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Preterm birth trends and risk factors in a multi-ethnic Asian population: A retrospective study from 2017 to 2023, can we screen and predict this?

Preterm birth (PTB) remains a leading cause of perinatal morbidity and mortality worldwide. This study examined PTB trends in Singapore and improved the predictive risk for spontaneous PTB using artificial intelligence (See full article, p.296).

Illustration by Maria De-Castro

Also in this issue

Omicron SARS-CoV-2 outcomes in vaccinated individuals with heart failure and ischaemic heart disease

Variations in management strategies for stable coronary artery disease in the Asia-Pacific region: Insights from a multinational survey

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Annals, Academy of Medicine, Singapore

Volume 54 | Number 5 | May 2025

EDITORIAL

Five years on post-COVID-19 pandemic: Importance of COVID-19 vaccination and the adult heart

Weien Chow 267

ORIGINAL ARTICLES

Omicron SARS-CoV-2 outcomes in vaccinated individuals with heart failure and ischaemic heart disease

Liang En Wee, Enoch Xueheng Loy, Jue Tao Lim, Yew Woon Chia, Shir Lynn Lim, Jonathan Yap, Khung Keong Yeo, Derek J Hausenloy, Mark Yan Yee Chan, David Chien Boon Lye, Kelvin Bryan Tan 270

Variations in management strategies for stable coronary artery disease in the Asia-Pacific region: Insights from a multinational survey

Lucky Cuenza, Satoshi Honda, Khi Yung Fong, Mitsuaki Sawano, F Aaysha Cader, Purich Surunchupakorn, Wishnu Aditya Widodo, Mayank Dalakoti, Jeehoon Kang, Misato Chimura, Mohammed Al-Omary, Zhen-Vin Lee, Novi Yanti Sari, Thanawat Suesat, Tanveer Ahmad, Jose Donato Magno, Chen Ting Tan, Badai Bhatara Tiksnadi, Uditha Hewarathna, Faisal Habib, Derek Pok Him Lee, Jonathan Yap 283

Preterm birth trends and risk factors in a multi-ethnic Asian population: A retrospective study from 2017 to 2023, can we screen and predict this?

Rachel Phoy Cheng Chun, Hiu Gwan Chan, Gilbert Yong San Lim, Devendra Kanagalingam, Pamela Partana, Kok Hian Tan, Tiong Ghee Teoh, Ilka Tan 296

COMMENTARIES

Supporting quadruple aim in primary care using artificial intelligence

Ngap Chuan Tan, Reid Heng Lip Lim, David Chee Chin Ng 305

Making better clinical decisions: How doctors can recognise and reduce bias and noise in medical practice

Isaac KS Ng, Wilson GW Goh, Norshima Nashi, Satya Gollamudi, Manjari Lahiri, Daniel J Morgan, Tow Keang Lim 310

LETTERS TO THE EDITOR

Strategic response to mpox in the Singapore Armed Forces: Military public health collaboration and preparedness

Goh Jit Khong Jake, M Premikha 314

Upper airway stimulation for obstructive sleep apnoea in Asians: A Singapore sleep centre experience

Shaun Ray Han Loh, Adele Chin Wei Ng, Benjamin Kye Jyn Tan, Brian Sheng Yep Yeo, Jaclyn Yu Ting Teo, Nurina Binte Mohd Isa, Maythad Uataya, Liang Chye Goh, Mimi Yow, Song Tar Toh 316

Annals, Academy of Medicine, Singapore

Volume 54 | Number 5 | May 2025

High acceptability of HPV self-sampling in a Singapore primary care setting

Grace Ming Fen Chan, Luan Seng Desmond Ong, Liang Shen,

Soon Yau Joseph Ng, Jen Hui Jeffrey Low, Li Min Lim 319

Managing uveitic glaucoma with the Hydrus Microstent: A paradigm shift in surgical solutions

Tina Yu Ting Shen, Dawn KA Lim 322

Five years on post-COVID-19 pandemic: Importance of COVID-19 vaccination and the adult heart

Weien Chow¹ MMed (Internal Medicine)

At the time of writing this editorial, it has been more than 5 years since the COVID-19 pandemic. As healthcare professionals, we can vividly remember how the COVID-19 pandemic disrupted the economy, society and our daily lives. More importantly, the COVID-19 pandemic struck the elderly and immunosuppressed patients or medically vulnerable persons the hardest. Medically vulnerable persons include persons with chronic diseases of the heart, lungs, kidney, liver and other organ systems. The last editorial on COVID-19 published in the *Annals* in 2023 was an insight piece titled “COVID-19: The virus, vaccine and paediatric heart”, which highlighted the importance of vaccination and the paediatric heart.¹

It is therefore timely that in this issue of *Annals*, Wee et al. published their research on Omicron SARS-CoV-2 outcomes in vaccinated individuals with heart failure (HF) and ischaemic heart disease (IHD).² This study demonstrated an increased risk of COVID-19-related hospitalisation and severe COVID-19 infections among HF/IHD patients compared with matched population controls. COVID-19 vaccination boosters were shown to attenuate the risk of COVID-19-related hospitalisation and severe COVID-19 infections. Using national databases, 15,426 HF patients were matched to 41,221 controls without HF, and 110,442 IHD patients were matched to 223,843 controls without IHD. The authors clearly demonstrated the effect of how COVID-19 booster vaccinations on HF and IHD patients reduced the risk of SARS-CoV-2 infection and adverse COVID-19 outcomes. It was also notable that there was a high percentage (>80%) of HF/IHD patients boosted (received ≥ 3 vaccine doses). Risk of SARS-CoV-2 infection and severe COVID-19 was found to be significantly lower in boosted groups who received ≥ 3 doses; IHD: adjusted hazard ratio (aHR) (95% confidence interval [CI]) 0.27 (0.23–0.32); HF (95% CI): aHR 0.35 (0.28–0.43), versus HF/IHD patients who had only completed a 2-dose primary vaccination series. Risks of SARS-CoV-2 infection, hospitalisation and severe disease were also lower in the ≥ 4 -dose

group compared with the 3-dose group, though CIs for infection overlapped.² The authors recommended that individuals with recurrent admissions should be prioritised for vaccination/boosting. The American College of Cardiology had published a health policy statement on cardiovascular disease considerations for COVID-19 vaccine prioritisation, which remains a useful reference today.³ In addition, it was heartening to note that vaccination rate was very high among the elderly during the Omicron wave. Even though the study was conducted during the Omicron wave (more than 3 years ago), the findings and recommendations remain relevant. The study also highlighted the importance of national vaccination databases that can inform and reinforce healthcare policies.

Effectiveness of vaccine boosters. Cardiac damage and myocardial injury can be sustained during viral infection of cardiomyocytes, which can result in decompensated heart failure and cardiac arrhythmias among other mechanisms. It is well established that mRNA vaccines stimulate both humoral and cellular immune responses. After inoculation of more than 1 dose of most vaccines, the efficacy rate increases. Thus, efforts should be made to maximise the effectiveness of the vaccine, with more than 1 dose among the vulnerable population. In another similar study that assessed the effectiveness of AZD1222, BNT162b2 and CoronaVac vaccines against the Omicron variant, the study showed that the administration of the booster doses is 95.4% effective in curbing COVID-19 infection, compared to non-boosted vaccination (87.2%).⁴ The authors concluded that boosters are effective in increasing protection against COVID-19, including the Omicron variant.⁴

A new problem of vaccine hesitancy. However, despite the strong scientific evidence and benefits of COVID-19 vaccination, a more recent study post-COVID-19 pandemic showed that the uptake of COVID-19 vaccines in the post-pandemic era in the US is low, with only 22.3% of adults and 37.4% of those aged at least 65 years receiving the updated 2023–2024 COVID-19 vaccine.⁵ Based on a written note from Singapore’s Ministry of Health (MOH) to

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a parliamentary question on 2 July 2024, as of June 2024, only about 15% of seniors aged 60 and above, have received more than 4 doses of COVID-19 vaccinations in Singapore. In the written answer, MOH explained that many Singaporeans are reluctant to take further doses of COVID-19 vaccine, probably contributed by vaccine fatigue. This is in turn due to the perceptions that COVID-19 is no longer a severe disease, and there are side effects to taking the vaccines. This poses significant concern to medically vulnerable persons, especially those with chronic diseases of the heart. There are several interventions such as full funding of COVID-19 vaccinations, sending of phone text reminders and deployment of mobile vaccination teams, to encourage vaccination especially among seniors. However, it is difficult to go against the current public perception and bring about a high vaccine uptake. Unlike many Western countries, Asian countries may not have a strong vaccination culture among adults. While influenza and pneumococcal vaccination rates have gone up since the roll out of Healthier SG (a nationwide initiative promoting overall healthier living), there is a need to continue to encourage more Healthier SG clinics to come on board to provide COVID-19 vaccination. By leveraging the relationship between family physicians and residents, it is hoped that Singapore can maintain societal resilience against COVID-19, as it will be here to stay.⁶

Policies and incentives to address vaccine hesitancy and improve vaccination rates. As a physician, we continue to face resistance and vaccine hesitancy among our patients to undergo not only COVID-19 vaccination but also other forms of vaccination such as influenza vaccination.⁷ As part of the Healthier SG initiative, Singapore's MOH has incentivised the subsidy of COVID-19 and influenza vaccinations. This is based on the 2024/2025 recommendation of the Expert Committee for Immunisation.⁸ COVID-19 vaccination is especially applicable to individuals at increased risk of severe COVID-19, such as seniors and those who are medically vulnerable. Singapore Citizens, Permanent Residents, Long-Term Pass Holders, and certain Short-Term Pass Holders aged 6 months and above are eligible to receive the COVID-19 vaccines for free under the National Vaccination Programme. For eligible Healthier SGenrolled Singapore Citizens (1) aged 65 years old and above and (2) adults with certain medical conditions, individuals are able to get fully subsidised flu vaccinations at their enrolled Healthier SG clinic.

What has changed since the COVID-19 pandemic and what can we do? While the virus strain has changed, the need to protect medically vulnerable persons remains unchanged. COVID-19 vaccination

rate is at a much lower rate than before. As more evidence emerge, it can help to increase COVID-19 vaccination rates and address vaccine hesitancy. Recent studies have demonstrated the effectiveness of COVID-19 vaccination on the development of post-COVID-19 condition symptoms in children aged 5 to 17 years¹⁰ as well as in adults as shown in the Vaccine Effectiveness, Networking, and Universal Safety (VENUS) study.¹¹ Findings presented by studies such as VENUS may provide an additional nudge for individuals to undergo COVID-19 vaccination. There is however limited research and evidence on the effectiveness of COVID-19 vaccine hesitancy interventions. A multiprong approach is therefore needed to improve vaccine acceptance, contextualised to the specific local population. More implementation science studies should also be carried out to better understand the effectiveness of various interventions and strategies of the national vaccination programme. This will help in the assessment and formulation of effective healthcare policies.

Call for action. As we continue to reinforce the importance of vaccination to our patients, it is not a matter of if but when the next pandemic will occur. One thing is certain: we must continue to vaccinate our patients and our residents as part of Healthier SG, so that we do not need to relearn the lessons learnt. We must not let our guard down and the time to action is now. This is especially important as Singapore continues to experience new waves of COVID-19 infections presently.

Ethics statement

Not applicable.

Declaration

The author(s) declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript. This study did not receive any specific funding.

Keywords: boosters, COVID-19 pandemic, heart failure, ischaemic heart disease, vaccination

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Omicron SARS-CoV-2 outcomes in vaccinated individuals with heart failure and ischaemic heart disease

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ABSTRACT

Introduction: Outcomes after SARS-CoV-2 Omicron infection in patients with heart failure (HF) and ischaemic heart disease (IHD) remain poorly defined.

Method: In a highly vaccinated cohort of adult Singapore citizens and permanent residents, we used Cox proportional hazards models (adjusted for sociodemographic variables and comorbidities) to compare the risks of Omicron infection, COVID-19-related hospitalisation, and severe COVID-19 between individuals with HF or IHD and matched controls without these conditions.

Results: From national databases, we identified 15,426 HF patients matched 1:~3 to 41,221 controls, and 110,442 IHD patients matched 1:~2 to 223,843 controls. Over 80% of HF and IHD patients had received at least 3 vaccine doses. During the Omicron-predominant period, both HF and IHD cohorts demonstrated higher adjusted risks of COVID-19 hospitalisation compared with matched controls (HF: adjusted hazard ratio [aHR] 1.77, 95% confidence interval [CI] 1.65–1.90; IHD: aHR 1.21, 95% CI 1.17–1.26). Among those with at least 1 HF- or IHD-related admission in the prior year, hospitalisation risk was further elevated (HF: aHR 1.27, 95% CI 1.13–1.42; IHD: aHR 1.11, 95% CI 1.01–1.23). Receipt of ≥3 vaccine doses was associated with substantially lower risk of severe COVID-19 versus only 2 doses (HF: aHR 0.35, 95% CI 0.28–0.43; IHD: aHR 0.27, 95% CI 0.23–0.32). A fourth dose conferred additional reductions in infection and adverse outcomes, though CIs for infection overlapped with those for 3 doses.

Conclusion: During Omicron predominance, HF and IHD patients experienced greater risk of COVID-19

hospitalisation and severe COVID-19 versus matched controls. Booster vaccinations attenuated these risks. Individuals with recent HF/IHD admissions should be prioritised for receipt of booster vaccine doses.

Keywords: boosters, cardiology, COVID-19, heart failure, infectious diseases, Omicron, SARS-CoV-2, vaccination

CLINICAL IMPACT

What is New

- This is the first population-based, matched case-control analysis in Singapore to examine how vaccination status influences COVID-19 outcomes in patients with heart failure (HF) or ischaemic heart disease (IHD) during the Omicron wave.
- Patients with HF or IHD faced higher rates of COVID-19-related hospitalisation and severe COVID-19 versus matched controls, but booster doses significantly mitigated these risks.

Clinical Implications

- Even in the Omicron-dominant and endemic phase of COVID-19, booster vaccination continues to provide meaningful protection for individuals with HF or IHD, underscoring the need to prioritise regular receipt of booster doses in this high-risk group.

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INTRODUCTION

Respiratory viral infections are a relatively common cause of heart failure (HF) exacerbations, with higher risk of adverse outcomes observed in HF episodes precipitated by infection.¹ Multiple reports from the initial phase of the COVID-19 pandemic reported higher mortality and in-hospital complications associated with a history of HF and ischaemic heart disease (IHD) among hospitalised patients with concurrent SARS-CoV-2 infection.^{2,3,4} In a multicentre cohort study of critically ill adult patients hospitalised for COVID-19, one-fourth had pre-existing cardiovascular conditions.⁵ This association is not just observed in hospitalised cohorts; in a population-based study involving >6 million English adults, marked gradients were still seen in the incidence of adverse COVID-19 outcomes by cardiovascular risk profile.⁶ Increased risk of adverse COVID-19 outcomes has been documented in HF regardless of left ventricular ejection fraction; in a cohort of HF patients with mildly reduced or preserved ejection fraction recruited into a large clinical trial spanning the pandemic period, ~10% of cases contracted SARS-CoV-2 infection on follow-up, with >50% of infections leading to hospitalisation or death.⁷

However, a significant limitation is that most studies on COVID-19 outcomes among HF/IHD patients were based on data from the early pre-Delta stages of the pandemic.¹⁻⁷ In a multicentre US registry of adults hospitalised with cardiovascular complications and concurrent SARS-CoV-2 infection, rates of in-hospital mortality progressively declined during the transition from pre-Delta to Delta-predominant transmission.⁸ Newer SARS-CoV-2 variants, such as Omicron, are associated with milder symptoms and higher proportions of non-severe disease;⁹ individuals hospitalised during the Omicron-predominant period were less likely to experience severe respiratory disease compared to those hospitalised during circulation of earlier SARS-CoV-2 variants.¹⁰ Data on COVID-19 outcomes among individuals with HF/IHD who were infected with SARS-CoV-2 during Omicron-predominant transmission remains lacking. Additionally, most studies pre-dated the rollout of vaccination or did not systematically record vaccination status.^{1-6,8} A single population-based cohort of adults with HF who were infected with SARS-CoV-2 during Omicron-predominant transmission reported significant reduction in risk of severe COVID-19 following receipt of a single booster dose, though restriction to only polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infections meant that a substantial proportion of mild infections may have been missed, thus limiting generalisability.¹¹ Additional studies are required in order to guide recommendations for vaccination and boosting in

patients with HF/IHD during COVID-19 endemicity. We contrasted outcomes of SARS-CoV-2 infection in a highly-vaccinated cohort of adults in Singapore with HF/IHD versus matched population controls, during waves of transmission driven by successive Omicron subvariants, including Omicron XBB.

METHOD

Study population, period and design

Population-wide national records of all confirmed SARS-CoV-2 infections, hospitalisations and vaccines administered in Singapore, a multi-ethnic Southeast Asian city state, were linked with national healthcare claims records for the study period of 1 January 2022 to 20 December 2023, corresponding to the wave of infections predominated by the SARS-CoV-2 Omicron variant. Omicron emerged in late 2021 to displace Delta as the predominant strain, and subsequently predominated community transmission by January 2022, with ≥90% of sequenced cases on national surveillance.¹² The Omicron XBB subvariant first emerged in Singapore at the end of 2022,¹³ replacing earlier Omicron subvariants in circulation; as such, 18 September 2022 was used as the cut-off date to further separate the Omicron period into XBB and pre-XBB (Omicron BA.1/2/3/4) transmission.

A retrospective case-control study design was utilised to match controls from the general population to every patient with HF/IHD in the study population (matched by age strata; sex; ethnicity; socioeconomic status [SES] based on housing type; cardiovascular risk factors including diabetes, hypertension, dyslipidaemia; and COVID-19 vaccination timing [respective months in which an individual was fully vaccinated, boosted and received a second booster dose]), during the Omicron wave in Singapore (Fig. 1). Data collected was capped at 20 December 2023. The study population included all adult Singapore citizens and permanent residents aged ≥18 years. Three controls from the general population were included for every patient with HF/IHD in each period for comparison, using exact matching with replacement. History of HF/IHD and other comorbidities such as cardiovascular risk factors, were defined based on International Classification of Diseases, Tenth Revision codes recorded in the national healthcare claims database. The national healthcare claims database encompasses all public and private healthcare providers in inpatient and outpatient settings; participation in the national government-administered medical-savings scheme (i.e. Medisave) is compulsory for all Singaporeans.¹⁴ Under the Chronic Disease Management Scheme, Medisave can be used to claim expenses for inpatient and outpatient treatment of various chronic diseases, including HF/

IHD, hypertension, diabetes and dyslipidaemia;¹⁴ this enabled comprehensive capture of diagnoses across different healthcare settings. Individuals with missing sociodemographic data, who demised or were infected prior to study start date, developed HF/IHD during the study period, or had no matching controls were excluded from the final study population (Fig. 1). Individuals vaccinated with non-messenger ribonucleic acid (mRNA) vaccines were also excluded as they formed a very small minority (<5%).

COVID-19 outcomes

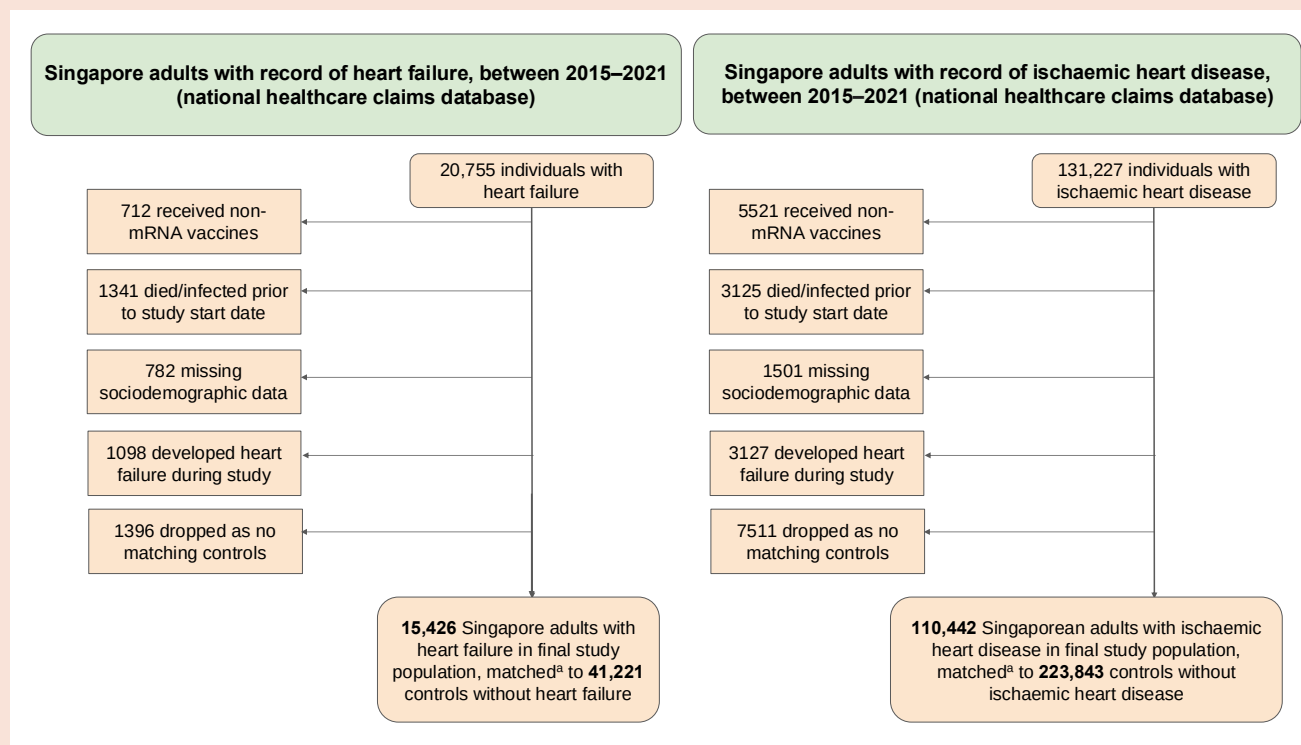
SARS-CoV-2 infection, COVID-19-related hospitalisation and severe COVID-19 disease were defined using the national COVID-19 registry. SARS-CoV-2 infection was defined as either a positive PCR test or rapid antigen test (RAT) result recorded in the national testing registry. During the study period, SARS-CoV-2 testing was widely available across all healthcare providers, including both public and private hospitals, public primary care clinics (polyclinics) and Public Health Preparedness Clinics, which formed a nationwide network of more than 1000 private general-practitioner clinics activated during pandemics to provide subsidised testing.¹⁵ By law, MOH was notified of all test-positive cases up to 1 March 2024, beyond the end of the study period.¹⁶ COVID-19-related hospitalisation was defined as all-cause hospitalisations occurring within 30 days from a positive

COVID-19 result. Severe COVID-19 disease was defined as those requiring oxygen supplementation or intensive care unit admission, or that resulting in death. Singapore's Ministry of Health (MOH) was notified of all COVID-19 hospitalisations and severe COVID-19 infections.^{15,16}

Covariates

The following covariates were extracted from national databases: demographics (age, sex, ethnicity), vaccination status, comorbidities and SES. SES was classified by housing type based on postal code. Most Singaporeans (≥90%) live in subsidised public housing; smaller-sized flats attract higher subsidy, with purchase eligibility linked to household income.¹⁷ SES has been shown to affect COVID-19 vaccination uptake and oral antiviral utilisation in the Singapore context,^{17,18} which can potentially affect risk of adverse COVID-19 outcomes. Vaccination status was defined by the number of mRNA vaccination doses recorded in the National Immunisation Registry, at the point of SARS-CoV-2 infection. In Singapore, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) were first approved for use in the national vaccination programme as a 2-dose primary series; ≥90% of the population received mRNA vaccines.¹⁹ Booster vaccinations (third and fourth vaccine doses) were concurrently rolled out in September 2021 during emergence of the Delta wave.¹⁹ From December 2022

Fig. 1. Cohort construction flowchart.



