



ANNALS

OFFICIAL JOURNAL OF THE ACADEMY OF MEDICINE, SINGAPORE

VOLUME 55

NUMBER 6

JUN 2026



Singapore expert consensus on optimising lipid-lowering strategies in acute coronary syndrome: A modified Delphi study

A 10-member panel developed 30 high-consensus statements for low-density lipoprotein cholesterol management in post-acute coronary syndrome. (See full article, p. 318)

Illustration by Maria De-Castro

Also in this issue

Association of estimated pulse wave velocity with 28-day mortality in sepsis: A MIMIC-IV study

Trends in healthcare costs and utilisation in SingHealth 2019–2024: The effects of an ageing population

Who seeks help? Factors associated with utilisation of primary care mental health services in Singapore

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ISSN 2972-4066

Annals, Academy of Medicine, Singapore

Volume 55 | Number 6 | June 2026

EDITORIAL

Vascular stiffness and sepsis mortality: A promising signal in search of clinical relevance

David M Allen 292

ORIGINAL ARTICLES

Association of estimated pulse wave velocity with 28-day mortality in sepsis: A MIMIC-IV study

Xiuxiu Ding, Chaochao Wei, Shuang Cai, Bingli Zhang, Jiwei Li, Dajia Fu 294

Trends in healthcare costs and utilisation in SingHealth 2019–2024: The effects of an ageing population

Joshua Kuan Tan, Yun Zhao, Zoey Hui Xian Lim, Boon Hwee Ang, Julian Thumboo, Ivan En-Howe Tan, Lian Leng Low, Marianne Kit Har Au 305

REVIEW ARTICLE

Singapore expert consensus on optimising lipid-lowering strategies in acute coronary syndrome: A modified Delphi study

Ru San Tan, Jonathan Yap, Colin Yeo, Kian Keong Poh, Peter Chee Hong Yan, Pow Li Chia, Michael Chun Leng Lim, David Foo, Fahim Haider Jafary, Natalie Si Ya Koh 318

LETTERS TO THE EDITOR

Who seeks help? Factors associated with utilisation of primary care mental health services in Singapore

Yu Cong Eugene Chua, Hui Li Koh, Poay Sian Sabrina Lee, Yijun Carol Lin, Sabrina Kay Wye Wong, Winnie Shok Wen Soon, Wern Ee Tang 332

Safety of independent discharge post-endoscopy with sedation: A 7-year retrospective observational study

Quan Rui Tan, Pei Yee Lim, Sherwyn Koh, Xin Tien Lee, Wee Khoon Ng 335

Decentralised germline genetic testing for epithelial ovarian cancer in a tertiary Asian centre

Poornima Bhadriraju, Pei Yi Ong, Li Min Lim, Jeffrey JH Low, Pearl Tong, Joseph Ng, David SP Tan, Yi Wan Lim, Natalie YL Ngoi, Siew Eng Lim, Gloria HJ Chan, Soo Chin Lee, Samuel GW Ow 339

Impact of artificial intelligence on novice endoscopists' colonoscopy training

Kristie Eliana Ramli, Leticia Jing Yee Wong, SingHealth General Surgery Residency, SingHealth Gastroenterology Residency, Fung-Joon Foo, Eng-Kiong Teo, Frederick Hong Xiang Koh, The SingHealth General Surgery Residency, The SingHealth Gastroenterology Residency 342

A novel opioid-sparing method for post-laparotomy pain management in gynaecologic oncology patients: Correspondence

Gee Huey Leong, Wah Tze Tan 345

Vascular stiffness and sepsis mortality: A promising signal in search of clinical relevance

David M Allen^{1,2,3} MD

Sepsis is a major contributor to all-cause mortality worldwide and is a leading cause of in-hospital deaths in Southeast Asia.¹ The emergence of SARS-CoV-2 significantly disrupted a steady trend of improving sepsis survival over the last 30 years; fortunately, that trend appears to have resumed in 2023.

Improvement in sepsis mortality outcomes has been attributed to early sepsis recognition and to protocolising a prompt response to sepsis, including moderate fluid resuscitation and early initiation of context-appropriate antibiotics. While outcome improvements are commendable, 30-day mortality due to septic shock still averages 34.7% (95% confidence interval [CI] 32.6–36.9%) and sepsis without shock averages 24.4% (95% CI 21.5–27.2%) with modest regional variation.² The potential utility of mortality prognostication seems clear. Accurate mortality prognostication could improve goals-of-care conversations, triage considerations, resource stewardship in the intensive care unit (ICU), and clinical trial enrolment. However, unlike the established benefits of early sepsis recognition and timely intervention, the extent to which improved mortality prognostication translates into better individual patient outcomes remains unclear. At present, its utility may be greater for population-level benchmarking rather than for bedside management.³

As the understanding of sepsis pathophysiology evolved from the 1980s into the 1990s, so did sepsis mortality prognostication. Starting with simple physiological scoring tools including Acute Physiology and Chronic Health Evaluation (APACHE), APACHE II, Simplified Acute Physiology Score (SAPS), SAPS II, and SAPS III, prognostic models subsequently progressed towards complex organ dysfunction assessment using Sequential Organ Failure Assessment (SOFA). These instruments were initially validated for use during the first 24 hours in the ICU (APACHE and SAPS families) or for serial use in the ICU (SOFA), but subsequent evaluation has supported their use outside the ICU in the emergency department and in general wards. The APACHE and SAPS tools demonstrate area under the receiver

operating characteristic (AUROC) values in the 0.75–0.90 range, whereas SOFA's AUROC value range is 0.80–0.92. AUROC values in these ranges reflect good-to-excellent discrimination for predicting mortality. Multiple approaches intending to incrementally improve mortality prognostication are underway: biomarker and physiological marker combinations (e.g. adjusted quick SOFA using lactate and procalcitonin), enhanced clinical scoring systems (e.g. National Early Warning Score and Modified Early Warning Score, APACHE IV), machine learning models, and transcriptomics.⁴

Estimated pulse wave velocity (ePWV) has recently entered the sepsis mortality prognostication landscape. Unlike carotid-femoral pulse wave velocity (cfPWV), which is measured using specialised equipment to directly quantify pressure wave speed along the aorta, a patient's ePWV value can be generated via several methods of varying accuracy. The method utilised by Ding et al. calculates ePWV (hereafter labelled "derived ePWV") using a regression equation that was empirically derived and validated in a pan-European reference population, which excluded subjects with diabetes mellitus, treated hypertension, treated dyslipidaemia or known cardiovascular disease. The calculation requires only mean blood pressure and patient age.⁵ cfPWV is the gold standard for measuring aortic stiffness and predicts cardiovascular events independently of traditional risk factors (age, sex, systolic blood pressure, body mass index, smoking, cholesterol).⁶ Derived ePWV's correlation with cfPWV is modest ($r=0.67$) and decreases further in patients with diabetes mellitus and those with chronic kidney disease.⁷ Derived ePWV independently predicts all-cause mortality, but not cardiovascular events.⁸ Derived ePWV is more accessible than cfPWV and other direct measures of pulse wave velocity. The rationale for investigating pulse wave metrics is grounded in observations of sepsis-related endothelial injury and vascular dysregulation.^{9,10} Both cfPWV and derived ePWV have been explored as tools for predicting sepsis-related mortality risk with mixed results.¹¹ In Ding et al., derived ePWV shows a signifi-

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¹ Division of Infectious Diseases, National University Hospital, Singapore

² Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

³ Infectious Diseases Translation Research Programme, National University of Singapore, Singapore

Correspondence: Associate Professor David M Allen, Division of Infectious Diseases, National University Hospital, 1E Kent Ridge Road, Singapore 119228; Email: mdcdma@nus.edu.sg

Accepted: 8 June 2026

Published Online First: 11 June 2026

cant linear positive association with 28-day mortality in septic ICU patients with some caveats.¹² Ding et al. present what appears to be a statistically strong case for derived ePWV to incrementally improve prediction, but the issue of clinical relevance remains. In their study, derived ePWV used alone had a poor AUROC value of 0.567. The 2 prediction models they compared head-to-head are the “combined LASSO model” and the “adjusted model”. Importantly, both the “adjusted model” and the “combined LASSO model” already include derived ePWV. The modest increase in AUROC from 0.815 to 0.823 likely reflects improved statistical discrimination from LASSO-based variable selection rather than a clearly demonstrated incremental contribution from ePWV itself. Notably, they do not provide head-to-head performance results of their 2 models with existing sepsis prognostic scores (SOFA, APACHE, etc.) or assess their 2 models without including ePWV. As such, the hypothesis that derived ePWV is useful as a sepsis mortality prognosticator alone or that it makes a clinically significant or practical contribution to sepsis mortality prognostication models or existing scoring systems is not established.¹²

The authors are to be commended for leveraging the Medical Information Mart for Intensive Care (MIMIC-IV) as a large real-world resource for studying septic ICU patients, strengthening evidence for an association—rather than a correlation—between ePWV and sepsis mortality that prior small cohort studies have demonstrated less convincingly, and demonstrating that ePWV retains statistical significance after extensive adjustment. However, because ePWV is mathematically derived from age and mean blood pressure, performs poorly as a standalone predictor (AUC 0.567), and was not directly compared against existing prognostic tools with and without its inclusion, its value remains uncertain.

With respect to the generalisability of this work to Asia, readers should be aware of the limitations of the tool and materials used to test the prognostication models by Ding et al.: derived ePWV and MIMIC-IV. Derived ePWV was empirically generated from a predominately non-Asian population, which excluded those with diabetes mellitus, treated hypertension, cardiovascular disease or treated dyslipidaemia. The MIMIC-IV database is derived from a single medical centre in the US where ICU practices, mortality rates, disease epidemiology, and end-of-life cultural perspectives may differ substantially from those encountered in Asia. Notably, Asians represent <5% of MIMIC-IV’s cohort. Although these limitations are not disqualifying, contextually relevant validation—with local ICU practices, appropriate ethnic representation, and prevalent regional comorbidities—would strengthen confidence in the findings.

In this context, the work by Ding et al. is best viewed as an exploratory effort that strengthens evidence for an association between derived ePWV and sepsis mortality while leaving its clinical value unresolved. Future studies should demonstrate not only improved statistical discrimination and generalisability but also meaningful impacts on clinical decision-making and patient outcomes.

Ethics statement

Not applicable, as no study participants were involved.

Declaration

The author declares that he has 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: *infectious diseases, mortality, prognostication, sepsis, short-term outcomes*

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Association of estimated pulse wave velocity with 28-day mortality in sepsis: A MIMIC-IV study

Xiuxiu Ding^{*1} MMed, Chaochao Wei^{*1,2,3} MMed, Shuang Cai¹ MMed, Bingli Zhang¹ MMed, Jiwei Li¹ MMed, Dajia Fu^{4,5} MM

ABSTRACT

Introduction: Despite the association between sepsis and carotid-femoral pulse wave velocity, the relationship between estimated pulse wave velocity (ePWV) and sepsis remains unclear. This study investigated the correlation between ePWV and 28-day mortality in patients with sepsis.

Methods: Using data from the Medical Information Mart for Intensive Care IV database between 2008 and 2019, the association between ePWV and 28-day mortality was analysed with Kaplan-Meier curves, Cox models, and restricted cubic splines (RCS). Subgroup analysis was performed to validate the findings. A combined model was constructed by screening variables via Cox-least absolute shrinkage and selection operator (LASSO), with its incremental predictive value evaluated using receiver operating characteristic (ROC) curves and decision curve analysis (DCA).

Results: Survival analysis showed an inverse association between ePWV and survival rates (log-rank test $P < 0.001$). Cox analysis demonstrated that each increase in ePWV was associated with a significantly higher risk of 28-day mortality in patients with sepsis (hazard ratio 1.905, 95% confidence interval 1.672–2.169, $P < 0.001$), with linearity confirmed by RCS analysis ($P_{\text{nonlinear}} = 0.3313$). Subgroup analysis indicated significant interaction effects of invasive ventilation ($P_{\text{interaction}} < 0.001$) and a history of malignant tumours ($P_{\text{interaction}} = 0.005$) on mortality. The combined model optimised by LASSO demonstrated the best discriminative performance (ROC = 0.823) and an improved net clinical benefit with the inclusion of ePWV, as confirmed by DCA.

Conclusion: ePWV was linearly and positively correlated with the risk of 28-day mortality in patients with sepsis.

Keywords: 28-day mortality, ePWV, MIMIC-IV, sepsis

INTRODUCTION

Among patients in intensive care units (ICUs), sepsis is a major cause of mortality.¹ In 2017, a disease burden study showed that there were approximately 48.9 million cases of sepsis worldwide, with 11

CLINICAL IMPACT

What is New

- Estimated pulse wave velocity (ePWV) is significantly positively correlated with 28-day mortality in patients with sepsis.
- Invasive ventilation and a history of malignancy influence the association between ePWV and 28-day mortality in patients with sepsis.

Clinical Implications

- ePWV may serve as a potential indicator for assessing the prognosis of patients with sepsis, aiding in the early identification of high-risk individuals in clinical practice and providing a reference for personalised management and prognostic evaluation.

million deaths, accounting for 19.7% of the total global mortality. Although the age-standardised incidence rate decreased by 37.0% and the mortality rate decreased by 52.8% compared to 1990, sepsis remains a major factor contributing to the global health burden.² Sepsis, which is characterised by systemic inflammatory responses that can escalate to organ dysfunction, significantly increases the risk of cardiovascular disease (CVD), including myocardial infarction, acute coronary syndrome, congestive heart failure, and atherosclerosis.^{3–5} Therefore, monitoring the risk of CVD and atherosclerosis in patients with sepsis is critical.

An independent predictor of CVD mortality, carotid-femoral pulse wave velocity (cf-PWV) is the gold standard for assessing arterial stiffness.⁶ A recent study also found a relationship between cf-PWV and sepsis, with higher levels associated with poorer survival in patients with sepsis.⁷ These data indicate that monitoring variations in cf-PWV may aid in

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¹ Department of Respiratory and Critical Care Medicine, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, China

² Department of Oncology, Xiangya Hospital Central South University, China

³ NHC Key Laboratory of Tropical Disease Control, Hainan Medical University, China

⁴ Department of Emergency Medicine, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, China

⁵ Department of Electrophysiology, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, China

* Joint first authors

Correspondence: Dr Dajia Fu, Department of Emergency Medicine, and Electrophysiology, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University, No. 19 Xiuhua Road, Xiuying District, Haikou City, Hainan Province, 570311, China. Email: dajiafu666@163.com

Accepted: 6 March 2026

Published Online First: 2 June 2026

predicting mortality risk in patients with sepsis. However, the clinical utility of cf-PWV is limited because it requires specific equipment and qualified personnel to measure.⁸ Estimated pulse wave velocity (ePWV) is a simple measure derived from mean blood pressure (MBP) and chronological age.⁹ Evidence suggests that ePWV has predictive value comparable to that of pulse wave velocity (PWV), with a risk prediction difference of -0.3% compared with cf-PWV and PWV in evaluating CVD risk in the Danish MONICA10 cohort.^{10,11}

Although recent research has initially explored the association between ePWV and sepsis outcomes using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database,¹² uncertainties persist regarding the precise nature of this relationship and its incremental predictive value beyond conventional clinical models, owing to differences in study designs and analytical approaches. Consequently, the present study aimed to further elucidate the correlation between ePWV and 28-day mortality in patients with sepsis through an independent, rigorous analysis and to investigate in depth the potential factors influencing this association.

METHODS

Data source

Data were obtained from the publicly accessible MIMIC-IV database (<https://mimic.mit.edu/>),¹³ which

comprises data on ICU-admitted patients at Beth Israel Deaconess Medical Center in Boston from 2008 to 2019. MIMIC-IV is publicly available and anonymised; thus, no ethical approval was necessary.

Study population

The study included patients diagnosed with sepsis or septic shock using Sepsis-3 criteria.¹⁴ Data were collected from 2008 to 2019. Exclusion criteria included (1) children <18 years old; (2) patients with multiple ICU admissions (only the first admission was included); and (3) patients with ICU stays shorter than 1 day. A total of 19,422 eligible patients were included, of whom 16,414 survived within 28 days of ICU admission, and 3008 died during the same period (Fig. 1).

ePWV assessment and primary endpoint

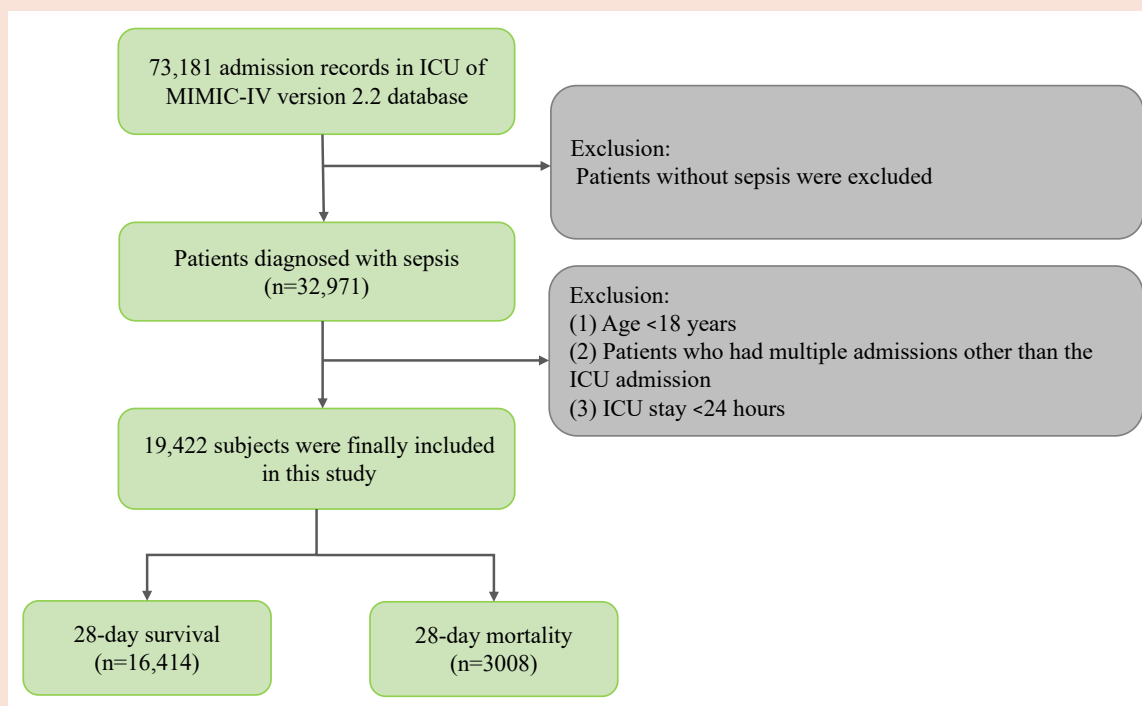
ePWV was computed using age and MBP with the formula from Greve et al.,¹¹ where $PWV = 9.587 - 0.402 \times \text{age} + 4.560 \times 10^{-3} \times \text{age}^2 - 2.621 \times 10^{-5} \times \text{age}^2 \times MBP + 3.176 \times 10^{-3} \times \text{age} \times MBP - 1.832 \times 10^{-2} \times MBP$. MBP was computed from diastolic blood pressure (DBP) and systolic blood pressure (SBP) as $MBP = DBP + 0.4 \times (SBP - DBP)$.¹⁵

The primary endpoint was 28-day mortality among patients with sepsis admitted to the ICU.

Variable collection

The MIMIC-IV database was used to collect patient data, including demographics, severity scores,

Fig. 1. Flowchart of study population selection.



ICU: intensive care unit; MIMIC-IV: Medical Information Mart for Intensive Care IV

comorbidities, vital signs, laboratory tests, and therapy information. Vital-sign and laboratory-test variables with missing values for more than 20% of the overall sample were eliminated. Missing values in other variables were handled using the random forest (RF) approach from the “mice” package. Supplementary Table S1 contains details on the variables that were included and eliminated. Severity scores were collected within 24 hours after ICU admission, whereas vital signs and laboratory tests were taken during the first 24 hours, with the most severe measurement used for variables with multiple values.

Statistical analysis

Structured Query Language queries were used to obtain data from MIMIC-IV (version 2.2), which was then analysed using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). The “tableone” package was used to create a baseline table, which displayed continuous variables as mean (standard deviation), and compared groups using t-tests. Categorical variables were reported as percentages (%) and compared using chi-squared test. A 2-tailed $P < 0.05$ indicated statistical significance.

The “jskm” package was used to generate Kaplan-Meier survival curves based on ePWV quartiles in patients with sepsis, as well as to perform log-rank testing. Variance inflation factor (VIF) was used to assess collinearity across variables, with VIF values greater than 4 suggesting collinearity. After accounting for multicollinearity, Cox proportional hazards models were created using the “survey” and “survival” packages to investigate the association between ePWV and 28-day mortality in patients with sepsis. A Cox proportional hazards model was created for ePWV quartiles and 28-day mortality in patients with sepsis. A trend test was used to determine whether there was a trend between ePWV and 28-day mortality in patients with sepsis, with $P < 0.05$ indicating a significant difference.

In the fully adjusted model, the “ms” package was used to perform restricted cubic spline (RCS) analysis to investigate the nonlinear association between ePWV and the 28-day mortality in patients with sepsis. All categorical variables were subjected to interaction and subgroup analysis.

To evaluate the predictive value of ePWV for mortality risk in ICU patients, the authors constructed multivariable survival prediction models. Initially, 59 candidate variables were included based on clinical relevance and prior literature¹⁶: age, race, vital signs (e.g. respiratory rate, temperature, SpO_2), laboratory parameters (e.g. lactate, creatinine, electrolytes, coagulation indicators), severity scores (Simplified Acute Physiology Score [SAPS] II, Acute Physiology

Score III, Logistic Organ Dysfunction System, Oxford Acute Severity of Illness Score), Glasgow Coma Scale score, Charlson Comorbidity Index, mechanical ventilation, and vasoactive drug use. Given potential multicollinearity among high-dimensional clinical variables, variable selection employed Cox-least absolute shrinkage and selection operator (LASSO) regression. Using 10-fold cross-validation, the optimal λ was selected based on the λ_{1se} criterion to balance model stability and overfitting risk.¹⁷ The final multivariable Cox joint model was constructed based on the 30 selected variables. To assess the predictive value of ePWV, the ePWV-only model, the ePWV-adjusted model, and a combined model were constructed, with their discriminative ability compared using time-dependent receiver operating characteristic (ROC) curves with area under the curve (AUC) and clinical utility evaluated using decision curve analysis (DCA). Statistical analyses were performed in R, with significance set at 2-tailed $P < 0.05$.

RESULTS

Baseline characteristics

This study included 19,422 patients, with 16,414 survivors within 28 days and 3008 deaths during the same period, corresponding to a mortality rate of 15.5%. The baseline characteristics are shown in Table 1. The overall cohort had a mean age of 66.67 years (standard deviation [SD] 16.28), with 58.1% male. Comparative analysis indicated that the deceased group had substantially higher ePWV values (10.60 [SD 2.75] versus [vs] 9.97 [SD 2.63], $P < 0.001$), were older (70.53 years [SD 15.18] vs 65.96 years [SD 16.38], $P < 0.001$), and had longer ICU stays (6.33 days [SD 5.25] vs 5.25 days [SD 6.55], $P < 0.001$) than the survivors. Furthermore, compared to the survivor group, the deceased group showed substantially lower SBP, DBP, and MBP values, higher severity scores, and a higher incidence of comorbidities (all $P < 0.001$).

Relationship between ePWV and 28-day mortality in patients with sepsis

Further investigation was undertaken into the relationship between ePWV and 28-day mortality in patients with sepsis. Kaplan-Meier survival curves showed a decrease in 28-day survival rates for patients with sepsis as ePWV levels increased, with significant intergroup differences (log-rank test, $P < 0.001$) (Fig. 2A).

Covariates associated with 28-day mortality in sepsis were selected, and after eliminating variables with multicollinearity, 35 variables were used to build a Cox proportional hazards model (Supplementary Table S2). Table 2 shows that ePWV, a continuous variable, was significantly associated with an elevated 28-day

Table 1. Characteristics of patients admitted to the intensive care unit for the first time.

