developing in individuals. Silver Ribbon (Singapore) and Fei Yue Community Services also provide online counselling and emotional support on COVID-related issues. Finally, a group of psychologists from the Singapore Psychological Society have been providing their services pro bono or at reduced rates to those who have been distressed by the outbreak.

In hospitals, psychiatrists have been providing additional clinic sessions to render psychiatric support to patients with emotional issues coming through the Emergency Departments. Nevertheless, there is still a need to combine resources to provide a comprehensive and integrated psychological service for patients and to enhance the psychological preparedness of the nation.

Conclusion

In the current pandemic, there is no agency that plans and coordinates psychological intervention for the country and her population. It would be worthwhile to consider involving psychiatrists and mental health professionals in the Task Force on COVID-19 to advise the government on mental health policies and psychological intervention. At this writing, the hospitals, polyclinics and SSA are working in silos to conduct psychological interventions in patients with little communication among them, leading to resource wastage and decreased efficacy of their interventions. It would be helpful to hospitals and SSA to align their goals and efforts by engaging each other in case discussions and training. Community health personnel can be trained to better identify and manage psychological distress in patients. Case discussions can promote seamless transfer of patient care across hospitals and community services. While patients with severe psychiatric morbidities will benefit from management in hospitals, mild to moderate cases or those who have recovered with treatment can be discharged to community services for continued management.

Past pandemics have provided Singapore valuable lessons on global responses to manage them. Consequently, the country is more medically prepared to deal with the COVID-19 outbreak with better medical infrastructure and technology and highly qualified health workers. However, it is crucial that we do not ignore the psychological impact the outbreak will have on individuals and society which can hamper their readiness to overcome the crisis, and the fact that the psychological ramifications can persist long after the pandemic has ended.

The outbreak of COVID-19 has highlighted the fragility of mental resilience and the need to have a nation-wide psychological intervention plan. We have suggested 6 strategies that local and overseas authorities could consider to improve their current plan. After their psychological defence is bolstered, countries will be equipped to succeed in their battle against COVID-19 and secure their future.

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Commentary

Counting Coronavirus Disease-2019 (COVID-19) Cases: Case Definitions, Screened Populations and Testing Techniques Matter

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Abstract

While counting cases of disease appears straightforward, there are issues to consider when enumerating disease counts during an epidemic. For example, for Coronavirus Disease-2019 (COVID-19), how is a case defined? Hubei province in China changed its case definition twice in a fortnight—from laboratory-confirmed cases to clinically-confirmed cases without laboratory tests, and back to laboratory-confirmed cases. This caused confusion in the reported number of cases. If a confirmed case requires laboratory testing, what is the population who are laboratory-tested? Due to limited laboratory testing capacity in the early phase of an emerging epidemic, only "suspected cases" are laboratory-tested in most countries. This will result in underdiagnosis of confirmed cases and also raises the question: how is a "suspect case" defined? With the passage of time and increased capability to perform laboratory tests, more people can be screened and the number of confirmed cases will increase. What are the technical considerations of laboratory testing? This includes specimen collection (variable collection methods), samples collected (upper or lower respiratory tract biospecimens), time of collection in relation to course of disease, different laboratory test methods and kits (not all of which may be standardised or approved by authorities such as the Food and Drug Administration). Are approved laboratory facilities and trained manpower available, and how are test results interpreted and false-negatives excluded? These issues will affect the accuracy of disease counts, which in turn will have implications on how we mount an appropriate response to the outbreak.

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Key words: Diagnosis, Laboratory testing, Outbreak, Pandemic, Screening

Introduction

Several factors determine the number counts of Coronavirus Disease-2019 (COVID-19)—one of which is the case definition. It was reported on 13 February 2020 that there was an overnight steep increase in COVID-19 in China—15,152 cases and 254 deaths. This was caused by the broadening of the case definition (only in Hubei province and not the rest of China or elsewhere in the world) to include not only the 1820 cases confirmed by laboratory testing on that day, but also 13,332 clinically-confirmed cases (on the basis of chest imaging, without the need for laboratory tests), which had accumulated in the weeks since the start of the outbreak.[1]

The reason given for recognising clinically-confirmed cases was to allow clinicians to report cases more quickly without waiting for laboratory confirmation, for which there was a backlog. This would allow for prompt clinical care and public health responses such as contact tracing and quarantine. Thus, the spike of 14,000 cases in a single day had been caused by a change in case definition. The case definition in Hubei has since been changed again on 20 February 2020 to consider only laboratory-confirmed cases.[2]

However, even the use of a case definition (which requires laboratory confirmation of the disease) has limitations as it may lead to underdiagnosis of cases due to various reasons.

Who Are Tested in the Population?

During the early stages of an outbreak of a novel disease, there are limited test kits and facilities, so not every person can be tested. Testing has to be prioritised for suspected

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cases. Infected persons who seek medical attention, but who do not fall under the category of "suspected cases" would not be tested. Those who do not come forward to seek medical treatment will also not be tested.

The term "suspected cases" has to be clearly defined. This is usually based on a history of relevant travel or contact with infected persons and specific symptoms such as pneumonia-like symptoms. The definition of a "suspected case" would vary from country to country and during different time periods of the outbreak. For example, in the initial phase of the outbreak in China, "suspected cases" were likely to have moderate or severe illness, with criteria such as atypical pneumonia and/or acute respiratory distress used to define "suspected cases".

