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Monkeypox is a global health emergency that is spreading across the world. Unlike previous outbreaks of monkeypox, which were zoonotically transmitted, cases of the current outbreak feature significant travel and sexual history.

A recent review of cases in Singapore highlights clinical clues to aid physicians narrow the broad differential diagnosis. Localised anogenital vesiculo-pustules are a common presentation in the current outbreak, and may occur unpredictably relative to other viral prodrome-like symptoms. Clinical vigilance and high index of suspicion can facilitate early detection to contain local transmission.

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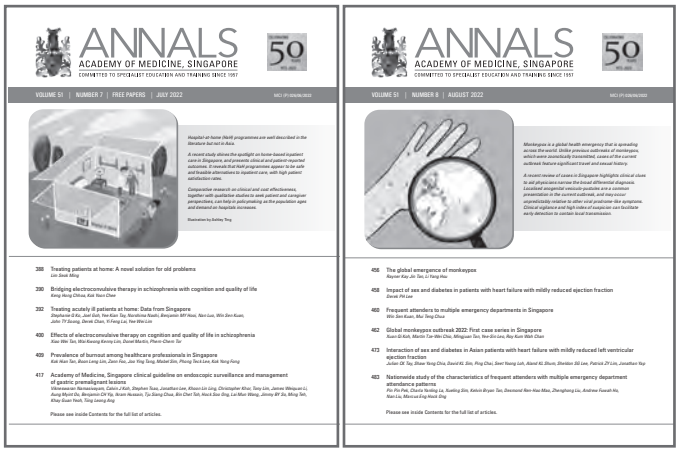

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EDITORIAL

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The global emergence of monkeypox

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Monkeypox is so named because the poxvirus was first identified in 2 outbreaks among cynomolgus monkeys housed at the Statens Serum Institut, Denmark, in 1958.[1] Both outbreaks occurred approximately 2 months after the monkeys arrived by plane from Singapore.[1] However, the natural reservoir of the virus is not monkeys from Asia, but is most likely rodents and other small mammals in West and Central Africa.[2]

Long regarded as a zoonosis with relatively inefficient human-to-human transmission, multiple small outbreaks of monkeypox had occurred in Africa between 1970 and 2017, largely believed to be due to zoonotic transmission.[2] Pre-2022, the largest human outbreak outside Africa occurred in 2003 in the US Midwest: 71 people were infected by prairie dogs kept as household pets, which had themselves been infected previously as a result of close contact with rodents from Ghana.[3]

However, this pattern of almost exclusive zoonotic transmission changed from September 2017, when Nigeria—which prior to that time had reported a grand total of 3 cases—experienced a large and extended outbreak involving mainly young adult men, most of whom had no animal exposure.[2] Household, nosocomial, intimate, and prison transmissions have been described in reports of the Nigerian epidemic,[2,4] backed by genomic evidence of human-to-human transmission.[4] The presence of genital ulcers also featured prominently in these reports,[2,5] along with tentative suggestions on the possibility of sexual transmission as a novel mode of spread for monkeypox.[2]

Dr Dimie Ogoina, lead author of these reports, recalled in a recent press interview that his warnings of monkeypox spreading via sexual transmission had been repeatedly ignored.[6] Indeed, the outbreak in Nigeria was also largely ignored by the global health community until the explosive spread of the virus from May 2022, with more than 36,000 cases and 11 deaths in 89 countries as of 15 August.[7] Genomic analysis of the monkeypox viruses isolated in 2022 linked them firmly to the Nigerian outbreak that began in 2017.[8] Singapore has not been spared from this epidemic, with 15 monkeypox cases diagnosed to date—5 imported and 10 local cases, of which 9 were not linked to any known cases.[9] The clinical features of these 15 cases are described in this issue of the *Annals*.[10]

The World Health Organization (WHO) declared the current outbreak a public health emergency of international concern on 23 July 2022, noting that the majority of cases had occurred in males who had identified themselves as gay, bisexual, or men who have sex with men (GBMSM), with clustering occurring in sexual networks.[10] However, along with other public health practitioners and researchers, WHO also warned against attaching any stigma to or blaming any specific groups for monkeypox, as this would jeopardise public health efforts to contain the virus.[11]

Monkeypox has spread and established itself through the vulnerability of social and sexual networks, but it is not inherently a GBMSM disease, and transmission is neither limited to this group nor to sexual activities in general. Specifically, stigma against GBMSM and other groups may drive individuals from these stigmatised populations away from health services, undermine prevention messaging among the general public, and therefore impede efforts to control the spread of monkeypox.

Can the global monkeypox epidemic be contained, or must we learn to live with another endemic infectious disease so soon after COVID-19?

Despite its extensive spread to date, there are still strong reasons to believe that the epidemic can be contained. It is certainly not as transmissible as COVID-19, with a reproductive number R that exceeds 1 (i.e. the point at which an outbreak will spread exponentially and sustain itself) only in GBMSM sexual networks, while other populations are less vulnerable to monkeypox transmission at current projections.[12] There are also vaccines and drugs designed against smallpox—a closely related virus—that are highly likely to be effective against monkeypox as well, although urgent clinical trials are currently being conducted to verify this. We have also eradicated smallpox—a more transmissible and deadlier disease—in 1980 through a global strategy of detection, isolation and ring vaccination,[13] the latter which involved vaccinating the close contacts of confirmed cases

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rather than mass public vaccination as in the case of COVID-19.

Because monkeypox also has a prolonged incubation period of 6–13 days, a strategy effective against smallpox might also be successful against this virus. Nonetheless, there are non-trivial challenges in implementing a strategy of detection, isolation and ring vaccination,[13] even in Singapore. Currently, there are insufficient smallpox vaccines stockpiled in many countries for the purpose of ring vaccination, even though manufacturing is being ramped up. Contact tracing can also be difficult when the predominant mode of spread is via sexual and social networks of GBMSM, in view of the stigmatisation and discrimination experienced by this population in many countries.[14] Effective outreach and communications are therefore critical in educating and reaching people at higher risk, as well as addressing any stigmatisation.

Thankfully, there is no need to reinvent the wheel when it comes to effective communications during an outbreak. The COVID-19 pandemic has highlighted the importance of effective public health and risk communication in optimising public health responses amid a rapidly evolving situation. In this regard, maintaining public trust, developing clear and culturally appropriate messaging that is delivered on the relevant platforms, and engaging community groups are essential in engendering effective responses.[15]

One way of ensuring communication of clear, consistent, and culturally appropriate information on monkeypox to the right populations is via a 2-pronged strategy. The first is ensuring that the public has accurate information of monkeypox: that anyone can be infected, and that while it can be sexually transmitted, it should not be labelled as a "sexually transmitted disease". This ensures that people understand they are potentially at risk even if they are not sexually active, while for those who are sexually active, traditional prevention methods for sexually transmitted diseases will not offer effective protection against monkeypox. The second is ensuring that community stakeholders are directly engaged to tailor such information to specific populations. These community stakeholders may be groups that serve GBMSM at this point in the global outbreak, but perhaps could also be schools or forums for pregnant mothers, in the event that the course of the outbreak subsequently shifts.

Even though the risk of a large monkeypox outbreak remains remote in Singapore, we will never be free of the threat of importation unless the global outbreak also comes to a close. This outbreak again highlights the risk of rapid infectious disease spread in an interconnected world, and reinforces the need for high-income countries and supranational organisations to support other countries in becoming better prepared against future outbreaks and any major epidemics.

REFERENCES

1. von Magnus P, Andersen EK, Petersen KB, et al. A pox-like disease in cynomolgus monkeys. Acta Pathol Microbiol Scand 1959;46:156-76.
2. Ogoina D, Izibewule JH, Ogunleye A, et al. The 2017 human monkeypox outbreak in Nigeria – report of outbreak experience and response in the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria. PLoS One 2019;14:e0214229.
3. Reynolds MG, Davidson WB, Curns AT, et al. Spectrum of infection and risk factors for human monkeypox, United States, 2003. Emerg Infect Dis 2007;13:1332-9.
4. Yinka-Ogunleye A, Aruna O, Dalhat M, et al. Outbreak of human monkeypox in Nigeria in 2017-18: a clinical and epidemiological report. Lancet Infect Dis 2019;19:872-9.
5. Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human monkeypox in Nigeria. Clin Infect Dis 2020;71:e210-4.
6. National Public Radio. He discovered the origin of the monkeypox outbreak – and tried to warn the world. Updated 29 July 2022. Available at: https://www.npr.org/sections/goatsandsoda/2022/07/28/1114183886/a-doctor-in-nigeria-tried-to-warn-the-world-that-monkeypox-had-become-a-global-t. Accessed on 15 August 2022.
7. Mathieu E, Spooner F, Dattani S, et al. Monkeypox, 2022. Available at: https://ourworldindata.org/monkeypox. Accessed on 15 August 2022.
8. Isidro J, Borges V, Pinto M, et al. Phylogenomic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus. Nat Med 2022;28:1568-72.
9. Ministry of Health, Singapore. Summary of confirmed monkeypox cases in Singapore, 2022. Available at: https://www.moh.gov.sg/docs/librariesprovider5/default-document-library/summary-of-monkeypox-casese17ab747df2f444ba56e8f13dbecc2df.pdf. Accessed on 15 August 2022.
10. Koh XQ, Chio M, Tan M, et al. Global monkeypox outbreak 2022: First series of cases in Singapore. Ann Acad Med Singap 2022;51:462-72.
11. World Health Organization. Second meeting of the International Health Regulations (2005) (IHR) Emergency Committee regarding the multi-country outbreak of monkeypox, 23 July 2022. Available at: https://www.who.int/news/item/23-07-2022-second-meeting-of-the-international-health-regulations-(2005)-(ihr)-emergency-committee-regarding-the-multi-country-outbreak-of-monkeypox. Accessed on 15 August 2022.
12. Endo A, Murayam H, Abbott S, et al. Heavy-tailed sexual contact networks and the epidemiology of monkeypox outbreak in non-endemic regions, May 2022. medRxiv 2022. https://doi.org/10.1101/2022.06.13.22276353.
13. Thèves C, Crubézy E, Biagini P. History of smallpox and its spread in human populations. Microbiol Spectr 2016;4.
14. Sah R, Abdelaal A, Asija A, et al. Monkeypox virus containment: the application of ring vaccination and possible challenges. J Travel Med 2022. doi: 10.1093/jtm/taac085.
15. Hyland-Wood B, Gardner J, Leask J, et al. Toward effective government communication strategies in the era of COVID-19. Humanit Soc Sci Commun 2021;8:30.

EDITORIAL

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Impact of sex and diabetes in patients with heart failure with mildly reduced ejection fraction

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With increasing global awareness of sex differences in the heart failure population and the new entity of heart failure with mildly reduced ejection fraction (HFmrEF), much has yet to be fully understood with regard to patient demographic, clinical presentation, response to guideline-directed heart failure therapies, and outcome across the spectrum of left ventricular ejection fraction (LVEF). A recent study from the UK found that HFmrEF constituted 15% of the entire spectrum of heart failure population, and 40% among this group had LVEF below 50%. The clinical characteristics and outcomes in HFmrEF population were found in a large part to be intermediate between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).[1] These findings were consistent with a previous analysis from European Society of Cardiology (ESC) heart failure long-term registry[2] as well as a prospective international multiethnic cohort study.[3] However, whether HFmrEF is a distinct entity from HFrEF and HFpEF remains a heated debate. On the therapeutic side, whether HFmrEF population demonstrates similar treatment response to guideline-directed heart failure therapies as HFrEF cohorts, requires further evidence from collaborative research efforts. Undoubtedly, the introduction of the HFmrEF entity by the ESC aimed to draw a conjoint effort in better characterisation and to establish a clear therapeutic strategy to this category.

Sex differences in heart failure population was another hot topic in the past decade. While male sex predominated in HFrEF and female sex predominated in HFpEF as shown in various studies, sex differences were also noted with respect to clinical characteristics, pathophysiology and therapeutic responses to heart failure treatment.[4] Increasing evidence showed that men were predisposed to macrovascular diseases and hence at higher risk of developing HFrEF, whereas women were predisposed to microvascular disease and endothelial inflammation, which were hypothesised to play a key role in HFpEF.[5] Apart from sex differences in the pathophysiology of heart failure, a number of sex-specific risk factors for heart failure such as peripartum cardiomyopathy and cancer therapy-induced cardiomyopathy also contributed to distinct sex differences in heart failure populations.

On the other hand, the presence of diabetes was known to be strongly associated with adverse outcomes in both acute and chronic ambulatory heart failure cohorts.[6,7] Diabetes constitutes an ever-increasing threat to global health as a debilitating and serious chronic disease that causes disabling and life-threatening complications. According to the International Diabetes Federation Diabetes Atlas[8] published in 2021, some 537 million adults (1 in 10) were living with diabetes in 2021, and the number is expected to rise to 643 million by 2030 and 783 million by 2045. Such an exponential rise in predicted numbers is also anticipated in the Southeast Asia population where 1 in 11 adults (90 million) were living with diabetes in 2021. The under-awareness of diabetes and its profound health consequences continues to be a major challenge to the global healthcare system.

In this issue of the *Annals*, we get an insight into the interplay between these 2 major factors—diabetic status and sex—in the outcome of HFmrEF patients.[9] The Asian context of this study further adds to the emerging data and understanding of our ethnic population. A systematic collection of data in a nationwide registry is crucial to improving both our understanding as well as clinical care of our heart failure patients. Regarding the clinical characteristics of Asian HFmrEF population shown in the current article, a slight male predominance was observed.[9] However, the sex predilection was not as clear as in HFrEF or HFpEF cohorts, which had been previously discussed. Obesity was noted to be more prevalent in the diabetic compared with non-diabetic group, and a clear sex predilection was not observed. There was a higher prevalence of prior coronary artery diseases and myocardial infarction in men than women, which was similar to HFrEF cohorts. A higher prevalence of diabetes was observed in women than in men. More importantly, a clear interaction between diabetic status and sex on the outcomes of HFmrEF was demonstrated in this study. Regardless of sex, the presence of diabetes was significantly associated with

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worse clinical outcomes in HFmrEF. However, compared to men, the presence of diabetes in women was found to be less strongly associated with all-cause mortality but more strongly associated with combined cardiovascular death and heart failure rehospitalisation.

While the most widely used classification of heart failure is currently based on the LVEF range and the heart failure treatments that we offer primarily target the physiological consequences of heart failure, little is known on how we can best categorise our heart failure patients. If we are to classify them by ejection fraction, what cutoffs should we use? What is the range that should be considered "normal"? And should we classify "normal" by the response to heart failure therapies in drug trials? Given that the most accepted "reduced ejection fraction group" came mainly from the substantial evidence of drug efficacies in major trials conducted in the past, the HFmrEF group in fact created a lot of enthusiasm and interest in how we can further refine our classification of general heart failure population to optimise the use of heart failure therapies, and perhaps open up a new era of heart failure treatments.

As we understand more about the interaction between sex and various risk factors in heart failure population, as in diabetes in this case, we are expecting to see more research on this topic. With accumulating evidence showing that women behave differently than men in disease processes, outcomes and treatment responses—not only in heart failure but also in other acute and chronic medical illnesses—sex-specific management strategies and guidelines will be one of the important future developments in medicine.

REFERENCES

1. Straw S, Cole, CA, McGinlay M, et al. Guideline-directed medical therapy is similarly effective in heart failure with mildly reduced ejection fraction. Clin Res Cardiol 2022. doi: 10.1007/s00392-022-02053-8.
2. Chioncel O, Lainscak M, Seferovic, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC heart failure long-term registry. Eur J Heart Fail 2017;19:1574-85.
3. Lam CSP, Gamble GD, Ling LH, et al. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. Eur Heart J 2018;39:1770-80.
4. Lam CSP, Arnott C, Beale AL, et al. Sex differences in heart failure. Eur Heart J 2019;40:3859-3868c.
5. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J 2018; 39:3439-50.
6. Dauriz M, Targher G, Laroche C, et al. Association Between Diabetes and 1-Year Adverse Clinical Outcomes in a Multinational Cohort of Ambulatory Patients With Chronic Heart Failure: Results From the ESC-HFA Heart Failure Long-Term Registry. Diabetes Care 2017;40:671-8.
7. Targher G, Dauriz M, Laroche C, et al. In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19:54-65.
8. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119.
9. Tay JCK, Chia SY, Sim DKL, et al. Interaction of sex and diabetes in Asian patients with heart failure and mildly reduced left ventricular ejection fraction. Ann Acad Med Singap 2022; 51:473-82.

EDITORIAL

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Frequent attenders to multiple emergency departments in Singapore

Win Sen Kuan [1,2]*MCI*, Mui Teng Chua [1,2]*MPH*

The problem of overcrowding, of which access block is one of the main causes, continues to plague emergency departments (EDs) worldwide.[1] Some of its negative effects include adverse impact on patient safety, medical errors and staff burnout. In addition, high volume of patients waiting to be seen (ED input) exacerbates overcrowding. Frequent attenders (FAs), defined as those having 4 or more visits to the ED per calendar year,[2] are known to utilise incommensurate amount of resources and drive up ED input.[3] The recognition of this issue prompted The Royal College of Emergency Medicine in the UK to publish a best practice guideline and recommendations to manage FAs.[4] Although numerous papers have been published from single-centre EDs to better understand the characteristics of these patients, several statewide studies highlighted the possibility for underestimation of the magnitude of the problem as FAs may have the propensity to visit multiple EDs in the same region.

In this issue of the *Annals*, Pek et al. characterised FAs at multiple Singapore public hospital EDs and compared them to those who only attend a single ED frequently.[5] The authors benefited from Singapore being an island nation, which enabled a retrospective analysis of nationwide ED de-identified electronic health database between 2006 and 2018. This is the longest longitudinal study on FAs in Singapore conducted thus far from a large database. They introduced a novel concept of "mixed" FAs—those who attend single and multiple EDs in different calendar years. This categorisation was made to anticipate the likelihood of variability in ED attendance patterns among these patients—which were indeed shown in some of the results—versus FAs of multiple EDs and single ED. The authors discovered that about half of FAs visited multiple EDs (38.9%) or were mixed FAs (12.6%), who would have otherwise been missed out from single-centre studies. Notwithstanding trend data showing a decline in proportion of FAs from 19.8% in 2006 to 17.1% in 2018, the absolute number is still substantial and warrants attention. Among factors found to be associated with multiple ED and mixed FAs were younger patients, males, multiple comorbidities, and median triage class of higher severity. These patients were also much more likely to visit EDs more than 7 times per year, contributing to a considerable and disproportionate strain on ED resources.

Despite not directly studying appropriateness of ED attendances, the authors found that FAs of multiple EDs and mixed ED were less likely to be admitted to inpatient units for further management. Overall, only around 40% of FAs had an admission rate of 0.5 or more, with a significantly lower proportion among FAs of multiple EDs, suggesting some level of inappropriateness in their multiple ED attendances that may have been avoided and adequately managed in the community setting. They postulated that the younger age and greater mobility of these FAs may be reasons behind the results, a discovery corroborated by a recent Singapore multicentre study.[6] However, the findings of more patients with multiple comorbidities and median triage class of higher severities among mixed FAs seem counter-intuitive to the lower admission rate, and require further investigation.

As with any other research using administrative databases, there will be limitations on the details of variables used for analysis. Quantifying the number of comorbidities rather than identification of specific comorbidities would likely limit its usefulness in understanding the reasons behind the differences between FAs of single ED versus multiple EDs or mixed FAs. Likewise, the broad categorisation of most common final diagnosis based on International Classification of Diseases codes, instead of specific conditions, hinders the ability for in-depth understanding of the ED attendance patterns of FAs. For example, the 2 main diagnosis categories of "respiratory system" and "symptoms, signs and ill-defined conditions" that were found in 41.6% of FAs of single EDs and 51.8% of mixed FAs are rather vague and not informative.

The efforts by the authors to approach this analysis from a nationwide perspective and comparing with single-centre ED FAs are both extremely important and commendable. A systematic review that evaluated effectiveness of interventions targeting FAs in reducing visit frequency and improving patient outcomes identified 24 out of 31 studies conducted at only a single institution.[7] There is likelihood of overestimation of the interventions' measured effectiveness in decreasing ED visits if these FAs visited other sites. Therefore, having

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all-encompassing data on FAs and perhaps other ED-related topics in the future could provide sound foundation for health services research to identify pertinent issues, and subsequently offer potential whole-system national approach to solutions rather than from individual institutions or healthcare clusters.[8]

Since EDs deal with undifferentiated patients coming through their doors, using a symptoms-based approach could be a viable alternative in dissecting diagnoses to more meaningful conditions, which may allow for planning of future interventions.[9] This strategy is further supported by the finding that heterogeneity of presenting complaint, particularly with history of mental disorder, was found to be associated with further attendance in a UK study.[10] The exclusion of patient visits to a specialised psychiatric facility in this study by Pek et al. restricts and potentially underestimates the rapidly increasing burden of mental illness among FAs. Overall, only 1.4% of FAs' reasons for visiting EDs were attributed to mental disorders, far lower than data published in the West where substance abuse and heavy drinking contribute significantly as reasons for visits to EDs by FAs.[2,3] Data on mode of arrival and referral were also unavailable in this study. These additional factors could provide further insight into ascertaining the health-seeking behaviour and mobility patterns, especially among younger patients who were at higher odds of attending multiple ED and mixed FAs.

Generalisability to other healthcare settings may be limited due to the unique geographical nature and healthcare system of Singapore, integrated with cultural and health-seeking behaviour in the society. For instance, FAs to multiple EDs in England were older and more likely to be admitted compared to Singapore.[8] Nevertheless, regions with similar electronic database capabilities could model after Pek et al.[5] and perform suitable analyses to comprehend patterns of their own FAs. After identifying attendance patterns, qualitative studies may be carried out to better understand the clinical, psychological and social profiles of these patients to ascertain if they are psychosocially vulnerable and heavily utilise other primary care services.[11] Some of the possible interventions implemented in other regions include having ED care plans, case management, multidisciplinary team conferences, primary care involvement and psychological therapy for patients with medically unexplained symptoms.[4]

Looking from the perspective of a complex system comprising ED patients, their social networks, wider society, and the healthcare system, a study from 2 regions in the UK of over 3.8 million ED attendances advocates that FAs should be seen as part of a continuum of attendance rather than a discrete problem of individuals.[12] Burton et al. showed that ED attendances follow a power law distribution and ED attendance patterns are stable at the level of the system, but unstable at the level of individual FAs. The consistency of their findings across a very socioeconomically diverse region suggests a generalisable process. These data further strengthen the argument that a whole-system view, together with individual solutions, would be required to evaluate interventions to reduce frequent attendances.

By 2023, 2 of the 3 health clusters in Singapore will be on board the Next Generation Electronic Medical Record, thus integrating ED datasets from majority of public institutions. This game-changing initiative would enable streamlined non-duplicative delivery of clinical care, which is particularly pertinent to multiple and mixed FAs. In addition, it could allow almost real-time monitoring of FA burden on a larger scale and effects of interventions that are instituted.

REFERENCES

1. Kelen GD, Wolfe R, D'Onofrio G, et al. Emergency department crowding: the canary in the health care system. NEJM Catalyst 2021;5.
2. Locker TE, Baston S, Mason SM, et al. Defining frequent use of an urban emergency department. Emerg Med J 2007;24:398-401.
3. Boh C, Li H, Finkelstein E, et al. Factors Contributing to Inappropriate Visits of Frequent Attenders and Their Economic Effects at an Emergency Department in Singapore. Acad Emerg Med 2015;22:1025-33.
4. The Royal College of Emergency Medicine Best Practice Guideline. Frequent Attenders in the Emergency Department, August 2017. Available at: https://rcem.ac.uk/wp-content/uploads/2021/10/Frequent_Attenders_in_the_ED_Aug2017.pdf. Accessed on 21 June 2022.
5. Pek PP, Lau YC, Sim X, et al. Nationwide Study of the Characteristics of Frequent Attenders with Multiple Emergency Department Attendance Patterns. Ann Acad Med Singap 2022;51:483-92.
6. Cheng L, Ng WM, Lin Z, et al. Factors reducing inappropriate attendances to emergency departments before and during the COVID-19 pandemic: A multicentre study. Ann Acad Med Singap 2021;50:818-26.
7. Moe J, Kirkland SW, Rawe E, et al. Effectiveness of Interventions to Decrease Emergency Department Visits by Adult Frequent Users: A Systematic Review. Acad Emerg Med 2017;24:40-52.
8. Greenfield G, Blair M, Aylin PP, et al. Frequent attendances at emergency departments in England. Emerg Med J 2020;37:597-99.
9. Kelly AM, Keijzers G, Klim S, et al. An Observational Study of Dyspnea in Emergency Departments: The Asia, Australia, and New Zealand Dyspnea in Emergency Departments Study (AANZDEM). Acad Emerg Med 2017;24:328-36.
10. Hotham R, O'Keeffe C, Stone T, et al. Heterogeneity of reasons for attendance in frequent attenders of emergency departments and its relationship to future attendance. Emerg Med J 2022;39:10-15.
11. Byrne M, Murphy AW, Plunkett PK, et al. Frequent attenders to an emergency department: a study of primary health care use, medical profile, and psychosocial characteristics. Ann Emerg Med 2003;41:309-18.
12. Burton C, Stone T, Oliver P, et al. Frequent attendance at the emergency department shows typical features of complex systems: analysis of multicentre linked data. Emerg Med J 2022;39:3-9.

ORIGINAL ARTICLE

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Global monkeypox outbreak 2022: First case series in Singapore

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ABSTRACT

Monkeypox is a global health emergency. Prior to 2022, there were few reports of monkeypox outside of endemic countries, which were mostly travel-related. Since May 2022, an exponential increase in monkeypox infections in previously non-endemic countries has been reported. Unlike previous outbreaks of monkeypox, which were zoonotically transmitted and presented with generalised vesicular eruptions after prodromal symptoms, cases of the current outbreak feature significant travel and sexual history, and atypical localised genital eruptions with unpredictable onset relative to viral prodrome-like symptoms. We summarise the 15 Singapore cases reported to date as of August 2022, and highlight salient clinical clues that may aid physicians in narrowing the broad differential diagnosis of an acute vesicular genital eruption. Although research into vaccination and antiviral strategies is ongoing, monkeypox is currently conservatively managed. Clinical vigilance and a high index of suspicion are required to facilitate early detection and isolation of cases to contain transmission in Singapore.

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INTRODUCTION

Monkeypox has been declared a public health emergency of international concern. Up until 2022, most cases of monkeypox have been reported in parts of Africa. On 7 May 2022, a returning traveller from Nigeria to the UK was confirmed to have contracted monkeypox. By the end of May 2022, 23 countries had reported cases of monkeypox to the World Health Organization (WHO), and many of these cases did not involve a recent visit to an endemic country. On 23 June 2022, WHO convened a meeting of the International Health Regulations (2005) Emergency Committee on the multinational monkeypox outbreak this year, bringing global attention to this disease.[1]

The monkeypox virus is a member of the *Poxviridae* family, genus *Orthopoxvirus*. There are 2 genetically distinct clades—the West African clade and the Basin clade (Central African). Transmission in endemic areas was largely zoonotic via consumption of uncooked small mammals and contact with diseased animals through impaired skin barrier or respiratory route, while human-to-human transmission through household contacts were observed in outbreaks.[2-5] Conventional signs included fever, chills, pharyngitis, conjunctivitis, generalised vesiculo-pustular eruption, and potential progression to pulmonary failure and encephalitis. A mortality rate of approximately 1% for the West African clade and up to 10% for the Congo Basin clade was observed; victims were predominantly children aged 3–5 years.[3,4] In 2003, an outbreak of 47 zoonotically transmitted monkeypox infections with household transmissions was reported in the US. Infected prairie dogs that had been temporarily kept in the vicinity of imported monkeypox-infected wild-caught rodents from Ghana were identified as the culprit animal reservoirs. Symptoms were similar to those observed in Africa. In this outbreak, however, there were no reported mortalities or interhuman transmissions.[5-7]

The first case of monkeypox in Singapore was diagnosed in 2019. A business traveller from Nigeria had presented with fever, chills, myalgia and a generalised pustular eruption. Infection was attributed to the consumption of contaminated bushmeat in Ebonyi State 2 weeks prior. Close contacts were quarantined, and

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CLINICAL IMPACT

What is New

- The current monkeypox epidemic differs from classic monkeypox in risk factors, transmission, clinical presentation and outcome.
- Travel and sexual history are important potential risk factors.
- Localised anogenital vesiculo-pustules are a common presentation in the current outbreak, and may occur unpredictably relative to other viral prodrome-like symptoms.

Clinical Implications

- Alternative diagnoses that may fully explain the symptoms should be excluded clinically or via point-of-care testing if available.
- A high index of suspicion should be maintained in such situations.

vaccination with smallpox live vaccine (ACAM2000, Emergent Product Development Gaithersburg Inc, Gaithersburg, US) was offered and administered to 14 people without serious adverse events. There was no local transmission and no further local cases of monkeypox until the current outbreak in 2022.[8]

Since the onset of the monkeypox outbreak this year, 15 cases of monkeypox have been diagnosed in Singapore as of 10 August 2022. Measures such as case isolation and contact tracing have been enforced to contain local transmission. As Singapore relaxes travel restrictions that were instituted during the COVID-19 pandemic, more cases of monkeypox are likely to be diagnosed in the country. The current monkeypox outbreak has demonstrated significant interhuman transmission of the disease, with clinical presentations that differ from those of previous outbreaks, emphasising the need to update our understanding of this evolving disease. We summarise the 15 local cases based on the Ministry of Health (MOH), Singapore's situation update,[9] and discuss factors that may differentiate monkeypox from other clinical differentials of an acute vesicular genital eruption.

Diagnosed cases to date in Singapore

All 15 diagnosed cases of monkeypox infection in Singapore (Table 1)[9] were male adults of 25–54 years (median 36 years, mean 38.4 years, interquartile range 15 years). Five cases had a positive history of travel and sexual contact in a country with reported monkeypox cases. Details regarding symptoms of the last 4 cases were not reported. Six of the first 11 cases developed skin lesions first, 5 of whom were located on the inguinal and anogenital regions, and the last on the lower abdomen. One of these 6 cases had concurrent anogenital and extragenital skin lesions as a first symptom, while the rest had more localised lesions. The other 5 patients initially developed fever (sole symptom in 2, accompanied by headache, anal discomfort and myalgia in 1), headache alone (n=1), or anal discomfort alone (n=1). All of the first 11 patients subsequently developed skin lesions in the course of their disease. Putting aside the time of appearance of skin lesions, 5 patients had skin lesions in the anogenital area; 3 had anogenital and extragenital skin lesions; 1 had anogenital and extragenital skin lesions localised to the lower abdomen; and 2 had lesions on unspecified locations. Additionally, 8 cases were reported to have fever and 2 were reported to have lymphadenopathy. These reported symptoms are based on MOH local situation update,[9] which may not accurately reflect the full range of symptoms experienced by these patients throughout the course of the disease as these reports are made only upon first confirmation of diagnosis.

Table 1 summarises the presentations of the diagnosed cases in Singapore since the start of the global monkeypox outbreak this year. Representative lesions from one of these cases are depicted in Fig. 1, demonstrating vesicles, pustules, erosions and scabs occurring contemporaneously.