^a Matched by age, sex, ethnicity, socioeconomic status, cardiovascular risk factors and vaccination status.

onwards, bivalent vaccine formulations fully replaced their monovalent predecessors;²⁰ updated monovalent XBB1.5 vaccines in turn replaced bivalent boosters in October 2023.²⁰

Statistical analysis

Differences in proportions were compared using chi-square test. Cox regressions were conducted to compare risks of SARS-CoV-2 infection, COVID-19-related hospitalisations, and severe COVID-19 disease between HF/IHD patients and population-based controls without a diagnosis of HF/IHD, adjusting for demographics, SES and comorbidities as covariates. Estimates of risk were grouped by number of vaccine doses received (zero/single-dose, 2-dose, 3-dose and ≥ 4 -dose groups). Hospitalisation for HF/IHD in the preceding year was taken as an indicator of disease severity in supplementary analyses. As an additional analysis, risk estimates for COVID-19 outcomes in individuals with HF/IHD infected during Omicron were stratified into XBB-predominant transmission and pre-XBB periods. Data were analysed using Python version 3.11.5 (Python Software Foundation, Wilmington, DE, US) and R statistical software version 4.3.1 (R Core Team 2023, R Foundation for Statistical Computing, Vienna, Austria). Python was used for data preprocessing, while R was used for statistical analysis; $P < 0.05$ was considered statistically significant.

This study was performed as part of national public health research under Singapore's Infectious Diseases Act. Separate individual informed consent and ethics review by an institutional review board was not required by law.

RESULTS

Overall, after applying inclusion and exclusion criteria, 15,426 HF patients were matched to 41,221 controls without HF, and 110,442 IHD patients were matched to 223,843 controls without IHD (Fig. 1). Sociodemographic characteristics of IHD/HF cases and controls, stratified by vaccination doses received, are reported in Tables 1 and 2. Around one-third of IHD/HF cases were female (IHD: 28.2%, 31,124/110,442; HF: 41.3%, 6364/15,426). The majority were aged ≥ 60 years (IHD: 75.9%, 83,824/110,442; HF: 81.7%, 12,603/15,426). Booster uptake (≥ 3 vaccine doses) was high in both IHD/HF cases aged ≥ 60 years (IHD: 92.9%, 77,904/83,824; HF: 83.8%, 10,567/12,603), as well as in those aged < 60 years (IHD: 95.0%, 25,279/26,618; HF: 87.9%, 2482/2823). Rates of vaccination throughout the Omicron wave among HF/IHD patients, compared against vaccination rates in controls and in the whole population, are reflected in Supplementary Table S1. At the onset

of Omicron, the majority (IHD: 74.4%; HF: 59.1%) had already received a booster dose; this rose to 94.8% of IHD patients and 88.1% of HF patients by the end of the study period (Supplementary Table S1).

The adjusted hazard ratio (aHR) for risk of SARS-CoV-2 infection, COVID-19-related hospitalisations and severe COVID-19 disease in HF/IHD patients grouped by number of vaccine doses received (zero/single-dose, 2-dose, 3-dose and ≥ 4 -dose groups) are shown in Table 3, with unadjusted incidence rates reported in Supplementary Table S2. During Omicron, significantly decreased risk of SARS-CoV-2 infection, but not COVID-19 hospitalisation or severe COVID-19, was noted in unvaccinated or partially-vaccinated patients compared with fully-vaccinated individuals, across both HF/IHD cases and healthy controls (Table 3). Risk of SARS-CoV-2 infection, COVID-19-related hospitalisation and severe COVID-19 disease was significantly lower in boosted HF/IHD patients (≥ 3 doses), compared against HF/IHD patients who had only completed a 2-dose primary vaccination series. Hazard ratios (HRs) of SARS-CoV-2 infection, hospitalisation and severe disease were lower in the ≥ 4 -dose group compared with the 3-dose group, though the confidence intervals (CIs) for infection overlapped (Table 3).

Compared with matched controls, higher risks of SARS-CoV-2 infection (HF: aHR 1.05 [95% CI 1.01–1.08]; IHD: aHR 1.10 [95% CI 1.09–1.12]) and COVID-19-related hospitalisation (HF: aHR 1.77 [95% CI 1.65–1.90]; IHD: aHR 1.21 [95% CI 1.17–1.26]) were observed among HF/IHD patients infected during Omicron (Table 4). Risk of COVID-19 hospitalisation remained elevated during both XBB-predominant transmission and prior circulation of other Omicron subvariants (BA.1/2/4/5). During the period of Omicron predominance, those with at least 1 HF/IHD-related admission in the preceding year had higher risk of COVID-19-related hospitalisation (IHD: aHR 1.11 [95% CI 1.01–1.23]; HF: aHR 1.27 [95% CI 1.13–1.42]) (Supplementary Table S3).

DISCUSSION

In a highly vaccinated/boosted population-based cohort of HF/IHD cases, elevated risk of COVID-19-related hospitalisation relative to matched population controls was still observed during Omicron-predominant transmission, persisting even into the XBB-predominant period. While risk of infection in the unvaccinated may have diminished during Omicron-predominant transmission due to the introduction of vaccine-differentiated social distancing measures, with greater restrictions placed on unvaccinated individuals,^{17,21} vaccination and boosting

Table 1. Characteristics of heart failure cases (n=15,426) and control populations without heart failure (n=41,221), stratified by total number of vaccine doses.

Sex, no. (%)	0/1 dose (Unvaccinated/partially vaccinated)		2 doses (Fully vaccinated, not boosted)		3 doses (Boosted)		≥4 doses (Double-boosted)	
	Heart failure ^a	Control	Heart failure ^a	Control	Heart failure ^a	Control	Heart failure ^a	Control
Female	442 (43.8)	1153 (44.7)	613 (44.8)	1455 (46.1)	3064 (41.3)	8313 (41.3)	2245 (39.9)	6124 (39.9)
Male	566 (56.2)	1426 (55.3)	756 (55.2)	1698 (53.9)	4354 (58.7)	11,839 (58.7)	3386 (60.1)	9213 (60.1)
Age, no. (%)								
18–29 years	3 (0.3)	9 (0.3)	3 (0.2)	9 (0.3)	27 (0.4)	79 (0.4)	5 (0.1)	13 (0.1)
30–39 years	7 (0.7)	18 (0.7)	15 (1.1)	39 (1.2)	127 (1.7)	353 (1.8)	44 (0.8)	118 (0.8)
40–49 years	31 (3.1)	82 (3.2)	31 (2.3)	62 (2.0)	431 (5.8)	1202 (6.0)	171 (3.0)	447 (2.9)
50–59 years	106 (10.5)	266 (10.3)	145 (10.6)	313 (9.9)	1080 (14.6)	2969 (14.7)	597 (10.6)	1615 (10.5)
60–69 years	203 (20.1)	536 (20.8)	322 (23.5)	743 (23.6)	2095 (28.2)	5758 (28.6)	1527 (27.1)	4230 (27.6)
70–79 years	224 (22.2)	585 (22.7)	392 (28.6)	899 (28.5)	1957 (26.4)	5348 (26.5)	1545 (27.4)	4256 (27.7)
≥80 years	434 (43.1)	1083 (42.0)	461 (33.7)	1088 (34.5)	1701 (22.9)	4443 (22.0)	1742 (30.9)	4658 (30.4)
Ethnicity, no. (%)								
Chinese	635 (63.0)	1712 (66.4)	843 (61.6)	2082 (66.0)	4841 (65.3)	13,459 (66.8)	4244 (75.4)	11,881 (77.5)
Indian	166 (16.5)	397 (15.4)	223 (16.3)	453 (14.4)	927 (12.5)	2376 (11.8)	428 (7.6)	1026 (6.7)
Malay	191 (18.9)	438 (17.0)	296 (21.6)	606 (19.2)	1590 (21.4)	4177 (20.7)	904 (16.1)	2295 (15.0)
Others	16 (1.6)	32 (1.2)	7 (0.5)	12 (0.4)	60 (0.8)	140 (0.7)	55 (1.0)	135 (0.9)
Socioeconomic status by housing type, no. (%) ^b								
Public, 1–2 rooms	165 (16.4)	406 (15.7)	231 (16.9)	492 (15.6)	945 (12.7)	2434 (12.1)	634 (11.3)	1609 (10.5)
Public, 3 rooms	266 (26.4)	652 (25.3)	337 (24.6)	799 (25.3)	1823 (24.6)	4923 (24.4)	1260 (22.4)	3462 (22.6)
Public, 4 rooms	255 (25.3)	675 (26.2)	443 (32.4)	1016 (32.2)	2536 (34.2)	6972 (34.6)	1876 (33.3)	5169 (33.7)
Public, 5 rooms	229 (22.7)	603 (23.4)	274 (20.0)	644 (20.4)	1770 (23.9)	4906 (24.3)	1490 (26.5)	4151 (27.1)
Others	13 (1.3)	32 (1.2)	9 (0.7)	20 (0.6)	19 (0.3)	44 (0.2)	87 (1.5)	181 (1.2)
Private housing	80 (7.9)	211 (8.2)	75 (5.5)	182 (5.8)	325 (4.4)	873 (4.3)	284 (5.0)	765 (5.0)

Table 1. Characteristics of heart failure cases (n=15,426) and control populations without heart failure (n=41,221), stratified by total number of vaccine doses. (Cont'd)

	0/1 dose (Unvaccinated/partially vaccinated)		2 doses (Fully vaccinated, not boosted)		3 doses (Boosted)		≥4 doses (Double-boosted)	
	Heart failure ^a	Control	Heart failure ^a	Control	Heart failure ^a	Control	Heart failure ^a	Control
Types of comorbidities no. (%)								
Ischaemic heart disease	654 (64.9)	488 (18.9)	944 (69.0)	662 (21.0)	4900 (66.1)	3772 (18.7)	3691 (65.5)	2737 (17.8)
Chronic obstructive pulmonary disease	137 (13.6)	188 (7.3)	229 (16.7)	306 (9.7)	861 (11.6)	1350 (6.7)	677 (12.0)	967 (6.3)
Cerebrovascular disorders	205 (20.3)	438 (17.0)	260 (19.0)	498 (15.8)	1127 (15.2)	2157 (10.7)	871 (15.5)	1414 (9.2)
Cancer	95 (9.4)	251 (9.7)	144 (10.5)	454 (14.4)	539 (7.3)	1489 (7.4)	464 (8.2)	1159 (7.6)
Chronic kidney disease	288 (28.6)	354 (13.7)	506 (37.0)	607 (19.3)	2126 (28.7)	2497 (12.4)	1481 (26.3)	1886 (12.3)
Chronic liver disease	39 (3.9)	36 (1.4)	41 (3.0)	64 (2.0)	192 (2.6)	271 (1.3)	135 (2.4)	182 (1.2)
Diabetes	538 (53.4)	1312 (50.9)	799 (58.4)	1749 (55.5)	4165 (56.1)	11,052 (54.8)	3008 (53.4)	8056 (52.5)
Hypertension	794 (78.8)	1974 (76.5)	1168 (85.3)	2637 (83.6)	6226 (83.9)	16,769 (83.2)	4815 (85.5)	13,071 (85.2)
Hyperlipidaemia	596 (59.1)	1483 (57.5)	886 (64.7)	2029 (64.4)	5069 (68.3)	13,743 (68.2)	3939 (70.0)	10,822 (70.6)
No. of comorbidities, no. (%)								
0 comorbidity	44 (4.4)	334 (13.0)	35 (2.6)	272 (8.6)	267 (3.6)	1628 (8.1)	188 (3.3)	1150 (7.5)
1 comorbidity	87 (8.6)	285 (11.1)	82 (6.0)	262 (8.3)	563 (7.6)	2278 (11.3)	408 (7.2)	1663 (10.8)
2 comorbidities	145 (14.4)	496 (19.2)	156 (11.4)	503 (16.0)	989 (13.3)	4206 (20.9)	752 (13.4)	3399 (22.2)
3–4 comorbidities	439 (43.6)	1120 (43.4)	577 (42.1)	1570 (49.8)	3517 (47.4)	10,151 (50.4)	2786 (49.5)	7821 (51.0)
≥5 comorbidities	293 (29.1)	344 (13.3)	519 (37.9)	546 (17.3)	2082 (28.1)	1889 (9.4)	1497 (26.6)	1304 (8.5)
COVID-19, no. (%)								
Infected ^c	398 (39.5)	735 (28.5)	626 (45.7)	1509 (47.9)	3162 (42.6)	8427 (41.8)	2432 (43.2)	6278 (40.9)
Hospitalised ^d	291 (28.9)	402 (15.6)	349 (25.5)	522 (16.6)	970 (13.1)	1111 (5.5)	589 (10.5)	615 (4.0)
Severe disease ^e	134 (13.3)	178 (6.9)	128 (9.3)	145 (4.6)	300 (4.0)	223 (1.1)	128 (2.3)	95 (0.6)
Death	42 (4.2)	72 (2.8)	28 (2.0)	47 (1.5)	31 (0.4)	26 (0.1)	5 (0.1)	6 (0.0)

^a Among cases of heart failure (n=15,426), 10,189 (66.1%) had a concurrent diagnosis of ischaemic heart disease.

^b Housing type was used as an indicator of socioeconomic status.

^c SARS-CoV-2 infection defined as positive test result (polymerase chain reaction [PCR] test or rapid antigen test [RAT]) recorded in the national COVID-19 registry.

^d COVID-19 hospitalisation was defined as all-cause hospitalisations occurring within 30 days from a positive COVID-19 result (PCR/RAT).

^e Severe disease was defined as COVID-19 infection with the resulting need for supplemental oxygen, intensive care admission or death.

Table 2. Characteristics of ischaemic heart disease cases (n=110,442) and control populations without ischaemic heart disease (n=223,843), stratified by total number of vaccine doses.

		0/1 dose (Unvaccinated/partially vaccinated)		2 doses (Fully vaccinated, not boosted)		3 doses (Boosted)		≥4 doses (Double boosted)	
		Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control
Sex, no. (%)									
Female		1173 (35.1)	2556 (39.8)	1479 (37.8)	2826 (43.0)	14,569 (28.8)	34,850 (33.9)	67,850 (26.5)	38,633 (31.3)
Male		2173 (64.9)	3868 (60.2)	2434 (62.2)	3744 (57.0)	36,078 (71.2)	67,850 (66.1)	38,633 (73.5)	74,333 (68.7)
Age, no. (%)									
18–29 years		2 (0.1)	6 (0.1)	4 (0.1)	12 (0.2)	59 (0.1)	167 (0.2)	17 (0.0)	47 (0.0)
30–39 years		19 (0.6)	48 (0.7)	31 (0.8)	79 (1.2)	631 (1.2)	1660 (1.6)	191 (0.4)	507 (0.5)
40–49 years		123 (3.7)	286 (4.5)	196 (5.0)	374 (5.7)	3801 (7.5)	9134 (8.9)	1660 (3.2)	4037 (3.7)
50–59 years		437 (13.1)	873 (13.6)	527 (13.5)	916 (13.9)	10,754 (21.2)	22,909 (22.3)	8166 (15.5)	17,841 (16.5)
60–69 years		848 (25.3)	1642 (25.6)	916 (23.4)	1521 (23.2)	17,134 (33.8)	33,759 (32.9)	18,564 (35.3)	38,094 (35.2)
70–79 years		865 (25.9)	1674 (26.1)	1094 (28.0)	1760 (26.8)	12,017 (23.7)	23,352 (22.7)	15,248 (29.0)	30,668 (28.4)
≥80 years		1052 (31.4)	1895 (29.5)	1145 (29.3)	1908 (29.0)	6251 (12.3)	11,719 (11.4)	8690 (16.5)	16,955 (15.7)
Ethnicity, no. (%)									
Chinese		2250 (67.2)	4532 (70.5)	2535 (64.8)	4583 (69.8)	35,455 (70.0)	75,130 (73.2)	41,756 (79.5)	88,599 (81.9)
Indian		570 (17.0)	925 (14.4)	698 (17.8)	958 (14.6)	6943 (13.7)	11,952 (11.6)	4265 (8.1)	7074 (6.5)
Malay		434 (13.0)	771 (12.0)	659 (16.8)	988 (15.0)	7772 (15.3)	14,732 (14.3)	5775 (11.0)	10,982 (10.2)
Others		92 (2.7)	196 (3.1)	21 (0.5)	41 (0.6)	477 (0.9)	886 (0.9)	740 (1.4)	1494 (1.4)
Socioeconomic status by housing type, no. (%)^b									
Public, 1–2 rooms		392 (11.7)	684 (10.6)	567 (14.5)	877 (13.3)	4283 (8.5)	8075 (7.9)	3710 (7.1)	7109 (6.6)
Public, 3 rooms		734 (21.9)	1360 (21.2)	938 (24.0)	1589 (24.2)	9796 (19.3)	19,732 (19.2)	9463 (18.0)	19,461 (18.0)
Public, 4 rooms		993 (29.7)	1862 (29.0)	1270 (32.5)	2104 (32.0)	17,008 (33.6)	34,756 (33.8)	16,239 (30.9)	33,561 (31.0)
Public, 5 rooms		833 (24.9)	1646 (25.6)	918 (23.5)	1576 (24.0)	16,285 (32.2)	33,494 (32.6)	18,630 (35.5)	38,926 (36.0)
Others		114 (3.4)	258 (4.0)	17 (0.4)	37 (0.6)	105 (0.2)	228 (0.2)	250 (0.5)	476 (0.4)
Private housing		280 (8.4)	614 (9.6)	203 (5.2)	387 (5.9)	3170 (6.3)	6415 (6.2)	4244 (8.1)	8616 (8.0)

Table 2. Characteristics of ischaemic heart disease cases (n=110,442) and control populations without ischaemic heart disease (n=223,843), stratified by total number of vaccine doses. (Cont'd)

	0/1 dose (Unvaccinated/partially vaccinated)		2 doses (Fully vaccinated, not boosted)		3 doses (Boosted)		≥4 doses (Double boosted)	
	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control	Ischaemic heart disease ^a	Control
Types of comorbidities no. (%)								
Heart failure	650 (19.4)	155 (2.4)	914 (23.4)	196 (3.0)	4848 (9.6)	942 (0.9)	3629 (6.9)	663 (0.6)
Chronic obstructive pulmonary disease	289 (8.6)	351 (5.5)	477 (12.2)	552 (8.4)	3597 (7.1)	5250 (5.1)	3640 (6.9)	5398 (5.0)
Cerebrovascular disorders	536 (16.0)	871 (13.6)	643 (16.4)	971 (14.8)	5040 (10.0)	8640 (8.4)	4947 (9.4)	8509 (7.9)
Cancer	297 (8.9)	612 (9.5)	504 (12.9)	950 (14.5)	2999 (5.9)	6194 (6.0)	3523 (6.7)	7134 (6.6)
Chronic kidney disease	609 (18.2)	635 (9.9)	987 (25.2)	963 (14.7)	6534 (12.9)	8642 (8.4)	6645 (12.6)	9747 (9.0)
Chronic liver disease	81 (2.4)	98 (1.5)	99 (2.5)	129 (2.0)	750 (1.5)	1162 (1.1)	750 (1.4)	1139 (1.1)
Diabetes	1504 (44.9)	2482 (38.6)	2040 (52.1)	2946 (44.8)	22,285 (44.0)	41,523 (40.4)	22,996 (43.8)	44,042 (40.7)
Hypertension	2433 (72.7)	4113 (64.0)	3180 (81.3)	4876 (74.2)	38,573 (76.2)	71,864 (70.0)	41,288 (78.6)	79,618 (73.6)
Hyperlipidaemia	2003 (59.9)	3243 (50.5)	2701 (69.0)	3961 (60.3)	37,407 (73.9)	69,387 (67.6)	40,139 (76.4)	77,229 (71.4)
No. of comorbidities, no. (%)								
0 comorbidity	349 (10.4)	1369 (21.3)	247 (6.3)	952 (14.5)	4426 (8.7)	14,950 (14.6)	4231 (8.1)	13,667 (12.6)
1 comorbidity	526 (15.7)	1076 (16.7)	383 (9.8)	815 (12.4)	7392 (14.6)	16,950 (16.5)	6964 (13.3)	16,066 (14.9)
2 comorbidities	707 (21.1)	1364 (21.2)	732 (18.7)	1286 (19.6)	13,630 (26.9)	27,969 (27.2)	14,582 (27.8)	30,659 (28.3)
3–4 comorbidities	1296 (38.7)	2162 (33.7)	1705 (43.6)	2797 (42.6)	21,256 (42.0)	39,088 (38.1)	23,279 (44.3)	44,139 (40.8)
≥5 comorbidities	468 (14.0)	453 (7.1)	846 (21.6)	720 (11.0)	3943 (7.8)	3743 (3.6)	3480 (6.6)	3618 (3.3)
COVID-19, no. (%)								
Infected ^c	1062 (31.7)	1567 (24.4)	1990 (50.9)	3155 (48.0)	22,977 (45.4)	43,344 (42.2)	22,773 (43.3)	43,673 (40.4)
Hospitalised ^d	617 (18.4)	788 (12.3)	799 (20.4)	972 (14.8)	2865 (5.7)	3506 (3.4)	2143 (4.1)	2731 (2.5)
Severe disease ^e	242 (7.2)	363 (5.7)	244 (6.2)	282 (4.3)	555 (1.1)	642 (0.6)	318 (0.6)	396 (0.4)
Death	83 (2.5)	139 (2.2)	70 (1.8)	95 (1.4)	71 (0.1)	95 (0.1)	20 (0.0)	35 (0.0)

^a Among cases of ischaemic heart disease (n=110,422), 10,041 (9.09%) had a concurrent diagnosis of heart failure.
^b Housing type was used as an indicator of socioeconomic status.
^c SARS-CoV-2 infection was defined as positive test result (polymerase chain reaction [PCR] test or rapid antigen testing [RAT]) recorded in the national COVID-19 registry
^d COVID-19 hospitalisation was defined as all-cause hospitalisations occurring within 30 days from a positive COVID-19 result (PCR/RAT).
^e Severe disease was defined as COVID-19 infection with resulting need for supplemental oxygen, intensive care admission or death.