Internationally, countries primarily concerned about imported cases may have broader criteria for defining a suspect case. This might consist of clinical symptoms such as cough and fever, and recent travel history to an affected region; contact with a confirmed or probable case; or working in a healthcare facility that treats probable/confirmed cases. Such surveillance would be able to identify clinically milder cases. On the other hand, restricting testing only to persons with relevant travel, contact or work history may result in missing symptomatic cases that may have occurred through local transmission.[3]

Relevant Travel History

The definition of "relevant travel history" in a suspect case has evolved over time, due to the spread of COVID-19 to different countries, and the changing risk of infection for travel in newly affected countries. This is illustrated in the case of Singapore, where the case definition of a "suspect case" was repeatedly updated as the outbreak unfolded. The definition of a "suspect case" first appeared on 2 January 2020 in Singapore. It had 2 criteria: 1) a person with clinical signs and symptoms suggestive of pneumonia or severe respiratory infection with breathlessness and travel to or residence in Wuhan city within the last 14 days, or 2) a person with an acute respiratory illness of any degree of severity who, within 14 days before onset of illness, had close contact[1] with a pneumonia case of unknown cause linked to the Wuhan cluster.

In view of the spread of COVID-19 to all parts of China, criterion number 1 was expanded to cover travel to any part of mainland China on 21 January 2020. This criterion was further extended to include travel to Daegu city or Cheongdo county, South Korea on 23 February 2020 because of the steep increase of cases in these locations. The list of countries was further enlarged on 3 March 2020 to include Iran, northern Italy, Japan and the Republic of Korea (and on 10 March, to any country outside of Singapore).

Criterion number 2 was expanded on 4 February 2020 to include "a person with an acute respiratory illness of any degree of severity who, within 14 days before onset of illness had" done any one of the following: 1) been to Hubei province (including Wuhan) or Zhejiang province (including Hangzhou), China; 2) been to a hospital in mainland China (this was further amended on 3 March to "a hospital in affected areas"); 3) had close contact with a case of COVID-19 infection; or 4) had frequent or close contact during work with recent travellers from mainland China (travel history in the last 14 days).

An expanded case definition for a "suspect case" will result in greater sensitivity for case detection and more number of cases being confirmed (while lowering the specificity). Having greater sensitivity will be important if cases have to be detected in order to institute early measures to contain the illness. Conversely, restricting the case definition may result in increased specificity, but will reduce the sensitivity of case detection and number of cases detected.

Symptoms of COVID-19

The symptoms that characterise COVID-19 can vary and some patients can even be asymptomatic. For example, gastrointestinal symptoms initially occur in about 10% of cases, and this is often not listed as a symptom that would define a suspect case. It was reported that a patient who initially presented with gastrointestinal symptoms was not suspected to have the illness and initially admitted to a surgical ward. This patient infected over 10 healthcare workers.[4]

A large Chinese case series (n = 72,314) has shown that 1.2% (n = 889) of cases are asymptomatic.[5] Another case report[6] has demonstrated an asymptomatic carrier transmission of COVID-19. However, much is still unknown about the asymptomatic transmission of the disease and as such, many countries are currently only testing patients who are symptomatic.

Should "Confirmed Cases" or "Probable Cases" Be Counted?

An internationally standard and rigorous case definition of a "confirmed case" will allow for comparison of case numbers in different parts of the world, or within a country during the course of an epidemic. This will assist in the calibration of an appropriate public health response at different stages of a disease outbreak.

On the other hand, a "probable case" is usually less rigorously defined, and the definition may vary from country to country. While this makes meaningful comparison of case numbers from various locations less feasible, it has its uses. For example, the introduction of a clinical case definition in Hubei province on 13 February 2020 resulted in a spike of cases in 1 day, and rendered comparisons with other Chinese provinces and the rest of the world invalid. However, the change in case definition in Hubei

was in response to delays in confirming the diagnosis with laboratory testing, due to inability of laboratory services to cope with the surge in demand for testing. Early confirmation of cases was needed, so that preventive control measures such as isolation, contact tracing, risk communication and quarantine could be instituted immediately since delays in these actions could prove detrimental. This is an important consideration in situations when there are few diagnostic kits available or in low- or middle-income countries where testing facilities can be limited.

What Biological Sample is Collected?

Samples required for initial diagnostic testing include both upper and lower respiratory tract samples[7] such as single or combined nose/throat swab, nasopharyngeal aspirate or sputum. A serum sample may also be useful for acute serological testing to rule out other causes of viral pneumonia (e.g. influenza, H1N1, H5N1, H7N9). Commercially produced serological tests for COVID-19 are beginning to be available. However, it would be useful to determine the levels of specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies (e.g. via enzyme-linked immunosorbent assay [ELISA]) and their ability to neutralise the virus (e.g. via microneutralisation assays).

The sample collection technique—nasal or throat swab, wash or aspirate—can vary and affect the amount of virus collected. The type of biological samples taken for testing also have different diagnostic yields. For example, lower respiratory specimens obtained from sputum, lower respiratory tract aspirate or bronchioalveolar lavage have higher diagnostic value than upper respiratory specimens. The World Health Organization recommends that if initial testing is negative in a patient who is strongly suspected to have COVID-19, the patient should be resampled and specimens collected from multiple respiratory tract sites. Additional specimens such as blood, urine and stool might also be collected to assess virus presence or shedding.[8]

When Are Biospecimens Collected?

The timing of the test is important. In the early stages of the disease, the viral load may be lower and thus might not be detectable. According to the Centers for Disease Control and Prevention (CDC), "In the early stages of infection, it is possible the virus will not be detected". It adds that "a negative test for a sample collected while a person has symptoms likely means [COVID-19] is not causing their illness"[9] (which describes a true negative result in a symptomatic person).

A woman travelled from Wuhan to Anyang on 10 January 2020 and visited several relatives. When 5 of her relatives developed COVID-19, she was isolated and tested for coronavirus. The woman tested negative on 26 January 2020, but a follow-up test on 28 January 2020 was positive. Computed tomography scans of the chest on 27 and 31 January 2020 showed no significant abnormalities and as of 11 February 2020, she had no elevated temperature or self-reported fever and no gastrointestinal or respiratory symptoms, including cough and sore throat.[6] This woman represents either an asymptomatic severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) carrier, or alternatively her second test result was a false-positive. However, the latter explanation is less likely as 5 of her relatives developed COVID-19 after interactions with her.