DISCUSSION

Clinical features of the current outbreak versus classic monkeypox

It has been highlighted that the clinical features of the current monkeypox outbreak differ from those reported in the classic version, in terms of mode of transmission, demographics of at-risk persons, sequence of symptom onset, morbidity and mortality.[10-12] Monkeypox infection, as described in outbreaks prior to 2022, had an incubation of 7–17 days. The disease was heralded by a prodrome of fever, headache, fatigue, malaise, backache, and severe localised or generalised lymphadenopathy. Patients developed skin lesions 1–3 days after the prodrome, usually starting as a synchronous maculopapular eruption with lesions of 2–5mm diameter, with centrifugal spread. The lesions became papular, vesicular, pustular and then crusted over the next 2–4 weeks, resolving with scarring and pigmentary change.[13,14]

The current outbreak of monkeypox differs in terms of epidemiology and clinical features. Firstly, a large proportion of cases occurring in non-endemic countries

Table 1. Summary of locally reported cases to date

n=15	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15
Age	42	45	36	30	48	41	46	26	31	28	32	59	33	25	54
Sex	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male
Travel history	Yes, location not reported	No	Yes, US	Yes, Germany	No	No	Yes, London	No	No	Yes, Canada	No	No	No	No	No
First symptom	Headache	Rash on lower abdomen	Anal discomfort	Groin rash	Perianal rash	Genital rash	Groin rash	Rash on genital region and other body regions	Fever	Fever, headache, anal pain and myalgia	Fever	Unreported	Unreported	Unreported	Unreported
Rash	Yes, location not reported	Yes, lower abdomen	Yes, rashes “typical of monkeypox”	Yes, groin rash	Yes, perianal rash	Yes, genital rash	Yes, groin rash	Yes, genital rash and rashes in other body regions	Rashes on face, perianal region that spread to other body parts	Yes, perianal rash	Yes, genital rashes that spread to other body regions	Unreported	Unreported	Unreported	Unreported
Fever	Yes	Yes	Unreported	Yes	Yes	Unreported	Yes	Unreported	Yes	Yes	Yes	Unreported	Unreported	Unreported	Unreported
Lymphadenopathy	Unreported	Yes	Unreported	Unreported	Unreported	Unreported	Yes	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported
Sore throat	Unreported	Yes	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported
Fatigue	Unreported	Yes	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported
Other symptoms	Unreported	Unreported	Yes, not specified	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported	Unreported

Source: Ministry of Health, Singapore. Monkeypox. Available at: https://www.moh.gov.sg/diseases-updates/monkeypox. Accessed on 13 August 2022.

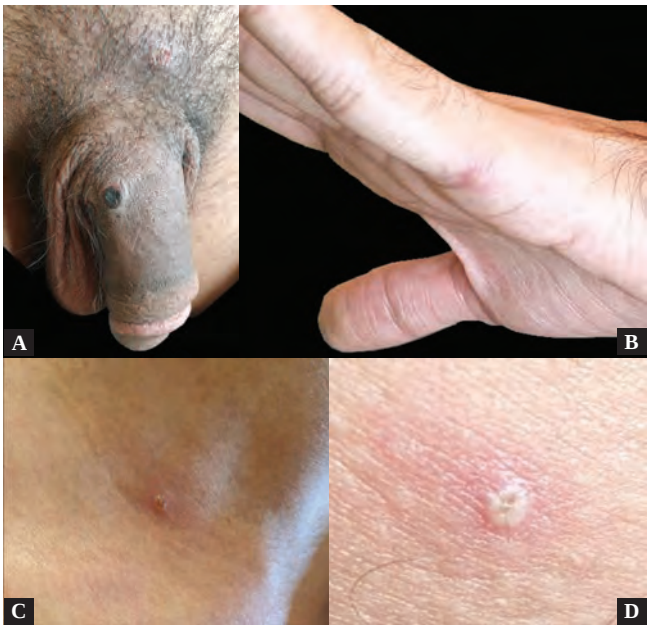

Fig. 1. Representative lesions from a locally diagnosed case demonstrating contemporaneous lesions at various stages of development.

(A) Epithelialising ulcer at the base of shaft of penis with another ulcer on pubis.
(B) Small vesicle on an erythematous base on the palmar aspect of the left 5th finger.
(C) Eroded vesiculo-pustule on an erythematous base over the right supraclavicular region.
(D) Close-up of a representative umbilicated pustule on an erythematous base.

are reported among men who had recent sexual interactions with a new male partner or multiple partners. Secondly, many cases had only a few lesions, which could be localised to the genital area including mucosal surfaces, and appear without prodrome. Lesions were asynchronous, and the presence of lesions at different stages of evolution was observed in some patients.[15] Some patients, on the other hand, did not have rashes. Anal pain and anal bleeding were other features different from the classic presentation. Associated symptoms such as fever, myalgia, fatigue, headache, sore throat and lymphadenopathy were common throughout the course of the disease, but the sequence of symptomatology varied.[15,16]

Case definition of suspected monkeypox

Given the varied presentation of the current monkeypox outbreak, the initial local guidance for defining a suspect case was relatively broad, casting a wide net to pick up possible cases (MOH Circular No. 63/2022, 20 May 2022).[17] Doctors were instructed to notify possible cases if they had fever, acute vesicular rash, and either a travel history to countries with reported monkeypox cases or a history of close contact with an infected person within 21 days before the onset of symptoms. This led to reports of cases where there was a clear probable alternative diagnosis for the symptoms.[17]

The latest Singapore guidance of when to suspect monkeypox (MOH Circular No. 79/2022, 1 July 2022)[18] reflects our evolving understanding of the current outbreak and refines the suspect case definition. Risk factors and clinical features taken into consideration in the current guidance include recent travel history to countries with confirmed cases of monkeypox, history of close contact (sexual or non-sexual) with an infected person or within a network with circulating monkeypox activity, an unexplained acute rash and constitutional symptom(s). Clinicians were additionally reminded to exercise clinical judgment to exclude other common conditions that may present similarly, such as varicella zoster virus (VZV), herpes zoster virus (HZV), enteroviral infections e.g. hand-foot-mouth disease (HFMD), measles, herpes simplex virus (HSV), other sexually transmitted diseases (STDs), molluscum contagiosum, dengue, and dermatitic conditions. Supplementary Table S1 (in the online version of this article) compares the Singapore suspect case definition to that used in selected other countries, which are relatively similar.

Disease mimics

It may be difficult for the clinician to differentiate potential causes of an acute rash in individuals with exposure history who become symptomatic, with compatible constitutional symptoms. A thorough history and examination, tailored to the patient's demographics and medical history, will provide clues to arriving at the correct diagnosis.

The majority of cases reported in this outbreak have been in men who have sex with men (MSM) who have recent sexual exposure, therefore STDs rank highly on the list of differentials and may also occur concomitantly.[16] The first is HSV infection.

Patients with HSV infection have tender, grouped vesicles or shallow erosions with an erythematous border. These may be preceded by a prodrome. When more severe, patients may have adjacent lymphadenopathy. Immunocompromised patients may present with more severe signs and constitutional symptoms, hence human immunodeficiency virus (HIV) tests should be performed in all patients who are not already known to have HIV. A swab for HSV polymerase chain reaction (PCR) should be taken. If available, a Tzanck test can be performed but may not differentiate between different *Herpesviridae* infections such as HSV, VZV or HZV.

The chancre of primary syphilis is classically described as a single painless ulcer with firm edges. Patients may have more than one chancre. Unlike monkeypox lesions, syphilitic chancres do not evolve through stages of tender vesicle or pustule, but are papules that ulcerate. Secondary syphilis in some cases may be difficult to differentiate from the vesiculopustular eruption of monkeypox. Pustular secondary syphilis is rare, estimated to occur in approximately 1.9% of patients with secondary syphilis.[19] Dark-field microscopy of skin lesions will demonstrate spirochetes of *Treponema pallidum* in moist lesions and can be a useful rapid test in a clinic with appropriate resources. A rapid plasma reagin test should be performed for all patients with anogenital ulcers. It is often positive in primary syphilis and always positive in secondary syphilis.

Disseminated gonococcal infection (DGI) is another important differential. Patients may develop oligoarticular septic arthritis, arthralgia, fever, and systemic complications such as meningitis and endocarditis. Petechial or pustular lesions are usually acrally distributed. Gram stain, culture and nucleic acid amplification test (NAAT) from swabs of pustular skin lesions or synovial fluid in suspected DGI are not sensitive.[20-22] Although the primary site of infection may not be clinically apparent, it is still advisable to obtain samples from all reported sites of sexual exposure. The gold standard investigation is a NAAT for *Neisseria gonorrhoea* from first-void urine, urethral discharge or secretions.[23]

Lymphogranuloma venereum (LGV), chancroid and granuloma inguinale are rarely diagnosed STDs in Singapore, but should also be considered when evaluating a patient with fever, genital lesions, and a compatible exposure history. LGV is similar to monkeypox in having prominent tender lymphadenopathy, but the genital lesion of LGV tends to be a single spontaneously resolving papule/vesicle/ulcer. Chancroid also presents with single or multiple inflamed genital papules that progress into painful ulcers, together with tender inguinal lymphadenopathy. Gram stain, albeit again insensitive, may demonstrate strands of Gram-negative rods in a "school of fish" appearance. The lesions of granuloma inguinale are characteristically beefy red, painless, slowly progressive genital ulcers without regional lymphadenopathy.[23,24]

Non-STDs that may present with a vesicular eruption on the anogenital area include VZV, enteroviral infections, HZV and impetigo. Both VZV and enteroviral infections may be preceded by a mild prodrome and have an oral enanthem. In VZV, there is a cephalocaudal spread of vesicles on an erythematous base, characteristically with lesions at different stages presenting simultaneously, and usually sparing the distal limbs and lower limbs. An example of enteroviral infection is HFMD, which presents with oral stomatitis and acral vesicles that may become generalised. HFMD is more common in children, although adults may also be affected. HZV that affects the S1–S3 dermatome may present with grouped vesicles that coalesce into bullae and erosions with scalloped borders over the anogenital region. Clues to this diagnosis include a preceding sensation of hyperaesthesia or hyperalgesia in the corresponding dermatome, and unilateral lesions that respect the midline. As aforementioned, Tzanck smear may be useful to support *Herpesviridae* infection as a point-of-care test, but lesional swabs for PCR for VZV, enteroviruses, and HSV should be obtained for confirmation of diagnosis. Impetigo is recognised by presence of golden crusting on erythematous erosions, typically over the face and extremities. It may be a primary cause of anogenital pustulation, or a secondary infection of pre-existing lesions of other causes. Pyogenic culture from lesional swab should be obtained to guide treatment.[24]

Lastly, insect bite reactions may give rise to pruritic, urticated papules that can progress to vesiculobullae or persistent prurigo nodularis-like lesions. The bites may correspond to sites of exposure, and a history of environmental exposures, pets and hobbies can be revealing. Some patients may develop a hypersensitivity reaction in the form of papular urticaria that can be generalised; lesions tend to be more urticated and erythematous rather than pustular, unless there is a secondary infection.[24]

Table 2 compares and contrasts selected differentials of monkeypox eruption.

Diagnosis of monkeypox

Monkeypox diagnosis can be made via NAAT. Singapore uses specific monkeypox virus (MPXV) PCR, which is preferable to the less specific *Orthopoxvirus* PCR. Genetic sequencing to determine the virus clade is recommended by WHO. Suitable samples include a vigorous swab of exudate or lesion, roof of lesion, or crusts. Sampling should be performed from at least 2 lesions of the same type, preferably of different appearance and at different locations of the body. Lesions of different types (e.g. exudate vs skin vs crust) should be collected in different tubes of viral transport media. Samples should be refrigerated at 2–8°C or frozen

Table 2. Selected differentials of current monkeypox outbreak[22,24,25,29]

Clinical differentials	Cutaneous features	Common extracutaneous features	Potential differentiating features	Potential confounding features	Laboratory tests (including point-of-care tests)
Monkeypox (current outbreak)	• Lesions at same stage of development, localised or generalised, frequently genital distribution • Sequential development from macules to papules to vesicles to pustules to scabs over 2–4 weeks • Papulovesicular/pustular stage consists of deep-seated discrete or grouped lesions, often with umbilication	• Tender lymphadenopathy • Viral prodrome-like symptoms may occur before, together or after onset of rash • May have anal discomfort	• Lesions were classically described to be at the same stage of development, although asynchronous lesions have been reported in the current outbreak • Epidemiologic risk factors in terms of travel, sexual history, and contact with dead/live African endemic exotic species	• Sequence of symptom onset is variable • Cases may not have relevant exposure history • May be clinically indistinguishable from less common presentations of SARS-CoV-2 infection or secondary syphilis, or atypical presentations of the other listed differentials	• Lesional swab for MPXV PCR • Consider opportunistic screening for other STIs, including syphilis (such as POC testing with RPR) and HIV (POC)
Herpes simplex	• Grouped vesicles on an erythematous base that may coalesce into bullae/erosions with scalloped borders • Can range from asymptomatic to excruciatingly painful	• Viral prodrome before onset of lesions • May be associated with regional lymphadenopathy	• Characteristically grouped lesions with scalloped border on erythematous base, unlike monkeypox lesions which can be discrete	• Similar sexual epidemiologic risk factor to monkeypox • Monkeypox may also have grouped vesicles on an erythematous base indistinguishable from HSV	• Lesional swab for Tzanck smear (POC) • Lesional swab for HSV PCR
Disseminated gonococcal disease	• Acral distribution of petechial or pustular eruptions	• Milky white or purulent discharge from exposed infected areas e.g. urethra, rectum, vagina, oropharynx • Fever • Arthralgia • Oligoarticular septic arthritis • May have complications such as perihepatitis, meningitis, pelvic inflammatory disease, endocarditis	• Genital discharge is not a feature of monkeypox • Swollen and tender oligoarthritis if septic gonococcal arthritis • Pustules do not demonstrate umbilication	• Similar sexual epidemiologic risk factor to monkeypox • Gram stain of pustules is not sufficiently sensitive to rule out gonococcal infection	• *Neisseria gonorrhoeae* PCR from relevant sites • *Neiserria gonorrhoeae* culture
Lymphogranuloma venereum (LGV)	• Causative organism: the L1, L2 and L3 serovars of *Chlamydia trachomatis* • Primary lesion seen in up to half of cases (1st stage of LGV) — herpetiform lesion that spontaneously resolves without scarring	• Constitutional symptoms are rare • Inguinal syndrome (second stage of LGV): suppurative unilateral inguinal lymphadenopathy with overlying erythema • Anogenito-rectal syndrome (3rd stage of LGV): proctocolitis, perirectal abscesses, urogenital fistulas	• Inguinal lymphadenopathy can be suppurative in LGV • LGV does not usually have multiple vesicles/pustules	• Similar sexual epidemiologic risk factor to monkeypox • Both LGV and monkeypox may cause tender lymphadenopathy • Monkeypox may rarely have no rash or only a single lesion	• Serological tests i.e. LGV complement fixation test • Culture from lymph node aspiration • *Chlamydia trachomatis* PCR from urine as well as other clinical sites as appropriate
Chancroid	• Causative organism: *Haemophilus ducreyi* • Single to multiple painful, purulent and deep genital ulcers with well-defined soft undermined edges	• Painful suppurative inguinal lymphadenopathy (buboes) • Scarring from recurrent buboes may result in urogenital or rectal fistulas	• Inguinal lymphadenopathy can be suppurative in chancroid • Ulcers in chancroid tend to be larger and deeper compared to the shallower erosions of ruptured vesicles and pustules in monkeypox	• Similar sexual epidemiologic risk factor to monkeypox • Both chancroid and monkeypox may cause tender lymphadenopathy	• Smear for direct microscopy (POC, although poor sensitivity) • Culture of smear from ulcer/aspirate from buboes • Smear for PCR

Table 2. Selected differentials of current monkeypox outbreak[22,24,25,29] (Cont'd)

Clinical differentials	Cutaneous features	Common extracutaneous features	Potential differentiating features	Potential confounding features	Laboratory tests (including point-of-care tests)
Granuloma inguinale	• Causative organism: *Klebsiella granulomatis* • Beefy vascular ulcers that began as small papules/nodules which slowly enlarged and ulcerated over weeks to months • Associated with odorous exudate • Subcutaneous granulomas (pseudobuboes) may be present	• Secondary dissemination may lead to involvement of any internal organ or bone	• Granuloma inguinale usually does not have regional lymphadenopathy, while lymphadenopathy is a common feature of monkeypox • Ulcers of granuloma inguinale are large, vascular, and foul smelling, unlike smaller lesions characteristic of monkeypox	• Similar sexual epidemiologic risk factor to monkeypox • Early stage of granuloma inguinale may be mistaken for monkeypox especially when lesions are still small and have not developed the characteristic beefy appearance	• Tissue smear from ulcer for intra-cellular Donovan bodies within histiocytes (not available at all institutions) • Biopsy of ulcer • Culture is difficult with no commercially available PCR
Primary syphilis	• Usually a single painless papule, which may develop into a well-circumscribed surface ulceration that is firm on palpation	• Regional lymphadenopathy	• Primary syphilis is frequently asymptomatic, whereas monkeypox usually has associated prodromal symptoms and tender cutaneous lesions	• Similar sexual epidemiologic risk factor to monkeypox • Chancres may infrequently be multiple and may mimic atypical monkeypox presentations that have few cutaneous lesions	• Lesional smear for darkfield microscopy (POC) • Non-treponemal tests e.g. RPR (POC) • Treponemal tests e.g. TPHA, TPAb • Consider opportunistic screening for other STIs as well, including HIV (POC)
Pustular secondary syphilis	• Miliary pustular syphilis: perifollicular pustules approximately 3–5mm diameter • Acneiform syphilis: acneiform papules and pustules on the face • Varioliform syphilis: umbilicated erythematous infiltrated papules and pustules with superficial erosions • Impetiginoid syphilis and ecthymiform syphilis have lesions similar to impetigo and ecthyma, respectively • Rupoid syphilis: papules and pustules with overlying thick hyperkeratotic crusts resembling oyster shells	• Prodromal symptoms • Lymphadenopathy	• Pustular secondary syphilis is a very rare presentation of syphilis. It is far more common for the rash of secondary syphilis to be a papulosquamous eruption. • There may be a history suggestive of previous primary syphilis	• Similar sexual epidemiologic risk factor to monkeypox • Cutaneous features and prodrome-like symptoms can be indistinguishable from monkeypox	• See above
Varicella zoster	• "Dew drops on a rose petal" appearance, describing clear 1–3mm vesicles with a narrow erythematous halo • Lesions at varying stages concurrently • Cephalocaudal spread • Usually spares distal limbs and lower limbs • Oral enanthem	• Mild viral prodrome • More severe presentation and higher risk of extracutaneous complications in adolescents and adults compared to children	• Lesions are at varying stages concurrently • No previous varicella vaccination or varicella zoster infection	• Generalised vesicular eruption, +/- umbilication may be difficult to differentiate from classic monkeypox eruption	• Lesional swab for Tzanck smear (POC) • Lesional swab for varicella zoster virus PCR

Table 2. Selected differentials of current monkeypox outbreak[22,24,25,29] (Cont'd)

Clinical differentials	Cutaneous features	Common extracutaneous features	Potential differentiating features	Potential confounding features	Laboratory tests (including point-of-care tests)
Herpes zoster	• Grouped vesicles that may coalesce into bullae/erosions with scalloped borders • Dermatomal distribution • May be preceded by hyperaesthesia/ hyperalgesia in the corresponding dermatome	• Neuropathic symptoms in the associated dermatome (may persist as postherpetic neuralgia)	• Dermatomal in nature • Does not cross midline • History of previous varicella zoster infection	• Disseminated zoster is not confined to the dermatome • Genital zoster is uncommon	• Lesional swab for Tzanck smear (POC) • Lesional swab for herpes zoster virus PCR
Hand-foot-mouth disease	• Acral erythematous vesicles with oral stomatitis • May become generalised, involving the face, perioral areas, trunk, buttocks and extremities	• Mild prodrome • Neurologic, cardiopulmonary complications, and death may occur in young children with hand-foot-mouth disease due to enterovirus 71 infection	• Usually affects young children • Oropharyngeal lesions are frequent, occurring on the tongue, buccal mucosae, palate, uvula, tonsillar pillars • Lesions may be more prominent in areas of pre-existing eczematous dermatitis (eczema coxsackium)	• Generalised vesicular eruption may be difficult to differentiate from classic monkeypox eruption	• Usually a clinical diagnosis • Swabs for cell culture or PCR for enterovirus or coxsackievirus can be done if aetiologic confirmation is necessary
Impetigo	• Early lesions begin as a single 2–4mm erythematous macule that quickly evolves into a short-lived vesicle or pustule • Late lesions present as superficial erosions with "honey yellow" crust, and direct extension of the infection to the surrounding skin • The less common bullous variant that presents with small vesicles, which then enlarge into superficial bullae (initially 1–2cm, later up to 5cm in diameter); with a collarette of scale after rupture	• May also have systemic symptoms like fever, weakness and mild lymphadenopathy	• More common in children • Predilection for face (around the nose or mouth) and extremities • Golden crusting is typical	• Less common bullous variant may also affect trunk, buttocks and genitals	• Swab lesions for pyogenic culture
Insect bites and insect bite reactions	• Pruritic urticated papules (usually 2–8mm) that may progress to vesiculobullae or persistent prurigo nodularis-like lesions • May develop papular urticaria, a hypersensitivity reaction to the initial bite(s) that can be localised to sites of bites or generalised	• May not have prodomal symptoms • Rarely associated with anaphylaxis	• Papules may have visible punctum • Patterns of eruption tend to correlate with exposure or exposed areas • History of outdoor exposures, pets, work and hobbies	• Patients may also have a travel history • Secondary infection (e.g. Staphylococcal) may appear more pustular	• Parasite smear may sometimes, but not often, yield arthropod parts (POC) • Swab lesions for pyogenic culture for secondary bacterial infection

HIV: human immunodeficiency virus; HSV: herpes simplex virus; LGV: lymphogranuloma venereum; MXPX: monkeypox virus; PCR: polymerase chain reaction; POC: point of care; RPR: rapid plasma regain; STI: sexually transmitted infection; TPAb: *Treponema pallidum* antibody; TPHA: *Treponema pallidum* haemagglutination
Superscript numbers: Refer to REFERENCES

to below -20°C within 1 hour of collection, and transported to the laboratory in triple packaging in accordance with local infectious disease control protocols. WHO recommends that it may be prudent to collect 2 sets of samples, in order to reduce sampling error. The second set may be tested if the first sample yields an inconclusive result.[25]

Other investigations, such as testing for acute and convalescent serum antibodies against the monkeypox virus, can be done if NAAT is inconclusive, but are not recommended as standalone tests. Viral culture and electron microscopy are currently not recommended for routine diagnostic testing either.[25]

Management of monkeypox

Prevention

Timely updates to the general public in Singapore are given via the media to educate on the symptoms and transmission of monkeypox and remind the public to practise strict personal hygiene.[26] At-risk groups such as MSM are advised by WHO to temporarily reduce the number of sexual partners and to exchange contacts with new partners to facilitate contact tracing.[27] Travellers to affected countries should additionally avoid contact with wild animals, and seek medical attention if new symptoms of fever, lymphadenopathy or rashes develop within 3 weeks of return from travel.[9] Close contacts of infected persons are quarantined and undergo appropriate regular surveillance for the development of symptoms.[28]

General measures

Supportive management is the current standard of care. This includes attention to wound care to prevent secondary skin infections, analgesics/antipyretics/antiemetics and other symptomatic treatment as necessary, monitoring for systemic complications, and addressing any psychosocial impact in a sensitive manner. Standard, contact, droplet and airborne precautions are currently advised to all persons who attend to confirmed cases of monkeypox.[18] If tolerable, exposed lesions should be covered when others come into the patient's isolation room. Environmental measures include segregation and disposal of infectious waste; machine-washing contaminated linen in hot water >60°C with laundry detergent and drying at high heat; and cleaning contaminated surfaces with detergent and water followed by an approved virucidal disinfectant. Such precautions should continue until all the lesions have scabbed over and all scabs have fallen off revealing intact new skin underneath.[29]

Pharmacologic treatment

Treatment of monkeypox is largely conservative at present. In the UK, US and Australia, smallpox vaccination has been approved in certain circumstances to reduce the risk of monkeypox. Smallpox vaccines contain the vaccinia virus, which also belongs to the *Orthopoxvirus* genus, and hence provide some cross-protection against monkeypox. The Smallpox Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN) is a non-replicating live-attenuated virus suitable for immunosuppressed persons, pregnant or breastfeeding women, children and those with atopic dermatitis. It is available in the UK, US and Australia, and involves 2 subcutaneous injections 4 weeks apart for primary vaccination. Side effects include local injection site reactions, and viral prodrome-like symptoms. ACAM2000 is a live vaccine that is an alternative to MVA-BN in the US and Australia currently. The side effect profile is similar to MVA-BN, but rare serious adverse events such as progressive vaccinia, generalised vaccinia, eczema vaccinatum, severe cutaneous adverse drug reactions, myocarditis, encephalitis, encephalomyelitis, or encephalopathy have also been reported. Furthermore, the vaccination site is an infectious lesion that may result in autoinoculation of other body parts or infection of other people.[30-32] In Singapore, smallpox vaccination may be offered as a post-exposure prophylaxis in close contacts of a confirmed person with monkeypox, although specific local guidance on eligible individuals is not yet available.[28]

As to the use of antivirals in confirmed monkeypox infection, WHO recommends that antiviral use be in the context of a randomised clinical trial. Tecovirimat is a p37 viral envelope protein inhibitor with clinical effectiveness against smallpox in animal models. It is administered orally 600mg twice daily for 2 weeks, based on phase 3 placebo-controlled pharmacokinetic and safety trial in humans.[33,34] It is licensed by the European Medicines Agency for the treatment of monkeypox, but is not approved by the US Food and Drug Administration or the Australian Therapeutic Goods Administration.[29] Nonetheless, Australian guidelines recommend considering the use of tecovirimat in those with or at high risk of severe disease (e.g. haemorrhagic complications, sepsis and encephalitis).[35] Other potential antiviral treatments that are also currently not approved for use against monkeypox include brincidofovir, cidofovir and NIOCH-14.[29] In Singapore, there are no approved antiviral medications for both infected persons and at-risk individuals.

CONCLUSION

Monkeypox is an emerging virus that has the potential to cause significant physical and psychosocial morbidity. Early stages may mimic other common infectious and non-infectious conditions. Moreover, significant variation in clinical presentations of persons infected in the current outbreak, many of whom do not develop the characteristic generalised vesiculo-pustular eruption of previous outbreaks, highlights the need for clinicians to take a detailed travel and sexual history, to maintain a high index of suspicion to detect cases, and isolate cases to prevent onward transmission to contain the local outbreak.

REFERENCES

1. World Health Organization. Meeting of the International Health Regulations (2005) Emergency Committee regarding the multi-country monkeypox outbreak. Updated 25 June 2022. Available at: https://www.who.int/news/item/25-06-2022-meeting-of-the-international-health-regulations-(2005)-emergency-committee--regarding-the-multi-country-monkeypox-outbreak. Accessed on 27 July 2022.
2. Nolen LD, Osadebe L, Katomba J, et al. Introduction of Monkeypox into a Community and Household: Risk Factors and Zoonotic Reservoirs in the Democratic Republic of the Congo. Am J Trop Med Hyg Aug 2015;93:410-5.
3. Khodakevich L, Jezek Z, Messinger D. Monkeypox virus: ecology and public health significance. Bull World Health Organ 1988; 66:747-52.
4. Meyer H, Perrichot M, Stemmler M, et al. Outbreaks of disease suspected of being due to human monkeypox virus infection in the Democratic Republic of Congo in 2001. J Clin Microbiol 2002;4 0:2919-21.
5. Sejvar JJ, Chowdary Y, Schomogyi M, et al. Human monkeypox infection: a family cluster in the midwestern United States. J Infect Dis 2004;190:1833-40.
6. Reynolds MG, Davidson WB, Curns AT, et al. Spectrum of infection and risk factors for human monkeypox, United States, 2003. Emerg Infect Dis 2007;13:1332-9.
7. Fleischauer AT, Kile JC, Davidson M, et al. Evaluation of human-to-human transmission of monkeypox from infected patients to health care workers. Clin Infect Dis 2005;40:689-94.
8. Yong SEF, Ng OT, Ho ZJM, et al. Imported Monkeypox, Singapore. Emerg Infect Dis 2020;26:1826-30.
9. Ministry of Health, Singapore. Monkeypox. Available at: https://www.moh.gov.sg/diseases-updates/monkeypox. Accessed on 13 August 2022.
10. World Health Organization. Surveillance, case investigation and contact tracing for monkeypox: interim guidance, 24 June 2022. available at: https://www.who.int/publications/i/item/WHO-MPX-Surveillance-2022.2. Accessed on 27 July 2022.
11. Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. PLoS Negl Trop Dis 2022;16:e0010141.
12. Girometti N, Byrne R, Bracchi M, et al. Demographic and clinical characteristics of confirmed human monkeypox virus cases in individuals attending a sexual health centre in London, UK: an observational analysis. Lancet Infect Dis 2022. doi:10.1016/S1473-3099(22)00411-X.
13. Di Giulio DB, Eckburg PB. Human monkeypox: an emerging zoonosis. Lancet Infect Dis 2004;4:15-25.
14. Centers for Disease Control and Prevention. Multistate outbreak of monkeypox--Illinois, Indiana, and Wisconsin, 2003. MMWR Morb Mortal Wkly Rep 2003;52:537-40.
15. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox Virus Infection in Humans across 16 Countries — April–June 2022. N Engl J Med 2022. doi:10.1056/nejmoa2207323.
16. World Health Organization. Multi-country monkeypox outbreak: situation update. World Health Organization. Updated 27 June 2022. Available at: https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON396. Accessed on 27 July 2022.
17. Ministry of Health, Singapore. Update on Monkeypox Cases in Europe and North America and Maintaining Vigilance against Monkeypox, MOH Circular No. 63/2022, 20 May 2022.
18. Ministry of Health, Singapore. Update on Suspect Case Definition and Notification Requirements for Monkeypox, MOH Circular No. 79/2022, 1 July 2022.
19. Kazlouskaya V, Wittmann C, Tsikhanouskaya I. Pustular secondary syphilis: report of three cases and review of the literature. Int J Dermatol 2014;53:e428-31.
20. Liebling MR, Arkfeld DG, Michelini GA, et al. Identification of Neisseria gonorrhoeae in synovial fluid using the polymerase chain reaction. Arthritis Rheum 1994;37:702-9.
21. Read P, Abbott R, Pantelidis P, et al. Disseminated gonococcal infection in a homosexual man diagnosed by nucleic acid amplification testing from a skin lesion swab. Sex Transm Infect Oct 2008;84:348-9.
22. Birrell JM, Gunathilake M, Singleton S, et al. Characteristics and Impact of Disseminated Gonococcal Infection in the "Top End" of Australia. Am J Trop Med Hyg 2019;101:753-60.
23. Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep 2021;70:1-187.
24. Bolognia J, Schaffer JV, Cerroni L. Dermatology. 4th edition. Elsevier, 2018.
25. World Health Organization. Laboratory testing for the monkeypox virus: Interim guidance. Updated 27 June 2022. Available at: https://www.who.int/publications/i/item/WHO-MPX-laboratory-2022.1. Accessed on 27 July 2022.
26. The Straits Times. Can monkeypox be transmitted asymptomatically? 21 July 2022. Available at: https://www.straitstimes.com/singapore/health/askst-how-long-is-the-isolation-period-for-monkeypox-patients. Accessed on 3 August 2022.
27. The Straits Times. Amid monkeypox surge, WHO urges reducing number of sexual partners, 28 July 2022. Available at: https://www.straitstimes.com/world/amid-monkeypox-surge-who-urges-reducing-number-of-sexual-partners. Accessed on 3 August 2022.
28. Ministry of Health, Singapore. Monkeypox. Updated 8 June 2022. Available at: https://ask.gov.sg/questions/958. Accessed on 10 July 2022.
29. World Health Organization. Clinical management and infection prevention and control for monkeypox: Interim rapid response

guidance, 10 June 2022. Available at: https://www.who.int/publications/i/item/WHO-MPX-Clinical-and-IPC-2022.1. Accessed on 27 July 2022.

