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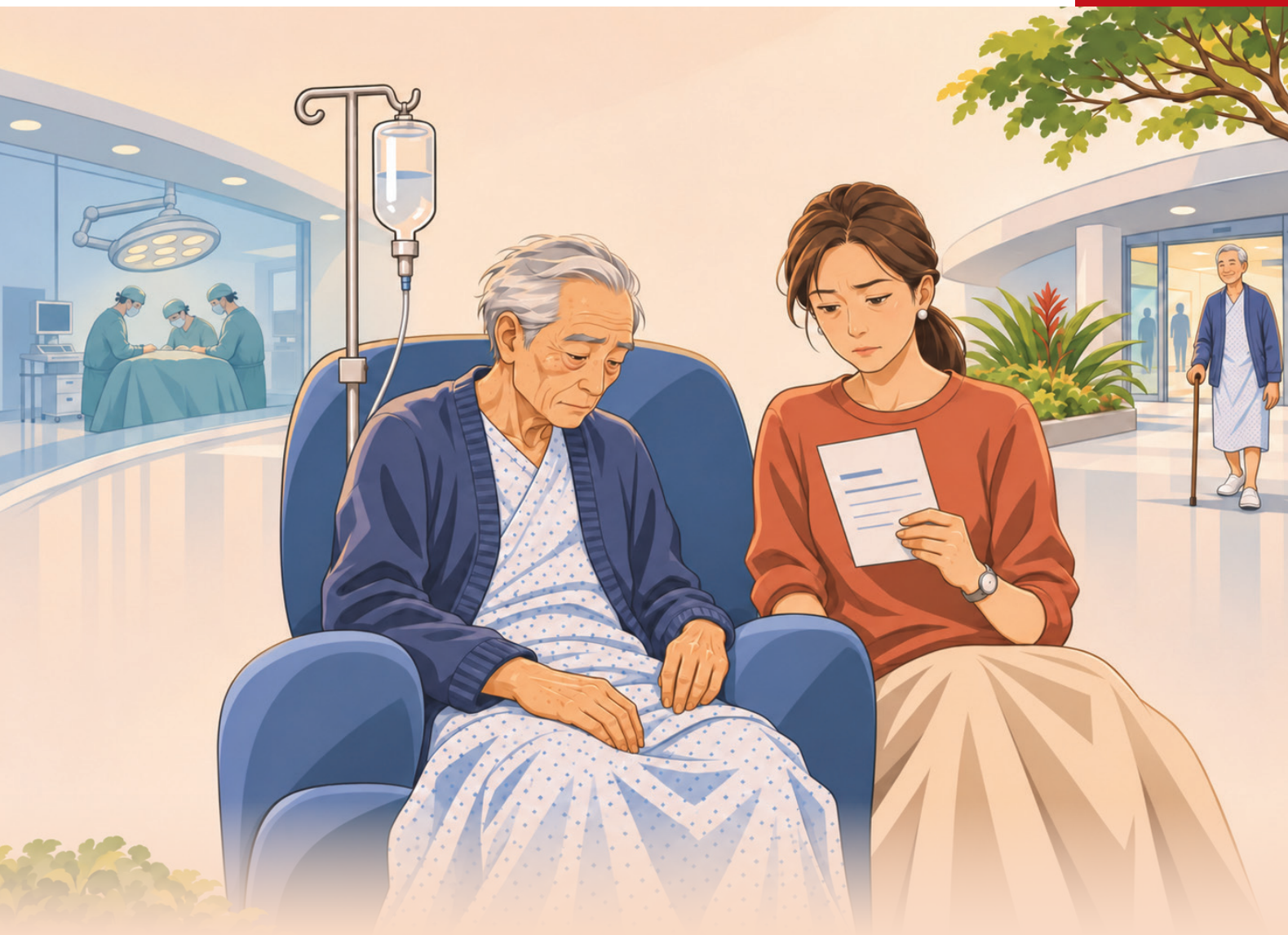

Identifying adults with serious illness in Singapore's surgical population and its impact on postoperative healthcare utilisation and costs

A Singapore cohort study demonstrates how routinely collected health data can identify seriously ill surgical patients at risk of greater healthcare utilisation and costs, informing targeted perioperative support and resource planning. (See full article, p. 563).

Illustration by Maria De-Castro

Also in this issue

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Lecanemab in Singapore: Appropriate use recommendations for early Alzheimer's disease

Efficacy of AI in the diagnosis of oral squamous cell carcinoma from clinical images

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Adolescent headache in a changing world: Diverging trends, shared challenges

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Headache disorders are among the most common neurological conditions worldwide and a leading cause of disability across the lifespan. Tension-type headache (TTH) is more prevalent, but migraine accounts for most headache-related disability.[1] Much of this burden is described in adults, although headache commonly begins much earlier and affects around 1 in 5 children and adolescents worldwide.[2] Recurrent headaches at this age can disrupt school attendance, learning, friendships, and quality of life, while migraine in this age group is associated with higher rates of anxiety and depressive symptoms.[3,4] Adolescence therefore matters twice over—it is a period in which the development of headache disorders can be observed, and one in which recognition and early management can limit the educational, psychological, and social impact.

In this issue of the *Annals*, Zhu et al.[5] used the Global Burden of Disease (GBD) 2021 data to compare migraine and TTH among adolescents aged 10–19 years in China, Germany, and the US between 1990 and 2021. They examined incidence, prevalence, years lived with disability (YLDs), age and sex patterns, temporal trends, and associations with the socio-demographic index (SDI). China had the largest absolute number of adolescents affected by migraine and TTH, despite having the lowest age-standardised rates (ASRs), while also experiencing the largest increases in age-standardised incidence and prevalence rates for both disorders. Germany had the highest age-standardised incidence, prevalence, and YLD rates for migraine, whereas the US had the highest corresponding rates for TTH. However, trends in both countries were generally stable or declining.[5]

This rise in ASRs in China is perhaps the most striking finding. There are at least 2 explanations, and they are not mutually exclusive. First, headache may genuinely be increasing in frequency. Earlier global analyses have also reported increasing incidence, prevalence, and disability among adolescents and young adults, with East Asia showing the fastest rise in TTH prevalence.[2,6] Shorter sleep, heavier academic demands, less physical activity, more screen exposure, and greater psychosocial stress are plausible contributors. Second, some of the apparent increase may reflect better recognition of existing cases. Because migraine and TTH are diagnosed clinically using symptom-based criteria, population estimates depend heavily on survey methods, disease awareness, and access to care—all of which affect the quality of the underlying data. A low recorded prevalence does not always mean a low true burden, and a rising one may reflect worsening disease, better recognition, or both.

The age-specific findings are particularly interesting. Migraine incidence was higher at 10–14 years of age, while prevalence and disability were greater at 15–19 years. This may represent different points on the same trajectory: migraine presenting earlier in adolescence, with greater accumulated burden later. TTH prevalence and disability were also greater in the older age group.[5] Biological changes, including puberty, are likely to be relevant, alongside the lifestyle and psychosocial changes of adolescence: sleep, schooling, social pressures, and mental health. Although the study identifies when the trends diverge, it cannot establish what drives these differences.

The findings should be read in a wider Asian context. Because of its population size, Asia carries an enormous absolute burden even where the ASRs appear modest. Across all age groups, Asia had an estimated 684 million people with migraine and 1.13 billion with TTH in 2021.[7] The financial consequences extend well beyond headache days. An adult population-based survey in China estimated the annual cost of primary headache disorders at 2.24% of gross domestic product, with indirect costs accounting for most of that burden.[8] In adolescents, analogous indirect costs may instead appear as missed classes, impaired performance, and parents taking time away from work—all of which are harder to quantify.

The relationship between SDI and headache burden needs to be interpreted with caution. Higher headache rates in more developed settings do not mean that socioeconomic development itself causes headache. Wealthier countries may have greater diagnostic awareness, better access to healthcare, and

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stronger epidemiological data. Rapidly developing societies may concomitantly experience major changes in education, lifestyle, and psychological well-being. In the article by Zhu et al., the slope index of inequality widened for migraine but narrowed slightly for TTH, while concentration indices rose for both—a reminder that absolute and relative measures of inequality can move in different directions within the same dataset.[5] SDI therefore helps contextualise the observed patterns but cannot explain the mechanisms underlying them.

The same caution applies to extrapolations from data collected during the COVID-19 pandemic. The pandemic simultaneously altered sleep, screen time, physical activity, schooling, and stress, all of which could influence headache patterns. However, the increase in China had begun before 2020, and some age- and sex-specific trends flattened in 2019–2021.[5] The study cannot determine how much of the observed change was caused by the pandemic.

GBD analyses are valuable because they allow comparisons across countries and decades using standardised methods, but they inherit the limitations of their inputs. Rural Chinese adolescents may be under-represented, diagnostic practice differs between countries, and population-level associations cannot establish causation. These limitations should temper causal explanations, but they are not a reason to wait.

Adolescent headache is still too readily normalised by young people, families, and clinicians alike. Improving awareness among adolescents, parents, teachers, and primary care clinicians may be one of the most accessible interventions available. Better recognition could lead to earlier assessment and management of headache, including associated disability, effects on sleep, mood, and impact on school and daily life. Medication overuse deserves particular attention, as frequent reliance on acute treatments can further complicate headache and is potentially preventable. Schools and primary care are well placed to identify adolescents whose headaches are frequent or disabling and to direct them towards appropriate care.

Historically, many randomised trials of preventive medication in children and adolescents have not shown clear superiority to placebo, and guidelines have therefore emphasised education, lifestyle and behavioural measures, management of comorbidities, and shared decision-making.[9] More recently, however, the emergence of therapies targeting the calcitonin gene-related peptide (CGRP) pathway has changed the treatment landscape of migraine in adults, and these therapies are increasingly positioned as first-line preventive options. Their role is now beginning to extend into paediatric migraine. Fremanezumab, an anti-CGRP monoclonal antibody, has demonstrated efficacy in children and adolescents with episodic migraine, with phase 3 evidence showing a modest reduction in migraine days and substantially higher 50% responder rates than placebo.[10] Other CGRP-targeted therapies are also being evaluated in paediatric populations, making the outlook increasingly promising. As treatment options expand, care should remain holistic, aiming not only to reduce headache frequency but also to restore the opportunities that headaches can disrupt in young people, including learning, social participation, psychological well-being, and everyday functioning.

Moving forward, advances in treatment should be matched by a better understanding of why adolescent headache burden is changing. Longitudinal studies following adolescents into adulthood are needed to understand how sleep, psychological health, school demands, physical activity, digital exposure, and healthcare access shape headache over time. The findings of Zhu et al.[5] show that adolescent headache is evolving differently across societies. The challenge now is to translate these trends into earlier recognition, better access to care, and timely intervention for adolescents living with headache.

Ethics statement

Not applicable, as no study participants were recruited.

Declaration

The authors 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. No funding was received for this work, and no artificial intelligence tools were used for the preparation of this manuscript.

Keywords: *adolescent, headache, migraine disorders, sociodemographic index, tension-type headache*

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Identifying adults with serious illness in Singapore's surgical population and its impact on postoperative healthcare utilisation and costs

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ABSTRACT

Introduction: Serious illness (SI) refers to life-limiting conditions that adversely affect quality of life. It is increasingly prevalent among ageing populations and has potential downstream repercussions for healthcare systems. Up to 40% of adults with SI undergo surgery, yet the burden of SI among adults undergoing surgery in Singapore remains poorly understood. In this study, the authors adapted a consensus-based definition of SI for the Singapore context and examined its association with postoperative healthcare utilisation and costs.

Methods: The authors used data from the registry of Singapore's largest healthcare cluster and included adults who underwent inpatient surgery between April 2019 and March 2023. First, they identified SI by mapping its consensus definition to locally adopted International Classification of Diseases, 10th Revision codes. Subsequently, they built multivariable regression models to test associations between SI and postoperative health-care utilisation and gross inpatient bill size.

Results: Among 228,687 adults who underwent inpatient surgery, 41,011 (17.9%) met the adapted SI definition. Compared with adults without SI, adults with SI had a longer length of stay (incidence rate ratio 1.81; 95% confidence interval [CI] 1.80–1.83), higher odds of 30-day hospital readmission (odds ratio [OR] 1.58; 95% CI 1.52–1.64), 1-year hospital readmission (OR 2.60; 95% CI 2.53–2.67), 30-day emergency department (ED) visits (OR 1.57; 95% CI 1.51–1.64), 1-year ED visits (OR 2.08; 95% CI 2.03–2.14), and higher relative bill size (relative ratio 1.64; 95% CI 1.62–1.67).

Conclusion: SI was associated with greater postoperative healthcare utilisation and higher gross inpatient bill size. The findings highlight the burden of SI in Singapore and the need for targeted interventions in this vulnerable population to decrease downstream adverse effects on Singapore's healthcare system.

Keywords: costs, healthcare utilisation, serious illness, Singapore, surgery

CLINICAL IMPACT

What is New

- In a large cohort study, the prevalence of serious illness (SI) was 17.9% among adults undergoing inpatient surgery.
- SI was independently associated with higher healthcare utilisation and costs following surgery.

Clinical Implications

- Routinely collected electronic health record data can identify seriously ill adults with high healthcare needs.
- Findings highlight the burden of SI on the healthcare system and the need for targeted perioperative supportive care interventions for this vulnerable cohort.

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INTRODUCTION

In developed and ageing populations globally, healthcare utilisation and expenditure are concentrated among a small proportion of individuals with complex healthcare needs.[1] These "super-utilisers" comprise only approximately 5% of the population but account for a disproportionate share of healthcare utilisation and an estimated 40–60% of total healthcare spending.[2-3] Many of these individuals live with serious illness (SI), characterised by high mortality risk, substantial symptom burden, impaired quality of life and function, and significant caregiver strain.[4] Adults with SI commonly include those with advanced cancer, dementia, end-stage renal, or heart or pulmonary disease, and other life-limiting conditions.[5,6] As populations age globally, the rising burden of SI has emerged as a major driver of healthcare utilisation, hospital admissions, and healthcare expenditure across multiple healthcare systems.

In response to escalating healthcare costs, healthcare systems internationally have increasingly focused on the prospective identification of populations with SI to enable earlier delivery of supportive and palliative care interventions. In the US, where healthcare expenditure exceeded 18% of gross domestic product in 2024, substantial efforts have been made to operationalise SI definitions using administrative data to identify high-need, high-cost populations.[7] Early identification of seriously ill adults enables the timely delivery of palliative care interventions, which have been shown to improve quality of life, support caregivers, and reduce healthcare utilisation and costs.[8]

Adults with SI account for an important proportion of the inpatient surgical population and may experience substantial postoperative healthcare burden.[9,10] Among adults with SI, those with unmet palliative care needs were more likely to experience increased hospital days, emergency readmissions, and emergency department (ED) visits within 1 year after surgery.[11] Healthcare costs after surgery have also been shown to double among seriously ill adults with unmet palliative care needs. These findings underscore the importance of identifying supportive-care needs and prospectively evaluating targeted interventions in surgical populations.