How Reliable and Comparable Are Test Kits?

A laboratory test commonly used to diagnose COVID-19 is real-time polymerase chain reaction (RT-PCR), which detects the presence of viral nucleic acids. This is a highly specific and sensitive assay which has been demonstrated to be superior in detecting novel coronavirus (nCoV) than other assays.[10] Probes are designed to bind to unique sequences in the pathogen for amplification and detection. Currently, diagnostic kits come from different sources, and different kits have different levels of test sensitivity and specificity. If the result of the RT-PCR test is positive for coronavirus, the sample can be sent for genome sequencing to confirm the findings. Patients are deemed to have a positive test if the genetic sequence of the virus in their blood or respiratory tract sample has a "high degree"of similarity with that of the virus. False-positives can only arise if there is contamination of the sample. This could arise during multiple sample collection and cross contamination. False-negatives are a more likely outcome which could be due to the time or site of sampling (e.g. viral load is below the limit of detection of the assay) or degradation of viral ribonucleic acid (RNA) during transport and storage. Xie et al[11] evaluated the effectiveness of PCR methods and found that viral nucleic acid could be detected in oropharyngeal swab samples (9/19 positive patients) and also stool samples (8/9 positives). None of the positive results were identified in blood and urine samples.

One example of a RT-PCR test is the CDC 2019-nCoV RT-PCR Diagnostic Panel, which contains 2019-nCoV_N1, 2019-nCoV_N2 and 2019-nCoV_N3 primers and probes that target the nucleocapsid (N) gene (designed for universal detection of SARS-like coronavirus as well as specific detection of the 2019-nCoV); RT primers and probes targeting the Human RNase P gene; and nCoVPC, the 2019-nCoV positive control used in the assay.[12] This test is not yet approved for use by the United States Food and Drug Administration (FDA). However, an Emergency Use Authorization (EUA) for this test is supported by the Secretary of Health and Human Service's declaration that circumstances exist to justify the use of in vitro diagnostics (IVD) under EUA for the detection and/or diagnosis of 2019-nCoV.[12] An IVD made available under an EUA has

not undergone the same type of review as an FDA-approved IVD. There has been a report of unreliable kits, where a number of faulty test kits were sent out by United States health authorities to laboratories across the country.[13] RT-PCR assays that target the RNA-dependent RNA polymerase (RdRp)/helicase (Hel) genes of SARS-CoV-2 have been recently shown to be more sensitive and specific than those that target the spike (S) and nucleocapsid (N) genes.[14]

Determining the levels of specific antibodies to SARS-CoV-2 is becoming possible and a rapid point-of-care test has been reported.[15] This assay uses a recombinant receptor binding domain of SARS-CoV-2 Spike Protein in a lateral flow immunoassay format. Xiang et al[16] also compared ELISA IgG and IgM antibodies colloidal gold-immunochromatographic assay with RT-PCR. Best results were obtained by combining IgM and IgG responses. The limited data to date indicates that immunoassay sensitivity is 83–88% compared to around 50% with RT-PCR.

Details of seroconversion of infected patients are largely unknown; however, it has been reported that IgM antibodies were detected 3–6 days after infection with SARS-CoV and IgG after 8 days. In addition, levels of cross-reaction with closely related CoV will need to be controlled for. A number of companies are developing immunoassay-based kits (e.g. Snibe Diagnostic received a CE Mark for their Maglumi 2019-nCoV [SARS-CoV-2] IgM/IgG kits recently).[17] Ultimately, neutralising antibody assays will be valuable but will require level 3 biosafety capacity.

Are Laboratory Facilities Certified and is the Laboratory Manpower Adequately Trained?

In addition to the availability and quality of test kits, laboratory personnel should be adequately trained to perform these tests accurately. For example, the CDC 2019-nCoV RT-PCR Diagnostic Panel is only authorised for use in qualified laboratories designated by the CDC as qualified, and certified under the Clinical Laboratory Improvement Amendments to perform high complexity tests.[18]

Many laboratories throughout the developing world may not have such capability, and there is a rush to develop such expertise and capacity.[19] The WHO has activated an international network of 16 referral laboratories that can support national efforts in confirming new cases.[20]

How Are the Results Interpreted?

RT-PCR is widely used in diagnostic virology and has yielded few false-positive outcomes.[21] A negative test result indicates that the viral RNA was not identified in the specimen above the limit of detection, but does not exclude the possibility of a false-negative test. False-negative tests should be considered if the patient's recent exposures or clinical presentation indicate that COVID-19 is likely, and diagnostic tests for other causes of illness are negative. In such cases, retesting should be considered.[12]

Conclusion

Accurate diagnosis of COVID-19 is extremely important for clinical management of cases, for early institution of preventive health measures such as isolation and contact tracing for quarantine measures and for understanding the pattern of disease transmission.

A significant proportion of cases are presently undiagnosed in many countries. This is probably due to limited testing of people due to restrictive case definitions of "suspect cases" in the early stages of the outbreak, where laboratory test kits are scarce, and testing is often only limited to "suspect cases". The fewer the laboratory tests are done, the fewer would be the number of confirmed cases and the larger the proportion of undiagnosed cases. As more laboratory test kits become available and laboratory testing is more widely done, the proportion of undiagnosed cases will decrease.

Counting the number of cases (including mild cases) is necessary in order to understand the pattern of disease transmission and for calibration of the epidemic response. However, the variability of case definitions, the populations that are screened (which will vary by location and timeline of the outbreak), testing techniques and interpretation of laboratory results will affect the number of cases enumerated. Given the above, the reliability of epidemiological characterisation of the disease—in terms of disease counts and comparability of numbers within and between countries—can never be completely accurate and unambiguous. Fortunately, it is often true that a close approximation of the true figures would suffice for adequate public health responses.