Table 3. Risk of Omicron SARS-CoV-2 infection, COVID-19 related-hospitalisation and severe disease by vaccination status, among heart failure/ischemic heart disease cases and matched controls.

No. of mRNA vaccine doses ^c	SARS-CoV-2 infection, aHR (95% CI) ^a		COVID-19 hospitalisation, aHR (95% CI) ^{a,b}		Severe COVID-19 disease, aHR (95% CI) ^{a,b}	
	Heart failure	Controls	Heart failure	Controls	Heart failure	Controls
Unvaccinated/partially vaccinated	0.81 (0.71–0.94)	0.54 (0.49–0.59)	0.98 (0.82–1.18)	0.90 (0.78–1.04)	1.18 (0.88–1.58)	1.51 (1.17–1.96)
Fully vaccinated, not boosted	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)
Boosted	0.81 (0.75–0.87)	0.89 (0.85–0.94)	0.42 (0.37–0.48)	0.31 (0.28–0.35)	0.35 (0.28–0.43)	0.25 (0.20–0.31)
Double boosted (≥4 doses)	0.79 (0.71–0.88)	0.92 (0.86–0.99)	0.28 (0.23–0.34)	0.18 (0.16–0.22)	0.19 (0.13, 0.27)	0.15 (0.10, 0.21)
No. of mRNA vaccine doses ^c	Ischaemic heart disease	Controls	Ischaemic heart disease	Controls	Ischaemic heart disease	Controls
Unvaccinated/partially vaccinated	0.57 (0.52–0.62)	0.51 (0.48, 0.54)	0.92 (0.81, 1.04)	0.85 (0.78, 0.93)	1.07 (0.85, 1.35)	1.23 (1.04–1.44)
Fully vaccinated, not boosted	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)	1.00 (NA)
Boosted	0.91 (0.87–0.95)	0.98 (0.95–1.00)	0.37 (0.34–0.40)	0.34 (0.32–0.36)	0.27 (0.23–0.32)	0.25 (0.22–0.28)
Double boosted (≥4 doses)	0.91 (0.87–0.96)	0.98 (0.95–1.01)	0.23 (0.20–0.25)	0.19 (0.18–0.21)	0.15 (0.12–0.19)	0.14 (0.12–0.17)

aHR: adjusted hazard ratio; CI: confidence interval; NA: not applicable

^a Calendar-time scale cox regression, controlling for age, sex, ethnicity, socioeconomic status (housing type), comorbidities, vaccination status.

^b Restricted to infected individuals only.

^c Individuals who received 0 mRNA vaccine dose were considered unvaccinated; individuals who received 1 mRNA vaccine dose only were considered partially vaccinated; full vaccination was defined as having completed a primary 2-dose vaccine series (either BNT162b2 or mRNA-1273, at least 8 weeks apart). Fully-vaccinated individuals who received additional mRNA vaccine doses at least 6 to 9 months after the second dose were considered boosted. Unvaccinated and partially vaccinated individuals were consolidated in the same category due to the small number of unvaccinated/partially vaccinated cases in our population.

Table 4. Comparing risk of SARS-CoV-2 infection and COVID-19-related hospitalisation and severe disease between individuals with heart failure/ ischaemic heart disease and matched controls who were infected during Omicron-predominant transmission.

Heart failure cases versus matched population controls (period of transmission)	SARS-CoV-2 infection, aHR (95% CI)^a	COVID-19 hospitalisation, aHR (95% CI)^{a,b}	Severe COVID-19 disease, aHR (95% CI)^{a,b}
Population controls (reference category)	1.00 (NA)	1.00 (NA)	1.00 (NA)
Heart failure cases (entire Omicron period) ^c	1.05 (1.01–1.08)	1.77 (1.65–1.90)	2.40 (2.10–2.75)
Heart failure cases (pre-Omicron XBB transmission) ^d	1.02 (0.98–1.06)	1.92 (1.76, 2.09)	2.56 (2.18, 2.99)
Heart failure cases (Omicron XBB transmission) ^d	1.14 (1.06–1.22)	1.58 (1.40–1.80)	2.17 (1.66–2.85)
Ischaemic heart disease cases versus matched population controls (period of transmission)	SARS-CoV-2 infection, aHR (95% CI)^a	COVID-19 hospitalisation, aHR (95% CI)^{a,b}	Severe COVID-19 disease, aHR (95% CI)^{a,b}
Population controls (reference category)	1.00 (NA)	1.00 (NA)	1.00 (NA)
Ischaemic heart disease cases (entire Omicron period) ^c	1.10 (1.09–1.12)	1.21 (1.17–1.26)	1.12 (1.03–1.21)
Ischaemic heart disease cases (pre-Omicron XBB transmission) ^d	1.09 (1.08–1.10)	1.24 (1.19–1.30)	1.14 (1.03–1.25)
Ischaemic heart disease cases (Omicron XBB transmission) ^d	1.15 (1.12–1.18)	1.15 (1.08–1.22)	0.98 (0.84–1.14)

aHR: adjusted hazard ratio; CI: confidence interval; NA: not applicable

^a Calendar-time scale cox regression, controlling for age, sex, ethnicity, socioeconomic status (housing type), comorbidities and vaccination status.^b Restricted to infected individuals only.^c Entire Omicron period refers to Omicron-predominant transmission period.^d 18 September 2022 was used as the cut-off date to further separate the Omicron period into XBB-predominant and pre-XBB (Omicron BA.1/2/3/4) transmission.

unequivocally attenuated risks of adverse COVID-19 outcomes in HF/IHD cases during the Omicron wave.

Elevated risk of infection, hospitalisation and severe COVID-19 among adults with HF/IHD compared to matched population controls was still observed during Omicron predominance, even though the Omicron variant was associated with relatively milder symptoms and lower risk of respiratory complications.^{9,10} Adverse COVID-19 outcomes in acute infection may arise not just from respiratory complications, but also cardiac damage sustained during viral infection of cardiomyocytes, which differentially express angiotensin-converting enzyme 2 required for SARS-CoV-2 viral entry. In an in-vitro study evaluating differential response of engineered human cardiac tissues to Delta and Omicron variants, Omicron pseudoviruses were still able to efficiently infect cardiomyocytes in a tissue-engineered cardiac muscle bundle model.²² Up to one-third of older adults infected with Omicron sustained concurrent myocardial injury (elevated troponin); myocardial injury was associated with higher risk of requiring intensive care.²³ Elevated risk of adverse COVID-19 outcomes in HF/IHD patients infected with Omicron is of concern, given that increased transmissibility of the Omicron variant results in a much greater number of infected individuals. Elevated risk of COVID-19

hospitalisation persisted even into XBB-predominant transmission, compared with other Omicron subvariants in historical circulation. In a population-based study of adults who tested positive for SARS-CoV-2 over successive pandemic phases, pre-existing cardiovascular conditions remained a significant predictor for adverse COVID-19 outcomes even during Omicron transmission, with HF being the most significant predictor for progression to severe COVID-19.²⁴

Our findings highlight the continued benefit of COVID-19 vaccination for patients with HF/IHD in the current era of COVID-19 endemicity and Omicron-predominant transmission. The majority of studies that documented adverse COVID-19 outcomes in patients with HF/IHD were conducted in the early pre-Omicron stages of the pandemic, prior to vaccination rollout.^{1–6} Improved outcomes for COVID-19 patients with elevated troponin and myocardial injury during Omicron was ascribed to the protective effect of vaccination, not available in earlier pandemic waves.²⁵ A single population-based cohort of adults in the Czech Republic with HF who were infected during Omicron-predominant transmission reported vaccine effectiveness estimates against severe COVID-19 of 41.9% in the fully vaccinated group and 76.6% in those who had received a single booster.¹¹ However,

generalisability was significantly limited by restriction to PCR-confirmed cases of SARS-CoV-2 infection, which may have introduced bias as milder RAT-confirmed infections may not have been recorded. Indeed, the reported infection rate (approx. 5%) in the Czech study was surprisingly low.¹¹ Significantly lower HRs against hospitalisation and severe disease in the 4-dose group compared with the 3-dose group suggests that regular boosting is beneficial for additional protection in individuals with HF/IHD. Hospitalisation for HF/IHD in the preceding year was associated with higher risk of COVID-19-related hospitalisation attributed to the Omicron variant, suggesting that individuals with recurrent admissions remain at-risk and should be prioritised for vaccination/boosting. However, vaccine hesitancy remains an issue in this at-risk population,²⁶ despite multiple studies unequivocally demonstrating the safety of mRNA COVID-19 vaccines for patients with HF/IHD.^{27–29} For instance, in a Danish cohort of HF patients matched to population-based controls, receipt of an mRNA COVID-19 vaccine was not associated with an increased risk of worsening heart failure, myocarditis, venous thromboembolism or all-cause mortality.²⁷ Similarly, in a population-based cohort of 32,490 adults in Hong Kong with HF, analysis using a self-controlled case series design did not demonstrate risk of hospitalisation for HF, major adverse cardiovascular events or all-cause hospitalisation after receiving the BNT162b2 mRNA vaccine.²⁸ COVID-19 vaccination in HF patients was associated with significant subsequent reduction in all-cause hospitalisation and mortality rates.²⁹ In our Singapore population, no increased risk of cardiovascular events was observed up to 180 days after any mRNA vaccination dose administered in the Omicron era,³⁰ and myocarditis cases reported post-COVID-19 vaccination were rare and clinically mild.³¹ Continued prioritisation of patients with HF/IHD for booster doses is crucial during COVID-19 endemicity. Such individuals at increased risk of severe COVID-19 should receive updated vaccine doses at an interval of around 1 year from the last vaccine dose,³² given that updated booster doses have been shown to decrease risk of severe COVID-19 in the acute phase of illness,²⁰ as well as long-term risk of cardiovascular complications (eg. thrombosis),³³ compared to ancestral vaccine doses.

Our study has the following strengths: usage of a comprehensive nationwide vaccination and testing database (PCR/RAT) during a period when diagnostic tests were widely available, subsidised and strongly encouraged, resulting in minimal misclassification bias for SARS-CoV-2 infection/vaccination status. National healthcare claims data were used to comprehensively

identify patients with HF/IHD. However, our study also has the following limitations. Unmeasured confounders could still have influenced estimates; in particular, several important comorbidities (e.g. smoking history) were not adjusted for, as this information was unavailable in the national electronic health records. Corroborative test data (e.g. echocardiography) was not available in the national electronic health record, hence we were unable to further stratify HF patients into groups with preserved or reduced ejection fraction for further comparison. This analysis was focused on outcomes of COVID-19 in the acute phase; post-acute long-term cardiovascular sequelae following SARS-CoV-2 infection was not evaluated, although increased long-term risk of dysrhythmias has been observed after Omicron infection in the general adult Singaporean population.^{34,35} Finally, our results may not be immediately generalisable to other populations with differing uptake of COVID-19 boosters/vaccination doses.

CONCLUSION

Persistently elevated risk of COVID-19-related hospitalisation was observed among patients with HF/IHD compared with matched population controls, during successive Omicron waves, including Omicron XBB. Boosting attenuated risk of serious COVID-19 outcomes, with lower risk of hospitalisation and severe disease in the double-boosted group compared to those who only received a single booster. Patients with HF/IHD would benefit from continued enrolment in vaccination programmes during the Omicron era.

Supplementary materials

Supplementary Table S1. Vaccination rates in patients with ischaemic heart disease/heart failure compared to controls and the general adult population.

Supplementary Table S2. Incidence rate of COVID-19 infection, hospitalisation and severe disease, by unvaccinated or partially vaccinated, fully vaccinated, and boosted subgroups.

Supplementary Table S3. Incidence rate of COVID-19 infection, hospitalisation and severe disease, by unvaccinated or partially vaccinated, fully vaccinated, and boosted subgroups.

Ethics statement

Not applicable.

Declaration

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Data sharing

The databases with individual-level information used for this study are not publicly available due to personal data protection. De-identified data can be made available for research, subject to approval by the Ministry of Health, Singapore. All inquiries should be sent to the corresponding author.

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Variations in management strategies for stable coronary artery disease in the Asia-Pacific region: Insights from a multinational survey

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ABSTRACT

Introduction: Randomised controlled trials (RCTs) have informed guideline recommendations for the management of stable coronary artery disease (CAD). However, the real-world impact of contemporary guidelines and trials on practising physicians in the Asia-Pacific region remains uncertain. We aimed to evaluate the knowledge, attitudes and practices among cardiovascular physicians in the region regarding stable CAD management.

Method: An anonymised cross-sectional electronic survey was administered to cardiovascular practitioners from the Asia Pacific, assessing 3 domains: 1) baseline knowledge on recent trials and society guideline, 2) attitudes towards stable CAD, and 3) case scenarios reflecting management preferences. Correlations among knowledge, attitudes and practice scores were assessed

between physicians from developed and developing countries using Pearson correlation.

Results: Overall, 713 respondents from 21 countries completed the survey. The mean knowledge score was 2.90 ± 1.18 (out of 4), with 37.3% of respondents answering all questions correctly, while 74.6% noted that guidelines have significant impact on their practice. Despite guidelines recommending optimal medical therapy, majority chose revascularisation (range 53.4–90.6%) as the preferred strategy for the case scenarios. Practitioners from developed regions had higher knowledge scores and lower attitude scores compared to developing regions, while practice scores were similar in both groups. Weakly positive correlations were noted between knowledge, attitude and practice scores.

Conclusion: Variations exist in knowledge and attitudes towards guideline recommendations and correspondingly

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actual clinical practice in the Asia Pacific, with most practitioners choosing an upfront invasive strategy for the treatment of stable CAD. These differences reflect real-world disparities in guideline interpretation and clinical adoption..

Keywords: Asia Pacific, cardiologists, coronary artery disease, coronary intervention, survey

CLINICAL IMPACT

What is New

- There is limited data in the Asia Pacific regarding how the results of studies and guidelines impact physicians' management preferences for stable coronary artery disease.
- While respondents showed favourable perceptions towards trials and guidelines, the majority of practitioners preferred revascularisation over optimal medical therapy in answering the hypothetical case scenarios, regardless of trial results and guideline recommendations.

Clinical Implications

- Further studies are required to assess factors associated with these variations and discrepancies to facilitate translation of evidence into real-world clinical practice.

INTRODUCTION

Ischaemic heart disease remains the leading cause of morbidity and mortality worldwide, and Asia being the most populous region in the world has shown an increasing prevalence of coronary artery disease (CAD) and related mortality compared to Western countries; 58% of cardiovascular deaths worldwide occurred in Asia in 2019 and 47% was due to ischaemic heart disease.¹ While advancements in management of CAD have progressively improved outcomes, the definitive management of patients with stable CAD can be a subject of debate, particularly with regard to options for revascularisation compared to optimal medical therapy (OMT). Results from landmark trials such as ISCHEMIA and COURAGE,^{2,3} which showed that revascularisation did not significantly reduce the incidence of death and myocardial infarction when compared to medical therapy, have helped inform guideline recommendations to aid physicians in the management of stable CAD.^{4,5} However, the real-world impact of these results and recommendations on clinical practice

has not been fully elucidated. Data is scarce on what factors influence physicians' decisions to recommend revascularisation over OMT, and vice versa. In Asia in particular, differences in prevalences of stable CAD across countries, varied implementation rates of OMT as well as updates on revascularisation decisions after the latest trials and guidelines represent unmet needs that exist between guideline recommendations and actual clinical application.⁶ The present study aimed to assess the knowledge, attitudes and practices of cardiologists towards managing stable CAD in the region.

METHOD

This study was conducted through an online electronic cross-sectional survey of cardiovascular practitioners in the Asia-Pacific region. Our target population consisted of a broad inclusion of cardiac practitioners (i.e. both interventional and non-interventional cardiologists, cardiac surgeons as well as trainees/cardiology fellows), meant to capture wider perspectives and increase representativeness. Only active cardiac practitioners with direct patient care practising in the Asia-Pacific region were included to maintain focus on the intended demographic. A waiver of ethics approval was obtained and granted by the Singhealth Centralised Institutional Review Board as the target respondents were anonymous and participation in the survey was voluntary.

An anonymised electronic survey (see Supplementary Material) was designed by an expert panel of experienced cardiologists based on a similar concept used in previous studies.^{7,8} The questionnaire was initially pilot-tested with 20 expert cardiologists to test for validity and reliability, ensuring proper wording of questions, appropriateness of content, clarity and sequence as well as establishing how the data will be sought from the respondents. Questions were carefully crafted using clear and unambiguous language with neutral wording to ensure more accurate and unbiased responses. The first section of the survey collected basic demographic information about the respondent. The second section consisted of 4 questions that assessed knowledge, notably on the COURAGE and ISCHEMIA trials, as well as the 2021 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on coronary revascularisation,⁹ with participants answering "yes", "no", or "unsure". For the knowledge section, 1 point was ascribed to each correct answer for a maximum of 4 points, and attaining 3–4 points was deemed as a high knowledge score. The third section assessed attitudes and perceptions towards the COURAGE and ISCHEMIA trials as well as contemporary guidelines available at the time the survey was

conducted. For the first 6 questions of the attitudes section, a response of “strongly agree” or “agree” was given a score of 1, and responses of “neutral”, “disagree” or “strongly disagree” were given a score of 0. An average attitude score was then calculated for each respondent. Additionally, on a 5-point Likert scale, clinicians assessed how 19 variables influence the choice of OMT versus [vs] revascularisation. The Likert-type responses were grouped into 3 categories either favouring OMT, favouring revascularisation, or neutral for ease of analysis. For the fourth section, we showed hypothetical case scenarios to understand practice patterns towards revascularisation vs OMT. The ideal and correct response to all 5 case scenarios based on current guidelines would be to offer OMT; 1 point was ascribed to each correct answer for a maximum of 5 points. The Japanese version of the questionnaire only had 3 case scenarios (i.e. they did not answer for cases 1D and 1E) due to technical issues that resulted in the last 2 scenarios not being displayed online. The average score from the respective case scenarios were calculated for each individual participant.

Selection of respondents from participating countries was guided by ascertainment of geographical diversity (i.e. efforts to ensure a mix of developed and developing countries with varying healthcare systems), stratification (i.e. participants were classified based on their country’s development status (developed vs developing) according to United Nations classifications,¹⁰ allowing for comparative analysis and voluntary participation (ensuring ethical standards were upheld). The final version of the questionnaire, which was available in both English and Japanese, was disseminated through professional networks shared within professional groups and associations as well as social media and messaging applications (i.e. Facebook, Viber and WhatsApp groups) to participants from member regions of the Asian Pacific Society of Cardiology from August 2022 to January 2023.

Statistical analysis

Categorical variables were expressed as number values and percentages. Continuous variables were analysed with 2 samples expressed as mean and standard deviation (SD) as appropriate. The relationships between knowledge, attitude and practice scores were explored via calculations of the Pearson correlation coefficient in bivariate analysis. Two subgroup comparisons were performed using the gathered data: 1) developed versus developing countries; and 2) knowledge score (0–2 vs 3–4 correct questions from section 2 of the survey. Two-way comparisons were performed using Student’s t-test for parametric data, Mann-Whitney U test for nonparametric data and chi-squared test for categorical data. All statistical analyses were

performed in RStudio using R-4.3.0 (Posit, Boston, MA, US), with a *P* value of <0.05 used to denote significance.