30. World Health Organization. Vaccines and immunization for monkeypox: Interim guidance, 14 June 2022. Available at: https://www.who.int/publications/i/item/who-mpx-immunization-2022.1. Accessed on 27 July 2022.
31. Centers for Disease Control and Prevention. Vaccines: Smallpox. Updated 8 August 2022. Available at: https://www.cdc.gov/smallpox/clinicians/vaccines.html. Accessed on 24 August 2022.
32. Australian Government Department of Health and Aged Care. ATAGI clinical guidance on vaccination against Monkeypox. Updated 1 August 2022. Available at: https://www.health.gov.au/resources/publications/atagi-clinical-guidance-on-vaccination-against-monkeypox. Accessed on 27 July 2022.
33. Grosenbach DW, Honeychurch K, Rose EA, et al. Oral Tecovirimat for the Treatment of Smallpox. N Engl J Med 2018;379:44-53.
34. Russo AT, Grosenbach DW, Chinsangaram J, et al. An overview of tecovirimat for smallpox treatment and expanded anti-orthopoxvirus applications. Expert Rev Anti Infect Ther 2021;19:331-44.
35. Australian Government Department of Health and Aged Care. Monkeypox treatment guidelines, 24 June 2022. Available at: https://www.health.gov.au/resources/publications/monkey pox-treatment-guidelines. Accessed on 27 July 2022.
36. Ministry of Health, Singapore. Update on Revised Schedule of Notifiable Infectious Diseases under the Amended Infectious Diseases Act, 2022.
37. Centers for Disease Control and Prevention. Monkeypox: Case Definitions. Updated 22 July 2022. Available at: https://www.cdc.gov/poxvirus/monkeypox/clinicians/case-definition.html. Accessed on 23 July 2022.
38. UK Health Security Agency. Monkeypox: case definitions - GOV.UK United Kingdoms. Updated 9 August 2022. Available at: https://www.gov.uk/guidance/monkeypox-case-definitions. Accessed on 10 August 2022.
39. Australian Government Department of Health and Aged Care. Monkeypox virus infection – Surveillance case definition, 1 August 2022. Available at: https://www.health.gov.au/resources/publications/monkeypox-virus-infection-surveillance-case-definition. Accessed on 23 August 2022.

ORIGINAL ARTICLE

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Interaction of sex and diabetes in Asian patients with heart failure with mildly reduced left ventricular ejection fraction

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ABSTRACT

Introduction: The impact of sex and diabetes mellitus (DM) on patients with heart failure with mildly reduced ejection fraction (HFmrEF) is not well elucidated. This study aims to evaluate sex differences in the clinical profile and outcomes in Asian HFmrEF patients with and without DM.

Methods: Patients admitted nationally for HFmrEF (ejection fraction 40–49%) between 2008 and 2014 were included and followed up until December 2016. The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular (CV) death and/or heart failure (HF) rehospitalisations.

Results: A total of 2,272 HFmrEF patients (56% male) were included. More women had DM than men (60% versus 55%, *P*=0.013). Regardless of DM status, HFmrEF females were older, less likely to smoke, had less coronary artery disease, narrower QRS and lower haemoglobin compared to men. The odds of having DM decreases in smokers who are women as opposed to men ($P_{interaction}$ =0.017).

In multivariate analysis, DM reached statistical analysis for all-cause mortality and combined CV mortality or HF rehospitalisation in both men and women. However, the results suggest that there may be sex differences in terms of outcomes. DM (vs non-DM) was less strongly associated with increased all-cause mortality (adjusted hazards ratio [adj HR] 1.234 vs adj HR 1.290, $P_{interaction}$ <0.001] but more strongly associated with the combined CV death/HF rehospitalisation (adj HR 1.429 vs adj HR 1.317, $P_{interaction}$ =0.027) in women (vs men).

Conclusion: Asian women with HFmrEF had a higher prevalence of DM, with differences in clinical characteristics, compared to men. While diabetes conferred poor outcomes regardless of sex, there were distinct sex differences. These highlight the need for sex-specific management strategies.

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Keywords: Asian, diabetes mellitus, heart failure with mildly reduced ejection fraction, sex

INTRODUCTION

Diabetes mellitus (DM) is a common comorbidity worldwide with global prevalence among adults above 18 years of age increasing from 4.7% in 1980 to 8.5% in 2014.[1] DM has been shown to be a common comorbidity in heart failure (HF) patients ranging from 4.3–28%[2] and when present, portends a poorer prognosis in these patients.[3,4]

There have been increasing epidemiologic data showing Asian patients with HF to be significantly younger, leaner and with a higher predisposition for DM compared to their Western counterparts.[5,6] Prior studies have also shown that Asian patients with HF with mildly reduced ejection fraction (HFmrEF) represent a distinct HF phenotype riddled with a high burden of cardiovascular diseases such as DM, peripheral vascular disease, and coronary artery disease with distinct major adverse cardiac events outcomes.[7-9] While research on sex differences among patients with both DM and other subtypes of HF has been gaining traction[10] with distinct

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CLINICAL IMPACT

What is New

- In our Asian cohort with heart failure with mildly reduced ejection fraction (HFmrEF), women with HFmrEF were found to have a higher prevalence of diabetes mellitus (DM), with differences in clinical characteristics, compared to men.
- While diabetes conferred poor outcomes regardless of sex, there were distinct sex differences with women experiencing a higher composite rate of cardiovascular mortality and heart failure readmission than men.
- We also found that women with HFmrEF, particularly those without DM, were less likely to be prescribed with guideline-directed medical therapy (GDMT) of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or beta-blockers despite having comparable baseline haemodynamics, mean left ventricular ejection fraction and mean serum creatinine levels.

Clinical Implications

- Our findings highlight the need for sex-specific management strategies for HFmrEF patients with DM to improve outcomes.
- Concerted effort should be made to review the discrepant GDMT prescribing practices by clinicians for women with HFmrEF to further reduce morbidity and mortality.

sex-specific differences noted, data in HFmrEF have been scarce. This study aimed to evaluate sex differences in the clinical profile and outcomes in Asian HFmrEF patients with/without DM.

METHODS

Study population and setting

The Singapore Cardiac Databank Heart Failure (SCDB-HF) registry is a nationwide prospective, observational data collection registry for all consecutive patients ≥21 years of age admitted for heart failure to all Singapore public hospitals. Comprehensive data collection at baseline such as demographics, clinical signs and symptoms, characteristics, biochemistry, treatments and discharge outcomes were captured in this registry. Details of the registry have been previously described with numerous publications ensuing from this registry.[11-15] Trained coordinators collected data with the use of a standardised case report form and entered these findings into an electronic database, which underwent internal and external validation. Registry participation was independent of medical care received. The study was approved by the Institutional Ethics Review Board. Consecutive unique patients who were admitted to the SCDB-HF registry from 1 January 2008 to 31 December 2014 were included. Only patients with a mildly reduced ejection fraction of 40–49% at index presentation were included in this study.

Outcomes

All patients were followed-up until 31 December 2016. DM was defined as having a prior history of diabetes and/or currently receiving antidiabetic therapies. The primary outcome measured was all-cause mortality. The secondary outcome was a composite of cardiovascular death and/or heart failure rehospitalisation. These outcomes were obtained from national registries.

Statistical analyses

Baseline characteristics of individual subgroups were described using frequencies and percentages for categorical variables, and as mean ± standard deviation (SD) or medians with interquartile range (IQR) for continuous variables. Differences between groups were tested using chi-square tests for categorical variables and independent samples t-tests or one-way analysis of variance for continuous variables. Differences in baseline demographics, clinical profile, comorbidities and pharmacotherapy were tested between DM and non-DM in men and women separately; and men and women in DM and non-DM groups separately. The significance of correlations among the factors was applied using the Benjamini-Hochberg procedure with a false discovery rate of 0.05. Variables with significant *P* values after correction were indicated with an asterisk.

To examine clinical correlates of DM, a multivariable logistic regression model using DM as a dependent variable was built with a stepwise approach, by considering variables with significant univariable *P* values ($P<0.05$) and a priori choice of clinically important factors to obtain the most parsimonious model. Male and female groups in the clinical correlates of DM were tested with an interaction term and main effect terms, and adjusted for other significant factors. Time-to-event analyses were examined using a multivariable Cox proportional hazards model in the absence of violation of the proportion hazard assumption. The endpoints of overall all-cause mortality, cardiovascular mortality and first HF rehospitalisation were censored at time of event; for those without event, the last date of follow-up was used. To determine if DM modifies the

relationship between sex and outcomes in HFmrEF, the interaction between DM and sex, adjusted for age, was examined in the Cox model. Patients with incomplete data on adjusted clinical and demographic factors were excluded from multivariable logistic and Cox regression analyses. SAS version 9.4 (SAS Institute Inc, Cary, US) was used to conduct the analyses.

RESULTS

Baseline demographics and clinical characteristics

A total of 2,272 Asian patients with HFmrEF were included in this study. The mean age was 70.6±12.7 years, and 56.1% were men. Among these patients, the prevalence of DM was higher in women than in men (60.4% versus 55.0%, respectively, P=0.013). For both DM and non-DM patients, women with HFmrEF were more likely to be older, less likely to smoke, had narrower QRS duration, lower mean haemoglobin on presentation, and less likely to have coronary artery disease compared to men (all P<0.05). Within the DM group, women had lower mean creatinine (147.2 vs 177.1mmol/L), and were less likely to have hyperlipidaemia (75.9 vs 82.0%) and prior myocardial infarction (20.6 vs 26.8%) than men. In the non-DM group, women had lower mean diastolic blood pressure than men (78.7 vs 82.3mmHg).

With regards to guideline-directed medical therapy, we also noted significant sex differences in the medication uptake particularly in patients without DM. Female patients without DM were less likely to be prescribed with angiotensin-converting enzyme inhibitors (ACEi) or angiotension receptor blockers (ARBs) and beta-blockers. Comparing DM and non-DM patients, DM patients were more likely to be prescribed with BBs, antiplatelets and statins but less likely to be prescribed with digoxin and warfarin (Table 1).

Clinical correlates of DM

In both men and women, multivariate correlates of DM included younger age, Indian ethnicity, lower haemoglobin levels, hypertension, hyperlipidaemia, absence of AF and peripheral vascular disease. Among the independent correlates for DM, those that differed between men and women were serum potassium levels and smoking history. DM was more strongly correlated with higher potassium levels in men vs women ($P_{interaction}$ =0.034), and was more strongly inversely correlated with smoking history in women vs men ($P_{interaction}$ =0.017) (Fig. 1).

Clinical outcomes

Follow-up data were available in all 2,272 patients with no loss to follow-up in any groups. On multivariable analysis, diabetes was a significant predictor of overall mortality, CV mortality, HF rehospitalisations, and the composite of CV mortality/HF rehospitalisations in both men and women. However, there were distinct sex-specific differences for the outcomes of mortality and composite of CV mortality/HF rehospitalisations. DM was more significantly associated with overall mortality in men compared to women (adjusted hazards ratio [adj HR] 1.290, 95% confidence interval [CI] 1.094–1.522 vs adj HR 1.234, 95% CI 1.032–1.476; $P_{interaction}$ <0.001) and with combined CV mortality/HF rehospitalisations in women compared to men (adj HR 1.429; 95% CI 1.195–1.710 vs adj HR 1.317; 95% 1.137–1.526; $P_{interaction}$ =0.027). There were no sex-specific differences for the individual outcomes of CV mortality and HF rehospitalisations. In the absence of DM as a comorbidity, women and men have similar outcomes for overall mortality (P=0.511), cardiovascular mortality (P=0.825), HF hospitalisation (P=0.074), and composite of cardiovascular mortality and HF hospitalisation (P=0.922) (Table 2 and Supplementary Table S1 in online Supplementary Material, and Fig. 2).

DISCUSSION

In this prospective observational cohort of 2,272 Asian patients with HFmrEF, we demonstrated several pertinent findings: (1) there is a higher prevalence of DM in women with HFmrEF than in men; (2) distinct sex differences exist in clinical characteristics in this cohort; and (3) DM is a potent disease modifier that worsens all outcomes of HFmrEF patients, with a differential effect of higher overall mortality in men, and a higher composite outcome of cardiovascular mortality and HF readmissions in women. No sex differences in outcomes were noted in our HFmrEF cohort in the absence of DM.

In our study, we observed an increased prevalence of DM in women than men despite a greater representation of men. The International Diabetes Federation reported that the current global prevalence of DM in women and men was 9.0% and 9.6%, respectively, with greater affliction for men up until the age of 69 years, followed by a reversal in trend with greater female preponderance in adults aged 70 years and above.[16] This could explain our findings given that the mean age of our cohort was 70.6 years. Furthermore, a recent study suggests that Asian females with HFrEF were more likely to have DM than males, despite having a lean body mass index.[10]

Table 1. Clinical characteristics of study population

	% missing	Men			Women			DM	No DM
		DM	No DM	*P* value	DM	No DM	*P* value	Men vs Women	Men vs Women
No. (%)		704 (55)	571 (45)		602 (60)	395 (40)		0.013	
Demographics									
Mean age (SD), years	0	68.1 (11.3)	69.3 (13.3)	0.069	71.6 (11.9)	75.2 (14.1)	<0.001*	<0.001*	<0.001*
Ethnicity, no. (%)	0			<0.001*			<0.001*	0.797	0.259
Chinese		425 (60.4)	417 (73.0)		351 (58.3)	302 (76.5)			
Malay		142 (20.2)	96 (16.8)		135 (22.4)	57 (14.4)			
Indian		112 (15.9)	34 (6.0)		95 (15.8)	27 (6.8)			
Others		25 (3.6)	24 (4.2)		21 (3.5)	9 (2.3)			
Clinical parameters									
Mean LVEF (SD), %	0	42.9 (2.7)	42.9 (2.7)	0.966	43.1 (2.7)	42.9 (2.7)	0.448	0.449	0.947
Mean systolic blood pressure (SD), mmHg	0	150.8 (31.4)	145.2 (31.0)	0.001*	153.6 (29.0)	147.3 (29.9)	0.001*	0.099	0.295
Mean diastolic blood pressure (SD), mmHg	0	80.8 (19.7)	82.3 (20.6)	0.176	78.7 (17.5)	78.7 (19.2)	0.957	0.045	0.007*
Mean heart rate (SD), beats/min	0	88.0 (21.6)	90.3 (24.3)	0.079	90.1 (20.9)	91.4 (24.5)	0.399	0.073	0.498
Mean BMI (SD), kg/m^2	58.1	26.3 (6.5)	24.6 (5.7)	0.001*	26.6 (5.7)	24.6 (6.8)	0.002*	0.582	0.943
BMI categories, kg/m^2	58.1			<0.001*			<0.001*	0.776	0.180
Underweight (<18.5)		10 (3.1)	31 (11.1)		7 (3.2)	20 (14.5)			
Normal (18.5–23)		96 (30.1)	88 (31.4)		56 (25.9)	45 (32.6)			
Overweight (23–27.5)		101 (31.7)	101 (36.1)		73 (33.8)	36 (26.1)			
Obese (≥27.5)		112 (35.1)	60 (21.4)		80 (37.0)	37 (26.8)			
Mean QRS duration (SD), ms	0.8	101.4 (22.1)	103.2 (23.0)	0.171	95.7 (21.0)	97.4 (22.6)	0.235	<0.001*	<0.001*
Mean creatinine (SD), mmol/L	0.4	177.1 (146.3)	132.4 (97.3)	<0.001*	147.2 (111.3)	126.5 (127.5)	0.007*	<0.001*	0.421
Mean sodium (SD), mmol/L	0.5	136.7 (4.7)	137.2 (4.3)	0.053	136.6 (5.1)	137.5 (4.7)	0.004*	0.628	0.307
Mean potassium (SD), mmol/L	0.5	4.3 (0.7)	4.1 (0.8)	<0.001*	4.2 (0.7)	4.2 (0.7)	0.051	0.379	0.302
Mean haemoglobin (SD), g/dL	1.7	11.9 (2.2)	12.6 (2.3)	<0.001*	10.9 (1.8)	11.8 (1.9)	<0.001*	<0.001*	<0.001*
Comorbidities, no. (%)									
Prior coronary artery disease	0	386 (54.8)	249 (43.6)	<0.001*	279 (46.3)	131 (33.2)	<0.001*	0.002*	0.001*
Prior myocardial infarction	0	189 (26.8)	108 (18.9)	0.001*	124 (20.6)	62 (15.7)	0.052	0.008*	0.197

Table 1. Clinical characteristics of study population (Cont'd)

	% missing	Men			Women			DM	No DM
		DM	No DM	*P* value	DM	No DM	*P* value	Men vs Women	Men vs Women
Atrial fibrillation	0	111 (15.8)	163 (28.5)	<0.001*	107 (17.8)	123 (31.1)	<0.001*	0.332	0.385
Hypertension	0	616 (87.5)	396 (69.4)	<0.001*	539 (89.5)	285 (72.2)	<0.001*	0.252	0.348
Hyperlipidaemia	0	577 (82.0)	326 (57.1)	<0.001*	457 (75.9)	215 (54.4)	<0.001*	0.007*	0.412
Stroke	0	120 (17.0)	63 (11.0)	0.002*	97 (16.1)	59 (14.9)	0.617	0.652	0.073
Peripheral vascular disease	0	78 (11.1)	11 (1.9)	<0.001*	58 (9.6)	9 (2.3)	<0.001*	0.394	0.706
Chronic obstructive pulmonary disease	0	63 (8.9)	78 (13.7)	0.008*	56 (9.3)	41 (10.4)	0.574	0.825	0.127
Ever smoker	0	409 (58.1)	326 (57.1)	0.718	36 (6.0)	49 (12.4)	<0.001*	<0.001*	<0.001*
Discharge medications									
ACEi	0	337 (47.9)	323 (56.6)	0.002*	280 (46.5)	176 (44.6)	0.545	0.624	<0.001*
ARB	0	159 (22.6)	82 (14.4)	<0.001*	142 (23.6)	65 (16.5)	0.007*	0.668	0.373
ACEi or ARB	0	488 (69.3)	402 (70.4)	0.675	409 (67.9)	241 (61.0)	0.025*	0.592	0.002*
Beta-blocker	0	551 (78.3)	413 (72.3)	0.014*	467 (77.6)	256 (64.8)	<0.001*	0.764	0.013*
Spironolactone/aldosterone antagonist	0	72 (10.2)	59 (10.3)	0.951	40 (6.6)	41 (10.4)	0.035	0.021	0.981
Nitrate	0	267 (37.9)	182 (31.9)	0.024*	222 (36.9)	97 (24.6)	<0.001*	0.696	0.014*
Diuretic	0	578 (82.1)	446 (78.1)	0.075	491 (81.6)	301 (76.2)	0.041	0.800	0.487
Digoxin	0	75 (10.7)	107 (18.7)	<0.001*	86 (14.3)	89 (22.5)	0.001*	0.047	0.150
Antiplatelets (aspirin, clopidogrel)	0	525 (74.6)	364 (63.7)	<0.001*	416 (69.1)	226 (57.2)	<0.001*	0.028	0.041
Anticoagulants (warfarin)	0	56 (8.0)	100 (17.5)	<0.001*	49 (8.1)	63 (15.9)	<0.001*	0.902	0.523
Statins (lipid-lowering)	0	582 (82.7)	403 (70.6)	<0.001*	495 (82.2)	255 (64.6)	<0.001*	0.833	0.048

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; DM: diabetes mellitus; LVEF: left ventricular ejection fraction; SD: standard deviation
Values are n (%) unless otherwise indicated. The *P* values are based on Pearson's chi-square test (for categorical variables) and t-tests or one-way analysis of variance (for continuous variables).
* Significant *P* values after Benjamini-Hochberg procedure with false discovery rate 0.05.

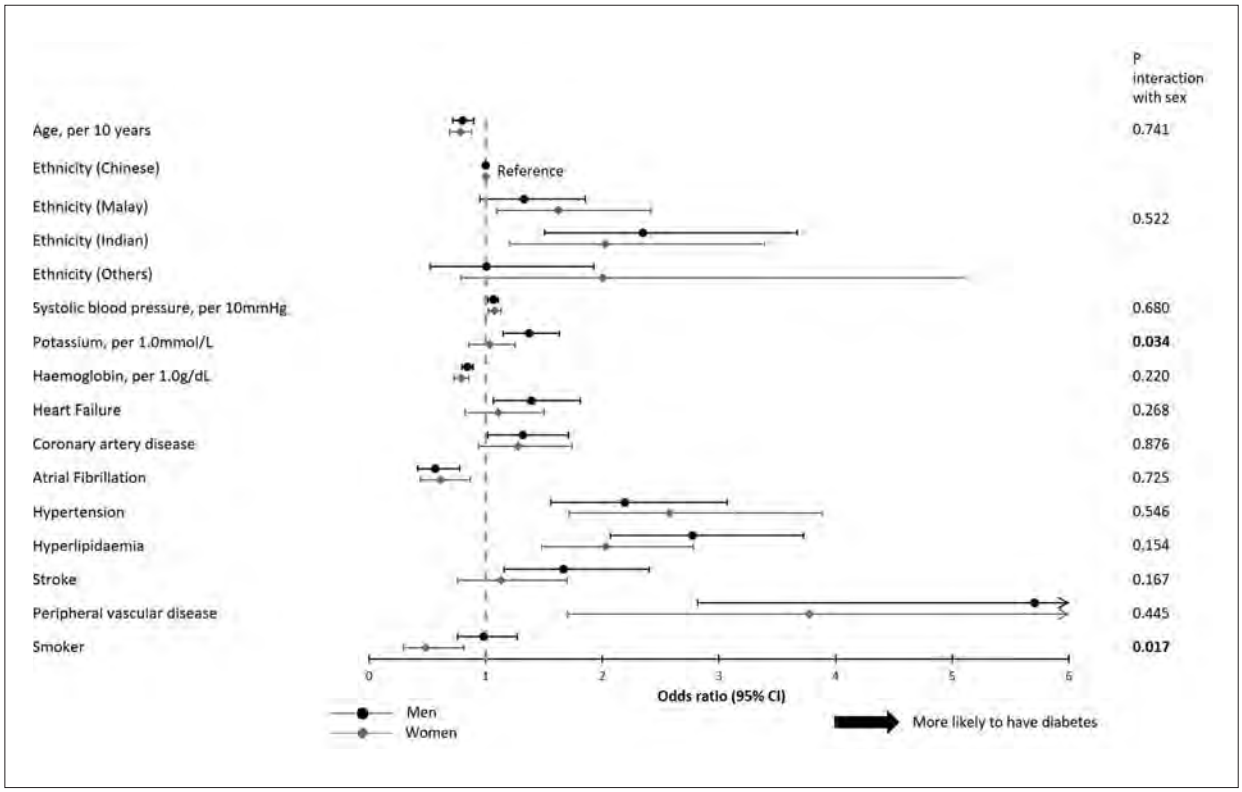

Fig. 1. Association of clinical correlates and diabetes mellitus. Odds ratio adjusted for age, ethnicity, systolic blood pressure, potassium, haemoglobin, heart failure, coronary artery disease, atrial fibrillation, hypertension, hyperlipidaemia, stroke, peripheral vascular disease and smoker.
CI: confidence interval

In our cohort, we found that sex differences did not alter outcomes in the absence of DM as a comorbidity. Previous studies assessing sex-based differences in HF prognosis have yielded conflicting results.[17-19] In the Swedish HF registry of 42,987 patients, Stolfo et al. demonstrated a higher crude risk of mortality/morbidity in female HFmrEF patients compared to their male cohorts, although this effect was lost upon adjustment for other variables with mortality outcomes favouring females instead. HF admission outcomes were similar for both males and females in this study.[17] In contrast, Martines-Selles et al. and O'Meara et al. demonstrated better survival in women than in men, irrespective of left ventricular ejection fraction (LVEF)[18,19] These differences may be explained by the complex interplay of biological variabilities in cardiac functional remodelling, role of sex hormones, different socioeconomic characteristics in women across geographical locations, as well as different adjustments used in studies worldwide.

On the contrary, our study showed that DM was a potent disease modifier of outcomes in HFmrEF. Distinct sex-specific differences were noted with higher risk of overall mortality in men and a higher risk of combined HF rehospitalisations/CV death in women. This finding is corroborated by contemporary studies evaluating the effects of DM on sex differences. Malmborg et al. recently reported that the relative rate of first-time cardiovascular complications associated with DM such as myocardial infarction, HF, ischaemic stroke, or cardiovascular death composite outcomes were higher in women than in men across all ages in a large Danish cohort.[20] In a meta-analysis of 47 cohorts totalling 12,142,998 HF patients, DM was also shown to increase the risk of incident HF in both men and women, with a 47% and 9% excess risk of HF in type 1 diabetes mellitus and type 2 diabetes mellitus, respectively, for women when compared to their male counterparts.[21]

In terms of HF pharmacotherapy prescription, the presence and severity of chronic kidney disease (CKD) could potentially limit the initiation of guideline-directed medical therapy such as ACEi/ARB. In our cohort, the mean serum creatinine levels in our study were in the range of 126.5–177.1mmol/L, which puts the average CKD severity as stage 3. Despite this,

Table 2. Association of diabetes mellitus with different group of outcomes: (A) all-cause mortality, (B) cardiovascular mortality, (C) heart failure rehospitalisation, and (D) heart failure rehospitalisation or cardiovascular mortality in men and women

	Age-adjusted $P_{interaction}$ with sex	Men				Women			
		Number at risk	Number of events (%)	Adjusted HR (95% CI)	*P* value	Number at risk	Number of events (%)	Adjusted HR (95% CI)	*P* value
All-cause mortality[a]									
Diabetes	**<0.001***	704	415 (58.9)	1.290 (1.094–1.522)	0.003*	602	387 (64.3)	1.234 (1.032–1.476)	0.021*
No diabetes		571	287 (50.3)	1.000 (reference)		395	227 (57.5)	1.000 (reference)	
Cardiovascular mortality[b]									
Diabetes	**0.131**	704	221 (31.4)	1.431 (1.148–1.783)	0.001*	602	183 (30.4)	1.423 (1.103–1.837)	0.007*
No diabetes		571	130 (22.8)	1.000 (reference)		395	96 (24.3)	1.000 (reference)	
Heart failure rehospitalisation[c]									
Diabetes	**0.054**	704	341 (48.4)	1.254 (1.060–1.485)	0.008*	602	275 (45.7)	1.480 (1.196–1.830)	<0.001*
No diabetes		571	244 (42.7)	1.000 (reference)		395	132 (33.4)	1.000 (reference)	
Cardiovascular mortality or heart failure rehospitalisation[d]									
Diabetes	**0.027***	704	443 (62.9)	1.317 (1.137–1.526)	<0.001*	602	360 (59.8)	1.429 (1.195–1.710)	<0.001*
No diabetes		571	303 (53.1)	1.000 (reference)		395	193 (48.9)	1.000 (reference)	

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CI: confidence interval; HR: hazard ratio

[a] HR adjusted for age, race, creatinine, sodium, haemoglobin, stroke, peripheral vascular disease, ACEi or ARB, beta-blockers, anticoagulants and lipid lowering.

[b] HR adjusted for age, prior myocardial infarction, systolic blood pressure, QRS duration and sodium.

[c] HR adjusted for age, prior coronary artery disease, diastolic blood pressure, QRS duration and creatinine.

[d] HR adjusted for prior coronary artery disease, ever smoker, QRS duration and spironolactone/aldosterone antagonist.

* Values were considered to be statistically significant when $P<0.05$.

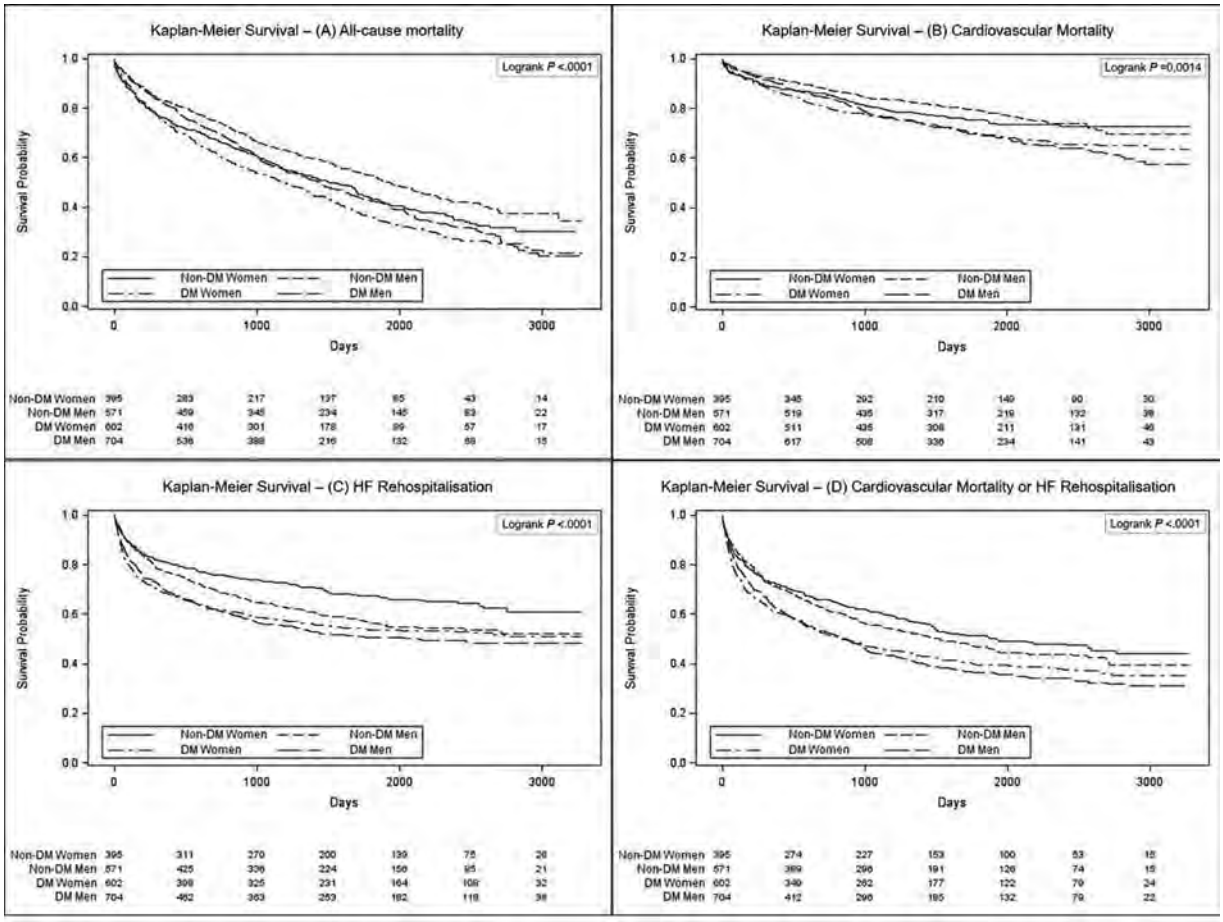

Fig. 2. Relationship between diabetes mellitus (DM) and (A) all-cause mortality (B) cardiovascular mortality, (C) heart failure (HF) rehospitalisation, and (D) cardiovascular mortality or HF rehospitalisation for men and women
DM: diabetes mellitus; HF: heart failure

the overall prescription of ACEi/ARB in our study was 67.8%, which was comparable to that of contemporary HFmrEF studies (58.8–86%).[17,22-24]

We did, however, note subtle sex-specific differences in HF pharmacotherapy prescription in our cohort. Non-DM females were less likely to be prescribed ACEi/ARB and BB than non-DM males although there were no significant differences in baseline haemodynamic (systolic/diastolic blood pressure and heart rate) as well as mean LVEF. A possible explanation could be the older mean age of non-DM females compared to males in our cohort (75.2 vs 69.3 years) and thus physicians were less likely to prescribe medications with antihypertensive effects. In terms of CKD severity, non-DM females in our cohort had comparable mean serum creatine to non-DM men (126.5 vs 132.4mmol/L, *P*=0.421), and even lower creatinine compared to females with DM (126.5 vs 147.2mmol/L, *P*=0.007), suggesting that CKD severity is less likely to be the contributing factor for this discrepant practice.