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Letter to the Editor

Emergency Laparotomy Outcomes: Higher First-Year Mortality in the Elderly

Dear Editor,

Emergency laparotomy (EL) is a common procedure in the treatment of a myriad of potentially life-threatening abdominal conditions. Unlike elective surgery, EL is associated with high morbidity and mortality.[1–3] Compared to their younger counterparts, elderly patients are at higher risk of postoperative complications and mortality that are attributed to multiple comorbidities and reduced physiological reserves.[3–5] Additionally, patients who require EL tend to be critically ill with limited time for preoperative optimisation. Studies on EL have revealed substantial variations in processes and lack of coordination of EL care.[6–8]

In the United Kingdom (UK), the National Emergency Laparotomy Audit (NELA) has shown a reduction in 30-day mortality from 11.8% to 9.5% since 2013.[6] In its third report, NELA described 9 key standards that can improve efficiency in the management of EL patients. To date, there is no standard practice in EL management in our institution and postoperative EL outcomes in Singapore are not known. In this study, we described EL outcomes in an acute hospital in Singapore, determined factors associated with 30-day mortality and explored perioperative outcomes in elderly patients.

Materials and Methods

We performed a retrospective cohort study of EL outcomes from January 2017 to December 2017 in a local institution. Patients ≥16 years old who underwent EL were included. Similar to NELA, the exclusion criteria included laparotomies for trauma, vascular or gynaecology emergencies. Relook laparotomies were also excluded.

Data collected included patient demographics, diagnoses and preoperative risk assessment such as Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (P-POSSUM) scores and efficiency outcomes. Patients were classified as either young (<65 years old) or elderly (≥65 years old). The American Society of Anaesthesiologists (ASA) Physical Status Classification System was used to assess the physical state of patients prior to EL. The priority (P) accorded to each EL was also recorded. In our institution, P1 refers to procedures that are performed within 1 hour, P2 for procedures undertaken within 4 hours and P3 denote those that take place within 24 hours. Postoperative complications were graded according to the Clavien-Dindo classification system. Data on length of stay (LOS), 30-day mortality and annual mean cost to hospital (total bill without subsidy awarded by the state) were evaluated.

Data analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). For categorical variables, counts and percentages were reported. Parametric data were reported in mean and standard deviation (SD). Differences were assessed using Student's t-test for continuous data; for categorical data, chi-square or Fisher's Exact test was used. A value of P <0.05 was considered statistically significant.

Results

A total of 152 patients were included in the study. Most of them were Chinese (74.3%). There were 96 (63.2%) men and 80 (52.6%) patients were >65 years old. A total of 73 (48.0%), 44 (28.9%) and 20 (13.2%) patients were graded ASA II, III and IV, respectively. Forty-nine (32.2%) patients had P-POSSUM mortality risk ≥10%. As shown in Table 1, the most common indications for EL were perforated peptic ulcer disease (22.4%), obstructed or perforated colonic tumours (20.4%) and adhesion-related intestinal obstruction (15.1%).

Preoperative computed tomography (CT) was performed on most patients (86.2%). Mean duration from booking of operative case to EL ranged from 92 (SD 26) minutes for P1 cases to 171 (SD 76) minutes for P2 cases and 510 (SD 319) minutes for P3 cases. The procedure was supervised by a senior anaesthetist and senior surgeon in 47 (30.9%) and 140 (92.1%) cases, respectively. A total of 71 (46.7%) EL were performed during the day (Table 2).

Postoperatively, 39 (25.7%) patients were monitored in Intensive Care Unit (ICU), 18 (11.8%) in High Dependency Unit (HDU) and the remainder in General Ward. In patients with P-POSSUM mortality risk

Table 1. Demographic and Preoperative Characteristics of Patients

Variable	Aggregate (n = 152)	<65 Years Old (n = 72)	≥65 Years Old (n = 80)	*P* Value
Mean age in years (SD)	63 (16)	49 (11)	75 (7)	<0.01
Gender (%)				0.49
Male	96 (63.2)	48 (66.7)	48 (60.0)	
Female	56 (36.8)	24 (33.3)	32 (40.0)	
Ethnicity (%)				
Chinese	113 (74.3)	45 (62.5)	68 (85.0)	<0.01
Malay	24 (15.8)	12 (16.7)	12 (15.0)	0.95
Indian	10 (6.6)	10 (13.9)	0 (0)	<0.01
Others	5 (3.3)	5 (6.9)	0 (0)	0.02
ASA Physical Status score (%)				
1	15 (9.9)	14 (19.5)	1 (1.3)	<0.01
2	73 (48.0)	38 (52.7)	35 (43.7)	0.34
3	44 (28.9)	14 (19.5)	30 (37.5)	0.02
4	20 (13.2)	6 (8.3)	14 (17.5)	0.15
Indication for surgery (%)				
Perforated gastric/duodenal ulcer	34 (22.4)	15 (20.8)	19 (23.8)	0.81
Colorectal cancer (obstructed/perforated)	31 (20.4)	17 (23.6)	14 (17.5)	0.46
Intestinal obstruction secondary to adhesions	23 (15.1)	10 (13.9)	13 (16.2)	0.86
Bowel ischaemia	16 (10.5)	8 (11.1)	8 (10.0)	0.82
Perforation of intestine	19 (12.5)	7 (9.7)	12 (15.0)	0.46
Anastomotic leak	12 (7.9)	7 (9.7)	5 (6.2)	0.62
Bleeding	4 (2.6)	4 (5.6)	0 (0)	0.048
Intestinal obstruction (bezoar/foreign bodies)	5 (3.3)	1 (1.4)	4 (5.0)	0.37
Non-malignant intestinal obstruction	5 (3.3)	3 (4.2)	2 (2.5)	0.67
Gallstone ileus	3 (2.0)	0 (0)	3 (3.8)	0.25
Preoperative P-POSSUM				
Mean morbidity score (SD)	65.0 (23.6)	58.7 (24.0)	70.7 (21.8)	<0.01
Mean mortality score (SD)	11.4 (14.2)	8.9 (13.9)	13.7 (14.1)	0.04
Low (<5%), %	74 (48.7)	43 (59.7)	31 (38.7)	0.02
Medium (5 – 10%), %	29 (19.1)	14 (19.5)	15 (18.8)	0.91
High (>10%), %	49 (32.2)	15 (20.8)	34 (42.5)	<0.01
Documentation of risk assessment and counselling (%)	0 (0)	0 (0)	0 (0)	NA
Preoperative CT (%)	131 (86.2)	65 (90.3)	66 (82.5)	0.25