RESULTS

Study population

In total, 713 unique respondents from 21 countries completed the survey. The majority of participants (61.5%) were ≤50 years old, and 11.2% were female. The highest proportion of respondents came from Japan (66.9%), followed by the Philippines (10.4%) (Table 1). Developed countries accounted for 76.2% of the respondents. Interventional cardiologists comprised 32.7% of respondents, and the duration of practice was >10 years in 74.8% of respondents. The majority practised in an urban setting (66%), and the respondents were well distributed between government, private and rural institutions (Table 2).

Table 1. Survey respondents (n=713).

Countries	Respondents	%
Japan	477	66.90%
Philippines	74	10.38%
Indonesia	32	4.49%
Hong Kong	24	3.37%
Singapore	21	2.95%
Vietnam	14	1.96%
Malaysia	10	1.40%
Thailand	10	1.40%
Nepal	9	1.26%
United Arab Emirates	9	1.26%
Taiwan	7	0.98%
Australia	6	0.84%
Sri Lanka	6	0.84%
South Korea	5	0.70%
Bangladesh	2	0.28%
Oman	2	0.28%
Egypt	1	0.14%
Jordan	1	0.14%
Mongolia	1	0.14%
Myanmar	1	0.14%
Saudi Arabia	1	0.14%

Table 2. Demographics of the study population (n=713).

	All (n=713)	Developed (n=543)	Developing (n=170)	P value
Country, no. (%)		543 (76.2)	170 (23.8)	<0.001
Gender, no. (%)				
Male	633 (88.8)	509 (93.7)	124 (72.9)	
Age, no. (%)				<0.001
21–30	18 (2.5)	13 (2.4)	5 (2.9)	
31–40	212 (29.7)	110 (20.3)	102 (60.0)	
41–50	209 (29.3)	173 (31.9)	36 (21.2)	
51–60	173 (24.3)	160 (29.5)	13 (7.6)	
Above 60	101 (14.2)	87 (16.0)	14 (8.2)	
Primary specialty				<0.001
Cardiology, non-interventional cardiology	385 (54.0)	308 (56.7)	77 (45.3)	
Fellow/trainee	54 (7.6)	19 (3.5)	35 (20.6)	
Interventional cardiology	233 (32.7)	181 (33.3)	52 (30.6)	
Others	41 (5.8)	35 (6.4)	6 (3.5)	
Duration of practice				<0.001
<5 years	91 (12.8)	15 (2.8)	76 (44.7)	
5–10 years	89 (12.5)	39 (7.2)	50 (29.4)	
11–20 years	183 (25.7)	169 (31.1)	14 (8.2)	
21–30 years	211 (29.6)	192 (35.4)	19 (11.2)	
>30 years	139 (19.5)	128 (23.6)	11 (6.5)	
Type of practice				<0.001
Government, academic	179 (25.1)	115 (21.2)	64 (37.6)	
Government, non-academic	104 (14.6)	81 (14.9)	23 (13.5)	
Private	269 (37.7)	187 (34.4)	82 (48.2)	
Rural	161 (22.6)	160 (29.5)	1 (0.6)	
Area of practice				
Rural	239 (33.5)	221 (40.7)	45 (26.5)	0.001
Urban	474 (66.5)	447 (82.3)	127 (74.7)	0.038

P values in bold denote significance.

Knowledge scores

The mean knowledge score was 2.90 ± 1.18 . Knowledge scores were higher in developed countries compared to developing countries (3.01 ± 1.13 vs 2.55 ± 1.28 , $P < 0.001$). Overall, 37.3% of respondents answered all questions correctly, and 51.3% had high

knowledge scores (3–4 points). The question with the highest number of incorrect answers was related to the ACC/AHA guidelines on revascularisation in patients with stable CAD and significant triple vessel disease without left main disease, with only 46.6% answering correctly (Table 3).

Table 3. Overall survey results stratified by developing vs developed countries and by knowledge scores.

Knowledge						
	Total (n=713)	Developed (n=543)	Developing (n=170)	P value	Knowledge score 0-2 (n=194)	Knowledge score 3-4 (n=519) P value
All knowledge questions correct, no. (%)	266 (37.3)	221 (40.7)	45 (26.5)	0.001	0 (0.0)	266 (51.3) <0.001
Q1	574 (80.5)	447 (82.3)	127 (74.7)	0.038	69 (35.6)	505 (97.3) <0.001
Q2	572 (80.2)	449 (82.7)	123 (72.4)	0.004	72 (37.1)	500 (96.3) <0.001
Q3	332 (46.6)	265 (48.8)	67 (39.4)	0.040	21 (10.8)	311 (59.9) <0.001
Q4	588 (82.5)	472 (86.9)	116 (68.2)	<0.001	81 (41.8)	507 (97.7) <0.001
Mean knowledge score, no. (%)	2.90 (1.18)	3.01 (1.13)	2.55 (1.28)	<0.001	1.25 (0.87)	3.51 (0.50) <0.001
By score						
0	54 (7.6)	37 (6.8)	17 (10.0)		54 (27.8)	0 (0.0)
1	37 (5.2)	16 (2.9)	21 (12.4)		37 (19.1)	0 (0.0)
2	103 (14.4)	74 (13.6)	29 (17.1)		103 (53.1)	0 (0.0)
3	253 (35.5)	195 (35.9)	58 (34.1)		0 (0.0)	253 (48.7)
4	266 (37.3)	221 (40.7)	45 (26.5)		0 (0.0)	266 (51.3)
Attitudes/perceptions						
	Total (n=713)	Developed (n=543)	Developing (n=170)	P value	Knowledge score 0-2 (n=194)	Knowledge score 3-4 (n=519) P value
Average A/P score, no. (%)	0.71 (0.34)	0.67 (0.35)	0.81 (0.31)	<0.001	0.70 (0.35)	0.71 (0.34) 0.637
Individual questions: no. of respondents with score = 1 (strongly agree/agree)						
I find the results of the COURAGE trial informative.	460 (64.5)	328 (60.4)	132 (77.6)	<0.001	121 (62.4)	339 (65.3) 0.520
The COURAGE trial has impacted my management of patients with stable CAD.	443 (62.1)	307 (56.5)	136 (80.0)	<0.001	120 (61.9)	323 (62.2) 0.995
I find the results of the ISCHEMIA trial informative.	523 (73.4)	383 (70.5)	140 (82.4)	0.003	139 (71.6)	384 (74.0) 0.594
The ISCHEMIA trial has impacted my management of patients with stable CAD.	504 (70.7)	370 (68.1)	134 (78.8)	0.01	134 (69.1)	370 (71.3) 0.626

Table 3. Overall survey results stratified by developing vs developed countries and by knowledge scores. (Cont'd)

Attitudes/perceptions							
	Total (n=713)	Developed (n=543)	Developing (n=170)	P value	Knowledge score 0-2 (n=194)	Knowledge score 3-4 (n=519)	P value
I find the recommendations of the guidelines informative.	561 (78.7)	415 (76.4)	146 (85.9)	0.012	153 (78.9)	408 (78.6)	>0.99
The guidelines have impacted my management of patients with stable CAD.	532 (74.6)	390 (71.8)	142 (83.5)	0.003	144 (74.2)	388 (74.8)	0.961
Variables influencing therapeutic decision (medical therapy/neutral/revascularisation)							
	Total (n=713)	Developed (n=543)	Developing (n=170)	P value	Knowledge score 0-2 (n=194)	Knowledge score 3-4 (n=519)	P value
Symptomatic, (%)	4.5/7.2/88.4	3.9/8.1/88	6.5/4.1/89.4	0.088	2.6/5.7/91.8	5.2/7.7/87.1	0.189
Asymptomatic, (%)	59.5/30/10.5	53.6/34.4/12	78.2/15.9/5.9	<0.001	50.5/36.1/13.4	62.8/27.7/9.4	0.011
Age <65, (%)	10.8/28.9/60.3	8.8/29.5/61.7	17.1/27.1/55.9	0.011	8.2/25.3/66.5	11.8/30.3/58	0.105
Age 65–80, (%)	20.2/38/41.8	16.4/37.9/45.7	32.4/38.2/29.4	<0.001	19.6/32.5/47.9	20.4/40.1/39.5	0.100
Age >80, (%)	51.8/30.7/17.5	49/32/19	60.6/26.5/12.9	0.025	44.3/28.9/26.8	54.5/31.4/14.1	<0.001
Presence of diabetes	10.2/22/67.7	9.9/24.9/65.2	11.2/12.9/75.9	0.005	9.3/19.1/71.6	10.6/23.1/66.3	0.388
Presence of multiple comorbidities	24.3/28.3/47.4	24.1/30.8/45.1	24.7/20.6/54.7	0.027	16.5/25.3/58.2	27.2/29.5/43.4	0.001
LVEF <35%	7.9/15/77.1	4.8/16/79.2	17.6/11.8/70.6	<0.001	12.4/20.1/67.5	6.2/13.1/80.7	0.001
LVEF 35–50%	4.6/18.2/77.1	3.7/20.3/76.1	7.6/11.8/80.6	0.007	4.6/19.6/75.8	4.6/17.7/77.6	0.847
LVEF >50%	21/42.6/36.3	18.4/46.4/35.2	29.4/30.6/40	<0.001	15.5/33/51.5	23.1/46.2/30.6	<0.001
LM disease	1.7/4.2/94.1	0.4/4.4/95.2	5.9/3.5/90.6	<0.001	2.6/8.2/89.2	1.3/2.7/96	0.002
Triple vessel disease	2.8/7.4/89.8	1.7/7.4/91	6.5/7.6/85.9	0.004	3.1/7.7/89.2	2.7/7.3/90	0.941
pLAD disease	3.4/6.5/90.2	2.2/6.6/91.2	7.1/5.9/87.1	0.009	3.1/8.8/88.1	3.5/5.6/90.9	0.303
mLAD disease	14.6/26.5/58.9	12.2/28.7/59.1	22.4/19.4/58.2	0.001	12.4/22.7/64.9	15.4/27.9/56.6	0.134
Single vessel disease not involving LAD	36.5/35.9/27.6	35.4/37.8/26.9	40/30/30	0.184	30.9/34/35.1	38.5/36.6/24.9	0.020
Double vessel disease not involving LAD	21.7/30.2/48.1	19.2/31.5/49.4	30/25.9/44.1	0.011	16.5/24.2/59.3	23.7/32.4/43.9	0.001

Table 3. Overall survey results stratified by developing vs developed countries and by knowledge scores. (Cont'd)

Variables influencing therapeutic decision (medical therapy/neutral/revascularisation)						
	Total (n=713)	Developed (n=543)	Developing (n=170)	P value	Knowledge score 0-2 (n=194)	Knowledge score 3-4 (n=519) P value
Mild ischaemia on stress test	43.6/30.7/25.7	39.4/33.9/26.7	57.1/20.6/22.4	<0.001	36.6/32/31.4	46.2/30.3/23.5 0.037
Moderate ischaemia on stress test	14.6/20.1/65.4	11.2/20.3/68.5	25.3/19.4/55.3	<0.001	10.8/18/71.1	16/20.8/63.2 0.106
Severe ischaemia on stress test	2.4/7/90.6	1.3/6.8/91.9	5.9/7.6/86.5	0.002	2.1/7.7/90.2	2.5/6.7/90.8 0.853
Practices/offering medical therapy ("correct" option) for the case below						
	Total (n=713)	Developed (n=543)	Developing (n=170)	P value	Knowledge score 0-2 (n=194)	Knowledge score 3-4 (n=519) P value
Case 1a	67 (9.4)	52 (9.6)	15 (8.8)	0.886	15 (7.7)	52 (10.0) 0.431
Case 1b	332 (46.6)	231 (42.5)	101 (59.4)	<0.001	82 (42.3)	250 (48.2) 0.186
Case 1c	177 (24.8)	133 (24.5)	44 (25.9)	0.792	35 (18.0)	142 (27.4) 0.014
Case 1d*	25 (10.1)	8 (10.3)	17 (10.0)	>0.99	5 (5.7)	20 (12.4) 0.148
Case 1e*	62 (25.0)	16 (20.5)	46 (27.1)	0.343	14 (16.1)	48 (29.8) 0.026
Average case scenario score	0.25 (0.29)	0.25 (0.30)	0.26 (0.24)	0.619	0.20 (0.25)	0.27 (0.30) 0.006

CAD: coronary artery disease; LAD: left anterior descending; LM disease: left main coronary artery disease; LVEF: left ventricular ejection fraction; mLAD: mid left anterior descending artery disease;
pLAD disease: proximal left anterior descending coronary artery disease
* Excluding 465 participants from Japan.
P values in bold denote significance.

Attitude scores

For the attitudes section, the majority of respondents found the guideline recommendations informative (78.7%) and felt that the guidelines impacted their clinical practice (74.6%). The average attitude score was 0.71 ± 0.34 and was lower in developed countries compared to developing (0.67 ± 0.35 vs 0.81 ± 0.31 , $P < 0.001$). Compared to developing countries, a lower percentage of respondents from developed countries noted that both COURAGE (56.5% vs 80.0%, $P < 0.001$) and ISCHEMIA trials (68.1% vs 78.8%, $P = 0.01$) impacted their management of patients with stable CAD. There were no differences in attitude scores when stratified by higher vs lower knowledge scores ($P = 0.637$) (Table 3).

For the variables influencing therapeutic decision-making in section 3 of the survey, the majority of respondents favoured the performance of coronary revascularisation compared to OMT for symptomatic patients (88.4% vs 4.5%), age < 65 (60.3% vs 10.8%), presence of diabetes (67.7% vs 10.2%) and multiple comorbidities (47.4% vs 24.3%). In addition, LVEF $< 50\%$, left main disease, triple vessel disease, proximal left anterior descending (LAD), mid-LAD, and patients with moderate and severe ischaemia on the stress test all showed a trend favouring revascularisation, and this appears consistent whether the respondent is from a developing or developed country (all P values < 0.05). When stratified based on knowledge scores, respondents with higher knowledge scores tended to favour OMT over revascularisation in the setting of asymptomatic status (62.8% vs 9.4%), age > 80 years (54.5% vs 14.1%), single vessel disease not involving the LAD (38.5% vs 24.9%) and mild ischaemia on stress testing (46.2% vs 23.5%, all P values < 0.05) (Table 3).

Practice scores

For the practice domain, the correct answer based on guideline recommendations for all clinical scenarios was OMT. The average practice score was 0.25 ± 0.29 , indicating that respondents on the whole favoured revascularisation for most scenarios. The distribution of the responses to the case scenarios of stable

with double vessel disease (89.9%). Notably, only 25% selected OMT for the fifth scenario of an asymptomatic patient with an abnormal treadmill test and proximal LAD stenosis. There were no significant differences in practice scores between developed and developing countries ($P = 0.619$) (Table 3). Overall, while OMT should technically be the correct answer to all the mentioned cases based on guidelines, the majority of respondents chose revascularisation as the preferred option.

Correlations between scores

The results of the correlation analysis are shown in Table 4. For the overall cohort, there was a weakly positive correlation between knowledge and practice scores ($r = 0.12$, $P = 0.001$) and attitude and practice scores ($r = 0.13$, $P < 0.001$). There was a positive correlation between knowledge and attitude scores ($r = 0.109$, $P = 0.016$), knowledge and practice scores ($r = 0.096$, $P = 0.025$), and attitude and practice scores ($r = 0.14$, $P = 0.001$), respectively, in developed countries; while in developing countries, the positive correlation was only noted between knowledge and practice scores ($r = 0.23$, $P = 0.003$). In those with higher knowledge scores, there was a positive but weak correlation between attitude and practice scores ($r = 0.18$, $P < 0.001$) but this was not seen in those with low knowledge scores.

DISCUSSION

This multinational survey of cardiovascular practitioners from the Asia-Pacific region reveals several important observations regarding the management of stable CAD. First, knowledge scores were in general favourable, with the majority of respondents scoring 3 or 4 points. Developed countries appear to have higher knowledge scores than developing countries. Second, the majority of respondents felt guideline recommendations were informative and impacted their management. Lower attitude scores were observed in developed compared to developing countries. Third, practice scores were overall low, indicating a preference for revascularisation over OMT in scenarios where guidelines do not recommend revascularisation. Practice scores were higher in respondents with high knowledge scores than those with low knowledge scores. Fourth, significant but only weakly positive correlations were seen between knowledge and practice as well as attitude and practice scores.

While overall knowledge scores were generally good, developed countries appear to have higher knowledge scores than developing countries. This may be due to differences in resource availability as well as feasibility to comply to guideline recommendations.

Fig.1. Responses to case scenarios.

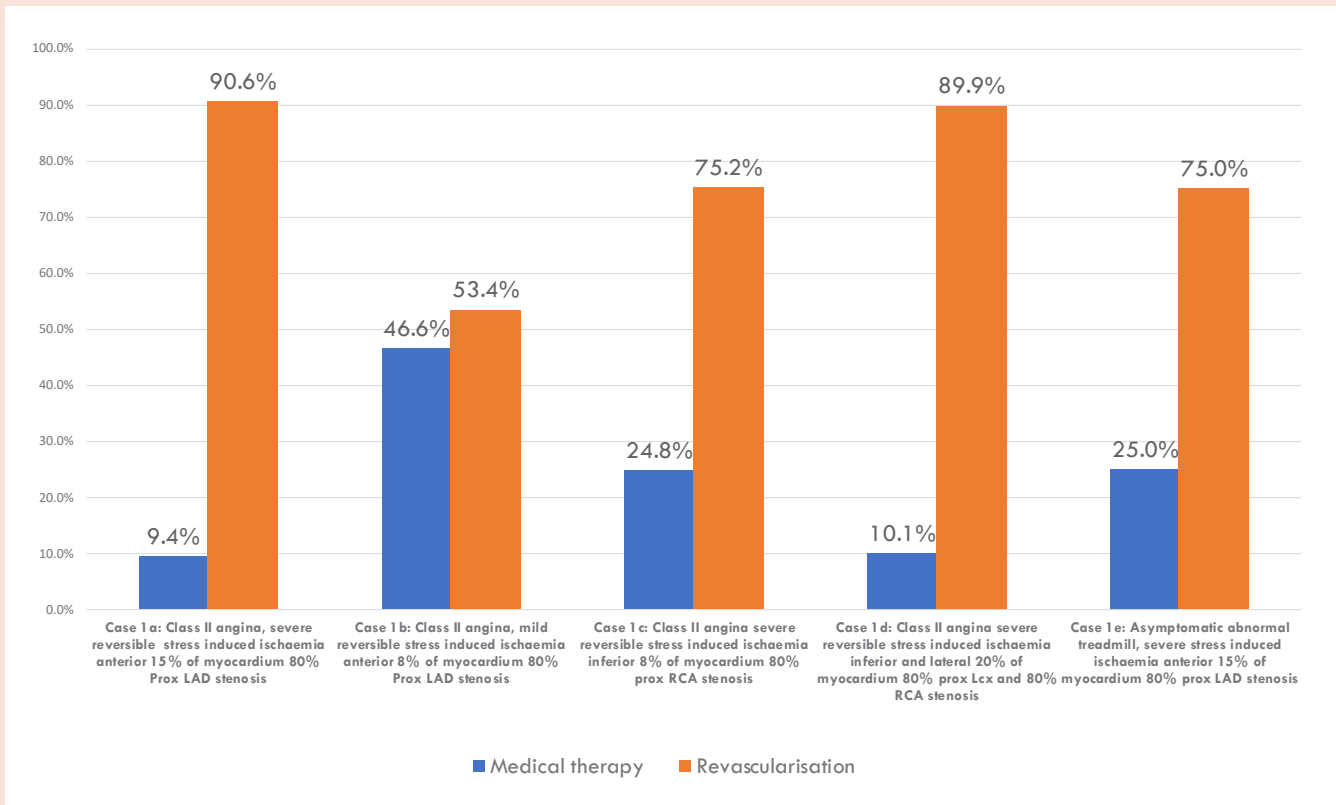


Table 4. Correlation between knowledge, attitude and practice scores.

Variable	t-statistic	Degrees of freedom	P value	Correlation coefficient	95% confidence interval
Knowledge score vs attitude score					
Overall	0.702	711	0.483	0.026	-0.047 to 0.10
Developing countries	-1.14	168	0.255	-0.088	-0.24 to 0.064
Developed countries	2.41	541	0.016	0.109	0.019–0.19
Knowledge score vs practice score					
Overall	3.21	711	0.001	0.12	0.046–0.19
Developing countries	3.04	168	0.003	0.23	0.080–0.37
Developed countries	2.25	541	0.025	0.096	0.012–0.18
Attitude score vs practice score					
Overall	3.47	711	<0.001	0.13	0.056–0.20
Developing countries	1.17	168	0.243	0.090	-0.061 to 0.24
Developed countries	3.20	541	0.001	0.14	0.053–0.22
Knowledge score 3–4	4.08	517	<0.001	0.18	0.092–0.26
Knowledge score 0–2	-0.28	192	0.781	-0.020	-0.16 to 0.12

Developed countries typically have more robust healthcare systems with better infrastructure, including advanced medical technologies and access to comprehensive medical education. Cardiologists from developed countries often benefit from structured training programmes and continuing medical education opportunities.¹¹ Developing countries also face unique challenges with regard to length and variability of training, education and research output inequity, especially in comparison with developed nations.¹² These socioeconomic disparities can influence healthcare delivery and education. Finally, it has been shown that availability and applicability of guidelines can differ between high-income and low-income nations, and applying the best evidence is often not feasible in the latter and may diverge from guideline recommendations in actual practice.¹³

The vast majority from both groups noted that the information provided by the guidelines was informative and impacted their practice. It has been shown that the knowledge and attitudes of healthcare providers may play a role in the usage of clinical practice guidelines.¹⁴ A study assessing attitudes and behaviours towards clinical guidelines showed that 77% of surveyed clinicians have a welcoming attitude towards guidelines, and clinicians' decisions to use them were based on the perceived value of the guideline.¹⁵ The variables that influenced the decision to revascularise among respondents appears congruent with the 2018 European Society of Cardiology/European Association of Cardio-Thoracic Surgery (ESC/EACTS) guidelines on myocardial revascularisation¹⁶ which are mostly Class I recommendations focused on the extent of CAD (either anatomical or functional) or symptomatology. These characteristics are frequently assessed by practitioners in the real world and influence their decision making.