Singapore faces similar pressures from an ageing population, rising multimorbidity, and increasing healthcare expenditure.[12] In 2025, recognising the growing burden of adults with complex healthcare needs, the Ministry of Health (MOH), Singapore established the Appropriate and Value-Based Care initiative aimed at improving healthcare value and optimising healthcare spending.[13] However, despite increasing policy emphasis on value-based care, there remains no operationalised or validated definition of SI in Singapore. This limits the ability to systematically identify high-need, high-cost populations; implement targeted health services interventions; and measure quality outcomes across healthcare systems.[14]

This study therefore applied an adapted International Classification of Diseases, 10th Revision (ICD-10) diagnosis code-based definition of SI within Singapore's healthcare context and examined its association with short- and long-term healthcare utilisation and costs following inpatient surgery in Singapore's largest healthcare cluster. By relying primarily on routinely recorded ICD-10 diagnostic codes, this approach is readily reproducible and potentially automatable within electronic health record systems in Singapore. By anchoring the analyses to a surgical admission, the authors sought to characterise the perioperative burden of SI and its relationship with subsequent healthcare utilisation and expenditure. This work provides a foundation for validation in Singapore and future prospective identification of surgical patients who may benefit from targeted supportive and palliative care interventions, while informing broader efforts to operationalise SI identification across Singapore's healthcare system.

METHODS

Study design and data source

The authors conducted a retrospective cohort study using the SingHealth Electronic Health Intelligence System (eHints), a population-based database comprising routinely collected healthcare data of Singapore's largest public healthcare cluster and covering approximately 35% of the national population.[15] The eHints registry houses demographics, disease, treatment, and out-come information. This study was reported in accordance with the Strengthening the Reporting of Cohort, Cross-sectional and Case-control Studies in Surgery guidelines and the REporting of studies Conducted using Observational Routinely-collected health Data extension of the Strengthening the Reporting of Observational Studies in Epidemiology statement.[16,38]

Study population

The authors included adults aged 21 years and older who underwent inpatient surgery and were discharged between April 2019 and March 2023. Surgical procedures and procedure types were identified using the Table of Surgical Procedures (TOSP) codes designated by MOH, Singapore.[17] For patients with more than 1 qualifying surgical admission during the study period, a single index admission was retained to avoid double-counting and ensure independence of observations. The admission associated with the highest TOSP code was selected as the index admission, with TOSP codes used as a pragmatic proxy for procedural complexity to identify the highest-

complexity perioperative episode during the study period. Where multiple admissions had the same highest TOSP code, the earliest admission was selected based on admission date and case number. Day-surgery and other non-inpatient cases were excluded. A sensitivity analysis was conducted using the first eligible surgical admission for each patient as the index admission.

Operationalising the SI definition in Singapore

The authors operationalised an ICD-10 diagnosis-only definition of SI derived from the US consensus-based definition of SI in surgery; this definition has been validated in several population-based studies.[18,19] Adults with any of the following diagnoses were considered to have SI: (1) advanced cancer (i.e. stage III or IV solid organ cancers), (2) advanced pulmonary disease, (3) heart failure, (4) cirrhosis, (5) end-stage renal disease on dialysis or eligible for dialysis, and (6) dementia.[5,6,20] ICD-10 codes used to identify these conditions in US Medicare claims were individually mapped to corresponding ICD-10 diagnostic codes used in Singapore. The mapping was reviewed and refined by the SingHealth study team against local ICD-10 descriptors to account for differences in coding terminology and classification. As an adaptation for use with routinely collected diagnostic data, the operational definition did not incorporate non-diagnostic criteria included in the original definition, such as healthcare utilisation or care-need triggers, frailty, nursing-home residence, or functional impairment, as these variables were not consistently available within the study dataset. The resulting ICD-10-based definition has not been validated against medical record review or a clinically adjudicated reference standard and should therefore be interpreted as an adapted operational definition of SI in Singapore's healthcare context. The mapped SI definitions and corresponding ICD-10 codes are provided in Supplementary Tables S1 and S2.

Outcomes: Healthcare utilisation and gross inpatient bill size

Healthcare utilisation outcomes were measured using the length of stay (LOS) for the index surgical admission, 30-day and 1-year hospital readmissions, and 30-day and 1-year ED visits following discharge from the index surgical admission. The financial outcome was the pre-subsidy gross inpatient bill size for the index surgical admission, derived from hospital billing records. It represents a hospital billing amount rather than an economic cost of care, payer expenditure, or patient out-of-pocket payment.[21] Gross inpatient bill sizes were adjusted for inflation (2020 Singapore Dollars [SGD]) based on the consumer price index.[22]

Study covariates

Patient characteristics, such as age, sex, and ethnicity, were included. Data on the qualifying SI condition, number of qualifying SI conditions, surgical procedure type, surgery nature (minor versus major), admission type, and financial year were also collected. Surgical procedure type was classified using MOH-defined TOSP codes, which organise surgical procedures into body system-based categories.[17] Additionally, surgery nature was classified as minor or major using the same TOSP coding system, which ranks surgical procedures from Table 1A to 7C, with higher numbers indicating greater procedural complexity.[17,23] Procedures coded as Table 4 and above were defined as major surgery, while those below Table 4 were considered minor surgery.[23]

Statistical analysis

The annual prevalence of SI among patients undergoing inpatient surgery was summarised descriptively. Patient characteristics were compared between adults with and without SI using standardised mean differences, given the sensitivity of conventional significance testing to small differences in large samples. Univariable and multivariable regression analyses were performed to evaluate the association between SI and postoperative healthcare utilisation and index-admission gross inpatient bill amounts. Negative binomial regression was used to model LOS to account for overdispersion in count data. Gamma regression with a log link was used for gross inpatient bill sizes because of their positive, right-skewed distribution, while logistic regression was used for binary outcomes, including hospital readmissions and ED visits.

Multivariable models were adjusted for age, sex, ethnicity, surgical procedure type, surgery nature, admission type, and financial year. Individual SI conditions and the number of qualifying SI conditions were not included in the primary models because they formed part of the operational definition of the primary exposure (SI status). For all multivariable models, 95% confidence intervals (CIs) were calculated using heteroskedasticity-consistent type 1. Adjusted marginal mean gross inpatient bill sizes were estimated from the multivariable models by averaging predicted values across the observed covariate distribution. Effect modification by surgery nature (major vs minor surgery) was evaluated by including an interaction term between SI status and surgery nature. Finally, as a sensitivity analysis, primary analyses were repeated using the first eligible surgical admission as the index admission, rather than the admission with the highest TOSP code. All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study participants

A total of 813,211 surgical cases were identified during the study period. After excluding patients aged <21 years and non-inpatient surgical cases, 315,171 inpatient surgical cases were identified. For patients with multiple surgical admissions during the study period, a single index admission corresponding to the highest TOSP-coded surgery was retained, resulting in a final study cohort of 228,687 unique patients. Fig. 1 depicts the study cohort flow.

In total, 41,011 (17.9%) met the operational definition of SI. Among patients with SI, advanced cancer was the most common qualifying condition (n=26,451; 64.5%), followed by end-stage renal disease (n=6669; 16.3%), heart failure (n=4856; 11.8%), dementia (n=2723; 6.6%), advanced pulmonary disease (n=2051; 5.0%), and cirrhosis (n=921; 2.2%). Most patients with SI had a single qualifying condition (n=38,480; 93.8%), while 2403 (5.9%) had 2 and 128 (0.3%) had 3 or more qualifying conditions. Study cohort characteristics are presented in Table 1.

Trend in the prevalence of SI among surgical patients

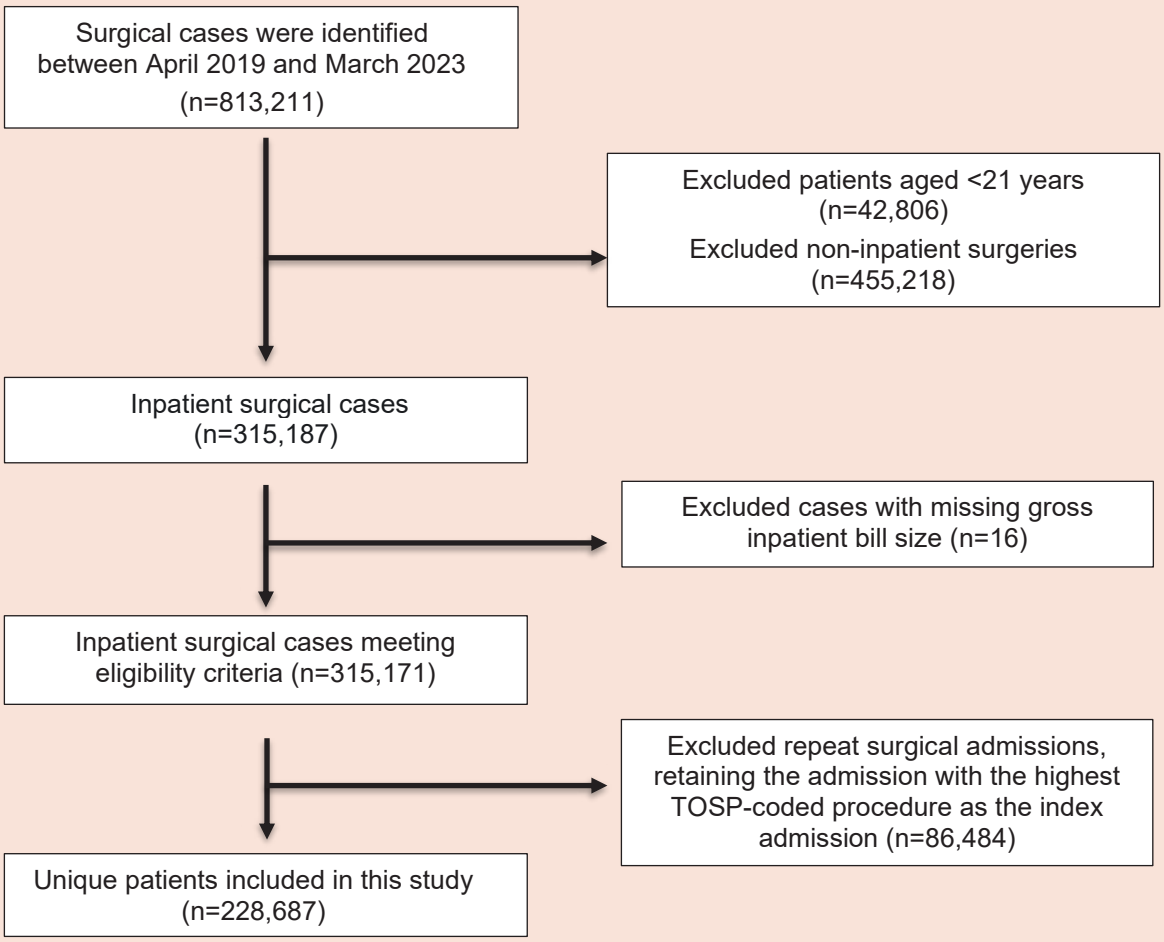
The proportion of adults undergoing inpatient surgery who met criteria for SI remained relatively stable across the 4-year study period, ranging from 17.1% to 18.3%. The annual prevalence was 17.6% in April 2019–March 2020, 17.1% in April 2020–March 2021, 18.3% in April 2021–March 2022, and 18.1% in April 2022–March 2023.

Healthcare utilisation

Table 2 presents the adjusted associations between SI and postoperative healthcare utilisation, including hospital LOS, hospital readmissions, and ED visits. Unadjusted analyses are presented in Supplementary Table S3.

The mean hospital LOS for the overall cohort was 6.3 days (standard deviation [SD] 12.0). Mean LOS was 11.8 days (SD 17.6) among adults with SI and 5.1

Fig. 1. Flow diagram for study cohort.



TOSP: Table of Surgical Procedures

Table 1. Baseline characteristics of adults with and without SI undergoing surgery (April 2019–March 2023, n=228,687).

Patient characteristics	Adults without SI (n=187,676)	Adults with SI (n=41,011)	Absolute SMD
Age in years, mean (SD)	52.1 (17.9)	66.2 (13.5)	0.89
Female sex, no. (%)	115,723 (61.7)	18,831 (45.9)	0.32
Qualifying serious illness,[a] no. (%)			-
Advanced cancer	-	26,451 (64.5)	
End-stage renal disease	-	6669 (16.3)	
Heart failure	-	4856 (11.8)	
Dementia	-	2723 (6.6)	
Advanced pulmonary disease	-	2051 (5.0)	
Cirrhosis	-	921 (2.2)	
No. of qualifying conditions, mean (SD)	-	1.065 (0.259)	
One condition, no. (%)	-	38,480 (93.8)	
Two conditions, no. (%)	-	2403 (5.9)	
At least 3 conditions, no. (%)	-	128 (0.3)	
Surgical procedure type, no. (%)			
Breast and soft tissue	14,418 (7.7)	3663 (8.9)	0.045
Cardiothoracic and vascular	23,860 (12.7)	9218 (22.5)	0.259
Central nervous system[b]	3165 (1.7)	778 (1.9)	0.016
Ear, nose, and throat	5536 (2.9)	686 (1.7)	0.085
Endocrine[c]	1495 (0.8)	882 (2.2)	0.113
Eye	1004 (0.5)	134 (0.3)	0.032
Gastrointestinal	32,911 (17.5)	12,527 (30.5)	0.308
Genito-urinary[d]	6280 (3.3)	3363 (8.2)	0.209
Gynaecological	63,264 (33.7)	2949 (7.2)	0.696
Musculoskeletal	32,757 (17.5)	2815 (6.9)	0.328
Respiratory	2108 (1.1)	3478 (8.5)	0.349
Others[e]	878 (0.5)	518 (1.3)	0.086
Surgery nature, no. (%)			
Major	92,864 (49.5)	25,026 (61.0)	0.234
Minor	94,812 (50.5)	15,985 (39.0)	0.234
Length of stay, days, mean (SD)	5.11 (9.93)	11.77 (17.56)	0.467
Length of stay, days, median (IQR)	3 (2–5)	6 (3–14)	-
30-day hospital readmission, any, no. (%)	13,491 (7.2)	3902 (9.5)	0.084
1-year hospital readmission, any, no. (%)	35,578 (19.0)	17,351 (42.3)	0.524
30-day ED visit, any, no. (%)	16,442 (8.8)	5981 (14.6)	0.182
1-year ED visit, any, no. (%)	43,091 (23.0)	19,264 (47.0)	0.520

ED: emergency department; IQR: interquartile range; SD: standard deviation; SI: serious illness; SMD: standard mean difference
[a] Does not sum up to 100% as a patient can have >1 serious illness condition
[b] Neurosurgery, spine
[c] Thyroid, adrenal
[d] This excludes female genital; female genital is under gynaecological procedure
[e] Lymphatics, spleen

Table 2. SI and healthcare utilisation and cost outcomes among adults undergoing surgery.