ASA: American Society of Anaesthesiologists; CT: Computed tomography; NA: Not applicable; P-POSSUM: Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and morbidity; SD: Standard deviation

≥10%, 38 (77.6%) of them were managed by the Critical Care team. For postoperative complications, 29 (19.1%) patients were graded III to V on Clavien-Dindo classification system. Mean LOS was 15.4 (SD 17.0) days. Mortality rates at 30 days and 1 year were 5.3% and 9.2%, respectively. Mean annual cost to the institution was S$14,152 (SD S$15,860) for each patient (Table 3).

Factors associated with increased mortality included P-POSSUM mortality risk ≥10% (odds ratio [OR] 4.217, P <0.05), ASA score of 4 (OR 9.265, P <0.01) and postoperative complications (OR 11.0, P <0.01). Subgroup analysis of 80 (52.6%) elderly patients revealed that they had higher ASA III scores than young patients (37.5% vs 19.5%, P = 0.02). P-POSSUM morbidity and mortality were also higher in elderly patients (P <0.01 and P = 0.04, respectively). Finally, more elderly (35.0%) patients were monitored in ICU than young (15.3%) patients (P <0.01).

Elderly (20.0%) patients had more severe postoperative complications—Clavien-Dindo IV—than younger (1.4%) patients (P <0.01). More elderly (7.5%) patients also had another unplanned procedure performed on them than on their younger (2.8%) counterparts (P = 0.28). As shown in Table 3, mean LOS in elderly patients was 19.0 (SD 21.6) days against 11.3 (SD 7.8) days in younger patients (P <0.01). In elderly patients, the 30-day mortality rate was 8.8% but only 1.4% in younger patients. More of them (35.1%) were discharged to stepdown care against 4.2% of younger patients who did so (P <0.01). However, readmissions at 30 days were similar in both groups: 6.2% in the elderly group and 6.9% in the younger group (P = 0.86). At 1 year, the mortality rate in the elderly and younger group was 15.0% and 2.8%, respectively (P = 0.01).

Discussion

Much effort has been made to improve outcomes following EL including NELA in the UK and ANZ Emergency Laparotomy Audit and Quality Improvement project in Australia and New Zealand.[9] In the UK, NELA had demonstrated a reduction in mortality rate from 11.8% in 2013 to 9.5% in 2018. In 2017, cost savings of up to 24 million pounds and 108,000 bed-days in acute public hospitals were achieved. In contrast, data on outcomes following EL in Asia is lacking. This is the first emergency laparotomy audit in an acute public hospital in Singapore that described care processes and patient outcomes following EL.

In our study, the finding of a 30-day mortality rate of 5.3% was lower than that found by NELA which was 9.5%. P-POSSUM and ASA scores were also accurate predictors of mortality and morbidity following emergency surgery and laparotomies, respectively.[10,11] These findings highlight the importance of a standardised preoperative risk assessment in the identification of high-risk patients who may benefit from reviews by senior anaesthetists and senior surgeons to reduce postoperative complications and mortality.

Table 2. Efficiency Outcomes

Outcome	Aggregate (n = 152)	<65 Years Old (n = 72)	≥65 Years Old (n = 80)	*P* Value
Mean duration to OT in minutes (SD)				
P1 (within 60 minutes)	92 (26)	95 (30)	90 (22)	0.68
P2 (within 240 minutes)	171 (76)	151 (58)	188 (85)	<0.01
P3 (within 720 minutes)	510 (319)	395 (295)	652 (326)	0.25
P-POSSUM ≥10%	27.5 (15.1)	30.1 (18.9)	26.5 (13.3)	0.46
Supervision by senior surgeon in OT (%)	140 (92.1)	68 (94.4)	72 (90.0)	0.38
P-POSSUM ≥10%	46 (93.9)	15 (100)	31 (91.2)	0.54
Supervision by senior anaesthetist in OT (%)	47 (30.9)	24 (33.3)	23 (28.8)	0.66
P-POSSUM ≥10%	12 (24.5)	4 (26.7)	8 (23.5)	1.0
Time of surgery (%)				0.71
0730 – 1700 hours	71 (46.7)	32 (44.4)	39 (48.8)	
1700 – 0730 hours	81 (53.3)	40 (55.6)	41 (51.2)	

OT: Operating theatre; P-POSSUM: Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and morbidity; SD: Standard deviation

Our study met 5 of 9 key standards on efficiency and organisational outcomes that were described in the third patient report by NELA. Most of our patients underwent preoperative CT that was performed by a radiologist who was of the registrar grade. Arrival at the operating theatre took place within the prescribed time interval and mean wait time for P2 and P3 cases were only about 1 hour.

Although P-POSSUM was performed retrospectively in our study, senior surgeons reviewed the results and supervised most procedures when the risk was ≥10%. In our institution, there is no consensus to direct all postoperative admissions to HDU/ICU when P-POSSUM mortality risk was ≥10%. The decision on HDU/ICU admission is based on a global assessment of the patient by the senior surgeon who uses P-POSSUM as a guide, but not as the sole determinant for doing so.