In addition, there were no specific guideline recommendations on pharmacotherapy in patients with HFmrEF until recently in 2021.[25] In fact, this phenomenon of guideline-directed medical therapy under-prescription in females is not new and has been reported by previous studies across all types of cardiovascular diseases.[26-28] Specific to HF patients, Tamargo et al. reviewed contemporary studies and discussed potential factors leading to this phenomenon such as sex differences in pharmacokinetics/pharmacodynamics, as well as the paucity of data on drug efficacy and safety, given female under-representation in HF clinical trials. In addition, women were found to experience adverse drug reactions either more frequently or at greater severity despite similar HF drug dosages compared to their male counterpart.[28] It is crucial to address this discordance in the sex-specific prescription of HF medications since ACEi/ARB and BB have shown some evidence of benefit in the HFmrEF population. From the same cohort, we recently demonstrated that ACEi/ARB and BB had a

relative risk reduction of 16% and 18%, respectively[9] on cardiovascular mortality in this group of patients. Randomised trials on ACEi/ARB and BB have also shown reduction in cardiovascular mortality for both, as well as overall survival for BB.[29,30]

A major challenge with analysing sex-specific data in HF patients is the under-representation of women in clinical trials due to low recruitment rates previously. Women constitute 43.9% of our cohort, which is comparatively higher than in previous studies. Since the inception of major randomised HF trials such as the CONSENSUS trial to the more recent PARADIGM-HF trial, women only represent 11–40% of these trial populations.[31] However, distinct sex differences have been shown to exist. For example, in a post hoc analysis of BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) study followed by a validation cohort in the ASIAN-HF registry, Santema et al. highlighted that women derive the greatest benefit of ACEi/ARB and BB at a lower percentage of recommended doses, with not only no incremental benefit but increased risk of developing adverse effects at higher doses.[26] It is thus critical that future HF clinical trials recruit an equal proportion of women such that more robust data on sex differences can be generated to guide sex-specific HF pharmacotherapy trials as we head towards an era of targeted and personalised medicine.

Limitations

While the strengths of our study hinge upon an ethnically diverse Asian HFmrEF population with an almost proportionate sex distribution, several limitations do exist. Inherent to any observational study, despite robust adjustment for confounders, there may be variables not evaluated that may influence the results. Secondly, this study included mainly hospitalised patients. Thirdly, data on haemoglobin A1c and diabetes control, as well as detailed echocardiographic data, were not available within the registry and these will be work for future studies. Lastly, the cohort was recruited up to 2016 with the impact of newer medications such as sodium-glucose transport protein 2 inhibitors on sex differences not evaluated.

CONCLUSION

In our Asian HFmrEF cohort, women with HFmrEF have a higher prevalence of DM, with differences in clinical characteristics, compared to men. While diabetes confers poor outcomes regardless of sex, there are distinct differences between the sexes. These highlight the need for sex-specific management strategies for HFmrEF patients with DM to improve outcomes.

REFERENCES

1. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215-22.
2. Seferović PM, Petrie MC, Filippatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2018;20:853-72.
3. Dauriz M, Targher G, Laroche C, et al. Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: Results from the ESC-HFA Heart Failure Long-Term Registry. Diabetes Care 2017;40:671-8.
4. Johansson I, Edner M, Dahlström U, et al. Is the prognosis in patients with diabetes and heart failure a matter of unsatisfactory management? An observational study from the Swedish Heart Failure Registry. Eur J Heart Fail 2014;16:409-18.
5. Lam CSP, Teng THK, Tay WT, et al. Regional and ethnic differences among patients with heart failure in Asia: The Asian sudden cardiac death in heart failure registry. Eur Heart J 2016;37:3141-53.
6. Bank IEM, Gijsberts CM, Teng THK, et al. Prevalence and Clinical Significance of Diabetes in Asian Versus White Patients With Heart Failure. JACC Hear Fail 2017;5:14-24.
7. Rickenbacher P, Kaufmann BA, Maeder MT, et al. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). Eur J Heart Fail 2017;19:1586-96.
8. Hsu JJ, Ziaeian B, Fonarow GC. Heart Failure With Mid-Range (Borderline) Ejection Fraction: Clinical Implications and Future Directions. JACC Hear Fail 2017;5:763-71.
9. Tay JCK, Chia SY, Koh SHM, et al. Clinical characteristics and outcomes in Asian patients with heart failure with mildly reduced ejection fraction. Singapore Med J (In Press 2022.)
10. Chandramouli C, Teng THK, Tay WT, et al. Impact of diabetes and sex in heart failure with reduced ejection fraction patients from the ASIAN-HF registry. Eur J Heart Fail 2019;21:297-307.
11. Go YY, Sellmair R, Allen JC, et al. Defining a 'frequent admitter' phenotype among patients with repeat heart failure admissions. Eur J Heart Fail 2019;21:311-8.
12. Go YY, Allen JC, Chia SY, et al. Predictors of mortality in acute heart failure: Interaction between diabetes and impaired left ventricular ejection fraction. Eur J Heart Fail 2014;16:1183-9.
13. Yap J, Sim D, Lim CP, et al. Predictors of two-year mortality in Asian patients with heart failure and preserved ejection fraction. Int J Cardiol 2015;183:33-8
14. Yap J, Lim FY, Chia SY, et al. Prediction of Survival in Asian Patients Hospitalized With Heart Failure: Validation of the OPTIMIZE-HF Risk Score. J Card Fail 2019;25:571-5
15. Yap J, Chia SY, Lim FY, et al. The Singapore Heart Failure Risk Score: Prediction of Survival in Southeast Asian Patients. Ann Acad Med Singap 2019;48:86-94.
16. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract 2019;157:107843
17. Stolfo D, Uijl A, Vedin O, et al. Sex-Based Differences in Heart Failure Across the Ejection Fraction Spectrum: Phenotyping, and Prognostic and Therapeutic Implications. JACC Hear Fail 2019;7:505-15.
18. Martinez-Selles M, Doughty R, Poppe K, et al. Influence of diabetes, sex, and ejection fraction on the risk of death in patients

with heart failure: Results from the MAGGIC individual patient meta-analysis. Eur Heart J 2012;14:473-9.

19. O'Meara E, Clayton T, McEntegart MB, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure - Results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation 2007;115:3111-20.
20. Malmborg M, Schmiegelow MDS, Nørgaard CH, et al. Does type 2 diabetes confer higher relative rates of cardiovascular events in women compared with men? Eur Heart J 2020;41:1346-53.
21. Ohkuma T, Komorita Y, Peters SAE et al. Diabetes as a risk factor for heart failure in women and men: a systematic review and meta-analysis of 47 cohorts including 12 million individuals. Diabetologia 2019;62:1550-60.
22. Ibrahim NE, Song Y, Cannon CP, et al. Heart failure with mid-range ejection fraction: characterization of patients from the PINNACLE Registry®. ESC Hear Fail 2019;6:784-92.
23. Webb J, Draper J, Fovargue L, et al. Is heart failure with mid range ejection fraction (HFmrEF) a distinct clinical entity or an overlap group? IJC Hear Vasc 2018;21:1-6.
24. Rastogi A, Novak E, Platts AE, et al. Epidemiology, pathophysiology and clinical outcomes for heart failure patients with a mid-range ejection fraction. Eur J Heart Fail 2017;19:1597-605.
25. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
26. Santema BT, Ouwerkerk W, Tromp J, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. Lancet 2019;394:1254-63.
27. Zhao M, Woodward M, Vaartjes I, et al. Sex differences in cardiovascular medication prescription in primary care: A systematic review and meta-analysis. J Am Heart Assoc 2020;9:e014742.
28. Tamargo J, Caballero R, Delpón E. Sex-related differences in the pharmacological treatment of heart failure. Pharmacol Ther 2022;229:107891.
29. Lund LH, Claggett B, Liu J, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail 2018;20:1230-9.
30. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: An individual patient-level analysis of double-blind randomized trials. Eur Heart J 2018;39:26-35.
31. Eisenberg E, Di Palo KE, Piña IL. Sex differences in heart failure. Clin Cardiol 2018;41:211-6.

ORIGINAL ARTICLE

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Nationwide study of the characteristics of frequent attenders with multiple emergency department attendance patterns

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ABSTRACT

Introduction: The burden of frequent attenders (FAs) of emergency departments (EDs) on healthcare resources is underestimated when single-centre analyses do not account for utilisation of multiple EDs by FAs. We aimed to quantify the extent of multiple ED use by FAs and to characterise FAs.

Methods: We reviewed nationwide ED attendance in Singapore data from 1 January 2006 to 31 December 2018 (13 years). FAs were defined as patients with ≥4 ED visits in any calendar year. Single ED FAs and multiple ED FAs were patients who attended a single ED exclusively and ≥2 distinct EDs within the year, respectively. Mixed ED FAs were patients who attended a mix of a single ED and multiple EDs in different calendar years. We compared the characteristics of FAs using multivariable logistic regression.

Results: We identified 200,130 (6.3%) FAs who contributed to1,865,704 visits (19.6%) and 2,959,935 (93.7%) non-FAs who contributed to 7,671,097 visits (80.4%). After missing data were excluded, the study population consisted of 199,283 unique FAs. Nationwide-linked data identified an additional 15.5% FAs and 29.7% FA visits, in addition to data from single centres. Multiple ED FAs and mixed ED FAs were associated with male sex, younger age, Malay or Indian ethnicity, multiple comorbidities, median triage class of higher severity, and a higher frequency of ED use.

Conclusion: A nationwide approach is needed to quantify the national FA burden. The multiple comorbidities and higher frequency of ED use associated with FAs who visited multiple EDs and mixed EDs, compared to those who visited a single ED, suggested a higher level of ED burden in these subgroups of patients. The distinct characteristics and needs of each FA subgroup should be considered in future healthcare interventions to reduce FA burden.

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Keywords: ED overcrowding, ED reattendance, emergency medicine, frequent attenders, frequent flyers, multiple emergency department attendance

INTRODUCTION

Emergency department (ED) overcrowding is a growing issue that threatens public health in various parts of the world,[1] including the US,[2] UK,[3] Australia,[4] Japan[5] and Taiwan.[6]

Individuals who visit the ED repeatedly, known as frequent attenders (FAs), have been identified as a possible driver of ED overcrowding. While the definition of a FA varies in the literature, a commonly used threshold is ≥4 ED presentations within a year.[7-10] FAs represent a small proportion of ED patients but contribute a disproportionate number of ED visits, exerting an excessive strain on ED resources[9] as well as related medical services.[11]

FAs may exacerbate the problem of poor quality of care, prolonged waiting times, insufficient admission

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CLINICAL IMPACT

What is New

- To the best of our knowledge, this is the first study in Singapore to compare characteristics associated with frequent attenders (FAs) who visited single emergency departments (EDs), multiple EDs and mixed EDs.
- Multiple ED FAs and mixed ED FAs were associated with ≥2 comorbidities, median triage class of higher severity (P2) and a higher frequency of ED use (>7 visits per year).

Clinical Implications

- Targeted healthcare interventions are needed to address the distinct characteristics of FA subgroups to reduce the burden of FA on healthcare resources.

beds and delayed care,[12] thereby leading to detrimental health outcomes. Moreover, studies have reported that FAs may not be using the ED appropriately.[9,10,13-15]

Most studies on repeated ED use by FAs have focused on single centres with limited multicentre assessment of ED use.[7] In the US, limited statewide studies reported 58% FAs in Massachusetts[16] and 62% FAs in Utah[17] visiting multiple EDs (≥2 different EDs). To the best of our knowledge, few studies on FAs have been conducted on a national level.[9,18-20] Without national data, the burden of FAs is likely to be underestimated when FAs visit multiple EDs within a country.[20] Furthermore, use of multiple EDs is associated with problems such as over-treating,[21] drug misuse,[22,23] and discontinuity of care.[24]

Consistent with global trends, Singapore faces an increase in ED attendances over the years[25,26] and ED overcrowding remains a chronic problem.[27] Currently, there are 10 public hospitals in Singapore (8 general hospitals and 2 specialised hospitals) with 24-hour emergency services that are easily accessible.

In the present study, data of nationwide ED attendance over a 13-year period across all public hospitals in Singapore were analysed to quantify the degree to which FAs sought care at EDs. Single hospital analyses were compared with nationwide data. We sought to determine how characteristics associated with ED attendance behaviour differed in (1) FAs who visited a single ED only; (2) FAs who visited multiple EDs; and (3) FAs who attended a mix of a single ED and multiple EDs in different calendar years.

METHODS

Study design and population

This was a retrospective review of ED attendance records from all public hospitals in Singapore from 1 January 2006 to 31 December 2018. The public healthcare system in Singapore comprises 3 integrated healthcare clusters—Singapore Health Services, National Healthcare Group, and National University Health System—with 8 public general hospitals under the clusters. In 2011, the National Electronic Health Record (NEHR) system, which consolidates all patients' electronic medical records across public (mandatory data contribution) and private (voluntary data contribution) healthcare institutions on a single secure platform, was implemented. Medical records on NEHR were anonymised to form Ministry of Health, Singapore's Omnibus database. In our study, we utilised nationwide ED de-identified electronic health data from Omnibus. Although patient identification was masked, repeated visits for the same patient could be tracked through a study identifier. Visits to specialised hospitals (a women's and children's hospital, and a psychiatric hospital) and visits with missing study identifiers were excluded from the analysis.

FAs were identified as patients with ≥4 ED visits in any calendar year, which was consistent with commonly reported definitions in FA studies.[9,10] FAs of a single ED (single ED FAs) were identified as FAs who sought care from 1 ED in any calendar year exclusively throughout the study period. FAs of multiple EDs (multiple ED FAs) referred to FAs who sought care in ≥2 distinct EDs in any calendar year exclusively throughout the study period. FAs who attended a mix of a single ED and multiple EDs in different calendar years of the study period were referred to as mixed ED FAs in this study. Institutional review board exemption was obtained for the study.

Data variables

Patient demographics (age, sex and ethnicity), ED attendance characteristics, and variables that were found in the literature to be associated with frequent ED visits[2,4-7,16,17,28] were included in our analysis. The age of patients at their first ED visit was categorised into 5 age groups (≤25, 26–45, 45–65, 66–85, >85 years old). Ethnicity was categorised into the 4 main ethnic groups in Singapore as Chinese, Malay, Indian and others. ED attendance characteristics included triage class (based on patient acuity category scale), number of comorbidities, admission rate, frequency of ED use, and final diagnosis that was based on World Health

Organization International Classification of Diseases Ninth Revision (ICD-9), Tenth Revision (ICD-10) and Australian Modification (ICD-10-AM).

For each patient, we computed the median triage category over all ED visits and the proportion of ED visits that resulted in hospital admission. Highly frequent use of ED was taken to be >7 ED visits within a calendar year.[29] The most common final diagnosis was identified for each patient and categorised into broad groups of conditions under each relevant ICD-9 chapter heading.[30]

Statistical analysis

We compared the demographics of FAs and their ED attendance characteristics using chi-square tests for categorical data and Mann-Whitney U test for continuous variables.

Multivariable logistic regression modelling, with unique individuals as the unit of analysis, was performed to determine characteristics associated with multiple and mixed ED use in FAs. Factors found significant in univariable analyses were included in the multivariable logistic regression model. A two-tailed *P* value of <0.05 was considered statistically significant. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were reported as applicable. All data analyses were performed using STATA version 15.1 (StataCorp, College Station, US).

RESULTS

From 1 January 2006 to 31 December 2018, a total of 11,641,406 ED visits were recorded. We excluded 17.5% of visits to specialised hospitals and 0.51% visits with missing study identifiers (Fig. 1). We identified 200,130 (6.3%) patients as FAs who contributed to 1,865,704 ED visits (19.6%), and 2,959,935 (93.7%) non-FAs who contributed to 7,671,097 (80.4%) ED visits. After excluding missing data, the final study population consisted of 199,283 unique FAs.

Fig. 2 shows the yearly trend of the total number of ED patients and corresponding ED visits. We observed an increase in the number of ED patients and ED visits by 39.7% and 34.8%, respectively, from 2006 to 2018. Consistent with this increasing trend, the number of FAs and their corresponding ED visits were also found to have increased over the study period by 24.9% and 16.4%, respectively.

Compared to 173,329 FAs identified from aggregating the numbers from all individual hospitals, nationwide linked data identified 200,130 FAs, which was an additional 15.5% of FAs identified (Table 1).

Table 2 shows the demographics and ED attendance characteristics of the FA population.

FAs of multiple EDs and mixed EDs were characterised by younger age, with a median age of 33 years (IQR [interquartile range] 21–62) and 47 years (IQR 22–67), respectively, compared to 52 years (IQR 23–73) for FAs of a single ED. A higher proportion of FAs who visited multiple EDs (72.4%) were males compared to those who visited single EDs (62.6%) and mixed EDs (67.2%). FAs of Chinese (59.5%) and other (14.3%) ethnicities tended to visit a single ED, while FAs of Malay (19.5%) and Indian (19.1%) ethnicities showed mixed ED attendance behaviour.

The majority of all FAs (59.5–69.6%) had 1 comorbid condition, with a higher proportion of mixed ED FAs (38.8%) having ≥2 comorbidities compared to FAs who visited single (25.6%) and multiple EDs (27.9%). The majority of FAs who visited multiple EDs had a median triage class of lowest severity, i.e. P3/P4 (58.8%), while the majority of mixed ED FAs had a median triage class of higher severity, i.e. P2 (51.0%). A higher proportion of mixed ED FAs (25.6%) had symptoms, signs and ill-defined conditions as the final diagnoses compared to FAs who visited a single ED (19.2%) and multiple EDs (20.2%).

Multivariable analysis showed that FAs who visited multiple EDs and mixed EDs were associated with male sex, younger age, Malay or Indian ethnicity, multiple comorbid conditions, median triage class of higher severity, and a higher frequency of ED use (Table 3).

Compared to FAs who were ≤25 years of age, the adjusted odds of multiple ED and mixed ED use were 0.33 time (95% CI 0.31–0.35) and 0.36 time (95% CI 0.33–0.39) lower, respectively, in FAs >85 years old. The odds of multiple ED and mixed ED use were 1.25 (95% CI 1.22–1.28) and 1.04 (95% CI 1.01–1.07) times higher, respectively, in male FAs compared to female FAs. FAs of Malay or Indian ethnicity had 1.06 (95% CI 1.03–1.09) and 1.17 times (95% CI 1.13–1.20) increased odds of visiting multiple EDs, respectively, compared to FAs who were Chinese. Similarly, FAs of Malay or Indian ethnicity had 1.40 (95% CI 1.34–1.45) and 1.74 times (95% CI 1.67–1.82) increased odds of visiting mixed EDs than FAs who were Chinese.

A highly frequent ED use of >7 visits per year was found to be most strongly associated with multiple ED (OR 2.15, 95% CI 2.09–2.22) and mixed ED (OR 4.61, 95% CI 4.45–4.79) use in FAs. The odds of multiple ED (OR 0.93, 95% CI 0.88–0.99) and mixed ED (OR 0.87, 95% CI 0.80–0.95) use were lower for FAs with a median triage class of P3/P4 (lowest severity), when

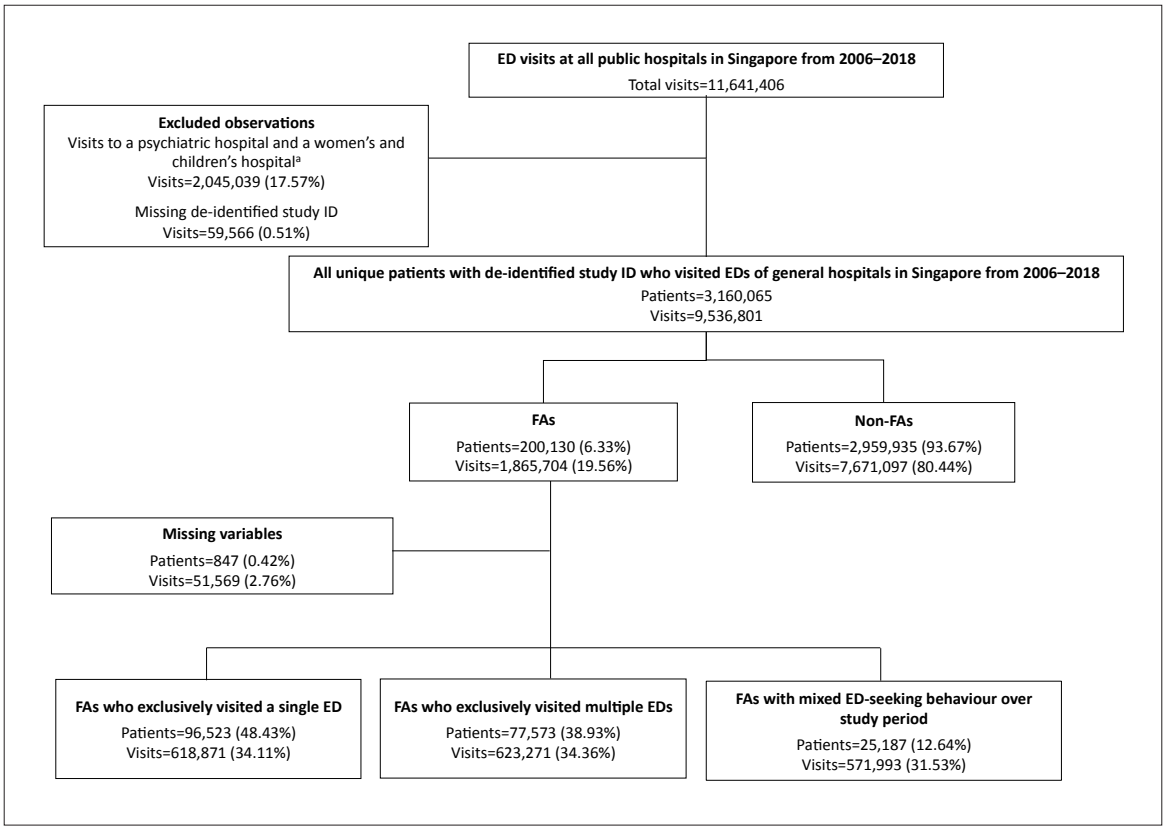

Fig. 1. Study population flowchart
ED: emergency department; FA: frequent attender; ID: identifier
[a] Institute of Mental Health, KK Women's and Children's Hospital, Singapore

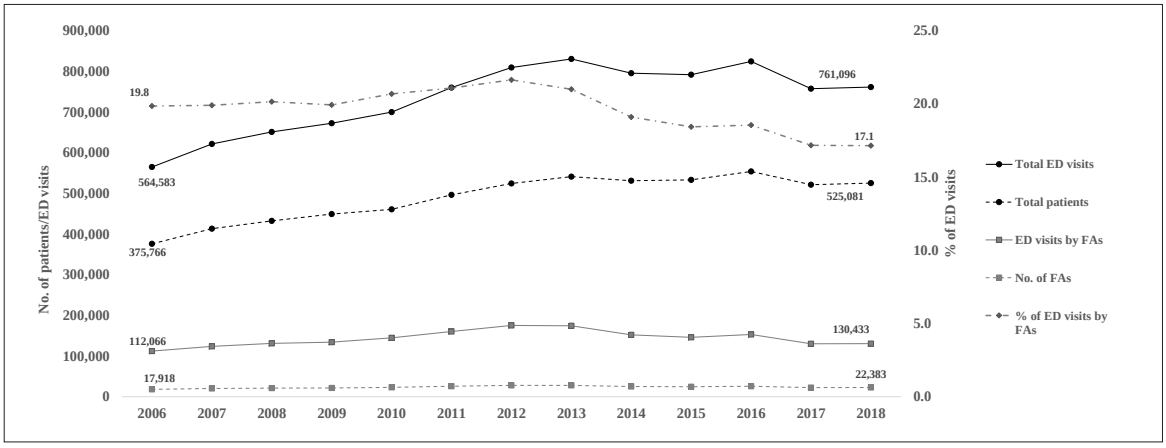

Fig. 2. Number of emergency department patients and emergency department visits at all public general hospitals in Singapore by calendar year from 2006 to 2018.
ED: emergency department; FA: frequent attender

compared to FAs with median triage class of P1 (highest severity), while the association between admission rate and multiple ED (P=0.92) and mixed ED (P=0.08) use in FAs became attenuated.

FAs who had ≥2 comorbidities had 1.07 times (95% CI 1.02–1.13) and 3.39 times (95% CI 3.05–3.76) increased odds of visiting multiple EDs and mixed EDs, respectively, than FAs without any comorbidities. Compared with infectious diseases as the reference category, the top 3 most common final diagnoses associated with FAs of multiple EDs were mental disorders (OR 1.87, 95% CI 1.71–2.04); injuries and

Table 1. Frequent attenders in Singapore and their attributable ED visits nationwide and at individual hospitals, 2006–2018

Hospital	No. of FAs	Total patients	Proportion of total patients (%)	No. of ED visits by FAs	Total ED visits	Proportion of total ED visits (%)
Nationwide	200,130[a]	3,160,065	6.33	1,865,704	9,536,801	19.56
Hospital A	28,662	821,017	3.49	237,483	1,764,082	13.46
Hospital B	36,834	759,458	4.85	328,765	1,905,645	17.25
Hospital C	37,554	900,773	4.17	315,071	2,056,402	15.32
Hospital D	22,751	506,410	4.49	196,303	1,124,899	17.45
Hospital E	30,703	813,569	3.77	231,344	1,777,142	13.02
Hospital F	11,341	279,943	4.05	92,648	563,521	16.44
Hospital G[b]	5,352	199,845	2.68	36,108	317,740	11.36
Hospital H[b]	132	23,855	0.55	684	27,370	2.50

ED: emergency department; FA: frequent attender
[a] Nationwide linked data identified 200,130 FAs, which was an additional 15.5% of FAs when compared to 173,329 FAs identified if the numbers from all individual hospitals were aggregated
[b] Limited data available as operations of these hospitals commenced officially in 2015 (G) and 2018 (H)

Table 2. Characteristics of frequent attenders in Singapore who visited a single emergency department versus multiple emergency departments versus mix of single and multiple emergency departments, 2006–2018

Characteristics	Overall, no. (%) N=199,283	FAs of single ED, no. (%) n=96,523	FAs of multiple EDs, no. (%) n=77,573	FAs of single and multiple EDs (mixed EDs), no. (%) n=25,187	*P* value
Demographic characteristics					
Age, median (IQR), years	44 (22–69)	52 (23–73)	33 (21–62)	47 (22–67)	<0.001
Age groups, years					
≤25	67,923 (34.1)	27,459 (28.5)	32,361 (41.7)	8,103 (32.2)	<0.001
26–45	33,988 (17.1)	16,086 (16.7)	13,755 (17.7)	4,147 (16.5)	
46–65	40,500 (20.3)	19,392 (20.1)	14,812 (19.1)	6,296 (25.0)	
66–85	46,751 (23.5)	26,876 (27.8)	14,020 (18.1)	5,855 (23.3)	
>85	10,121 (5.1)	6,710 (7.0)	2,625 (3.4)	786 (3.1)	
Male	133,593 (67.0)	60,466 (62.6)	56,193 (72.4)	16,934 (67.2)	<0.001
Ethnicity					
Chinese	113,617 (57.0)	57,418 (59.5)	43,522 (56.1)	12,677 (50.3)	<0.001
Malay	31,749 (15.9)	14,149 (14.7)	12,803 (16.5)	4,922 (19.5)	
Indian	27,405 (13.8)	11,125 (11.5)	11,358 (14.6)	4,797 (19.1)	
Others	26,512 (13.3)	13,831 (14.3)	9,890 (12.8)	2,791 (11.1)	
Attendance characteristics					
Median triage class					
P1	8,231 (4.1)	4,852 (5.0)	2,529 (3.3)	850 (3.4)	<0.001
P2	85,453 (42.9)	43,152 (44.7)	29,455 (38.0)	12,846 (51.0)	
P3/P4	105,599 (53.0)	48,519 (50.3)	45,589 (58.8)	11,491 (45.6)	

Table 2. Characteristics of frequent attenders in Singapore who visited a single emergency department versus multiple emergency departments versus mix of single and multiple emergency departments, 2006–2018 (Cont'd)

Characteristics	Overall, no. (%) N=199,283	FAs of single ED, no. (%) n=96,523	FAs of multiple EDs, no. (%) n=77,573	FAs of single and multiple EDs (mixed EDs), no. (%) n=25,187	*P* value
No. of comorbidities					
0	8,332 (4.2)	4,620 (4.8)	3,302 (4.3)	410 (1.6)	<0.001
1	134,812 (67.7)	67,191 (69.6)	52,626 (67.8)	14,995 (59.5)	
≥2	56,139 (28.2)	24,712 (25.6)	21,645 (27.9)	9,782 (38.8)	
Admission rate					
<0.5	118,189 (59.3)	52,869 (54.8)	50,883 (65.6)	14,437 (57.3)	<0.001
≥0.5	81,094 (40.7)	43,654 (45.2)	26,690 (34.4)	10,750 (42.7)	
Frequency of ED use					
4–7 visits per year	169,116 (84.9)	90,056 (93.3)	65,277 (84.2)	17,244 (68.5)	<0.001
>7 visits per year	30,167 (15.1)	6,467 (6.7)	12,296 (15.9)	7,943 (31.5)	
Most common final diagnosis related to					
Infectious diseases	19,261 (9.7)	10,736 (11.1)	7,195 (9.3)	1,330 (5.3)	<0.001
Neoplasms	3,513 (1.8)	1,890 (2.0)	1,531 (2.0)	92 (0.4)	
Endocrine, nutritional and related diseases	8,295 (4.2)	4,260 (4.4)	2,791 (3.6)	1,244 (4.9)	
Mental disorders	2,846 (1.4)	1,093 (1.1)	1,399 (1.8)	354 (1.4)	
Nervous system and sense organs	7,528 (3.8)	3,297 (3.4)	3,604 (4.7)	627 (2.5)	
Circulatory system	14,032 (7.0)	7,300 (7.6)	4,880 (6.3)	1,852 (7.4)	
Respiratory system	44,640 (22.4)	21,592 (22.4)	16,440 (21.2)	6,608 (26.2)	
Digestive system	13,884 (7.0)	7,103 (7.4)	5,322 (6.9)	1,459 (5.8)	
Genitourinary system	7,161 (3.6)	4,112 (4.3)	2,185 (2.8)	864 (3.4)	
Skin and subcutaneous tissue	6,220 (3.6)	3,275 (3.4)	2,189 (2.8)	756 (3.0)	
Musculoskeletal system and connective tissue	9,134 (3.1)	4,212 (4.4)	3,828 (4.9)	1,094 (4.3)	
Symptoms, signs and ill-defined conditions	40,635 (20.4)	18,490 (19.2)	15,696 (20.2)	6,449 (25.6)	
Injury and poisoning	20,287 (10.2)	8,101 (8.4)	9,893 (12.8)	2,293 (9.1)	
Others	1,846 (0.9)	1,062 (1.1)	620 (0.8)	164 (0.7)	

ED: emergency department; FA: frequent attender; IQR: interquartile range

poisoning (OR 1.61, 95% CI 1.54–1.68); and neoplasms (OR 1.55, 95% CI 1.44–1.68). For mixed FAs, they were symptoms, signs and ill-defined conditions (OR 2.37, 95% CI 2.22–2.53); endocrine, nutritional and related diseases (OR 2.14, 95% CI 1.96–2.34); and injury and poisoning (OR 2.11, 95% CI 1.96–2.28).

DISCUSSION

Our study provided a comprehensive perspective on FAs using nationwide, longitudinal ED attendance data and highlighted the heterogeneity among FAs with different ED attendance patterns. It affirmed single-centre studies[9,18,19] that FAs account for a disproportionately large share of ED attendances and the magnitude was previously underestimated when comparing nationwide data and data aggregated from individual hospitals. Addition of the number of FAs from the ED of each hospital underestimated the actual FA use of EDs.