SI status	Length of stay (IRR,[a] 95% CI)	30-day hospital readmission, any (OR,[a] 95% CI)	1-year hospital readmission, any (OR,[a] 95% CI)	30-day ED visits, any (OR,[a] 95% CI)	1-year ED visits, any (OR,[a] 95% CI)	Gross inpatient bill size (relative ratio,[a] 95% CI)
SI vs non-SI	1.81 (1.79–1.83)	1.58 (1.52–1.64)	2.60 (2.53–2.67)	1.57 (1.51–1.64)	2.08 (2.03–2.138)	1.64 (1.61–1.67)

CI: confidence interval; ED: emergency department; IRR: incidence rate ratio; OR: odds ratio; SI serious illness
[a] Models are adjusted for age, sex, ethnicity, TOSP, surgery nature, admission type, and financial year.

days (SD 9.9) among adults without SI. SI was independently associated with longer LOS following inpatient surgery (adjusted incidence rate ratio [IRR] 1.81, 95% CI 1.80–1.83).

The 30-day hospital readmission rate was 9.5% among adults with SI and 7.2% among adults without SI, while the corresponding 1-year readmission rates were 42.3% and 19.0%, respectively. SI was independently associated with higher odds of hospital readmission at both 30 days (adjusted OR 1.58, 95% CI 1.52–1.64) and 1 year (adjusted OR 2.60, 95% CI 2.53–2.67) following inpatient surgery.

Similarly, 30-day ED visit rates were 14.6% and 8.8%, while 1-year ED visit rates were 47.0% and 23.0% among adults with and without SI, respectively. SI was also independently associated with higher odds of ED visits at 30 days (adjusted OR 1.57, 95% CI 1.51–1.64) and 1 year (adjusted OR 2.08, 95% CI 2.03–2.14).

Fig. 2 presents the associations between SI and healthcare utilisation outcomes, stratified by surgery nature. The association between SI and LOS differed by surgery nature, with a stronger association among adults undergoing minor surgery (adjusted IRR 2.00, 95% CI 1.97–2.03) than among those undergoing major surgery (adjusted IRR 1.70, 95% CI 1.68–1.72; *P* for interaction <0.001). In contrast, there was no evidence of effect modification by surgery nature for 1-year hospital readmission (adjusted OR 2.63 for major surgery vs 2.55 for minor surgery; *P* for interaction=0.193) or 1-year ED visits (adjusted OR 2.12 for major surgery vs 2.04 for minor surgery; *P* for interaction=0.109).

Gross inpatient bill size

The adjusted mean gross inpatient bill size was SGD25,648.08 (standard error [SE] 154.22; 95% CI 25,345.81–25,950.35) among adults with SI and SGD15,615.66 (SE 48.50; 95% CI 15,520.60–15,710.72) among those without SI. SI was independently associated with a 1.64-fold higher gross inpatient bill size following inpatient surgery (adjusted relative ratio 1.64, 95% CI 1.62–1.67).

When stratified by surgery nature, the adjusted marginal mean gross inpatient bill size following major surgery was SGD34,586.24 (SE 206.97) among adults with SI and SGD21,217.42 (SE 65.11) among adults without SI. Following minor surgery, the adjusted marginal mean gross inpatient bill sizes were SGD15,338.97 (SE 175.22) and SGD9630.46 (SE 50.82) among adults with and without SI, respectively. There was no evidence of effect modification by surgery nature, with similar associations between SI and gross inpatient bill size following major surgery (adjusted relative ratio 1.65, 95% CI 1.62–1.67) and minor surgery (adjusted relative ratio 1.64, 95% CI 1.59–1.69; *P* for interaction=0.682).

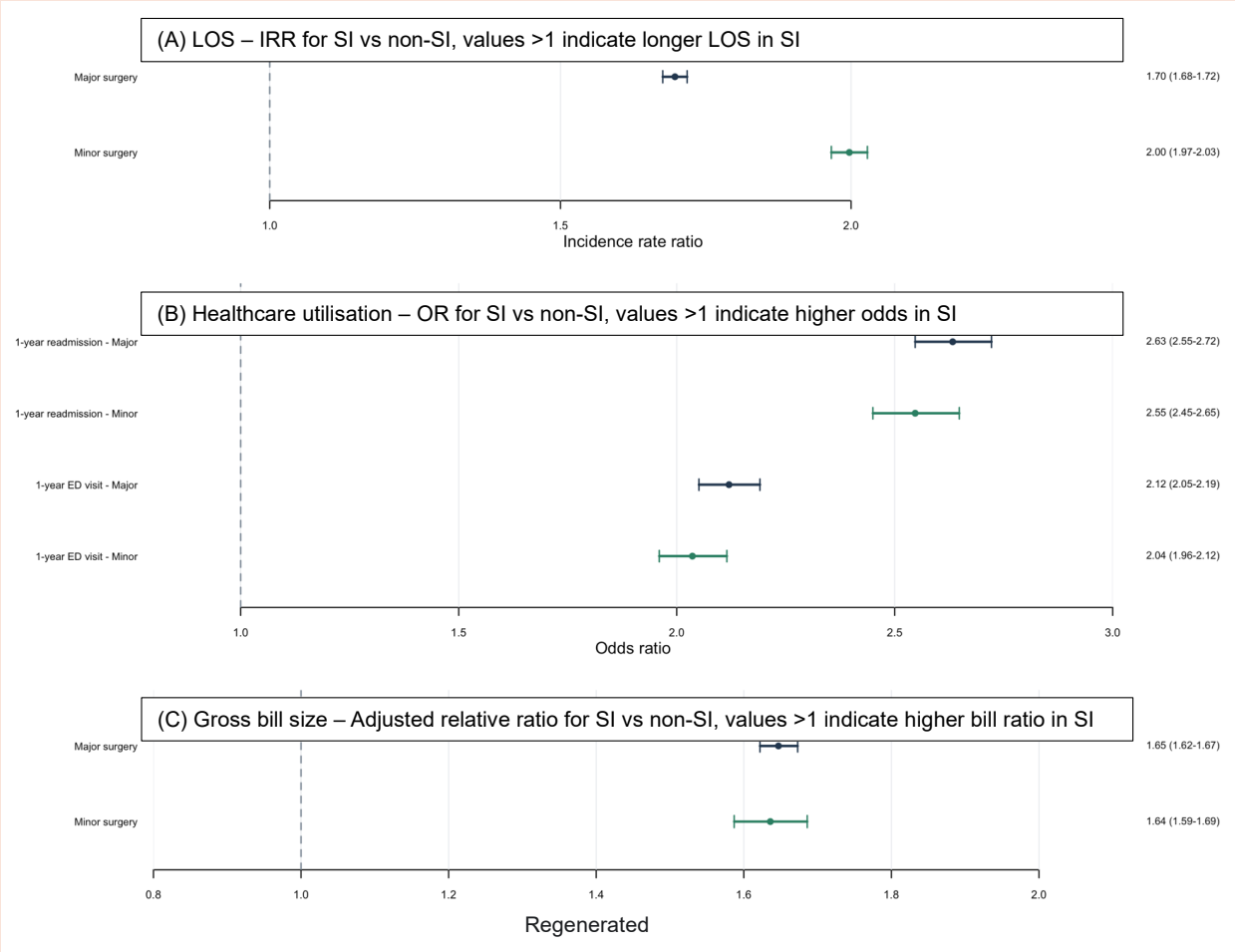
Sensitivity analysis using the first eligible surgical admission as the index admission yielded findings consistent with the primary analysis for all healthcare utilisation outcomes and gross inpatient bill sizes (Supplementary Table S4).

DISCUSSION

In this population-based study of adults undergoing inpatient surgery in Singapore, nearly 1 in 5 patients (17.9%) met the adapted ICD-10-based definition of SI, with advanced cancer being the qualifying condition in almost two-thirds of adults with SI. The proportion of surgical patients with SI remained relatively stable over the 4-year study period. Compared with adults without SI, those with SI experienced substantially greater postoperative healthcare utilisation, including longer hospital stays and higher rates of hospital readmissions and ED visits, with differences persisting up to 1 year after surgery. SI was also associated with substantially higher gross inpatient bill sizes. Collectively, these findings demonstrate the considerable and sustained healthcare burden associated with SI among adults undergoing inpatient surgery.

This study represents one of the first efforts to operationalise and evaluate an SI definition among adults undergoing surgery outside the US healthcare system. Although consensus-based SI definitions have been developed and evaluated in the US, their

Fig. 2. Differences in outcomes: (A) length of stay, (B) 1-year hospital readmission and 1-year emergency department visits, and (C) inpatient healthcare costs in adults with and without serious illness by surgery nature (minor vs major).



CI: confidence interval; ED: emergency department; IRR: incidence rate ratio; LOS: length of stay; OR: odds ratio; SI: serious illness
Note: Points represent relative estimates for adults with SI versus adults without SI within each surgery nature group (minor vs major); horizontal lines represent 95% CIs

application in other healthcare systems remains limited despite the growing global burden of ageing, multimorbidity, and healthcare utilisation.[24-26] The authors adapted a US-based definition of SI in surgery definition into an ICD-10-only approach using routinely collected diagnostic data available within Singapore's largest public healthcare cluster. The ability of this pragmatic definition to identify a sizeable surgical population with substantially greater subsequent healthcare needs supports its potential utility as a scalable approach for identifying SI within routinely collected health data.

This study highlights the substantial short- and longer-term healthcare utilisation associated with SI among adults undergoing surgery. Adults with SI were more likely to visit the ED or experience hospital readmission at 30 days and 1 year after surgery. This increased healthcare utilisation was accompanied by substantially higher inpatient costs, with adjusted gross inpatient bill sizes approximately 64% higher among adults with SI. The findings align well with prior US-based studies, which demonstrated similar trends in healthcare utilisation.[11,27-29] In a cohort of seriously ill older adults undergoing major elective surgery, those with unmet palliative care needs, such as pain, functional dependence, depression, or care-partner needs, had the highest risk of increased healthcare utilisation and costs at 1 year after surgery.[11]

Notably, the relative increase in LOS associated with SI was greater among adults undergoing minor surgery than among those undergoing major surgery. One possible explanation is that the expected LOS following minor surgery is relatively short, such that additional perioperative complexity associated with SI may result in a proportionally larger increase in hospital stay.[30,31] In contrast, major surgery is inherently associated with longer postoperative recovery and hospitalisation, which may attenuate the relative

difference in LOS attributable to SI.[32] Despite this difference in LOS, the associations between SI and longer-term hospital readmissions and ED visits were similar following major and minor surgeries. This suggests that while procedural complexity may influence the immediate perioperative impact of SI, longer-term healthcare utilisation may be driven to a greater extent by patients' underlying SI and associated healthcare needs. Given the observational nature of this study and the absence of detailed perioperative clinical variables, these findings remain hypothesis-generating and warrant further investigation.

This study specifically focused on adults undergoing surgery because perioperative care represents a clinically intensive episode frequently associated with substantial healthcare utilisation, care transitions, and postoperative morbidity among patients with SI.[33-35] Although surgery may not represent the primary treatment modality for all SI conditions included in this study, such as dementia or advanced cancer, these individuals nevertheless commonly undergo surgical interventions for diagnostic, therapeutic, symptom-directed, or emergency indications.[36,37] Thus, restricting the cohort to inpatient surgical patients within a single public healthcare cluster allowed the authors to evaluate the perioperative burden of SI within a clinically important and resource-intensive healthcare context. However, the lack of data from other public healthcare clusters, private hospitals, and community settings limits generalisability to the national surgical population and to all adults with SI across the broader healthcare system.

This study has several limitations. First, although the authors adapted a previously established US-based consensus definition of SI in surgery,[5,6,20] they were unable to fully replicate all original criteria because of differences in available registry variables between the US and Singapore healthcare systems. In particular, measures relating to frailty, nursing home residence, functional or cognitive impairment, and certain healthcare utilisation-based criteria were unavailable within the SingHealth eHints dataset. As a result, the adapted Singapore definition relied predominantly on ICD-10 diagnosis-based criteria and may have misclassified some adults with SI, particularly frail or functionally impaired individuals without qualifying diagnostic codes. Consequently, the estimated prevalence of SI and its observed associations with healthcare utilisation may differ from studies using more comprehensive multidimensional definitions. Future work should validate this operational definition against medical record review or a clinically adjudicated reference standard in the Singapore population.

Second, for individuals with multiple qualifying surgical admissions, the authors retained a single index admission based on the highest TOSP code. Although this provided a pragmatic approach to identifying the highest-complexity surgical episode, it may have preferentially selected more resource-intensive admissions and may not necessarily represent the most clinically meaningful episode for individual patients. Nevertheless, sensitivity analyses using the first eligible surgical admission as the index admission demonstrated findings consistent with the primary analysis.

Third, several limitations relate to the scope of data captured within eHints. Death data were unavailable, so the authors were unable to assess postoperative mortality or perform competing-risk analyses. Mortality rates are likely higher among adults with SI, and differential mortality may have influenced longer-term estimates of readmissions and ED utilisation, as patients who died earlier had less opportunity to experience these outcomes. As the eHints registry captures healthcare utilisation within the SingHealth cluster, healthcare encounters occurring in other public healthcare clusters, private institutions, or community settings were not captured. Similarly, the gross inpatient bill size examined in this study represents the pre-subsidy bill for the index surgical admission rather than an economic cost or total healthcare-system expenditure. Costs associated with subsequent readmissions and ED visits were unavailable, and the financial estimates should therefore not be interpreted as the total downstream healthcare expenditure associated with SI.

Finally, the observational nature of this study precludes causal inference. While SI was associated with increased healthcare utilisation and inpatient costs, the findings do not establish that earlier identification or intervention would necessarily reduce downstream utilisation or expenditures. Further prospective interventional studies are required to evaluate whether targeted perioperative supportive care models can improve outcomes among seriously ill surgical populations.

CONCLUSION

An adapted ICD-10-based definition of SI identified a substantial population of adults undergoing inpatient surgery with high healthcare needs. SI was associated with greater short- and longer-term healthcare utilisation, including longer hospital stays, increased ED visits and hospital readmissions, and higher index-admission gross inpatient bill sizes. The findings support the potential utility of an ICD-10-based approach for the systematic identification of SI within surgical populations and provide a foundation for developing and prospectively evaluating targeted perioperative supportive care strategies to improve outcomes and address healthcare utilisation and costs.

Supplementary materials

Table S1. Adaptation of the definitions of serious illness in surgery in Singapore.

Table S2. International Classification of Diseases, 10th Edition codes used to define serious illness.

Table S3. Univariable analysis for serious illness and healthcare utilisation and cost outcomes among adults undergoing surgery.

Table S4. Sensitivity analysis of the association between serious illness and postoperative healthcare utilisation and gross inpatient bill size using the first eligible surgical admission as the index admission.

Ethics statement

This study was deemed "Not Human Subjects Research" by the SingHealth Centralised Institutional Review Board (ECOS reference number: 2024-4525).

Declaration

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Temporal trends of migraine and tension-type headache in adolescents across China, Germany and the US

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ABSTRACT

Introduction: Adolescence (10–19 years) is a critical neurodevelopmental window. This study aimed to describe long-term temporal trends and disease burden of migraine and tension-type headache (TTH) and explore sociodemographic inequality among adolescents in China, the US, and Germany from 1990 to 2021.

Methods: Incidence, prevalence, and years lived with disability (YLDs) were extracted from the Global Burden of Disease 2021 study stratified by country, age (10–14 and 15–19 years), and sex. Joinpoint regression calculated average annual percent changes (AAPCs) for age-standardised incidence, prevalence, and YLD rates (ASIR, ASPR, ASYR, respectively). Frontier analysis, slope index of inequality, and concentration index assessed socio-demographic index (SDI) associations and inequalities.