Characteristic	Total (n=19,422)	28-day survival (n=16,414)	28-day mortality (n=3008)	P value
ePWW	10.07 (2.66)	9.97 (2.63)	10.60 (2.75)	<0.001
Sex				0.006
Female	8140 (41.9)	6811 (41.5)	1329 (44.2)	
Male	11,282 (58.1)	9603 (58.5)	1679 (55.8)	
Age, years	66.67 (16.28)	65.96 (16.38)	70.53 (15.18)	<0.001
Race				<0.001
White	13,054 (67.2)	11,245 (68.5)	1809 (60.1)	
Black	1537 (7.9)	1307 (8.0)	230 (7.6)	
Other race	4831 (24.9)	3862 (23.5)	969 (32.2)	
Marital status				<0.001
Married	10,676 (55.0)	8878 (54.1)	1798 (59.8)	
Unmarried	8746 (45.0)	7536 (45.9)	1210 (40.2)	
LOS, days	5.42 (6.38)	5.25 (6.55)	6.33 (5.25)	<0.001
Heart rate, times/min	86.77 (15.96)	86.04 (15.46)	90.76 (17.98)	<0.001
SBP, mmHg	115.64 (15.06)	116.20 (14.78)	112.56 (16.17)	<0.001
DBP, mmHg	61.24 (10.16)	61.39 (10.05)	60.40 (10.68)	<0.001
MBP, mmHg	76.58 (10.05)	76.85 (9.89)	75.11 (10.77)	<0.001
Respiratory rate, times/min	19.59 (4.03)	19.25 (3.85)	21.44 (4.49)	<0.001
Temperature, °C	36.88 (0.61)	36.91 (0.55)	36.72 (0.86)	<0.001
SpO₂	97.03 (2.20)	97.15 (1.94)	96.36 (3.20)	<0.001
Glucose, mg/dL	324.15 (9033.27)	292.09 (8790.39)	499.10 (10257.69)	0.248
SAPS II	40.18 (14.11)	38.16 (12.82)	51.20 (15.61)	<0.001
SOFA	5.89 (3.47)	5.45 (3.10)	8.31 (4.30)	<0.001
APS III	49.61 (22.05)	46.17 (19.35)	68.37 (26.07)	<0.001
Anion gap, mmol/L	16.64 (5.27)	16.07 (4.81)	19.71 (6.49)	<0.001
Bicarbonate, mmol/L	21.16 (4.89)	21.52 (4.58)	19.21 (5.93)	<0.001
Chloride, mmol/L	106.70 (6.65)	106.85 (6.35)	105.88 (8.06)	<0.001
Haematocrit, µmol/L	29.66 (6.35)	29.66 (6.26)	29.65 (6.82)	0.945
Haemoglobin, g/dL	9.84 (2.14)	9.87 (2.10)	9.66 (2.30)	<0.001
Platelet, K/µL	177.20 (102.25)	177.69 (99.63)	174.54 (115.47)	0.121
Potassium, K/µL	4.64 (0.88)	4.60 (0.85)	4.86 (0.98)	<0.001
PTT, seconds	43.84 (29.49)	42.10 (27.62)	53.37 (36.67)	<0.001
INR	1.65 (1.16)	1.58 (1.04)	2.04 (1.59)	<0.001
PT, seconds	17.93 (11.78)	17.20 (10.58)	21.92 (16.35)	<0.001
Sodium, mEq/L	136.72 (5.35)	136.79 (5.16)	136.36 (6.26)	<0.001
BUN, mg/dL	30.48 (24.12)	28.48 (22.66)	41.43 (28.51)	<0.001
WBC, K/µL	15.75 (12.31)	15.37 (11.25)	17.84 (16.81)	<0.001

Table 1. Characteristics of patients admitted to the intensive care unit for the first time. (Cont'd)

Characteristic	Total (n=19,422)	28-day survival (n=16,414)	28-day mortality (n=3008)	P value
RBC, m/μL	3.28 (0.73)	3.29 (0.72)	3.22 (0.80)	<0.001
MCH, pg	29.81 (2.61)	29.80 (2.54)	29.87 (2.94)	0.181
MCHC, g/L	32.53 (1.68)	32.64 (1.63)	31.90 (1.78)	<0.001
MCV, fL	90.34 (7.00)	90.06 (6.76)	91.85 (7.99)	<0.001
RDW	15.38 (2.44)	15.18 (2.30)	16.49 (2.85)	<0.001
Creatinine, mg/dL	1.65 (1.64)	1.57 (1.62)	2.10 (1.70)	<0.001
Invasive ventilation				<0.001
No	8375 (43.1)	7302 (44.5)	1073 (35.7)	
Yes	11,047 (56.9)	9112 (55.5)	1935 (64.3)	
Dialysis				<0.001
No	18,470 (95.1)	15,776 (96.1)	2694 (89.6)	
Yes	952 (4.9)	638 (3.9)	314 (10.4)	
Vasopression				<0.001
No	18,098 (93.2)	15,665 (95.4)	2433 (80.9)	
Yes	1324 (6.8)	749 (4.6)	575 (19.1)	
Antibiotics				<0.001
No	2502 (12.9)	2009 (12.2)	493 (16.4)	
Yes	16,920 (87.1)	14,405 (87.8)	2515 (83.6)	
Congestive heart failure				<0.001
No	13,799 (71.0)	11,870 (72.3)	1929 (64.1)	
Yes	5623 (29.0)	4544 (27.7)	1079 (35.9)	
Peripheral vascular disease				0.001
No	17,119 (88.1)	14,521 (88.5)	2598 (86.4)	
Yes	2303 (11.9)	1893 (11.5)	410 (13.6)	
Chronic lung disease				<0.001
No	14,425 (74.3)	12,292 (74.9)	2133 (70.9)	
Yes	4997 (25.7)	4122 (25.1)	875 (29.1)	
Chronic kidney disease				<0.001
No	15,274 (78.6)	13,099 (79.8)	2175 (72.3)	
Yes	4148 (21.4)	3315 (20.2)	833 (27.7)	
Malignant tumour				<0.001
No	16,822 (86.6)	14,436 (87.9)	2386 (79.3)	
Yes	2600 (13.4)	1978 (12.1)	622 (20.7)	

APS III: Acute Physiology and Chronic Health Evaluation III; BUN: blood urea nitrogen; DBP: diastolic blood pressure; ePWV: estimated pulse wave velocity; INR: international normalised ratio; LOS: length of stay; MBP: mean blood pressure; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean corpuscular volume; PT: prothrombin time; PTT: partial thromboplastin time; RBC: red blood cell; RDW: red cell volume distribution width; SAPS II: Simplified Acute Physiology Score II; SBP: systolic blood pressure; SOFA: Sequential Organ Failure Assessment; SpO₂: peripheral oxygen saturation; WBC: white blood cell

Continuous variables are displayed as mean (standard deviation) and compared between groups using t-tests. Categorical variables are reported as percentages (%) and compared by chi-squared test. $P < 0.05$ indicates statistical significance. Variables having missing values greater than 20% of the overall sample size in vital signs and laboratory tests were eliminated. Missing values in other variables were handled with the Random Forest.

mortality in patients with sepsis in the fully adjusted model (hazard ratio [HR] 1.096, 95% confidence interval [CI] 1.076–1.115, $P < 0.001$). A multivariate-adjusted Cox proportional hazards model was created by classifying ePWV into quartiles. As shown in Table 2, increasing ePWV levels increased the risk of 28-day mortality in patients with sepsis across all 3 models ($P < 0.001$). In the fully adjusted model, the risk for Q2, Q3, and Q4 increased by 18.2% (HR 1.182, 95% CI 1.052–1.329, $P = 0.005$), 43.6% (HR 1.436, 95% CI 1.269–1.626, $P < 0.001$), and 90.5% (HR 1.905, 95% CI 1.672–2.169, $P < 0.001$), respectively, compared to Q1.

In the RCS analysis, an increase in ePWV was associated with an increase in 28-day mortality in patients with sepsis (P -overall < 0.0001), with no significant nonlinear association (P -nonlinear = 0.3313) (Fig. 2B).

Subgroup analysis of the relationship between ePWV and 28-day mortality in patients with sepsis

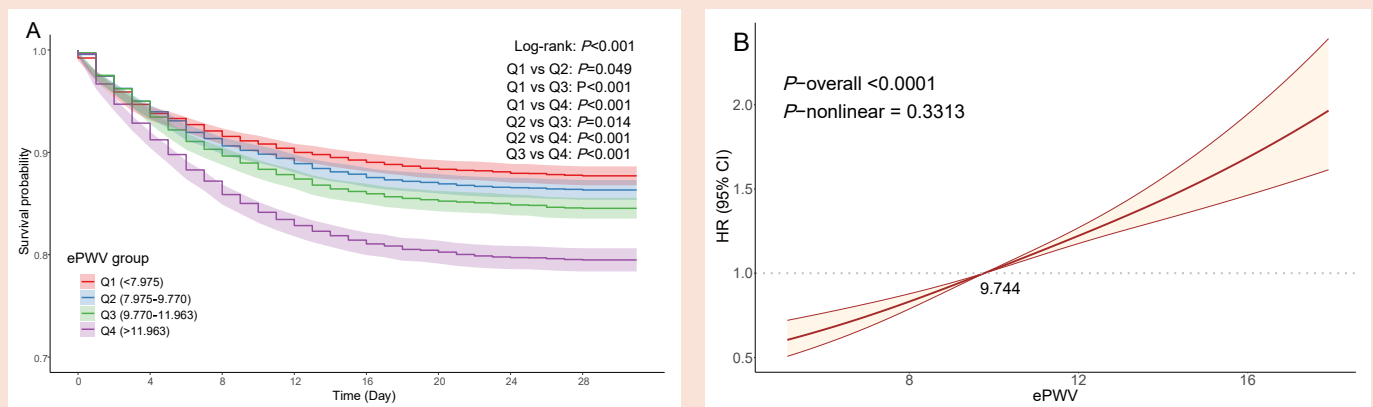
A subgroup analysis investigated other factors that influence the association between ePWV and 28-day mortality in patients with sepsis. As shown in Fig. 3, after controlling for all confounding factors, a significant association was detected between ePWV and the 28-day mortality risk in all patient subgroups except

Table 2. Association of ePWV with 28-day mortality in patients with sepsis.

Characteristic	HR (95% CI), P		
	Crude model	Model 1	Model 2
28-day mortality			
ePWV (continuous)	1.082 (1.068–1.096), < 0.001	1.088 (1.074–1.103), < 0.001	1.096 (1.076–1.115), < 0.001
ePWV (categorical)			
Q1 (< 7.975)	Ref	Ref	Ref
Q2 (7.975–9.770)	1.118 (1.001–1.248), 0.049	1.191 (1.066–1.331), 0.002	1.182 (1.052–1.329), 0.005
Q3 (9.770–11.963)	1.274 (1.144–1.419), < 0.001	1.369 (1.228–1.526), < 0.001	1.436 (1.269–1.626), < 0.001
Q4 (> 11.963)	1.740 (1.573–1.926), < 0.001	1.853 (1.228–1.526), < 0.001	1.905 (1.672–2.169), < 0.001
P for trend	< 0.001	< 0.001	< 0.001

Note: Crude - unadjusted; Model 1 - adjusted for race, sex, marital status; Model 2 - adjusted for race, sex, marital status, Sequential Organ Failure Assessment, Simplified Acute Physiology Score II, Acute Physiology and Chronic Health Evaluation III, heart rate, respiratory rate, temperature, SpO_2 , glucose, anion gap, bicarbonate, chloride, platelet, potassium, partial thromboplastin time, international normalised ratio, prothrombin time, sodium, blood urea nitrogen, white blood cell, mean corpuscular haemoglobin concentration, red cell volume distribution width, creatinine, invasive ventilation, dialysis, vasopressin, antibiotics, congestive heart failure, peripheral vascular disease, chronic lung disease, chronic kidney disease, malignant tumour.

Fig. 2. Survival analysis and restricted cubic spline analysis. (A) Kaplan-Meier curve of 28-day survival rate in patients with sepsis at different ePWV levels. (B) Restricted cubic spline plot of the relationship between ePWV and 28-day mortality in patients with sepsis.



CI: confidence interval; ePWV: estimated pulse wave velocity; HR: hazard ratio

Black patients and patients with malignant tumours. Invasive ventilation use (P -interaction <0.001) and a history of malignancy (P -interaction = 0.005) showed significant interactions with mortality.

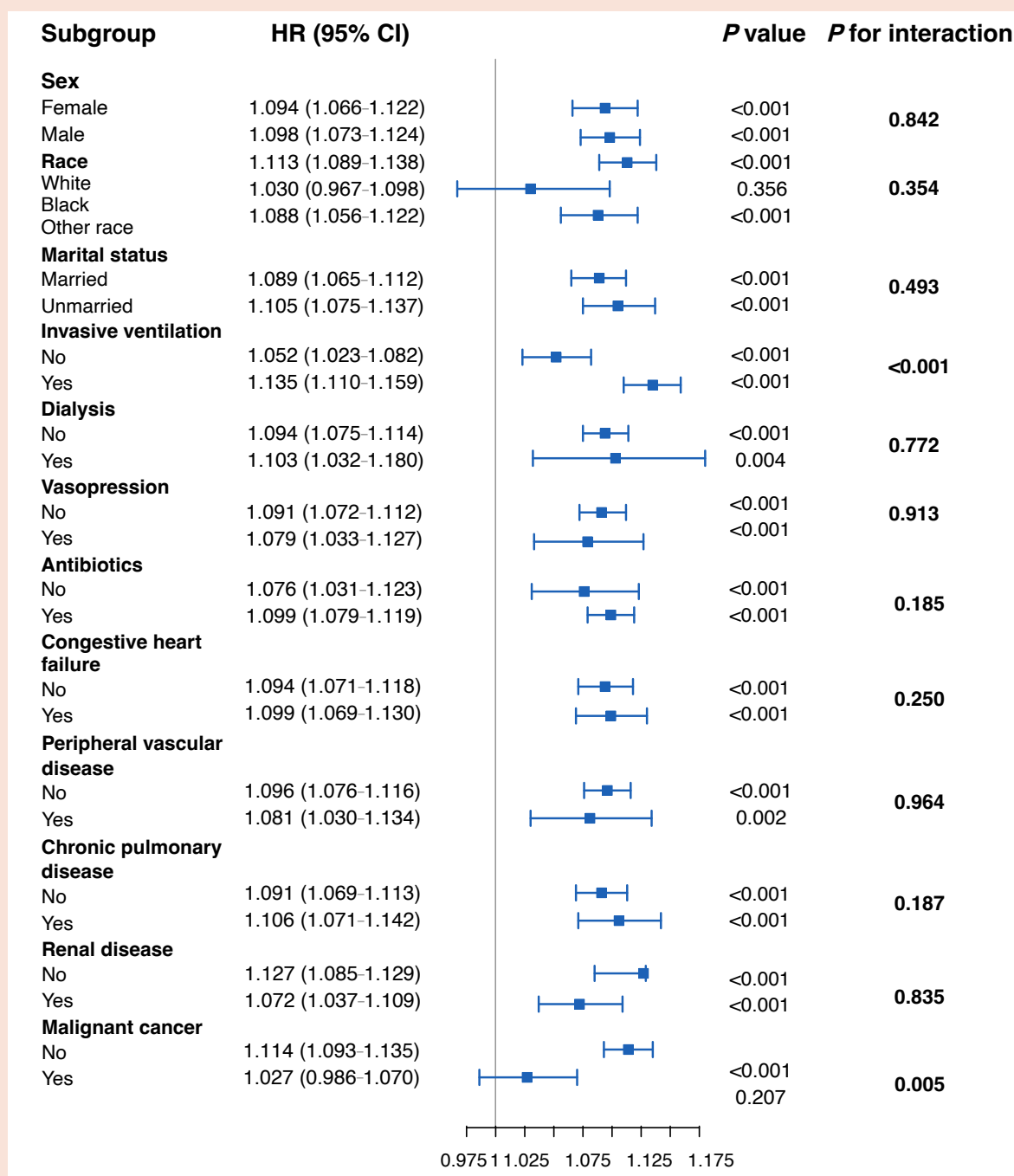
Evaluation of ePWV for predicting 28-day mortality in ICU patients

Using Cox-LASSO regression to screen 59 candidate variables, ePWV, together with traditional prognostic factors such as lactate, SAPS II score, and GCS score, was retained after determining the optimal penalty

parameter via cross-validation (Supplementary Fig. S1), indicating its independent predictive value in a multivariable context.

Time-dependent ROC analysis showed improvement in the AUC for 28-day mortality prediction from 0.567 for the ePWV-only model to 0.815 after adjusting for traditional clinical variables. The LASSO-optimised joint model achieved the highest discriminative ability, with an AUC of 0.823 (Fig. 4A), indicating that ePWV provides significant incremental prognostic value to the existing predictive framework. DCA showed

Fig. 3. Forest plot of subgroup analysis.



CI: confidence interval; HR: hazard ratio

that across a 20–80% risk threshold range, the joint model consistently yielded a higher net benefit than the ePWV-only model, adjusted model, or treat-all/treat-none strategies, with the advantage most pronounced in the intermediate-to-high risk range (Fig. 4B). This indicates that incorporating ePWV into existing predictive systems enhances clinical risk stratification.

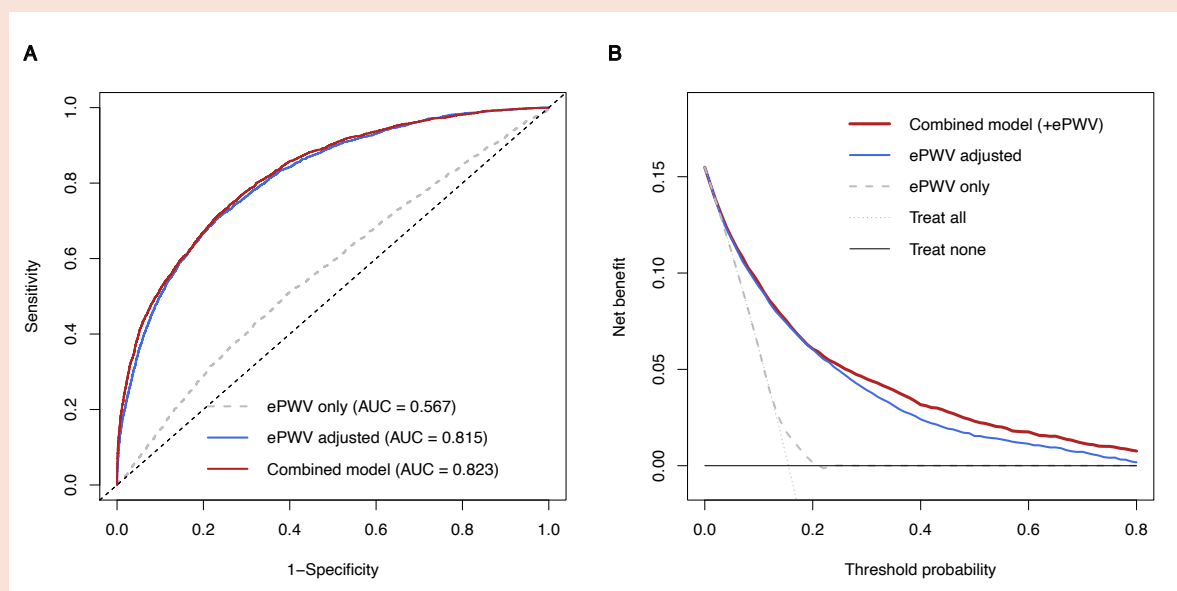
DISCUSSION

The findings show a positive correlation between ePWV and 28-day mortality in patients with sepsis, and this association is modified by the use of invasive ventilation and the absence of malignant tumours. The LASSO-optimised joint model exhibited optimal discriminative ability, with DCA confirming a significant improvement in net clinical benefit after the inclusion of ePWV.

The predictive value of ePWV as a simple clinical parameter for risk prediction in critically ill patients in the ICU has been established. ePWV is a reliable prognostic biomarker for critically ill patients with coronary artery disease, independently predicting short- and long-term mortality risk. Incorporating ePWV into standard risk assessments improves the predictive power of 1-year and in-hospital mortality risk in critically ill coronary artery disease patients.¹⁸ In addition, research has found a substantial connection

between ePWV and higher in-hospital mortality risk in critically ill patients with acute kidney injury, with ePWV functioning as an independent predictor of in-hospital mortality.¹⁹ Similar findings have been reported in critically ill patients with chronic kidney disease and associated atherosclerotic heart disease, in which ePWV appears to be a possible marker for measuring in-hospital and one-year mortality, with its elevation closely linked to increased mortality risk.²⁰ The present data also show a substantial positive relationship between ePWV and 28-day mortality risk in patients with sepsis, further highlighting the prognostic value of ePWV in critical illnesses. Notably, a recent study by Liu et al.¹² based on the same database also corroborated the prognostic value of ePWV, thereby supporting the accuracy of the present findings. However, while they identified a nonlinear (U-shaped) relationship between ePWV and 30-day mortality risk, the present study's analysis employing RCS revealed a linear positive association between ePWV and 28-day mortality. This discrepancy in conclusions may be attributable to differences in outcome definitions and patient selection strategies, further underscoring the scientific necessity of independently validating the predictive characteristics of ePWV. Of note, ePWV is a key prognostic biomarker rather than a direct therapeutic intervention. Its primary value lies in enabling early identification of high-risk patients, facilitating precise

Fig. 4. Performance evaluation and decision curve analysis of 28-day mortality prediction models.



(A) Receiver operating characteristic curve comparing discriminative ability of the ePWV-only model, ePWV-adjusted model, and combined model. (B) Decision curve analysis evaluating net clinical benefit across threshold probabilities for different models.

AUC: area under the curve; ePWV: estimated pulse wave velocity

Note: The ePWV-adjusted model included covariates from the final association analysis model; the combined model included predictors selected by LASSO.

risk stratification and guiding individualised treatment strategies and management optimisation. Future research should explore the potential of ePWV for risk prediction in other critical illnesses, with the goal of integrating it into clinical decision-making to improve patient outcomes.

The processes driving the rise in ePWV in sepsis are not well understood and may include 3 components. Patients with sepsis have elevated levels of inflammatory mediators, including TNF- α and IL-1 β ,²¹ which can cause endothelial dysfunction and thrombosis.²² This may lead to an increase in ePWV. Furthermore, during sepsis, levels of high-density lipoprotein cholesterol and low-density lipoprotein cholesterol decrease, while oxidation of low-density lipoprotein cholesterol increases, increasing the risk of cellular apoptosis and atherosclerosis.²³ This may also increase ePWV. Finally, patients with sepsis often have hypotension, which can cause reduced tissue perfusion pressure²⁴ and hypoxia-induced vascular smooth muscle cell proliferation and migration, both of which contribute to atherosclerosis.²⁵ Several studies have found a link between chronic hypoxic conditions (e.g. chronic obstructive pulmonary disease, obstructive sleep apnoea syndrome) and an increase in PWV.^{26,27}

Furthermore, the present study's subgroup analysis reported that invasive ventilation and the absence of malignant tumours increase the risk of 28-day mortality in patients with sepsis. The need for invasive ventilation is a factor associated with higher mortality in patients with sepsis.²⁸ Patients with sepsis who require invasive ventilation have much higher mortality rates (41.33% vs 8.91%).²⁹ This may be because invasive ventilation can cause ventilator-associated pneumonia,³⁰ which worsens the course of sepsis. Invasive ventilation might cause haemodynamic instability after intubation,^{31,32} which may worsen the prognosis for patients with sepsis who already have circulatory dysfunction.³³ The greater mortality risk among patients without malignant tumours may be related to different treatment strategies or monitoring intensity received by patients with malignancy, though these hypotheses require further validation.

Notably, the subgroup analysis revealed variation in the association between ePWV and 28-day mortality across racial groups. Among White patients, ePWV was significantly positively associated with mortality risk; no significant association was observed in Black patients. Several factors may explain this finding. First, the relatively small sample size of the Black subgroup may have limited the statistical power to detect a significant association. Second, prior evidence indicates racial differences in arterial stiffness; for instance, one study found that Black boys had significantly higher carotid-radial, carotid-femoral, and carotid-dorsal foot PWVs, along with greater carotid intima-media thickness, than their White counterparts,³⁴

indicating that Black individuals may have inherently higher baseline arterial stiffness, which could influence the predictive value of ePWV in this population. Additionally, racial differences in socioeconomic factors, healthcare access, dietary intake, and comorbidity distribution may have confounded the results.^{35,36} Therefore, these racial subgroup findings, particularly the null result in Black patients, should be interpreted with caution. Future prospective studies across diverse racial populations, including Asian and African cohorts, are needed to validate the generalisability of ePWV's predictive value and explore the possibility of race-specific thresholds.