For the clinical case scenarios, we aimed to understand what decisions clinicians would make in real-world practice. The majority of respondents chose revascularisation despite guidelines and RCTs indicating OMT as the correct answer and firstline treatment for these scenarios. On average, approximately only around a quarter of the respondents chose OMT, suggesting a discrepancy between current guidelines and actual clinical practice. Despite good knowledge and generally positive attitude scores, practice scores overall were poor. There was only a weakly positive correlation between knowledge and practice scores as well as attitude and practice scores. While it is expected that good knowledge forms the basis of a good foundation for better attitudes and practices, the weakly positive correlations suggest that factors beyond these behavioural aspects such

as demographics and socioeconomic status also exert influence in the clinician's decision-making.¹⁷ Cardiologists who answered a survey about ESC guidelines for heart failure showed that while awareness of the guidelines was high and respondents found the guidelines relevant to their treatment choices, only around 25% of the responses in clinical case scenarios were in agreement with the guidelines.¹⁸ A study by Karbach et al.¹⁹ that assessed primary care physicians' knowledge and compliance with guidelines also showed that adequacy of physician's knowledge does not in itself always lead to better guideline implementation.

It is difficult to ascertain how the trials and guidelines for stable CAD management influence real-world practice, but some data suggest it has had minimal impact. Despite the results of COURAGE, there was little to no significant change in OMT prescription patterns noted by Borden et al.²⁰ while Inohara et al. compared 2 national registries and even noted an increase in volume of PCIs in the US by 15.8% and in Japan by 36%, respectively, after publication of COURAGE.²¹ The ORBITA²² trial showed PCI having no significant improvement in exercise capacity or angina frequency compared to sham procedure, and generated considerable debate and controversy regarding the symptom benefits of PCI.²³ Despite these results, data from the UK showed no impact on elective PCI rates for stable angina, and interventionists did not alter their practice before and after publication of both COURAGE and ORBITA.²⁴ While the results of ISCHEMIA encouraged calls for a paradigm shift as reflected in the guidelines on the contemporary management of stable ischaemic heart disease,²⁵ it is acknowledged that due to unique characteristics of these types of patients in the Asia-Pacific region as well as heterogenous approaches, differences in resources along with low number of patients from the region in pivotal studies, international guidelines cannot be routinely applied in Asia Pacific countries.²⁶

The physician's decision-making process for the treatment of stable CAD is complex and cannot be simply explained by quantitative factors or trial results alone. While it can be assumed that fee for service healthcare systems may create financial incentivisation to perform procedures, there is evidence which shows that even cardiologists in capitated settings still prefer revascularisation, indicating that factors other than payment play a role in the decision to perform invasive management.²⁷ Many practitioners may also feel that the results of trials like ISCHEMIA and COURAGE represent a homogeneous population that is not fully applicable to real-world patients.²⁸ Analysis of an Italian registry which assessed a real-world, large-scale evaluation of the applicability

of ISCHEMIA showed that 84.7% did not fulfil ISCHEMIA criteria, and that only 3.8% were “ISCHEMIA like”.²⁹ Findings from trials represent a small fraction of patients routinely encountered in clinical practice, thus requiring a more nuanced approach with equipoise.³⁰ The way the benefits of revascularisation are perceived by the physician and presented to the patient may also affect management preferences,³¹ such as the “open artery hypothesis” (i.e. the notion that an open artery is better than a stenosed artery).³² Lastly, psychological and emotional factors play a role in decisions that prevail over evidence from clinical trials and cultural bias towards the use of technology compared to more conservative measures.³³

Results from our survey among cardiovascular practitioners in the Asia Pacific suggest that while the knowledge and attitudes to guidelines and trials regarding stable CAD are positive, there is discordance between cardiologists’ clinical knowledge and beliefs about the benefits of revascularisation for stable CAD and how they apply evidence into practice. This suggests that these clinical practice guidelines may have limited effect on changing physician behaviour.³⁴ There is high awareness regarding guidelines and recommendations but there is data that suggest that large-scale dissemination of guidelines may not contribute to improvement in practice,³⁵ and physicians may continue to ignore the results of studies that may be in conflict with their own clinical practice beliefs and practise selective-based medicine.³⁶ Attempts to address and resolve these differences of translating results from research studies to practice are complex and challenging³⁷ and beyond the scope of this paper but may involve improvement in the characteristics of future studies that methodologically reconcile randomised and pragmatic designs while assessing endpoints to make them more comparable to real world data found in registries.³⁸ The review by Van Spall et al. also provides some guidance to overcome suboptimal uptake of evidence-based cardiovascular therapies after trial results by improving implementation science and execution, which includes engagement of broad stakeholders (i.e. patients, clinicians and decision-makers) in trial advisory boards as well as integrating trial execution with the healthcare system while evaluating and addressing barriers and facilitators to deployment of the intervention.³⁹ These measures may allow adoption of guidelines and trial results for better implementation of research findings into clinical practice and ultimately better patient care.

Limitations of this study exist. The results may not be fully generalisable and representative. A large percentage of survey respondents were from one

country (Japan), and the majority of respondents are from developed countries, which may possibly lead to an underrepresentation of practitioners most notably from other developing countries. Any regional differences and inferential tests noted at this stage are exploratory in nature and will need to be further studied. Moreover, being limited to the Asia-Pacific region, this survey cannot account for knowledge, attitudes and practices in other regions such as Europe and the Americas. Due to the anonymous nature of the survey and mass sent dissemination via social media channels, we were not able to account for non-responders to ascertain the actual response rates. Despite our best efforts to design and administer the survey, we cannot totally remove nonresponse bias, which may also affect the generalisability of our results. Lastly, most of the knowledge that the respondents based their responses were from data up to 2022. The latest guidelines on chronic coronary syndromes published by the ESC not only reflect changes in nomenclature but also provide updated recommendations on the role of revascularisation on a variety of clinical scenarios while emphasising the role of guideline directed medical therapy.⁴⁰ It is uncertain how clinician interpretation of the evidence in these guidelines will affect clinical practice moving forward. Nevertheless, the results of this study contribute to a better understanding of physicians’ attitudes and practices related to the management of stable CAD in the Asia-Pacific region, of which data are currently lacking at present. In addition, how these results translate into practical measures to bridge the gaps between trial results and guidelines with that of clinical practice will be the work of future research.

CONCLUSION

In the management of stable CAD, variations exist in knowledge and attitudes towards guideline recommendations and correspondingly actual clinical practice in the Asia-Pacific. These differences reflect real-world disparities in relation to guideline interpretation and subsequent adoption.

Supplementary material: Appendix S1. Survey questions and Appendix S2. Case scenarios/practice

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Ethics statement

A waiver of ethics approval was obtained and granted by the SingHealth Centralised Institutional Review Board (2022/2356).

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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Preterm birth trends and risk factors in a multi-ethnic Asian population: A retrospective study from 2017 to 2023, can we screen and predict this?

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ABSTRACT

Introduction: Preterm birth (PTB) remains a leading cause of perinatal morbidity and mortality worldwide. Understanding Singapore's PTB trends and associated risk factors can inform effective strategies for screening and intervention. This study analyses PTB trends in Singapore from 2017 to 2023, identifies risk factors in this multi-ethnic population and evaluates a predictive model for PTB.

Method: A retrospective analysis of all PTBs between 22+0 and 36+6 weeks of gestation, from 1 January 2017 to 31 December 2023, was performed by extracting maternal and neonatal data from electronic medical records. These PTBs were taken from the registry of births for Singapore and SingHealth cluster data. Cochran-Armitage trend test and multinomial logistic regression were used. An extreme gradient boosting (XGBoost) model was developed to test and predict the risk of PTB.

Results: The PTB rate in Singapore did not show a significant change. However, there was modest downward trend in the SingHealth population from 11.3% to 10.2%, mainly in late spontaneous PTBs (sPTBs). sPTBs accounted for ~60% of PTBs. Risk factors for very/extreme sPTB included Chinese ethnicity, age ≥ 35 years, body mass index (BMI) ≥ 23 kg/m², being unmarried, primiparity, twin pregnancy and maternal blood group AB. The XGBoost model achieved an area under the receiver operating characteristic curve of 0.75, indicating moderate ability to predict PTB.

Conclusion: The overall PTB rate in Singapore has not improved. This study underscores the importance of local factors, particularly advanced maternal age, BMI, primiparity, unmarried, Chinese ethnicity and maternal blood group AB influencing PTB risk. Artificial intelligence methods show promise in improving PTB risk stratification, ultimately supporting personalised care and intervention.

Keywords: obstetrics and gynaecology, preterm birth, prediction model, risk factors, Singapore, trends

CLINICAL IMPACT

What is New

- The incidence of preterm birth (PTB) globally (10%) and in Singapore (8.1%) has not improved in the last 10 years.
- Using artificial intelligence, we have modestly improved the predictive risk for spontaneous PTB. Notable risk factors include Chinese ethnicity, single mother and maternal blood group AB.

Clinical Implications

- Our findings can better guide risk stratification and predict the population at risk of spontaneous PTB. This will improve neonatal outcomes through targeted management, monitoring and early intervention.

INTRODUCTION

Preterm birth (PTB), defined by the World Health Organization as delivery before 37 weeks of gestation, is the primary contributor to perinatal morbidity and mortality worldwide.¹⁻³ Despite advances in clinical and public health interventions, global PTB rates have remained relatively constant at approximately 10%.⁴ Rates vary by region and ethnicity; for instance, the US reported a 10.4% PTB rate in 2022,⁵ the UK 7.6% in 2021,⁶ and the Netherlands 6.9% in 2015.⁷ While there have been slight decreases in some regions, disparities persist.⁸ In Asia, PTB rates also differ widely; Bangladesh (16.2%), Pakistan (14.4%) and India (13.0%) report higher rates, while China's rate is lower (6.1%).⁴ Singapore's PTB rate was 8.12% in 2023.⁹ Ethnic disparities in PTB are well-documented in countries such as the US and UK, where black women

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experience disproportionately higher PTB rates.^{10–12} Singapore's population comprises 74.0% Chinese, 13.5% Malay, 9.0% Indian and 3.4% from other ethnicities,¹³ but the role of ethnicity in Singapore's PTB rates has not been explored in detail previously.

PTB can be further categorised by gestational age: (1) extreme preterm birth (ExPTB, <28 weeks), (2) very preterm birth (vPTB, 28 to <32 weeks), (3) late preterm (32 to <37 weeks). Although most PTBs occur in the late preterm category,¹⁴ ExPTB and vPTB are disproportionately linked to mortality and severe long-term complications.^{15–17} PTB is also subdivided by clinical subtype into (1) iatrogenic PTB (iPTB), where delivery is indicated for maternal or foetal reasons, and (2) spontaneous PTB (sPTB), which includes spontaneous labour or pre-labour premature rupture of membranes (PPROM).^{14,18}

A history of PTB is the strongest risk factor for recurrent PTB.^{14,19} Maternal age over 35 years, abnormal body mass index (BMI), tobacco use, single marital status and medical comorbidities have all been linked to an increased risk of PTB.^{14,20–26} Short interpregnancy intervals (<6 months) further increase PTB risk.^{27,28} In multiple pregnancies, especially twins, PTB rates can be as high as 60%, with ~40% being spontaneous.¹⁴ Emerging research also suggests an association between maternal ABO blood group and PTB.^{29,30} Given the multifactorial aetiology of PTB and its significant burden on neonates, the healthcare system and families, a deeper understanding of local PTB risk profiles is needed to develop timely and targeted interventions. This study represents the first large-scale analysis of PTB in a large multi-ethnic, high-income Asian setting (Singapore), focusing on trends and risk factors. We used our findings to develop a predictive model for screening high-risk women. To our knowledge, this is the first study to include maternal blood group in a large multi-ethnic population using machine learning methods to predict risk of sPTB.

METHOD

Study design and setting

This retrospective cohort study analysed all PTBs between 22+0 and 36+6 weeks of gestation within the Obstetrics units of SingHealth institutions, namely, the 2 restructured hospitals—KK Women's and Children's Hospital (KKH) and Singapore General Hospital (SGH)—from 1 January 2017 to 31 December 2023. Both hospitals provide a significant portion of Singapore's maternity and neonatal care, including the management of early gestational deliveries. Prior to 2017, paper notes formed the majority of data many of which were incomplete, and it was decided to use electronic data from 2017 to the present to best predict trends in PTB. The Singapore PTB was obtained

from the births and deaths registry published by the Immigration and Checkpoints Authority of Singapore.

Data collection

We extracted maternal and neonatal data from electronic medical records. Collected variables included (1) maternal factors: age, ethnicity, parity, booking BMI, blood group, marital status, obstetric history (previous PTB and PPRM), medical conditions (hypertension, diabetes), cervical surgery history, use of cerclage or progesterone, smoking, illicit drug use, and interpregnancy interval; (2) pregnancy and delivery details: gestational age, mode of delivery, clinical subtype of PTB (spontaneous or iatrogenic), singleton or twin pregnancy; (3) neonatal outcomes: birth weight, sex and neonatal intensive care unit admission; (4) socioeconomic status: data for this were incomplete. Private and subsidised care was initially thought of to differentiate financial status. However, this was challenging to differentiate in the context of KK Women's and Children's Hospital and Singapore General Hospital, as almost all private patients opted for subsidised status when admitted to both hospitals. This was due to the high differential costs of neonatal care between the 2 groups of patients. As such, average household income among the different ethnicities as determined by the Singapore Department of Statistics Census of Population 2020 was used as proxy.

Inclusion and exclusion criteria

We included PTBs between 22+0 and 36+6 weeks of gestation. For multiple pregnancies, only twin gestations were included; higher-order multiples were excluded due to their distinct risk profile and rarity.

Classification of PTBs

PTBs were categorised by gestational age into (1) ExPTB: <28 weeks, (2) vPTB: 28 to <32 weeks, (3) late preterm: 32 to <37 weeks. Given their significant contribution to neonatal complications but with their comparatively smaller numbers, ExPTB and vPTB were grouped together for analysis in this paper.^{16,17} PTBs were also classified by clinical subtypes into (1) sPTB: onset of labour or PPRM before 37 weeks; (2) iPTB: deliveries induced due to maternal or foetal complications.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Maternal age was grouped as <30, 30–34 and ≥35 years. Booking BMI was divided into <23 kg/m² and ≥23 kg/m² using Asian cut-off points.³¹ Race was categorised into Chinese, Malay, Indian and Others. Parity was classified as 1 (primiparous), 2 and ≥3 births (multiparous including current pregnancy). Marital status was dichotomised into married versus (vs) single/divorced, and birth type into singleton vs twin.

We used the Cochran-Armitage trend test to assess yearly PTB incidence trends. Multinomial logistic regression was performed to examine risk factors for late PTB vs term birth, and ExPTB/vPTB vs term birth. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported.

Development of the prediction model

A risk score prediction model for sPTB was developed based on the identified risk factors, using an extreme gradient boosting (XGBoost) classifier. XGBoost operates by sequentially expanding an ensemble of decision tree models, with each new tree model correcting for residual errors from the previous ensemble. The training of the ensemble is performed with gradient descent optimisation to minimise prediction error. The XGBoost classifier was first trained on the training set with 5-fold cross-validation to optimise the model hyperparameters. The final model was then trained using the optimised hyperparameters on the training set data and evaluated on the held-out test set.

For this study, data were available for PTBs from 2017 to 2023 inclusive, and term births from 2017 to 2019 inclusive. Data from 2017 and 2018 inclusive were designated as the training set (2503 PTB cases and 20,827 term birth cases), and from 2019 onwards as the test set (5615 PTB cases and 10,145 term birth cases). The model included 7 maternal features (age, race, marital status, blood group, BMI at booking, multiple pregnancy and parity) as its input features, with the target variable being PTB. A second risk score prediction model for sPTB was developed based

on identified risk factors (excluding multiple pregnancy). The test set for this model has 4814 PTB and 10,136 term births.

Ethical considerations

Ethical approval was obtained from the SingHealth Institutional Review Board (2023-2278). Patient confidentiality was maintained, and data were anonymised prior to analysis.

RESULTS

PTB incidence and trends

From 2017 to 2023, SingHealth institutions recorded 91,174 births, accounting for 34.5% of all births in Singapore during that period. Of Singapore's total PTBs, 44.1% were managed in SingHealth, with an increase from 42.5% in 2020 to 47.3% in 2023.

SingHealth delivered 42.9% of late preterm infants and 79.3% of ExPTB/vPTB infants in 2023. Due to the specialised tertiary neonatal care that is provided by SingHealth institutions, more extreme and very PTB babies were delivered in our hospitals (Table 1). ExPTB and vPTB constituted 18.3% of the total PTBs in SingHealth and 0.7% of total births nationwide.

Overall PTB rates and subtypes

Although there was no statistically significant shift in PTB rates in Singapore, a slight downward trend from 11.3% to 10.2% (2017–2023) was observed within SingHealth institutions ($P<0.001$). This decline was mostly due to fewer late sPTBs being born in SingHealth institutions (from 9.3% to 8.2%, $P<0.001$),

Table 1. Total term births and PTBs according to gestational age at delivery in SingHealth (KK Women's and Children's Hospital and Singapore General Hospital) and Singapore (singleton and twin pregnancies).

Year	Total births		Late PTBs		ExPTBs and vPTBs	
	SingHealth, no. (% of PTB)	Singapore, no. (% of PTB)	SingHealth, no. (% of PTB)	Singapore, no. (% of PTB)	SingHealth, no. (% of PTB)	Singapore, no. (% of PTB)
2017	13,218 (11.3)	39,615 (8.9)	1230 (9.3)	3139 (7.9)	266 (2.0)	367 (0.9)
2018	13,251 (10.7)	39,039 (8.4)	1159 (8.7)	2900 (7.4)	255 (1.9)	381 (1.0)
2019	13,001 (10.5)	39,279 (8.1)	1132 (8.7)	2851 (7.3)	228 (1.8)	316 (0.8)
2020	12,989 (9.3)	38,590 (7.4)	999 (7.7)	2544 (6.6)	212 (1.6)	305 (0.8)
2021	13,168 (10.3)	38,672 (7.9)	1097 (8.3)	2683 (6.9)	256 (1.9)	353 (0.9)
2022	12,907 (10.2)	35,605 (8.1)	1071 (8.3)	2549 (7.2)	250 (1.9)	323 (0.9)
2023	12,640 (10.3)	33,541 (8.2)	1037 (8.2)	2415 (7.2)	264 (2.1)	333 (1.0)

ExPTBs: extreme preterm births; PTB: preterm births; vPTBs: very preterm births

while rates of ExPTB/vPTB and iPTB remained unchanged. Approximately 60% of PTBs were spontaneous, and 40% were iatrogenic (Table 2).

Multiple pregnancies

Among twin pregnancies, the PTB rate exhibited a significant upward trend from 11.6% in 2017, dropping to 6.8% in 2020, and increasing again to 12.2% in 2023 ($P<0.001$). This fluctuation likely reflects the temporary suspension of assisted reproductive technology (ART) services during the COVID-19 pandemic, followed by a post-pandemic rebound. With adjustment for potential risk factors such as age, race, booking BMI, parity and marital status, women who gave birth in 2023 were 2.21 times (95% CI 1.31–3.75) more likely to have a PTB as compared to 2020, but it was not statistically significant when compared with 2017 (adjusted OR 1.07; 95% CI 0.58–1.98). In twin pregnancies, 62.6% of PTBs were iatrogenic, while 37.4% were spontaneous.

Maternal and neonatal characteristics

Table 3 summarises the demographic characteristics of patients delivering at SingHealth in 2017 to 2023 who experienced sPTB, stratified by gestational age.

Risk factors for sPTB

Multinomial logistic regression identified several key risk factors (Table 4). Advanced maternal age (≥ 35 years), booking BMI ≥ 23 kg/m², single/divorced marital status, primiparity, twin pregnancy and Chinese ethnicity were associated with increased odds of very/extreme sPTB.

ABO blood group and PTB

Univariable logistic regression revealed that mothers with blood group AB were 13% more likely to experience PTB compared to blood group O (OR 1.13,

95% CI 1.03–1.24). Blood groups A and B showed slightly lower elevations in risk (Table 5).

Neonatal sex

No association was found between neonatal sex and sPTB risk ($P=0.589$).

Risk prediction model for sPTB

Using maternal age, ethnicity, marital status, blood group, booking BMI, multiple birth indicator and parity, our XGBoost-based risk prediction model achieved sensitivity of 0.7040 (95% CI 0.6919–0.7159) and specificity of 0.6647 (95% CI 0.6554–0.6739), with an area under the receiver operating characteristic (AUROC) curve of 0.7491 (95% CI 0.7414–0.7568) on the test set (Fig. 1). The most important predictors (based on Shapley Additive Explanation values) were booking BMI, ethnicity, age and blood group. When multiple pregnancy indicator was excluded from the database, we had a similar predictive AUROC of 0.7392 (95% CI 0.7309–0.7479) on the test set (Fig. 1).

DISCUSSION

Principal findings

Our analysis showed that Singapore's and SingHealth's PTB rates remained relatively unchanged during the study period.

There was a modest decline only in the number of late sPTBs within the SingHealth population. A possible explanation is that most maternity units in Singapore are able to care for late PTBs in their own units while higher risk PTBs less than 32 weeks are referred into SingHealth for tertiary care. This supports the recognition of better prognosis of in-utero rather than ex-utero transfer of PTB to specialist neonatal units.