Results: China had the largest absolute case numbers but lowest age-standardised rates (migraine AAPC = 0.27%, TTH = 0.31%).). Girls carried a substantially higher burden than boys across all 3 countries. The US and Germany showed higher ASRs with generally stable or declining trends. Migraine was more common in 10–14-year-olds, while TTH was more frequent in 15–19-year-olds. Migraine burden became increasingly concentrated in higher-SDI countries with widening absolute and relative inequalities, whereas TTH-related inequalities slightly attenuated over the study period.

Conclusion: China's rapidly rising SDI and population structure were associated with the increase in headache burden. High-SDI countries maintained a relatively stable burden, likely due to mature health services. Worsening socio-economic inequalities were observed for migraine, while TTH showed a mild mitigating trend. Potential targeted strategies include school-based screening for headache in China, expanded youth telehealth in the US, and stress manage-ment programmes in Germany.

Keywords: adolescent, headache, migraine, sociodemographic index, tension-type headache

CLINICAL IMPACT

What is New

- This study provides a 30-year cross-national comparison of adolescent migraine and tension-type headache (TTH) trends across China, the US, and Germany, capturing distinct sociodemographic index trajectories.
- Migraine was more common among younger adolescents (10–14 years), while TTH predominated among older adolescents (15–19 years).
- Socioeconomic inequalities widened for migraine but slightly attenuated for TTH.

Clinical Implications

- China: Rising headache burden highlights the need for school-based headache screening and earlier access to preventive care.
- US: Stable or declining rates support strengthening headache-care pathways and expanding youth telehealth access.
- Germany: The higher TTH burden among older adolescents supports age-specific stress-management and early psychosocial interventions.

INTRODUCTION

Adolescence is a pivotal period of neurodevelopment, hormonal fluctuation, and psychosocial transition, all of which converge to elevate vulnerability to migraine and tension-type headache (TTH).[1,2] Recurrent headache in this age group disrupts school attendance, impairs peer relationships, and increases the risk of comorbid mental health disorders.[3-5] Although the global headache burden has been studied, few analyses have focused specifically on the 10–19-year subgroup with long-term trend decomposition, age–sex stratification, cross-national comparison at different socio-demographic index (SDI) stages, and formal inequality metrics.

China, Germany, and the US were selected because they represent distinct SDI trajectories and health system models. China's rapidly rising SDI may exacer-bate urban–rural disparities in paediatric headache care, while Germany and the US remain high-SDI nations.[6] China faces unique challenges, including intense academic competition among adolescents

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aged 15–19 years and uneven access to paediatric headache care between urban and rural regions.[7,8] Germany, a high-income country with universal healthcare, offers structured adolescent health services but grapples with rising mental health stressors among adolescents aged 10–14 years.[9] The US, also a high-income country, exhibits stark disparities in access to paediatric headache care and high levels of adolescent screen time, both of which have been linked to TTH exacerbation.[10,11] Comparisons across these 3 nations allow exploration of how context-specific factors, including SDI-driven resource disparities and population subgroup differences, may influence headache trends among adolescents aged 10–19 years over 3 decades.

The Global Burden of Disease (GBD) 2021 study provides standardised, comparable estimates of headache burden across countries. Secondary analysis of GBD public data is a legitimate and widely accepted approach in epidemiological research to generate context-specific insights not reported in the original GBD publications.[12] Using GBD 2021, the authors aimed to compare age-specific temporal trends of migraine and TTH across 3 countries representing different SDI levels, examine population-level changes in migraine and TTH during the COVID-19 period as an ecological observation, quantify the inequalities in relation to context-specific factors, and provide tailored public health recommendations.

METHODS

Data source

The anonymised data used in this study were extracted from GBD 2021. GBD 2021 provides standardised estimates of disease burden and attributable risk factors across 371 diseases and injuries, alongside 87 risk factors, covering 204 countries and territories and 811 subnational locations from 1990 to 2021. The estimates were systematically synthesised from global data sources, including peer-reviewed literature, vital registration systems, population-based surveys, national censuses, administrative health records, disease registries, individual research studies, official reports, and satellite imagery.[13]

China, Germany, and the US were selected based on 3 key criteria: (1) they represent distinct SDI trajectories—China's SDI has risen rapidly into the high-middle range, while Germany and the US have remained within the high-SDI range, allowing comparison across different stages of socioeconomic development; (2) the countries represent diverse healthcare paradigms, including China's expanding mixed public–private system, Germany's universal healthcare with structured adolescent services, and the US healthcare system, with its private insurance-based structure and disparities in insurance coverage; (3) they have distinct adolescent risk profiles—intense academic pressure in China, rising mental health stress in Germany, and high screen time plus care gaps in the US—which facilitate the identification of context-specific burden drivers.

For the current analysis, which focuses on migraine and TTH in adolescents, 3 core measures of disease burden were extracted: incidence, prevalence, and YLDs. In the context of this study, YLDs, a key metric for quantifying non-fatal disease burden, reflect the healthy life years lost due to disability caused by migraine or TTH. As migraine and TTH are predominantly non-fatal disorders, their burden is primarily reflected in the disability and reduced quality of life they impose. Therefore, YLDs were selected as the key burden metric to capture their impact on health. All indicators were obtained as both absolute numbers and age-standardised rates (ASRs) and were stratified by: (1) geography at the global level and for the 3 focal countries (China, Germany, the US); (2) time, with annual data from 1990 to 2021; (3) age, including adolescents aged 10–19 years, and 2 age subgroups (10–14 and 15–19 years); and (4) sex, including boys and girls.

Definition of diseases

For case definition, codes from the International Classification of Diseases, 10th Revision (ICD-10), corresponding to migraine and TTH were used. These include G43–G43.919 for migraine and G44.2–G44.229, G44.4–G44.41 for TTH.[14] In standard clinical classification, G44.4 denotes drug-induced headache and is not classified as a primary TTH subtype. The GBD study includes this range of codes in its TTH definition because medication-overuse headache cannot be reliably separated from primary TTH in aggregated population-level datasets. This coding convention has been widely adopted in peer-reviewed GBD-based headache epidemiological research.[15,16]

Sociodemographic index

In GBD 2021, SDI was calculated for each country and territory worldwide.[12] As a composite metric, SDI quantifies key sociocultural and macroeconomic determinants that shape population health outcomes across different geographic settings. Specifically, the index integrates 3 core indicators: total fertility rate (capturing population reproductive patterns), mean years of schooling among adults aged ≥15 years (reflecting educational attainment), and lag-distributed income per capita adjusted for purchasing power parity (accounting for economic development). These 3 metrics are aggregated using a geometric mean to generate the final SDI score.[12]

Frontier analysis

Frontier analysis was performed to further assess the relationship between the burden of migraine and

TTH and SDI development, among adolescents aged 10–19 years, using data for both sexes combined. A nonlinear frontier was constructed to represent the lowest observed burden of migraine and TTH attainable at different SDI levels, thereby reflecting the minimum burden associated with each stage of sociodemographic development. Non-parametric data envelopment analysis was used to construct this frontier.[17]

Analysis of cross-country inequalities

To quantify cross-country inequalities in migraine and TTH burden among adolescents aged 10–19 years, 3 standardised metrics, the slope index of inequality (SII; for absolute inequality), and the concentration index (CIX; for relative inequality), were used based on crude incidence, prevalence, and YLD rates.[18] Analyses drew on GBD 2021 data for all countries (to calculate global inequality) but focused on contrasts between the global average and 3 focal countries (China, Germany, the US) for result presentation. Specifically, SII was calculated by regressing national crude rates among adolescents aged 10–19 years against countries' relative positions in the SDI-ranked distribution, defined as the midpoint of the cumulative population share. The SII quantifies the absolute difference in disease burden across the socioeconomic spectrum. The CIX was calculated as twice the area between the Lorenz concentration curve (cumulative proportion of the global 10–19-year-old population versus disease burden, sorted by SDI) and the equality line to quantify relative burden distribution. The authors used 95% confidence intervals (1000 bootstrap iterations) to assess significance, with the sign of the SII indicating the direction of the burden gradient by SDI (positive = higher burden in high-SDI countries) and the CIX (range −1 to 1) reflecting the degree of inequality (0 = even distribution, positive/negative = concentration in high-low-SDI countries).

Statistical analysis

All statistical analyses were conducted using migraine and TTH burden data extracted from GBD 2021, covering 3 core metrics: incidence, prevalence, and YLDs. For each metric, both absolute numbers (to reflect the overall population-level disease burden) and ASRs were calculated, including age-standardised incidence rate (ASIR), age-standardised prevalence rate (ASPR), and age-standardised YLD rate (ASYR), to account for differences in population age structure. ASRs were computed in accordance with the GBD standard-population structure,[19] with rates expressed per 100,000 person-years.

The Joinpoint Regression Program version 4.9.0.0 (Surveillance Research Program, National Cancer Institute, US) was used to quantify temporal trends in ASIR, ASPR, and ASYR, and corresponding absolute counts for migraine and TTH from 1990 to 2021. The core principle of this method is to partition the entire time series into multiple continuous segments using "joinpoints" (points where the trend slope changes significantly) and fit a linear regression model to each segment to estimate trend direction and magnitude. The Monte Carlo permutation test (significance level $P<0.05$) was used to identify the number and position of joinpoints, ensuring that only statistically meaningful trend changes were retained. For each segment, the annual percent change (APC) was calculated to describe the average annual rate of change in burden within that period. For the overall 1990–2021 period, the authors computed the average annual percent change (AAPC), a geometric weighted average of APCs across all segments, to summarise the long-term trend, with 95% confidence intervals (CIs) reported for both APC and AAPC to reflect statistical uncertainty. The 95% CIs for APC and AAPC were derived by the Joinpoint Regression Program using the standard errors of the fitted regression model, and are distinct from the 95% uncertainty intervals (UIs) reported for GBD burden estimates; the latter integrate uncertainty from sampling error, model specification, and data quality rather than a single regression model. This analysis was conducted separately for each combination of disease and geography to capture subgroup-specific trend differences.[20]

The core statistical assumptions of the joinpoint regression model include: (1) temporal trends of ASRs follow a piecewise linear pattern within each segment; (2) error terms are independently and identically distributed; and (3) the optimal number of joinpoints is determined by the Monte Carlo permutation test with correction for multiple comparisons.

To assess the robustness of the main findings, 2 pre-specified sensitivity analyses were conducted: (1) the authors excluded data from 2020 to 2021 (the COVID-19 pandemic period) and recalculated AAPCs for 1990–2019 to verify long-term trend stability; and (2) the maximum number of joinpoints was restricted to 3 (from the default maximum of 5) to evaluate the consistency of trend change points. Full AAPC results from both sensitivity analyses are provided in Table S1 for direct comparison with the primary analysis. All sensitivity analyses yielded results consistent with the primary analysis, supporting the robustness of the estimated temporal trends.

RESULTS

Global and country-specific burden (China, the US, Germany) of migraine and TTH among adolescents (10–19 years) in 2021

In 2021, among adolescents aged 10–19 years globally, the burden of migraine and TTH differed in scale. For migraine, the global incidence was 25,713,886 cases (ASIR: 1992.37), prevalence was

188,274,040 cases (ASPR: 14,587.92 per 100,000), and YLDs were 6,930,930 (ASYR: 537.03) (Table 1). For TTH, the global incidence reached 135,457,152 (ASIR: 10,495.54), prevalence 346,026,054 (ASPR: 26,810.93), and YLDs 531,662 (ASYR: 41.19) (Table 2).

Among the 3 focal countries, China had the largest migraine incidence (2,557,730 cases), prevalence (16,542,731 cases), and YLDs (613,794). This was followed by the US (incidence: 1,124,890; prevalence: 7,057,157; YLDs: 253,318) and Germany (incidence: 218,232; prevalence: 1,579,898; YLDs: 56,651). For ASRs, Germany had the highest migraine values for ASIR, ASPR, and ASYR (2774.98, 20,089.51, 720.36, respectively), followed by the US (2618.87, 16,429.83, 589.75, respectively), while China had the lowest (1589.98, 10,283.6, 381.56, respectively). From 1990 to 2021, temporal trends (AAPC) showed that China's burden increased across incidence (AAPC = 0.27%), prevalence (AAPC = 0.08%), and YLDs (AAPC = 0.07%). In contrast, the US had a decreasing trend in YLDs (AAPC = −0.12%), while Germany's migraine incidence remained nearly stable (AAPC = 0.003%) and its prevalence showed a slight increase (AAPC = 0.03%) (Table 1).

In terms of TTH case counts, China had the largest incidence (12,957,217), prevalence (33,211,545), and YLDs (51,627) among the 3 countries, followed by the US (incidence: 6,312,654; prevalence: 15,768,559; YLDs: 23,235) and Germany (incidence: 1,029,171; prevalence: 2,640,669; YLDs: 3965). For ASRs, the US had the highest ASIR (14,696.55), ASPR (36,710.93), and ASYR (54.09), followed by Germany (ASIR: 13,086.63; ASPR: 33,577.95; ASYR: 50.42), while China had the lowest (ASIR: 8054.71; ASPR: 20,645.59; ASYR: 32.09). From 1990 to 2021, temporal trends showed that China's incidence (AAPC = 0.31%) and prevalence (AAPC = 0.21%) had increased. The US, however, had decreasing trends across incidence (AAPC = −0.04%), prevalence (AAPC = −0.05%), and YLDs (AAPC = −0.03%). Germany's TTH incidence showed a slight increase (AAPC = 0.02%), but its prevalence was nearly stable (AAPC = −0.002%) and YLDs decreased slightly (AAPC = −0.01%) (Table 2).

As shown in Fig. 1, China had the highest numbers of incident cases, prevalent cases and YLDs for migraine and TTH in both age groups (10–14 and 15–19 years) in 2021, followed by the US and Germany. For migraine, incident cases and ASIR were higher in the 10–14 years group, whereas prevalent cases, YLDs, and the corresponding ASRs were higher in the 15–19 years group. ASRs for migraine were highest in Germany, followed by the US and China (Fig. 1A, C, E). For TTH, only incidence and ASIR in China's 10–14 years group exceeded those in the US and Germany. ASRs for TTH were highest in the US, followed by Germany and China (Fig. 1B, D, F).

Temporal trends in migraine among adolescents (aged 10–19 years) globally and in China, the US, and Germany from 1990 to 2021

For migraine cases, China exhibited multi-stage fluctuations. Incidence declined in 1990–1994 (APC = −2.4%), rose in 1994–2002 (1.64%), declined non-significantly in 2002–2005 (−0.86%), dropped sharply in 2005–2012 (−4.73%), declined again in 2012–2015 (−2.18%), and rose in 2015–2021 (2.36%). Prevalence showed a decline in 1990–1995 (−2.9%), a sharp rise in 1995–2004 (2%), a decline from 2004 to 2016 (2004–2007: −2.48%, 2007–2013: −5.1%, 2013–2016: −1.61%) and a rise from 2016 to 2021 (1.82%); YLDs mirrored the trends of prevalence. In the US, the number of migraine cases mostly rose in the middle-to-late periods (2000–2015). Incidence increased from 1992 to 2018 (1992–2004: 0.83%, 2004–2011: 0.41%, 2011–2014: 1.57%, 2014–2018: 0.56%), and then declined slightly from 2018 to 2021 (−0.31%). Prevalence rose from 1992 to 2015 (0.69%, 0.23%, 0.84%, 1.57%) and grew mildly from 2015 to 2021 (0.13%), while the trend of YLDs mirrored that of prevalence. In Germany, migraine burden increased during the early period, with incidence rising from 1990 to 1998 (APC = 1.74%), prevalence from 1992 to 1999 (1.53%), and YLDs from 1992 to 1999 (1.55%), followed by declines in the middle and later periods (Fig. 2, Table S2). In all 3 countries, the number of migraine cases was substantially higher among girls than boys, and the temporal trends were broadly similar between the sexes (Fig. S1).