While this study has several strengths, some limitations exist. First, because this was a retrospective study, recall and information bias could not be avoided. Despite adjusting for confounding variables as much as possible, there may still be confounding factors affecting the association between ePWV and mortality, such as lifestyle factors and genetic susceptibility. Second, the authors investigated only the association of ePWV with in-hospital mortality in patients with sepsis. Whether changes in ePWV have long-term effects on patients with sepsis should be investigated, and prospective cohort studies could enable more precise temporal tracking of the impact of ePWV on septic mortality and prognosis. Third, this study included only patients with sepsis admitted to the ICU, which may influence patients' haemodynamic status. Future research that directly measures ePWV under stable conditions, could provide a more accurate and comprehensive understanding of the relationship between ePWV and septic patient mortality. Finally, the data in MIMIC primarily comprise patients from a single geographic region, limiting the generalisability of results to other populations, and the associations identified in this study need further validation in different populations.

CONCLUSION

The results identify ePWV as an independent mortality predictor in sepsis. Future external validation studies across diverse racial and geographic populations are urgently needed to confirm the generalisability and robustness of ePWV and provide stronger evidence supporting its use as a clinical risk stratification tool.

Supplementary materials

Fig. S1. Variable selection using Cox-LASSO regression.

Table S1. Number and proportion of missing variables.

Table S2. Variance inflation factor of variables for multivariate Cox regression.

Ethics statement

The data used in this study were obtained from the publicly available MIMIC-IV database. Ethical

approval and consent were not required for this study in accordance with national guidelines.

Declarations

The authors declare they have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. This paper was supported by the Hainan Provincial Natural Science Foundation High-Level Talents Program (823RC571), Hainan Provincial Natural Science Foundation of China (824QN374), and NHC Key Laboratory of Tropical Disease Control, Hainan Medical University (2023NHCTDCKFKT11002). There is no conflict of interest to declare.

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Trends in healthcare costs and utilisation in SingHealth 2019–2024: The effects of an ageing population

Joshua Kuan Tan^{*1} MPH, Yun Zhao^{*2} PhD, Zoey Hui Xian Lim² BAcc, Boon Hwee Ang² BAcc, Julian Thumboo^{1,3,4} MMed, Ivan En-Howe Tan² MBA, Lian Leng Low⁵ MMed, Marianne Kit Har Au^{2,6} BBus

ABSTRACT

Introduction: Despite rising healthcare expenditure in Singapore, detailed utilisation patterns are not well characterised. We analyse utilisation within SingHealth, the country's largest public healthcare cluster.

Methods: We conducted a retrospective observational study using patient-level data from 2019 to 2024, across inpatient, outpatient specialist, and primary care settings. Patients were categorised using the Modified British Columbia (ModBC) Population Segmentation Framework, and inpatient diagnoses were classified using a locally adapted version of the Clinical Classifications Software Refined (CCSR). Healthcare costs were reported in inflation-adjusted 2024 Singapore dollars (SGD). Descriptive statistics and temporal trend analyses were performed.

Results: The patient population increased from 1.21 million in 2019 to 1.37 million in 2024, while total healthcare expenditure rose from SGD 4.37 billion to SGD 6.05 billion. Inpatient care remained the dominant cost driver, accounting for 63.8% of total expenditure in 2024, with a stable relative share over time. Expenditure increased disproportionately among older adults, with the steepest per-user growth in those aged ≥ 80 years, consistent with age-related acceleration in healthcare spending. Absolute utilisation increased among adults aged ≥ 60 years, while utilisation rates within age groups remained stable, suggesting that growth was associated with changes in population composition rather than utilisation intensity. Patients in the ModBC high-complex chronic conditions and cancer segments accounted for 46.7% of total expenditure. Diagnosis-level analyses using CCSR revealed age-related differences in utilisation patterns within these segments.

Conclusion: Rising healthcare expenditure appears consistent with population ageing and the increasing complexity of chronic diseases. Addressing these challenges will require a sustained shift towards preventive, community-based, and value-driven models of care to ensure long-term system sustainability.

Keywords: health finance, healthcare costs, healthcare expenditure, healthcare utilisation, population health analytics, public health

CLINICAL IMPACT

What is New

- This is the first comprehensive, patient-level, longitudinal analysis of healthcare utilisation and costs across the full continuum of care in SingHealth, Singapore's largest public healthcare cluster.
- The findings support a pathway in which population ageing and secular advances in medical care increase the number of clinically complex patients, thereby driving healthcare utilisation and expenditure.

Clinical Implications

- Addressing the rising healthcare expenditure will require a sustained shift towards preventive, community-based, and value-driven models of care to ensure long-term system sustainability.

INTRODUCTION

Healthcare utilisation and expenditure have risen globally, placing increasing strain on the health system.¹ Global health spending reached approximately United States Dollars (USD) 9.8 trillion (9.9% of global gross domestic product [GDP]) in 2022,¹ while OECD health expenditure increased from 8.8% of GDP in 2019 to 9.2% in 2023.² These trends are driven by population ageing, rising non-communicable disease burden, emerging health risks, and advances in medical technology, underscoring the need for sustainable health system reforms.^{1,2}

Singapore's healthcare system, often regarded as cost-effective, is not immune to these pressures. It achieves universal health coverage through its "3M" framework—MediShield Life, MediSave, and MediFund—which combines mandatory medical savings, subsidised insurance, and a public safety

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¹ Health Services Research Unit, Singapore General Hospital, Singapore

² Group Finance Analytics, Singapore Health Services, Singapore

³ Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁴ Duke-NUS Medical School, Singapore

⁵ Population Health and Integrated Care Division, Singapore General Hospital, Singapore

⁶ Finance, Regional Health System & Strategic Finance, Singapore Health Services, Singapore

*Joint first authors

Correspondence: Dr Joshua Tan Kuan, Health Services Research Unit, Singapore General Hospital, Outram Road, Singapore 169608.

Email: joshua.tan.kuan@singhealth.com.sg

Accepted: 28 May 2026

Published online first: 25 June 2026

net.^{3,4} This approach has supported strong health outcomes, while maintaining relatively low national health expenditure (4–5% of GDP).⁵ However, healthcare expenditures have risen in both absolute and relative terms. Government health expenditure increased from Singapore dollars (SGD) 3.9 billion (2.0% of GDP) in 2010 to SGD 11.1 billion (2.2%) in 2019, exceeding SGD 15 billion (>2.9% of GDP) in both 2020 and 2021 during the COVID-19 pandemic,⁶ and is projected to rise from SGD 21 billion in 2025 to SGD 30 billion by 2030.

In response, the Healthier SG initiative was launched in 2023 to strengthen preventive health and chronic disease management. It promotes longitudinal primary care, public–private collaboration, and a shift towards capitation-based financing to support preventive care and population-level health management across Singapore's 3 healthcare clusters—Singapore Health Services (SingHealth), National University Health System, and National Healthcare Group (NHG) Health.⁷

Despite well-documented national trends, the granular patterns of healthcare utilisation across care settings remain less well understood. Such insights are critical for identifying utilisation trajectories, evolving care needs, and service gaps, and for informing value-based care strategies. This study examines healthcare utilisation within SingHealth, Singapore's largest healthcare cluster, comprising 4 acute hospitals, 5 national specialty centres, 3 community hospitals, and 10 primary care polyclinics, serving nearly half of the population. Specifically, we examine how demographic change and clinical complexity, as characterised by a population segmentation framework, relate to patterns of healthcare utilisation and expenditure across care settings. Using longitudinal data from 2019 to 2024 across inpatient, outpatient specialist, and primary care services, and leveraging diagnosis-level analyses using the Clinical Classifications Software Refined (CCSR) to characterise inpatient utilisation patterns, this study aims to inform resource planning and support the development of targeted strategies to ensure the sustainability of Singapore's largest healthcare delivery system.

METHODS

Study setting and data sources

This was a retrospective, population-based observational study of all individuals with at least 1 healthcare encounter within SingHealth between 2019 and 2024. Patient-level data were obtained from the SingHealth Integrated Electronic Health Records database, which consolidates administrative, clinical, and billing information across all SingHealth institutions and care settings.

Inclusion and exclusion criteria

The study included all individuals with at least 1 recorded healthcare encounter at any SingHealth institution between 1 January 2019 and 31 December 2024. The study population therefore comprises patients who utilised SingHealth services and does not represent the resident population of any defined catchment area. The cohort spanned all age groups, sexes, and major ethnic groups. Complete case analysis was conducted, with no exclusion criteria applied.

Variables and measures

Demographic variables included sex, ethnicity, and age, categorised into 7 groups: 0–4 years, 5–17 years, 18–39 years, 40–59 years, 60–69 years, 70–79 years, and 80 years or older—reflecting meaningful life stages and healthcare utilisation patterns across the lifespan.

Healthcare costs were captured comprehensively across 3 main care settings. Inpatient costs included all expenses associated with hospital admissions, such as room charges, procedures, medications, and professional fees. Outpatient costs comprised expenditures for specialist clinic visits and ambulatory services, while primary care costs covered public sector primary care services within SingHealth (i.e., polyclinic visits) and did not include private general practitioner services. Total healthcare costs were calculated as the sum of expenditures across all 3 settings for each calendar year, providing a complete picture of healthcare resource utilisation.

Modified British Columbia Population Segmentation Framework

The Modified British Columbia Population Segmentation Framework (ModBC), adapted from the British Columbia Health System Matrix, was used to stratify a heterogeneous population into mutually exclusive subgroups based on healthcare needs and complexity,^{8,9} enabling utilisation trends to be interpreted in relation to underlying care needs. The framework uses a hierarchical classification algorithm that assigns individuals to segments based on their most significant healthcare need, ensuring that patients with multiple conditions are classified by their highest level of complexity. Within these segments, we examined demand-driving utilisation patterns to inform targeted, needs-based interventions and service planning.

In this study, patients were classified into 7 ModBC categories (detailed in Supplementary Table S1):

1. Healthy with outpatient utilisation;
2. Healthy with inpatient admission;
3. Low-complex chronic conditions;

4. Medium-complex chronic conditions;
5. Mental health conditions;
6. High-complex chronic conditions; and
7. Cancer

These analytic categories were consolidated from the original 12 ModBC segments to improve interpretability. They are intended for population health planning and should not be interpreted as a linear hierarchy of disease severity, but rather as reflecting distinct patterns of healthcare needs and utilisation. For example, the mental health segment is defined using prespecified diagnosis and procedure codes within the adapted ModBC algorithm, rather than symptom scores or screening instruments, while the cancer segment is defined using cancer-related coding rules, including malignant and metastatic disease where applicable, and is analysed separately because of its distinct care pathways and resource requirements.

The classification algorithm draws on healthcare data from the current year and the preceding 4 years to account for each patient's chronic disease complexity. Patients may transition between segments over time as their clinical status evolves. Diagnostic information was drawn from all healthcare encounters, including primary care diagnoses, primary and secondary ICD-10 codes, and surgical procedure codes. As part of the internal assignment logic of the ModBC algorithm, patients without chronic disease complexity tags were further stratified based on their healthcare utilisation intensity (as measured by emergency visits, hospitalisations, and specialist consultations) for the current year of assessment; this stratification was used solely for segment assignment and was not independently reported in the results section.

Clinical Classifications Software Refined

To enable clinically meaningful analysis of inpatient utilisation patterns, primary inpatient diagnoses were classified using a locally adapted version of the Clinical Classifications Software Refined (CCSR), originally developed by the US Agency for Healthcare Research and Quality.¹⁰ While ICD-10 codes provide granular diagnostic detail, their high dimensionality and clinical specificity can limit interpretability for population-level analyses. The CCSR addresses this by grouping ICD-10 Clinical Modification (ICD-10-CM) codes into approximately 530 clinically meaningful categories providing insights into disease-specific healthcare utilisation and outcomes.^{10,11} As Singapore uses the ICD-10 Australian Modification (ICD-10-AM), a customised mapping algorithm was used to align ICD-10-AM codes to CCSR categories.¹²

Cost and statistical analysis

Healthcare costs were defined as gross bill charges before government subsidies, insurance disburse-

ments, or patient co-payments, and therefore reflect the provider's perspective. Costs were expressed in 2024 SGD and adjusted for inflation using the Singapore Consumer Price Index. This enabled year-on-year comparisons while accounting for changes in purchasing power over the study period. Descriptive statistics summarised population characteristics and healthcare costs. Trends from 2019 to 2024 were examined by care setting, demographic subgroup, and ModBC category. Analyses were conducted in R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

Ethics approval was obtained from the SingHealth Centralised Institutional Review Board (CIRB) prior to initiating this study (SingHealth CIRB reference number: 2022/00892). As all participant data were de-identified, a waiver for participant consent was also obtained.

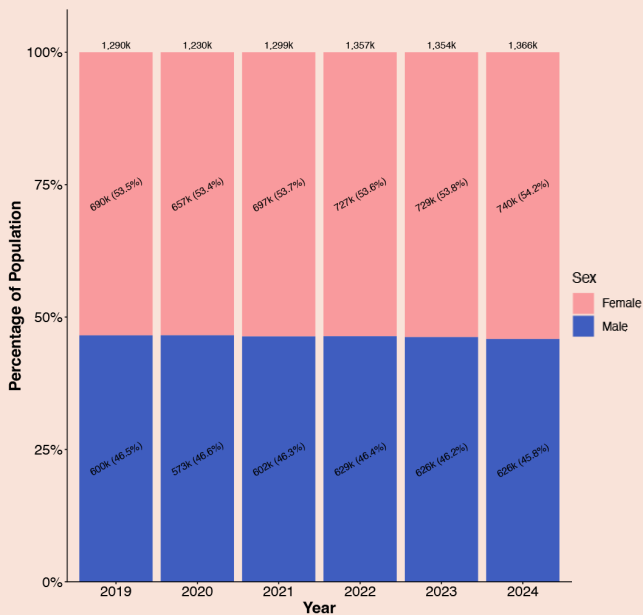
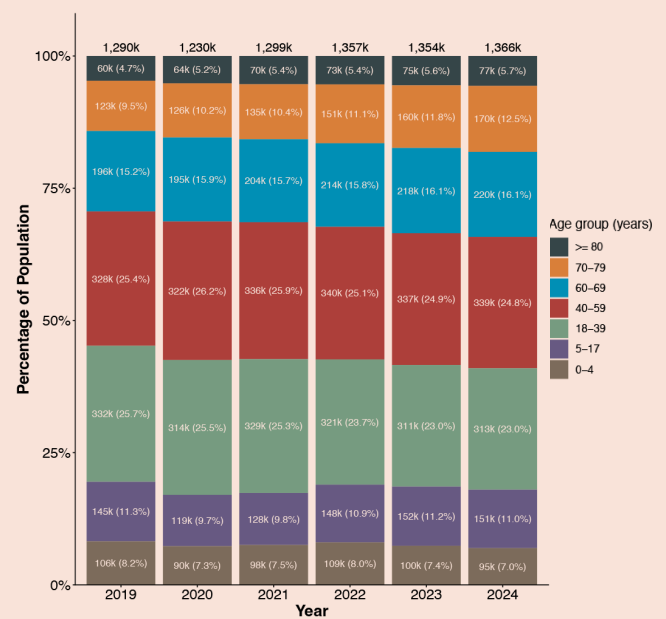
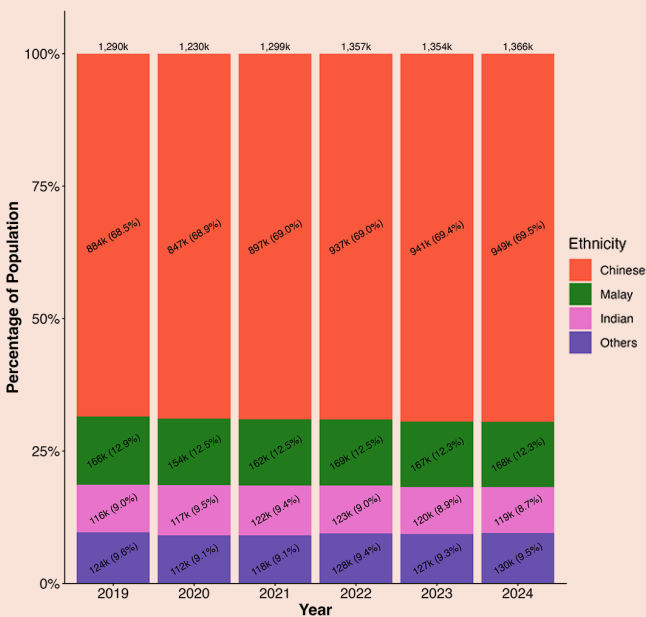
RESULTS

Across the study period, the number of patients served by SingHealth increased from 1.21 million in 2019 to 1.37 million in 2024 (Fig. 1A). The proportion of female patients remained relatively stable (53.4–54.2%), and the ethnic distribution closely mirrored that of the national population (Fig. 1B).¹³ The population of Chinese patients exhibited modestly higher growth (Supplementary Fig. S1). The patient cohort became progressively older over time, with patients aged ≥60 years increasing from 379,275 (29.4%) in 2019 to 467,186 (34.2%) in 2024 (Fig. 1C and Supplementary Fig. S2).

Total inflation-adjusted healthcare expenditure increased steadily over the study period, rising from SGD 4.37 billion in 2019 to SGD 6.05 billion in 2024 (Fig. 2A). Inpatient care remained the largest cost component, accounting for 63.8% of total expenditure in 2024, with a stable share over time (63.2% in 2019 to 63.8% in 2024), indicating growth in absolute but not relative terms.

In 2024, females accounted for slightly higher total expenditure than males (SGD 2.22 billion versus SGD 2.15 billion, respectively). On aggregate, males had a higher proportion of their total spending attributed to inpatient care and a lower proportion to outpatient services (Fig. 2A). Across ethnic groups, the distribution of healthcare expenditure by type of care remained broadly stable over time (Fig. 2B). However, Chinese patients exhibited the largest overall increase in healthcare expenditure, with consistently higher growth across most care settings compared with other ethnic groups (Supplementary Fig. S3). Similarly, across age groups, the distribution of healthcare expenditure by type of care remained broadly stable over time (Fig. 2C). However, older

Fig. 1. Demographic composition of patients utilising SingHealth services by (A) sex, (B) ethnicity, (C) age group.

(A) Population Composition by Sex**(C) Population Composition by Age Group****(B) Population Composition by Ethnicity**

patients aged 70–79 years and ≥ 80 years exhibited the largest overall increases in healthcare expenditure, with consistently higher growth across all care settings (Supplementary Fig. S4).

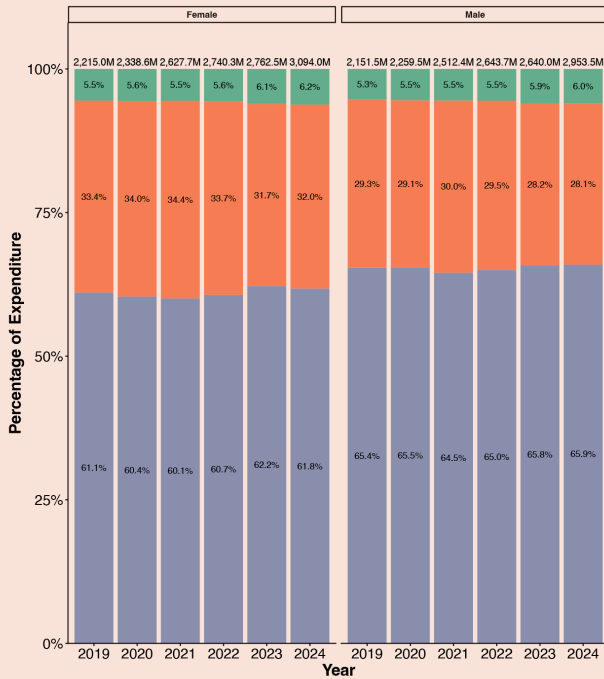
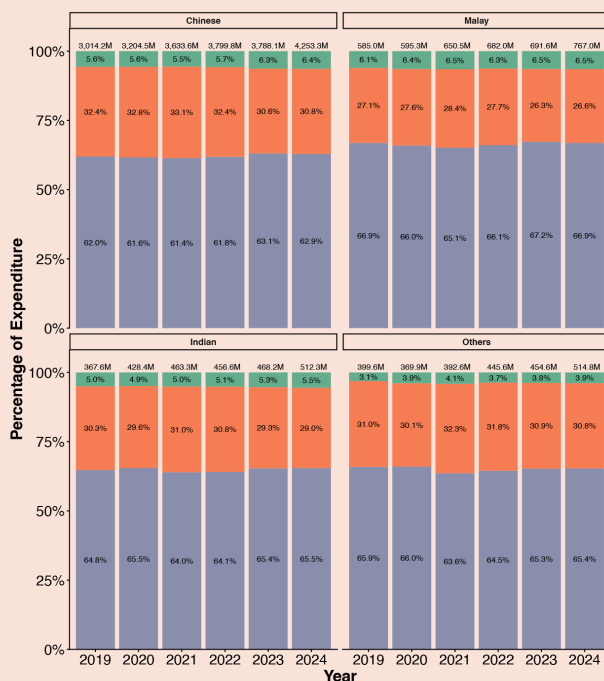
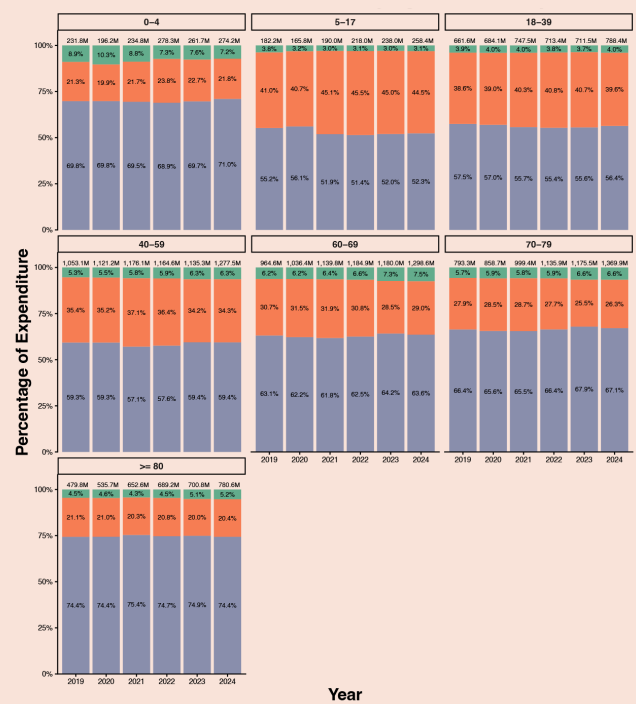
Absolute utilisation of inpatient, outpatient, and primary care services (defined as the number of patients utilising each service) increased over time for patients aged ≥ 60 years and especially for those aged 70–79 years (Fig. 3A, Supplementary Fig. S5). In contrast, service-specific utilisation rates within age groups (defined as the number of patients utilising

a given service divided by the number of patients in that age group utilising any service) remained relatively stable across most services (Fig. 3B). These findings are consistent with rising service use being associated more with shifts in population composition (Fig. 1C) than with increased utilisation intensity within age groups.

Inpatient care had the highest per-user expenditure (calculated as the total service expenditure divided by the number of patients who utilised the service in a given year), followed by outpatient and then primary care (Fig. 4). Inpatient per-user expenditure was higher in males than in females, showed minimal variation across ethnic groups, and increased with age, particularly among individuals aged ≥ 60 years. Notably, inpatient per-user expenditure increased over time, with the greatest growth observed in older age groups (Fig. 4C and Supplementary Table S3). In contrast, per-user expenditure for outpatient and primary care remained relatively consistent across age groups and did not exhibit substantial increases over time.

The distribution of patients by ModBC segment (Fig. 5A) showed increasing absolute counts and modest proportional growth in the high-complex chronic conditions and cancer segments over the study period, consistent with a shift towards higher clinical complexity. In 2024, patients in the cancer segment accounted for 24.0% of healthcare expenditure, followed by patients with high-complexity chronic conditions (22.7%) and patients in the healthy with inpatient admission segment (16.3%) (Fig. 5B).

Fig. 2. Distribution of healthcare expenditure (in SGD millions) by type of care and demographic characteristics by (A) sex, (B) ethnicity, (C) age group.

(A) Healthcare Expenditure Breakdown by Sex and Type of Care**(B) Healthcare Expenditure Breakdown by Ethnicity and Type of Care****(C) Healthcare Expenditure Breakdown by Age Group and Type of Care****Type of Care**

Primary Care
Outpatient
Inpatient

with inpatient admissions had higher per-user costs than patients in the medium- and low-complexity chronic conditions segment.

Distribution of top hospital admission diagnoses by patient segment

Table 1 presents the top 10 most common reasons from inpatient admissions in 2024 characterised using the CCSR and stratified by modified BC segment. Additional details including the ICD-10-AM codes are provided in Supplementary Tables S6–S12.