ExPTB and vPTB rates were unchanged, posing a continued challenge in PTB prevention as this is the

Table 2. Total PTBs in SingHealth (KK Women's and Children's Hospital and Singapore General Hospital) according to subtype (singleton and twin pregnancies).

Year	Total PTBs, no. (%)	sPTBs, no. (%)	iPTBs, no. (%)
2017	1496 (11.3)	956 (63.9)	540 (36.1)
2018	1410 (10.6)	876 (62.1)	534 (37.9)
2019	1351 (10.4)	849 (62.8)	502 (37.2)
2020	1197 (9.2)	793 (66.2)	404 (33.8)
2021	1334 (10.1)	814 (61.0)	520 (39.0)
2022	1303 (10.1)	827 (63.5)	476 (36.5)
2023	1281 (10.2)	737 (57.5)	544 (42.5)

iPTBs: iatrogenic preterm births; PTBs: preterm births; sPTBs: spontaneous preterm births

Table 3. Demographic characteristics of patients by type of sPTB.

Characteristics	Term births (n=59,548)	Late PTBs (n=3186)	ExPTBs/vPTBs (n=610)
Ethnicity, no. (%)			
Chinese	24,033 (40.4)	1223 (38.4)	303 (49.7)
Malay	16,623 (27.9)	934 (29.3)	118 (19.3)
Indian	6406 (10.8)	357 (11.2)	72 (11.8)
Others	12,486 (21.0)	672 (21.1)	117 (19.2)
Age, no. (%)			
<30 years	20,424 (34.3)	1102 (34.6)	131 (21.5)
30–34 years	22,991 (38.6)	1129 (35.4)	232 (38.0)
≥35 years	16,133 (27.1)	955 (30.0)	247 (40.5)
Parity, no. (%)			
1	27,332 (45.9)	1457 (45.7)	338 (55.4)
2	18,726 (31.5)	932 (29.3)	173 (28.4)
≥3	13,490 (22.7)	797 (25.0)	99 (16.2)
Booking BMI, no. (%)			
<23 kg/m ²	24,604 (41.3)	1181 (37.1)	218 (35.7)
≥23 kg/m ²	34,944 (58.7)	2005 (62.9)	392 (64.3)
Marital status, no. (%)			
Married	57,660 (96.8)	3010 (94.5)	575 (94.3)
Single/divorced	1888 (3.2)	176 (5.5)	35 (5.7)
Type of birth, no. (%)			
Singleton	59,241 (99.5)	2960 (92.9)	554 (90.8)
Twins	307 (0.5)	226 (7.1)	56 (9.2)

BMI: body mass index; ExPTBs: extreme preterm births; PTBs: preterm births; sPTB: spontaneous preterm birth; vPTBs: very preterm births

group with significant effects on neonatal mortality and morbidity.^{16,17} Notably, SingHealth managed a growing proportion of PTBs in earlier gestation (78% in 2023), highlighting the cluster's expanding role in caring for high-risk pregnancies.

SingHealth has set up a PTB clinic in 2022 in attempt to provide specialised care for patients at risk of PTB. We will now apply our prediction model to identify women at risk of PTB and provide personalised and early intervention.

Comparisons with other studies

The PTB rates we observed align with global trends, where overall PTB rates have not declined significantly.⁴ The higher PTB rates among Chinese

mothers in Singapore compared to China (6.1%)⁴ may reflect distinct environmental or lifestyle factors. In addition, although socioeconomic status is associated with higher risk of PTB, this may not necessarily apply to our Singapore population. This is highlighted when we used the monthly median household income differentiated by ethnic groups as our proxy for socioeconomic status. Here, the Indian ethnic group had the highest monthly median income followed by the Chinese and Malay ethnic groups. Meanwhile, Malay women had relatively lower PTB rates, which is intriguing given potential socioeconomic disadvantages.³² These findings underscore the complexity of PTB aetiology, where genetic, cultural and healthcare access variables interact.

Table 4. Multinomial logistic regression analysis of risk factors for sPTB.

Characteristics	Late PTBs vs term birth OR (95% CI)		ExPTBs/vPTBs vs term birth OR (95% CI)	
	Singleton and twin pregnancies	Singleton pregnancies	Singleton and twin pregnancies	Singleton pregnancies
Ethnicity				
Chinese (Reference)	1.00	1.00	1.00	1.00
Malay	1.08 (0.99–1.19)	1.09 (0.99–1.20)	0.73 (0.58–0.92)	0.70 (0.55–0.89)
Indian	1.09 (0.96–1.23)	1.09 (0.96–1.23)	0.99 (0.76–1.29)	0.93 (0.71–1.23)
Others	1.06 (0.96–1.17)	1.07 (0.97–1.19)	0.89 (0.71–1.11)	0.83 (0.66–1.05)
Age				
<30 years (Reference)	1.00	1.00	1.00	1.00
30–34 years	0.92 (0.84–1.00)	0.92 (0.84–1.01)	1.66 (1.32–2.07)	1.69 (1.34–2.14)
≥35 years	1.07 (0.97–1.18)	1.08 (0.98–1.20)	2.59 (2.06–3.26)	2.79 (2.20–3.55)
Parity				
1 (Reference)	1.00	1.00	1.00	1.00
2	0.92 (0.84–1.01)	0.91 (0.84–1.00)	0.65 (0.54–0.78)	0.63 (0.51–0.76)
≥3	1.07 (0.97–1.18)	1.07 (0.97–1.18)	0.50 (0.39–0.63)	0.48 (0.37–0.61)
Booking BMI				
<23 kg/m ² (Reference)	1.00	1.00	1.00	1.00
≥23 kg/m ²	1.18 (1.09–1.28)	1.18 (1.09–1.27)	1.38 (1.16–1.64)	1.37 (1.15–1.64)
Marital status				
Married (Reference)	1.00	1.00	1.00	1.00
Single/divorced	1.84 (1.57–2.17)	1.84 (1.56–2.17)	2.36 (1.66–3.36)	2.33 (1.62–3.35)
Type of birth				
Singleton (Reference)	1.00		1.00	
Twins	15.21 (12.74–18.15)		16.99 (12.57–22.97)	

BMI: body mass index; CI: confidence interval; ExPTBs: extreme preterm births; OR: odds ratio; PTBs: preterm births; sPTB: spontaneous preterm birth; vPTBs: very preterm births

Table 5. Association between blood groups and PTB.

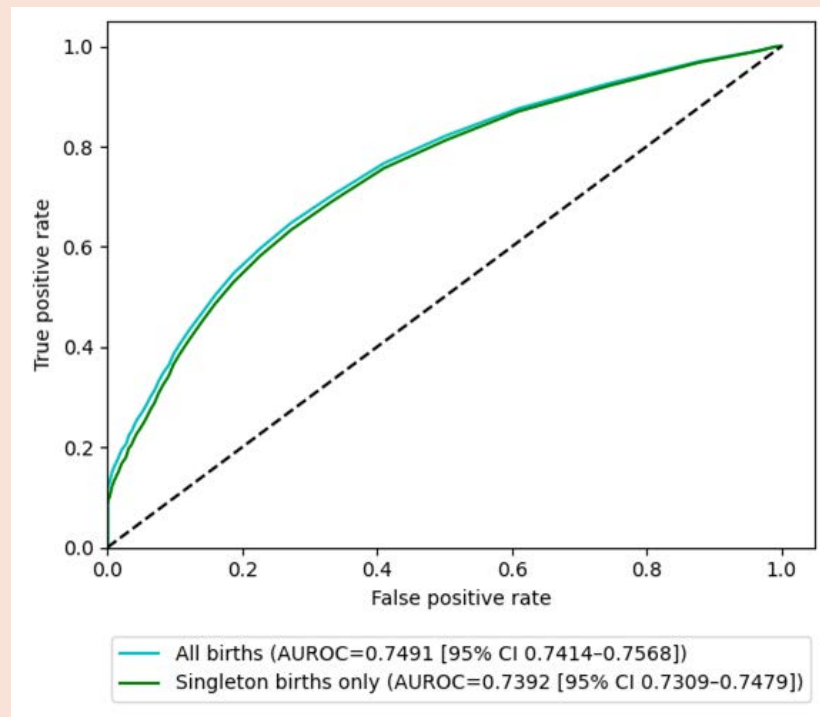
Blood group	OR (95% CI)
O	Reference
AB	1.13 (1.03–1.24)
A	1.09 (1.02–1.15)
B	1.06 (1.00–1.13)

CI: confidence interval; OR: odds ratio; PTB: preterm birth

Risk factors

Advanced maternal age (≥35 years), higher booking BMI (≥23 kg/m²) and single/divorced marital status were all found to significantly increase PTB risk, consistent with existing evidence.^{14,20–23,25,26} Our results also point to primiparity as a risk factor and identify Chinese ethnicity as an important consideration. The role of ABO blood group in influencing PTB risk, particularly blood group AB conferring a higher risk than blood group O, warrants further mechanistic investigation.^{29,30,33}

Fig. 1. Area under the receiver operating curve for preterm birth detection.



CI: confidence interval

Multiple pregnancies

Twin pregnancies were associated with considerably elevated PTB risk.^{14,18} The observed fluctuations in twin PTB rates, especially around 2020, likely reflect changes in ART availability during the pandemic, followed by increased demand post-pandemic.

Risk prediction model

Our XGBoost model demonstrated moderate performance (AUROC $\approx$ 0.75) in identifying women at risk for sPTB using demographic and basic clinical features alone. This is the first reported paper using a machine learning model to predict risk of sPTB incorporating maternal blood group in a large study (n=30,827) of a multi-ethnic population, and it underlies the potential benefit of including more information to improve predictive accuracy. Due to the multifactorial associations with PTB, it is envisaged that prospective studies incorporating more detailed clinical information, such as cervical length measurements, previously identified biomarkers, microbiota flora and possible multi-omics in pregnancy associated with PTB, would certainly enhance the goal of early risk stratification to provide personalised care in diverse populations.

Strengths and limitations

A key strength of this study is the large sample size and comprehensive data collection from these 2

maternity centres with specialist neonatal units on-site. Specifically, as SingHealth accounts for approximately 80% of ExPTBs and vPTBs, we are better able to study the characteristics of this population with the highest risk of perinatal and infant mortality, enhancing the generalisability of the findings for this group within Singapore. However, limitations include the retrospective design and potential for unmeasured confounding factors. Incomplete data on certain variables (e.g. smoking status, illicit drug use, prior cervical procedures, cervical length measurement) may have limited the analysis. Additionally, data prior to 2017 were unavailable due to transition from hardcopy to electronic record. In our risk predictive model, we only included information that we could accurately obtain to form our database for artificial intelligence model analysis. In addition, there was no second set of data available for validation.

Implications for practice and research

The findings demonstrate that there are geographical and cultural differences to the multifactorial cause of PTB. This highlights the need for targeted interventions to reduce PTB rates specific for each region, particularly among high-risk groups identified in this study.

Personalised screening could help identify those who may benefit from preventive strategies. Those currently available are of limited success or perhaps misdirected as demonstrated by the stable PTB rates.

Our predictive model could be refined further by incorporating multiomics in pregnancy, biomarkers and cervical length measurements, together with emerging and improving technologies in machine learning. Further research is needed to explore the role of ABO blood groups and other novel risk factors in PTB aetiology.

CONCLUSION

Despite a slight decline in late PTBs in the SingHealth population, the overall PTB rate in Singapore has remained relatively unchanged between 2017 and 2023. This study highlights several key risk factors—Chinese ethnicity, advanced maternal age, higher BMI, primiparity, single/divorced marital status and maternal blood group AB. This points to opportunities for tailored screening and interventions. Our machine learning model provides moderate predictive value, underscoring the need for further refinements. Ongoing research integrating additional clinical and biological markers may enhance PTB prevention efforts and improve neonatal outcomes both in Singapore and globally.

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Ethics statement

Ethical approval was obtained from the SingHealth Institutional Review Board (2023-2278).

Declaration

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Supporting quadruple aim in primary care using artificial intelligence

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Global healthcare challenges are pervasive, hindering delivery of effective, high-quality and sustainable care to populations worldwide. The quadruple aim in healthcare is a strategy to address these challenges by (1) improving population health, (2) enhancing the patient care experience, (3) reducing per capita healthcare costs, and (4) promoting the well-being of healthcare workers.¹ A resilient health system relies on sufficient, well-trained health workers, yet the World Health Organization estimates a global shortfall of 11 million by 2030, affecting all countries to varying degrees.² Achieving these aims requires innovative technologies and tools, such as artificial intelligence (AI).

AI enables machines to simulate aspects of human learning, problem-solving, decision-making and pattern recognition.³ Early AI, based on neural networks inspired by the human brain, comprises interconnected nodes that learn from data to make predictions before it evolved to machine learning (ML). ML enables computers to learn from data and make decisions without explicit programming. It is widely used for data analysis, predictive analytics and risk assessment in healthcare.⁴

Deep learning (DL), a subset of ML, employs multilayered neural networks to analyse complex patterns, excelling in tasks like medical imaging and natural language processing. Transformer models have accelerated AI, particularly in language processing and multimodal applications like image and video generation. These breakthroughs have been escalated by graphics processing units (GPUs),⁵ which enable efficient large-scale training and sophisticated model development to solve complex challenges across industries, including healthcare.⁴

Singapore is rapidly emerging as a global AI hub, adopting the National Artificial Intelligence Strategy (NAIS) in 2019 for AI development, use and governance.⁶ The local clusters of academic public primary care clinics have tapped their vast patient data and electronic medical records (EMR) systems and dovetailed NAIS to develop and test AI solutions.

Such applications, if proven to address the issues, will spread to the private general practice clinics through the primary care networks.

The current impetus to apply AI originates from a surge in chronic complex diseases amid an ageing population. Managing geriatric patients with multimorbidity is tough, compounded by the growing burden of administrative documentation in electronic systems, which are inundated with information from multiple healthcare partners. This strain contributes to widespread burnout in an overstretched healthcare ecosystem. AI is widely perceived as a tool to address these challenges, but requires clear goals, high-quality data collection, appropriate technology selection, pilot testing and ongoing evaluation.⁷ Collaboration with primary care professionals (PCPs), training and regular ethical reviews help mitigate AI bias. However, AI deployment must align with local healthcare priorities, policy directives and supported by AI expertise and resources within the primary healthcare system.⁸

Improving the health of the population

Individuals from diverse demographic, clinical and socioeconomic backgrounds can benefit from AI applications in primary care. AI facilitates diagnosis of medical conditions by speeding up reporting of laboratory and imaging results. For example, diabetic retinopathy is the leading cause of blindness in Singapore. The AI-based SELENA+ system now allows diabetic retinal imaging in primary care to be reported within minutes, which facilitates prompt referral of patients with such complication to ophthalmologists for treatment (Table 1).⁹

Neonatal jaundice (NNJ), which can cause severe cerebral damage from kernicterus in infants, is commonly evaluated in primary care facilities. BiliSG, an AI-enabled smartphone-based application, has been developed and validated to assess NNJ.¹³ It aims to decentralise NNJ management for its assessment by parents conveniently at home (Table 1).

Millions of in-person consultations were completed annually in primary care, generating huge volumes of

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Table 1. Summary of AI tools.

Tool name	Function	Aim	Data and preparation	Model type	Evaluation stages	Deploy plan
SELENA+ ¹⁰	Enable rapid reporting of diabetic retinal imaging	Improve patient and provider experience Improve health outcome Reduction of cost	Trained on more than half a million non-identifiable images from the Singapore Integrated Diabetic Retinopathy Programme, a screening initiative that was launched in 2010	Deep learning system	Completed extensive validation and is now commercialised	SELENA+ is currently implemented as a tool for routine diabetic retinal screening nationwide across all polyclinics
BiliSG ¹¹	Decentralisation of NNJ management	Improve patient and provider experience Improve health outcome Reduction of cost	Currently the largest study population on mobile health app to assess NNJ in the world with the data from over 500 neonates to develop the AI software	Machine learning system	Completed local validation study; commencing validation for different phone types and initiating implementation for scaling up	BiliSG will be rolled out to primary care clinics across Singapore and beyond, pending outcome of the implementation study
PREDICT.AI ¹²	To enable patients with T2DM to understand their complication risks using real-world data, and allow providers to use narrative to counsel patients on lifestyle modifications and medication adherence	Improve patient and provider experience Improve health outcome Reduction of cost	The software leverages EMR data of over 80,000 patients with T2DM who are managed in a large primary care institution	Machine learning system	Predict.AI is currently being evaluated in a randomised controlled trial	Primary healthcare professionals will be trained to use Predict.AI for scaling up across primary care clinics, pending outcome of the randomised controlled trial

AI: artificial intelligence; EMR: electronic medical record; NNJ: neonatal jaundice; T2DM: type 2 diabetes mellitus

patients' clinical, prescription, laboratory and imaging data to create risk stratification or predictive models using ML and deep learning. PERDICT.AI is a software that enables primary care professionals (PCPs) to quickly identify high-risk patients with poor diabetic control, recommend medications based on real-world effectiveness data, discuss person-centric lifestyle modifications, and facilitate shared medical decision-making.¹⁴ It is currently being evaluated in a randomised controlled trial. The intention is to adopt it as an additional tool to personalise diabetes care in the community (Table 1), which aligns with the recommendations of the Health Foundation in the UK, on harnessing AI potential in clinical practice.¹⁵

Enhancing care experience

Long wait times and limited accessibility are common barriers in primary care. AI-powered tools can improve access by streamlining remote appointment scheduling, diagnostics, and follow-ups through AI-chatbots.¹⁶ These tools relieve mundane tasks such as answering frequently asked questions like operating hours and service costs, while AI chatbots provide intuitive and personalised responses, accommodating diverse text constructs, sequencing and languages, including voice annotations. These tools empower patients and the public to access timely, affordable healthcare services efficiently.

Virtual health assistants (VHAs) are AI tools that triage and identify individuals' care needs and direct them to appropriate providers for timely management.¹⁶ With their personalisation and portability, VHAs also serve as patient companions, fostering continuity of care and empowering self-efficacy through knowledge sharing and positive motivation. These VHAs offer tailored, easy-to-understand information about specific conditions, actionable care plans, and guidance towards health goals, allowing users to address concerns on demand. Currently, these VHAs are being evaluated for the acceptance, utility, safety and effectiveness in disease management by target users.

Reducing healthcare per-capita cost

Chronic diseases are lifelong conditions requiring regular monitoring to maintain disease control and prevent complications. With their increasing prevalence in an ageing population, episodic in-person medical reviews will place increasing strain on the healthcare system. Remote telemonitoring, where patients use reliable, licensed devices to track clinical parameters and transmit data to their healthcare providers, ensures continuity of care in between clinician-patient interactions. Real-time analysis of telemonitoring data using AI can detect

abnormal trends, identify at-risk individuals for timely interventions, and address defaulters.¹⁷ AI tools further enhance telemedicine by optimising operational efficiency, reducing no-shows, managing medication supply and demand, and enabling agile deployment of trained telehealth professionals. On a per-patient basis, AI is expected to be cost-efficient, offering scalable solutions to mitigate rising shortage in healthcare manpower.

Boosting healthcare workers' well-being

During in-person consultations, AI-enabled ambient dictation technology is used in automated voice-to-text transcription, seamlessly documenting clinical notes into EMR systems.¹⁸ These digital scribes alleviate PCPs from time-consuming documentation, allowing them to focus on face-to-face interactions with patients, fostering rapport and enhancing clinician-patient relationships. Auditing the transcripts generated by these scribes requires effort, but it also creates an opportunity for PCPs to reflect on their prior patient interaction and care delivery and, if necessary, take remedial measures to address any missteps or lapses. Hence, allowing AI tools to replace repetitive manual tasks without compromising care provision and job security, which can improve staff morale and well-being, both physically and psychologically. These tools free up valuable time, enabling PCPs to spend more time with their families or pursue training for higher-value roles, enhancing their career growth and work-life balance. However, the non-deterministic nature of generative AI can introduce hallucinated or inaccurate content, which poses downstream risks to clinical decision-making. Hallucination can be mitigated through the careful use of guardrails, such as precise prompt engineering, retrieval-augmented generation and clinical finetuning. Therefore, robust validation and clinical studies are essential to select the appropriate AI solutions to ensure safety, minimise verification, and support responsible adoption.¹⁵

AI is transforming learning beyond traditional rote memorisation. AI-powered platforms, trained on extensive knowledge corpus from textbooks and medical journals, provide deep insights across a wide range of specialties.¹⁹ Instead of spending hours combing through books and papers, PCPs can now access precise, real-time answers and the latest updates through natural language platforms. Moreover, AI streamlines medical literature search and review, enabling quick access to relevant journal articles. As an e-learning companion, AI adapts to the nuances of various medical topics and personalises the learning experience, teaching PCPs intuitively and effectively to enhance their understanding and application of medical knowledge.

Transforming primary care using AI: Steps ahead

The transition to an AI-powered primary care practice requires a phased approach that integrates advanced technologies while ensuring quality care and regulatory compliance. The process begins with a comprehensive technology audit, reviewing existing systems, such as EMRs, billing software and telemedicine platforms to identify areas compatible with AI-solutions. Simultaneously, workflow and system interoperability analyses are critical to achieving seamless integration of AI tools into the practice's operations. Since many AI solutions are cloud-based, robust cybersecurity measures must be implemented to safeguard sensitive health data and prevent tampering, ensuring secure and scalable data storage systems that uphold patient confidentiality and trust.

Engaging stakeholders early to gather feedback is crucial to identify pain points within the system and prioritise areas where AI can add value. Healthcare leaders' support is vital for end-to-end AI implementation in clinical practice.²⁰ The leaders must understand the various AI systems, proactively integrating or modifying existing work routines and processes, and reviewing its deployment progress using efficiency, safety and access metric-indicators.²⁰

Equally important is training staff, including PCPs and administrators, to elevate their AI literacy.²¹ PCPs need to understand that AI is designed to assist, not replace their work. Emphasising human-AI collaboration in clinical practice can help reduce adoption resistance. PCPs should receive regular updates on emerging capabilities and new applications to stay informed and keep up with rapid AI advancements.^{21,22} Their capacity for innovative AI adoption should be considered a key attribute when hiring in the healthcare industry.