FAs who visited multiple EDs and mixed EDs were not captured in hospital-specific data but could be

Table 3. Univariable and multivariable analysis of factors associated with frequent attenders in Singapore who visited multiple emergency departments and a mix of single and multiple emergency departments (versus a single emergency department)

Parameters	Univariable, OR (95% CI)		Multivariable adjusted, OR (95% CI)[a]	
	FAs of multiple EDs	FAs of single and multiple EDs (mixed EDs)	FAs of multiple EDs	FAs of single and multiple EDs (mixed EDs)
Age groups, years				
≤25 (reference)	1.00	1.00	1.00	1.00
26–45	0.73 (0.71–0.75)	0.87 (0.84–0.91)	0.76 (0.74–0.79)	0.94 (0.90–0.99)
46–65	0.65 (0.63–0.67)	1.10 (1.06–1.14)	0.60 (0.58–0.62)	0.92 (0.88–0.97)
66–85	0.44 (0.43–0.45)	0.74 (0.71–0.77)	0.42 (0.40–0.43)	0.64 (0.60–0.67)
>85	0.33 (0.32–0.35)	0.40 (0.32–0.35)	0.33 (0.31–0.35)	0.36 (0.33–0.39)
Sex				
Female (reference)	1.00	1.00	1.00	1.00
Male	1.57 (1.54–1.60)	1.22 (1.19–1.26)	1.25 (1.22–1.28)	1.04 (1.01–1.07)
Ethnicity				
Chinese (reference)	1.00	1.00	1.00	1.00
Malay	1.19 (1.16–1.23)	1.54 (1.48–1.60)	1.06 (1.03–1.09)	1.40 (1.34–1.45)
Indian	1.35 (1.31–1.39)	2.00 (1.93–2.08)	1.17 (1.13–1.20)	1.74 (1.67–1.82)
Others	0.94 (0.92–0.97)	0.91 (0.87–0.96)	0.78 (0.76–0.81)	0.91 (0.87–0.96)
Median triage class				
P1 (reference)	1.00	1.00	1.00	1.00
P2	1.31 (1.25–1.38)	1.70 (1.58–1.83)	1.15 (1.09–1.21)	1.62 (1.50–1.76)
P3/P4	1.80 (1.72–1.89)	1.35 (1.25–1.46)	0.93 (0.88–0.99)	0.87 (0.80–0.95)
No. of comorbidities				
None (reference)	1.00	1.00	1.00	1.00
1	1.10 (1.05–1.15)	2.51 (2.27–2.79)	1.05 (1.00–1.10)	2.24 (2.02–2.48)
≥2	1.23 (1.17–1.29)	4.46 (4.02–4.95)	1.07 (1.02–1.13)	3.39 (3.05–3.76)
Admission rate				
<0.5 (reference)	1.00	1.00	1.00	1.00
≥0.5	0.64 (0.62–0.65)	0.90 (0.88–0.93)	1.00 (0.97–1.03)	1.04 (0.99–1.09)
Frequency of ED use				
4–7 visits per year (reference)	1.00	1.00	1.00	1.00
>7 visits per year	2.54 (2.47–2.62)	5.17 (4.99–5.35)	2.15 (2. 09–2.22)	4.61 (4.45–4.79)
Most common final diagnosis related to				
Infectious diseases (reference)	1.00	1.00	1.00	1.00
Neoplasms	1.21 (1.12–1.30)	0.39 (0.31–0.49)	1.55 (1.44–1.68)	0.36 (0.29–0.45)
Endocrine, nutritional and related diseases	0.98 (0.92–1.03)	2.36 (2.17–2.57)	1.30 (1.22–1.38)	2.14 (1.96–2.34)
Mental disorders	1.91 (1.76–2.08)	2.61 (2.28–2.99)	1.87 (1.71–2.04)	1.93 (1.68–2.22)
Nervous system and sense organs	1.63 (1.54–1.72)	1.54 (1.39–1.70)	1.50 (1.41–1.58)	1.47 (1.32–1.63)

Table 3. Univariable and multivariable analysis of factors associated with frequent attenders in Singapore who visited multiple emergency departments and a mix of single and multiple emergency departments (versus a single emergency department) (Cont'd)

Parameters	Univariable, OR (95% CI)		Multivariable adjusted, OR (95% CI)[a]	
	FAs of multiple EDs	FAs of single and multiple EDs (mixed EDs)	FAs of multiple EDs	FAs of single and multiple EDs (mixed EDs)
Circulatory system	1.00 (0.95–1.05)	2.05 (1.90–2.21)	1.33 (1.27–1.40)	1.89 (1.74–2.05)
Respiratory system	1.14 (1.10–1.18)	2.47 (2.32–2.63)	0.95 (0.92–0.99)	2.06 (1.93–2.20)
Digestive system	1.11 (1.07–1.17)	1.66 (1.53–1.80)	1.17 (1.12–1.23)	1.53 (1.40–1.66)
Genitourinary system	0.79 (0.75–0.84)	1.70 (1.55–1.86)	0.96 (0.91–1.02)	1.58 (1.44–1.74)
Skin and subcutaneous tissue	1.00 (0.94–1.06)	1.86 (1.69–2.05)	1.07 (1.01–1.14)	1.86 (1.68–2.06)
Musculoskeletal system and connective tissue	1.36 (1.29–1.43)	2.10 (1.92–2.29)	1.29 (1.22–1.37)	1.96 (1.79–2.14)
Symptoms, signs and ill-defined conditions	1.27 (1.22–1.31)	2.82 (2.64–3.00)	1.39 (1.33–1.44)	2.37 (2.22–2.53)
Injury and poisoning	1.82 (1.75–1.90)	2.28 (2.12–2.46)	1.61 (1.54–1.68)	2.11 (1.96–2.28)
Others	0.87 (0.79–0.97)	1.25 (1.05–1.48)	1.00 (0.90–1.11)	1.19 (1.00–1.42)

CI: confidence interval; FA: frequent attender; OR: odds ratio

[a] Using stepwise logistic regression controlling for age, sex, ethnicity, median triage class, number of comorbidities, proportion of admissions, frequency of ED use and most common final diagnosis

accounted for using nationwide linked data. Although majority of FAs (48.4%) visited a single ED, half of the FAs (51.6%) visited multiple EDs or had mixed ED attendance behaviour. These findings signified that a substantial number of FAs would not be accounted for if only data at a single hospital were analysed. As such, integrated datasets that include all EDs in a given region or country is important to realise the full extent of the FA burden.

A failure to consider the overlapping pattern of ED use has various implications. The costs of multiple ED utilisation by FAs are higher compared to aggregate costs from a single ED.[29] Multiple ED use poses a challenge in settings where ED physicians need to make rapid decisions under stressful conditions despite insufficient knowledge with regards to previous care at EDs. This may result in duplicative, unnecessary or suboptimal patient care.[31]

Our findings showed that younger age (≤25 years old) and male sex were associated with FAs who visited multiple EDs and mixed EDs. In contrast, studies based on single-centre assessments of ED use reported FAs as being older adults and >65 years old.[9,18,19] This suggested that single ED analyses failed to capture a whole FA population, particularly younger aged FAs who may have greater mobility and may visit EDs at multiple locations.[32] Our findings corroborated with Chan et al. who observed higher rates of frequent attendance in younger males (16–25 years old) in Singapore.[18] The authors postulated that this was likely due to the prevalence of conscripted soldiers seeking treatment at the ED. Similarly, a study in 1 tertiary hospital reported that 7% of their annual ED workload was contributed by conscripted soldiers.[19] In Singapore, all males aged ≥18 years are required to serve 2 years of mandatory military service. These military personnel can access ED services without fees, which may explain the higher consumption of ED services by this group of FAs.[33]

FAs with 2 or more comorbidities tended to visit multiple EDs or mixed EDs (>3 times increased odds) compared to those with no comorbidities, suggesting that these groups of FAs were characterised by more complex medical profiles. Interestingly, only 30–40% FAs of multiple ED and mixed ED attendance had an admission rate of >0.5, i.e., they were less likely to be admitted as inpatients for further management and this may be related to their younger age. Further research may be needed to determine if these FAs could be better managed in the community.

FAs of multiple EDs and mixed EDs were highly frequent users of EDs compared to FAs of a single ED, with 16% of multiple ED FAs and one third of mixed ED FAs having >7 visits per year. This observation was consistent with existing literature on multiple ED use.[32] This tendency could in part be attributed to an increase in random chance of visiting more than 1 ED as the frequency of ED use was increased.[29]

Importantly, our findings showed a strong association between mental disorders (including alcohol/substance abuse) and the use of multiple EDs by FAs, a finding that was aligned with prior literature on multiple ED use.[31,32] This suggested that EDs in Singapore could be facing the effects of unavailable or insufficient treatment opportunities for mental disorders. FAs who presented with such diagnoses were likely sent to the ED during times of crisis, and often by third parties (e.g. law enforcement or ambulance). These patients would then be conveyed to the nearest ED, increasing the likelihood of visiting different EDs.[32] Stronger infrastructure to address issues of mental health and substance use may be critical to mitigate the use of multiple EDs.[32]

For mixed ED FAs, a strong association was found for the final diagnoses of general symptoms/ill-defined conditions (including syncope, nausea and chest pain), which may be related to the higher proportion of individuals with multiple comorbidities seen in this group. Our observation that mixed ED FAs were the heaviest users of EDs with a significant proportion of them visiting the ED >7 times in a year, corroborated previous studies which demonstrated an increased ED/acute care utilisation with increased number of comorbidities.[34,35] Further studies are needed to elucidate the reasons for ED care seeking instead of primary care for this group of patients.

The FA population was found to be not demographically or clinically homogeneous, with each of the 3 groups of FAs having distinct characteristics and needs.[16] This is an important consideration that should guide the development of future health interventions to reduce FA numbers, improve patient outcomes and encourage the use of finite ED resources more efficiently, especially when ED visits continue to rise. The magnitude of the FA population overlap among EDs suggests that coordination of care across multiple institutions is warranted to address the FA burden.

Future research

The scope for future research includes investigating the persistence of multiple and mixed ED use over time and conducting qualitative studies to explore reasons for ED use in terms of the healthcare system (e.g. ambulance transport policies, accessibility and quality of primary care services) and personal preference factors, so as to better assess the extent to which FA behaviour may be problematic, inappropriate or preventable.[29] Future research should also seek to understand and evaluate the impact of multiple and mixed ED use on patient care utilisation and outcomes.[31]

Study limitations

There were several methodological limitations in our study. Firstly, there was a lack of critical variables that may influence ED-seeking behaviour, such as education level, socioeconomic status, employment status, social history and mode of arrival to the ED. Social circumstances such as homelessness or isolation may specifically increase the risk of multiple ED use but these were unavailable in the dataset.

Secondly, the study was subjected to the common limitations of using existing datasets collected for clinical and administrative purposes. These included missing data and a potential misclassification of information, especially when data could be collected under stress conditions at the ED.

Lastly, our findings may not be generalisable to other settings as health-seeking behaviour of FAs are intricately related to factors such as healthcare funding and delivery models, which differ across regions or countries.

CONCLUSION

To our knowledge, this is the first study in Singapore to compare factors associated with FAs who visited single EDs, multiple EDs and mixed EDs. The use of nationwide data provided a comprehensive perspective on FAs. A nationwide approach is needed to quantify the national FA burden, as single hospital studies may greatly underestimate the problem.

The multiple comorbidities and higher frequency of ED use associated with FAs who visited multiple EDs and mixed EDs, compared to those who visited a single ED, suggested a higher level of ED burden in these subgroups of patients. The distinct characteristics and needs of these patients should be considered in future healthcare interventions to reduce FA of EDs.

REFERENCES

1. Di Somma S, Paladino L, Vaughan L, et al. Overcrowding in emergency department: an international issue. Intern Emerg Med 2015;10:171-5.
2. Vinton DT, Capp R, Rooks SP, et al. Frequent users of US emergency departments: Characteristics and opportunities for intervention. Emerg Med J 2014;31:526-32.
3. Dent A, Hunter G, Webster AP. The impact of frequent attenders on a UK emergency department. Eur J Emerg Med 2010;17:332-6.
4. Markham D, Graudins A. Characteristics of frequent emergency department presenters to an Australian emergency medicine network. BMC Emerg Med 2011;11:21.
5. Takeuchi S, Funakoshi H, Nakashima Y, et al. Unique characteristics of frequent presenters to the emergency department in a Japanese population: a retrospective analysis. Acute Med Surg 2019;6:145-51.

6. Hsu CM, Liang LL, Chang Y Te, et al. Emergency department overcrowding: Quality improvement in a Taiwan Medical Center. J Formos Med Assoc 2019;118:186-93.
7. Pines JM, Asplin BR, Kaji AH, et al. Frequent users of emergency department services: Gaps in knowledge and a proposed research agenda. Acad Emerg Med 2011;18:e64-9.
8. Chiu Y, Racine-Hemmings F, Dufour I, et al. Statistical tools used for analyses of frequent users of emergency department: A scoping review. BMJ Open 2019;9:e027750.
9. Boh C, Li H, Finkelstein E, et al. Factors Contributing to Inappropriate Visits of Frequent Attenders and Their Economic Effects at an Emergency Department in Singapore. Acad Emerg Med 2015;22:1025-33.
10. Oh HC, Chow WL, Gao Y, et al. Factors associated with inappropriate attendances at the emergency department of a tertiary hospital in Singapore. Singapore Med J 2020;61:75-80.
11. Kuek BJW, Li H, Yap S, et al. Characteristics of Frequent Users of Emergency Medical Services in Singapore. Prehospital Emerg Care 2019;23:215-24.
12. Dunn R. Reduced access block causes shorter emergency department waiting times: An historical control observational study. Emerg Med 2003;15:232-8.
13. McHale P, Wood S, Hughes K, et al. Who uses emergency departments inappropriately and when - a national cross-sectional study using a monitoring data system. BMC Med 2013;11:258.
14. Miyazawa A, Maeno T, Shaku F, et al. Inappropriate use of the emergency department for nonurgent conditions: Patient characteristics and associated factors at a Japanese hospital. J Gen Fam Med 2019;20:146-53.
15. Cheng L, Ng WM, Lin Z, et al. Factors reducing inappropriate attendances to emergency departments before and during the COVID-19 pandemic: A multicentre study. Ann Acad Med Singap 2021;50:818-26.
16. Fuda KK, Immekus R. Frequent Users of Massachusetts Emergency Departments: A Statewide Analysis. Ann Emerg Med 2006;48:9-16.
17. Cook LJ, Knight S, Junkins EP, et al. Repeat Patients to the Emergency Department in a Statewide Database. Acad Emerg Med 2004;11:256-63.
18. Chan JS, Tin AS, Chow WL, et al. Frequent attenders at the emergency department: an analysis of characteristics and utilisation trends. Proc Singapore Healthc 2018;27:12-9.
19. Paul P, Heng BH, Seow E, et al. Predictors of frequent attenders of emergency department at an acute general hospital in Singapore. Emerg Med J 2010;27:843-8.
20. Shen Y, Teo EWK, Liu N, et al. Data-driven approach to defining the emergency department frequent attender using a cohort of 10 years. J Acute Med 2018;8:6-16.
21. Sansone RA, Sansone LA. Doctor shopping: a phenomenon of many themes. Innov Clin Neurosci 2012;9:42-6.
22. Paulozzi LJ, Strickler GK, Kreiner PW, et al.; Centers for Disease Control and Prevention (CDC). Controlled Substance Prescribing Patterns - Prescription Behavior Surveillance System, Eight States, 2013. MMWR Surveill Summ 2015;64:1-14.
23. Hall AJ, Logan JE, Toblin RL, et al. Patterns of Abuse Among Unintentional Pharmaceutical Overdose Fatalities. JAMA 2008;300:2613-20.
24. Biernikiewicz M, Taieb V, Toumi M. Characteristics of doctor-shoppers: a systematic literature review. J Mark Access Heal Policy 2019;7:1595953.
25. Data.gov.sg. Attendances at Accident & Emergency Departments, Specialist Outpatient Clinics, Polyclinics and Public Sector Dental Clinics, 31 May 2021. Available at: https://data.gov.sg/dataset/attendances-at-accident-emergency-departments-specialist-outpatient-clinics-and-polyclinics. Accessed on 27 April 2021.
26. Tang XR, Pek PP, Siddiqui FJ, et al. Determinants of emergency department utilisation by older adults in Singapore: A systematic review. Ann Acad Med Singap 2022;51:170-9.
27. Schoenenberger LK, Bayer S, Ansah JP, et al. Emergency department crowding in Singapore: Insights from a systems thinking approach. SAGE Open Med 2016;4:205031211667195.
28. Uí Bhroin S, Kinahan J, Murphy A. Profiling frequent attenders at an inner city emergency department. Ir J Med Sci 2019;188:1013-9.
29. Fertel BS, Hart KW, Lindsell CJ, et al. Patients who use multiple EDs: Quantifying the degree of overlap between ED populations. West J Emerg Med 2015;16:229-33.
30. World Health Organization. International classification of diseases: [9th] ninth revision, basic tabulation list with alphabetic index. Available at: https://apps.who.int/iris/handle/10665/39473. Accessed on 31 March 2022.
31. Lyons TW, Olson KL, Palmer NP, et al. Patients Visiting Multiple Emergency Departments: Patterns, Costs, and Risk Factors. Acad Emerg Med 2017;24:1349-57.
32. Giannouchos TV, Washburn DJ, Kum HC, et al. Predictors of Multiple Emergency Department Utilization among Frequent Emergency Department Users in 3 States. Med Care 2020;58:137-45.
33. Oktay C, Cete Y, Eray O, et al. Appropriateness of emergency department visits in a Turkish university hospital. Croat Med J 2003;44:585-91.
34. Gruneir A, Griffith LE, Fisher K, et al. Increasing comorbidity and health services utilization in older adults with prior stroke. Neurology 2016;87:2091-8.
35. Griffith LE, Gruneir A, Fisher K, et al. Insights on multimorbidity and associated health service use and costs from three population-based studies of older adults in Ontario with diabetes, dementia and stroke. BMC Health Serv Res 2019;19:313.

REVIEW ARTICLE

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Barriers to breast cancer screening in Singapore: A literature review

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ABSTRACT

Introduction: Breast cancer is a leading cause of cancer death among women, and its age-standardised incidence rate is one of the highest in Asia. We aimed to review studies on barriers to breast cancer screening to inform future policies in Singapore.

Method: This was a literature review of both quantitative and qualitative studies published between 2012 and 2020 using PubMed, Google Scholar and Cochrane databases, which analysed the perceptions and behaviours of women towards breast cancer screening in Singapore.

Results: Through a thematic analysis based on the Health Belief Model, significant themes associated with low breast cancer screening uptake in Singapore were identified. The themes are: (1) high perceived barriers versus benefits, including fear of the breast cancer screening procedure and its possible outcomes, (2) personal challenges that impede screening attendance and paying for screening and treatment, and (3) low perceived susceptibility to breast cancer.

Conclusion: Perceived costs/barriers vs benefits of screening appear to be the most common barriers to breast cancer screening in Singapore. Based on the barriers identified, increasing convenience to get screened, reducing mammogram and treatment costs, and improving engagement with support groups are recommended to improve the screening uptake rate in Singapore.

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Keywords: Barriers, breast cancer, mammography, screening programme

INTRODUCTION

Breast cancer is a major public health concern and a leading cause of cancer death among women worldwide, including Singapore.[1] According to the 2018 Singapore Cancer Registry report, breast cancer has been consistently ranked as a leading cancer (29.3% of all cancers in Singapore) among women in Singapore women for the past 50 years.[2] Additionally, the age-standardised incidence rate of invasive breast cancer in Singapore has increased 3.5-fold to 70.7 per 100,000 population in 2014 to 2018.[2] Despite these alarming figures, breast cancer screening rates in Singapore have remained relatively low.

Early detection significantly reduces mortality since breast cancer detected at earlier stages has a better prognosis. Mammography screening is the only breast cancer screening method that has proven to be effective, with more than 40% reduction in the risk of breast cancer deaths in high-income countries.[3,4] While it is costly, it is also cost-effective and feasible in countries with good healthcare infrastructure that can afford long-term organised population-based screening programmes.[5]

Singapore's approach to breast cancer screening

Singapore's approach to promoting breast cancer screening follows a multipronged strategy comprising a national breast cancer screening programme, together with targeted health education through family, healthcare providers (HCPs), cultural leaders, and community engagement groups (e.g. Breast Cancer Foundation, Singapore).

The National Breast Cancer Screening Programme, BreastScreen Singapore (BSS), managed by the Health

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CLINICAL IMPACT

What is New

- High perceived barriers versus benefits, personal challenges that impede screening attendance, payment for screening and low perceived susceptibility to breast cancer were identified as major barriers to breast cancer screening.

Clinical Implications

- Sensitivity, cultural and communication training of healthcare providers (HCPs) may help overcome embarrassment and distrust of HCPs felt by some women as deterrents to screening.
- Based on identified barriers to screening, this study provides suggestions and informs healthcare policymakers on how to improve breast cancer screening uptake in Singapore.

Promotion Board, Singapore, has been providing subsidised breast cancer screening to the population since 2002.[6] However, BSS is not a fully organised programme, and improvements have been made to determine screening eligibility using different parameters since 2019.[7]

There is also a national campaign to raise awareness of breast cancer and screening. It takes place every October as part of Breast Cancer Awareness Month. During the campaign, partnering voluntary welfare organisations make additional subsidies available to eligible women, which in turn encourages higher take-up rates of screening mammogram.

Information on screening are readily accessible via websites such as HealthHub, the national population enablement platform for digital health.[7] Seetoh et al. found that a similar multipronged approach, including physician reminders, tailored education and cost reduction, is an effective solution in overcoming attitudinal barriers to increase screening uptake.[8]

However, despite publicity and encouragement from the Singapore health authorities, the screening uptake rate in Singapore has remained low at about 40% (Fig. 1A).[7] This is lower compared to other countries (Fig. 1B).[10-12] Both Singapore and international studies have shown that possible reasons for the relatively low screening rates include cultural, economic, and technological factors that often minimise participation in screening procedures by those at high risk for breast cancer.[8-11]

Fig. 1. (A) Women aged 50–69 years who underwent mammography in the last 2 years.
BSS: BreastScreen Singapore
Data source: Ministry of Health, Singapore. National Population Health Survey 2019. Available at: https://www.hpb.gov.sg/docs/default-source/default-document-library/national-population-health-survey-2019.pdf. Accessed on 5 August 2022.

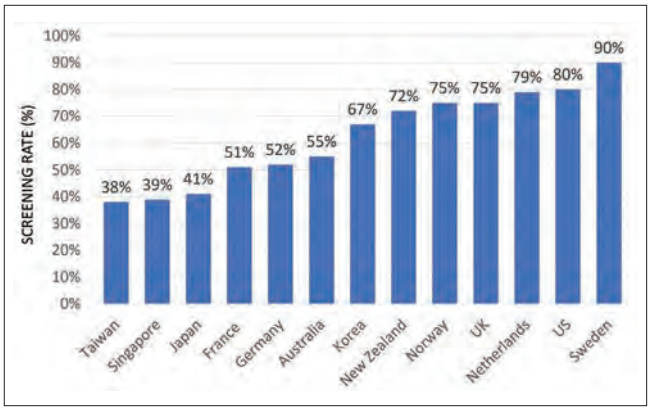

Fig. 1. (B) Breast cancer screening rates in countries with national screening programme, 2015 (or nearest years).[10-12]
Superscript numbers: Refer to REFERENCES

While there have been numerous studies performed in Singapore to explore these barriers contributing to poor breast cancer screening uptake, none to our knowledge have attempted to provide a consolidated view of these barriers relative to one another. Thus, our study aimed to consolidate identified barriers leading to low screening uptake in Singapore, and propose for programme development and policymaking.

METHOD

We performed a literature review of studies on breast cancer screening in Singapore between 2012 and 2020 using PubMed, Google Scholar and Cochrane databases. Studies were identified using the key terms: "breast cancer screening", "motivators", "barriers", and "Singapore screening". To expand the scope and breadth of studies reviewed, studies screened from the bibliographies of articles identified based on the key terms were also reviewed.

We also only included studies where women have either undergone screening or have never been screened before. Studies on breast self-examination or presentation of breast cancer upon breast self-examination were excluded. Editorial, letters, conference abstracts and personal views were excluded. One coder was used to identify themes using the constructs described in the Health Belief Model (HBM) for easier understanding.[17]

HBM is based on the understanding that individuals will adopt health-related actions if they believe they are faced with risk and have the potential to reduce that risk. The model postulates that behaviour change occurs according to constructs of perceived susceptibility to a condition, perceived severity of the condition, perceived benefits outweighing the risks, and perceived self-efficacy and cues to perform an available course of action.[17]

Recurrent themes that emerged as barriers to breast cancer screening were mapped and ranked according to these HBM constructs.

RESULTS

A total of 10 studies were included for the thematic analysis (Fig. 2). The ranked themes are described in Table 1 and online Supplementary Table S1.[17]

Perceived costs/barriers versus the benefits of breast cancer screening

High perceived costs/barriers vs the benefits of breast cancer screening among women in Singapore was identified as the most common obstacle to breast cancer screening in Singapore.

1. Fear

Fear was the most common subtheme elicited. Perceived fear of the screening components (fear of procedural pain and fear of radiation from mammograms),[18,19] and perceived fear of screening outcomes (fear of cancer diagnosis leading to high out-of-pocket cost of treatment, fear of poor quality of life, fear of treatment side effects, fear of lifetime medication and fear of social stigma) are the most widely reported barriers to breast cancer screening among women in Singapore.[8,18,20]

2. Personal challenges

Women with perceived inability to attend screening due to personal challenges were also less likely to attend breast cancer screening. Such challenges included having "no time" due to personal or professional responsibilities and "inconvenience" in having to personally attend the screening that may or may not be nearby.[18,20-22]

3. Cost

The financial cost of screening and being a financial burden to their families due to the high cost of treatment were also identified as deterrents to screening attendance. Bilger et al. found that among various factors, women were more concerned about outcomes of screening and treatment cost if tested positive than by screening attributes, which include the cost of screening or monetary incentives to screen.[23]

While previous studies have emphasised that the cost of screening had a minor effect on the decision to go for breast cancer screening, one study highlighted that women in Singapore who do not undergo regular mammograms were in fact only willing to pay an average amount of only SGD29 for screening vs the subsidised price of S$50 (for Singapore citizens aged ≥50 years).[7,24] Even those who underwent regular mammograms were willing to pay an average of only SGD33.[24] Furthermore, Lim et al. showed that a large proportion (71.4%) of women in their study population were worried about cost and also not aware that MediSave, a compulsory national medical savings scheme, could be used to pay for screening mammograms. This was apparent in low-income families and among women who did not have any personal experience with breast cancer.[18]

4. Modesty/embarrassment and distrust

In several studies, cultural beliefs on modesty and embarrassment during the procedure emerged as strong reasons for not undergoing screening. The involvement of male staff, previous negative personal experiences and negative experiences by others were specifically mentioned as barriers to screening.[18,22] These experiences could have contributed to distrust felt towards HCPs and screening methods.[22,25]

Perceived susceptibility to breast cancer

"I'm healthy" was commonly cited as a reason for avoiding breast cancer screening among women who have and have not undergone for a mammogram before. Malay women were found to indicate this more often as a reason to avoid screening compared with their Chinese and Indian counterparts.[24-26]

"I'm not at risk" was also commonly cited, as women perceived a lack of family history, feeling well and having undergone a prior mammogram with normal results, meant that they were exempted from regular

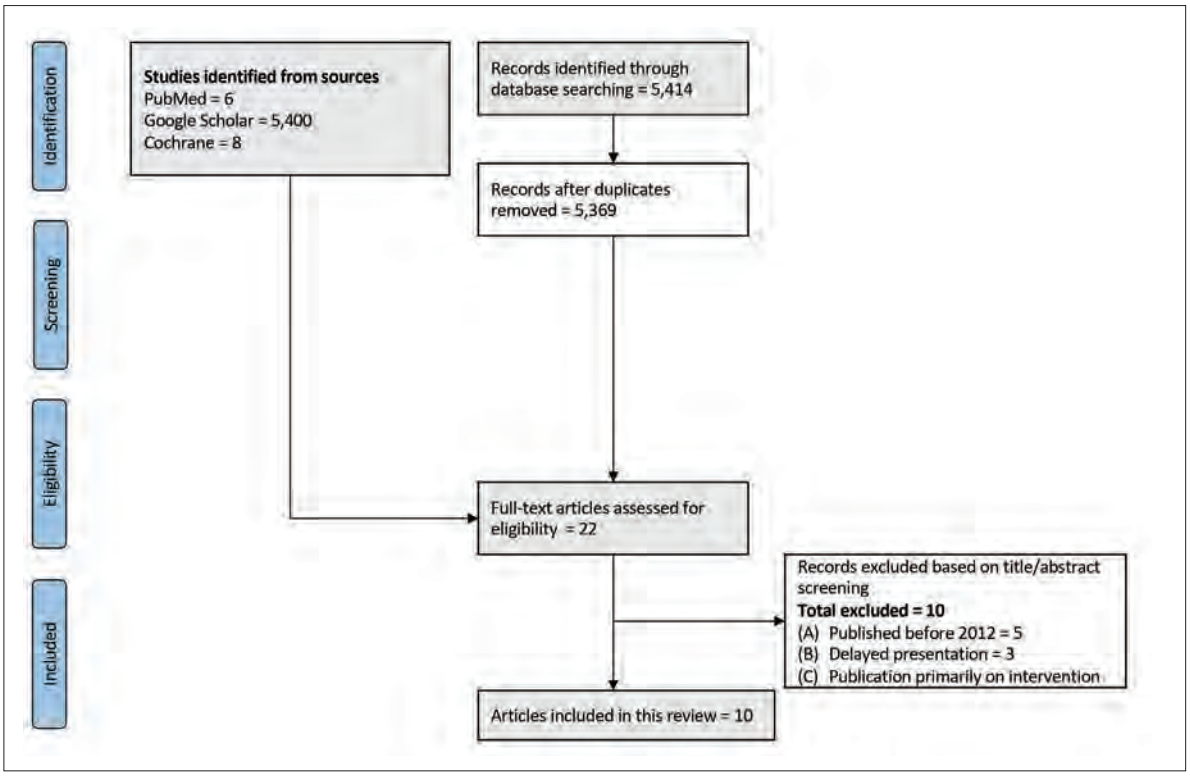

Fig. 2. Identification of studies for the thematic analysis.

screening. Women also expressed the perception that one will get cancer if one is looking for it, and that getting screened meant that something was wrong with them.[8,18,20,21]

Perceived severity of breast cancer and cues to undergo breast cancer screening

Physicians are the main source of information for screening mammogram among women.[24] The doctor-patient relationship is an important cue for women in Singapore to take action and undergo breast cancer screening—particularly, doctors who are trusted by women, and those who provide regular reminders and information on screening to allay patient fears.[8,18,27] Fatalistic beliefs that one's health outcomes were beyond one's control was also cited as a reason for poor screening uptake in this study. This factor has been observed as a barrier for women across ethnicities (Chinese, Malay and Indian), but more so among Malay women.[21,25] In addition, women ≥60 years were found to cite fatalism as one of the barriers more frequently vs younger women.[21]

Studies have showed that the majority of women in Singapore were aware of the severity of breast cancer and the importance of breast cancer screening.[28] However, Lim et al. found that while 81.6% of women participants were aware that breast cancer is one of the most common female cancers in Singapore, approximately one-third (33.4%) were not aware of the BSS programme and more than half (51.2%) did not know that screening was for asymptomatic women.[18] In addition, 46.3% of the women were not aware of the starting age for screening, and nearly one-fifth (19.5%) could not name a single screening centre.[18]

Perceived self-efficacy

Women who perceived themselves to be important to family members, and who were encouraged by their loved ones to be screened were more likely to accept and adopt breast cancer screening.[18,25]

DISCUSSION

There have been numerous studies that have explored the barriers to breast cancer screening in Singapore. To our knowledge, this is the first Singapore review that has attempted to consolidate findings across studies and identify each barrier's importance relative to others as perceived by women in Singapore. This will serve to guide prioritisation efforts towards increasing breast cancer screening rates in Singapore (Table 2).