The top 10 most common reasons for admission across ModBC patient segments accounted for 21–33% of all admissions and varied by segment, suggesting differing clinical profiles. Among patients classified as healthy with inpatient admission, admissions were primarily for low-acuity conditions such as benign neoplasms, intestinal infections (i.e. gastroenteritis-related conditions), abdominal pain and related symptoms, and upper respiratory infections.

In the low- and medium-complex chronic conditions segments, admissions were characterised by a broader mix of acute and chronic conditions, including upper respiratory disease (i.e. otorhinolaryngology-related

Despite differences in total expenditure, patients in the cancer and high-complex chronic conditions segments incurred substantially higher per-user costs, calculated as total expenditure within a segment divided by the number of patients in that segment in a given year (Fig. 5C). Interestingly, healthy patients

Fig. 3. Service utilisation trends by age group and type of care (A) absolute utilisation, (B) utilisation rates.

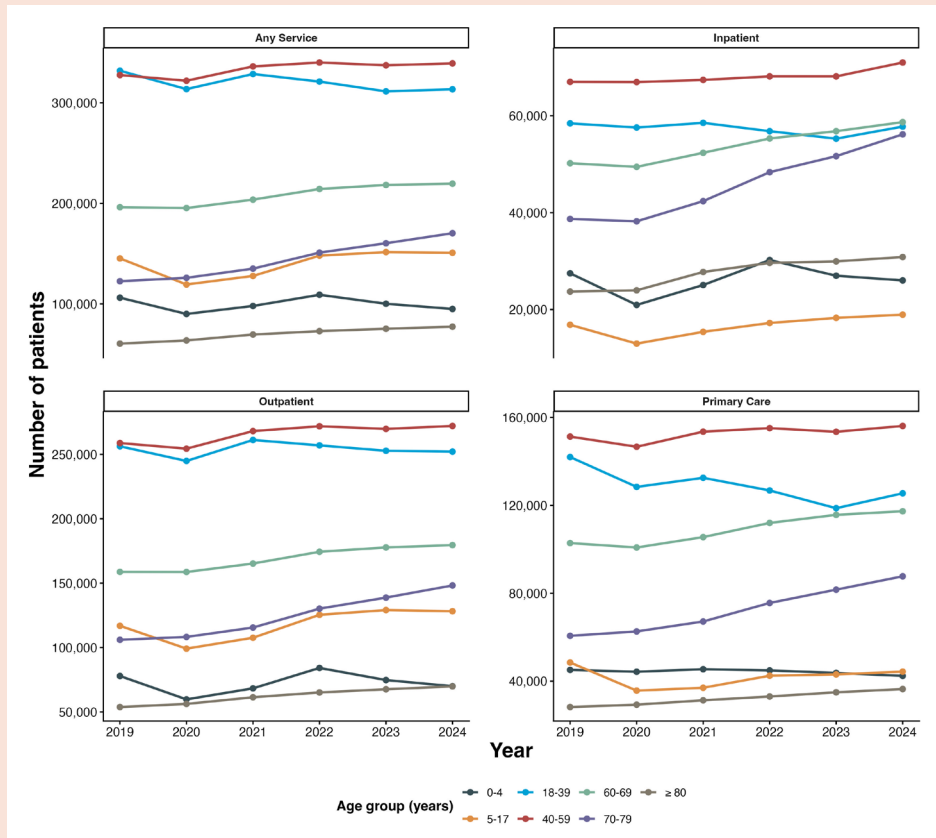
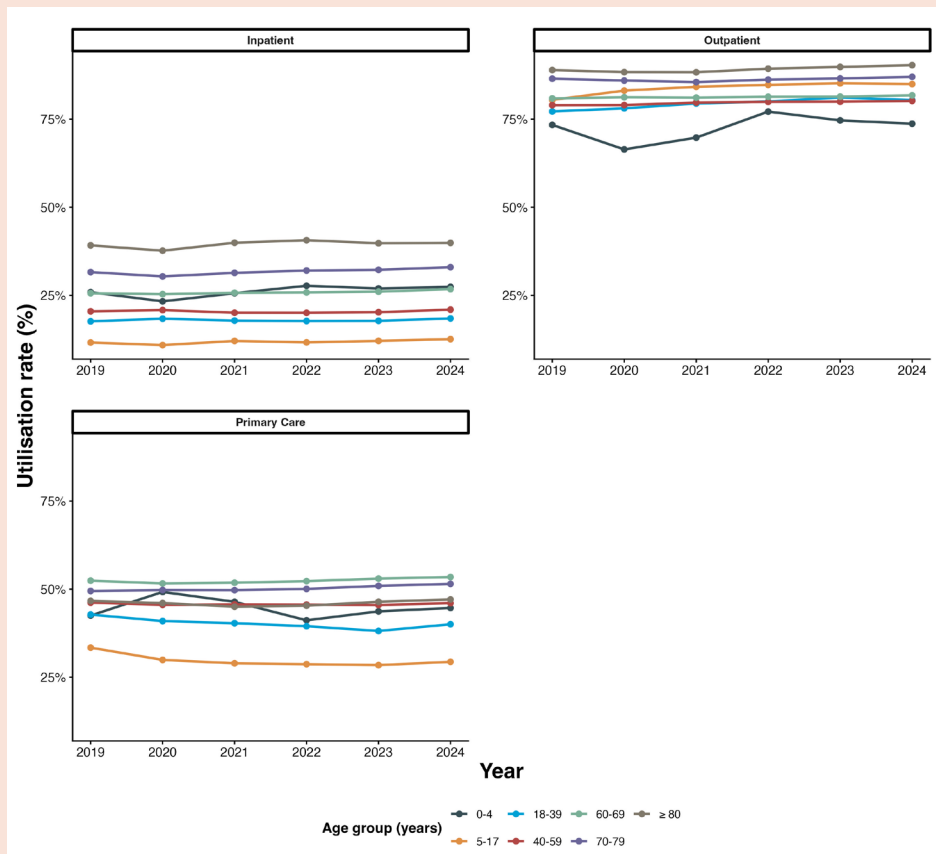
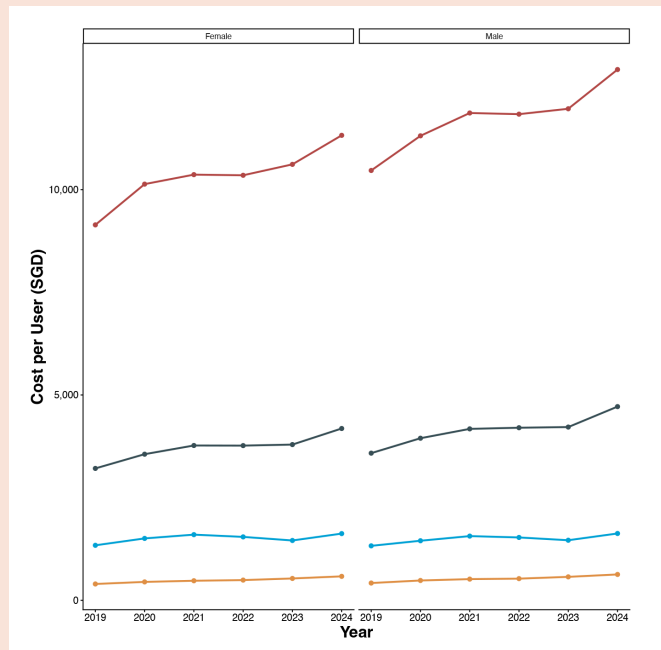
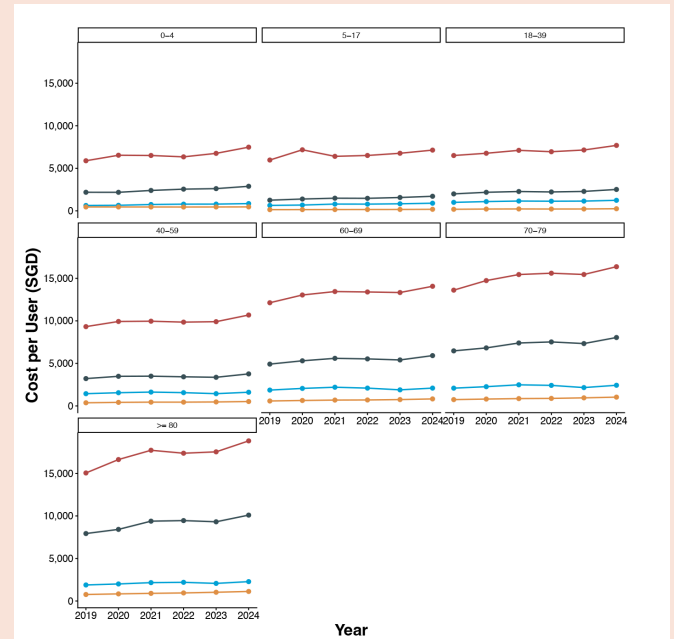
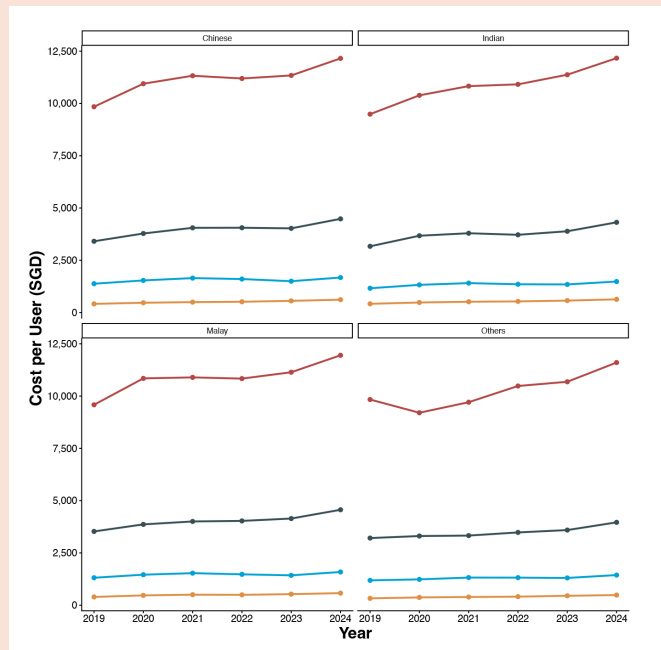
(A) Absolute Service Utilisation by Age Group and Type of Care**(B) Service Utilisation Rates by Age Group and Type of Care**

Fig. 4. Per-user healthcare expenditure by type of care and demographic characteristics by (A) sex, (B) ethnicity, (C) age group.

(A) Per-User Healthcare Expenditure by Type and Sex**(C) Per-User Healthcare Expenditure by Type of Encounter and Age Group****(B) Per-User Healthcare Expenditure by Type of Encounter and Ethnicity****Type of Encounter**

- All Services
- Primary Care
- Outpatient
- Inpatient

conditions), abdominal pain and related symptoms, benign neoplasms, pneumonia, coronary artery disease, and nonspecific chest pain.

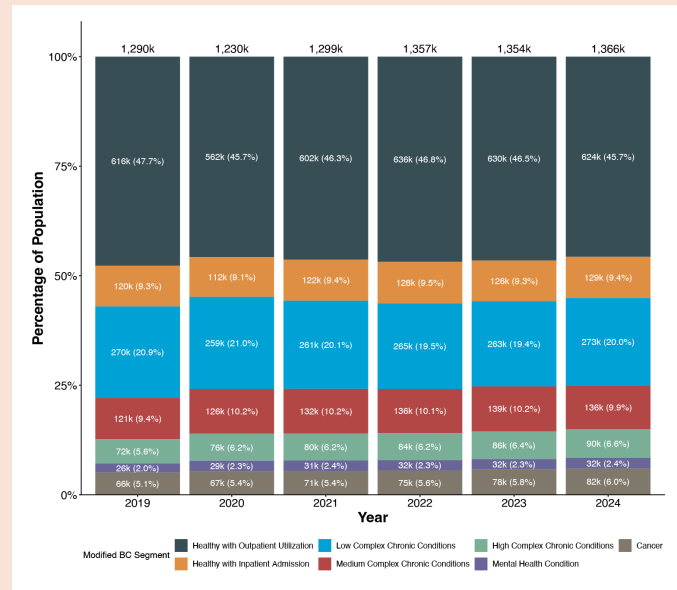
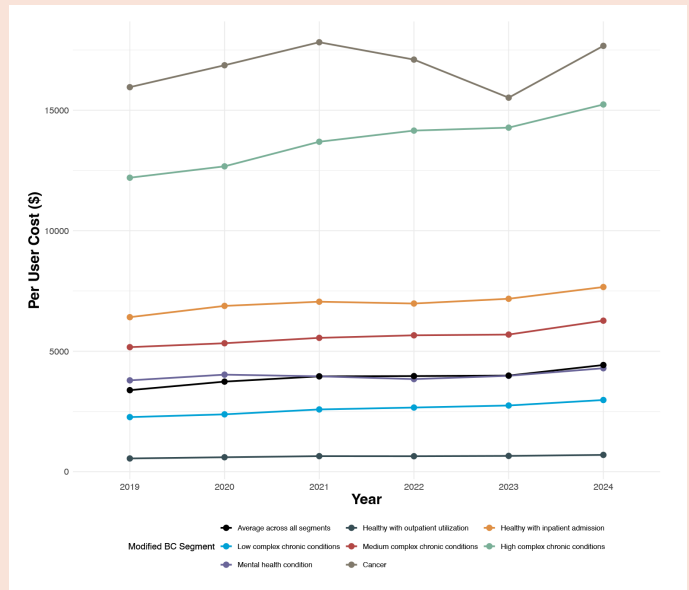
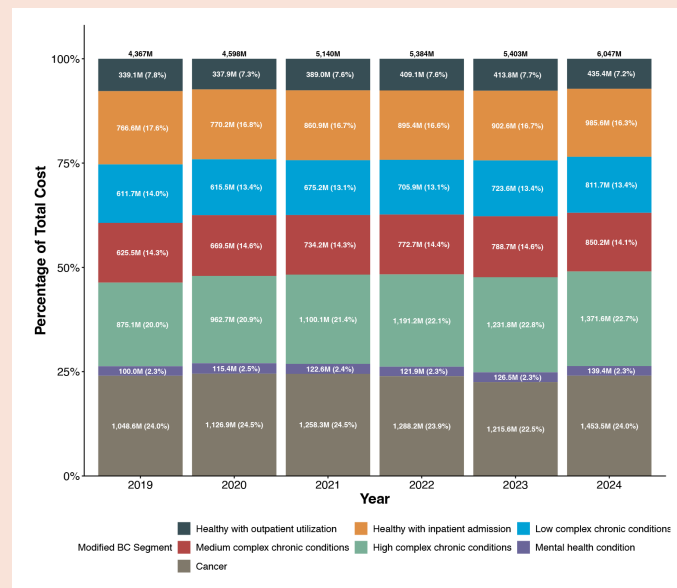
For patients in the high-complex chronic conditions segment, admissions were predominantly for pneumonia and complications of chronic diseases. These included diabetes with complications, cerebral

infarction, heart failure, fluid and electrolyte disorders, and cardiovascular implant-related complications.

Among patients with mental health conditions, common causes of admission included poisoning by drugs and other low-acuity conditions. In the cancer segment, the most common admissions were for encounters related to antineoplastic therapies, as well as primary and secondary malignancies, particularly breast, colorectal, and respiratory cancers.

Additionally, we compared the top 10 most common CCSR reasons for inpatient admissions in 2024 between adults aged 18–59 years and those aged ≥60 years (Supplementary Tables S4 and S5). Among patients with medium-complexity chronic conditions, there was substantial overlap, with 9 of the top 10 CCSR categories shared between age groups. In contrast, clearer age-related differences were observed among patients with high-complex chronic conditions. Adults aged <60 years were more likely to be admitted for chronic kidney disease, coronary atherosclerosis, nonspecific chest pain, and cutaneous infections, whereas those aged ≥60 years were more frequently admitted for osteoarthritis, pneumonia, and urinary tract infections.

Fig. 5. (A) Population composition by ModBC segment, (B) total healthcare expenditure by ModBC segment, (C) per-user cost by ModBC segment.

(A) Population Composition by Modified BC Segment**(C) Per-User Cost by Modified BC Segment****(B) Total Healthcare Costs by Modified BC Segment**

ModBC: Modified British Columbia Population Segmentation Framework

DISCUSSION

In this study, we examined healthcare utilisation across the SingHealth cluster, providing a comprehensive view of utilisation trends and factors associated with rising healthcare demand. Leveraging a large longitudinal dataset across the continuum of care, we found that inpatient care remained the largest cost component, increasing substantially in absolute terms while its share of total expenditure remained stable. Healthcare expenditure grew most markedly among patients aged 70–79 years and ≥80 years, with inpatient care accounting for most of this increase. This pattern is consistent with demographic shifts, with increased service use attributable to a growing older population rather than increased utilisation intensity within age groups. Concurrently, inpatient per-user expenditure rose over time, particularly among adults aged ≥60 years, while outpatient and primary care per-user costs remained relatively stable.

Using the ModBC population segmentation framework, we observed a shift towards greater clinical complexity, with growth in the high-complex chronic conditions and cancer segments. Together, these segments accounted for over 40% of total expenditure and were associated with substantially higher per-user costs. Diagnosis-level analyses using CCSR further revealed age-related differences in utilisation patterns within these groups. Taken together, these findings

Within the cancer segment, younger adults were more commonly admitted for ductal breast cancer, endocrine system cancers, female reproductive system cancers, and non-Hodgkin lymphoma, while older adults were more likely to be admitted for male reproductive system cancers, respiratory cancers, pneumonia, and urinary tract infections. Overall, diagnosis-level analyses revealed age-related differences in utilisation patterns, particularly within the high-complex chronic and cancer segments.

Table 1. Distribution of top 10 CCSR codes (in square brackets) for all inpatient admissions in FY24 by patient segment, with counts and percentage of admissions in brackets.

Whole cohort		ModBC Segment					
Healthy with inpatient admission		Low-complex chronic conditions		Medium-complex chronic conditions	High-complex chronic conditions	Mental health condition	Cancer
1	Pneumonia (except that caused by tuberculosis) [RSP002]: 9626 (3.1)	Benign neoplasms [NEO073]: 4332 (4.2)	Other specified and unspecified upper respiratory disease [RSP007]: 2482 (5)	Coronary atherosclerosis and other heart disease [CIR011]: 2384 (6.1)	Pneumonia (except that caused by tuberculosis) [RSP002]: 3191 (5.5)	Poisoning by drugs, initial encounter [INJ022]: 308 (3.4)	Encounter for antineoplastic therapies [FAC006]: 2837 (5.2)
2	Benign neoplasms [NEO073]: 9247 (2.9)	Intestinal infection [DIG001]: 4111 (4)	Abdominal pain and other digestive/abdomen signs and symptoms [SYM006]: 1905 (3.9)	Nonspecific chest pain [CIR012]: 1215 (3.1)	Diabetes mellitus with complication [END003]: 3092 (5.3)	Abdominal pain and other digestive/abdomen signs and symptoms [SYM006]: 300 (3.3)	Breast cancer - all other types [NEO030]: 2412 (4.5)
3	Abdominal pain and other digestive/abdomen signs and symptoms [SYM006]: 8199 (2.6)	Abdominal pain and other digestive/abdomen signs and symptoms [SYM006]: 3303 (3.2)	Benign neoplasms [NEO073]: 1793 (3.6)	Osteoarthritis [MUS006]: 1204 (3.1)	Cerebral infarction [CIR020]: 2287 (3.9)	Gastritis and duodenitis [DIG007]: 256 (2.8)	Gastrointestinal cancers - colorectal [NEO015]: 2061 (3.8)
4	Intestinal infection [DIG001]: 7887 (2.5)	Other specified upper respiratory infections [RSP006]: 3197 (3.1)	Osteoarthritis [MUS006]: 1533 (3.1)	Acute myocardial infarction [CIR009]: 1192 (3)	Heart failure [CIR019]: 2015 (3.5)	Intestinal infection [DIG001]: 246 (2.7)	Secondary malignancies [NEO070]: 1928 (3.6)
5	Gastritis and duodenitis [DIG007]: 6381 (2)	Encounter for observation and examination for conditions ruled out (excludes infectious disease, neoplasm, mental disorders) [FAC003]: 2738 (2.6)	Gastritis and duodenitis [DIG007]: 1475 (3)	Diabetes mellitus with complication [END003]: 1172 (3)	Fluid and electrolyte disorders [END011]: 1861 (3.2)	Nonspecific chest pain [CIR012]: 224 (2.5)	Pneumonia (except that caused by tuberculosis) [RSP002]: 1508 (2.8)
6	Other specified upper respiratory infections [RSP006]: 5863 (1.9)	Other specified female genital disorders [GEN025]: 2683 (2.6)	Respiratory signs and symptoms [SYM013]: 1424 (2.9)	Abdominal pain and other digestive/abdomen signs and symptoms [SYM006]: 1138 (2.9)	Complication of cardiovascular device, implant or graft, initial encounter [INJ033]: 1762 (3)	Respiratory signs and symptoms [SYM013]: 195 (2.2)	Benign neoplasms [NEO073]: 1316 (2.4)
7	Skin and subcutaneous tissue infections [SKN001]: 5776 (1.8)	Pneumonia (except that caused by tuberculosis) [RSP002]: 2608 (2.5)	Asthma [RSP009]: 1403 (2.9)	Benign neoplasms [NEO073]: 1053 (2.7)	Urinary tract infections [GEN004]: 1515 (2.6)	Other specified and unspecified upper respiratory disease [RSP007]: 187 (2.1)	Respiratory cancers [NEO022]: 1269 (2.3)
8	Diabetes mellitus with complication [END003]: 5697 (1.8)	Gastritis and duodenitis [DIG007]: 2395 (2.3)	Skin and subcutaneous tissue infections [SKN001]: 1320 (2.7)	Pneumonia (except that caused by tuberculosis) [RSP002]: 1019 (2.6)	Other general signs and symptoms [SYM016]: 1342 (2.3)	Benign neoplasms [NEO073]: 176 (2)	Non-Hodgkin lymphoma [NEO058]: 1109 (2)
9	Other specified and unspecified upper respiratory disease [RSP007]: 4941 (1.6)	Haemolytic jaundice and perinatal jaundice [PNL007]: 2143 (2.1)	Intestinal infection [DIG001]: 1146 (2.3)	Gastritis and duodenitis [DIG007]: 1004 (2.6)	Acute myocardial infarction [CIR009]: 1256 (2.2)	Pneumonia (except that caused by tuberculosis) [RSP002]: 175 (1.9)	Implant, device or graft related encounter [FAC009]: 1071 (2)
10	Respiratory signs and symptoms [SYM013]: 4892 (1.6)	Acute bronchitis [RSP005]: 2028 (2)	Pneumonia (except that caused by tuberculosis) [RSP002]: 1125 (2.3)	Skin and subcutaneous tissue infections [SKN001]: 915 (2.3)	Coronary atherosclerosis and other heart disease [CIR011]: 1237 (2.1)	Other general signs and symptoms [SYM016]: 172 (1.9)	Male reproductive system cancers - prostate [NEO039]: 1048 (1.9)

CCSR: Clinical Classifications Software Refined; FY: financial year; ModBC: Modified British Columbia Population Segmentation Framework

suggest that demographic change and increasing clinical complexity are important factors associated with healthcare utilisation and expenditure.

Demographic shifts and the steepening hypothesis

The demographic shifts observed in our cohort mirror national ageing trends. Singapore is among the world's fastest ageing societies and is projected to become a super-aged society by 2030.¹⁴ Between 2019 and 2024, the proportion of residents aged ≥ 60 years increased nationally from 21.4% to 25.1%,¹⁵ while rising more rapidly in our healthcare cohort from 29.4% to 34.2%. Over the same period, healthcare expenditure for this group in SingHealth increased from SGD 2.24 billion (51.2% of total expenditure) to SGD 3.45 billion (57.0%) (Supplementary Table S3).

Our findings show that population ageing is amplified within healthcare cohorts, with a disproportionate concentration of utilisation and expenditure among older adults. Patients aged ≥ 60 years had higher total and per-user expenditures and experienced faster expenditure growth over time (Supplementary Fig. S4; Fig. 4C). This is consistent with the steepening hypothesis, which posits that age-specific healthcare spending increases more rapidly among older individuals over time,^{16,17} as reported in other developed settings.^{16,18,19}

Central to the steepening hypothesis are the dimensions of chronological age, per-user expenditure, and time.¹⁶ Over time, demographic shifts are associated with a greater proportion of older individuals within the population, while advances in medical care have extended life expectancy and expanded treatment options for older adults, potentially increasing maintenance costs over the life course.^{19,20}

We did not examine time-to-death and therefore could not assess the widely discussed “red herring” hypothesis, which posits that ageing may not substantially influence healthcare expenditure when adjusted for an individual's proximity to death.^{17,21} Nevertheless, the patterns observed in our study remain consistent with several plausible explanations.