Patients and the public are also key stakeholders in AI adoption.²³ Ensuring that AI solutions are explainable fosters transparency, builds confidence and promotes wider acceptance in the community. Engaging the community through forums, continuing medical education and community platforms allows PCPs and institutional leaders to demonstrate how AI can enhance care and decision-making, debunk misconceptions, address concerns and set realistic expectations for its role in primary care.²⁴

AI implementation in healthcare has its challenges. Algorithmic bias can lead to disparities in patient outcomes, while data privacy and cybersecurity risks raise concerns about the security of sensitive medical information. Clinician resistance, often driven by trust issues and workflow disruptions, can hinder adoption. Rigorous validation is essential to ensure AI systems are accurate, reliable and aligned with clinical standards.²⁵ Addressing these challenges eases

the responsible and effective integration of AI into healthcare.²⁶

AI in primary care will evolve as developers translate innovative ideas into novel applications. Collaborating with AI solution providers and medical technology companies to co-create and adopt cutting-edge solutions is essential to stay ahead of the curve.²⁷ Partnering governmental policymakers and insurance providers to conduct cost-effectiveness analyses of AI interventions and care models will ensure fiscal sustainability for an AI-driven primary healthcare ecosystem.²⁸ Establishing AI-specific performance metric-indicators, such as patient outcomes, operational efficiency and employee satisfaction, is equally critical.²⁹ Regular audits of AI tools and systems, guided by AI engineers, experts and ethicists, minimise bias and ensure ethical use.³⁰

Primary care in Singapore is currently at the crossroads of AI transformation. Upskilling AI-trained PCPs and addressing AI fallacies improve implementation outcomes, mitigates bias risk and expedites quadruple aim achievement.

Ethics statement

Not applicable.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Keywords: artificial intelligence, care experience, healthcare cost, population health, primary care, quadruple aim, workforce well-being

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Making better clinical decisions: How doctors can recognise and reduce bias and noise in medical practice

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ABSTRACT

Clinical reasoning and decision-making are essential to medical practice, where poor clinical judgement can lead to serious diagnostic errors, suboptimal use of diagnostic tests and investigations, flawed management strategies and ultimately, adverse patient outcomes. It is known that in real-world clinical environments, clinicians often rely on intuitive judgements for decision-making, due to natural proclivities for pattern-recognition and retrieval of pre-existing illness scripts, as well as out of practical necessity to be efficient in fast-paced work environments with high patient volume and cognitive load. Yet, an over-reliance on intuitive judgements can result in cognitive errors. While biases associated with heuristics-based or intuitive thought processes are often discussed in literature, there is also a lesser entity of noise that affects consistency and reliability of clinical decision-making. In this article, we highlight the importance of learning foundational principles of clinical reasoning and understanding how cognitive errors happen in medical training, and suggest a series of educational pedagogies and workplace-based interventions that could help to cultivate and optimise medical decision-making in real-world practice.

Keywords: *clinical decision-making, clinical reasoning, cognitive bias, diagnostic errors, medical education, noise*

INTRODUCTION

In 1999, the US Institute of Medicine released a landmark report “To Err is Human: Building a Safer Health System” where it highlighted the high prevalence of preventable medical errors,¹ which led to concrete measures that resulted in significant improvement in patient safety standards. Two

decades later, there has now been a call to address the epidemic of diagnostic errors,^{2,3} where it has been reported that nearly 800,000 Americans suffer from disability or mortality annually due to misdiagnoses.² Apart from diagnostic errors, clinicians also often make poor decisions in other areas of medical practice, such as ordering of inappropriate investigations,⁴ making unnecessary subspecialty referrals,⁵ and lack of person-centred clinical management,⁶ which are attributable to suboptimal clinical reasoning and decision-making skills in real-world practice environments.⁷ As internal medicine physicians from different subspecialties who are heavily involved in both undergraduate and postgraduate medical education, we realised that the present focus on developing foundational content knowledge, clinical skills and expertise within the confines of a competency-based medical education system is by itself, inadequate in helping trainees navigate the complexities of real-world clinical decision-making. Therefore, in this article, we sought to discuss the importance of teaching and learning foundational principles of clinical reasoning, and understanding of how cognitive errors happen. We also propose educational pedagogies and workplace-based interventions that could help to cultivate and optimise physicians’ decision-making in real-world practice.

Clinical reasoning and sources of error in medical decision-making

Clinical reasoning can simply be defined as the thinking and decision-making processes associated with clinical practice,⁸ which involves systematically observing, collecting, analysing and interpreting patient information to arrive at a diagnosis and

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management plan.⁹ Yet this process is highly influenced by one's cognitive capacity, capabilities, habits, biases and limitations, emotional/affective overlay, and other external influences,⁷ thereby resulting in heterogeneous standards of clinical decision-making in real-world practice.

Conventionally, clinical decision-making can be understood from the traditional 2-system model of cognition, which comprises a fast-paced, unconscious, pattern recognition-based intuitive thinking (system 1) and a slower, deliberate, more analytical form of cognition (system 2).^{3,10,11} In practice, intuitive thinking remains, by far, the predominant mode of clinical reasoning because they are more naturistic (clinicians as trained diagnosticians), practical (in busy, high-acuity clinical environments) and potentially more accurate in complex or uncertain clinical situations (i.e. less-is-more by excluding irrelevant cues).¹² In fact, physicians are fundamentally intuitive Bayesian diagnosticians who subconsciously form probabilistic estimates of likelihood of disease and treatment success in every patient encounter, based on clinical and investigative cues, and constantly refine and recalibrate with new incoming environmental signals.¹³

Nonetheless, intuitive clinical judgements can often lead to decisional errors, which are attributable to the presence of cognitive bias and noise.¹⁴

Cognitive bias in clinical judgements refer to uniformly skewed patterns of systematic errors arising from common cognitive dispositions to respond.^{14,16} Till date, there have been more than 100 cognitive biases described in clinical practice.¹⁷ For example, anchoring bias occurs when physicians quickly latch on to key features early in the encounter and focus further evaluation purely on proving or disproving the generated hypotheses—which can lead to premature diagnostic closure.¹¹ Similarly, confirmation bias happens when physicians choose to pay selective attention to clinical cues that support their provisional diagnosis while neglecting or minimising conflicting evidence.¹¹ In availability bias, physicians may overestimate the likelihood of diseases that are easily recalled such as conditions that they have recently treated, whereas in representative heuristic bias, atypical disease manifestations may be neglected due to a tendency to look for prototypical illness patterns.¹¹ In recent years, implicit biases—which are inherent stereotypes against certain patient populations—such as marginalised persons, psychiatric patients, drug or alcohol abusers, those with health-seeking behaviours, are increasingly recognised as a root cause of inappropriate dismissal of valid clinical concerns (i.e. medical gaslighting).^{11,18} Similarly, visceral bias occurs when physicians' judgements are clouded/influenced by their emotional responses to the patient encounter such as presence

of counter-transference or specific liking/dislike of the patient.¹¹

In contrast, noise refers to an unacceptable degree of practice variability that occurs when different individuals or the same individual under different circumstances make significantly different decisions on a similar problem.¹⁵ In clinical practice, this not only leads to decisional errors but also causes inconsistent, unreliable medical decision-making that erodes patient confidence.¹⁹ Causes of inter-clinician variance may be attributable to differences in knowledge, expertise, resources, medical training, past/recent experiences, unique clinical consultation or management styles, subjectivity of the clinical entity being evaluated and different weightage given to cue relevancy.^{12, 15, 19} For example, a previous cohort study of Medicare beneficiaries in the US found significant regional differences in Medicare spending and health services rendered (e.g. inpatient consultations, major/minor procedures, patient disposition) for similar medical conditions.²⁰ Interestingly, there is also an intra-clinician variability when the same physician makes different judgements for an exact same clinical scenario but under different circumstances.¹⁹ This can happen due to changes in the individual's physical and mental state, such as fatigue or prevailing emotions,¹⁹ as well as other situational/environmental factors.²¹ For example, a previous study found that decision fatigue led to primary care physicians prescribing more antibiotics for acute respiratory illness towards the end of clinic sessions.²² Overall, in a healthcare system with excessive, unregulated noise, patients will face unacceptably high degrees of variability and inconsistency in clinical practices, management standards and eventual outcomes depending on where and with whom they seek medical consultation.

Pedagogical and workplace-based interventions to reduce bias and noise

We herein propose pedagogical and workplace-based interventions that may help to mitigate the problems of bias and noise in real-world clinical practice.

First, foundational teaching on Bayesian rules in clinical decision-making¹⁴ could potentially mitigate both bias and noise, as it addresses base-rate neglect and inter-clinician variability in decision-making through the use of common first principles. To standardise intuitive thinking when faced with clinical problems, clinicians may make use of simple Bayesian rule-of-thumbs such as testing and treatment thresholds to standardise clinical decision-making.¹⁴ For example, patients with clinical presentations that give rise to a low pre-test probability below testing threshold would be worked up for alternative diagnoses, whereas those with high pre-test likelihood of disease crossing

treatment threshold may be empirically started on treatment. For patients who are between testing and treatment thresholds, rule-in and rule-out tests may be selected depending on the likelihood of disease and management intention.

To improve the accuracy of clinical predictions in an intuitive Bayesian model, medical educational pedagogies can emphasise illness scripts development through problem-based learning (ideally with real cases contextualised to a local setting), self-explanations, concept mapping and script concordance tests.²⁶ Moreover, in constructing illness scripts, trainees must be specifically taught the base-rate prevalence in specific patient populations, as well as how the presence or absence of clinical risk factors and/or symptoms/signs will affect pre-test probabilities.²⁷ Then, to cultivate self-regulated learning and recalibration of internal clinical judgements/predictions, metacognitive practice should be encouraged, through think-aloud exercises,²⁸ verbalisation of propositional confidence of one's clinical assessments,²⁹ and retrospective chart-stimulated recall sessions³⁰ as part of workplace-based pedagogy.

Over the years, many cognitive de-biasing or forcing strategies have been proposed to deal with specific, identified biases in decision-making.¹⁶ However, in busy clinical environments, we contend that a heuristics-based debiasing approach is likely more efficient and effective than having to perform deliberate analyses of all possible options. For example, to counter anchoring bias and premature diagnostic closure, simple techniques such as ruling out worst case scenario (e.g. to rule out dangerous diagnoses, clinical red flags)¹⁰ or simple aetiological mnemonics (e.g. Vascular, Infection/Inflammatory, Traumatic, Autoimmune, Metabolic, Iatrogenic/Idiopathic, Neoplastic, Congenital, Degenerative, Endocrine)¹¹ can be adopted. In 2012, Shimizu and Tokuda described a novel pivot-and-cluster debiasing strategy, where physicians come up with an initial intuitive (pivotal) diagnosis based on the clinical presentation and surround this diagnosis with a cluster of differentials with similar manifestations.³¹ They further advocate the contemplation of diagnostic confidence, where a greater degree of diagnostic uncertainty would lead to the expansion of the clusters of differential diagnoses, including those with lesser diagnostic similarities to also be considered.³¹ To avoid confirmation bias that leads to tunnelled vision, actively framing differentials using factors for and against each diagnosis is a useful countermeasure.¹¹ Last, implicit bias can be mitigated through improved awareness of its entity, reflective practice and even undergoing implicit association tests, which are

psychological assessments developed to reveal subconscious associations and biases held by individuals towards other people or entities.³²

To counter the more pervasive noise (i.e. inconsistencies) in clinical practice, a multi-pronged approach is needed through both pedagogical and workplace-based interventions. First, medical trainees must learn to craft accurate problem statements/representations with the right semantic qualifiers to actively sieve out pertinent information amid irrelevant details (background noise).³³ Second, institutional/consensus guidelines, protocols and decision pathways¹⁹ are needed to improve standardisation of clinical decision-making at the local practice. Third, decision hygiene can be optimised through aggregate judgements,¹⁵ such as round-table discussions, departmental grand rounds or meetings to evaluate complex clinical cases. However, the effectiveness of aggregate judgements in optimising decision-making is contingent on avoidance of groupthink, and requires an open culture of holding objective and frank clinical discussions without fear of reprisal.¹⁹ Finally, to mitigate intra-clinician variability in decision-making due to situational or emotional influences on clinical judgement, cognitive-behavioural self-regulation techniques and external environmental modifications are important. To avoid letting emotional encounters cloud clinical judgement, physicians may practise mindfulness (acceptance of current emotions without pre-judgements) and adopt cognitive-behavioural techniques aimed at reframing negative thoughts and avoiding maladaptive actions. For example, instead of engaging in conflicts or avoidance behaviours in a difficult patient encounter, the physician may attempt to directly address the ongoing tension and identify the underlying reason(s) for the patient's behaviour. Lastly, workplace-based interventions such as mandated rest or mental breaks, reduction in work intensity/interruptions, adequate clinical consultation time, and better clinical support systems are important to reduce errors from excessive cognitive load and decisional fatigue. Behavioural nudges, such as pre-set default options to optimise medication prescriptions,³⁴ can also be useful to facilitate improved decision-making under rushed or stressful situations.

CONCLUSION

In summary, we highlighted the importance of understanding foundational Bayesian principles of clinical reasoning, and sources of cognitive errors in the form of bias and noise. We further discussed a series of practical pedagogical and workplace-based interventions that could strengthen clinical reasoning and fidelity of decisional processes in real-world clinical practice.

Ethics statement

Not applicable.

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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Strategic response to mpox in the Singapore Armed Forces: Military public health collaboration and preparedness

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Dear Editor,

The Singapore Armed Forces (SAF) has long prioritised infectious disease management as a critical component of military readiness. Mpox, a zoonotic viral disease caused by the monkeypox virus, presents unique challenges due to its transmissibility, potential for severe outcomes, and the logistical vulnerabilities of military environments. With frequent deployments to diverse regions and close living conditions, military personnel are particularly susceptible to outbreaks of emerging infectious diseases.^{1,2} In response to the global mpox outbreaks in 2022 and 2024, the SAF implemented a phased and adaptive strategy that underscores the value of proactive military health planning and robust civil-military collaboration.

The SAF's initial response in 2022 followed the World Health Organization's (WHO) declaration of mpox as a public health emergency of international concern.³ During this phase, early containment measures were paramount. Routine health screenings and symptom checks—targeting signs such as fever, rash and lymphadenopathy—were instituted to facilitate early detection of potential cases.⁴ Educational campaigns emphasised routes of transmission, such as contact with infectious lesions and respiratory droplets, and the importance of personal hygiene practices and symptom reporting.⁴ SAF commanders played a pivotal role in reinforcing compliance with preventive measures, cultivating a culture of vigilance across all ranks. The SAF also established isolation facilities to manage suspected cases and maintained robust personal protective equipment stocks to protect healthcare providers.

Although the SAF did not experience mpox outbreaks in 2022, contingency plans were developed for targeted vaccination of high-risk personnel, including healthcare workers and potential servicemen deployed to regions with active outbreaks. A vaccination census conducted in 2024 found that most active personnel were young, full-time national

servicemen. Due to operational constraints, we are unable to disclose the exact percentage of personnel who had received smallpox vaccination, but the overall rate was low. This highlighted the need for ongoing risk assessments and preventive strategies. Collaboration with Singapore's Ministry of Health (MOH) enabled SAF to access national vaccine reserves and integrate vaccination strategies into broader public health efforts.⁵

The 2024 mpox outbreak presented additional challenges due to the emergence of the Congo Basin/clade I, which was initially believed to be highly virulent but has since been reassessed as having varying severity between sublineages.⁶ In response, the SAF expanded its measures, building on the lessons learned in 2022. Border control protocols were strengthened, incorporating intensified health declarations, enhanced temperature screenings, and monitoring of personnel returning from high-risk regions. These measures were implemented primarily for early identification of potential cases among returning servicemen.

Risk assessments became a cornerstone of the SAF's response strategy in 2024, conducted in close partnership with the MOH. These assessments evaluated the epidemiological risks of deployment destinations, enabling SAF to tailor preventive measures and prepare contingency plans for potential mpox cases. Personnel returning from high-risk areas were subjected to additional monitoring, including health checks and symptom surveillance, ensuring rapid identification and containment of suspected cases.

A notable enhancement was the establishment of in-house diagnostic capabilities. Through collaboration with the Defence Science Organisation (DSO), the SAF procured and deployed diagnostic tools within its medical facilities, enabling rapid mpox testing. This initiative significantly reduced reliance on external laboratories, ensuring swift case identification and containment—particularly critical for military forces

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operating in remote or resource-limited environments. In-house diagnostics also enhanced operational resilience, aligning with SAF's broader strategy of minimising disruptions to military readiness during public health emergencies.⁷ While DSO had the capability to augment national testing, it was not required as Singapore's national testing capacity was sufficient, and no cases of mpox were detected within the SAF.

Communication strategies were also refined during the 2024 response, with regular updates and educational briefings delivered through multiple channels. These efforts reinforced awareness of personal hygiene practices, the importance of symptom reporting, and compliance with preventive measures. This comprehensive approach ensured that personnel across all ranks remained informed and engaged in mpox prevention efforts, particularly in dispersed or overseas deployments where communication gaps could otherwise hinder compliance.

The SAF's response to mpox was underpinned by strong partnerships with national agencies, particularly the MOH. This collaboration enabled SAF to align its strategies with Singapore's public health objectives, leveraging access to real-time epidemiological data, vaccine reserves and public health expertise. MOH's guidance also informed SAF's public health messaging, ensuring that communication efforts were scientifically accurate and sensitive. The SAF's Infectious Disease Specialist Advisory Board further contributed by providing technical expertise on infection control protocols, ensuring alignment with national standards and enhancing SAF's overall capacity to manage infectious disease threats.

Despite its successes, the SAF's response to mpox highlighted areas for improvement. The global shortage of mpox vaccines during the 2022 and 2024 outbreaks showed the importance of strategic vaccine stockpiling and pre-arranged procurement agreements.⁸ Such measures would mitigate the impact of future supply chain disruptions, ensuring timely access to critical resources. Furthermore, while in-house diagnostic capabilities provided a significant advantage, the nature of military operations emphasises the need for portable diagnostic solutions that can be rapidly deployed in remote or austere settings.⁷

Future efforts should also explore enhanced digital communication platforms to improve real-time information dissemination. Such tools would enable infection control updates and preventive guidelines to reach personnel more efficiently, particularly those in geographically dispersed locations. By integrating digital solutions with existing communication networks, military organisations can further enhance their capacity to respond to emerging infectious disease threats.

The SAF's phased response to the 2022 and 2024 mpox outbreaks demonstrates the critical importance of adaptability, collaboration and proactive planning in managing emerging infectious diseases. By aligning its efforts with national public health strategies, the SAF safeguarded personnel health while maintaining operational readiness. This approach provides valuable lessons for other military organisations and public health agencies seeking to enhance their preparedness frameworks for emerging infectious diseases.

Ethics statement

Not applicable.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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Keywords: *infectious diseases, military medicine, mpox, operational readiness, public health, surveillance, zoonotic*

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Upper airway stimulation for obstructive sleep apnoea in Asians: A Singapore sleep centre experience

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Dear Editor,

Obstructive sleep apnoea (OSA) is the most prevalent sleep-related breathing disorder, affecting approximately 15% of the global population.¹ In Singapore, 30.5% of the population has moderate-to-severe OSA.² The gold standard treatment, continuous positive airway pressure (CPAP) therapy, often has poor adherence, with only 13.8% of Singaporeans diagnosed with OSA adhering to CPAP therapy after 1 year.³

Upper airway stimulation (UAS), a novel treatment for patients with moderate-to-severe OSA who are intolerant of CPAP therapy, has shown promising results in Europe and America over the last 10 years.⁴⁻⁸ Various studies have shown that UAS, specifically hypoglossal nerve stimulation (HGNS) has high surgical success rates,⁴⁻⁶ compliance rates^{4,5} and patient satisfaction.⁷ HGNS is as effective as CPAP in reducing the apnoea-hypopnoea index (AHI), and may even be more effective in reducing daytime sleepiness.⁸

However, current HGNS registries primarily reflect results from Caucasian patients.⁹ Data from Asian populations are lacking. Asians frequently have distinct craniofacial characteristics (e.g. smaller upper airways and greater neck adiposity), which may affect HGNS efficacy. Therefore, understanding HGNS performance in Asians is essential for delivering equitable care across patient groups.

In Asia, HGNS was first introduced in 2022. Here, we report the clinical characteristics and outcomes of HGNS in Asian patients at a single tertiary Singaporean sleep centre. This study was approved by the SingHealth Centralised Institutional Review Board (IRB 2019–2011). We retrospectively reviewed charts of Asian patients who had undergone UAS

with a unilateral hypoglossal nerve implant (Inspire Medical Systems, Maple Grove, MN, US) and had completed a post-implantation fine-tune sleep study between May 2022 and October 2023.

All patients were diagnosed with OSA based on a preoperative polysomnographic sleep study, conducted as a level 1 in-laboratory attended study (scored according to American Association of Sleep Medicine 2012 guidelines),¹⁰ or a level 3 unattended peripheral arterial tonometry home sleep apnoea test (HSAT; WatchPAT, ZOLL-Iltamar, Caesarea, Israel). Preoperative drug-induced sleep endoscopy (DISE) was routine, and lateral cephalometry done in selected patients.