Table 1. Themes on breast cancer screening barriers in Singapore

Themes	Subthemes	No. of times cited	Teo et al.[24] 2013	Wee et al.[20] 2012	Seetoh et al.[8] 2014	Lim et al.[18] 2015	Wee et al.[27] 2016	Wee et al.[21] 2016	Malhotra et al.[22] 2016	Wong et al.[19] 2017	Shaw et al.[25] 2018	Bilger et al.[23] 2020
Perceived cost/barriers versus the benefits of breast screening	Fear	8										
	Fear of screening procedure	4			✓	✓		✓		✓		
	Fear of screening outcomes/diagnosis	4		✓				✓	✓			✓
	Personal challenges	7										
	No time	4	✓	✓		✓		✓				
	Inconvenience	3		✓				✓	✓			
	Cost	6										
	Screening costs	4	✓	✓		✓		✓				
	Treatment costs	2						✓				✓
	Modesty /embarrassment	4				✓	✓		✓		✓	
	Distrust	3						✓	✓		✓	
Perceived susceptibility to breast cancer	“I’m not at risk”	5		✓	✓	✓		✓		✓		
	“I’m healthy”	5		✓	✓	✓	✓	✓				
	Fatalistic/cultural beliefs	3						✓	✓		✓	
Perceived severity and cues to undergo breast cancer screening	Doctor-patient relationship	4				✓	✓	✓	✓			
	Forgetfulness	3							✓	✓	✓	
	Awareness on seriousness of breast cancer and importance of screening	2		✓					✓			
Perceived self-efficacy	Self-worth and influence of family	3				✓		✓			✓	

Superscript numbers: Refer to REFERENCES

Based on our study, perceived costs/barriers vs benefits of screening emerged as the predominant theme (subthemes: fear, personal challenges, cost, modesty/embarrassment and distrust) cited by studies to explain low screening rates. This is followed by levels of perceived susceptibility (subthemes: "I'm healthy" and "I'm not at risk"), perceived severity and inadequate cues to screening (subthemes: doctor-patient relationship, fatalistic/cultural beliefs, forgetfulness, and awareness on seriousness breast cancer) and perceived self-efficacy (subtheme: self-worth and influence of family). These findings are similar to studies done in other countries, including a meta-synthesis of qualitative studies across 22 countries on breast cancer screening.[29]

Table 2. Recommendations to improve breast cancer screening in Singapore

1.	Messaging that addresses fears of the screening procedure and its outcomes should be considered for inclusion in BSS and BCAM health education materials.
2.	Modern screening modalities could be used to improve first-time screening rates, as well as subsequent drop-out rates, on a case-by-case basis.
3.	Decentralising screening appointments from clinics to the Mammobus and having more of such buses islandwide operating in easily accessible locations, could enable more women to adopt preventive breast screening as part of their normal routine.
4.	Out-of-pocket payment for subsidised screening mammograms could be reviewed to incentivise uptake. To address concerns relating to affordability, more publicity on the use of MediSave to absorb costs could assist in improving screening rates.
5.	Regular training is crucial for healthcare providers on culturally sensitive communication, and improving awareness to patients on breast cancer screening
6.	Training of Singapore doctors on how to communicate information with appropriate interpersonal skills could potentially go a long way in increasing screening rates.
7.	Targeted health campaigns to increase screening among Malay-Muslim women could include educational materials and messaging in the mother tongue, and engaging mosques and religious leaders for dissemination.

BCAM: Breast Cancer Awareness Month; BSS: BreastScreen Singapore

Fear was the most common subtheme elicited in our study as an explanation to low screening rates. Emotions are well-documented motivators[30] central to both self-regulation, health behaviour,[31] and the acceptance of health-promoting messages.[32] Fear in particular can act as both a barrier and facilitator for screening.[33]

These fears can be addressed through interpersonal communication between women and their family members, HCPs and/or community members, and facilitated by public health institutions. Professionals should be provided with skills and training on how to deliver the content. Other studies also suggest that message appeals, such as in utilising testimonials taken from real survivors of breast cancer are effective in increasing willingness and alleviating fears towards mammograms.[34]

Women who undergo screening mammogram often complain of pain, discomfort in their breasts, and anxiety as a reason to forgo consecutive screenings. However, anxiety could also be attributed to fear of the outcome. Studies have shown that modern screening modalities can be performed with less compression, which can reduce anxiety and pain levels for women without compromising the image quality.[35]

Personal challenges due to lack of time and inconvenience of accessing screening sites, which emerged strongly as a subtheme in this study has also been identified in other studies.[28] Screening sites have been brought closer to target populations through the use of a mobile Mammobus, a mobile mammography service that has shown promise in improving screening rates, both in community and workplace settings.[36] Notably, weekday take-up rates were noted to be lower compared to weekends, reinforcing the importance of time and convenience on women's decision-making.

Decentralising screening appointments from clinics to the Mammobus, and having more of such buses islandwide operating in easily accessible locations could enable more women to adopt preventive breast cancer screening as part of their normal routine.[26]

The cost of screening, though not the most common theme elicited across the studies, is still important in women's consideration in getting screened, especially in the lower socioeconomic groups in Singapore.[20] Higher breast cancer screening rates can be achieved when screening is provided free of charge or at low cost.[20] It is prudent to note that as part of the national screening programme, Screen for Life, the cost of Pap smears and faecal immunochemical test for cervical and colorectal screening respectively have been reduced to ≤SGD5 based on eligibility criteria and screening centre.[7] Yet, the subsidised cost for a mammogram remains at SGD50 under the same programme for eligible Singapore citizens.[7]

As identified in our study, women from low-income groups or who have not had personal experience with breast cancer were less likely to be aware that mammograms can be paid for using MediSave. Bilger

et al. found that a decrease in treatment costs in their study (quantitative pilot from $250,000 to $0) led to an increase in predicted screening uptake rates.[23] This stems from the fact that women greatly fear the cost of treatment if tested positive for breast cancer, as shown in our study. Hence, alleviating these costs may be essential and effective.

Out-of-pocket payment for subsidised screening mammograms could be reviewed to incentivise uptake. To address concerns relating to affordability, more publicity on the use of MediSave to absorb costs could assist in improving screening rates.[18]

Modesty, embarrassment and distrust also emerged as common subthemes in our study. This is coherent with findings from other countries.[29] Asian women may be less comfortable with exposing their private parts, even if it is to a HCP.[37] It is therefore not surprising that negative experiences with HCPs emerged under this subtheme. This issue is confounded by any indifferent behaviour that may be exhibited by HCPs.[18,25]

Low perceived susceptibility to breast cancer emerged as the next most common theme, though this is often linked with one's perceived severity of the disease or lack thereof.[28] The doctor-patient relationship is particularly important in overcoming this. This is especially important as BSS is not a fully organised programme—reminders are not sent to women who miss their first invitation and successful/missed screening attendance are not tracked. Physicians were found to be the main sources of information on breast cancer for Singapore women, and were crucial at allaying their fears and correcting misunderstandings regarding mammograms and breast cancer. Previous studies suggest that having a gynaecologist as a HPC is an important predictor for breast cancer screening.[38]

Fatalism, often associated with cultural beliefs, was also cited as a subtheme in our study. This was seen in older women and across ethnicities, although more prominently in Malay women. Shirazi et al. highlight that members of underrepresented minority groups are at higher risk of experiencing greater breast cancer-related morbidity and mortality.[39] Further to this, Tan et al. observe that Malay women in Singapore usually present with histologically more aggressive breast cancer, at a more advanced stage, and with higher risk of breast cancer-related deaths.[40] They were also more likely to perceive their susceptibility to breast cancer as low, partly due to feeling healthy along with cultural and fatalistic beliefs.[25] Given these attitudes/beliefs, developing cancer is viewed as inevitable, and consequently, these women would not get screened because of their belief that they cannot avoid their fate.[41]

Targeted health campaigns to increase screening among Malay-Muslim women, as suggested by Islam et al. could include educational materials and messages in the mother tongue, and engaging mosques and religious leaders for dissemination.[41] The effectiveness of such campaigns would be strengthened if key stakeholders are actively engaged, particularly imams (religious leaders) and female leaders within mosques.[41] Involvement of imams is of high importance as women frequently visit them at mosques and strongly believe in them.

Women's perceived self-efficacy for following through with screening emerged as a theme, though less prominently compared to other themes. It was found to be largely associated with family influence and self-worth of women. Family members and friends can contribute positively to women accepting breast cancer screening in 2 ways: family members can act as messengers on the importance of screening as women are likely to trust them; and with perceived sense of importance in her family, women are more inclined to sustain their health status in order to continue contributing to the family.[42]

There are a few limitations to our study. We included a limited number of studies, with a widely distributed participant population (N=20–740) and only identified studies in a 10-year range from 2012–2020 (of note, BSS started in 2002). The Screening Test Review Committee was set up by the Academy of Medicine, Singapore in 2010 to provide evidence-based recommendations on appropriate use of screening tests; mammogram as a suitable population-level screening was recommended in 2011.[43] Hence, we included studies published after 2012. Most of the studies also lacked comparator arms. In our analysis, we found some barriers had been reiterated more so in some articles compared to others. The degree of impact of individual barriers is difficult to ascertain given the heterogeneity of study design and analysis. In fact, there was a high level of heterogeneity across studies that were mostly qualitative in nature, and there were few quantitative studies. Furthermore, our study had only analysed findings from studies and was not focused on their methodology. As such, we are unable to ascertain the validity of the studies. However, this allowed inclusivity, for us to analyse both qualitative and quantitative studies.

We also chose to use the constructs of HBM to elicit themes and organise our findings. While HBM has been shown to be most useful to promote and describe less

entrenched and simple preventive behaviour changes such as health screening, there have also been many criticisms of HBM and its constructs in explaining health-seeking behaviours.[44] Since we have detailed the relevant subthemes under each construct, we do not view this as a major limitation to our study. However, collapsing and condensing the findings into key overarching themes and subthemes may result in the full range of findings not being captured accurately as a trade-off.

Finally, only one coder was used to identify the themes, which may have introduced subjective bias to our findings. Although we could not ascertain intercoder reliability, studies have shown that the reliability check does not necessarily establish that codes are objective, as 2 people can apply a similarly subjective perspective to the text.[45] Therefore, a better way to judge the quality of findings in a thematic analysis is to analyse whether the study has improved the understanding of a particular phenomenon or provided information for practical actions,[46] both of which we believe our study has achieved. The ranking of themes and subthemes elicited from the studies we reviewed can serve to guide prioritisation efforts in programme development and policymaking in Singapore.

CONCLUSION

Using constructs from HBM to analyse studies on addressing barriers to breast cancer screening in the Singapore context, we identified a high perceived costs/barriers vs benefits (especially with regards to fear of screening and its impact), and a low perceived susceptibility to breast cancer, as main underlying reasons for poor breast cancer screening uptake in Singapore. Based on findings from this study, Singapore's multipronged approach to encourage breast cancer screening can be further enhanced through increased convenience to get screened, further reduction of mammogram and treatment costs, and improved engagement with families, HCPs and specific ethnic groups with disparate cancer incidence. The way health communication content and messages are crafted as part of these interventions should also consider fear and cultural differences among women in Singapore to improve the acceptability of breast cancer screening.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Health Promotion Board, National Registry of Diseases Office. Singapore Cancer Registry Annual Report 2018, 31 March 2021. Available at: https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/scr-annual-report-2018.pdf. Accessed on 17 July 2021.
3. Coldman A, Phillips N, Wilson C, et al. Pan-Canadian study of mammography screening and mortality from breast cancer. J Natl Cancer Inst 2014;106:dju261. Erratum in: J Natl Cancer Inst 2015;107:dju404.
4. Hofvind S, Ursin G, Tretli S, et al. Breast cancer mortality in participants of the Norwegian Breast Cancer Screening Program. Cancer 2013;119:3106-12.
5. World Health Organization. WHO position paper on mammography screening, 2014. Available at: https://apps.who.int/iris/handle/10665/137339. Accessed on 1 July 2021.
6. Loy EY, Molinar D, Chow KY, et al. National Breast Cancer Screening Programme, Singapore: evaluation of participation and performance indicators. J Med Screen 2015;22:194-200.
7. Ministry of Health, Singapore. HealthHub. Available at: https://www.healthhub.sg. Accessed on 12 November 2021.
8. Seetoh T, Siew WF, Koh A, et al. Overcoming Barriers to Mammography Screening: A Quasi-randomised Pragmatic Trial in a Community-based Primary Care Setting. Ann Acad Med Singap 2014;43:588-94.
9. Ministry of Health, Singapore. Screening rate for breast cancer, 5 October 2020. Available at: https://www.moh.gov.sg/news-highlights/details/screening-rate-for-breast-cancer. Accessed on 26 July 2021.
10. The Commonwealth Fund. What Is the Status of Women's Health and Health Care in the U.S. Compared to Ten Other Countries? Survey Brief, December 2018. Available at: https://www.commonwealthfund.org/sites/default/files/2018-12/Gunja_status_womens_health_sb.pdf. Accessed on 26 July 2021.
11. Ministry of Health, Singapore. Percentage of women aged 50-69 years who have gone for mammography in the last 2 years. Available at: https://data.gov.sg/dataset/preventive-health-screening-statistics?view_id=d3fadaaa-6f06-4080-8de8-2b53f845f480&resource_id=ae7613d6-8e7c-45a7-a134-0b403c9d9023. Accessed on 26 July 2021.
12. OECD. Screening, survival and mortality for breast cancer. In: Health at a Glance 2017: OECD Indicators. Paris: OECD Publishing; 2017.
13. Jibaja-Weiss ML, Volk RJ, Smith QW, et al. Differential effects of messages for breast and cervical cancer screening. J Health Care Poor Underserved 2005;16:42-52.
14. Hiatt RA, Pasick RJ, Stewart S, et al. Community-based cancer screening for underserved women: Design and baseline findings from the Breast and Cervical Cancer Intervention Study. Prev Med 2001;33:190-203.
15. Jones KO, Denham BE, Springston JK. Effects of mass and interpersonal communication on breast cancer screening: Advancing agenda-setting theory in health contexts. J Appl Commun Res 2006;34:94-113.
16. Ballard-Barbash R, Klabunde C, Paci E, et al. Breast cancer screening in 21 countries: Delivery of services, notification of results and outcomes ascertainment. Eur J Cancer Prev 1999;8:417-26.
17. Rosenstock IM, Strecher VJ, Becker MH. Social Learning Theory and the Health Belief Model. Health Educ Q 1988;15:175-83.

18. Lim SK, Teo XL, Ng JL, et al. A Survey on Singaporean Women's Knowledge, Perception and Practices of Mammogram Screening. Ann Acad Med Singap 2015;44:317-25.
19. Wong XY, Chong KJ, van Til JA, et al. A qualitative study on Singaporean women's views towards breast cancer screening and Single Nucleotide Polymorphisms (SNPs) gene testing to guide personalised screening strategies. BMC Cancer 2017;17:776.
20. Wee LE, Koh GC, Chin RT, et al. Socioeconomic factors affecting colorectal, breast and cervical cancer screening in an Asian urban low-income setting at baseline and post-intervention. Prev Med 2012;55:61-7.
21. Wee LE, Lim LY, Koh GCH. Two sides of the coin: A qualitative study of patient and provider perspectives on colorectal, breast and cervical cancer screening in a low-income Asian community. Proc Singapore Healthc 2016;25:80-91.
22. Malhotra C, Bilger M, Liu J, et al. Barriers to Breast and Cervical Cancer Screening in Singapore: a Mixed Methods Analysis. Asian Pac J Cancer Prev 2016;17:3887-95.
23. Bilger M, Özdemir S, Finkelstein EA. Demand for Cancer Screening Services: Results From Randomized Controlled Discrete Choice Experiments. Value Health 2020;23:1246-55.
24. Teo CT, Yeo YWS, Lee SC. Screening Mammography Behavior and Barriers in Singaporean Asian Women. Am J Health Behav 2013;37:667-82.
25. Shaw T, Ishak D, Lie D, et al. The influence of Malay cultural beliefs on breast cancer screening and genetic testing: A focus group study. Psychooncology 2018;27:2855-61.
26. Straughan PT, Seow A. Attitudes as barriers in breast screening: a prospective study among Singapore women. Soc Sci Med 2000; 51:1695-703.
27. Wee LE, Cher WQ, Sin D, et al. Primary care characteristics and their association with health screening in a low-socioeconomic status public rental-flat population in Singapore-a mixed methods study. BMC Fam Pract 2016;17.
28. Sim HL, Seah M, Tan SM. Breast cancer knowledge and screening practices: a survey of 1,000 Asian women. Singapore Med J 2009;50:132-8.
29. Özkan İ, Taylan S. Barriers to women's breast cancer screening behaviors in several countries: A meta-synthesis study. Health Care Women Int 2021;42:1013-43.
30. Consedine NS, Magai C, Bonanno GA. Moderators of the Emotion Inhibition-Health Relationship: A Review and Research Agenda. Rev Gen Psychol 2002;6:204-28.
31. Thomas LR, Fox SA, Leake BG, et al. The effects of health beliefs on screening mammography utilization among a diverse sample of older women. Women Health 1996;24:77-94.
32. Witte K, Allen M. A meta-analysis of fear appeals: implications for effective public health campaigns. Heal Educ Behav 2000; 27:591-615.
33. Hay JL, McCaul KD, Magnan RE. Does worry about breast cancer predict screening behaviors? A meta-analysis of the prospective evidence. Prev Med 2006;42:401-8.
34. Frisby CM. A matter of life and death: Effects of emotional message strategies on African American women's attitudes about preventative breast cancer screenings. JBS 2006;37:103-26.
35. Abdullah Suhaimi SA, Mohamed A, Ahmad M,et al. Effects of Reduced Compression in Digital Breast Tomosynthesis on Pain, Anxiety, and Image Quality. Malays J Med Sci 2015;22:40-6.
36. Singapore Cancer Society. Community Mammobus Programme. Available at: https://www.singaporecancersociety.org.sg/get-screened/breast-cancer/community-mammobus-programme.html. Accessed on 22 July 2021.
37. Bedi M, Devins GM. Cultural considerations for South Asian women with breast cancer. J Cancer Surviv 2016;10:31-50.
38. Chong PN, Krishnan M, Hong CY, et al. Knowledge and practice of breast cancer screening amongst public health nurses in Singapore. Singapore Med J 2002;43:509-16.
39. Shirazi M, Engelman KK, Mbah O, et al. Targeting and tailoring health communications in breast screening interventions. Prog Community Health Partnersh 2015;9:83-9.
40. Tan EY, Wong HB, Ang BK, et al. Locally advanced and metastatic breast cancer in a tertiary hospital. Ann Acad Med Singap 2005; 34:595-601.
41. Islam N, Patel S, Brooks-Griffin Q, et al. Understanding Barriers and Facilitators to Breast and Cervical Cancer Screening among Muslim Women in New York City: Perspectives from Key Informants. SM J Community Med 2017;3:1022.
42. Chang G, Chan CW, Hartman M. A commentry on delayed presentation of breast cancer in Singapore. Asian Pac J Cancer Prev 2011;12:1635-9.
43. Academy of Medicine, Singapore. Report of the Screening Test Review Committee, March 2019. Available at: https://www.ams.edu.sg/view-pdf.aspx?file=media%5c4817_fi_59.pdf&ofile=STRC+Report+March+2019.pdf. Accessed on 1 February 2022.
44. Lewis G, Sheringham J, Bernal J, et al. Mastering Public Health: A Postgraduate Guide to Examinations and Revalidation. 2nd Ed. Boca Raton: CRC Press; 2014.
45. Ballinger C, Yardley L, Payne S. Observation and action research. In: Research Methods for Clinical and Health Psychology. 1st Ed. London: Sage Publications; 2004.
46. Krippendorff K. Content Analysis: An Introduction to Its Methodology. 2nd Ed. Thousand Oaks: Sage Publications; 2004.

COMMENTARY

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Activating Code Crimson in the emergency department: Expediting definitive care for trauma patients with severe haemorrhage in Singapore

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ABSTRACT

"Trauma activation" is a process adopted across all emergency departments of public healthcare institutions in Singapore, with the aim of rapidly mobilising personnel and resources to care for patients with major trauma. A subset of trauma patients with exsanguinating haemorrhage has a particularly high mortality rate, and they require an additional response beyond the usual trauma activation for definitive haemorrhage control. To address this need, Code Crimson has been developed at Auckland City Hospital in New Zealand and other jurisdictions as a step-up response. This is aimed at early activation of the massive transfusion protocol for haemostatic resuscitation, involvement of additional multidisciplinary teams for rapid decision-making, and expediting definitive haemorrhage control. At present, there is no protocol for activation of Code Crimson in Singapore. Code Crimson may be effective in Singapore, as it has been in other jurisdictions, to reduce morbidity and mortality in major trauma patients with severe haemorrhage.

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Keywords: Code Crimson, definitive control, emergency department, haemorrhage, massive transfusion protocol

Public healthcare institutions (PHIs) in Singapore have a range of policies and guidelines for the management of patients presenting to the emergency department (ED) with blunt or penetrating major trauma. "Trauma team activation" is initiated by the ED specialist through the hospital call-centre, and is a process that mobilises key personnel (ED specialist, doctor and nurses; as well as surgical registrar, orthopaedics registrar, diagnostic radiology doctor and radiographer) who are initially required for assessment and management of these patients. This activation is based on predefined criteria that include an initial assessment of the mechanism of injury, anatomical injuries and/or physiological criteria (Table 1). The activation either occurs directly after prehospital notification of arrival of a trauma patient by the Singapore Civil Defence Force (SCDF) paramedics, or upon the patient's arrival in ED and assessment by the ED specialist.

In patients with major trauma, severe or exsanguinating haemorrhage is a leading cause of potentially preventable death. These patients only form a small subset of the total trauma activations. Along with advancements in resuscitation strategies for bleeding control (direct pressure, tourniquets, pelvic binders, tranexamic acid, permissive hypotension, haemostatic resuscitation and prevention of the lethal triad of coagulopathy, acidosis and hypothermia), these patients also require a timely decision on the best method of haemorrhage control, and prompt transfer to the site where that can be effected.

To address this need, Code Crimson has been developed as an additional form of trauma activation in ED. It has been integrated into a number of hospitals

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in Australia and New Zealand.[1-3] PHIs in Singapore have yet to initiate this form of step-up trauma activation. Code Crimson activation mobilises additional personnel and resources who are specifically required for decision-making, above those that are required for most major trauma activations. This step-up response is aimed at early activation of the massive transfusion protocol and expediting definitive haemorrhage control by transferring the patient to the operating theatre (OT) or interventional radiology (IR) suite. A retrospective study to evaluate the impact of Code Crimson activation in patients with exsanguinating truncal trauma reported high blood transfusion rate and that they were very likely to undergo operative or angiographic intervention. Moreover, Code Crimson at Westmead Hospital in Sydney, Australia significantly reduced the median time from ED to OT to 23 minutes versus 59 minutes in patients with major haemorrhage in whom the code was not activated.[1] In 2018, Critical Haemorrhage to Operation Room Patient (CHOP) protocol was implemented by the Department of General Surgery at Khoo Teck Puat Hospital in Singapore, with a goal of bringing a severely injured patient rapidly to definitive care within 90 minutes. Analysis of the first 10 cases of CHOP protocol activation reported an average time of 73 minutes from the time of patient's arrival at ED to transfer to OT or IR suite.[4]

The activation of Code Crimson at Auckland City Hospital is currently based on the Assessment of Blood Consumption (ABC) Score, which is validated to predict the need for a massive transfusion protocol (MTP) in patients with major haemorrhage.[5] The patient should meet 2 out of 4 criteria of ABC score for activation, namely, (1) heart rate >120 beats per minute, (2) systolic blood pressure <90mmHg, (3) penetrating injuries to head, neck, chest, abdomen and/or proximal extremities, and (4) positive focused abdominal sonography in trauma (FAST) imaging indicating haemoperitoneum or haemopericardium. There were a total of 3,002 trauma activations at Auckland City Hospital from August 2015 to February 2021, out of which 148 patients (4.93%) met the criteria for Code Crimson activation. The clinical data of Code Crimson during this period are described in Table 2. The majority of patients (73%) suffered from blunt trauma. The average Injury Severity Score for these patients was 25, indicating its utility for patients with major trauma. Code Crimson managed to significantly reduce the average time from arrival in ED to transfer to OT or IR for definitive intervention to a mean of 54 minutes. The mean length of stay of these patients in the intensive care unit was 6 days, and the mortality rate was 19.6%.

In Singapore, blunt trauma is the predominant mechanism of injury in about 98% of trauma patients, either secondary to road traffic crashes, fall from height, interpersonal violence or industrial incidents.[6] High-energy blunt injuries such as pelvic disruption, massive haemothorax, uncontrolled maxillo-facial haemorrhage or amputation of limbs lead to massive haemorrhage and haemodynamic instability. The high mortality rate in this group of patients is usually contributed by coagulopathy. Thus, rapid initiation of a massive transfusion protocol is relevant.[7,8] By activating Code Crimson, the patients with high-risk blunt trauma would benefit from early access to MTP and definitive intervention to control haemorrhage.[7]

Activation of Code Crimson in the ED requires consideration of both penetrating as well as high-energy blunt trauma injuries, and should meet 2 out of the 4 criteria aforementioned.

A proposed workflow for Code Crimson activation from the ED is described in Fig. 1. Code Crimson can be activated by the ED specialist or the trauma team leader (trauma surgeon or general surgeon). This second-tier activation through the hospital call centre, in addition to the usual trauma activation, should automatically lead to activation of MTP from the blood bank and delivery to the ED resuscitation room, commencement of E-blood (emergency O-negative blood) stored in the ED and priming of a rapid infuser or fluid warmer in ED. It should also lead to activation of the following additional on-call specialists: trauma or general surgery consultant, anaesthesiologist, intensive care specialist, interventional radiology (IR) specialist, OT in-charge nurse to designate the emergency OT, and stand-by OT staff and IR suite in-charge nurse. Thus, critical communication across the key decision makers is made more efficient by incorporating a single activation code, eliminating the need for multiple calls to the individual personnel, which often leads to delay. Activation of Code Crimson identifies the patient who requires evaluation by the relevant specialists for quick decision-making and plans for definitive control of major haemorrhage and subsequent care. The trauma or surgery consultant, anaesthesiologist, intensivist and IR consultant should arrive in the ED rapidly upon activation. After discussion among all these relevant specialists, the trauma team leader, who is the overall team leader for the case, should make a decision for rapid transport of the patient to the OT or IR suite for definitive haemorrhage control, ideally within 30 minutes from the time of activation of Code Crimson.

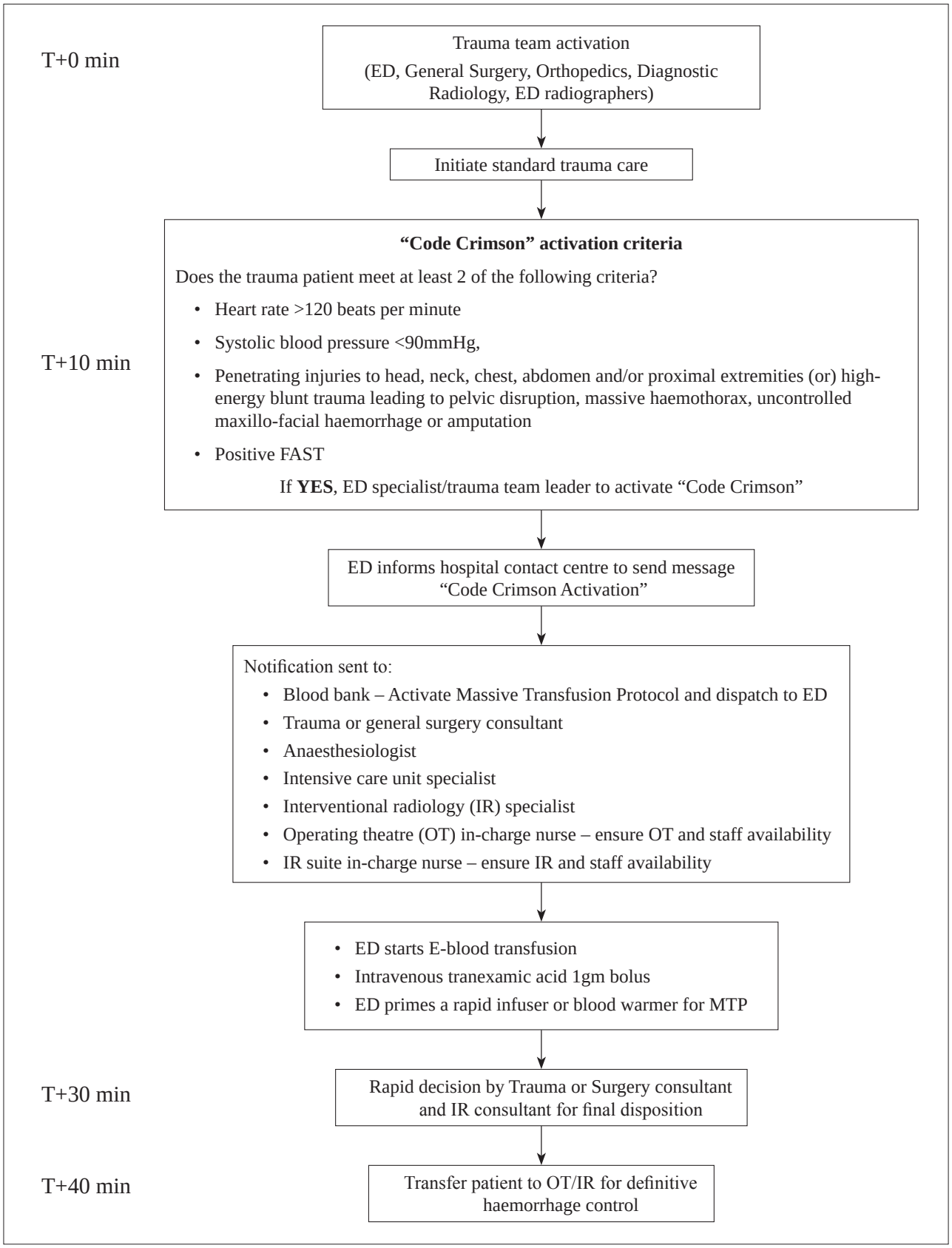

Fig. 1. Workflow of Code Crimson activation in the emergency department.
ED: emergency department; FAST: focused abdominal sonography in trauma; IR: interventional radiology; MTP: massive transfusion protocol; OT: operating theatre

In Auckland, prehospital Emergency Medical Services (EMS), ambulance EMS and helicopter EMS can activate Code Crimson if the patient meets the activation criteria. It would also be possible for prehospital activation of Code Crimson by SCDF paramedics in Singapore. Currently, the SCDF paramedics do not use portable ultrasound for FAST in the prehospital setting. The EMS will be able to activate Code Crimson if the patient met any 2 of the 3 criteria suggested (criteria 1, 2 and 3). In the future, when the SCDF paramedics are trained to perform FAST in the prehospital setting, they would be able to activate if the patient meets any 2 of the 4 criteria, similar to the activation of Code Crimson from the ED.

The following key performance indicators (KPIs) are recommended to be part of the ongoing evaluation of Code Crimson activation by the trauma service of a hospital:

- Code Crimson activation within 10 minutes of initial assessment of the patient with ongoing haemorrhage in ED;
- Transferring the patient to the OT or IR suite within 30 minutes of Code Crimson activation (total 40 minutes from the time of trauma activation).