First, technological innovation is closely linked to both health outcomes and healthcare costs, highlighting the importance of cost-effective, value-based adoption to support sustainable expenditure growth.¹⁷ Second, the interplay between longevity, healthcare innovation, and expenditure suggests that extended survival may be associated with higher long-term costs. Taken together, these findings support a life-course approach to care, which may support informed, value-based decisions that promote healthy ageing and appropriate resource use over time. Within this context, advance care planning and end-of-life discussions remain important to help align

care with patients' values and preferences, and may also shape healthcare utilisation and expenditure.²¹

Insights from service utilisation rates

Inpatient utilisation remained the dominant driver of healthcare expenditure. Absolute inpatient service utilisation increased markedly over time, particularly among patients aged 70–79 years and ≥ 80 years (Fig. 3A; Supplementary Fig. S4). However, relatively stable inpatient utilisation rates (Fig. 3B) suggest that this growth is more consistent with the expansion of older age groups rather than with increased utilisation intensity within age groups. This stability may reflect the effectiveness of ongoing efforts to manage demand despite demographic shifts. Notably, the study period spans the COVID-19 pandemic (2020–2022) and post-pandemic recovery. Despite this, we did not observe a clear rebound pattern in utilisation or expenditure, characterised by a transient spike followed by a decline; but rather broadly consistent year-on-year growth throughout the study period. While pandemic-related effects cannot be fully disentangled from underlying secular trends, extending the study period to 2024 provides a longer post-pandemic observation window, improving the interpretability of temporal trends.

Considered alongside rising inpatient per-patient expenditure among older adults aged ≥ 60 years (Fig. 4), these findings suggest that increasing costs reflect not only population ageing and technological advances but also greater resource intensity per patient, potentially related to increasing clinical complexity and multimorbidity. While CCSR-based analyses provide insight into utilisation reasons, they do not fully capture clinical complexity, and more advanced methods are needed to assess its evolution over time.

Although stable inpatient utilisation rates are desirable, greater utilisation of primary care may be preferable from a system perspective, as it reflects a shift towards lower-cost, community-based care. In the context of Healthier SG, our data include only public-sector primary care utilisation, with private-sector data not yet available. Nevertheless, strengthening primary and community-based care remains critical to moderating inpatient expenditure growth. The success of Healthier SG will depend on addressing persistent barriers to primary care access, including limited consultation time, long waiting times, gaps in continuity of care, provider workload, and administrative burden.²²

Clinical complexity as a driver of healthcare expenditure

Clinical complexity, as characterised by the ModBC population segmentation framework, provides an

important lens for interpreting patterns of healthcare utilisation and expenditure. By incorporating information from the index year and the preceding 4 years, ModBC assigns patients to mutually exclusive segments as a pragmatic proxy for underlying complexity. Patients in the high-complex chronic conditions and cancer segments accounted for nearly half of total healthcare expenditure, with per-user costs more than twice those of other segments, consistent with an important association between clinical complexity and higher costs.

Diagnosis-level analyses using CCSR further demonstrated that inpatient admissions were increasingly characterised by more complex conditions as ModBC segment severity increases. While ModBC enables identification of high-need patients, the marked heterogeneity in CCSR diagnoses within segments suggests that segmentation alone may be insufficient to guide actionable interventions, consistent with prior studies.²³ However, the dimensionality reduction afforded by CCSR allows clinically related conditions to be grouped and could be incorporated into predictive models^{24,25} as both inputs and outputs. This would enable the development of models that jointly capture utilisation risk and underlying clinical factors—an approach that would be difficult using highly granular ICD-10 codes alone.

Integrating demographic change, healthcare utilisation, and clinical complexity

Taken together, our findings are consistent with a pathway in which population ageing and secular advances in medical care increase the number of clinically complex patients, alongside higher healthcare utilisation and expenditure. Stable utilisation rates across age groups suggest that rising absolute utilisation is more closely associated with shifts in population composition, while increasing inpatient per-user expenditure points to greater resource intensity per patient. In this context, population ageing is a distal, non-modifiable driver of demand, whereas clinical complexity is a more proximal, potentially actionable factor.

Strengths and limitations

This study has several strengths. It uses a large, contemporary patient-level dataset spanning 6 years and the full continuum of care within Singapore's largest healthcare cluster, enabling robust longitudinal analyses of healthcare utilisation and expenditure. Through patient-level linkage across care settings and application of a population segmentation framework at cluster scale, it provides a granular post-pandemic baseline for system-level planning. These data offer a comprehensive view of utilisation, complexity, and

expenditure patterns, with relevance for national policy on healthcare financing, system capacity, and resource planning.

Nevertheless, several limitations should be acknowledged. First, as an observational analysis using routinely collected administrative and clinical data, causal relationships cannot be established. Temporal associations do not imply causality, and the effects of policy changes, demographic shifts, technological advances, and health-seeking behaviours cannot be fully disentangled. Residual confounding, variation in coding practices, and data completeness may introduce bias.

Second, the study period encompasses the COVID-19 pandemic, which disrupted healthcare delivery and utilisation patterns. Although the year-stratified results allow descriptive comparisons across pre-, during-, and post-pandemic phases, we did not perform a formal causal analysis of COVID-19 effects. While isolating its specific impact is challenging, the inclusion of data beyond the acute phase enhances the generalisability of our findings.

Third, this analysis was confined to patients who utilised SingHealth's services. Although SingHealth serves nearly half of Singapore's population, utilisation patterns may differ across clusters and geographic areas due to variations in demographics, service configurations, and referral patterns, limiting generalisability.

Fourth, the analysis did not account for patient mobility across clusters or private-sector utilisation, potentially underestimating total healthcare use. Care delivered outside the SingHealth system, including private specialist services, traditional medicine, and overseas treatment, was not captured.

Fifth, this study focused on utilisation and expenditures rather than clinical outcomes such as mortality, disease progression, or functional status. Cost estimates reflect the provider's perspective and do not capture broader societal costs such as productivity losses or informal caregiving.

Sixth, although comprehensive, the dataset lacks detailed clinical information on disease severity, functional status, comorbidity burden, and quality-of-care metrics, limiting the assessment of the appropriateness and effectiveness of care. While CCSR enables clinically meaningful categorisation, it does not fully capture variation in clinical complexity or resource use over time. This study also did not assess admission avoidability; thus, observed inpatient utilisation and expenditure should not be assumed to represent preventable care. Future work could apply existing MOH frameworks to avoidable admissions to better identify modifiable drivers of inpatient use.

Finally, population segmentation approaches have inherent limitations. While they provide useful strategic insights, patients within each segment remain heterogeneous and findings cannot be directly translated into intervention strategies without more sophisticated analysis.

In summary, rising healthcare utilisation and expenditure appear to be driven by a combination of population ageing and increasing clinical complexity. Advances in medical care have extended life expectancy and expanded treatment options, but have also increased long-term maintenance costs, particularly among older adults. Addressing these challenges will require a sustained shift towards preventive, community-based, and value-driven models of care to ensure long-term system sustainability.

Supplementary Materials

Supplementary Table S1. Detailed classification criteria for Modified British Columbia Population Segmentation Framework.

Supplementary Table S2. Service utilisation rate (%), with year-on-year change (percentage points) in brackets.

Supplementary Table S3. Expenditure (in SGD millions), with year-on-year change (percentage points) in brackets.

Supplementary Table S4. Distribution of top 10 CCSR codes for inpatient admissions in FY24 and for patients age ≥60 years, by patient segment, with counts and percent of admissions in brackets.

Supplementary Table S5. Distribution of top 10 CCSR codes for inpatient admissions in FY24 and for patients age 18–59 years, by patient segment, with counts and percent of admissions in brackets.

Supplementary Table S6. The 10 most prevalent ICD-10 codes within the 10 most common CCSR categories for the entire SingHealth cohort in Financial Year (FY) 2024.

Supplementary Table S7. The 10 most prevalent ICD-10 codes within the 10 most common CCSR categories for patients in the Modified British Columbia (ModBC) segment—Healthy with inpatient admission.

Supplementary Table S8. The 10 most prevalent ICD-10 codes within the 10 most common CCSR categories for patients in the ModBC segment—Low complex chronic conditions.

Supplementary Table S9. The 10 most prevalent ICD-10 codes within the 10 most common CCSR categories for patients in the ModBC segment—Medium complex chronic conditions.

Supplementary Table S10. The 10 most prevalent ICD-10 codes within the 10 most common CCSR categories for patients in the ModBC segment—High complex chronic conditions.

Supplementary Table S11. The 10 most prevalent ICD-10 codes within the 10 most common CCSR categories for patients in the ModBC segment—Mental health condition.

Supplementary Table S12. The 10 most prevalent ICD-10 codes within the 10 most common CCSR categories for patients in the ModBC segment—Cancer.

Supplementary Fig. S1. Indexed population growth by ethnicity.

Supplementary Fig. S2. Indexed population growth by age band.

Supplementary Fig. S3. Indexed healthcare expenditure growth by ethnicity and type of care.

Supplementary Fig. S4. Indexed healthcare expenditure growth by age group and type of care.

Supplementary Fig. S5. Indexed service utilisation (absolute counts) by age group and type of care.

Ethics statement

Ethics approval was obtained from the SingHealth Centralised Institutional Review Board (CIRB) prior to initiating this study (SingHealth CIRB reference number: 2022/00892). As all participant data were de-identified, a waiver for participant consent was also obtained.

Acknowledgments

This research is supported by the National Medical Research Council Population Health Research Grant (Award No.: MON-PHRGTC-7-0001). The funder was not involved in the design of the study; the collection, analysis, and interpretation of data; writing the report; and did not impose any restrictions regarding the publication of the report.

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.

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Singapore expert consensus on optimising lipid-lowering strategies in acute coronary syndrome: A modified Delphi study

Ru San Tan^{1,2} MD, Jonathan Yap^{1,2} MBBS, Colin Yeo³ MBBS, Kian Keong Poh^{4,5} MBBSChir, Peter Chee Hong Yan⁶ MBBS, Pow Li Chia⁷ MBBS, Michael Chun Leng Lim⁸ MBBS, David Foo⁷ MBBS, Fahim Haider Jafary⁷ MD, Natalie Si Ya Koh^{1,2} MBBS

ABSTRACT

Introduction: Acute coronary syndrome (ACS) carries a high early risk of recurrent events, yet time-to-target low-density lipoprotein cholesterol (LDL-C) is often prolonged, and goal attainment is suboptimal in real-world practice. The authors aimed to develop expert consensus recommendations for post-ACS lipid management in Singapore, focusing on LDL-C targets, pharmacotherapy, escalation strategies, and implementation tools to improve adherence and reduce therapeutic inertia.

Methods: A modified Delphi methodology was employed with a panel of 10 members. Evidence was synthesised from guidelines, randomised trials, meta-analyses, and observational studies. Thirty-two statements were drafted across 5 domains (LDL-C targets; timing/monitoring; pharmacotherapy; special populations; implementation/adherence/health-system strategies) and rated anonymously on a 5-point Likert scale. Consensus thresholds were defined as high ($\geq 75\%$ concordant), moderate (55–74%), and low ($< 55\%$).

Results: After the final round, 30 of 32 statements achieved high consensus, and 2 received low consensus. Key agreements included measuring lipids within 24 hours of admission and retesting at 4–6 weeks, early initiation of high-intensity statins, and upfront combination therapy with statin + ezetimibe when monotherapy is unlikely to achieve the goals. Consideration of a proprotein convertase subtilisin/kexin type 9 inhibitor at discharge was recommended if LDL-C remained > 1.4 mmol/L. Special considerations included older adults, familial hypercholesterolaemia, lower statin adherence among women, and the role of lipoprotein(a). The panel recommended adopting objective metrics, integrating electronic health record prompts, and developing localised pathways to harmonise care transitions.

Conclusions: The consensus recommendations provide a tailored approach for Singapore, emphasising early

action, proactive escalation, and systems-level interventions to improve post-ACS outcomes.

Keywords: cholesterol, ezetimibe, LDL, PCSK9 inhibitor, statins

CLINICAL IMPACT

What is New

- This expert consensus provides structured, Delphi-based recommendations for optimising post-acute coronary syndrome (ACS) low-density lipoprotein cholesterol management in Singapore.
- It highlights key gaps in current practice and provides tailored, context-specific recommendations across diagnosis, treatment initiation, follow-up, and system-level implementation.

Clinical Implications

- The recommendations advocate for early combination therapy, timely reassessment, and proactive treatment intensification, particularly in very high-risk ACS patients.
- This guidance may improve clinical outcomes, reduce recurrent events, and support national efforts to standardise lipid management practices.

INTRODUCTION

Among ischaemic heart diseases (IHDs), acute coronary syndrome (ACS) remains the leading cause of death

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¹ Department of Cardiology, National Heart Centre Singapore, Singapore

² Duke-NUS Medical School, Singapore

³ Department of Cardiology, Changi General Hospital, Singapore

⁴ Department of Cardiology, National University Heart Centre Singapore, Singapore

⁵ Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁶ Gleneagles Hospital Singapore, Singapore

⁷ Department of Cardiology, Tan Tock Seng Hospital, Singapore

⁸ Singapore Heart, Stroke & Cancer Centre Pte Ltd, Singapore

Correspondence: Dr Ru San Tan, Department of Cardiology, National Heart Centre Singapore, Duke-NUS Medical School, Singapore, Singapore.

Email: tan.ru.san@singhealth.com.sg

Accepted: 21 May 2026

Published Online First: 3 June 2026

worldwide, with nearly half of cases arising from the Asia-Pacific region.¹ In Singapore, IHD accounted for 19.7% of all deaths in 2023.² Beyond mortality, ACS imposes substantial direct healthcare costs and indirect losses through impaired productivity and reduced quality of life.³

Low-density lipoprotein cholesterol (LDL-C) is the primary modifiable therapeutic target, especially in individuals at high risk of future events.⁴ Yet many patients fail to achieve recommended LDL-C goals after an ACS. Guidelines advocate a stepwise escalation of lipid-lowering therapy (LLT): initiation with high-intensity statin, followed by ezetimibe, and subsequent escalation with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (PCSK9i) when targets remain unmet. In practice, however, this approach may delay LDL-C goal achievement, especially during the high-risk post-ACS phase.³

Emerging evidence suggests that faster, more intensive strategies can improve both timeliness of control and clinical outcomes. A “PCSK9i fast-track” approach has been reported as safe and effective for achieving LDL-C targets more rapidly than the conventional stepwise pathway in real-world ACS cohorts.⁵ Achieving LDL-C targets within 12 weeks after ACS is associated with significantly fewer cardiovascular events.⁶ Likewise, systematic adoption of a personalised “strike early and strong” LLT strategy has yielded higher goal-achievement rates and lower risk of major adverse cardiovascular events (MACE) at 1 year compared with a stepwise approach.⁷ Real-world data from Korean patients further show that reaching the LDL-C goal within 4–12 weeks after discharge is linked to fewer recurrent MACE in very-high-risk atherosclerotic cardiovascular disease (ASCVD), particularly in ACS.⁶

International guidance increasingly reflects this urgency. European guidance supports intensifying the use of a PCSK9i by 4–6 weeks after ACS if lipid goals are unmet. In contrast, the current Singapore lipid guidelines emphasise reassessment after 12 weeks of maximally tolerated statin plus ezetimibe, without ACS-specific escalation advice.^{8,9} Such differences are likely to contribute to greater practice variability, slower time-to-target LDL-C, and missed opportunities for early risk reduction.

Data from the Singapore cohort of the Dyslipidaemia International Study II reported suboptimal statin doses and infrequent use of combination therapy among patients admitted with ACS.¹⁰ Collectively, these observations suggest the need for better systems for monitoring, timely reassessment, and therapy intensification.

To address these gaps, a structured, modified Delphi process was undertaken to formulate practical,

evidence-based recommendations tailored to Singapore for optimising LDL-C management in the post-ACS setting. This consensus was ACS-specific, rather than a general ASCVD framework. The focus was on gathering insights on early LLT optimisation and appropriate follow-up to enable timely treatment intensification. In addition, implementation-oriented aspects, such as auditable quality metrics, care-transition processes, and system-level approaches aimed at reducing therapeutic inertia and improving LDL-C goal attainment in routine clinical practice were also included.

METHODS

This study aimed to develop consensus-based recommendations on lipid management among patients with ACS, focusing on recent therapeutic advances. To achieve this, a modified Delphi-based approach was employed, designed to harness collective expertise and refine understanding through iterative feedback. While this study was not prospectively registered, it adhered to a transparent process in alignment with established consensus development practices. The outcomes are reported in accordance with the ACCORD guidelines (Supplementary Annex S1). An overview of the workflow is summarised in (Fig. 1).

Selection of the expert panel and finalising core objectives

A panel of 10 experts with diverse clinical backgrounds was invited to participate in the voting and structured discussions (Supplementary Annex S2). Panellists were selected based on: (1) established subject-matter expertise, (2) peer-reviewed research contributions, and (3) substantial clinical experience in the management of ACS. One member with extensive experience in the relevant domain was designated as chair. The chair outlined the methodological approach, oversaw the process, and moderated all proceedings to ensure balanced participation. To minimise bias, the chair abstained from all voting.

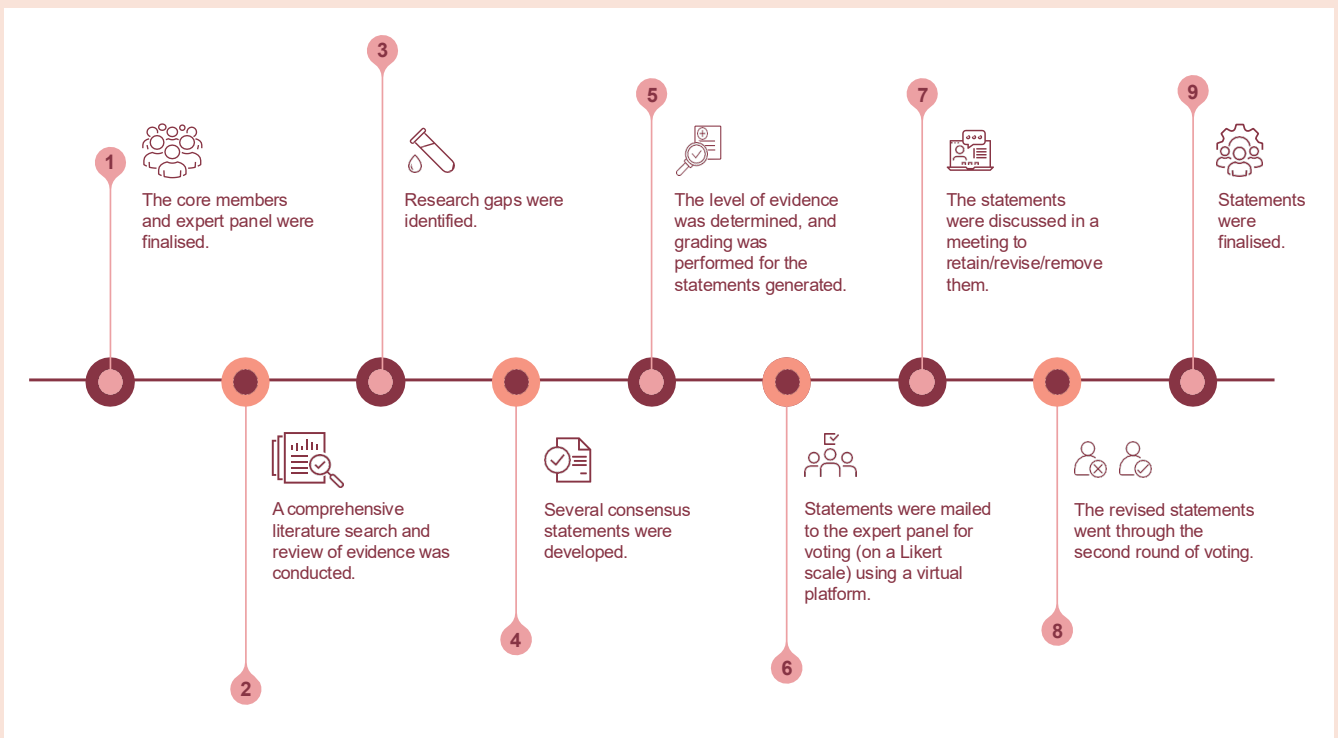
At the outset, the panel agreed on the objectives of the consensus exercise, which were to:

- (1) Analyse current clinical practices in lipid management after ACS.
- (2) Evaluate existing international and Singapore recommendations and supporting evidence.
- (3) Develop consensus statements to facilitate optimal, locally relevant care for patients with ACS in Singapore.

Review of evidence and formulation of consensus statements

A comprehensive search of the PubMed database was conducted to identify relevant literature

Fig. 1. Overview of the consensus development process.



published in English in the last 10 years. A scoping review of identified articles was conducted to inform the development of consensus statements. Broad domains were identified, and consensus statements were drafted. Studies with adequate methodological rigour were included (e.g. randomised controlled trials [RCTs], systematic reviews, meta-analyses, and cohort studies). Major guidelines/consensus statements were also reviewed. A summary of the literature search was shared with the expert panel as a pre-read. Separate piloting of the survey instrument was not conducted.

Delphi survey rounds and consensus thresholds

The draft statements were formatted into a structured questionnaire and circulated to the expert panel via a secure online survey platform. Each panellist completed the survey anonymously. Panellists recorded their position on each statement using a 5-point Likert scale: strongly agree, agree, neither agree nor disagree, disagree, and strongly disagree.

For every statement, responses were quantified and classified according to predefined consensus levels: (1) high agreement: $\geq 75\%$ agreement or disagreement; (2) moderate agreement: 55–74% agreement or disagreement; low agreement: $<55\%$ agreement or disagreement.

Consensus development process

A modified Delphi approach was used, combining 2 survey rounds with a consensus meeting. In round 1,

panellists completed the anonymised questionnaire (5-point Likert scale). The responses were aggregated and classified using the prespecified consensus thresholds. A meeting was then convened to review the results of round 1. The panel discussed each statement to decide whether to retain as is, revise, or remove. Following the meeting, all panellists were invited to participate in revoting.

The session chair ensured balanced participation and explicitly captured disagreements. Before finalising recommendations, the panel reviewed a summary of majority positions and documented minority opinions where relevant so that differing viewpoints were addressed and reflected transparently in the final manuscript.

RESULTS

This consensus was carried out between March and June 2025. The participants were provided with 15 days to complete the questionnaire. The participation rate was 100% for all rounds. The initial Delphi round comprised 32 statements organised into 5 thematic sections: LDL-C targets ($n=3$); timing and monitoring of therapy ($n=5$); pharmacotherapy ($n=11$); special considerations ($n=4$); and implementation, adherence, and health-system strategies ($n=9$). Of these 32 statements, 28 achieved high consensus, while 4 achieved moderate consensus in round 1. The panel reviewed the aggregate responses and the accompanying evidence at the subsequent

meeting. Based on the discussion, 6 statements were modified to improve clarity and scope and to align the recommendation with the strength of evidence.

All 6 revised statements were recirculated for a second vote. Four of the 6 attained high consensus after revision, while 2 fell to low consensus on revote. The 2 statements with low consensus were reported as areas of divergent expert opinion and/or targets for future research. The finalised consensus statements are presented in Tables 1–5.

DISCUSSION

Lipid management in the post-ACS phase remains critical. Several studies have suggested the importance of aggressive LDL-C lowering. The concept of a “strike early-strike strong” approach, initiating intensive LLT soon after ACS, has shown significant reductions in LDL-C levels and cardiovascular events.¹¹ However, discrepancies in the timing of therapy escalation, selection of combination regimens, and system-level implementation call for further standardisation of Singapore protocols for lipid management to ensure optimal patient outcomes.

LDL-C targets for ACS (Table 1)

In routine care, post-ACS lipid surveillance remains inconsistent. A considerable proportion of patients do not have a repeat LDL-C measurement after discharge, and among those who were retested, fewer than half have been reported to achieve guideline LDL-C goals. This highlights a substantial opportunity to improve post-ACS lipid management in community practice.^{10,12} The panel agreed that there was a need to optimise lipid management in patients with ACS.