Postoperatively, elderly patients were not routinely reviewed by a dedicated team headed by a geriatrician. By 2030, the population of Singaporeans >65 years old

Table 3. Clinical Outcomes

Outcome	Aggregate (n = 152)	<65 Years Old (n = 72)	≥65 Years Old (n = 80)	*P* Value
Postoperative admission (%)				
GW	95 (62.5)	51 (70.8)	44 (55.0)	0.06
HDU	18 (11.8)	10 (13.9)	8 (10.0)	0.62
ICU	39 (25.7)	11 (15.3)	28 (35.0)	<0.01
ICU/HDU (P-POSSUM ≥10%)	38/49 (77.6)	11/15 (73.3)	27/34 (79.4)	0.72
CD complications score (%)				
III	7 (4.6)	4 (5.6)	3 (3.8)	0.71
IV	17 (11.2)	1 (1.4)	16 (20.0)	<0.01
V	5 (3.3)	1 (1.4)	4 (5)	0.37
III – V	29 (19.1)	6 (8.3)	23 (28.8)	<0.01
Hospital discharge (%)				
Against medical advice	3 (2.1)	2 (2.8)	1 (1.3)	0.60
Normal discharge	6 (4.1)	5 (7.1)	1 (1.4)	0.10
Outpatient follow-up	106 (73.1)	61 (85.9)	45 (60.8)	<0.01
Community hospital	29 (20.0)	3 (4.2)	26 (35.1)	<0.01
Nursing home	1 (0.7)	0 (0)	1 (1.4)	1.0
Mean length of stay (SD)				
ICU	6.5 (6.2)	6.1 (6.7)	6.7 (6.2)	0.78
HDU	3.1 (3.9)	1.9 (1.2)	3.8 (4.6)	0.052
Overall	15.4 (17.0)	11.3 (7.8)	19.0 (21.6)	<0.01
Unplanned return to OT (%)	8 (5.3)	2 (2.8)	6 (7.5)	0.28
Unplanned percutaneous abdominal drainage (%)	18 (11.8)	6 (8.3)	12 (15.0)	0.31
Unanticipated admission/return to ICU/HDU (%)	4 (2.6)	0 (0)	4 (5.0)	0.12
30-day readmission (%)	10 (6.6)	5 (6.9)	5 (6.2)	0.86
30-day mortality (%)	8 (5.3)	1 (1.4)	7 (8.8)	0.07
1-year mortality (%)	14 (9.2)	2 (2.8)	12 (15.0)	0.01
Mean hospital cost in SGD (SD)	14,152 (15,860)	12,157 (12,222)	15,947 (18,430)	0.13

CD: Clavien-Dindo; GW: General ward; HDU: High dependency unit; ICU: Intensive care unit; OT: Operating theatre; P-POSSUM: Portsmouth Physiological and Operative Severity Score for the enumeration of Mortality and morbidity; SD: Standard deviation; SGD: Singapore dollars

is expected to reach 25%.[12] The elderly represents a vulnerable group of patients with lower physiological reserves and higher risk of morbidity and mortality than younger patients; at 1 year, all-cause mortality from EL was higher in them (15.0%) than in the latter (2.8%, $P = 0.01$). Using the key standards laid out by NELA as benchmarks in our study, our findings have highlighted opportunities for improvement.

A limitation of our study includes the inherent biases found in a retrospective study. For example, the presence of senior anaesthetists and senior surgeons were determined based solely on operative records. Consequently, the actual duration and extent of their involvement may be variable. Also, parameters such as intraoperative findings, degree of contamination and actual procedure were not examined since they may potentially enhance our understanding of postoperative outcomes in patients. Future studies could include standardised perioperative management of EL and comparison of multicentre data.

Conclusion

This is the first EL audit from our institution that reported a 30-day mortality of 5.3%. Postoperative complications and mortality at 1 year were significantly higher in elderly patients. More studies and collaborative initiatives from Singapore are needed to evaluate the efficacy of outcome-driven, multidisciplinary perioperative care.

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The Neonatal Transport Service in Singapore: A 5-Year Review

Dear Editor,

In-utero transfers of high-risk pregnancies are associated with better neonatal survival and outcomes.[1–3] However, ex-utero transfers cannot be avoided altogether and an effective neonatal transport network is essential to provide intensive care support to these newborns in transit.[4] In bigger countries, dedicated neonatal services are available and it is a common finding that such services are necessary to improve neonatal survival.

Singapore is a city-state with a land area of 724 square kilometres and has a resident population of 5.7 million.[5–6] With advancements in medical care, perinatal and neonatal mortality in Singapore has declined significantly.[7] In Singapore, neonatal care is concentrated in 3 public acute hospitals and 7 private hospitals that have neonatal intensive care unit (NICU) facilities.

The Children's Hospital Emergency Transport Service (CHETS) is managed by KK Women's and Children's Hospital—a tertiary perinatal centre in Singapore—and provides inter-hospital neonatal transfers in the city-state. The team comprises doctors, nurses and respiratory therapists trained in neonatal transport. In bigger countries such as Portugal and Switzerland where perinatal care is offered in different regions,[8,9] similar neonatal transport services are offered by tertiary centres to serve populations that are spread over a vast area. As Singapore is vastly smaller in size, the area served by CHETS encompasses not only the city-state but her neighbouring countries such as Indonesia and Malaysia as well. In this study, we report the epidemiological characteristics of neonates who required transport provided by CHETS.

Materials and Methods

A retrospective review of the medical records of neonates ≤28 days old who were referred to CHETS for transport between 1 January 2011 and 31 December 2015 was performed. Data on ethnicity, gender, gestational age and weight at time of transfer, indication for transfer, referral source, mode of transport and disposition were collected and analysed using Microsoft Excel (2013). The study was approved by the SingHealth Centralised Institutional Review Board (reference number 2015/2926).

Results

A total of 164 neonates were transported over the study period. Transport was not undertaken in 7 (4.3%) neonates and the reasons cited included being too ill for transport, lack of NICU beds in receiving hospitals, financial cost, resolution of medical condition or subsequent planned transfer to another region. All of them were born before the arrival of the transport team; 4 were from twin pregnancies and the remainder were singleton babies.