Upon arrival in the resuscitation room, ED nurses should immediately assess vital signs of the trauma patient and commence continuous physiologic monitoring. Simultaneously, ED doctors should conduct a rapid primary survey for identification of life-threatening injuries and severe haemorrhage, including FAST for identifying haemoperitoneum

Table 1. Trauma team activation criteria

Physiological criteria	• Cardiorespiratory arrest • Unstable vital signs (heart rate <50 or >100 beats/min, respiratory rate <8 or >20 breaths/min, systolic blood pressure <90mmHg, SpO_2 <90%) • Compromised neurological status (Glasgow Coma Scale <13) or lateralising neurological signs • Airway obstruction or anticipation of difficult airway • Pregnancy
Anatomical criteria	• Penetrating wound to the head, neck, chest, abdomen, pelvis or groin, extremity above knee or elbow • Injuries involving 2 or more body regions • Major blunt chest or abdominal trauma • Flail chest, major chest wall injury or pulmonary contusion • Suspicion of vascular or cardiac injury • Severe maxillo-facial injury • Near or complete amputation proximal to wrist or ankle • 2 or more proximal long bone fractures • Pelvic fracture • Open or depressed skull fracture • Evidence of spinal cord injury with or without paralysis • Burns >15% body surface area
Mechanism of injury	• Fall >10 feet • Fall from 2nd floor or higher • Motor vehicle collision with: - High speed crash - Rollover of vehicle - Intrusion of vehicle >12-inch occupant side or 18-inch any side - Entrapment or prolonged extrication >20 minutes - Death of an occupant - Ejection (partial or complete from vehicle) - Auto versus pedestrian/bicyclist thrown, run over, or with significant impact >30kph - Motorcycle crash >50kph • Explosion • High voltage injury

Table 2. Clinical data of Code Crimson at Auckland City Hospital from August 2015 to February 2021

Parameters	Median (range) N=148
Patient demographics	
Age, years	35 (15–83)
Sex, no. (%)	
Male	110 (74.3)
Female	38 (25.7)
Presentation during office hours (0800–2159 hours), no. (%)	102 (68.9)
Mechanism of injury, no. (%)	
Blunt trauma	108 (73.0)
Penetrating trauma	40 (27.0)
Injury Severity Score	25 (1–59)
Management, no. (%)	
E-blood/MTP usage at ED	148 (100)
Intervention	92 (62.2)
- Operating theatre	88 (95.6)
- Interventional radiology	3 (3.3)
- Combined	1 (1.1)
Time to intervention, minutes	54 (26–189)
Mortality, no. (%)	
Alive	119 (80.4)
Death	29 (19.6)
Length of hospital stay, days	
Intensive care unit	6 (1–56)
Total	16.5 (1–120)

E-blood: emergency O-negative blood; ED: emergency department; MTP: massive transfusion protocol

or haemopericardium. The current trauma activation response in PHIs should enable adherence of the proposed 10-minute KPI for activation of Code Crimson in patients identified to have severe external or internal haemorrhage. All cases where Code Crimson was activated should be subsequently evaluated, and the review should include the appropriateness of patient inclusion, interventions performed in ED/OT/IR, and whether the set KPIs were met.[9] This ensures appropriate utilisation of additional resources for trauma patients with severe haemorrhage to achieve improved outcomes.

Trauma patients with uncontrolled haemorrhage benefit from a second-tier of response in addition to the standard trauma team activation. Activation of Code Crimson in the ED for these patients helps put processes in place, with the aim of expediting the time for rapid diagnosis of major haemorrhage, initiation of haemostatic resuscitation using the MTP, as well as rapid operative or radiological intervention for definitive haemorrhage control. Introduction of Code Crimson in the trauma system of all EDs may be effective in Singapore, as it has been in other jurisdictions, as an effective step-up strategy to reduce morbidity and mortality in major trauma patients with severe haemorrhage.

REFERENCES

1. Tovmassian D, Hameed AM, Ly J, et al. Process measure aimed at reducing time to haemorrhage control: outcomes associated with Code Crimson activation in exsanguinating truncal trauma. ANZ J Surg 2020;90:481-5.
2. Grabs AJ, May AN, Fulde GWO, et al. Code crimson: A life-saving measure to treat exsanguinating emergencies in trauma. ANZ J Surg 2008;78:523-5.
3. Trauma Guidelines for Auckland City Hospital, 2018. Available at: https://www.trauma.co.nz/guidelines.html. Accessed on 1 March 2022.
4. Kang ML, Goo JTT, Lee DJK. CHOP Protocol: Streamlining access to definitive intervention for major trauma victims. Singapore Med J 2021;62:620-2.
5. Nunez TC, Voskresensky IV, Dossett LA, et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma 2009;66:346-52.
6. Wui LW, Shaun GE, Ramalingam G, et al. Epidemiology of trauma in an acute care hospital in Singapore. J Emerg Trauma Shock 2014;7:174-9.
7. Yeates EO, Grigorian A, Inaba K, et al. Blunt trauma massive transfusion (B-MaT) score: A novel scoring tool. J Surg Res 2022;270:321-6.
8. Givergis R, Munnangi S, Fayaz M Fomani K, et al. Evaluation of massive transfusion protocol practices by type of trauma at a level I trauma center. Chin J Traumatol 2018;21:261-6.
9. NSW Institute of Trauma and Injury Management. Trauma 'Code Crimson' pathway, 2017. Available at: https://aci.health.nsw.gov.au/networks/institute-of-trauma-and-injury-management/clinical/trauma-guidelines/Guidelines/trauma-code-crimson-pathway. Accessed on 1 March 2022.

LETTER TO THE EDITOR

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Screening for somatisation in an Asian children's hospital emergency setting

Dear Editor,

In recent years, self-harm is the leading cause of morbidity and mortality among adolescents in Singapore.[1,2] This is just the tip of the iceberg as youths with undiagnosed mental health disorders often present to the healthcare system with non-psychiatric symptoms.[3] These psychosomatic symptoms do not have an organic pathology but are often unrecognised and over-medicalised. Early recognition and interventions can prevent progression to more serious psychiatric disorders.[4,5]

Emergency physicians are typically ill-equipped to manage adolescents with psychosocial and mental health distress. Face-to-face psychosocial evaluation is time consuming and close to impossible in the busy emergency department (ED). However, psychosocial evaluation remains crucial because the ED is often their last safety net for seeking help.[6]

We describe the development of a self-administered Youth Well-Being (YWB) questionnaire (Appendix in online Supplementary Material) tool for efficient adolescent psychosocial evaluation, and how this tool is used efficiently in the Paediatric ED of KK Women's and Children's Hospital (KKH), Singapore.

The YWB questionnaire is modelled after the HEADS-ED, which is the ED version of the well-established Home, Education, peer group Activities, Drugs, Sexuality and Suicidality interview instrument (HEADSS).[7] HEADSS is a systematic approach to psychosocial assessment of adolescents.[8] The aim of our study is to efficiently identify psychosocial distress and to facilitate early intervention.

A multidisciplinary workgroup was convened in 2019 to develop the YWB questionnaire and the workflow for its use. The team comprised physicians trained in paediatric emergency medicine, adolescent medicine and paediatric psychiatry, as well as paediatric advanced practitioner nurses, clinical psychologists and medical social workers. A clinical guideline on the workflow for the administration of the questionnaire in the ED was also established. Based on clinical audit review of questionnaire responses documented in the electronic medical records, qualitative feedback from the ED medical and nursing team, and patient focus group discussion via the SingHealth Patient Advocacy Network (SPAN)@KKH, iterative changes were made to the questionnaire design and workflow.

The YWB questionnaire is designed to be relevant to the sociocultural context of Singapore adolescents. The questions are phrased in a non-judgmental and empathetic manner. Adolescents are required to answer questions under the 9 domains: home, school, activities, safety, habits, recreational screen time, sleep, mood and suicidality, and access to support network. Concerning responses prompt the clinician to probe deeper as part of the clinical consultation. Disclosures of low mood or thoughts of self-harm require a face-to-face Suicide Risk Screening.[9] The tool is designed to give the troubled adolescent a psychologically safe "space" for confidential disclosures of their psychosocial difficulties. As a communication tool, it serves to guide a subsequent face-to-face interview that is more empathetic and targeted. It is not designed to be a diagnostic tool. Hence, there is no scoring system, nor measures of reliability and construct validity.

Since February 2020, the YWB questionnaire has been administered to clinically stable adolescents aged 10–18 years who present to KKH Paediatric ED with possible somatic symptoms such as headache, chest pain, abdominal pain, syncope, breathlessness or non-traumatic musculoskeletal pain. These symptoms remain medically unexplained after careful clinical evaluation. Adolescents with intellectual disability are excluded (Fig. 1 for YWB workflow). Based on the findings, attending ED physicians can organise psychosocial and mental health support, in tandem with medical care. Patients with mild issues require only self-help and psychoeducation resources that are given to patients and parents at the point of the ED discharge counselling. Adolescents with moderate difficulties are referred to counsellors in schools or youth social service agencies funded by the Agency for Integrated Care. Youths with serious mental health or social problems are given appropriate referrals to medical social work, psychology or adolescent psychiatry services.

The YWB questionnaire has been integrated into routine clinical care in KKH Paediatric ED since February 2020. The questionnaire design and workflows have been regularly audited for face validity and revised throughout the period of the local COVID-19 pandemic, which also saw increased ED attendances by adolescents with psychosocial problems. It is currently administered in hardcopy format.

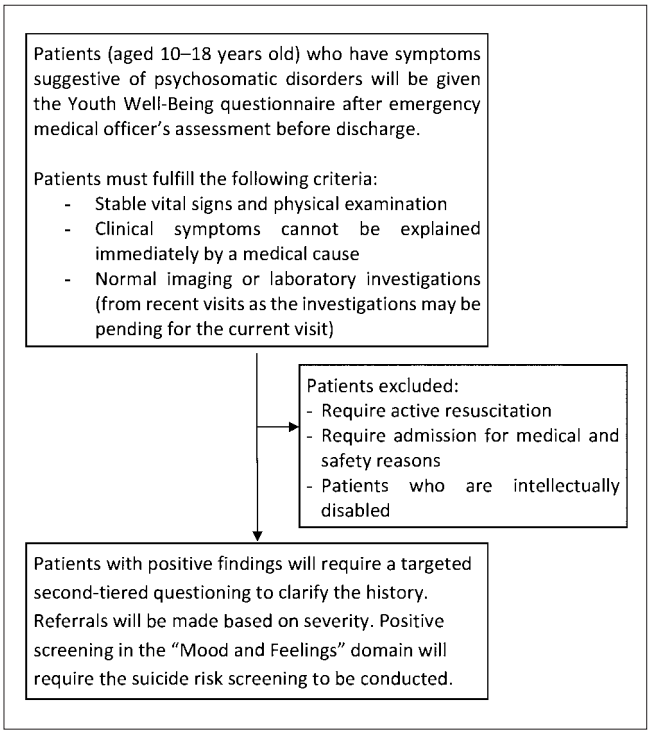

Fig. 1. Youth Well-Being workflow.

Discussion. Diagnosing somatic symptoms is challenging in the ED setting due to time constraints. Another hurdle is the inherent reluctance of youths to disclose stigmatising mental health difficulties or disapproved behaviours. However, given the magnitude of Singapore's youth mental health problem, failure to recognise psychological distress and social safety concerns can lead to disastrous consequences for the individual, wasteful consumption of healthcare resources, and long-term loss of human potential. Therefore, the YWB questionnaire provides an efficient solution to enhance capacity for early identification of adolescents with psychosocial distress. In terms of risk management, the YWB questionnaire enables identification of adolescents who present with somatic symptoms but do not disclose their suicidal thoughts to the ED triage nurse. As there are insufficient resources for universal screening, using the YWB questionnaire to identify the subset of adolescents for face-to-face Suicide Risk Screening provides the most sustainable solution to prevention of adolescent suicide as a sentinel event.

The YWB questionnaire differs from HEADS-ED in that HEADS-ED is conducted via a face-to-face interview, which would impose a huge inefficiency on the ED physician, whereas the YWB questionnaire is self-administered. This time-saving feature enables efficient psychosocial evaluation in our paediatric ED, which has an average attendance of more than 150,000 patients annually. Secondly, additional domains like recreational screen-time and sleep hygiene that commonly impact mental health are incorporated into the YWB questionnaire, but are not found in HEADS-ED.

Guided by evidence that adolescents prefer to disclose personal difficulties through a digital interface, the team is in the final stages of developing a digital version of the YWB questionnaire.[10] The software application is interactive and encourages disclosures through the use of relaxing music, animated graphics and an algorithm that asks relevant deeper questions based on the disclosures to first-tier questions. Future plans include working with multidisciplinary and inter-agency stakeholders to explore the use of the tool in other settings such as polyclinics, specialist clinics, other EDs and social service agencies.

The YWB questionnaire has great potential to impact Singapore's adolescent behavioural and mental health through early recognition and early interventions.

REFERENCES

1. World Health Organization. WHO Global Health Estimates Adolescent DALYS ranking. Available at: https://www.who.int/data/maternal-newborn-child-adolescent-ageing/indicator-explorer-new/mca/adolescent-dalys-ranking---top-5-causes-(country). Accessed on 30 October 2021.
2. World Health Organization. WHO Global Health Estimates Adolescent mortality ranking. Available at: https://www.who.int/data/maternal-newborn-child-adolescent-ageing/indicator-explorer-new/mca/adolescent-mortality-ranking---top-5-causes-(country). Accessed on 30 October 2021.
3. Andresen JM, Woolfolk RL, Allen LA, et al. Physical symptoms and psychosocial correlates of somatization in pediatric primary care. Clin Pediatr (Phila) 2011;50:904-9.
4. Chun TH, Mace SE, Katz ER, et al. Executive Summary: Evaluation and Management of Children With Acute Mental Health or Behavioral Problems. Part II: Recognition of Clinically Challenging Mental Health Related Conditions Presenting With Medical or Uncertain Symptoms. Pediatrics 2016;138:e20161574.
5. Barsky AJ, Orav EJ, Bates DW. Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. Arch Gen Psychiatry 2005;62:903-10.
6. The Lancet. Making the most out of crisis: child and adolescent mental health in the emergency department. Lancet 2016;388:935.
7. Cappelli M, Gray C, Zemek R, et al. The HEADS-ED: a rapid mental health screening tool for pediatric patients in the emergency department. Pediatrics 2012;130:e321-7.
8. Smith GL, McGuinness TM. Adolescent Psychosocial Assessment: The HEEADSSS. J Psychosoc Nurs Ment Health Serv 2017;55:24-7.
9. Horowitz LM, Bridge JA, Teach SJ, et al. Ask Suicide-Screening Questions (ASQ): a brief instrument for the pediatric emergency department. Arch Pediatr Adolesc Med 2012;166:1170-6.
10. Bradford S, Rickwood D. Acceptability and utility of an electronic psychosocial assessment (myAssessment) to increase self-disclosure in youth mental healthcare: a quasi-experimental study. BMC Psychiatry 2015;15:305.

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Teaching and learning during the COVID-19 pandemic: Perspectives of medical students in Singapore

Dear Editor,

The coronavirus disease 2019 (COVID-19) pandemic has resulted in many changes to medical education, including the site and mode of teaching, conducting of examinations and a shift towards prioritising the mastery of clinical skills relevant to infection control. Hence, Ng et al.'s suggestions on how to maximise learning in preparation for the final year medical school examinations piqued our interest.[1] As the pandemic becomes endemic, some of these changes emphasised in the delivery of education are likely to stay, perhaps longer than expected when they were first implemented as interim measures at the height of the pandemic. Furthermore, these changes have impacted medical students at all levels, including students who had begun their educational journeys during the pandemic itself ("COVID-generation" medical students, as we identify ourselves). In this letter, we propose additional strategies that may be of utility to younger medical students and their educators (Fig. 1).

Acknowledging the limitations posed by the pandemic and their conflict with the Oslerian method of bedside teaching, Ng et al.[1] recommend making the most of every clinical encounter by committing fully to patient care and comprehensive clinical examination. Since the era of Sir William Osler, however, technology has advanced remarkably, allowing us to bring the patient, virtual or real, to the classroom. Our school, Lee Kong Chian School of Medicine, a joint medical school of 2 universities, has invested in state-of-the-art tools that have allowed the continuation of clinical skills practice sessions in spite of restrictions to clinical placements. For instance, the AURiS Stethoscope (Echo Healthcare, Sarasota, US), a sensor-driven simulation stethoscope, allows students to appreciate and recognise subtle acoustic cues in the safe environment of a mannikin or a patient actor. At our partner institution, Imperial College London, the HoloLens headset (Microsoft Corp, Redmond, US) is being pioneered to reduce the crowding of students at the bedside.[2] The headset is a pair of augmented reality goggles with the capability of generating holographic projections of bedside clinical findings and radiological images. While simulation-based teaching is unlikely to replace the richness of in-person clinical clerkships, results of a review by Okuda et al. show that it leads to clinical improvement in specific scenarios and comfort in procedures.[3] In addition to clinical skills, ethical decision-making and professionalism may also be instilled through simulated scenarios that pose ethical dilemmas to students.[4] Having tested and optimised these tools for education enables educators to shift to virtual or online objective structured clinical examinations, which have been successfully implemented at several institutions, with a review showing moderate agreement between remote assessments and conventional on-site assessments.[5]

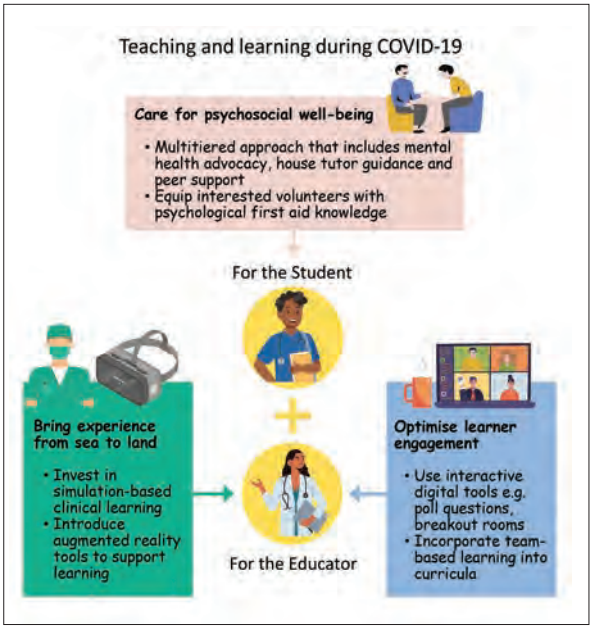

Fig. 1. Recommendations for teaching and learning during COVID-19 (created with Canva).

The pandemic has also driven the adoption of innovative technologies in the clinical setting. For example, a prospective study at Imperial College London found that the use of the HoloLens headset among staff caring for COVID-19 patients reduced the depletion of personal protective equipment and minimised staff exposure to infection.[6] As telemedicine becomes more widely adopted, it is imperative that students leverage this opportunity to become proficient in this emerging mode of patient interaction, and appreciate the nuances of and subtle differences between physical and virtual consultation modalities.

New technologies have also been adopted in the pre-clinical phase of our training. In 2021, an iPad (Apple Inc) application comprising 3D models of specimens in the anatomy laboratory was developed in our institution to allow students to study anatomy specimens remotely with remarkable precision. Students can access this

application from any location and at any time, providing a great sense of flexibility in revision outside the scheduled curriculum. The built-in labelling has also reduced reliance on supplementary faculty consults.

While the pandemic has presented unique opportunities for learning, it has also posed challenges to psychosocial well-being, through isolation (physical and social) and the pressure of self-directed learning. We acknowledge recent data that link online learning with lower emotional engagement,[7] and the latter's significant positive relationship with academic performance among learners.[8] These findings may be explained by the lack of student-lecturer and student-student social interaction within the online classroom. Take for example the small talk and side-to-side discussion between students in the traditional classroom, which seem to disappear when the same lecture is delivered in a webinar format.

As student-raised questions improve learning and fill knowledge gaps,[9] we echo Ng et al.'s suggestion for learners to prepare questions prior to home-based learning sessions. However, in our experience, students are less likely to speak in front of an entire cohort of students compared to small-scale conversations between classmates in physical vicinity. To tackle this increased barrier to entry, we recommend that educators leverage interactive features such as camera usage, poll questions, question-and-answer platforms, breakout room functions and open annotation tools to promote constructive question-asking behaviour and enhance learning. At our school, team-based learning (TBL) was implemented even before the pandemic. Our experience is that TBL primes students to be curious learners and fulfils their psychological needs for autonomy and interaction. Hence, we support the restructuring of academic curricula to incorporate TBL in addition to didactic teaching.

Moreover, we recommend safety nets for psychological well-being through ground-up initiatives. It is vital to dispel stereotypes surrounding mental health conditions, which discourage youth-in-need from reaching out for help and support.[10] This year, our student-run medical society invited professional coaches to inculcate psychological first aid skills to volunteer peer helpers. The society also created postcards with psychological aid information. Each student in our school is also paired with a personal house tutor for guidance and mentorship over the 5-year undergraduate medical education journey. With a multitiered support system, students have many avenues to seek help. Our hope is that no student gets left behind.

Ultimately, recent changes to medical education have inspired us to take ownership of our educational journeys as active participants, peers and advocates, which we realise in retrospect is the heart of a university education. It is a paradox indeed, that the pandemic has urged a shift from instructor-led pedagogical approaches to student-driven andragogical solutions. To facilitate this shift, we have reflected upon our unique experiences as "COVID-generation" medical students and dissected out recommendations for students and educators. We hope that these recommendations will shape various aspects of medical education to better prepare medical students for a COVID-endemic future.

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REFERENCES

1. Ng IK, Zhang VRY, Tseng FS, et al. Learning during the pandemic: Perspectives of medical students in Singapore. Ann Acad Med Singap 2021;50:638-42.
2. Monaghan AM. Medical Teaching and Assessment in the Era of COVID-19. J Med Educ Curric Dev 2020;7:2382120520965255.
3. Okuda Y, Bryson EO, DeMaria S Jr, et al. The utility of simulation in medical education: what is the evidence? Mt Sinai J Med 2009;76:330-43.
4. Thirumoorthy T. The Ethics of Medical Education - The Ethical and Professional Issues in Teaching and Learning Medicine. Ann Acad Med Singap 2017;46:331-2.
5. Kunutsor SK, Metcalf EP, Westacott R, et al. Are remote clinical assessments a feasible and acceptable method of assessment? A systematic review. Med Teach 2022;44:300-8.
6. Martin G, Koizia L, Kooner A, et al. Use of the HoloLens2 Mixed Reality Headset for Protecting Health Care Workers During the COVID-19 Pandemic: Prospective, Observational Evaluation. J Med Internet Res 2020;22:e21486.
7. Salta K, Paschalidou K, Tsetseri M, et al. Shift From a Traditional to a Distance Learning Environment during the COVID-19 Pandemic: University Students' Engagement and Interactions. Sci Educ (Dordr) 2022;31:93-122.
8. Lackmann S, Léger PM, Charland P, et al. The Influence of Video Format on Engagement and Performance in Online Learning. Brain Sci 2021;11:128.
9. Chin C, Osborne J. Students' questions: a potential resource for teaching and learning science. Stud Sci Educ 2008;44:1-39.
10. Pang S, Liu J, Mahesh M, et al. Stigma among Singaporean youth: a cross-sectional study on adolescent attitudes towards serious mental illness and social tolerance in a multiethnic population. BMJ Open 2017;7:e016432.

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A case of rapidly progressive insomnia and dysautonomia

Dear Editor,

A 43-year-old woman with no past medical history presented with 8 months of progressive memory loss and irritability, which led to her resigning from her office job. She frequently misplaced belongings, asked for deceased relatives, and could no longer bathe herself. When listening to conversations around her, she found them "strange and difficult to understand, as though in a dream".

She had developed secondary amenorrhoea in the past 4 months and had lost 12kg over a year despite eating well. She felt fatigued, and could take up to 3 hours to fall asleep nightly, with a reduced total sleep duration. While asleep, her mother observed that she would slowly raise her arms intermittently, while her legs made small jerking movements. No involuntary movements were seen when she was awake.

Her own father had died at 53 after a year of rapidly progressive dementia, weight loss, paucity of speech and jerky limb movements. A paternal uncle who was in his 70s had experienced behavioural changes and unsteady gait over the last 6 years.

On examination, she was alert but disoriented. She had a postural tremor, symmetrically brisk reflexes and down-going plantars. She was unsteady on tandem gait and had difficulty turning. Her neck was supple. Mini-mental state examination score was 18/28. She showed deficits in executive function, verbal fluency, attention and processing speed.

Blood count, metabolic panel, erythrocyte sedimentation rate, as well as ammonia and lactate levels were normal. Contrasted magnetic resonance imaging (MRI) of the brain showed no abnormal enhancement, with no diffusion-weighted imaging or fluid-attenuated inversion recovery hyperintensities (Fig. 1). Initial electroencephalography (EEG) showed generalised periodic epileptiform discharges, but a later EEG was merely consistent with a mild diffuse encephalopathy. Cerebrospinal fluid (CSF) composition was normal. Human immunodeficiency virus and syphilis screens, microbiology and a pan-scan for malignancy were unremarkable. CSF 14-3-3 quantification and real-time quaking-induced conversion tests were not available. The patient was treated empirically with pulsed methylprednisolone given initial suspicion for an autoimmune encephalitis. In keeping with her poor response to steroids, autoimmune and paraneoplastic panels later returned negative.

Given inconclusive investigations and a positive family history, genetic testing was performed. This identified a heterozygous pathogenic variant in the *PRNP* gene, c.532G>A (D178N), which co-segregates with methionine at codon 129. This mutation causes fatal familial insomnia (FFI), and is inherited in an autosomal dominant fashion.[1]

Over a few months, the patient developed progressive urinary retention, tachycardia and high fevers without clear sources of infection. She was treated with paracetamol, non-steroidal anti-inflammatory drugs, bisoprolol and intermittent catheterisation. As she became increasingly withdrawn and bedbound, home care services were engaged. With their support, the patient was able to avoid readmission, in keeping with her wishes. She died 11 months after symptom onset, and only 3 months after diagnosis.

FFI is a rare inherited prion disease characterised by focal neuronal loss first from the thalamus, and later from the medulla and cortex. A single other Singapore case of FFI has been reported,[2] although details of the *PRNP* mutation identified were not available. Definitive diagnostic criteria for FFI have been proposed.[3] FFI is associated with sleep disturbances—such as insomnia, sleep-related involuntary movements, stridor and dyspnoea—psychiatric symptoms, weight loss and sympathetic overactivity.[4] Features of endocrine dysfunction such as hypercortisolism, female amenorrhoea or male impotence can arise from

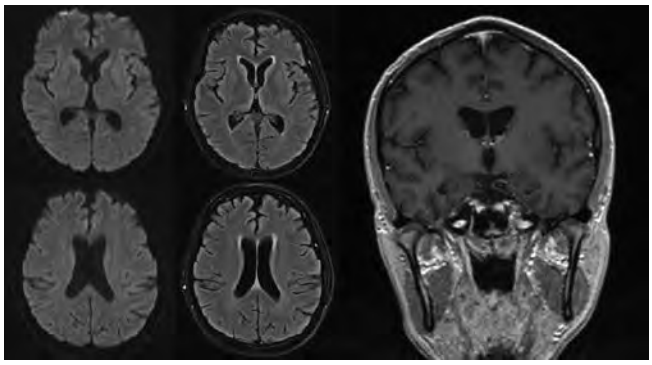

Fig. 1. Magnetic resonance imaging of the brain showed no hyperintensities on diffusion weighted imaging (left), fluid-attenuated inversion recovery sequences (middle column), and no abnormal contrast enhancement in the meninges or temporal lobes (rightmost image).

hypothalamic involvement.[5] In Asians diagnosed with FFI, neuropsychiatric symptoms, dysautonomia and sleep apnoea are more common than in non-Asians.[6] This patient's abrupt disease course is consistent with that described in an FFI cohort, where death occurred on average 13 months from disease onset.[6]

Certain differential diagnoses of rapidly progressive, early-onset dementia should be considered, including sporadic Creutzfeldt-Jakob disease (CJD). As with FFI, sporadic CJD can also be associated with the *PRNP* variant D178N, but in the latter, valine instead of methionine is found at codon 129. Sporadic CJD is associated with more florid ataxia, visual and extrapyramidal deficits[7] than what this patient demonstrated. IgLON5 disease was also considered, but the onset of IgLON5 is usually more insidious, and its disease trajectory includes oculomotor and bulbar dysfunction.[8] Other differentials of agrypnia excitata were also excluded systematically; this patient did not have neuromyotonia, anti-CASPR2 antibodies and malignancy seen in Morvan syndrome, or any identifiable causes of delirium tremens.

Some features in our patient were unusual for FFI. Cognitive impairment and motor features often occur later than dysautonomia in the course of FFI,[9] although the converse was true for this patient. It is conceivable that different genetic subtypes of FFI lead to different disease phenotypes.[10] Interestingly also, the patient's father had developed myoclonus, while her uncle deteriorated at an older age and over a longer disease course. These features resembled sporadic CJD more so than FFI. Nevertheless, it is possible that a single *PRNP* variant can give rise to a spectrum of phenotypes.[11]

Conventional MRI, EEG and CSF 14-3-3 may not be specific for FFI.[12] In fact, these are neither necessary nor sufficient in proposed criteria for diagnosing FFI.[3] The prion burden in FFI is lower than in sporadic CJD, and its distribution within brain tissue is more restricted, thus these tests may only show abnormalities in very advanced disease. Certain alternative investigations could have been considered in this patient. Even in earlier stages of FFI, polysomnography may help to detect reduced total sleep time, absent sleep spindles and lack of rapid eye movement atonia,[13] while fluorodeoxyglucose-positron emission tomography imaging may show thalamic and cingulate hypometabolism.[2]

There remains no definitive treatment for FFI. A formal genetic diagnosis helped the team to pre-empt the patient's disease trajectory and explore her preferences for end-of-life care. This provided some closure for her family.

REFERENCES

1. Goldfarb LG, Petersen RB, Tabaton M, et al. Fatal familial insomnia and familial Creutzfeldt-Jakob disease: disease phenotype determined by a DNA polymorphism. Science 1992;258:806-8.
2. Tham WY, Thian YL, Ratnagopal P, et al. 18F-FDG PET Brain in a Patient with Fatal Familial Insomnia. Clin Nucl Med 2018; 43:e274-5.
3. Wu LY, Zhan SQ, Huang ZY, et al. Expert Consensus on Clinical Diagnostic Criteria for Fatal Familial Insomnia. Chin Med J (Engl) 2018;131:1613-7.
4. Krasnianski A, Juan S, Ponto C, et al. A proposal of new diagnostic pathway for fatal familial insomnia. J Neurol Neurosurg Psychiatry 2014;85:654-9.
5. Tabernero C, Polo JM, Sevillano MD, et al. Fatal familial insomnia: clinical, neuropathological, and genetic description of a Spanish family. J Neurol Neurosurg Psychiatry 2000;68:774-7.
6. Zhang J, Chu M, Tian Z, et al. Clinical profile of fatal familial insomnia: phenotypic variation in 129 polymorphisms and geographical regions. J Neurol Neurosurg Psychiatry 2022;93:291-7.
7. See SJ, Pan A, Seah A, et al. Case reports of two biopsy-proven patients with Creutzfeldt-Jakob disease in Singapore. Ann Acad Med Singap 2004;33:651-5.
8. Gaig C, Iranzo A, Santamarí J, et al. Sleep disorder associated with antibodies to IgLON5: parasomnia or agrypnia? - Authors' reply. Lancet Neurol 2014;13:864-5.
9. Takada LT, Kim MO, Cleveland RW, et al. Genetic prion disease: Experience of a rapidly progressive dementia center in the United States and a review of the literature. Am J Med Genet Part B Neuropsychiatr Genet 2017;174:36-69.
10. Cortelli P, Fabbri M, Calandra-Buonaura G, et al. Gait disorders in fatal familial insomnia. Mov Disord 2014;29:420-4.
11. Chen B, Zhang S, Xiao Y, et al. Genetic Creutzfeldt-Jakob disease shows fatal family insomnia phenotype. Prion 2021;15:177-82.
12. Llorens F, Zarranz JJ, Fischer A, et al. Fatal Familial Insomnia: Clinical Aspects and Molecular Alterations. Curr Neurol Neurosci Rep 2017;17:30.
13. Yang TW, Park B, Kim KT, et al. Fatal familial insomnia presenting with agrypnia excitata and very low atonia index level. Medicine (Baltimore) 2018;97:e0646.

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LETTER TO THE EDITOR

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Development and feasibility of a mobile-based vestibular rehabilitation therapy application for healthy older adults

Dear Editor,

Vestibular hypofunction (VH) is the clinical condition where there is partial or complete loss of the vestibular organs and/or vestibular nerves. Symptoms of VH include vertigo, postural unsteadiness, and oscillopsia with head movements.[1,2] These symptoms, if untreated, can affect an individual's daily activities, occupational performance and mobility, leading to deconditioning and withdrawal from social activities.[3] VH in the elderly is a major risk factor for falls and reduction of physical activity.[4]

Vestibular rehabilitation therapy (VRT) is the recommended exercise-based treatment for patients with VH.[5] A comprehensive customised VRT programme consists of adaptive training of the vestibular ocular reflex (VOR) through gaze stabilisation exercises, balance and gait training, and habituation exercises for symptoms reduction.[2,5]

Current VRT programmes involve patients being taught home exercises by trained therapists, with exercise performance feedback received only during follow-up sessions (average 4–6). Without timely feedback, patients who perform home exercises suboptimally may aggravate their symptoms and prematurely stop their exercise programme.[5] Furthermore, patients rely on their therapists to progress further into their exercise programme during follow-up sessions, resulting in multiple and costly visits to the clinic.