Randomised trials and meta-analyses consistently indicate that pushing LDL-C lower than previously

recommended thresholds has yielded additional clinical benefit.^{13,14} An approximately 22% reduction in major vascular events per 1.0 mmol/L decrease in LDL-C at 1 year has been reported, with significant relative reductions of approximately 25% during each subsequent year of continued therapy.¹⁴

In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial among patients hospitalised for ACS, assignment to simvastatin 40 mg + ezetimibe 10 mg achieved a median time-weighted LDL-C of 1.4 mmol/L versus 1.8 mmol/L with simvastatin 40 mg alone ($P<0.001$). Over a median 6-year follow-up, the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction [MI], re-hospitalisation for unstable angina, coronary revascularisation, or nonfatal stroke) occurred in 32.7% with combination therapy versus 34.7% with statin monotherapy (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.89–0.99; $P=0.016$).¹³ These findings, reinforced by pivotal trials such as Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES), establish the value of intensive therapy, particularly in patients at the highest risk.

Beyond absolute thresholds, the magnitude of LDL-C reduction is also critical. Achieving a $\geq 50\%$ decrease is independently associated with fewer cardiovascular events in ACS, even among patients who have reached a level of <55 mg/dL (1.4 mmol/L). Conversely, suboptimal LDL-C lowering ($<50\%$) predicts higher event rates even when the on-treatment absolute LDL-C appears low, signalling residual risk from insufficient relative reduction.¹⁵ Long-term observational data after percutaneous coronary

Table 1. Consensus statements on LDL-C targets for ACS.

Statement no.	Finalised statement	Level of evidence	Finalised in round	Level of agreement
1	Despite recommendations on aggressive lipid-lowering therapy, real-world data indicate that suboptimal lipid management in ACS patients remains prevalent, justifying the urgency to address this issue.	2b ¹²	1	100%
2	In patients with ACS, an LDL-C reduction of $\geq 50\%$ from baseline [†] and a therapeutic target of <55 mg/dL (1.4 mmol/L) [‡] are recommended.	[†] 1b ¹³ ; [‡] 2b ¹⁵	1	100%
3	An LDL-C reduction below 40 mg/dL (1.0 mmol/L) should be considered in patients with a second vascular event within 2 years while taking maximally tolerated statin-based therapy.	1b ¹⁶	1	78%

ACS: acute coronary syndrome; LDL-C: low-density lipoprotein cholesterol

^{†,‡} Portions of the statement are indicated with respective supporting evidence.

Superscript numbers: refer to REFERENCES

intervention (PCI) showed that patients achieving >50% LDL-C reduction and LDL-C <1.4 mmol/L experienced the lowest 7-year risk of major adverse cardiac and cerebrovascular events, suggesting that both absolute and relative reductions may provide additional benefit.¹⁷ The panellists therefore agreed that a ≥50% reduction should remain a fundamental objective for any patient presenting with high LDL-C levels, even if the absolute target is met.

The European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommendations are based mainly on the findings of the IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES trials, which showed significant risk reduction in patients at a higher risk of future cardiovascular events.^{13,16,18} The ESC/EAS guidelines recommend considering an LDL-C target of <1.0 mmol/L (<40 mg/dL) for patients with a second cardiovascular event within 2 years. No attenuation of the clinical benefit of lowering LDL-C below 1.0 mmol/L has been reported.¹⁹ The panel members reached consensus on using this threshold for patients with a second vascular event within 2 years. During the discussion, some panellists pointed out that patients with ACS who also have diabetes, polyvascular disease, multivessel PCI, or a high-risk genetic profile should be directed to an even lower LDL-C target, although data remain limited for these specific phenotypes.

Timing and monitoring of therapy (Table 2)

Despite its established importance, lipid testing is often underutilised in patients presenting with ACS. Baseline lipids carry prognostic value and should

be measured within 24 hours of admission.²⁰ The panel emphasised that measurement within 24 hours of admission is important, as LDL-C levels fall by approximately 10–20% within 24–48 hours of acute MI. An “acute-phase dip” underestimates the true baseline and can mask the need for earlier therapy intensification.

A follow-up LDL-C assessment at 4–6 weeks after an event is essential to judge the response to initial therapy and to escalate promptly when needed.⁶ The panel put forth the pharmacokinetic rationale that the full statin effect is realised by approximately 4 weeks, and the MI-related lipid dip rebounds by that time. Although direct outcome data tied to the 4–6-week measurement are limited, earlier reassessment shortens the time to intensification, which is clinically meaningful in the high-risk early post-ACS window.

Failure to achieve LDL-C goals during the first year after ACS is associated with higher risk of recurrent cardiovascular events and re-hospitalisation, reinforcing the need for proactive, aggressive lipid-lowering early in recovery.²¹ Conversely, achieving LDL-C targets within 4–12 weeks has been linked to reduced risk of MACE, sustained LDL-C control, and lower healthcare utilisation and costs.⁶ These observations argue against therapeutic inertia and favour the timely escalation of therapy.

Along these lines, more frequent follow-up facilitates closer monitoring, supports medication adherence, and enables earlier treatment adjustments. Patients with multiple follow-ups are more likely to meet LDL-C targets than those seen only once at 12 months.²²

Table 2. Consensus statements on timing and monitoring of therapy.

Statement no.	Finalised statement	Level of evidence	Finalised in round	Level of agreement
4	LDL-C measurement should be performed within the first 24 hours of hospitalisation to establish a treatment baseline and support early therapy optimisation.	2b ²⁰	2	100%
5	For ACS patients, LDL-C levels should be re-evaluated at 4–6 weeks post-event to assess the effectiveness of lipid-lowering therapy and guide intensification.	2b ⁶	1	100%
6	Suboptimal LDL-C control in the first 12 months post-ACS is a major driver of recurrent events and re-hospitalisation.	2b ²¹	1	100%
7	Early achievement of LDL-C targets (4–12 weeks) is associated with a lower risk of recurrent MACE, sustained lower LDL-C levels over the long term, and lower healthcare resource utilisation among those with ACS.	2b ⁶	1	100%
8	Patients with more frequent follow-up visits show a greater reduction in LDL-C levels compared to those with only 1 visit, 12 months after hospital discharge.	2b ²²	1	100%

ACS: acute coronary syndrome; LDL-C: low-density lipoprotein cholesterol; MACE: major adverse cardiovascular events
Superscript numbers: refer to REFERENCES

The panel emphasised that lipid therapy should be fully optimised before transferring patients into shared-care models. In the panel discussion, it was highlighted that current hospital practices vary in timing and intensity, and harmonisation is needed to ensure consistent early goal attainment.

Pharmacologic therapy (Table 3)

Initiation of high-intensity statin therapy as early as possible in statin-naïve patients with ACS, irrespective of baseline LDL-C levels, is supported by robust

evidence and international guideline recommendations.²³ The panel agreed that every patient should leave the hospital on at least a moderate- to high-intensity statin, and that tracking this proportion at discharge should serve as a core quality metric to reduce unwarranted variation in care.

PCI remains the preferred reperfusion strategy in ACS but is occasionally complicated by the no-reflow phenomenon, which is associated with poor prognosis, reduced left ventricular ejection fraction, and adverse remodelling. The panel agreed on the use of high-

Table 3. Consensus statements on pharmacologic therapy.

Statement no.	Finalised statement	Level of evidence	Finalised in round	Level of agreement
9	High-intensity statins should be initiated in statin-naïve patients with ACS as early as possible, irrespective of LDL-C values.	1b ²⁴	1	100%
10	In patients with ACS, it is recommended to initiate combination therapy upfront, especially when statin monotherapy is unlikely to achieve LDL-C targets.	1a ²⁵	1	100%
11	PCSK9 inhibitors should be considered at the time of discharge for patients with ACS with LDL-C >1.4 mmol/L despite statin + ezetimibe therapy to avoid delays in optimisation.	1a ^{26,27}	1	78%
12	In patients with ACS, the combination of statin and PCSK9 inhibitors can facilitate favourable changes in coronary atherosclerosis consistent with stabilisation and regression by 12 months.	1b ^{28,29}	1	100%
13	The early introduction of the PCSK9 inhibitor alongside statin therapy in patients with ACS can ameliorate plaque phenotype, ^{††} effects that are closely linked to a more substantial lowering of LDL-C levels even within a short-term period [‡] (i.e. 4–12 weeks) following the acute event.	†2b ³⁰ ; †2a ³¹	1	100%
14	In statin-intolerant patients, greater LDL-C reductions can be observed with PCSK9 inhibitors compared to ezetimibe, with lower rates of musculoskeletal adverse events.	1b ³²	1	100%
15	Bempedoic acid could be a useful treatment option [†] in statin-intolerant patients for addressing both residual cholesterol and inflammatory risk after ACS. [‡]	†1b ³³ ; †2b ³⁴	1	100%
16	Elevated inflammatory markers, such as hsCRP (e.g. >2 mg/L), during follow-up of ACS may prompt consideration of more intensive lipid-lowering therapies even when LDL-C is at goal.	1b ³⁵	2	44%
17	Elevated apoB in patients during post-ACS follow-up with metabolic disease may prompt consideration of more aggressive lipid-lowering therapy even when LDL-C is at goal.	2a ³⁶	2	44%
18	Assessing lipoprotein(a) levels appears promising for risk stratification in ACS, offering valuable insights for tailoring secondary prevention strategies. For patients with ACS, a lipoprotein(a) level above 50 mg/dL (or 125 nmol/L) can be considered elevated and associated with increased cardiovascular risk.	2a ³⁷	2	100%
19	Acute high-dose statin therapy administered prior to PCI significantly reduces the risk of post-PCI no-events in patients presenting with ACS.	2a ³⁸	1	89%

ACS: acute coronary syndrome; apoB: apolipoprotein B; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; PCI: percutaneous coronary intervention; PCSK9: proprotein convertase subtilisin/kexin type 9

†,† Portions of the statement are indicated with respective supporting evidence.

Superscript numbers: refer to REFERENCES

dose statin therapy before PCI in patients with ACS to mitigate this risk, as it has been shown to significantly reduce post-PCI no-reflow events.³⁸

Although a sequential pathway (statin → add ezetimibe → consider PCSK9i) is biologically and economically intuitive, it assumes adequately resourced post-hospital care and cardiac rehabilitation. However, these services remain limited, with only a minority of eligible patients participating.³⁹

Given that high-intensity statin monotherapy often fails to deliver recommended targets in ACS, up-front combination LLT, particularly with ezetimibe, has been recommended.²⁵ In the IMPROVE-IT trial, adding ezetimibe 10 mg to simvastatin 40 mg after ACS achieved a lower median time-weighted LDL-C level (1.4 versus [vs] 1.8 mmol/L; $P < 0.001$) and a modest but significant reduction in the composite endpoint over 6 years (HR 0.94, 95% CI 0.89–0.99). Notably, even with the ezetimibe add-on, LDL-C was lowered by approximately 40%, indicating that further intensification is frequently required to reach the dual goal of < 1.4 mmol/L and $\geq 50\%$ reduction in this population.

Cholesterol-lowering agents that target PCSK9 include monoclonal antibodies (mAbs) (alirocumab and evolocumab) and inclisiran. When added to statins ± ezetimibe, both classes demonstrate considerable LDL-C-lowering potential. Biweekly alicumab biweekly lowers LDL-C by approximately 45–60% (dose-dependent, 75 vs 150 mg) and by approximately 50% with 300 mg monthly. Evolocumab reduces LDL-C by approximately 60% with 140 mg biweekly and by approximately 55% with 420 mg monthly. Inclisiran achieves approximately 50% peak reduction at approximately 30 days after the dose, with approximately 53% reduction still observed around day 180. However, interindividual variability in LDL-C response can be seen with both mAbs and inclisiran, requiring further characterisation of predictors of response.⁴⁰

For patients with LDL-C > 1.4 mmol/L despite dual therapy (statin + ezetimibe), the panel recommended considering a PCSK9i at discharge to avoid therapeutic inertia.^{26,27} Existing data suggest differences in effectiveness between PCSK9is, with some evidence pointing towards a more pronounced effect with evolocumab.^{41,42} However, head-to-head, outcome-focused evidence remains limited.

Beyond LDL-C metrics, the combination of statins + PCSK9i has shown consistent efficacy in promoting plaque stabilisation/regression. Intravascular imaging studies, Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound (also known as GLAGOV) and High-Resolution Assessment of Coronary Plaques in a

Global Evolocumab Randomized Study (also known as HUYGENS), demonstrated favourable changes in percent atheroma volume and fibrous-cap thickness when evolocumab was added to statins in patients with established ASCVD, including recent ACS.^{28,29}

In patients with statin intolerance, PCSK9is provide substantially greater LDL-C reductions than ezetimibe and are associated with fewer musculoskeletal adverse events, making them the preferred nonstatin backbone in this setting.³² Bempedoic acid also offers a nonstatin option to address residual LDL-C and inflammation.³³ The Cholesterol Lowering via Bempedoic Acid (ECT1002), an ACL-Inhibiting Regimen (CLEAR) Harmony trial highlighted significant LDL-C reductions with bempedoic acid alongside notable high-sensitivity C-reactive protein (hsCRP) lowering.³⁴ A single 180 mg daily dose reduces LDL-C by approximately 24.5% as monotherapy and by approximately 38–40% in a fixed-dose combination with ezetimibe.⁴³ However, the evidence is stronger in primary prevention, with more conclusive secondary prevention data still needed.⁴⁴ A post hoc reconstruction of the CLEAR Outcomes trial suggested 30% lower all-cause mortality with bempedoic acid in the primary prevention subgroup, whereas in secondary prevention, there was a nonsignificant trend toward higher all-cause mortality (approximately 15%). A similar pattern was reported for cardiovascular mortality, warranting careful interpretation and further study.⁴⁵

Biomarkers for risk assessment (Table 3)

Assessment of lipoprotein(a) or Lp(a) has emerged as a valuable tool for post-ACS risk stratification. Elevated levels of Lp(a) are linked to higher recurrent-event risk and may guide the choice and intensity of LLT, especially in patients with a family history of premature ASCVD or when residual risk persists.³⁷ The panel aligned on ≥ 125 nmol/L (approximately 50 mg/dL) as the “elevated” threshold and advised measuring outside the acute phase because Lp(a) drops transiently during MI.^{46,47} The optimal timing for Lp(a) measurement is not well defined.⁴⁶

While achieving LDL-C targets remains paramount, the panel also discussed hsCRP and apolipoprotein B (apoB) as potential risk markers. However, the panel felt that evidence is limited for therapy guidance based on these markers in post-ACS care. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (also known as JUPITER) trial, which is often cited for hsCRP, did not study the ACS population,³⁵ likely explaining the group’s mixed view. A practical barrier noted was access to testing, with many hospitals not having the resources for the hsCRP test. Some panellists favoured using hsCRP as a risk enhancer, particularly when hsCRP is high without alternative inflammatory causes,

while acknowledging that multiple conditions can elevate hsCRP and definitions of “elevated” can vary. For apoB, the panellists felt that the rationale was strong, but evidence for directing therapy based on apoB was not well established.

Special considerations (Table 4)

Meta-analyses show that LLTs, including statins, ezetimibe, and PCSK9is, are effective in older adults (age ≥ 75 years), significantly reducing cardiovascular events. Although relative risk reductions may be modest compared with those in younger cohorts, absolute benefits are comparable because the baseline risk is higher in this age group.⁴⁸ The panel agreed that age alone should not preclude intensive LDL-C lowering.

Lower adherence to statin therapy has been reported among women, often driven by perceived or real side effects and differences in risk perception.⁴⁹ The panel agreed that tailored adherence strategies, including targeted patient education, lower initial statin doses, and judicious use of nonstatin alternatives (e.g. ezetimibe, bempedoic acid), can improve adherence. These approaches aim to maintain momentum toward both absolute LDL-C targets and $\geq 50\%$ reductions.

Very high LDL-C levels in hospitalised patients with ACS should trigger evaluation for familial hypercholesterolaemia (FH), particularly in those < 65 years of age.⁵⁰ Early identification enables the timely initiation of intensive LLT, including high-intensity statin, ezetimibe, and/or PCSK9is.

The phenotype of heterozygous FH (HeFH) is variable, and many people with the condition are unaware of it unless they undergo genetic testing or experience an ischaemic event. Patients with HeFH often fail to achieve LDL-C targets. PCSK9is can be effective and safe for LDL-C reduction in such patients. Data from the Reduction of LDL-C With PCSK9

Inhibition in Heterozygous Familial Hypercholesterolemia Disorder-2 (also known as RUTHERFORD-2) trial showed approximately 60% LDL-C reductions in patients with HeFH treated with evolocumab.⁵¹

Patients with homozygous FH (HoFH) also exhibit a variable phenotype but are generally easier to recognise. They show a reduced and more variable LDL-C response. It has been reported that inclisiran does not meaningfully reduce LDL-C in HoFH, despite lowering circulating PCSK9.⁵² The panel agreed that early identification will enable the timely initiation of intensive LLT (high-intensity statin, ezetimibe, and/or PCSK9 inhibition).

Implementation, adherence, and health system strategies (Table 5)

Poor adherence and treatment discontinuation remain major barriers to LDL-C control. Patient misinformation or fear about statin adverse effects can be a leading contributor to suboptimal outcomes. For example, the perception that Asians are more susceptible to high-intensity statin side effects can hinder adherence. Patient-centred education about the proven benefits of statins and clarity on potential adverse effects can help mitigate noncompliance.⁵³ Implementing a dedicated lipid adherence pro-gramme, such as pharmacist-led interventions or follow-up by trained healthcare professionals, can considerably improve medication adherence and clinical outcomes.⁵⁴ The expert panel agreed that there is a need to implement such structured, evidence-driven interventions as effective strategies to bridge adherence gaps. Despite clear eligibility and benefit, many high-risk patients remain undertreated with PCSK9is, even after suboptimal response to maximally tolerated statin plus ezetimibe.⁵⁵ This gap indicates the need for system-wide strategies to improve identification and referral pathways to ensure that appropriate patients are escalated promptly.

Table 4. Consensus statements on special considerations.

Statement no.	Finalised statement	Level of evidence	Finalised in round	Level of agreement
20	Lipid-lowering therapy is equally effective in reducing cardiovascular events in patients aged ≥ 75 years as in younger populations, substantiating its use, including nonstatin treatment, in older patients.	1a ⁴⁸	1	89%
21	Lower adherence to statins in women, often due to side effects, may necessitate tailored strategies such as dose adjustment.	2a ⁴⁹	1	78%
22	During hospitalisation for ACS, very high LDL-C levels should prompt an investigation of familial hypercholesterolaemia.	2b ⁵⁰	1	100%
23	In patients with heterozygous familial hypercholesterolemia with inadequate control of LDL-C, PCSK9 inhibitors can be considered.	1b ⁵¹	1	100%

ACS: acute coronary syndrome; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9

Superscript numbers: refer to REFERENCES

Table 5. Consensus statements on implementation, adherence, and health system strategies.

Statement no.	Finalised statement	Level of evidence	Finalised in round	Level of agreement
24	In cases of non-compliance, patients should be counselled on the risks and benefits of statins, as misinformation is a common cause for lack of compliance.	2b ⁵³	1	100%
25	Dedicated lipid adherence programmes (e.g. pharmacist-led interventions) should be implemented to improve post-discharge adherence.	1a ⁵⁴	1	100%
26	A considerable proportion of patients eligible for PCSK9 inhibitors remain undertreated, underscoring the need for targeted identification and intervention.	2b ⁵⁵	1	100%
27	When cost remains a concern, it is important to select patients with the highest baseline risk who would gain the most from further intensification of lipid-lowering therapy with PCSK9 inhibitors.	2b ⁵⁶	1	100%
28	A nonstatin lipid-lowering agent can be recommended for patients already on a maximally tolerated statin who have an LDL-C level of ≥ 70 mg/dL (1.8 mmol/L).	1b ^{13,16,57}	1	100%
29	Singapore protocols similar to ACS lipid EuroPath tool should be developed to identify optimisation opportunities and support standardised lipid management in post-ACS patients.	4 ⁵⁸	2	100%
30	Tracking metrics, such as high-intensity statin use at discharge, should be used as a quality indicator.	4 ⁵⁹	2	89%
31	A structured discharge planning programme for patients with ACS can facilitate higher satisfaction and reduce unexpected readmissions.	1b ⁶⁰	1	100%
32	Electronic health records and clinical decision-support tools should be leveraged to prompt lipid testing and therapy optimisation.	1b ⁶¹	1	89%

ACS: acute coronary syndrome; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9

Superscript numbers: refer to REFERENCES

The cost of PCSK9is remains a principal constraint. However, prioritising therapy for the highest-risk patients is both clinically and economically rational.⁵⁶ The panel was in consensus that in cost-sensitive settings, an LDL-C level of ≥ 1.8 mmol/L can serve as a trigger for intensification, balancing benefit and cost impact. The broader use of PCSK9is, inclisiran, and bempedoic acid requires consideration of real-world constraints, including cost, reimbursement variability, and long-term adherence to complex treatment regimens, especially for injectables. In November 2023, the National Drug Advisory Committee listed evolocumab for subsidy under the Medication Assistance Fund in Singapore, aiming to increase its prescription among eligible patients. However, audits will be essential to determine whether this cost-subsidy strategy has led to improved LDL-C goal attainment.

Singapore protocols modelled on frameworks such as ACS EuroPath can help establish best practices, standardise algorithms, and enable clinicians to identify optimisation opportunities at every transition of

care.⁵⁸ The panel noted that current clinical practice guidelines lack a step-by-step ACS lipid protocol to guide clinicians. Recognising the gap in Singapore, the panel highlighted the need to design better tools to suit the Singapore context. The panel recognised that localised protocols could support consistent lipid management, especially during acute-to-long-term care transition.

Quality improvement initiatives should include tracking metrics, such as the proportion of patients discharged on high-intensity statins, as these serve as process indicators of care quality and adherence to guidelines.⁵⁹ Similarly, structured discharge planning programmes have demonstrated efficacy in improving patient satisfaction and reducing unplanned readmissions by ensuring continuity of care and appropriate medication titration.⁶⁰ The metrics suggested by the panel included (1) prescription of moderate/high-intensity statin (or documented intolerance) at discharge and (2) LDL-C retested by 6 weeks and at 3 months. The discussion highlighted the need for metrics that can be audited objectively. Conducting

regular audits and providing feedback to providers may help close the gap between research and practice.²³ Integrating electronic health records (EHRs) and clinical decision-support systems can significantly enhance lipid management by providing real-time alerts for lipid testing, flagging suboptimal LDL-C values, and prompting timely intensification of therapy.⁶¹ Together, these tools can help close care gaps and ensure that high-risk patients are not lost to follow-up.

Study limitations

This study had some limitations. The literature review relied only on PubMed with English language as a filter, which may have resulted in the exclusion of a few other relevant studies indexed in other databases. The modified Delphi approach ensured systematic refinement, but some recommendations lacked high-quality RCT evidence, making them reliant on lower levels of evidence. Additionally, some statements received a proportion of “neither agree nor disagree” responses, highlighting areas of ongoing uncertainty that need further research.

Key insights from the discussion

The recommendations presented in this consensus are broadly aligned with contemporary ESC/EAS and American College of Cardiology/American Heart Association guidance in emphasising early initiation of high-intensity statin therapy, aggressive LDL-C lowering, and the need for treatment intensification in patients who do not achieve recommended targets (Table 6).^{62,63} The present consensus builds on this evidence base by providing guidance on the timing of lipid assessment (including measurement within 24 hours and reassessment at 4–6 weeks), earlier consideration of combination therapy in patients unlikely to achieve targets with statin monotherapy, and explicit guidance on treatment decision-making at hospital discharge (Fig. 2). In addition, it incorporates implementation-oriented considerations, including structured follow-up, care-transition processes, and the use of system-level tools such as auditable metrics and EHR-supported prompts to facilitate timely treatment intensification in routine clinical practice. From a Singapore perspective, the panel identified several priorities for post-ACS lipid management:

- (1) **Evidence-based biomarker use:** Clinically actionable data are required before hsCRP or apoB can guide LLT titration. Currently, these biomarkers are useful for risk assessment but are not ready for routine, protocol-driven therapy decisions.
- (2) **Localised lipid pathways:** Singapore would benefit from context-aware, locally adapted lipid

protocols specifying testing intervals, LDL-C thresholds, and therapy escalation steps, aligned with regional healthcare constraints.

- (3) **Harmonisation across care transitions:** Standardising care from hospital to primary care is essential to ensure continuity and timely optimisation of therapy.
- (4) **Objective, auditable metrics:** Implementation should be supported by measurable indicators, enabling tracking, benchmarking, and quality improvement.
- (5) **Granular implementation tools:** Effective operationalisation of pathways requires discharge planning, EHR prompts, escalation algorithms, and patient education to minimise therapeutic inertia and close existing practice gaps.