A total of 123 (75.0%) referrals were from private hospitals, 31 (18.9%) were from a public acute hospital and 10 (6.1%) were from international hospitals. Table 1 shows the gender, race and disposition of the neonates and modes of transport that were deployed.

Within 3 days of their birth, 115 (70%) neonates were transferred. Figure 1 illustrates the gestational ages of the neonates at birth and at transfer. Overall mean birth gestation was 35.7 weeks (median 37.0 weeks, range 21.0–40.0 weeks) and overall mean corrected gestational age at time of transfer was 36.1 weeks (median 38.0 weeks, range 21.0–42.0 weeks). At time of transfer, mean weight of neonates was 2.540 kg (median 2.625 kg, range 0.655–4.750 kg). Table 1 provides an overview of weight of neonates at the time of referral.

The reasons cited for transport included continuity of care in a tertiary hospital (50%), surgery (29.2%), lack of facilities—such as high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO), inhaled nitric oxide and total body cooling for neonatal hypoxic ischaemic encephalopathy—in the referring hospital (13.4%) and need for further subspecialty evaluation (7.3%).

Table 2 provides a breakdown of the specific medical conditions and principal issues that prompted referrals to CHETS. Most transfers (23.2%) were provided to neonates who required surgical intervention and 30 (18.3%) neonates were referred for respiratory issues.

Of the 157 neonates who were transported, 64 (40.8%) were intubated on mechanical ventilation during transport, 17 (10.8%) were on non-invasive ventilation—continuous positive airway pressure or bilevel positive airway pressure—and 33 (20.1%) were supported with

oxygen via nasal cannula or hood box. Four (2.5%) neonates required surfactant during stabilisation and transport. During intra-transport, 11 (7.0%) of them required inotropic support. Fluid boluses were also administered in 11 (7.0%) neonates during transport.

A total of 126 neonates were admitted to our centre and 94 (74.6%) of them were discharged back home while another 13 (10.3%) passed away. The outcome in 19 (15.1%) neonates was not known and was attributed to incomplete data. Most of the neonates who were deceased were either extremely preterm or had underlying congenital malformations.

Discussion

To the best of our knowledge, no studies have been published on emergency neonatal transport services in Southeast Asia. Consequently, our study aimed to fill the gap in the literature on this subject and to profile the epidemiological characteristics of neonates who required such services in Singapore.

Table 1. Baseline Characteristics of Neonates Referred to CHETS

Variable	n	%
Gender		
Male	91	55.5
Female	72	43.9
Undetermined	1	0.6
Race		
Chinese	85	51.8
Malay	26	15.9
Indian	20	12.2
Others	33	20.1
Weight at time of referral (kg)		
<1.000	13	7.9
1.000 – 1.499	10	6.1
1.500 – 2.499	44	26.8
≥2.500	92	56.1
Unknown	5	3.0
Disposition		
Admission to KKH	126	76.8
Admission to other hospital	31	18.9
Activated but not transferred	7	4.3
Mode of transport*		
Land	154	98.0
Air	3	2.0

CHETS: Children's Hospital Emergency Transport Service; KKH: KK Women's and Children's Hospital
*7 neonates were not transported.

Most of the neonates were transferred from private hospitals to our centre for continuity of care. Prematurity was the sole diagnosis in 27 (16.5%) neonates. Notably, 16 (9.8%) neonates were born before 28 weeks of gestation and half of them required CHETS within 3 days of their birth. The reasons cited for ex-utero transfer of these neonates included financial constraints secondary to high costs of health services in private centres and lack of specialised management, especially when prolonged intensive care support was anticipated in cases of extreme prematurity. Additionally, some private centres lacked critical services such as ECMO and HFOV.

The next most cited reason (29.2%) for neonatal transfers was need for surgical expertise. Eleven of the 17 neonates transferred for cardiac diagnoses were scheduled for cardiothoracic surgery. This finding highlighted the need for skilled paediatric surgical expertise in private practice or early referral of antenatally diagnosed structural malformations to a tertiary centre with paediatric surgery expertise.

However, some conditions that necessitate neonatal transport—such as spontaneous preterm delivery or neonatal encephalopathy, for which in-utero transport may not be possible—cannot be anticipated. Additionally, certain surgical conditions may only be detected postnatally. Nevertheless, in view of the risks associated with neonatal transport,[1–3] more effort could be directed at identification of high-risk pregnancies with early antenatal and financial counselling. Such cases would include antenatally diagnosed congenital malformations and in-utero transfer is recommended over ex-utero transfer since there is lower morbidity and mortality and shorter length of stay.[10,11]

The findings of our study have demonstrated the importance for tertiary centres to collaborate with private and public hospitals to ensure that neonates are transported with appropriate care. The establishment of an effective referral system can also facilitate timely initiation and coordination of maternal transfers to a tertiary hospital. There is also a need to develop existing perinatal networks to facilitate emergency neonatal transfers and in-utero transfers in high-risk pregnancies.[12]

Although most centres believe that the use of specialised neonatal transport teams could improve quality of neonatal stabilisation and care,[13,14] a Cochrane review by Chang et al[15] did not find any reliable evidence to support or refute the efficacy and clinical outcomes of specialised neonatal transport. Nevertheless, the

finding of a large number of neonates in our study who required invasive (40.8%) and non-invasive (10.8%) ventilation during transport do emphasise the need for adequate training in airway management and use of resuscitation equipment by CHETS staff.

A significant limitation of our study was the lack of complete data since it relied on handwritten documents maintained by the CHETS team for analysis. For example, the primary diagnosis or purpose of transfer was not always clearly documented or easily identifiable in every neonate. Also, for cases that presented with multiple diagnoses but without a principal diagnosis, the first diagnosis that was documented was designated the principal condition.