For migraine ASRs, China showed fluctuating growth in ASIR and ASPR. ASIR increased in 1990–1996 (APC = 0.29%), decreased in 1996–2000 (−0.57%), and increased again in 2000–2019 (0.23%, 1.4%). ASPR decreased in 1990–2000 (−0.75%), increased sharply in 2000–2009 (1.93%, 0.8%), decreased in 2009–2015 (−0.6%), and increased again in 2015–2021 (0.14%). ASYR trends mirrored those of ASPR. In the US, ASIR, ASPR, and ASYR transitioned from early declines to sustained increases; ASIR declined in 1990–2005 (−0.6%, −1.11%, −0.1%) but increased in 2005–2021 (0.25%, 1.62%, 0.07%). Similarly, ASPR declined in 1990–2004 (−1.17%, −1.59%, −0.06%) but increased in 2004–2021 (0.71%, 1.86%, 0.09%), while ASYR declined in 1990–2003 (−1.12%, −2.09%) and then increased in 2003–2021 (0.69%, 1.84%, 0.01%). Germany's ASRs increased initially, declined during the middle period, and showed minor increases in the later period (Fig. 2). Across the 3 countries, migraine ASRs were substantially higher among girls

Table 1. Migraine burden among adolescents aged 10–19 years in 2021 and long-term trends (1990–2021).

Location	Incidence			Prevalence			YLDs		
	No. (95% UI)	ASIR (95% UI)	AAPC (95% CI), %	No. (95% UI)	ASPR (95% UI)	AAPC (95% CI), %	No. (95% UI)	ASYR (95% UI)	AAPC (95% CI), %
Global	25,713,886 (19,145,764–33,778,528)	1992.37 (1483.46–2617.24)	0.04 (0.01–0.07)	188,274,040 (144,988,898–241,499,918)	14,587.92 (11,234.09–18,711.99)	0.07 (0.05–0.08)	6,930,930 (475,886–16,967,500)	537.03 (36.87–1314.68)	0.06 (0.04–0.09)
China	2,557,730 (1,886,725–3,392,373)	1589.98 (1172.86–2108.83)	0.27 (0.24–0.3)	16,542,731 (12,466,583–21,444,877)	10,283.6 (7749.71–13,330.97)	0.08 (0.01–0.15)	613,794 (47,167–1,491,603)	381.56 (29.32–927.24)	0.07 (0.002–0.14)
US	1,124,890 (837,381–1,484,786)	2618.87 (1949.51–3456.74)	0.05 (0.03–0.08)	7,057,157 (5,317,086–8,991,403)	16,429.83 (12,378.76–20,932.97)	−0.09 (−0.15 to −0.02)	253,318 (17,047–609,563)	589.75 (39.69–1419.13)	−0.12 (−0.18 to −0.05)
Germany	218,232 (154,119–292,304)	2774.98 (1959.74–3716.85)	0.003 (−0.02 to 0.03)	1,579,898 (1,170,519–2,017,543)	20,089.51 (14,883.97–25,654.47)	0.03 (−0.04 to 0.11)	56,651 (3062–141,204)	720.36 (38.94–1795.51)	0.03 (−0.06 to 0.13)

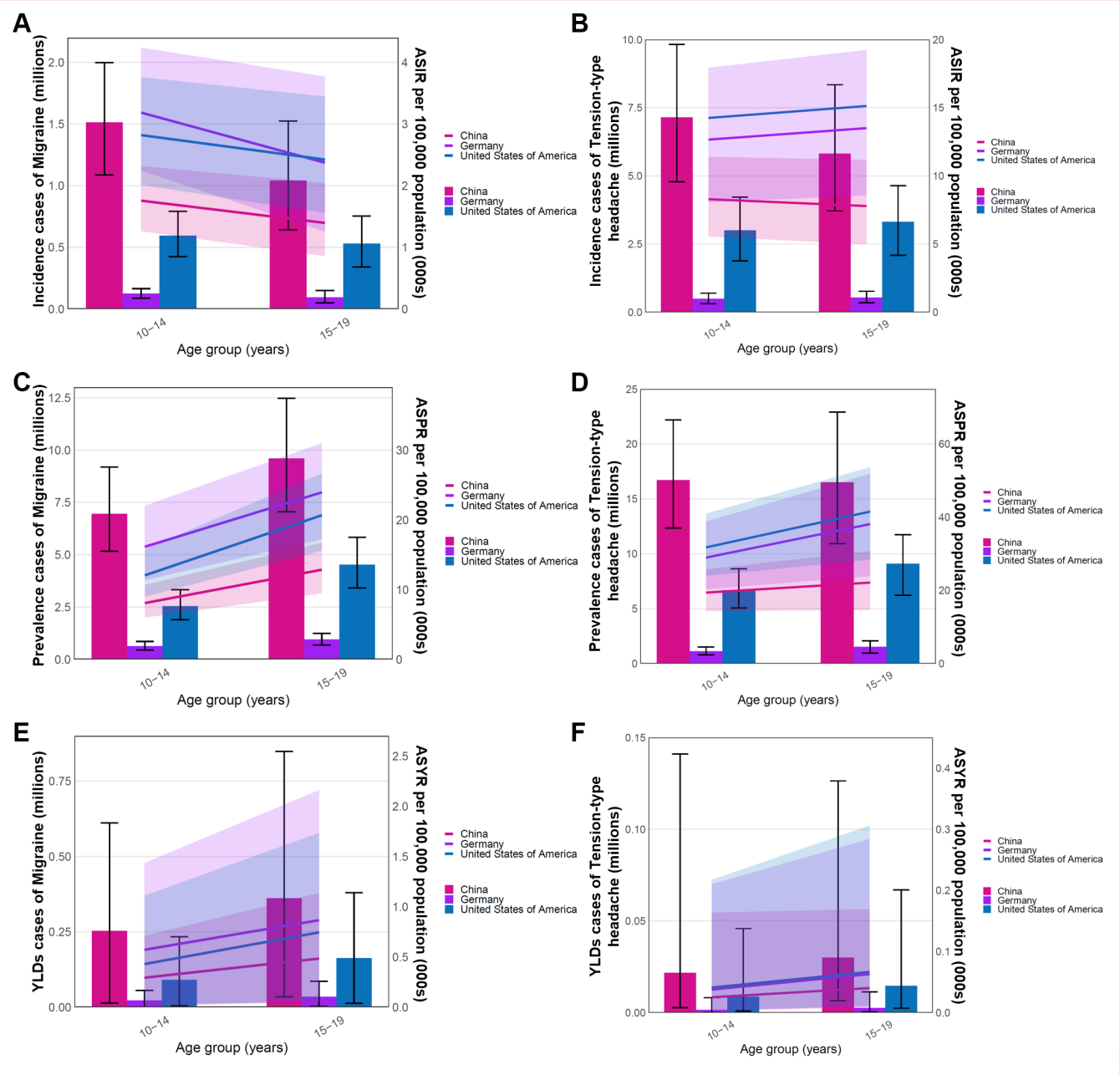
AAPC: average annual percent change; ASIR: age-standardised incidence rate; ASPR: age-standardised prevalence rate; ASYR: age-standardised YLD rate; UI: uncertainty interval; YLDs: years lived with disability
All rates are expressed per 100,000 population.

Table 2. Tension-type headache burden among adolescents aged 10–19 years in 2021 and long-term trends (1990–2021).

Location	Incidence			Prevalence			YLDs		
	No. (95% UI)	ASIR (95% UI)	AAPC (95% CI), %	No. (95% UI)	ASPR (95% UI)	AAPC (95% CI), %	No. (95% UI)	ASYR (95% UI)	AAPC (95% CI), %
Global	135,457,152 (95,795,037–176,341,550)	10,495.54 (7422.43–13,663.36)	0.04 (0.02–0.06)	346,026,054 (256,330,678–443,093,783)	26,810.93 (19,861.11–34,331.97)	0.03 (0.01–0.04)	531,662 (89,559–2,606,793)	41.19 (6.94–201.98)	0.03 (0.02–0.05)
China	12,957,217 (8,997,277–17,184,303)	8054.71 (5593.06–10,682.43)	0.31 (0.25–0.33)	33,211,545 (24,778,357–43,127,657)	20,645.59 (15,403.19–26,809.83)	0.21 (0.19–0.24)	51,627 (9330–255,412)	32.09 (5.8–158.77)	0.05 (−0.01 to 0.11)
US	6,312,654 (4,491,626–8,091,919)	14,696.55 (10,457–18,838.87)	−0.04 (−0.05 to −0.04)	15,768,559 (11,975,767–19,746,501)	36,710.93 (27,880.89–45,972.01)	−0.05 (−0.06 to −0.03)	23,235 (3243–113,990)	54.09 (7.55–265.38)	−0.03 (−0.05 to 0)
Germany	1,029,171 (728,023–1,338,941)	13,086.63 (9257.32–17,025.57)	0.02 (0–0.04)	2,640,669 (1,913,743–3,450,213)	33,577.95 (24,334.58–43,871.87)	−0.002 (−0.04 to 0.04)	3965 (550–18,837)	50.42 (6.99–239.52)	−0.01 (−0.09 to 0.07)

AAPC: average annual percent change; ASIR: age-standardised incidence rate; ASPR: age-standardised prevalence rate; ASYR: age-standardised YLD rate; UI: uncertainty interval; YLDs: years lived with disability
All rates are expressed per 100,000 population

Fig. 1. Burden of migraine and tension-type headache among adolescents aged 10–14 and 15–19 years in China, Germany, and the US in 2021. (A, B) Incidence cases (left axis, bars) and age-standardised incidence rate (ASIR, right axis, lines) for migraine and TTH, respectively. (C, D) Prevalence cases (left axis, bars) and age-standardised prevalence rate (ASPR, right axis, lines) for migraine and TTH, respectively. (E, F) YLDs cases (left axis, bars) and age-standardised YLD rate (ASYR, right axis, lines) for migraine and TTH, respectively.



ASIR: age-standardised incidence rate; ASPR: age-standardised prevalence rate; ASYR: age-standardised YLD rate; YLDs: years lived with disability

than boys, with overall trends broadly consistent with those described above (Fig. S2).

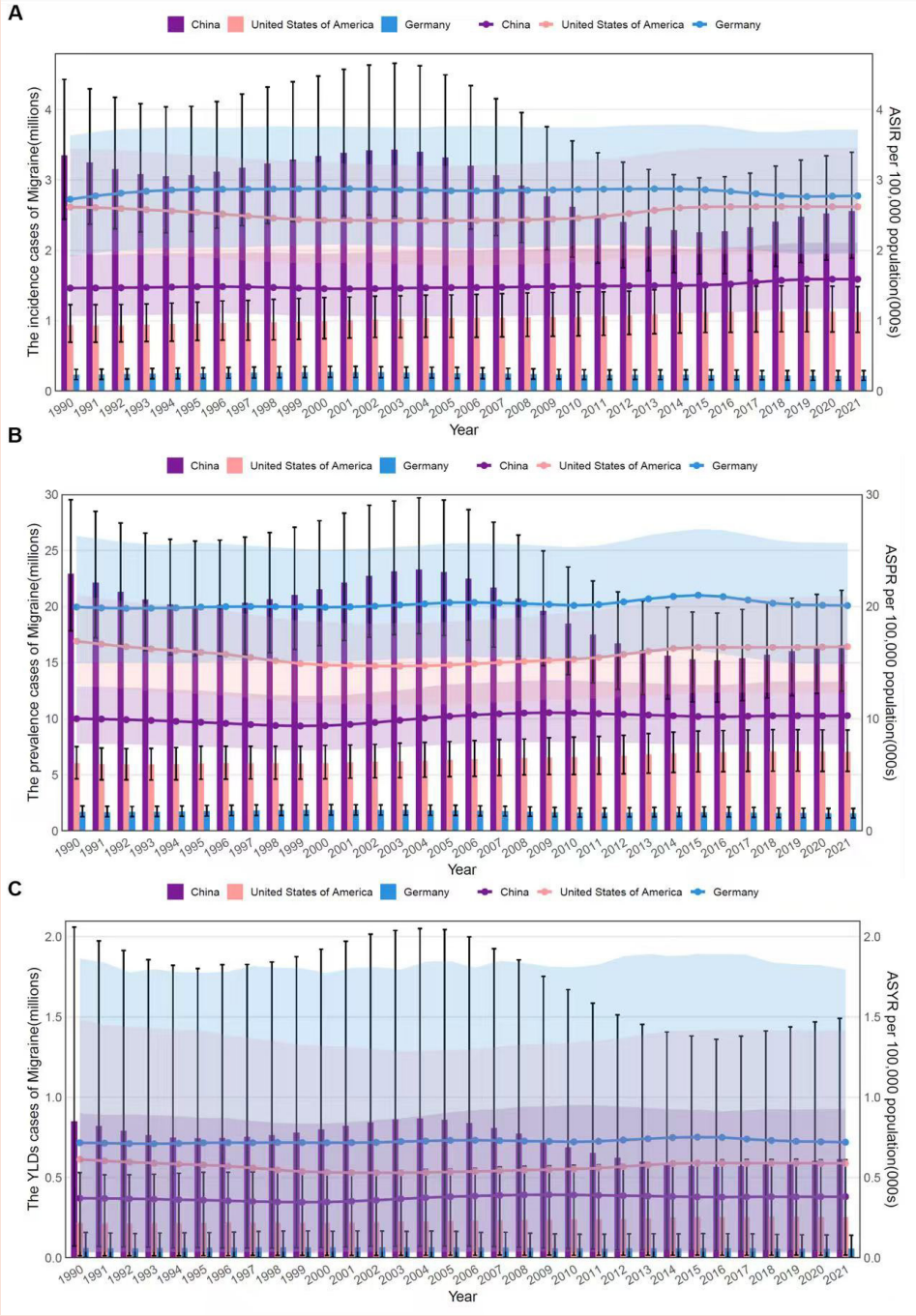
Migraine ASRs were further stratified by sex and age subgroups. Globally, ASIR among girls aged 10–14 years showed no clear trend (AAPC = −0.01) but declined continuously from 2010 to 2021 (APC = −0.11). In contrast, ASIR among 15–19-year-old girls decreased overall (AAPC = −0.03) but rose from 2003 to 2018 (APC = 0.06, 0.29) before flattening. For boys worldwide, both age groups showed increasing ASIR, with a larger increase in the 15–19-year group (AAPC = 0.13%). Increases in ASPR and ASYR were also greater in boys than girls, and in older than in younger adolescents. Notably, ASRs in the 15–19 years group flattened or declined during the COVID-19 pandemic. Among the 3 countries, China recorded the largest increases in all ASRs across both age and sex subgroups, Germany showed modest increases,

and the US showed mainly declines, primarily in the 10–14 years group. In China, all ASR increases were greater in boys than girls in both age groups, with the largest difference observed in ASIR among 10–14-year-olds. ASYR was consistently higher in the 15–19 years group for both sexes, with other metrics showing similar patterns associated with sex within each age group. China's ASIR also showed a downward trend during the pandemic (Tables S3–S5).