Patients who met the following criteria were offered UAS: moderate-to-severe OSA (AHI ≥ 15), age ≥ 21 years, body mass index (BMI) < 32 kg/m², intolerant of CPAP therapy, and absence of complete concentric palatal collapse on DISE. Patients underwent unilateral hypoglossal nerve implant via a dual incision approach (neck and chest). The cuff electrode, pressure-sensing lead and implantable pulse generator were placed on the right hypoglossal nerve, the second or third right intercostal space and a right chest subcutaneous pocket, respectively. UAS delivers phasic stimulation to the protruder branches of the hypoglossal nerve, resulting in tongue stiffening via intrinsic transverse/vertical tongue muscle activation and tongue protrusion via genioglossus/hyoglossus activation. This increases retroglossal airway diameter prior to inspiration, thus preventing upper airway collapse in OSA. Patients were observed for 1 night and discharged the next day. The implant was switched on 1 month postoperatively and titration polysomnography (PSG) was performed at 6 months postoperatively.

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Data collected included demographics, BMI, neck circumference, surgical history, Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), PSG parameters, cephalometry and complications. Post-implantation AHI was derived from the in-laboratory titration PSG segment with the fewest respiratory events and tolerable stimulation amplitude. Sleep time for this segment averaged 118.3 ± 77.4 minutes (range 39.4–351.1 min).

Pre- and post-implantation AHI, ESS and FOSQ were compared using paired t-tests. Sleep parameters between patients with skeletal class II (patients with retrognathism) and patients with skeletal class I+III (no retrognathism) were compared using the Mann-Whitney U test. A significance level of $P < 0.05$ was considered statistically significant. Analyses were performed using R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Fifteen Asian patients were included (Table 1), comprising 13 males (88.7%) and 2 females (13.3%), mostly of Chinese ethnicity (80%). The mean age was 53.7 ± 10.0 years (range 34–67 years). The mean BMI was 25.2 ± 2.5 kg/m² (range 21.7–30.2 kg/m²). The mean neck circumference was 38.7 ± 2.6 cm (range 33.9–42.0 cm). Seven and 8 patients underwent preoperative in-laboratory PSG and HSAT, respectively.

At baseline, the mean AHI was 33.6 ± 13.2 events per hour (range 17.0–60.6 events per hour). There were 7 and 8 patients with moderate and severe OSA, respectively. The mean AHI significantly decreased from 33.6 ± 13.2 events per hour pre-implantation to 7.1 ± 5.6 events per hour post-implantation ($P < 0.001$). All 15 patients (100%)

achieved surgical success, defined as $\geq 50\%$ AHI reduction from baseline and a postoperative AHI of < 20 events per hour.¹¹ However, there were no significant changes in the ESS score (from 7.5 ± 4.5 to 7.5 ± 4.8 ; $P = 0.535$) or the FOSQ score (29.6 ± 6.6 to 27.93 ± 9.0 ; $P = 0.309$) post-implantation.

Implant surgeries were uneventful in 87% of cases (13/15). One patient had transient hypoglossal neuropraxia; another had transient marginal mandibular neuropraxia. set as new paragraph were available for 11 patients, of whom 36.4% ($n = 4$) were classified as skeletal class I, 36.4% ($n = 4$) as skeletal class II and 27.3% ($n = 3$) as skeletal class III. A comparative analysis between patients in class II versus those in class I and III revealed no significant differences in all sleep parameters and outcomes.

This study represents the first report of the outcomes of HGNS in an Asian population. For the same severity of OSA, Caucasian patients are known to have higher BMIs and less skeletal restriction than Asians.¹² Our cohort displayed these characteristic differences, with a lower mean BMI and higher mean AHI compared to Caucasian-predominant registries.⁹ Our hypothesis was that skeletal restriction may limit room for tongue protrusion, which could conceivably limit the effectiveness of HGNS. As our initial case series was small, the sample size was likely insufficiently powered to compare AHI reductions between skeletal classes. One key study limitation was the use of postoperative titration PSGs to derive the post-operative AHI, which may not be fully reflective of the whole night's AHI. With a larger sample size and longer-term PSG and patient-reported outcome

Table 1. Characteristics among study participants ($n = 15$).

Characteristics	Mean $\pm$ SD			P value
	Preoperative	Postoperative	Difference	
Age, years		53.7 ± 10.0		NA
Sex, male, no. (%)		13 (88.7%)		NA
Ethnicity		12 Chinese, 1 Malay, 1 Indian, 1 Burmese		NA
BMI, kg/m ²		25.2 ± 2.5		NA
Neck circumference, cm		38.7 ± 2.6		NA
ESS	7.5 ± 4.5	7.5 ± 4.8	-0.46 ± 2.6	0.535
FOSQ	29.6 ± 6.6	27.93 ± 9.0	1.31 ± 4.4	0.309
AHI	33.6 ± 13.2	7.1 ± 5.6	-27.3 ± 11.2	< 0.001

AHI: apnoea-hypopnoea index; BMI: body mass index; ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; NA: not applicable; SD: standard deviation

in future, we aimed to determine if factors such as baseline PSG characteristics, OSA phenotype, and clinical or anatomical differences may impact HGNS success.

In conclusion, our early experience suggests that HGNS is safe and effective in Asian patients with OSA who meet implantation criteria. As HGNS becomes more widely adopted in Asian sleep centres where skeletal restriction is prevalent, future research should focus on whether these anatomical differences warrant adjustments to treatment protocols or eligibility criteria. Addressing these gaps is critical to delivering equitable care and optimising outcomes across ethnicities. We aim to update our analysis with a larger sample size soon.

Ethics statement

Ethics approval was granted by the SingHealth Centralised Institutional Review Board (IRB 2019-2011).

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript. This study did not receive any specific funding.

Availability of data

Additional data may reasonably be requested from the corresponding author.

Keywords: *apnoea-hypopnea index, hypoglossal nerve implant, otorhinolaryngology, respiratory medicine, short-term outcomes, sleep apnoea, sleep surgery*

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High acceptability of HPV self-sampling in a Singapore primary care setting

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Dear Editor,

Cervical cancer, caused by persistent oncogenic human papillomavirus (HPV) infection, is a preventable disease with screening and vaccination.¹ However, there was an alarming decline in cervical cancer screening rates from 57.9% in 2007 to 43.1% in 2022² in Singapore. Women who do not attend cervical screening are at the highest risk of developing cervical cancer, and disparities in screening practices among ethnic and socioeconomic groups further drive health inequities in cervical cancer incidence.³ As conventional cervical cancer screening includes a pelvic examination by a health professional, barriers to screening include fear, discomfort and lack of time.⁴ HPV self-sampling, or self-collection with a vaginal swab, has equivalent accuracy with physician-sampling⁵ and may overcome these barriers to improve screening uptake. We had previously conducted a pilot study that demonstrated the acceptability of self-sampling among women attending a tertiary centre in Singapore,⁶ but data in the community is lacking. Our primary objective is to establish the acceptability of HPV self-sampling for cervical screening in primary care in Singapore, with a secondary aim to compare the concordance between self-sampling and nurse-sampling.

This was a qualitative acceptability study conducted at a polyclinic in Singapore from February 2023 to October 2024. Ethics approval from the National Healthcare Group's Domain Specific Review Board (2022/00191) and informed consent from all participants were obtained. Participants were recruited from a convenience sample of patients who attended the polyclinic. The inclusion criteria were Singaporean women aged 30–69 years who were scheduled to attend cervical cancer screening. The exclusion criteria were pregnancy, previous total hysterectomy, cervical cancer, immunosuppression and virgo intacta. We utilised a crossover trial design, with participants being randomised into 2 groups by block randomisation in a 1:1 ratio. A computer-generated randomi-

sation schedule was created and recorded on a concealed allocation list, which was strictly followed. Participants in Group 1 underwent nurse-sampling as per standard of care, followed by self-sampling with the COPAN FLOQswab® (Copan Diagnostics, CA, US; Supplementary Fig. S1); while Group 2 underwent the reverse sequence. All swabs were processed using Roche-Cobas 6800 HPV assay. Subsequently, participants completed an anonymous questionnaire on their experience (Supplementary Appendix 1). The participants' clinical management was not affected by the study.

Acceptability of self-sampling was quantified in terms of favourable perception among participants, and the likelihood for women to take up cervical screening with self-sampling. We estimated the acceptance rate for HPV self-sampling to be 85% with a precision of 5%, resulting in a sample size of 200. All data were analysed using SPSS version 20.0 (IBM Corp, Armonk, NY, US). Agreement of self- and nurse-collected HPV swab results were assessed using McNemar-Bowker test.

Out of the 228 enrolled participants, 28 (12.3%) women declined to complete the survey and survey data was analysed for the remaining 200 patients (Supplementary Fig. S2). The characteristics of the participants are summarised in Supplementary Table S1. The ethnic composition of the study population closely mirrored that of the Singapore population. Regarding practices of cervical cancer screening and prevention, a quarter of the women were never-screeners (25%), and most participants (90.5%) have not received the HPV vaccine. Only 18.5% of women reported ever using tampons.

Table 1 shows the breakdown of the participants' preferences regarding HPV sampling. The majority of them found self-sampling easy to perform (88%), and experienced minimal discomfort (88%). Only a minority reported to have felt anxious (4.5%), unpleasant (6.5%) or embarrassed (1.5%) during the process. When asked about their preferences for

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Table 1. Study participants' preferences regarding the 2 sampling collection methods (n=200).

	Yes	No		
Have you had any cervical cancer vaccinations?	19 (9.5%)	181 (90.5%)		
Have you ever had cervical cancer screening done (HPV ^a or PAP ^b smear)?	150 (75.0%)	50 (25.0%)		
Have you ever used tampons?	37 (18.5%)	163 (81.5%)		
Have you ever smoked?	18 (9.0%)	182 (91.0%)		
Experience on HPV self-sampling				
	Strongly agree	Agree	Neither agree nor disagree	Disagree
When taking my own HPV sample today, I found it easy	141 (70.5%)	35 (17.5%)	18 (9.0%)	4 (2.0%)
I felt comfortable taking my own HPV sample	143 (71.5%)	33 (16.5%)	16 (8.0%)	6 (3.0%)
I did not feel anxious taking my own HPV sample	146 (73.0%)	36 (18.0%)	9 (4.5%)	7 (3.5%)
I did not feel embarrassed taking my own HPV sample	177 (88.5%)	18 (9.0%)	2 (1.0%)	1 (0.5%)
It was not unpleasant for me to take my own HPV sample	156 (78.0%)	26 (13.0%)	5 (2.5%)	8 (4.0%)
If self-sampling and sampling by a doctor/nurse are equally good, what would you prefer in a future screening programme? (More than 1 option can be selected)				
Self-sampling at home	141 (56.6%)			
Self-sampling at health centre	56 (22.5%)			
Sampling by a doctor/nurse	20 (8.0%)			
Does not matter	32 (12.9%)			
Are you likely to participate in future cervical cancer screening if you have the option of self-sampling?				
Yes	183 (91.5%)			
No	17 (8.5%)			
If you have the option of self-sampling, would you be willing to pay for it?				
Yes	148 (74.0%)			
No	52 (26.0%)			

^a Human papillomavirus^b Papanicolaou

future screening, the majority preferred self-sampling at home (56.6%) or in a health centre (22.5%), over physician-sampling (8%). Most participants (91.5%) were more likely to participate in future cervical cancer screening if the option of self-sampling was available, and 74% of women were willing to pay for the self-sampling swab.

The HPV results of the self-sampling and nurse-sampling swabs are shown in Supplementary Table S2. Out of the 228 study participants, 10 women did not undergo nurse-sampling as they were currently menstruating and did not qualify for screening as per the polyclinic protocol. Nine self-collected samples yielded invalid results (4.1%), all of which were HPV-negative on nurse-sampling. Women who did not

undergo nurse-sampling or had invalid samples were excluded from the final analysis. Discordant results were only observed in 5 samples, with a concordance rate of 98.4% (95% confidence interval 95.3%–99.7%). There was no significant difference between the detection of HPV in the self-sampled and nurse-sampled results ($P=0.37$, McNemar test).

This study demonstrated the acceptability of HPV self-sampling among women who attended a primary care setting in Singapore. This supports findings from our pilot study,⁶ as well as studies in Asian countries with similar ethnic groups.⁷ Singapore is a multiracial country with a unique sociocultural context that influences women's attitudes towards self-examination and health literacy.⁸ These include cultural taboos,

traditional views of women's modesty and a preference for female physicians. Self-sampling in the primary care setting is able to circumvent these barriers by providing women with an acceptable method to undergo cervical screening without a pelvic examination. Furthermore, despite a low use of tampon products among our study population, this was not a barrier to self-sampling, which similarly required the insertion of a foreign body into the woman's vagina.

Our study findings from women who attended primary healthcare are encouraging, with a significant proportion of participants reported to have been never-screeners for cervical cancer. Primary care attendance has been shown to be positively associated with preventative health measures,⁹ hence offering HPV self-sampling as an alternative option for cervical cancer screening within primary care has the potential to engage under-screened women.¹⁰ More research is needed on cost-effective self-sampling delivery strategies and robust follow-up plans, to guide national policymaking. Future large-scale randomised control trials or real-world implementation studies are essential for this purpose.

In conclusion, the acceptability of HPV self-sampling among Singapore women in primary care is high. HPV self-sampling overcomes barriers of conventional cervical screening, and is the preferred choice for cervical cancer screening in our study population. The introduction of self-sampling will increase accessibility of screening to women at highest risk of cancer, thus strengthening Singapore's efforts to eliminate cervical cancer.

Supplementary materials

Table S1. Baseline demographic characteristics of study participants and non-participants.

Table S2. Breakdown of self-collected and nurse-collected HPV results (n=218).

Fig. S1. COPAN FLOQswab used for HPV DNA self-sampling test.

Fig. S2. CONSORT flow diagram on the enrolment of study participants.

Appendix 1. Participant survey.

Appendix 2. Non-participant survey.

Ethics statement

Ethical approval from the National Healthcare Group's Domain Specific Review Board (2022/00191) and informed consent from all participants were obtained.

Declaration

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Keywords: cervical neoplasms, cervix uteri, early detection of cancer, human papillomavirus viruses, patient preference

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Managing uveitic glaucoma with the Hydrus Microstent: A paradigm shift in surgical solutions

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Dear Editor,

In this case series, we share our experience with the Hydrus Microstent (Ivantis, Irvine, CA, US) as an innovative approach in the management of uveitic glaucoma, to address a critical gap in the current literature.

Uveitic glaucoma—affecting approximately 7.6% of patients with acute uveitis and 6.5–11.1% with chronic uveitis¹—remains a therapeutic challenge due to its multifactorial nature, including steroid response and the typical age of onset (between the third and sixth decades of life).² The limited long-term success reported with traditional glaucoma surgeries^{3,4} and alternative treatment options, such as micropulse transscleral cyclophototherapy (MPTCP),⁵ further complicate decision-making when efficacy of initial surgical interventions diminishes over time.

The emergence of minimally invasive glaucoma surgery (MIGS) devices has caused a paradigm shift in glaucoma management. Designed to provide safer and more effective options by creating alternative aqueous outflow pathways, these devices offer distinct advantages. Among them, the Hydrus Microstent has garnered attention as a potential treatment option for uveitic glaucoma. This flexible aqueous drainage device comprises alternating spines for structural support and windows for aqueous outflow. It is inserted into Schlemm's canal, where it dilates the canal—countering its tendency to collapse under elevated intraocular pressure (IOP)⁶—and bypasses resistance at the juxtacanalicular segment of the trabecular meshwork and the inner wall of Schlemm's canal, thereby providing an intracanalicular scaffold for aqueous outflow to multiple collector channels.⁷

While studies have demonstrated its efficacy in surgically naive eyes with primary open-angle glaucoma (POAG), reporting significant reductions in IOP and medication burden,^{7,8} its application in uveitic or secondary glaucoma remains underexplored. The COMPARE study⁸ reported that 78% of patients were medication-free after 12-months post-Hydrus implantation, and the HORIZON trial⁹ found that

66% remained medication-free at 5 years. Given the challenges posed by chronic inflammation and prolonged steroid requirements in uveitic glaucoma, innovative conjunctiva-sparing solutions are needed. The Hydrus Microstent represents a potential paradigm shift in this context.

In the first case, a 37-year-old man with chronic myeloid leukaemia and HLA-B27-associated anterior uveitis developed bilateral chronic anterior uveitis with elevated IOP despite topical steroid therapy. Despite maximal medical therapy for glaucoma—including a combination of brinzolamide and timolol maleate (Azarga, Novartis, Switzerland), brimonidine tartrate (Alphagan, Allergan, Australia), tafluprost (Taflotan, Santen, Japan), and oral acetazolamide 250 mg twice daily—IOP control remained suboptimal (33 mmHg in the right eye and 37 mmHg in the left eye), with continuous deterioration in visual acuity and worsening glaucomatous field defects on Humphrey Visual Field (HVF) testing. The patient initially underwent Ahmed tube implantation in the right eye and MPTCP in the left eye. Gonioscopic evaluation revealed open angles (grade 3–4 on the modified Shaffer grading system) without peripheral anterior synechiae (PAS). Despite transient improvement, IOP rebounded to 42 mmHg in the left eye 2 weeks later, necessitating Ahmed tube implantation. He remained stable on Azarga and a lower-potency topical steroid of loteprednol etabonate (Lotemax, Bausch & Lomb, US) twice daily. Subsequent development of a white cataract with borderline IOP (23 mmHg) in the left eye prompted cataract surgery, performed in combination with Hydrus Microstent implantation. Postoperative IOP was 8 mmHg at 1 week and maintained around 15 mmHg without any glaucoma medications for nearly 2 years.

In the second case, a 54-year-old man with a history of bilateral laser-assisted in situ keratomileusis presented with recurrent episodes of left eye Posner-Schlossman Syndrome (PSS); viral tetraplex studies from anterior chamber tap were negative. Initially managed during acute flares with Alphagan

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and timolol maleate (Timolol, Santen, Japan), he gradually developed ocular hypertension with an IOP of 34 mmHg, a borderline cup-to-disc ratio of 0.6 and a normal HVF. Treatment with Azarga and Alphagan was initiated; however, the patient's intolerance to Azarga necessitated switching to Taflotan. Repeated courses of topical steroid therapy were required to manage recurrent PSS flares, leading to spikes of IOP to 30 mmHg, prompting the addition of oral acetazolamide. Gonioscopy consistently demonstrated open angles (grade 4) without PAS. In an effort to reduce medication burden and achieve better IOP control, combined phacoemulsification with Hydrus Microstent implantation was performed. Postoperative IOP was well-controlled at about 12 mmHg without glaucoma medications for 16 months. However, an eventual IOP rise to 22 mmHg prompted the reinitiation of topical glaucoma medications—specifically brinzolamide (Azopt, Novartis, Switzerland) from 16–19 months postoperatively, and the addition of Alphagan and latanoprost (Xalatan, Pfizer, New York, NY, US) after. He was subsequently scheduled for trabeculectomy about 2 years after surgery.

In the third case, a 46-year-old male with bilateral uveitic glaucoma had 2 previous Ahmed tube implantations in the right eye (1 combined with phacoemulsification), and combined Ahmed tube implantation and phacoemulsification in the left eye. Persistent mild inflammation required ongoing topical steroid therapy (Pred Forte [Allergan, Irvine, CA, US] twice daily) with anti-glaucoma medications (timolol and Alphagan). Steroid response led to borderline IOP of 24 mmHg in the right eye and 20 mmHg in the left eye, with recurrence of inflammation upon attempts at steroid tapering or switching from Pred Forte to Lotemax. Eventual escalation to maximum medical therapy was required, consisting combinations of bimatoprost and timolol maleate (Ganfort, Allergan, Ireland), and brinzolamide and brimonidine tartrate (Simbrinza, Novartis, Switzerland). The development of right eye corneal decompensation prompted Ahmed tube explantation and Paul's glaucoma implant (Advanced Ophthalmic Innovations, Singapore) implantation, reducing the IOP from 24 mmHg preoperatively to around 7–10 mmHg. After subsequent penetrating keratoplasty, IOP remained stable with Pred Forte and Ganfort.

In contrast, the left eye exhibited an elevated IOP of 34 mmHg despite maximal medical therapy. Gonioscopic evaluation confirmed open angles (grade 4) without PAS. Left eye Hydrus Microstent implantation was subsequently performed, achieving initial good postoperative IOP control at 16–17 mmHg. An increase to 24 mmHg 3 weeks later coincided with increased steroid frequency in the fellow eye for early corneal graft rejection, which prompted reinitiation of Ganfort in the left eye. The IOP remained stable

over the next 18 months until the addition of ripasudil (Glanatec, Kowa, Japan) was required. Right eye repeat penetrating keratoplasty was performed for graft failure approximately 2 years after the left eye Hydrus Microstent implantation. Left eye IOP subsequently reduced to 17 mmHg and remained stable on the same anti-glaucoma medications with ongoing topical steroid therapy of Pred Forte 4 times a day in the right eye up until the latest review. This case demonstrates that while the Hydrus Microstent reduces medication burden, complete independence from glaucoma medications may not be achieved. Patients should hence be counselled preoperatively and informed that adjunctive eyedrop therapy may still be necessary to potentiate the IOP-lowering effect and achieve optimal IOP control.

Hydrus Microstent has been established in several prospective studies as a useful surgical option in IOP control, especially when performed in combination with cataract surgery.^{9,10} It has also been favourably compared to similar Schlemm's canal-based MIGS devices, specifically iStent (Glaukos Corporation, Laguna Hills, CA, US),⁸ though current evidence is largely limited to eyes with POAG.

These cases illustrate the potential of Hydrus Microstent as an effective surgical modality in managing uveitic glaucoma that addresses the limitations of traditional glaucoma surgeries, particularly with its conjunctiva-sparing properties. By achieving good medium-term IOP control (up to close to 2 years) and reducing medication burden, the Hydrus Microstent enhances patient compliance and quality of life, thereby representing a promising conjunctiva-sparing option and paradigm shift in the management of these patients.

Ethics statement

Not applicable.

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: Hydrus Microstent, minimally invasive glaucoma surgery, ophthalmology, secondary glaucoma, uveitic glaucoma

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