An incidental finding of our study was that data on activation and transport time (36.3%) and inter-transport temperature (58.0%) was incomplete in a large number of cases. Consequently, we could not perform a secondary analysis of the data that can meaningfully benchmark or compare the quality of CHETS against that of other neonatal transport units. The lack of data could be attributed to time and manpower constraints in a demanding intensive care unit or lack of familiarity with documentation of transport records. These issues can be addressed with standardised medical records through the use of a simplified data collection form or introduction of electronic tools or applications that aid in record-keeping. Accurate documentation is helpful in future statistical analyses and in efforts to enhance patient safety and care. Finally, the dearth of data on neonatal transport in other centres throughout Singapore had precluded more indepth study of the subject. It is hoped that this gap can be addressed by the collection and inclusion of information on neonatal transport in national health statistics in the immediate future.

In our study, post-transfer outcomes were not evaluated. Future studies could focus on such outcomes by examining length of stay, mortality or development of respiratory or neurologic morbidities such as bronchopulmonary dysplasia or intraventricular haemorrhage.

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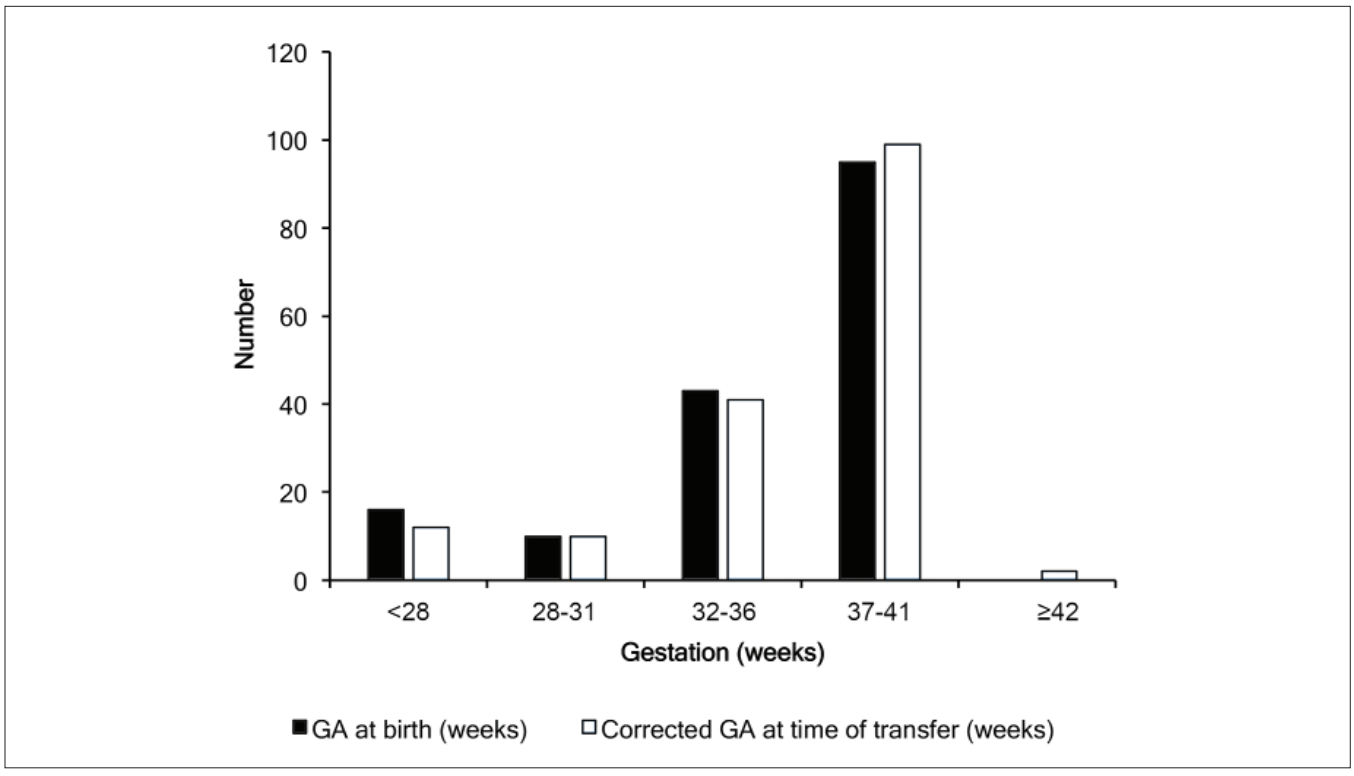

Fig. 1. Gestational age (GA) at birth and at time of transfer, in weeks, of neonates referred to Children's Hospital Emergency Transport Service.

Table 2. Medical Conditions of Neonates that Prompted Referral to Children's Hospital Emergency Transport Service

Variable	n	%
Surgical	38	23.2
Imperforate anus/anorectal malformation	11	
Intestinal atresia/obstruction	7	
Congenital diaphragmatic hernia	6	
Omphalocele	3	
Hirschsprung's disease	3	
Tracheo-oesophageal fistula	3	
Others	5	
Respiratory	30	18.3
Unspecified respiratory distress/stridor for investigation	8	
Persistent pulmonary hypertension	7	
Hyaline membrane disease	6	
Pneumothorax	5	
Others	4	
Prematurity	27	16.5
Neurology	26	15.9
Neonatal encephalopathy	16	
Seizures	5	
Intracranial thrombosis/ haemorrhage	2	
Others	3	
Others	26	15.9
Metabolic	10	
Haematologic	5	
Infection	3	
Renal	3	
Congenital anomalies	2	
Cardiology	17	10.4
Complex heart disease or congenital heart disease	4	
Pulmonary stenosis/atresia	3	
Tetralogy of Fallot	2	
Patent ductus arteriosus	2	
Coarctation/hypoplastic aortic arch	2	
Arrhythmia	2	
Others	2	

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