Temporal trends in TTH among adolescents (10–19 years) globally and in China, the US, and Germany from 1990 to 2021

For TTH cases, China exhibited multi-stage fluctuations followed by late-period increases. Incidence decreased in 1990–1994 (APC = −2.77%) but increased in 1994–2004 (1.99%), decreased in subsequent intervals (−3.58%, −5.26%), and increased again in

Fig. 2. Temporal trends and joinpoint regression analysis of migraine among adolescents aged 10–19 years in China, the US, and Germany from 1990 to 2021.



ASRs: age-standardised rates; ASIR: age-standardised incidence rate; ASPR: age-standardised prevalence rate; ASYR: age-standardised YLD rate; YLDs: years lived with disability

Absolute cases (left axis, bars), age-standardised rates (ASRs, right axis, lines).

2016–2021 (2.16%). Prevalence and YLDs showed similar temporal patterns, with early declines, mid-period increases, subsequent declines, and late-period increases. In the US, case numbers generally increased in the middle-to-late periods. Incidence generally increased in 1992–2018 (1.72%, 0.52%, −0.21%, 0.45%) before decreasing slightly in 2018–2021 (−0.24%). Prevalence and YLDs also increased in multiple intervals, with late-period decreases. Finally, case numbers in Germany increased early but declined in the middle-to-late periods (Fig. 3, Table S6). Across the 3 countries, the number of TTH cases was slightly higher among girls than boys, with overall trends broadly consistent with those described above (Fig. S3).

For TTH ASRs, China showed an overall increasing trend in ASIR, with increases in most segments of the study period (APCs = 0.13%, −0.39%, 1.86%, 0.05%, 0.73%). ASPR decreased slightly in 1990–2000 (−0.1%, −0.36%), increased sharply in 2000–2005 (1.84%), decreased modestly in 2005–2019 (−0.14%), and increased again in 2019–2021 (0.84%). ASYR trends mirrored those of ASPR. The US ASRs transitioned from early declines to mild or stable trends. ASIR decreased in 1990–1992 (−0.08%) and 2000–2004 (−0.31%) before showing a minor decline through 2021 (−0.01%). ASPR and ASYR showed similar patterns, with early declines followed by non-significant changes. Germany's ASRs increased in the middle intervals but decreased in the early and late periods (Fig. 3). Across the 3 countries, TTH ASRs were slightly higher among girls than boys, with overall trends broadly consistent with those described above (Fig. S4).

Globally, TTH ASRs in the 10–14 years group showed no clear trend from 1990 to 2021. In contrast, the 15–19 years group exhibited a marked upward trend, with greater increases among boys than girls, particularly for ASIR and ASPR. Similar to migraine, ASRs in the 15–19 years group flattened or declined during the COVID-19 pandemic. Among the 3 countries, China again showed the largest increases in all TTH ASRs across age and sex subgroups, whereas Germany and the US showed modest increases or slight declines, primarily in the 15–19 years group. In China, all ASR increases were greater in boys than girls and in older than in younger adolescents. China's TTH ASIR showed an upward trend during the pandemic (Tables S7–S9).

SDI trends and inequalities of migraine and TTH among adolescents (10–19 years) globally and in China, the US, and Germany from 1990 to 2021

All ASRs for both migraine and TTH in China were initially closest to the optimal frontier curve but gradually increased and deviated from the curve as SDI rose from 1990 to 2021, with the global level showing a similar pattern (Fig. 4). SDI increased only modestly in Germany and the US compared with China, and their ASR trajectories were consistent with those described earlier.

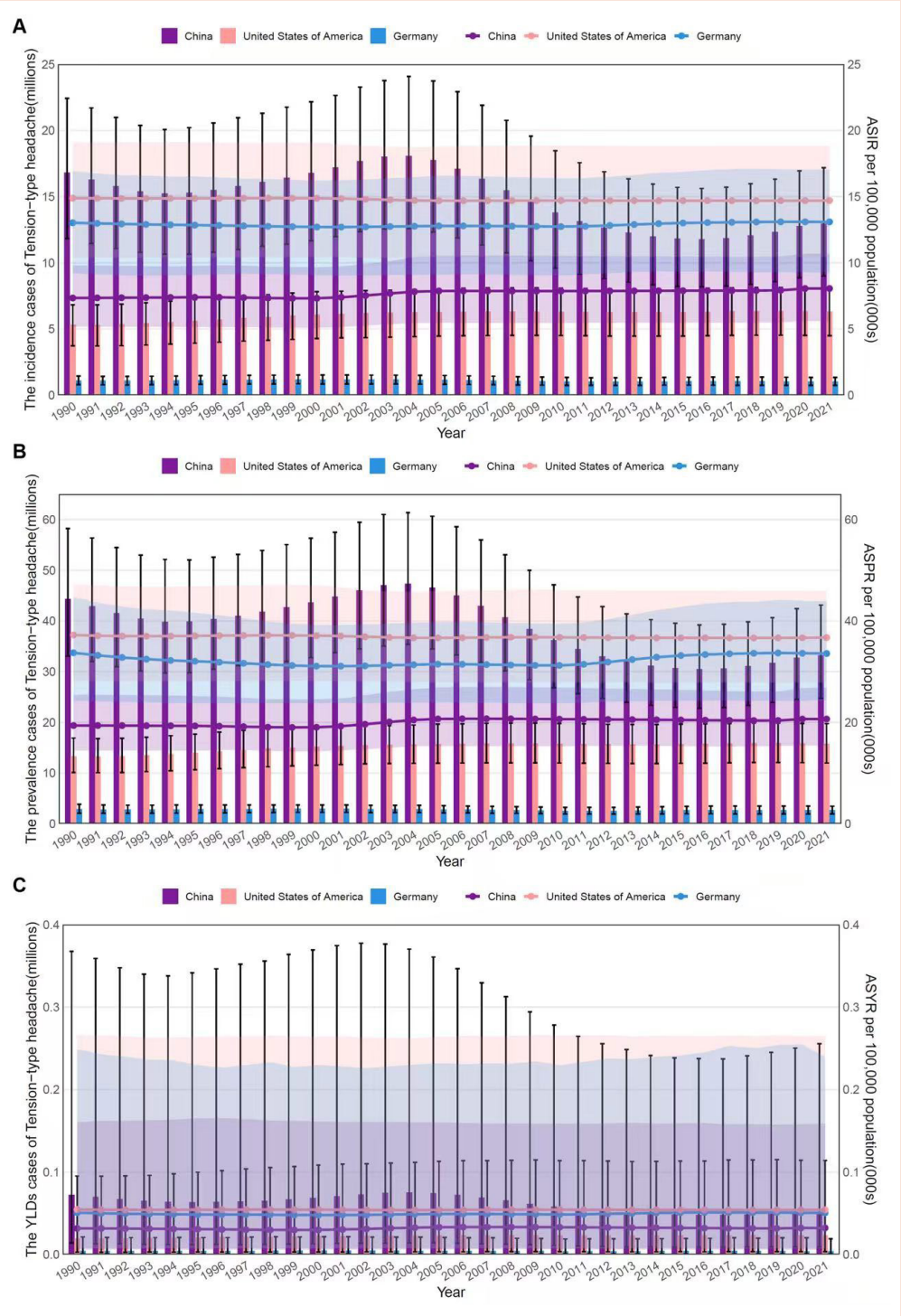
According to the inequality analysis, the crude rates of incidence, prevalence, and YLDs in China remained relatively low compared with the global average. Although China's relative rank of SDI increased significantly from 1990 to 2021, it remained below those of the US and Germany, whereas its crude rates were relatively low. The crude rates of incidence, prevalence, and YLDs in the US and Germany ranked relatively high globally. The relative SDI ranks of both countries increased slightly from 1990 to 2021. Of these, the crude rates of incidence, prevalence, and YLDs in the US showed a slightly decreasing trend, while those of Germany showed no obvious overall change. Overall, the SII for migraine indicated increasing inequality from 1990 to 2021, whereas that for TTH indicated slightly decreasing inequality. In addition, the SII for both indicated that the higher the SDI rank, the greater the burden of migraine and TTH (Fig. S5).

The CIX for migraine rose from 1990 to 2021, indicating that the incidence, prevalence, and YLDs of headache became increasingly concentrated in populations with higher SDI globally, and the social inequality of disease burden intensified significantly. In contrast, the CIX for TTH showed only a slight increase in the early period, with TTH-related inequality attenuating in the later periods, suggesting a mild mitigating trend in TTH-related inequality. Based on the curve distribution, in 2021, the cumulative incidence, prevalence and YLDs curves of Germany and the US were closer to the upper part of the graph, reflecting that these countries, which had higher SDI levels, had higher cumulative proportions of incidence, prevalence, and YLDs in their populations. China's curves were relatively flat but still showed a trend of increasing cumulative incidence, prevalence and YLDs with rising SDI (Fig. S6).

DISCUSSION

This study used data from the GBD 2021 to systematically examine trends in incidence, prevalence, and YLDs of migraine and TTH among adolescents aged 10–19 years in China, the US, and Germany, as well as their associations with SDI and patterns of inequality in disease burden. Importantly, as an ecological analysis of aggregated population-level data, this study can only identify associations and not establish causal relationships. All subsequent interpretations of potential drivers are based on existing epidemiological evidence and should be considered hypotheses requiring further validation in prospective individual-level studies. The findings illuminate distinct epide-

Fig. 3. Temporal trends and joinpoint regression analysis of tension-type headache among adolescents aged 10–19 years in China, the US, and Germany from 1990 to 2021.



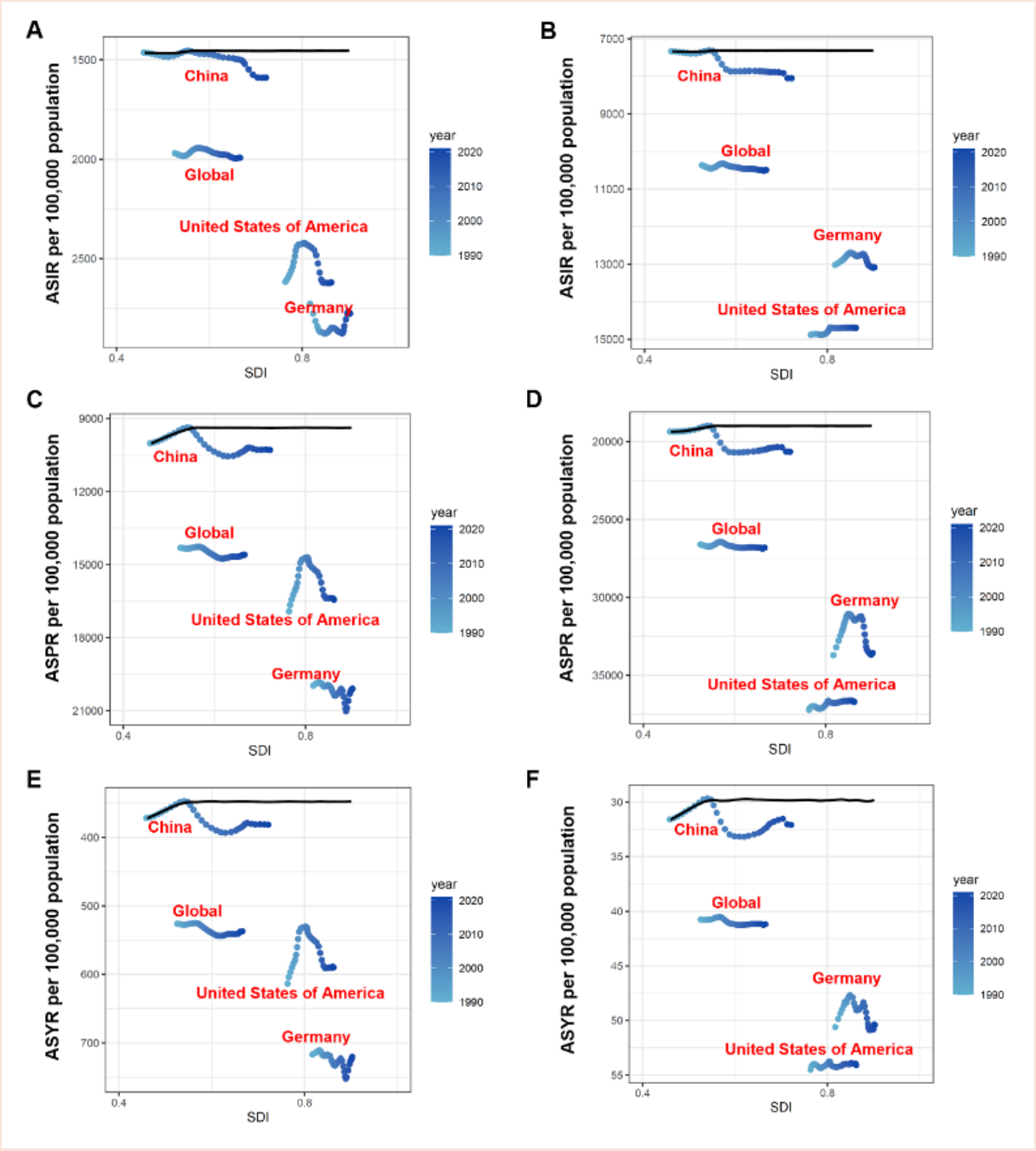
ASIR: age-standardised incidence rate; ASPR: age-standardised prevalence rate; ASRs: age-standardised rates; ASYR: age-standardised YLD rate; YLDs: years lived with disability

Absolute cases (left axis, bars), age-standardised rates (ASRs, right axis, lines).

miological profiles and public health imperatives of headache disorders in nations at varying SDI stages, which provide critical insights for developing age-specific and region-adapted prevention strategies for adolescents during this critical developmental stage.

Adolescents aged 10–19 years are in a critical period of academic advancement and psychological maturation, during which headache disorders can substantially disrupt learning, social functioning, and long-term well-being.[21] This analysis revealed that,

Fig. 4. Frontier analysis of migraine and TTH burden by SDI among adolescents aged 10–19 years in China, Germany, the US, and globally from 1990 to 2021. (A, C, and E) ASIR, ASPR, and ASYR for migraine by SDI, respectively. (B, D, and F) Corresponding rates for TTH by SDI.