CONCLUSION

This expert consensus underscores the critical role of timely LLT in patients with ACS to reduce recurrent cardiovascular events and optimise long-term outcomes. Evidence supports early initiation of high-intensity statins, combination therapy with ezetimibe or PCSK9is when indicated, and consideration of nonstatin alternatives in statin-intolerant patients. Special populations, including older adults, women, and patients with FH, require tailored approaches to maximise benefit. By synthesising the available evidence and expert experience, these recommendations provide a structured, evidence-informed framework for post-ACS lipid management in Singapore.

Supplementary materials

Annex S1. ACCurate CONsensus Reporting Document (ACCORD) guidelines.

Annex S2. Panel of experts.

Acknowledgements

The authors would like to thank BioQuest Solutions Pvt Ltd for its editorial support.

Ethics statement

Not applicable as no study subjects were recruited. All data were derived from expert opinion and literature review as part of a structured Delphi consensus process.

Declaration

Amgen provided financial support exclusively for the purpose of publication and had no role in the conception, study design, data interpretation, or the decision to submit this manuscript. Ru San Tan received an honorarium for chairing meetings. Jonathan Yap received speaker honoraria from Abbott, Biosensors, Biotronik, Boston Scientific, Edwards, Johnson &

Table 6. Comparison of ACS-specific lipid management guidelines with this consensus.

Domain	ESC/EAS 2025 Focused update of 2019 guidelines	ACC/AHA (2026 dyslipidaemia)	Present consensus (Singapore ACS)
Overall approach	Emphasises early and intensive lipid lowering after ACS	Recommends high-intensity statin with stepwise addition of nonstatin therapy	Emphasises early lipid lowering with consideration of timely intensification
LDL-C targets	<55 mg/dL (1.4 mmol/L); consider <40 mg/dL in recurrent events	<55 mg/dL for very-high-risk ASCVD; thresholds used to guide therapy escalation	<55 mg/dL with ≥50% reduction; <40 mg/dL considered for recurrent events
LDL-C reduction target (relative)	Recommends ≥50% reduction from baseline in addition to absolute LDL-C target	High-intensity statins defined by ≥50% LDL-C reduction; percentage reduction used to assess treatment response	Recommends ≥50% reduction from baseline in addition to absolute LDL-C target
Initial therapy	High-intensity statin for all patients with ACS	High-intensity statin for all patients with ACS	High-intensity statin for all patients with ACS
Combination therapy	Consider statin + ezetimibe early if targets unlikely with statin alone	Add ezetimibe and/or PCSK9 mAb if LDL-C remains above goal despite statin	Consider early combination therapy when statin monotherapy is unlikely to achieve targets
PCSK9 inhibitors	Consider if targets not achieved after initial therapy	Consider after statin if LDL-C remains above threshold	Consider in patients not achieving targets despite statin + ezetimibe; may be considered at discharge in selected patients
Timing of lipid testing	Early measurement recommended; reassessment at 4–6 weeks	Reassessment recommended at 4–12 weeks	Measurement within 24 hours; reassessment at 4–6 weeks
Treatment intensification	Encourages early intensification based on LDL-C response	Stepwise intensification based on LDL-C thresholds	Emphasises timely reassessment and treatment intensification
Follow-up	Reassessment after initiation or adjustment of therapy	Follow-up recommended to assess LDL-C response	Early follow-up (4–6 weeks) with further monitoring as needed
Implementation considerations	Limited discussion of implementation strategies	Limited discussion of implementation strategies	Includes considerations for care pathways, follow-up processes, and adherence
Adherence strategies	General emphasis on adherence	General emphasis on adherence	Highlights adherence support and follow-up strategies
Care transitions	Not specifically detailed	Not specifically detailed	Notes the importance of coordination across care settings
Biomarkers	Lp(a) recognised for risk assessment	Lp(a) recommended at least once; apoB selectively used	Lp(a) considered for risk stratification; limited role for hsCRP and apoB
Special populations	Addressed (e.g. elderly, FH)	Addressed (e.g. elderly, FH)	Addressed (e.g. elderly, women, FH, polyvascular disease)

ACC: American college of cardiology; ACS: acute coronary syndrome; AHA: American heart association; FH: familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein(a); mAb: monoclonal antibody; PCSK9: proprotein convertase subtilisin/kexin type 9

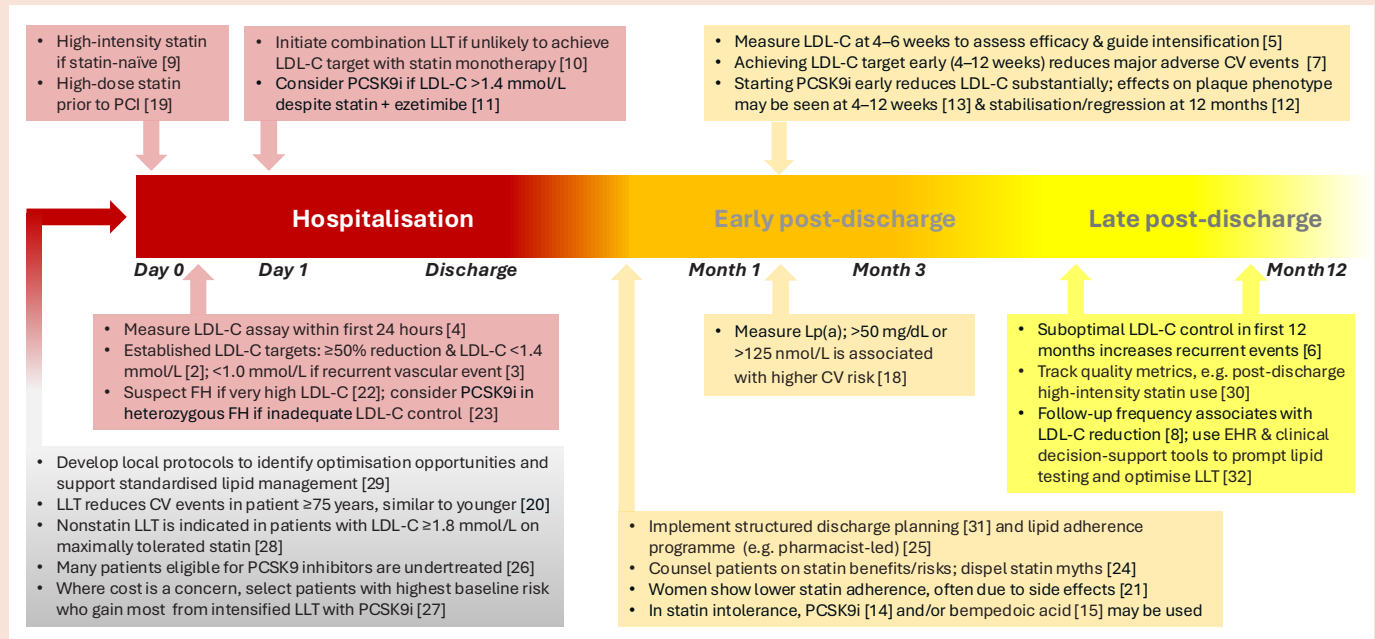
Johnson, Medtronic, and Terumo. Colin Yeo received honoraria from Amgen. Kian Keong Poh, Peter Chee Hong Yan, Pow Li Chia, Michael Chun Leng Lim, David Foo, Fahim Haider Jafary, and Natalie Si Ya Koh declare that they have no affiliations with or involvement in any organisation or entity with any financial

interest in the subject matter or materials discussed in this manuscript.

Data availability statement

All data generated or analysed during this study are included in this article and its supplementary files.

Fig. 2. Acute coronary syndrome lipid management consensus workflow. Consensus statements (statement numbers within square brackets) with high degrees of agreement ($\geq 75\%$) are condensed and mapped onto sequential epochs during a typical acute coronary syndrome event: hospitalisation (red), early post-discharge (orange), and late post-discharge (yellow), bounded by non-linearly scaled timepoints. Non-time-specific statements that outline the clinical justification for the workflow development in the grey box.



CV: cardiovascular; EHR: electronic health record; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; PCI: percutaneous coronary intervention; PCSK9i: proprotein convertase subtilisin/kexin type 9 inhibitor

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Who seeks help? Factors associated with utilisation of primary care mental health services in Singapore

Yu Cong Eugene Chua¹ FCFP (Singapore), Hui Li Koh² BSc (Psych) Hons, Poay Sian Sabrina Lee² PhD (Med), Yijun Carol Lin³ MPsych (Clinical), Sabrina Kay Wye Wong² PhD, Winnie Shok Wen Soon⁴ FCFP (Singapore), Wern Ee Tang² FCFP (Singapore)

Dear Editor,

Mental health screening in primary care aims to identify depression and anxiety early, but its effectiveness depends on whether patients accept follow-up services.¹ Despite the increasing accessibility of integrated mental health care in Singapore through the expansion of community and primary care mental health services, there are few studies that have evaluated the uptake of follow-up mental health services after mental health screening in primary care settings in Singapore. We examined the proportion of patients who attended the Health and Mind Service (HMS)—a multidisciplinary primary care mental health service—after a positive screen for depression or anxiety, and compared the characteristics of those who attended with those who did not.

This secondary analysis drew on data from a cross-sectional study of patients aged 21 years and above who attended NHG Polyclinics (NHGP) between December 2021 and April 2022.² Using systematic sampling, participants completed sociodemographic and validated screening questionnaires, i.e. the Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7). Those with scores ≥ 10 on either scale were considered screen-positive.^{3–5} These patients were offered a referral to the HMS by their attending family physician, and any attendance at HMS within 3 months was tracked. Multivariable logistic regression was performed to identify socio-demographic and clinical correlates of HMS attendance. Exemption approval was granted from the NHG Domain Specific Review Board (reference number 2024/00066).

Among the 3330 respondents, 353 screened positive. Among the 353 respondents, 12.7% ($n=45$) attended HMS. HMS attendees were predominantly young adults aged 21 to 36 years, and most had co-existing clinically significant depression and anxiety of moderate severity as well as at least 1 chronic condition. Regression analysis showed that unemployment (odds ratio [OR]

2.50, 95% confidence interval [CI] 1.08–5.77, $P=0.03$) and chronic disease burden (1–2 chronic conditions [OR 4.22, 95% CI 1.34–13.27, $P=0.01$]; ≥ 3 chronic conditions [OR 4.80, 95% CI: 1.29–17.86, $P=0.02$]) were significantly associated with higher odds of HMS attendance (Table 1).

Our findings highlight that despite the ready availability of services, most primary care patients who screened positive for depression or anxiety did not use mental health services within the primary care setting. This low uptake mirrors international trends. For instance, Hacker et al. reported that 9.4% of clients who screened positive completed a face-to-face mental health visit within 180 days,⁶ while Geyti et al. found a 29% mental healthcare initiation rate in Denmark within one year of a population-based screening.⁷ Whitton et al. reported a 36.8% uptake of at least 1 form of mental health treatment, including digital interventions, for patients who screened positive via a primary care-based screening programme in Australia within 18 weeks.⁸ While differences in healthcare models, follow-up periods, and mental health services complicate direct comparisons, all studies point to suboptimal engagement or preference for other forms of follow-up.

Our data also shows that HMS at NHGP is reaching more individuals with multiple chronic diseases and those who are unemployed—populations consistently cited in the literature as more vulnerable to adverse mental health outcomes. Patients with multimorbidity often face complex care needs and higher psychological burden,⁹ while unemployment is strongly associated with psychosocial stressors that compromise well-being.¹⁰ By supporting these vulnerable populations within a primary care setting, HMS fulfils its role as an accessible and integrated service addressing both medical and psychosocial needs.

These findings also reinforce that improving mental health support must extend beyond screening. Without adequate uptake of follow-up services, the

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¹ Hougang Polyclinic, NHG Polyclinics, Singapore

² Clinical Research Unit, NHG Polyclinics, Singapore

³ Psychology Services, NHG Polyclinics, Singapore

⁴ Clinical Services, NHG Polyclinics, Singapore

Correspondence: Dr Chua Yu Cong Eugene, Hougang Polyclinic, 89 Hougang Ave 4, Singapore 538829. Email: eugene.yc.chua@nhghealth.com.sg

Accepted: 4 April 2026

Published online first: 24 April 2026

Table 1. Factors associated with attendance at the Health and Mind Service (HMS) among respondents screening positive for depression or anxiety (PHQ-9 or GAD-7 ≥ 10 ; n=353).

Independent variables	Odds ratio (95% CI)	P value
Age (as of 2022)	1.00 (0.96–1.03)	0.82
Sex		
Male	Ref	
Female	1.41 (0.68–2.93)	0.36
Ethnicity		
Chinese	Ref	
Malay	0.69 (0.28–1.74)	0.44
Indian	1.38 (0.52–3.68)	0.52
Others	1.47 (0.38–5.62)	0.57
Current marital status		
Currently married	Ref	
Never married / single	1.29 (0.49–3.39)	0.60
Separated / divorced / widowed / others	1.83 (0.54–6.13)	0.33
Highest level of education attained		
Lower secondary & below	Ref	
Upper secondary / pre-university	1.88 (0.49–7.24)	0.36
Diploma and professional qualification	3.62 (0.88–14.78)	0.07
Degree & above	2.66 (0.65–10.80)	0.17
Main work status, over the last 12 months		
Employed	Ref	
Unemployed	2.50 (1.08–5.77)	0.03
Type of dwelling		
HDB 1-room / 2-room apartment	Ref	
Others	1.60 (0.39–6.54)	0.51
Overall social support (mMOS-SS)	1.00 (0.99–1.02)	0.89
Number of chronic diseases		
None	Ref	
1–2	4.22 (1.34–13.27)	0.01
≥ 3	4.80 (1.29–17.86)	0.02
PHQ-9, GAD-7 category		
PHQ-9 & GAD-7 ≥ 10	Ref	
PHQ-9 ≥ 10 & GAD-7 <10	1.22 (0.35–4.30)	0.75
PHQ-9 <10 & GAD-7 ≥ 10	0.40 (0.08–1.89)	0.25
PHQ-9 score	1.04 (0.94–1.16)	0.43
GAD-7 score	1.03 (0.91–1.17)	0.62

CI: confidence interval; GAD-7: Generalised Anxiety Disorder-7; HDB: Housing & Development Board; mMOS-SS: Modified Medical Outcomes Study Social Support Survey; OR: odds ratio; PHQ-9: Patient Health Questionnaire-9

P values in bold denote significance.

value of screening is diminished. Efforts should focus on addressing barriers to seeking mental health support, reducing stigma, improving mental health literacy, and developing services in the community.

This secondary analysis has several limitations. The single-service follow-up option may underestimate help-seeking behaviour if patients accessed community-based, private, hospital-based, or digital services. The three-month observation period may have missed delayed uptake, such as patients who accessed the HMS beyond this period. In addition, our quantitative analysis cannot fully capture patient decision-making, underscoring the need for qualitative studies to explore barriers to engagement. Furthermore, the relatively small number of participants who attended HMS may result in wider confidence intervals and greater uncertainty in the estimated associations, and therefore, these findings should be interpreted with caution.

Despite these constraints, this study provides important real-world insights from a large primary care population across multiple sites in Singapore. It is among the first to examine actual service uptake following routine mental health screening in this setting. The findings can guide allocation of resources, inform further study on patient preferences for mental health support, and strengthen the case for HMS for people with chronic conditions.

While only a minority of individuals who screened positive proceeded to attend HMS, our findings show that those who did—particularly unemployed persons and those with multimorbidity—belong to groups consistently identified in the literature as being at high risk of poor mental health outcomes. This demonstrates that HMS is reaching populations with psychosocial and health-related vulnerabilities. In addition to HMS, other mental health interventions should be developed to address patient needs and sustain and strengthen support for these groups, ensuring equitable access to timely and affordable mental health care within the community.

Acknowledgements

The team would like to thank all our NHGP colleagues, clinic staff, and patients who contributed to this study. Special thanks to Adj A/Prof Lee Eng Sing, Mr Jeremy Kaiwei Lew, A/Prof Mythily Subramaniam,

Dr Edimansyah Abdin, and Ms Debbie Ng Yanling for their support.

Ethics statement

Waiver of patient consent for this study was approved by National Healthcare Group Domain Specific Review Board (2024/00066)

Declaration

No funding was received for this study. 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: *anxiety, depression, family medicine, mental health, primary care*

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Safety of independent discharge post-endoscopy with sedation: A 7-year retrospective observational study

Quan Rui Tan¹ MBBS (Singapore), Pei Yee Lim² MSc (Nursing), Sherwyn Koh³ MBBS (Singapore), Xin Tien Lee³ MBBS (Singapore), Wee Khoo Ng^{2,4} FRCP (Edinburgh)

Dear Editor,

Sedation is widely administered during endoscopic procedures, and it would always be safest if patients are accompanied home after discharge, due to potential residual effects on cognition and psychomotor skills after sedation.¹ There are concerns for patient safety and the residual effects of sedative agents on cognition post-endoscopy. Given the concerns about patient safety, recent American and European guidelines from major gastroenterology and anaesthesiology societies recommend that patients discharged after receiving sedation should be accompanied by a responsible adult, such as a family member, guardian or friend.²⁻³ In the Singapore context where this study was performed, there are varied practices between hospitals, with some requiring the patient to postpone the procedure or be admitted post-sedation if there is no accompaniment. The current guideline suggests accompanied discharge for patients sedated with midazolam and fentanyl, but leaves individual institutions to decide on independent discharge for those sedated with propofol.⁴

However, this requirement often imposes a significant logistical burden on patients, especially those without family or social support. It was found that only 46% of patients completed a colonoscopy within 6 months of abnormal faecal immunochemical test results, with 57.1% attributing this to a lack of transportation, with remarks that patients lacked access to accompaniment.⁵ This threatens to be an ever-growing challenge, with increased social mobility, reduced intergenerational living, delayed marriages, dual-career families, and fewer children.

An opposing view has challenged the status quo, with a growing body of literature finding that escorts for sedated patients may be unnecessary, with no increase in adverse outcomes.⁶⁻⁷ These studies found that patients sedated with propofol who fulfilled

discharge criteria, such as the ability to walk in a straight line and an appropriate level of consciousness, had no significant increase in traffic accidents and no impairment in driving ability when discharged home alone.⁸ These findings underscore the need for evidence-based policy refinement that balances patient autonomy, access to care, and procedural safety.

The authors conducted a retrospective observational study using data from the electronic health record of Tan Tock Seng Hospital, Singapore, covering the period from January 2017 to January 2024. The study population included patients who underwent sedated endoscopic procedures, and were subsequently discharged without an escort. Eligibility for unaccompanied discharge was determined by trained clinical staff based on predefined clinical and social criteria, such as being able to ambulate independently, ability to take public transport, and lack of cognitive impairment. Following the procedure, patients were monitored in the recovery area, and only patients who achieved a Post Anaesthetic Discharge Scoring System score meeting the discharge threshold were permitted to leave without an escort. To assess post-discharge outcomes, a random subset of patients received a follow-up phone call within 24 hours. The follow-up aimed to identify any adverse events or complications. Patient-reported symptoms were categorised using the Adverse Events in Gastrointestinal Endoscopy (AGREE) classification, which stratifies complications into minor and major events.

From January 2017 to January 2024, 10,281 patients were recorded to have been discharged home unaccompanied. This represents 9.3% of all patients who underwent endoscopy. A total of 3066 patients (29.8%) were successfully contacted, of whom only 36 (1.2%) reported any complications, and only 3 (0.1%) had major classifications based on the AGREE classification of Grade II and above (Table 1). None of the complications were directly linked to being

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¹ Internal Medicine Residency Programme, National Healthcare Group, Singapore

² Endoscopy Centre, Tan Tock Seng Hospital, Singapore

³ Lee Kong Chian School of Medicine, Singapore

⁴ Department of Gastroenterology and Hepatology, Tan Tock Seng Hospital, Singapore

Correspondence: Dr Quan Rui Tan, National Healthcare Group, 11 Jalan Tan Tock Seng, Singapore 308433. Email: Quanrui97@gmail.com

Accepted: 7 April 2026

Published Online First: 24 April 2026

Table 1. Percentage of patients who went home alone and had symptoms on follow-up call.

Year	2017	2018	2019	2020	2021	2023	2024 ^a	Total
Total endoscopy patients	18,501	18,847	16,171	13,209	15,389	26,242	2295	110,654
Total home alone, no. (%)	1789 (9.7)	1723 (9.1)	1601 (9.9)	1542 (11.7)	899 (5.8)	2455 (9.4)	272 (11.9)	10,281 (9.3)
Sampled patients who could be contacted, no. (%)	116 (6.5)	555 (32.2)	648 (40.5)	541 (35.1)	212 (23.9)	864 (35.2)	127 (46.7)	3066 (29.8)
All complications, no. (%)	2 (1.7)	6 (1.1)	13 (2.0)	3 (0.6)	3 (1.4)	5 (0.6)	4 (3.1)	36 (1.2)
Complications related to going home alone, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
List of minor complications	1. Vomiting 2. Nausea and loss of appetite	1. Fever 2. Sore throat 3. Fever and chest pain 4. Epigastric pain 5. Post-scope haematochezia 6. Pain over anus	1. Sore throat and epigastric pain 2. Sore throat 3. Epigastric pain 4. Haematochezia 5. Sore throat 6. Abdominal pain 7. Abdominal pain and backache 8. Pruritus 9. Sore throat and mouth ulcer 10. Vomiting + small amount of haemetemesis 11. Abdominal pain 12. Right upper limb swelling	1. Cough and pain over ribs 2. Abdominal pain 3. Abdominal bloating	1. Chest pain 2. Fever	1. Unspecified/generalised pain 2. Fever and rhinorrhoea 3. Stomach pain 4. Fever	1. Nausea and neck pain 2. Sore throat 3. Sore throat 4. Headache	
Major complications, no. (%)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.5)	1 (0.1)	0 (0.0)	3 (0.1)
Types of major complications			Haematochezia secondary to haemorrhoids		Dyspnoea secondary to pneumonia	Pain over hands and legs		

^a Data for 2024 were only collected in January.

discharged home unaccompanied. The most common reported complications included abdominal pain (13.9% of total complications), sore throat (11.1%), fever (5.6%), and nausea (5.6%). The major complications reported were haematochezia due to haemorrhoids, dyspnoea due to pneumonia, and pain in the limbs that required admission. There were no complications related to the patients going home without accompaniment, for example, involvement in accidents such as falls or getting lost on the way home (Table 1).

These results of few, minor, and transient complications are consistent with a study by Martin et al.⁹ Our study corroborates a driving-simulation study of cognitive function, which found that driving abilities on a simulator were fully restored 4 hours after propofol sedation,¹⁰ suggesting that the dangers of travelling home alone post-sedation on public transport without an escort may not be associated with significant complications.

The findings have several important implications for clinical practice. The requirement for an escort can be a significant barrier to care, particularly for elderly patients, those with limited social support, or individuals living alone. Often, these individuals are faced with the prospect of having to call a friend or social worker to accompany them to and from procedures, which increases their barrier to undergoing procedures. Patients who are unable to find an escort may be admitted to the hospital for overnight monitoring after the procedure, potentially exacerbating the long wait times for an inpatient bed. This implies a significant percentage of resource wastage and inefficient use of resources. In a selected group of patients with independent function and good cognitive function, and in a city with good public and private transport infrastructure, and a good network of healthcare facilities such as Singapore, this practice could contribute to better resource utilisation in ambulatory settings without compromising patient safety. Good pre-selection of patients, an appropriate discharge screening tool, clear post-discharge advice, staff assistance with transportation options for selected patients, and a robust post-discharge follow-up plan can further enhance safety and allow patients to return home without accompaniment.

However, this study has limitations. First, due to manpower constraints, the authors could only focus on contacting the higher-risk individuals (29.8% of total patients successfully contacted), which may introduce response bias. Second, this is a single-centre study, and while the cohort size is large, institutional practices, staffing, and patient demographics may limit generalisability. Last, data loss in 2022 due to technical issues could have excluded relevant events,

although the proportion of lost data was small relative to the total study period.

In conclusion, while it is safer to discharge all patients post-sedation-assisted endoscopic procedures with an escort, careful selection of lower-risk patients with appropriate clinical safeguards will likely allow a significant proportion of patients to be discharged safely without an escort, reducing barriers to care without additional risks.

Ethics statement

Approval of the research protocol was obtained from the National Healthcare Group Domain Specific Review Board (2023/00995).

Declaration

The authors have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. There is no conflict of interest and funding to declare.

Acknowledgements

The authors would like to extend their gratitude to Tan Tock Seng Hospital, Singapore for allowing them to conduct their research at the hospital.