Virtual reality has a favourable potential to optimise the outcomes of patients with VH during VRT. The use of virtual reality and conventional VRT has demonstrated better results, sustained at 1 year compared to the sole use of conventional VRT programmes.[6]

Earlier home VRT mobile applications (apps) are purely instructional, thus providing no feedback for end users,[7,8] and do not facilitate clinicians' monitoring and assessment of end users' participation in home VRT.

Recent innovations have incorporated virtual reality via smartphone apps, used together with low-cost devices, to include gamifications aimed at improving visual and vestibular stimulation,[9] and gaze stability and balance training in VRT.[10] The level of difficulty of the games is determined at the clinicians' discretion.[10]

Development of a mobile-based vestibular rehabilitation therapy app (mobile VRT): The study team developed a mobile VRT prototype, which aims to empower patients with subacute to chronic VH to administer and progress home VOR exercises correctly and safely.

VOR exercises involve patients moving their head horizontally or vertically, while focusing their eyes on a target, and keeping the target clear at all times at a prescribed rate and intensity. Patients need to slow down their head movement when the target becomes blurred or dizziness increases.

The mobile VRT uses an Android operating system and deep learning technology to accurately track and measure head and eye movement, to consequently determine horizontal and vertical VOR performance. The mobile camera system measures (1) head rotation angles, (2) frequency of on-target visual fixation, and (3) frequency of head rotations achieving a minimum angle, to compute therapy routine performance.

Users receive immediate on-screen feedback on their performance of the VOR exercises, which empowers self-progression according to the severity of their symptoms (Fig. 1). They will be informed to modify the speed of their head movement based on self-perceived dizziness severity rating. Other feedback includes keeping their eyes focused on the target, if not maintained consistently throughout the VOR exercises.

Cloud-based service can be incorporated to enable remote supervision and monitoring of individual compliance and performance of VOR by clinicians. The number of horizontal and vertical head movement per minute will be recorded per training session to track users' performance. Dizziness intensity will be rated on a visual analogue scale of 1–10.

From 2012 to 2014, there was a 30% increase in smartphone internet usage among senior citizens aged 50–59 years, and a 19% increase among adults aged ≥60 years.[10] Given senior citizens' increasing familiarity with the use of smartphones in Singapore, the introduction of the mobile VRT for therapy in older adults is a timely idea.

We sought to test the experience and acceptance of older adults towards the mobile VRT, particularly given that these are unknown for apps that allow users to self-progress in VOR exercises.

Sixteen healthy older adults (mean age 57±7 years, 11 females) with no prior experience with vestibular rehabilitation consented to participate based on the

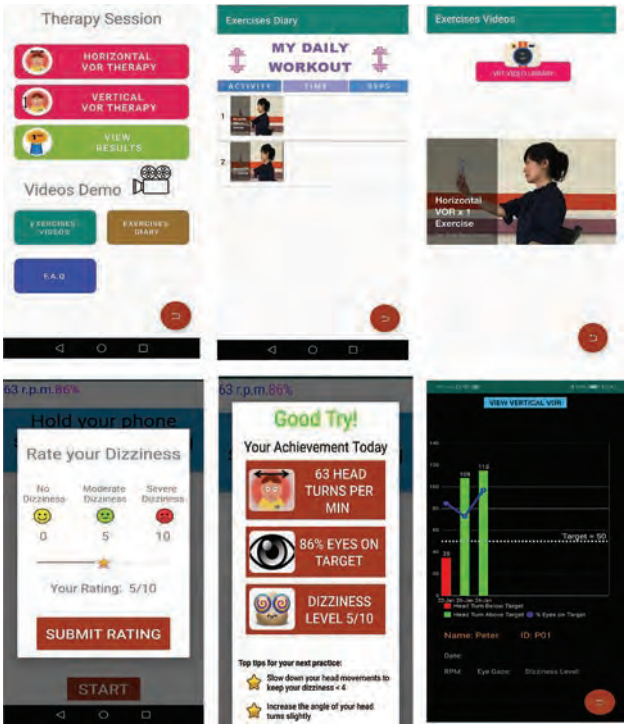

Fig. 1. Screenshots of the mobile VRT on a smartphone. Top (from left): home page, subject's customised exercise diary, and video sample of one of the home exercises. Bottom (from left): subjective rating of dizziness post-adaptive VOR exercise, on-screen feedback to users about their adaptive VOR exercises performance, and graphical representation of users' performance of adaptive VOR exercises.

National Healthcare Group Human Research Ethics Committee guidelines, to test and provide feedback on the mobile VRT. Subjects were taught to follow a series of exercise tasks over one 30-minute session, supervised by study team members before completing a questionnaire.

A 13-item questionnaire, with a combination of Likert scale and 1 open ended-question, was developed to evaluate users' experience and feedback on the ease of use, clarity of instructions, and intuitiveness of progression between exercise intensity levels.

Data were analysed using SPSS Statistics software version 27.0 (IBM Corp, Armonk, US). Descriptive statistics were used to present participants' characteristics and questionnaire responses. Categorical variables were presented as frequencies and percentages.

All recruited users found the mobile VRT easy to learn and navigate, and instructions and exercise videos simple to understand. All users also agreed that its use for rehabilitation is an innovative idea. A total of 93% reported confidence in using the app and would be keen to use it (Table 1).

Further enhancements were proposed following thematic feedback analysis. These include: fine-tuning of vertical VOR, development of instruction videos and development of a troubleshooting guide during calibration process.

Table 1. Questionnaire responses from the participants

	Questions	**Frequency (%)**			
		Strongly agree	**Agree**	**Disagree**	**Strongly disagree**
1	The process of learning the mobile VRT is easy	14 (87.5)	2 (12.5)	0	0
2	The navigation of the mobile VRT is easy	15 (93.8)	1 (6.3)	0	0
3	Instructions of the mobile VRT are easy to understand	11 (68.8)	5 (31.3)	0	0
4	Exercise videos are clear and easy to understand	13 (81.3)	3 (18.8)	0	0
5	The font and size of the text are readable	12 (75.0)	3 (18.8)	1 (6.3)	0
6	The voice of the mobile VRT can be heard clearly	14 (87.5)	2 (12.5)	0	0
7	The weight and distance of the mobile VRT prototype are comfortable to me	4 (25.0)	8 (50.0)	4 (25.0)	0
8	The speed between each interface is fast	6 (37.5)	6 (37.5)	4 (25.0)	0
9	The visual appeal of the mobile VRT looks interesting	11 (68.8)	5 (31.6)	0	0
10	The use of mobile VRT programme for rehabilitation is an innovative idea	13 (81.3)	3 (18.8)	0	0
11	If I were a patient, I will be keen to use the mobile VRT as part of my rehabilitation	13 (81.3)	2 (12.5)	1 (6.3)	0
12	If I were a patient, I will be confident to use the mobile VRT to perform home rehabilitation exercises independently	11 (68.8)	4 (25.0)	1 (6.3)	0
13	I will recommend the use of the mobile VRT to patients with inner ear imbalance for their rehabilitation	12 (75.0)	3 (18.8)	1 (6.3)	0

Mobile VRT: mobile-based vestibular rehabilitation therapy application

This study has preliminarily demonstrated the feasibility and usability of the mobile VRT in healthy older adults. Following further enhancements to the mobile VRT, the team plans to evaluate its potential for virtual reality gamifications to optimise VOR, visual and vestibular stimulation, and balance training in patients with VH.

The mobile RT facilitates cost-efficiency and remote supervision of users' home exercise programmes. Thus, it can potentially complement conventional VRT with such benefits and more enjoyable experiences.

Our study has some limitations. Only English-speaking older adults were recruited and currently, only the Android version of the app is available. Development of an iPhone-compatible version and in other languages would expand the usability of the mobile VRT.

Education and cognitive levels may be potential confounding variables in determining feasibility of the mobile VRT. Future feasibility studies may recruit users from different socioeconomic backgrounds, and age and ethnic groups to better represent the population in Singapore.

The mobile VRT was found to be easy to use, innovative and favourable by healthy older adults. Findings from this study will be considered for further development of the app.

REFERENCES

1. Bisdorff A, Von Breven M, Lempert T, et al. Classification of vestibular symptoms: towards an international classification of vestibular disorders. J Vestib Res 2009;19:1-13.
2. Herdman SJ. Vestibular rehabilitation. Curr Opin Neurol 2013;26:96-101.
3. Neuhauser HK, Radtke A, Brevern MV, et al. Burden of dizziness and vertigo in the community. Arch Intern Med 2008;168:2118-24.
4. Fernández L, Breinbauer HA, Delano PH. Vertigo and Dizziness in the Elderly. Frontiers Neurol 2015;6:1-6.
5. Hall CD, Herdman SJ, Whitney SL, et al. Vestibular Rehabilitation for Peripheral Vestibular Hypofunction: An Updated Clinical Practice Guideline From the Academy of Neurologic Physical Therapy of the American Physical Therapy Association. J Neurol Phys Ther 2022;46:118-77.
6. Viziano A, Micarelli A, Augimeri I, et al. Long-term effects of vestibular rehabilitation and head-mounted gaming task procedure in unilateral vestibular hypofunction: a 12-month follow-up of a randomized controlled trial. Clin Rehabil 2019;33:24-33.
7. Bergeron M, Lortie CL, Guitton MJ. Use of Virtual Reality Tools for Vestibular Disorders Rehabilitation: A Comprehensive Analysis. Adv Med 2015;2015:916735.
8. Wu P, Wan Y, Zhuang Y, et al. WeChat-based vestibular rehabilitation for patients with chronic vestibular syndrome: protocol for a randomised controlled trial. BMJ Open 2021;11:e042637.
9. Pereira E, Ferreira B, Menezes P. A VR-Based Vestibular Rehabilitation Therapeutic Game. International Conference on Graphics and Interaction 2021:1-8.
10. DSilva LJ, Skop KM, Pickle NT, et al. Use of Stakeholder Feedback to Develop an App for Vestibular Rehabilitation–Input From Clinicians and Healthy Older Adults. Front Neurol 2022;13:836571.

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White precipitate in a dialysis circuit

An 81-year-old man who had been fully vaccinated against COVID-19 was admitted to the medical intensive care unit on day 5 of his COVID-19-induced pneumonia for high flow nasal oxygen treatment. He had hypoxaemic respiratory failure secondary to acute respiratory distress syndrome (ARDS) from the COVID-19-induced pneumonia. He had a past medical history of hyperlipidaemia, hypertension, type 2 diabetes mellitus and stage 3 chronic kidney disease. He was treated with an extended 14-day course of dexamethasone and tocilizumab (the latter, an anti-interleukin-6 [IL-6] antagonist). His hypoxaemic respiratory failure continued to worsen despite these therapies, and he had to be intubated and mechanically ventilated on day 11 of his admission. He was started on propofol infusion for sedation post intubation, ventilated using a lung-protective ventilation strategy and placed on prone positioning for severe ARDS. He was also started on enteral feeding. The second day after intubation, his renal function continued to worsen with refractory hyperkalaemia, and he was initiated on continuous renal replacement therapy (CRRT). The CRRT circuit began to frequently clot 2 days after the initiation of dialysis, despite the use of regional citrate anticoagulation. A whitish discolouration was noted in the patient's blood and dialysis circuits, indicated by the arrows in Fig. 1 (taken on day 7 of intubation).

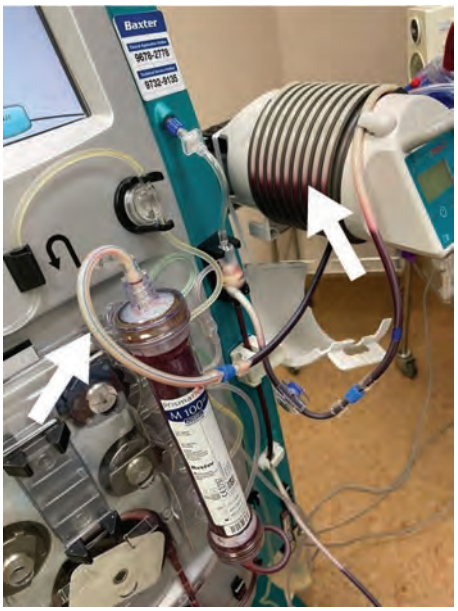

Fig. 1. Whitish appearance of dialyser tubing (left arrow) and tubing line access (right arrow).

Fig. 2. White precipitate in the arterial port (left arrow) and venous port (right arrow) of the dialysis line access due to hypertriglyceridaemia.

What is the cause of the whitish appearance of blood that led to frequent CRRT circuit clotting in this patient?

A. Sepsis-induced coagulopathy
B. Tocilizumab-induced hypertriglyceridaemia
C. Propofol-induced hypertriglyceridaemia
D. COVID-19-induced thrombosis
E. Fat emboli

The cause of the whitish appearance of blood/tubing that led to frequent CRRT clotting in this patient was propofol-induced hypertriglyceridaemia (Figs. 1 and 2, and online Supplementary Figs. S1 and S2).

Diagnosis. Lipid emulsion layering was seen in the CRRT circuit. It also clotted the filter on day 7 of intubation. This led us to suspect that this was caused by propofol infusion, which the patient was initiated on to ensure adequate sedation while on mechanical ventilation. Earlier, the patient had received high daily doses of propofol of 250–300mg (patient's weight 80kg) with an infusion rate of 3.1–3.75mg/kg/h. High doses of propofol were required to achieve adequate sedation due to ventilator dyssynchrony from poor lung

Answer: C

compliance as a result of severe ARDS. During this time, there was no evidence of propofol-related infusion syndrome such as bradycardia, arrythmias, hepatomegaly or rhabdomyolysis.

A serum lipid panel was checked on the same day the lipid emulsion layering was seen, and the triglyceride (TG) level recorded was 21.2mmol/L. Our patient had a baseline TG level of 5.98mmol/L, and he was on atorvastatin prior to admission. The high-dose propofol infusion was stopped and switched to midazolam infusion. The femoral dialysis line was also replaced, and the appearance of the whitish blood in the CRRT circuit resolved 4 days after propofol infusion was stopped, corresponding to a reduction in a serum TG level of 7.1mmol/L, repeated 2 days later. This confirmed the diagnosis of propofol-induced hypertriglyceridaemia (Table 1).

Discussion. Hypertriglyceridaemia and severe hypertriglyceridaemia are defined as serum TG concentrations ≥3mmol/L and >5mmol/L, respectively.[1] Propofol is emulsified in a lipid-based solution,[1] and when administered at high doses for prolonged duration, is associated with adverse effects such as bradycardia, hypotension, propofol-related infusion syndrome, and metabolic side effects such as hypertriglyceridaemia.[2] Other side effects include clotting of CRRT filters or extracorporeal membrane oxygenation (ECMO) circuits, deranged liver enzymes and hypertriglyceridaemia-induced pancreatitis.[3]

In severe stages of COVID-19, patients frequently develop respiratory failure requiring intensive care unit (ICU) admission and intubation with mechanical ventilatory support. Acute hypoxaemic respiratory failure from ARDS is the most common complication in patients admitted to the ICU. Propofol is a popular choice for sedation due to its rapid onset of action and easy titratability. Sedation with propofol decreases the incidence of ventilator dyssynchrony and is used as part of lung-protective ventilatory strategies. A review of studies points to an estimated 18–45% incidence of hypertriglyceridaemia with propofol.[3] A Swiss study of 220 patients in the ICU showed that the median dose of propofol associated with hypertriglyceridaemia was 2.04mg/kg/h after a median of 4 days with higher dose propofol.[1] A US study involving 552 patients found that approximately one third of patients developed hypertriglyceridaemia within a median time of 72 hours of propofol administration. The cumulative propofol dose was identified as a significant predictor of the development of hypertriglyceridaemia.[4]

In our patient, another potential cause to consider for the increase in triglyceride levels would be the use of an IL-6 inhibitor, tocilizumab. Tocilizumab is an IL-6 inhibitor used in the treatment of rheumatoid arthritis.[5] Case reports have described that IL-6 inflammatory cytokine blockade results in greater production of apolipoproteins, which lead to higher cholesterol levels.[1] Studies show that the use of tocilizumab in the treatment of rheumatoid arthritis leads to higher overall cholesterol, low-density lipoprotein (LDL) and triglyceride levels compared to patients treated with other disease-modifying anti-rheumatic drugs,[6] but not to the extent that it causes severe hypertriglyceridaemia. The exact mechanism is unclear. However, one hypothesis is that decreased IL-6 levels lead to decreased expression of LDL receptor, very-low-density lipoprotein (VLDL) receptor and scavenger receptor leading to decreased internalisation of lipids.[9] These findings are all consistent with previous studies.[7,8]

Application. Early detection and recognition of hypertriglyceridaemia helps to avoid complications such as CRRT and ECMO circuit clotting; pancreatitis; dyslipidaemia; and increased risk of stroke and myocardial infarction. We propose daily weaning of sedation, optimising sedation practices through the use of minimal doses, and limiting the duration and amount of lipid content delivered to patients. Other alternatives to propofol, such as dexmedetomidine can be considered. A multicentre, double-blinded randomised controlled trial showed that the use of dexmedetomidine compared to propofol did not result in any difference in weaning off ventilator use or mortality at 90 days.[10] In patients at particular risk for propofol-induced hypertriglyceridaemia, we re-commend monitoring of TG levels to avoid hypertriglyceridaemia-associated complications.

Table 1. Timeline of triglyceride levels and propofol administration

	Prior to intubation	Day 11	Day 12–15	Day 16–17	Day 18	Day 19	Day 20
Triglycerides (mmol/L)	5.98	-	-	21.18	7.08	8.93	7.17
Propofol dose (mg)	0	250	300	300		Stopped	
Tocilizumab				Administered			

REFERENCES

1. Devaud JC, Berger MM, Pannatier A, et al. Hypertriglyceridemia: A Potential Side Effect of Propofol Sedation in Critical Illness. Intensive Care Med 2012;38:1990-8.
2. Kovacevic MP, Dube KM, Lupi KE, et al. Evaluation of Hypertriglyceridemia in Critically Ill Patients with Coronavirus Disease 2019 Receiving Propofol. Crit Care Explor 2021;3:e0330.
3. Haffar S, Kaur RJ, Garg SK, et al. Acute Pancreatitis Associated with Intravenous Administration of Propofol: Evaluation of Causality in a Systematic Review of the Literature. Gastroenterol Rep (Oxf) 2019;7:13-23.
4. Corrado MJ, Kovacevic MP, Dube KM, et al. The Incidence of Propofol-Induced Hypertriglyceridemia and Identification of Associated Risk Factors. Crit Care Explor 2020;2:e0282.
5. McInnes IB, Thompson L, Giles JT, et al. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. Ann Rheum Dis 2015;74:694-702.
6. Pierini FS, Botta E, Soriano ER, et al. Effect of Tocilizumab on LDL and HDL Characteristics in Patients with Rheumatoid Arthritis. An Observational Study. Rheumatol Ther 2021;8:803-15.
7. Cacciapaglia F, Anelli MG, Rinaldi A, et al. Lipids and atherogenic indices fluctuation in rheumatoid arthritis patients on long-term tocilizumab treatment. Mediators Inflamm 2018;14:2453265.
8. Hoffman E, Rahat MA, Feld J, et al. Effects of Tocilizumab, an Anti-Interleukin-6 Receptor Antibody, on Serum Lipid and Adipokine Levels in Patients with Rheumatoid Arthritis. Int J Mol Sci 2019;20:4633.
9. Schultz O, Oberhauser F, Saech J, et al. Effects of Inhibition of Interleukin-6 Signalling on Insulin Sensitivity and Lipoprotein (a) Levels in Human Subjects with Rheumatoid Diseases. PLoS One 2010;5:e14328.
10. Hughes CG, Mailloux PT, Devlin JW, et al. Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. N Engl J Med 2021;382:1424-36.

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Neck pain with prevertebral soft tissue thickening

A 37-year-old man presented with a history of sudden-onset neck pain, which was worse on movement and neck extension. He reported no history of trauma or infection. He denied any neurological symptoms. A physical examination showed limited neck motion in all directions due to pain. Blood tests showed total white blood cell count to be within normal limits (10.1 x 10^9/L); raised inflammatory markers with C-reactive protein (CRP) of 59.8mg/L; and erythrocyte sedimentation rate (ESR) of 38mm/h. A cervical spine radiograph showed swelling in both the retropharyngeal and prevertebral spaces with ill-defined faint calcification anterior to C2 (Fig. 1). Magnetic resonance imaging (MRI) of the cervical spine showed low signal calcific density just inferior to the anterior arch of C1, with marked swelling and effusion in the retropharyngeal and prevertebral spaces (Figs. 2A and 2B). There were also associated inflammatory changes in the right longus colli muscle and to a lesser extent, along the adjacent longus capitis muscle.

What is the most likely diagnosis of this prevertebral soft tissue thickening?

A. Retropharyngeal abscess
B. Acute calcific tendinitis of the longus colli
C. Nasopharyngeal carcinoma
D. Cervical spondylosis with a large detached osteophyte
E. Prevertebral abscess

The patient was given a course of non-steroidal anti-inflammatory drugs (NSAIDs) and then reviewed by the otolaryngology department the week after, where a further physical examination showed no palpable lymph nodes. Nasoendoscopy revealed a central posterior nasal space (PNS) mass extending to the bilateral fossa of Rossenmüller with no posterior pharyngeal wall bulge. A biopsy of the PNS mass showed reactive lymphoid tissue, likely due to incidental adenoid enlargement. A further evaluation with a dedicated MRI of the nasopharynx was considered then to assess an underlying structural abnormality but our patient declined it as his neck pain had completely resolved following the short course of NSAIDs.

Both prevertebral and retropharyngeal abscesses can appear as prevertebral soft tissue thickening on a lateral neck radiograph, and are important considerations

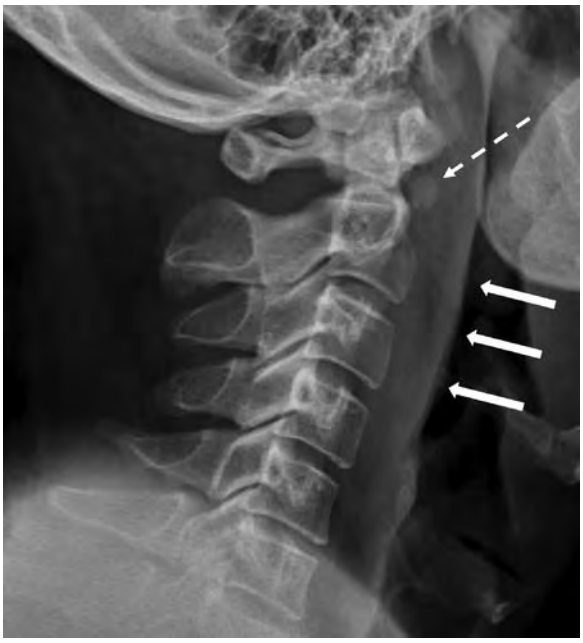

Fig. 1. Lateral neck radiograph demonstrating prevertebral soft tissue thickening at the level C1–C4 (white arrows), with a faint calcific density (dotted white arrow) seen just inferior to the anterior arch of the C1 vertebral body.

in patients with such imaging findings. However, patients with abscesses usually present with fever and malaise, in addition to significantly raised inflammatory markers, which were not present in our patient. Patients with prevertebral abscesses may have accompanying imaging findings of spondylodiscitis, which was also not seen in our patient. Another key differentiation is the presence of rim-enhancement in the prevertebral or retropharyngeal fluid on post-contrast MRI sequences, although its absence does not completely exclude an underlying infective process in early phases before infection evolves into a walled abscess.[1] For our patient, no post-contrast study was performed as the clinical suspicion for infection was very low.

Nasopharyngeal carcinoma (NPC) is another important consideration that may result in prevertebral soft tissue thickening.[2] However, patients with NPC usually present with nasal and ear-related symptoms including epistaxis or conductive hearing loss, and may have neck swelling from nodal metastases. MRI may show a nasopharyngeal mass with enlarged retropharyngeal and cervical lymph nodes, which were absent in our patient.

Answer: B

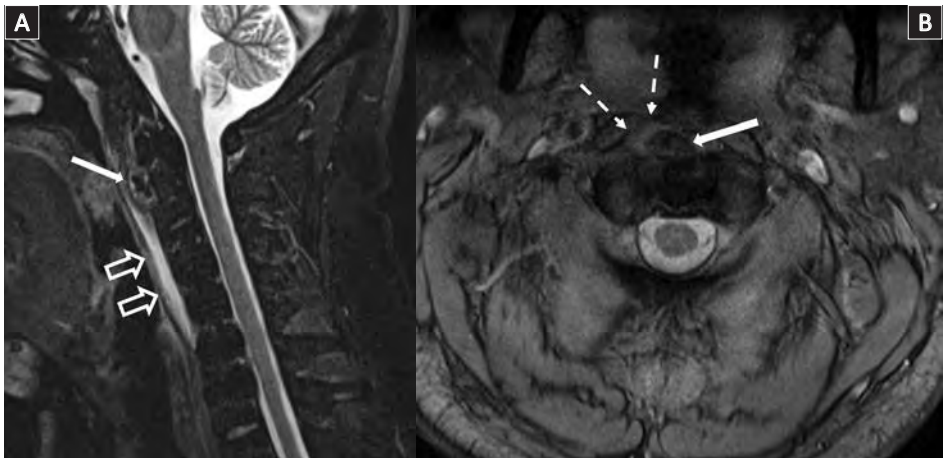

Fig. 2. (A) Coronal T2W-STIR and (B) axial T2W-MEDIC magnetic resonance imaging of the cervical spine.

(A) Marked oedema/fluid in the retropharyngeal region (empty white arrows), with an irregular rounded structure with low signal and a mildly hyperintense rim corresponding to the faint calcific density just inferior to the anterior arch of C1 (white arrow).

(B) Associated increased T2W signal is seen along the right longus colli muscle and adjacent longus capitis muscle (dotted white arrows). The low signal, faint calcific density is seen just inferior to the anterior arch of C1 (white arrow).

MEDIC: multi-echo data image combination; STIR: short tau inversion recovery; T2W: T2-weighted

Detached osteophytes from cervical spondylosis usually appear well-corticated on radiographs, and do not appear as faint calcific densities. In addition, the absence of significant degenerative change and no prior trauma make cervical spondylosis with a large detached osteophyte or fracture fragment less likely.

Acute calcific tendinitis of the longus colli (ACTLC), also known as retropharyngeal calcific tendinitis or acute calcific prevertebral tendinitis,[3] is a rare and benign condition caused by basic calcium phosphate deposition in the tendons of the longus colli muscle that is accompanied by an aseptic inflammatory process.[4] The specific aetiology of the condition is unknown, but some postulated mechanisms involve excessive mechanical strain in conjunction with degenerative spinal disease, collagen vascular or chronic renal disease, which can result in deposition of calcium crystals in muscle tendons.[5]

Patients with ACTLC typically present with acute or subacute onset of neck pain and restricted range of neck movements. Other reported symptoms include dysphagia, odynophagia, sore throat and even low-grade fever.[6] Laboratory findings may include normal or mild leukocytosis, and slightly elevated inflammatory markers including CRP and ESR.[7] Clinical presentation and initial radiographic findings can be confused with more serious conditions such as retropharyngeal abscess, infectious spondylitis, trauma or a foreign body, and hence awareness of ACTLC is important.[8] Cross-sectional imaging with computed tomography (CT) or MRI can be diagnostic in the appropriate clinical setting, with typical imaging findings including prevertebral soft tissue swelling extending from C1–C4 and amorphous calcification anterior to C1–C2 at the superior insertion of the longus colli muscle tendon.[3,8,9] CT may be superior to MRI in demonstrating the calcification, and is usually sufficient for diagnosis in the acute setting especially when MRI is not readily available. The benefits of MRI over CT are better soft tissue resolution, additional sequences that aid in differentiating oedema or effusion from retropharyngeal infection, and improved detection of spondylodiscitis, effusion or synovitis in the facet or uncovertebral joints of the spine.[6]

Symptoms of ACTLC usually improve spontaneously over the course of 1–2 weeks, with conservative treatment that includes a short course of NSAIDs and avoidance of ACTLC exacerbating neck movements. Follow-up imaging is usually unnecessary due to the self-limiting nature of the condition, although a repeat radiograph will typically demonstrate resolution of the characteristic prevertebral soft tissue swelling and amorphous calcification.[8]

In conclusion, ACTLC is a rare cause of acute neck pain. Recognising this benign entity is important to prevent misdiagnosis of other serious life-threatening conditions that present similarly, such as retropharyngeal abscess that could result in unnecessary antibiotics and surgical intervention instead of conservative treatment.[10]

REFERENCES

1. Hoang JK, Branstetter BF 4th, Eastwood JD, et al. Multiplanar CT and MRI of collections in the retropharyngeal space: is it an abscess? AJR Am J Roentgenol 2011;196:W426-32.
2. Chan SH. Aetiology of nasopharyngeal carcinoma. Ann Acad Med Singap 1990;19:201-7.
3. Abdelbaki A, Abdelbaki S, Bhatt N, et al. Acute calcific tendinitis of the longus colli muscle: report of two cases and review of the literature. Cureus 2017;9:e1597.
4. Hartley J. Acute cervical pain associated with retropharyngeal calcium deposit. A case report. J Bone Joint Surg Am 1964;46:1753-4.
5. Kaplan MJ, Eavey RD. Calcific tendinitis of the longus colli muscle. Ann Otol Rhinol Laryngol 1984;93:215-9.
6. Ahmed OH, German MA, Handwerker J, et al. Radiology quiz case 2. Acute calcific tendinitis of the longus colli (also known as calcific retropharyngeal/prevertebral tendinitis). Arch Otolaryngol Head Neck Surg 2012;138:599-600.
7. Kim YJ, Park JY, Choi KY, et al. Case reports about an overlooked cause of neck pain: calcific tendinitis of the longus colli: Case reports. Medicine (Baltimore) 2017;96:e8343.
8. Ellika SK, Payne SC, Patel SC, et al. Acute calcific tendinitis of the longus colli: an imaging diagnosis. Dentomaxillofac Radiol 2008;37:121-4.
9. Zibis AH, Giannis D, Malizos KN, et al. Acute calcific tendinitis of the longus colli muscle: case report and review of the literature. Eur Spine J 2013;22:S434-8.
10. Alamoudi U, Al-Sayed AA, AlSallumi Y, et al. Acute calcific tendinitis of the longus colli muscle masquerading as a retropharyngeal abscess: A case report and review of the literature. Int J Surg Case Rep 2017;41:343-6.

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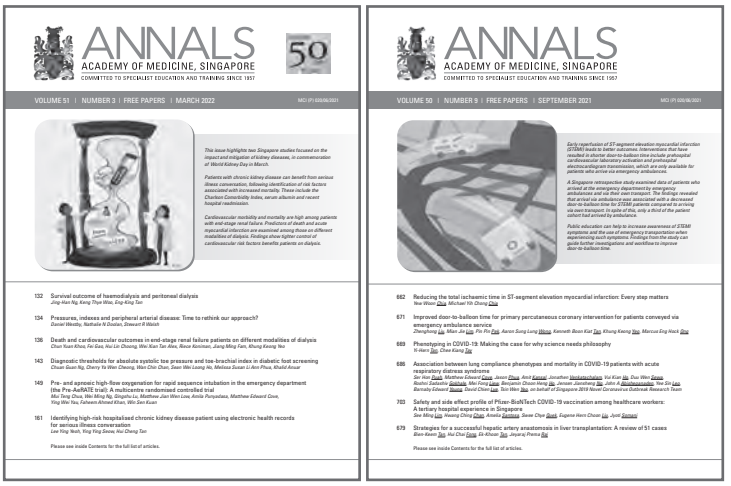

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