ASIR: age-standardised incidence rate; ASPR: age-standardised prevalence rate; ASYR: age-standardised YLD rate; SDI: socio-demographic index; TTH: tension-type headache; YLDs: years lived with disability

for this age group, the ASIR, ASPR, and ASYR in China for both migraine and TTH remained lower than the global average throughout the study period. Despite China's substantial increase in relative SDI ranking from 1990 to 2021, the increases in ASIR, ASPR, and ASYR were notably outpaced by SDI growth. This pattern may reflect 2 opposing dynamics: on the one hand, lifestyle shifts amid rapid urbanisation, including escalating academic pressure, reduced sleep duration, and heightened screen time among adolescents, are hypothesised to have contributed to headache incidence and prevalence.[22] On the other hand, the low diagnostic accuracy of migraine in China may lead to underestimation of the true incidence, while inadequate recognition of headache subtypes in primary care further dampens the apparent rise in incidence.[23] In contrast, the US and Germany, as high-SDI nations, consistently held top global rankings in

ASIR, ASPR, and ASYR for migraine and TTH in adolescents, yet their SDI growth was modest. The US exhibited slight declines in ASIR, ASPR, and ASYR whereas Germany remained stable overall. These trends may partly reflect differences in medical resources, access to specific therapeutics such as calcitonin generelated peptide receptor antagonists, and the maturity of headache management frameworks in high-SDI settings.[24] A study on neurological disease burden in the US similarly reported a gradual decline in migraine incidence, which may have been driven by enhanced preventive interventions and improved self-management among adolescents, with migraine remaining a leading contributor to YLDs in this population.[25]

This study's findings also revealed distinct age-specific patterns across the 2 headache disorders. Migraine burden was higher in the 10–14 years age group, while TTH was more concentrated in the 15–19 years group. This divergence may reflect differing drivers across stages of adolescent development, though these interpretations remain speculative and cannot be confirmed by the aggregated ecological data. Migraine is hypothesised to peak earlier in adolescence in association with pubertal neuroendocrine changes and the maturation of the trigeminovascular system—processes that predominantly occur during early to mid-adolescence.[26] For TTH, the rising burden in older adolescents could be linked to the gradual accumulation of psychosocial stressors, including intensifying academic pressure and expanding social responsibilities, which become more prominent during late adolescence.[27] Future individual-level prospective studies are needed to verify these potential mechanisms.

Notably, the 2019–2021 segment of the study period overlaps with the global COVID-19 pandemic, a disruption that may have impacted headache burden trends in adolescents aged 10–19 years, although its impacts varied across the 3 nations as reflected in the results. In China, migraine incidence showed an accelerated increase in 2015–2021, while TTH incidence similarly increased in 2016–2021. The pandemic period (2019–2021) coincided with a continuation of these upward trajectories, with ASRs also showing marginal increases. This may be related to pandemic-specific stressors for Chinese adolescents, including prolonged home-based online learning, reduced physical activity, social isolation, and anxiety about health—factors previously linked to increased headache frequency in youth.[28] In contrast, the US showed a slight decline in both migraine and TTH incidence during 2018–2021. This stability or mild reduction may be attributed to the nation's established remote healthcare infrastructure, which may have facilitated continued access to headache diagnostics and preventive interventions amid in-person care disruptions.[29] Germany, meanwhile, maintained overall stable migraine and TTH burden in 2019–2021—a pattern that may have been supported by its universal healthcare system's ability to sustain mental health and headache management services for adolescents, including school-based psychological support.[30] It is important to note, however, that GBD 2021 data for this period may partially rely on modelling to address potential gaps in real-world data collection, which could introduce modest uncertainty in capturing the full pandemic impact.

Analyses of the relationship between SDI and headache burden showed that both migraine and TTH followed a pattern in which higher SDI rankings were associated with greater disease burden among adolescents, consistent with global evidence that headache disorder burden increases with social development.[12] However, notable differences were observed in inequality trends between migraine and TTH: the SII and CIX indicated worsening disease burden inequality for migraine from 1990 to 2021, whereas inequality in TTH burden slightly decreased. This divergence may stem from fundamental differences in pathophysiology: migraine is closely linked to neuropathological processes (e.g. trigeminovascular activation, cortical spreading depression) and relies more heavily on medical resources for diagnosis and management, potentially making it more readily identified in high-SDI adolescent populations.[31] In contrast, TTH relates more to universal stressors that affect adolescents across SDI groups relatively evenly, thus attenuating inequality.[32] Notably, despite China's rapid SDI ascent, its headache burden inequality in adolescents remained lower than that in the US and Germany, possibly reflecting unique advantages of middle-SDI nations during disease burden transition.

Temporal trend analyses further revealed distinct phases across the 3 countries in the 10–19-year age group. In China, the incidence, prevalence, and YLDs of migraine and TTH showed multi-stage, fluctuating but overall upward trends, with accelerated growth after 2015, consistent with reports of the highest global estimated annual percentage change (EAPC) for adolescent headache burden in East Asia.[33] The US experienced a burden peak from 1990 to 2010, followed by a gradual decline, a trend that may be associated with widespread triptan use and school-based stress management interventions.[34,35] Germany remained relatively stable, a pattern that may be attributable to its long-standing standardised headache care system for youth.[36]

Limitations of this study should be acknowledged. First, GBD 2021 data for China's rural adolescents are underrepresented, potentially underestimating burden in low-income regions. Prospective population-based surveys in rural China are therefore urgently needed to validate and extend current estimates.

Such surveys would use standardised, face-to-face diagnostic assessments based on the ICD-10 criteria and could reduce uncertainty inherent in GBD model-derived estimates. They could also provide more direct estimates of the prevalence and incidence of headache disorders in underserved rural populations and identify region-specific risk factors, including unique lifestyle patterns, limited access to paediatric neurology care, and rural-specific psychosocial stressors that may not be fully captured in aggregated national datasets. Furthermore, longitudinal prospective studies could elucidate the natural history of adolescent headache in rural settings and inform the development of tailored prevention and management strategies to reduce the growing urban–rural disparity in headache care.

Second, this study is subject to the ecological fallacy, in that national-level associations between SDI, healthcare systems, and headache burden cannot be directly extrapolated to individual adolescents. Third, GBD 2021 estimates have inherent modelling uncertainty due to heterogeneous data sources and varying data quality across countries, with greater reliance on modelling in China than in the US and Germany. Fourth, cross-national variability in diagnostic practices exists. Although standardised ICD-10 codes were used, the clinical application of these criteria may differ across countries, particularly in primary care settings in China, potentially introducing bias into cross-country comparisons. Fifth, generalisability is limited to the 3 focal countries, which represent distinct SDI levels and healthcare systems, and may not extend to low-income regions or other cultural contexts. Sixth, individual-level risk factor data were unavailable, precluding causal inference and adjustment for potential confounders such as sleep quality, physical activity levels, and comorbid mental health conditions. All observed associations between population-level factors and headache burden trends should be interpreted as hypotheses requiring validation in prospective cohort studies. Seventh, the inflection points identified by joinpoint regression may temporally coincide with a range of national policy adjustments, healthcare service reforms, updates to diagnostic criteria, and socioeconomic shifts across the 3 focal countries. Given the ecological study design, the authors cannot disentangle the independent effects of individual policies or contextual events on the observed changes in trends. These concurrent factors may have contributed to the identified joinpoints but could not be separately evaluated. Eighth, COVID-19 impacts were inferred from temporal trends, as GBD 2021 lacks pandemic-specific covariates. Future research should conduct prospective surveys in rural China to validate GBD estimates and incorporate individual-level risk factors to quantify their contributions to burden inequalities. Studies should also evaluate the effectiveness of interventions, such as school-based stress manage-ment in China and telemedicine in the US, in reducing adolescent headache burden, while extending analyses to a broader range of countries to improve global generalisability.

CONCLUSION

Adolescent migraine and TTH showed distinct cross-national trends across different SDI levels. China experienced an increasing disease burden in absolute terms, whereas high-SDI countries showed stable or declining rates. The 2019–2021 period coincided with changes in cross-national inequality patterns, although pandemic-specific effects could not be confirmed from the available data. Future studies using primary data are needed to validate these findings, identify individual-level risk factors, and evaluate the effects of targeted interventions.

Supplementary materials

Table S1. Comparison of average annual percent change values between primary analysis and 2 sensitivity analyses for migraine and tension-type headache among adolescents aged 10–19 years in China, the US, and Germany from 1990 to 2021.

Table S2. Segment-specific annual percent change with 95% confidence intervals from joinpoint regression analysis for migraine among adolescents aged 10–19 years in China, the US, and Germany from 1990 to 2021.

Table S3. Annual percent change and average annual percent change of migraine incidence rates among adolescents aged 10–19 years, globally and in China, Germany, and the US, stratified by age and sex.

Table S4. Annual percent change and average annual percent change of migraine prevalence rates among adolescents aged 10–19 years, globally and in China, Germany, and the US, stratified by age and sex.

Table S5. Annual percent change and average annual percent change of migraine years lived with disability rates among adolescents aged 10–19 years, globally and in China, Germany, and the US, stratified by age and sex.

Table S6. Segment-specific annual percent change with 95% confidence intervals from joinpoint regression analysis for tension-type headache among adolescents aged 10–19 years in China, the US, and Germany from 1990 to 2021.

Table S7. Annual percent change and average annual percent change of tension-type headache incidence rates among adolescents aged 10–19 years, globally and in China, Germany, and the US, stratified by age and sex.

Table S8. Annual percent change and average annual percent change of tension-type headache prevalence rates among adolescents aged 10–19 years, globally and in China, Germany, and the US, stratified by age and sex.

Table S9. Annual percent change and average annual percent change of tension-type headache years lived with disability rates among adolescents aged 10–19 years, globally and in China, Germany, and the US, stratified by age and sex.

Fig. S1. Temporal trends in migraine cases among adolescents aged 10–19 years in China, the US, and Germany from 1990 to 2021, stratified by sex.

Fig. S2. Temporal trends in age-standardised rates of migraine among adolescents aged 10–19 years in China, the US, and Germany from 1990 to 2021, stratified by sex.

Fig. S3. Temporal trends in tension-type headache cases among adolescents aged 10–19 years in China, the US, and Germany from 1990 to 2021, stratified by sex.

Fig. S4. Temporal trends in age-standardised rates of tension-type headache among adolescents aged 10–19 years in China, the US, and Germany from 1990 to 2021, stratified by sex.

Fig. S5. Sociodemographic inequalities in migraine and tension-type headache burden among adolescents aged 10–19 years at the global level and in 3 countries from 1990 to 2021.

Fig. S6. Concentration curves of migraine and tension-type headache burden by sociodemographic index among adolescents aged 10–19 years globally and in 3 countries in 1990 and 2021.

Ethics statement

This study was a secondary analysis of publicly available, de-identified, aggregated population-level data from the GBD 2021 database. No identifiable individual-level data or human participant procedures were involved. Therefore, ethics committee approval and informed consent were not required.

Declarations

The authors 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. No funding was received for this study.

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Data availability

The data were extracted from the GBD 2021 platform (http://ghdx.healthdata.org/gbd-results-tool).

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Lecanemab in Singapore: Appropriate use recommendations for early Alzheimer's disease

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ABSTRACT

Introduction: Lecanemab, a monoclonal antibody targeting β-amyloid oligomers, protofibrils, and insoluble fibrils, has been approved for Alzheimer's disease (AD) treatment in Singapore, based on the phase 3 Clarity AD study. In this paper, the Singapore-adapted Appropriate Use Recommendations (AURs) serve to assist Singapore physicians in identifying patients who will likely benefit from treatment while ensuring effective monitoring.

Methods: The AURs are based on the Singapore-approved prescribing information combined with lecanemab phase 2 and 3 clinical trials and real-world data up to April 2026.

Results: The decision to initiate lecanemab should be based on careful evaluation of individuals, including Singapore-validated cognitive status tests to identify mild cognitive impairment (MCI) due to AD and mild AD dementia. Other important evaluations include baseline brain magnetic resonance imaging (MRI), assessment of the apolipoprotein E ε4 (*APOEε4*) genotype, and amyloid pathology confirmation. Guidance on identifying patients at increased risk of amyloid-related imaging abnormalities (ARIA) during treatment and other patient profiles warranting additional caution is provided. Recommendations for monitoring patients, managing infusion-related reactions, and identifying lecanemab discontinuation scenarios are included.

Conclusion: Lecanemab should only be prescribed for patients with MCI due to AD or mild AD dementia following careful clinical evaluation confirming AD pathology, with caution exercised in patients at increased ARIA risk (e.g. *APOEε4* gene carriers). During treatment, patients should receive regular monitoring for ARIA symptoms including follow-up MRI scans. Future directions include the development of a Singapore-specific registry to monitor patients and gather long-term data to support a consensus-driven framework to inform and optimise the use of lecanemab in Singapore.

Keywords: Alzheimer's disease, amyloid beta-peptides, anti-amyloid, antibodies, cognitive dysfunction, dementia, lecanemab, monoclonal, Singapore

CLINICAL IMPACT

What is New

- These Appropriate Use Recommendations (AURs) for lecanemab provide a structured approach to patient selection using Singapore-validated cognitive assessments, amyloid pathology confirmation, baseline MRI, and APOEε4 genotyping.
- These AURs provide guidance on ARIA risk stratification, treatment monitoring, infusion-reaction management, and criteria for treatment discontinuation.
- The checklist included in this paper details treatment candidate evaluation, comprising guidance for safety monitoring and adverse event management.

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Clinical Implications

- These AURs support Singapore physicians in identifying suitable candidates for lecanemab by individualising risk–benefit assessments and guiding safety monitoring throughout treatment.

INTRODUCTION

Lecanemab is a recombinant humanised immunoglobulin gamma 1 monoclonal antibody (mAB), targeting β-amyloid oligomers, protofibrils, and insoluble fibrils, facilitating their clearance, and thereby reducing amyloid plaques in the brain.[1-4] In January 2023, the US Food and Drug Administration (FDA) approved lecanemab under the accelerated approval pathway for the treatment of mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD), which was later converted to a traditional approval in July 2023.[5] Subsequently, lecanemab was approved by regulatory authorities in other territories, including the European Union,[6] Japan,[7] and Korea.[8] In Singapore, lecanemab was approved for slowing progression in patients at the MCI or mild dementia stage of AD in May 2025.[9]

To ensure that patients in Singapore who may benefit from lecanemab treatment can be appropriately identified and effectively monitored during treatment, guidance in addition to the prescribing information and guideline publications is needed. International guidance is available—notably, appropriate use recommendations (AURs) published in the US, France, and South Korea.[6,8,10]

Due to differences in healthcare systems and patient-specific factors, such as education, ethnicity, and language influencing cognitive performance tests,[11] guidance tailored to the Singapore clinical landscape and population is needed. Therefore, clinicians with expertise in the diagnosis and management of AD have formulated AURs for lecanemab in Singapore to optimise patient selection and monitoring and minimise risks of adverse events. This AUR does not discuss reimbursement or the monitoring of lecanemab efficacy in clinical practice.

METHODS

The AURs for lecanemab were developed by the author group to ensure its appropriate use in Singapore. The author group comprised 9 clinicians in Singapore with extensive experience in the management of AD. After a series of face-to-face explorations in November 2023, April 2023, and June 2025, involving some of the authors, a collective decision to develop a formal AUR to support Singaporean clinicians was made. The drafting of the AURs commenced through online circulation among the authors from July 2025 onwards. The recommendations described within this AUR are based primarily on the Singapore prescribing information for lecanemab,[9] with reference to important details from the Clarity AD trial and its Asian sub-study.[3] Recommendations based entirely on expert opinions are not described here. Additional publications to guide the discussion were identified through literature review focusing on "lecanemab" and its associated "clinical" and "real-world studies" using PubMed up to April 2026, the US prescribing information (USPI),[12] and the European Summary of Product Characteristics (SmPC).[13] All decisions were reached collaboratively by the author group, who were in full alignment with all the recommendations described.