Keywords: accompaniment, discharge, endoscopy, safety, sedation

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Decentralised germline genetic testing for epithelial ovarian cancer in a tertiary Asian centre

Poornima Bhadriraju^{1*} MBBS, Pei Yi Ong^{2*} BSc(Hons), Li Min Lim¹ MBBS, Jeffrey JH Low¹ MBBS, Pearl Tong¹ MBBS, Joseph Ng¹ MBBS, David SP Tan¹ MBBS, Yi Wan Lim¹ MBBS, Natalie YL Ngoi¹ MBBS, Siew Eng Lim¹ MBBS, Gloria HJ Chan¹ MBBS, Soo Chin Lee¹ MBBS, Samuel GW Ow¹ MBBS

Dear Editor,

This letter shares findings from the implementation of a decentralised gynaecology genetics clinic for epithelial ovarian cancer (EOC) patients at the National University Hospital, Singapore. This model addresses a critical gap in genetic testing (GT) access while maintaining quality standards through strategic collaboration between gynaecologic oncology and cancer genetics services.

Approximately 15% of EOC patients have an inherited germline mutation with profound implications for treatment selection and family risk assessment.^{1,2} Current guidelines recommend universal GT for all EOC patients.^{3,4} However, implementation remains challenging due to prolonged waiting time to see cancer genetics specialists. These delays significantly impact treatment decisions, particularly first-line poly (ADP-ribose) polymerase inhibitors (PARPi) selection as well as the role of concomitant anti-angiogenic therapy.^{5,6}

Two gynaecologic oncology specialists received training with the Cancer Genetics Service at the National University Cancer Institute, Singapore in 2020, including a 1.5-day workshop on hereditary breast and ovarian cancer syndrome (HBOC), including hands-on training in risk assessment, counselling, and result interpretation, followed by a 1-month clinical attachment. Both achieved competency in providing GT services for HBOC patients.

All patients with histologically proven EOC identified at the weekly multidisciplinary tumour board meeting (see workflow in Supplementary Fig. S1) were referred to the decentralised gynaecology genetics clinic for early genetic counselling by the trained gynaecologists, and offered multigene panel testing using a 49-gene next-generation sequencing panel including *BRCA1/2*, homologous recombination deficiency, and mismatch repair genes (see full gene list in Supplementary Table S1) performed at a College of

American Pathologists-accredited laboratory in line with regulation set out by the Clinical Laboratory Improvement Amendments of 1988 (Invitae Corporation, US). Patients found to have pathogenic variants (PV) or variants of uncertain significance (VUS) were reviewed by the cancer genetics service within 2–4 weeks for post-test counselling, while those testing negative received counselling directly in the decentralised clinic. Patients with suspicious family history or further queries post-GT were also offered referral to the cancer genetics service for further evaluation.

Eighty-eight EOC patients were counselled in the decentralised gynaecology genetics clinic during the study period (Supplementary Table S2). Among them, 52/88 (59.1%) agreed to undergo germline GT, comparable to baseline rates (66.6%; $P=0.44$). Of those tested, 12/52 (23.1%) had PV across multiple genes: *BRCA1* ($n=3$), *BRCA2* ($n=2$), *RAD51C* ($n=2$), *RAD51D* ($n=3$), *MSH2* ($n=1$), and *TP53* ($n=1$) (Supplementary Table S3). Eleven patients had 15 VUS across 12 genes (Supplementary Table S4).

The median waiting time for genetic counselling reduced drastically from 90 days (interquartile range [IQR] 3–192 days) to 45 days (IQR 4–94 days), representing a 50% reduction from historical data ($P<0.001$). This enhanced access enabled more timely integration of genetic results into treatment planning.

Fifty patients (56.8%) had the tumour specimen sent for somatic testing. Details of germline and somatic testing as well as maintenance PARPi therapy are shown in Fig. 1 and in Supplementary Table S5. Among 36 patients with concomitant germline and somatic testing, 57.1% showed concordant results, with 100% of patients with germline PV having corresponding somatic variants detected. Cascade testing was offered to family members of PV carriers, with 14 relatives of 5 patients underwent testing, identifying 2 additional carriers.

Several cases exemplify the critical importance of universal GT. One patient with germline *BRCA2*

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¹ Department of Obstetrics and Gynaecology, Division of Gynaecology Oncology, National University Health System, Singapore

² Department of Hematology-Oncology, National University Cancer Institute, Singapore

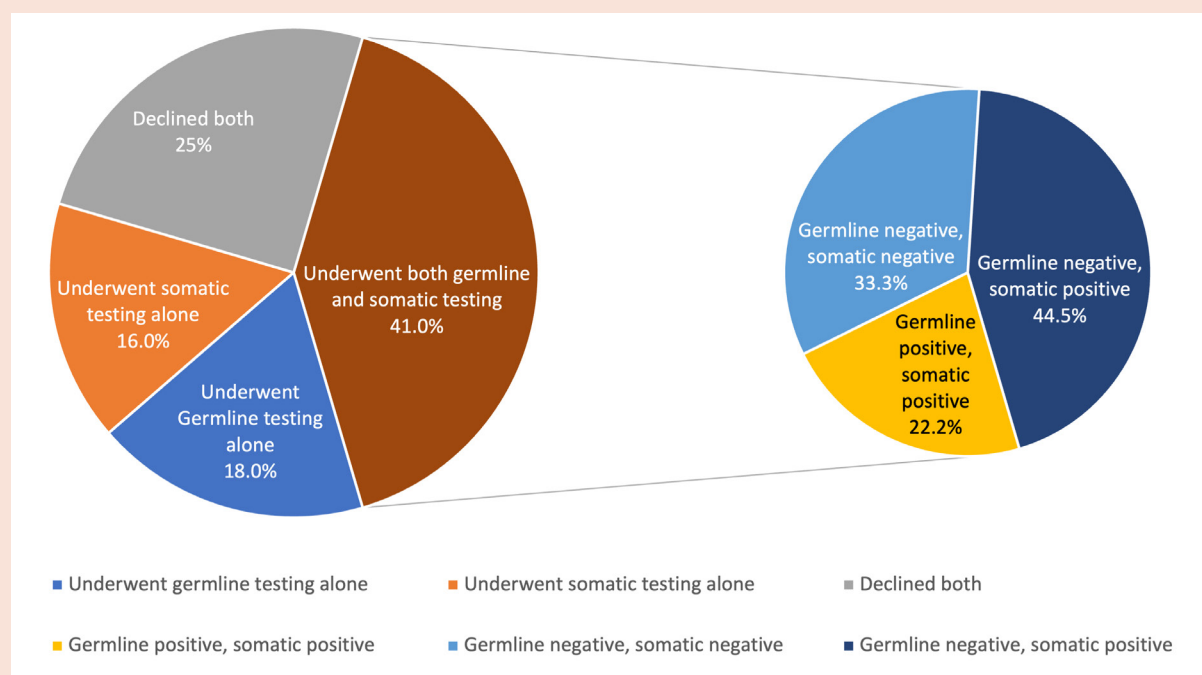
* Joint first authors

Correspondence: Dr Samuel GW Ow, Department of Haematology-Oncology, National University Cancer Institute, 5 Lower Kent Ridge Road, Singapore 119074. Email: samuel_ow@nuhs.edu.sg

Accepted: 24 March 2026

Published online first: 9 April 2026

Fig. 1. Summary of 88 patients with germline testing, somatic testing.



germline positive: tested positive for pathogenic variant on germline testing; germline negative: no pathogenic variants found on germline testing; somatic positive: tested positive for homologous recombination deficiency on somatic testing; somatic negative: tested negative for homologous recombination deficiency on somatic testing

PV had insufficient tumour tissue for somatic testing and would have missed PARPi therapy opportunity without germline testing. Another patient with Lynch syndrome (*MSH2* PV) who declined somatic testing demonstrates how germline testing identifies hereditary cancer syndromes beyond *BRCA1/2* with significant treatment and family screening implications.

Most remarkably, the identification of a *TP53* PV diagnostic of Li-Fraumeni syndrome in a patient without suggestive personal or family history underscores the limitations of family history-based screening approaches. Given that somatic *TP53* mutations are among the most common alterations in ovarian cancer, this finding highlights the unique value of systematic germline testing in revealing unexpected hereditary cancer syndromes requiring specialised management.

This study's "germline first" approach offers pragmatic benefits, with germline testing costing approximately USD250 compared to comprehensive somatic testing, which costs more than USD3500 per test. This supports prioritising germline testing, particularly in resource-constrained healthcare systems, while improving access through reduced waiting times.⁷

This care model differs from traditional mainstreaming approaches by decentralising genetic counselling

within established gynaecologic oncology pathways, leveraging existing patient-provider relationships.^{8,9} Integration with the cancer genetics service ensures patients with PV or VUS receive specialist counselling and cascade testing. This hybrid approach maintains quality standards through periodic audit. It also provides a safety net for the 40.9% of patients who initially declined testing, allowing reconsideration through subsequent cancer genetics service consultations.

The success of this model of care hinges on the close collaboration between the department of obstetrics and gynaecology and the cancer genetics service, which is possible in the author's tertiary cancer centre. This framework could serve as a template for other institutions seeking similar implementations, with potential for expansion to other cancer types (e.g. endometrial and breast cancers), representing opportunities for optimisation. As guidelines increasingly recommend universal or expanded testing across multiple cancer types, decentralised models may become essential for meeting growing demand while maintaining quality standards.

This is a single institutional study limited by the relatively small number of patients seen over 2 years. Additionally, the lack of formal patient-reported outcome measures restricts understanding of patient satisfaction and psychological impact. Future research

should include formal cost-effectiveness analyses and longer-term follow-up to evaluate cascade testing uptake and clinical outcomes. Multi-institutional studies will be useful in enhancing generalisability across diverse healthcare settings.

To the best of the authors' knowledge, this is the first time genetic counselling and testing for EOC patients is being offered by trained gynaecologists in a decentralised clinic at a tertiary cancer centre in Asia, demonstrating feasibility and timely access with meaningful clinical impact. This approach offers a scalable solution for healthcare systems seeking to implement universal GT while managing resource limitations. The model's success underscores the importance of collaborative care pathways in delivering comprehensive cancer genetics services.

Supplementary materials

Table S1. List of 49 cancer predisposition genes tested.

Table S2. Patient demographics.

Table S3. Clinical characteristics of patients with germline pathogenic variants (n=12).

Table S4. List of VUS identified.

Table S5. Summary of 88 patients with germline testing, somatic testing, and maintenance therapy.

Fig. S1. Workflow for decentralised gynaecology genetics clinic.

Ethics statement

Patient consent was sought for this study. Ethics approval was obtained from Domain Specific Review Board (DSRB) of National Healthcare Group (DSRB Ref: 2000/00511; date of approval on 8 December 2000).

Declaration

No funding was received for this study. 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: cancer, genetics, haematology, obstetrics and gynaecology, oncology

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Impact of artificial intelligence on novice endoscopists' colonoscopy training

Kristie Eliana Ramli¹, Leticia Jing Yee Wong¹, SingHealth General Surgery Residency², SingHealth Gastroenterology Residency³, Fung-Joon Foo^{2,4,6} FRCS, Eng-Kiong Teo^{2,5,6} FRCP, Frederick Hong Xiang Koh^{1,2,4,6,7,8,9,10} PhD

The SingHealth General Surgery Residency comprises, in alphabetical order:

Aditya Stephen, Basu Pallavi, Cheng Stephanie, Cheok Hui Xian Sabrina, Cheong Jie Ying Ellis, Chi Hannah Yee Shuen, Choo Li En Amadora, Chong Yvette, Ho Geok Eng Carolyn, Koh Han Jie, Koh Ming Yen Gabrielle Eloise, Khoo Chun Yuet, Khoo Shi Qing Michelle, Lee Jia Hui, Lim Sheng Hao Joshua, Lim Teik Wen, Lim Xin Yan, Lim Yen Yan, Lim Yuan Wei, Lin Yu, Lin Yun Le, Low Ying Xin, Lu Yao, Luo Zhentao, Malishree Dharmaratnam Vanessa, Moon Eui Whan, Ng Ai Ting Irene, Ng Wee Kiat Daniel, Ong Suet Yan, Palanisamy Prasad, Pang Jolyn Hui Qing, Sia Jin Yang Crystal, Sim Pei Yin Dayna, Soh Hann Natalie, Soong Erica Lauren, Tan Hui Lin, Tan Jun Kiat Thaddaeus, Tan Poh Poh Audrey, Tay Chin Lin Clarissa, Wang Ying Chi Francine, Xu Hongyun, Xue Luxi, Yen Dulcena Yu, Zhao Yue

The SingHealth Gastroenterology Residency comprises, in alphabetical order:

Carkarine Sushmitha, Chew Tian Wei Valerie, Chu Michael CY, Elangovan Sakktivel, Ho Ren Yi Jonas, Huang Yu Wei Cheryl, Kuang Zi Chuen, Lim Yan Zheng Daniel, Loi Pooi Ling, Morvil Gayathry, Ng Pei Xuan Jeanette, Ong Yan Ling, Soni Rajit, Tan Hui Ru Charlene, Yeo Li Xin Charlene

Dear Editor,

Artificial intelligence (AI) has been increasingly utilised by endoscopists worldwide in recent years to enhance adenoma detection rates (ADR).¹ Currently, endoscopy presents a steep learning curve, requiring novice endoscopists to acquire numerous cognitive and motor skills during hurried procedures.² Studies have examined the knowledge, beliefs, and perceptions of experienced endoscopists regarding the use of AI in endoscopy but have not examined long-term skill acquisition or potential deskilling among novices.³ In this letter, the authors aim to survey novice endoscopists' attitudes towards knowledge and utilisation of AI in their training.

An online survey was conducted in October 2025 to examine perceptions of AI use in colonoscopy training. According to the Joint Advisory Group on Gastrointestinal Endoscopy in the UK, the number of

colonoscopies required to achieve a caecal intubation rate of $\geq 90\%$ was 200.⁴ Hence, the eligibility criteria for this study included general surgery and gastroenterology residents from 3 tertiary healthcare institutions in Singapore who had performed fewer than 200 colonoscopies. The survey evaluated the demographics, educational background, and professional characteristics of the residents. The questions regarding colonoscopy skills and perspectives on AI were adapted from the American Society for Gastrointestinal Endoscopy training guide and Tham et al.⁵ The main software utilised by the residents was computer-aided detection (CADe) and computer-aided diagnosis, specifically GI Genius (Medtronic) and CAD-EYE (Fujifilm).³

The questionnaire included 4 thematic domains: (1) current perspectives on endoscopy training, (2) knowledge and perception of AI, (3) current use of

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¹ Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

² Department of General Surgery, SingHealth, Singapore

³ Department of Gastroenterology, SingHealth, Singapore

⁴ Colorectal Service, Department of General Surgery, Sengkang General Hospital, SingHealth Services, Singapore

⁵ Department of Gastroenterology and Hepatology, Sengkang General Hospital, SingHealth Services, Singapore

⁶ Endoscopy Centre, Division of Hyperacute Care, Sengkang General Hospital, Singapore

⁷ SingHealth Duke-NUS Muscle Health Programme, Singapore

⁸ Duke-NUS Medical School, National University of Singapore, Singapore

⁹ Yong Loo Lin School of Medicine, National University of Singapore, Singapore

¹⁰ Department of Surgery & Cancer, Faculty of Medicine, Imperial College London, UK

Correspondence: A/Prof Frederick Hong Xiang Koh, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886.

Email: frederickkohhx@gmail.com

Accepted: 24 March 2026

Published Online First: 8 May 2026

AI in endoscopy training, (4) general perceptions of the use of AI in clinical work. Question formats included 5-point Likert-scale items (e.g. from “Strongly agree” to “Strongly disagree” and from “Always” to “Never”), yes-or-no questions, and open-ended questions. Quantitative data analysis employed descriptive statistics. Qualitative analysis was conducted by the first and senior authors, following extensive discussion, using thematic analysis of the survey responses, guided by Braun and Clarke’s 6-phase framework.⁶ This included familiarisation with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and writing the report to categorise responses to open-ended questions. A semantic and latent interpretation of the survey’s verbatim results was also employed in the qualitative analysis.

The majority of the 50 endoscopists surveyed found it challenging to acquire endoscopy-related cognitive and motor skills. Participants believed that they were familiar with AI and large language models (LLMs). However, only a small percentage genuinely understood how different algorithms functioned. A majority (64.0%) reported limited exposure to AI but expressed interest in understanding it (86.0%). When asked about their perspectives on the current utilisation of AI, 88.0% expressed interest in learning how AI worked. Furthermore, 52.0% agreed that AI has improved colonoscopy quality, which is lower than the 62.5–97% of experienced endoscopists who believed that AI would positively impact endoscopic performance. Some agree that AI has improved endoscopy quality (48.0%) and will aid in developing skills (56.0%). Concerns remain regarding accuracy (16.0%) and potential deskilling (20.0%).

As many skills must be developed simultaneously, it is more challenging to acquire them all at once. Therefore, by easing the burden of developing cognitive skills such as polyp recognition, AI may help novice endoscopists refine their motor skills while also increasing their ADR.¹²

Although some residents self-reported having some knowledge, most of their answers were inaccurate, especially regarding neural networks, as shown in Table 1. This indicates insufficient understanding of the algorithms currently used in medical AI, machine learning, and LLMs, especially neural networks and deep learning.¹³ However, some residents still understood how AI and LLMs work. This may be due to the rapid rise in the popularity of LLMs among medical practitioners worldwide (see explanations for each of the different AI models in Supplementary Table S1).¹¹ The rate of digital literacy is lower than that observed among senior endoscopists (50.0%). Many also raised the concern that they rarely or never used AI in their practice. Furthermore, for those who learned to utilise CADe, this was only at a superficial level during actual hands-on colonoscopy procedures, while they were still expected to learn other motor and cognitive skills simultaneously. Therefore, they might not know how to optimise CADe functionality. Many also reported not having formal lessons on the use of AI. This highlights the need for greater efforts at medical schools and during residency training to upskill novice endoscopists in AI.

In total, 44.0% believe that AI can improve colonoscopy training by enhancing the ability to recognise polyps. As multiple studies have shown, using CADe can improve ADRs by detecting polyps and highlighting them in real time. It can also aid in recognising caecal landmarks and give feedback on adequate mucosal exposure. By taking on the cognitive burden of recognising ADRs at the outset, novices can focus on developing the multiple motor skills required to manoeuvre the scope safely. Others also noted that AI makes it easier to provide real-time feedback on missed lesions, thereby reinforcing visual pattern recognition and reducing the reinforcement of false negatives.¹⁴ Furthermore, CADe systems can help generate metrics for time to lesion recognition, missed lesions and mucosal inspection completeness, allowing for objective longitudinal tracking of perceptual

Table 1. Understanding of different artificial intelligence algorithms.

	No. of residents who have the correct explanation of each algorithm, (%)	No. of residents with an inaccurate explanation of how each algorithm works, (%)	No. of residents who mentioned that they do not understand the algorithm, (%)
Artificial intelligence	8 (16.0)	12 (24.0)	30 (60.0)
Machine learning	4 (8.0)	9 (18.0)	37 (74.0)
Neural networks	0 (0.0)	2 (4.0)	48 (96.0)
Deep learning	0 (0.0)	5 (10.0)	45 (90)
Large language models	3 (6.0)	6 (12.0)	41 (82.0)

improvement for the trainees. As seniors may have to guide multiple trainees simultaneously, this allows them to quickly track, recognise, and focus on each novice's weak points to address.

Despite a positive overall perception, 10.0% cited AI as likely to result in insufficient skill development in detecting precancerous polyps. A study reported that faster polyp detection increased CADe misinterpretation of normal mucosa by reducing the eye travel distance.¹⁵ Another showed that experienced endoscopists who used AI continuously led to a 22.4–28.4% reduction in endoscopist capability, suggesting a detrimental effect on endoscopist capability.¹⁶ Another common concern was that CADe was inaccurate in diagnosing lesions. As CADe is a neural network, it has been trained on many adenoma images; hence, it can detect adenomas more accurately than humans. Although CADe has improved detection rates, it has not been trained on sessile serrated lesions, which carry a risk of malignant transformation. This aligns with residents' suggestions that AI should be trained to detect lesions beyond adenomas. AI has also been linked to sensory and cognitive overload, as residents may be overwhelmed by excessive alerts and false positives. Other concerns raised by experienced endoscopists include prolonged withdrawal times and the long-term cost-effectiveness of AI systems.

The relatively small sample size of 50 makes it challenging to conduct statistically significant analyses across groups defined by various metrics that inherently affect their views on AI. As such, the authors recommend conducting such a survey on a larger scale, involving more countries in the region in subsequent iterations.

In conclusion, novice endoscopists have limited exposure to AI during colonoscopy training but are open to learning and utilising it further. They remain optimistic about AI's role as an adjunct to enhance endoscopic training and patient outcomes. However, reservations about deskilling and programme accuracy present barriers to fully integrating AI into colonoscopy training.

Supplementary material

Table S1. Definitions of different artificial intelligence algorithms.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2022/2695).

Declaration

All authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript. Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore provided reimbursement to study participants and funding for this paper.

Keywords: artificial intelligence, colonoscopy, endoscopy, gastroenterology, general surgery, medical education

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A novel opioid-sparing method for post-laparotomy pain management in gynaecologic oncology patients: Correspondence

Gee Huey Leong¹ MD (UKM), Wah Tze Tan² FAMS

Dear Editor,

We refer to the article "A novel opioid-sparing method for post-laparotomy pain management in gynaecologic oncology patients" published in a recent issue of the *Annals*.¹

The authors conducted a retrospective review on women undergoing gynaecologic oncologic surgeries via midline laparotomy. Two groups were compared: 119 patients with only intravenous patient-controlled analgesia (IV PCA) and 133 patients receiving preperitoneal wound catheters (PPWC) with or without IV PCA. The percentage of patients on PPWC who did not receive PCA was reported as 17.3%.

We wonder if the authors could have excluded the 17.3% of patients on PPWC who did not receive IV PCA, so that the comparison between the 2 groups could be less complicated, i.e. only IV PCA versus IV PCA and PPWC. The inclusion of patients on PPWC who did not receive IV PCA potentially introduced bias and confounding. Furthermore, there was no standardisation in the infusion protocol of PPWC administration as patients received continuous infusion at 5, 7 or 12 mL/hour based on clinical needs. This further increased the risk of bias and heterogeneity in the study results.

In the article, the authors reported the following: (1) opioid consumption among IV PCA users in both groups were comparable in terms of milligrams per kilogram of body weight per day after surgery for the first 72 hours postoperatively; (2) the pain scores at rest and during movement were similar between the 2 groups; (3) there were no significant differences in time to ambulation and bowel function between the 2 groups; and (4) opioid-related side effects were similar between the 2 groups. These findings suggest that the addition of PPWC to IV PCA did not make any difference to the measured endpoints. In addition, it was reported that PPWC patients had longer times to oral intake and hospital stay. This questions the overall efficacy of the PPWC. Despite these results, the authors concluded that PPWC is a novel and effective method for postoperative pain relief.

Anatomically, the innervation of the anterior abdominal wall arises from the anterior rami of spinal nerves T7 to L1. The branches from the anterior rami include the intercostal nerves (T7 to T11), the subcostal nerve (T12), and the iliohypogastric/ilioinguinal nerves (L1). These nerves run in the plane between the internal oblique and the transversus abdominis muscles. The nerves continue anteriorly from the transversus plane to pierce the rectus sheath and end as anterior cutaneous nerves. Local anaesthetic drugs deposited within the posterior rectus sheath bilaterally can thus provide analgesia over the middle anterior wall from the xiphoid process to the symphysis pubis.²

Based on this anatomy, local anaesthetic drugs deposited in the posterior rectus sheath will be useful for surgery with midline abdominal incisions. To our knowledge, the use of wound catheters for patients undergoing gynaecology oncologic surgery has been reported more than a decade ago.³ There are also numerous articles on the effectiveness of local anaesthetic deposition in the rectus sheath to help with postoperative pain control in both open and laparoscopic surgeries.⁴⁻¹⁰

In the article, the authors placed their wound catheter preperitoneally rather than in the rectus sheath. We wonder if this has contributed to the absence of significant differences between the 2 studied groups for the measured outcomes.

Ethics statement

Not applicable, as no study participants were recruited.

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: anaesthesiology, gynaecology oncology, laparotomy, obstetrics and gynaecology, postoperative pain

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¹ Department of Anaesthesia, National Healthcare Group, Singapore

² Mount Elizabeth Medical Centre, Singapore

Correspondence: Dr Gee Huey Leong, Department of Anaesthesia, National Healthcare Group, 1 Mandalay Road, Singapore 308205.

Email: geehuey.leong@mohh.com.sg

Accepted: 19 March 2026

Published Online First: 13 April 2026

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81 Kim Keat Road, #11-00 & #12-00 NKF Centre, Singapore 328836

Email: annals@ams.edu.sg | Website: <https://www.annals.edu.sg>