Efficacy and safety of lecanemab in clinical development and real-world studies

Lecanemab initially received accelerated FDA approval based on a phase 2b placebo-controlled trial that showed a reduction in amyloid plaques as assessed by positron emission tomography (PET) scans of participants.[3,5,14] Confirmatory data for standard FDA approval were from the phase 3 Clarity AD trial, which enrolled early AD patients with MCI or mild dementia and evidence of amyloid pathology.[3] The mean age of participants was 71 years, and 69% were carriers of the apolipoprotein E ε4 allele (*APOEε4*). Patients were randomised to intravenous (IV) lecanemab (10 mg/kg every 2 weeks, n=898) or placebo (n=897).[3] Efficacy analyses were conducted on the modified intention-to-treat population (859 and 874 participants in the lecanemab and placebo groups, respectively).[3]

At 18 months, changes from baseline in the primary endpoint, the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score, were 1.21 with lecanemab and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI] −0.67 to −0.23; $P<0.001$).[3] Changes favouring lecanemab were also noted in several secondary endpoints, including the Alzheimer's Disease Assessment Scale, Alzheimer's Disease Composite Score, and Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment.[3] An imaging sub-study found a greater decrease in brain amyloid burden in the lecanemab group than in controls.[3] Notable adverse events in the lecanemab group were infusion-related reactions (IRRs) (26.4% versus [vs] 7.4% with placebo) and amyloid-related imaging abnormalities with oedema (ARIA-edema [ARIA-E], 12.6% vs 1.7% with placebo) or with haemorrhage (ARIA-hemosiderin [ARIA-H], 17.3% vs 9.0%).[3]

As randomisation in Clarity AD was stratified by geographic region (i.e. North America, Europe, and

Asia), an Asian sub-study of Clarity AD could be conducted to assess the efficacy and safety of lecanemab in the 294 patients from Japan (n=152), South Korea (n=129), and Singapore (n=13) who were enrolled in the study.[15]

In this Asian regional subset, the adjusted mean difference in CDR-SB at 18 months was −0.349 (95% CI −0.773 to +0.076), representing a 24% slowing of decline (compared to placebo) that was directionally consistent with the core trial but not statistically significant at the subgroup level, reflecting limited power in this 294-patient subset.[15] Common adverse event of special interest in Asian participants included IRRs (12.3% vs 1.4%, lecanemab vs placebo) and ARIA-E (6.2% vs 1.4%). Rates of ARIA-H were numerically higher in the placebo group (16.2% vs 14.4% in the lecanemab group); however, this is likely attributable to the effect of a small sample size.[15] Relative to the overall population, the incidence of adverse events leading to lecanemab interruption or withdrawal was lower in Asian patients (7.1% vs 0.7% for withdrawal, and 19.5% vs 10.3% for interruptions).[15] A 36-month open-label extension (OLE) of Clarity AD demonstrated that patients continued to benefit from ongoing lecanemab treatment for up to 36 months.[16] Furthermore, this OLE suggests that early initiation of lecanemab at early-stage AD, based on low-tau status (PET standardised uptake value ratio <1.06), may be associated with clinical stability.[16] The OLE identified no new safety signals, and after the first 6 months, rates of ARIA were low and comparable between treatment and placebo groups.[16]

Observational data on lecanemab in clinical practice are increasing. A retrospective study in a US centre has reported initial data for 71 AD patients treated with up to 14 infusions of lecanemab.[17] Of those with safety monitoring imaging available, 12/50 (24%) had ARIA, and 26/71 (37%) experienced IRRs after their first infusion.[17] A retrospective study in Israel that included 86 patients treated with lecanemab reported that 22.1% of patients experienced IRRs (all mild and transient), and 18.6% of patients developed ARIA.[18]

Other retrospective data on experience with lecanemab therapy are available from the US, including an analysis of 234 patients that reported IRRs in 37% of patients and ARIA in 22%.[19] Another retrospective analysis of the first 70 patients treated with lecanemab at a single centre reported a 20% ARIA rate, and the incidence of ARIAs was significantly associated with APOE genotype.[20]

Emerging real-world data from Japan show rates of ARIA that are approximately half of those seen in the US. In clinical usage so far, approximately 7% of Japanese patients developed ARIA (ARIA-E in 3% and ARIA-H in 5.2%),[21] consistent with reported rates among the Japanese population enrolled in Clarity AD.[22] In contrast to this Japanese real-world finding, another Japanese single-centre real-world study reported higher rates of ARIA (20%), all of which were asymptomatic.[23] The authors suggested that this could be due to a higher prevalence of baseline microhaemorrhage and inclusion of patients with white matter lesions as well as the higher sensitivity for detecting microhaemorrhages (susceptibility weighted imaging [SWI] vs T2-weighted gradient recall echo [T2*GRE] used in Clarity AD).[23]

A Chinese real-world study also showed lower rates of ARIA, with 6.9% of patients developing ARIA-E with or without ARIA-H and 10% developing isolated ARIA-H.[24] Moreover, another ongoing real-world Chinese study reported similar findings, with 3.1% of ARIA-E and 9.4% of ARIA-H among the 64 patients enrolled.[25]

Serious adverse events and mortality

Serious adverse events occurred in 14% (n=126) of participants in the lecanemab arm of the main Clarity AD trial, and no deaths related to lecanemab were reported.[3] However, in the Clarity AD OLE, which had no untreated control arm, there were 9 deaths, 4 of which were deemed due to lecanemab.[26]

From the safety analysis of the combined core Clarity AD study and its OLE, there was a total of 24 deaths, 3 of which were due to intracranial haemorrhage.[26] A case report by Solopova et al. described the index case of fatal iatrogenic cerebral β-amyloid-related arteritis in a patient treated with lecanemab.[27] Reish et al. reported another fatal case of multiple cerebral haemorrhages that developed after treatment with tissue plasminogen activator in a patient receiving lecanemab.[28] It is therefore essential that patients being treated with lecanemab carry a patient alert card, and setting up alerts in electronic medical records should also be considered, as previously suggested.[29]

Which patients should receive lecanemab?

The recommendations for patient evaluations, lecanemab infusion, and monitoring discussed below are summarised in a checklist document included as Supplementary Annex S1.

In Singapore, lecanemab is indicated for slowing progression in patients at the MCI or mild dementia stage of AD.[9] This is aligned with the USPI indication, whereas the European indication specifies that patients should be *APOEε4* non-carriers or heterozygotes.[12,13]

Amyloid-beta pathology should be confirmed using a validated test prior to initiation. These criteria are based on the population included in Clarity AD, which enrolled patients 50–90 years of age with

AD and MCI/mild dementia, with amyloid pathology confirmed by PET scans or cerebrospinal fluid (CSF) testing.[3]

Potential cognitive assessment tools suitable for use in Singapore

Neither Singapore nor international prescribing information specifies which tests should be used to diagnose MCI or mild dementia.[9,12,13] The mild severity of AD used as an enrolment criterion for Clarity AD was based on several evaluations.[3] Specifically, those with MCI due to AD had to meet the National Institute on Aging–Alzheimer's Association's (NIA-AA) core criteria for MCI and have a global CDR score of 0.5 and a CDR Memory Box score ≥0.5 at screening and baseline.[3] Additionally, a history of subjective memory decline with gradual onset and slow progression over the last year prior to screening was required.[3] Those with mild AD dementia had to meet NIA-AA core clinical criteria for probable AD dementia and have a global CDR score of 1.0 and a CDR Memory Box score of ≥0.5 at screening and baseline.[3] Additional inclusion criteria for all participants in Clarity AD were a Mini Mental State Examination (MMSE) score of 22–30, and objective impairment in episodic memory as indicated by at least 1 standard deviation below the age-adjusted mean in the Wechsler Memory Scale IV–Logical Memory II.[3]

In Singapore, several tests are available for screening of cognitive status, such as the MMSE (various languages available),[30] Frontal Assessment Battery,[31] a Singapore-adapted version of the Montreal Cognitive Assessment (MoCA),[32,33] and the Visual Cognitive Assessment Test.[34]

However, physicians should apply these scales cautiously and note that the MMSE alone is not sufficient to identify candidates for treatment. Data from cohorts in Singapore and Korea suggest that conventional MMSE thresholds are inaccurate in these populations for identifying those with early dementia, particularly when testing less educated patients.[11,35] The Quick Dementia Rating System (QDRS) may be a useful adjunct, as it has been validated in a cohort of older Singaporeans, with and without MCI/dementia, and it demonstrated good internal consistency and correlation with other scores, including the CDR.[35]

Emerging digital tools for cognitive evaluation that are less dependent on the patient's literacy levels may be of particular value in multiethnic populations with diverse literacy rates, such as in Singapore. Examples of less literacy-dependent testing approaches that have been investigated in Singapore cohorts include tools based on drawing and on-screen games.[36,37] If validated, digital testing may assist screening, but it would complement, rather than replace, in-person tests such as MMSE, MoCA, or QDRS.

Currently, the diagnosis of MCI or mild dementia in AD varies in Singapore clinical practice, with clinicians often selecting the screening tools they are most familiar with. In line with AURs from South Korea and the Clarity AD study,[3,8] the author group suggests that clinicians select 1 or more tools to identify patients with AD and MCI/mild dementia with clinical staging corresponding to a CDR score of 0.5–1.0 as candidates for treatment. However, in practice, multiple cognitive tests in combination with the physician's clinical judgement may provide a more complete picture of the patient's suitability. Considering the importance of timely lecanemab initiation suggested by the OLE data,[16] clinicians should promptly identify those eligible for treatment.

How should amyloid pathology be evaluated?

Although the prescribing information from Singapore, the US, and Europe notes that amyloid pathology should be confirmed before initiation, a testing method is not specified. In Clarity AD, amyloid pathology was confirmed prior to enrolment by PET scan or CSF testing.[3] In Singapore, amyloid PET scans are available at both public and private institutions, and local testing of AD biomarkers in CSF is also available. Furthermore, assays of plasma tau phosphorylated at threonine 217 (p-tau217) have shown strong performance as a diagnostic and prognostic biomarker in diverse populations, including Asian cohorts.[38-40] Because biomarker levels can be influenced by demographic factors such as ethnicity, body mass index, and kidney function, population-specific cutoffs may need to be established.[41] A simplified approach to determining plasma p-tau217 cutoffs using finite mixture modelling in place of more invasive or costlier approaches has been reported.[41] Plasma p-tau217 assays can reduce the invasiveness and costs of evaluating amyloid pathology and may play an important role in the diagnosis and monitoring of AD in the near future. At the time of writing, 2 plasma assays have been cleared by the FDA to assist the diagnosis of AD,[42] and multiple others are in development.[43]

What is the role of *APOEε4* testing?

The *APOEε4* allele is the strongest genetic risk factor for the onset of AD, with heterozygotes having an approximately 2–3-fold increased lifetime risk of AD, and homozygotes having an approximately 60% lifetime risk of AD dementia by 85 years of age, with near-complete biomarker-defined AD biology by 90 years of age.[44] *APOEε4* homozygosity is increasingly characterised as a genetic risk for AD with implications for cascade counselling. Additionally, *APOEε4* carriers treated with anti-amyloid therapies, including lecanemab, are at increased risk of developing ARIA, with homozygous individuals at greatest risk (see

section below).[45] In accordance with the Singapore prescribing information, the author group recommends that all patients undergo *APOEε4* genotyping prior to treatment to assist in the evaluation of risk–benefit profile for each patient. A notable difference between the Singapore prescribing information and USPI versus the European SmPC is that the latter limits the indication of lecanemab to *APOEε4* non-carriers and heterozygotes only, due to the higher risk of ARIA in homozygous patients.[6,9,12,13]

Currently, only one *APOEε4* test has received FDA clearance,[46] and commercial testing kits with local approval are not available in Singapore. Direct-to-consumer test kits are available, but these vary in accuracy and are not intended for clinical use. Genetic counselling should be available to patients and their carers to ensure they understand the impact of their genotype on disease prognosis and treatment risk. Furthermore, as the patient's *APOEε4* status has implications for the genetic risk of all first-degree relatives,[47] counselling and testing of family members should also be discussed. Specialist memory clinics in Singapore may need to develop resources for counselling, as local availability of genetic counselling services is currently limited and focused on other diseases. Since *APOEε4* homozygotes are not excluded from the approved Singapore lecanemab indication, the author group recommends physicians to take additional precautions, including more risk discussion and informed decision-making when treating this high-risk patient group.

Which patients should be excluded from treatment?

Although the Singapore prescribing information only lists serious hypersensitivity to lecanemab or its excipients as a contraindication,[9] caution should be exercised in several subgroups of patients. Notable exclusion criteria in Clarity AD were psychiatric conditions that could interfere with study procedures in the subject, and cognitive impairment caused by neurological and medical causes other than AD.[3] Patients with contraindications to MRI scanning (e.g. intracranial and cardiac devices not approved for safe use in MRI scanners) were also excluded.[3] Patients were also excluded based on findings of the screening brain MRI suggestive of increased risk of ARIA, or brain lesions that could indicate forms of dementia other than AD.[3] Additionally, those with immunological diseases that were not adequately controlled or those needing treatment with immunoglobulins or systemic mABs were also excluded.[3]

Patients in Clarity AD on approved AD treatments at a stable dose for ≥12 weeks were permitted in the study, as were those on concomitant drugs for other conditions for ≥4 weeks prior to baseline assessment.[3] Due to its mode of action, lecanemab is not expected to interact with small-molecule drugs.[9] Patients with uncontrolled bleeding disorders and those on anticoagulants not at a stable dose for >4 weeks were excluded due to increased risks of haemorrhage. A detailed list of the Clarity AD inclusion/exclusion criteria and the author group recommendations for Singaporean AD patients are included in Table 1. In general, the recommendations are aligned with the inclusion/exclusion criteria of Clarity AD. Physicians who are considering the initiation of lecanemab must be aware that although the only absolute contraindication to lecanemab is hypersensitivity, lecanemab must be prescribed on an individualised basis due to the selected clinical trial population of Clarity AD. The authors propose various criteria for excluding patients from treatment, for example, those with untreated bleeding disorders, and those with neurological or medical conditions other than AD that may be a primary cause of cognitive impairment.

How should candidates for treatment be radiologically evaluated?

Baseline brain MRI is recommended in the prescribing information to assess a patient's eligibility for treatment and to exclude patients with brain lesions that may be associated with dementia independently of AD. International expert groups recommend non-contrast MRI with a minimum of 3 sequences: T2 fluid-attenuated inversion recovery (FLAIR), T2*GRE or equivalent sequences (e.g. SWI and diffusion-weighted imaging [DWI]), preferably using a 3 T scanner, and minimally on a 1.5 T scanner, with ≤5 mm slice thickness.[8,10] Where a GRE sequence is performed, an echo time of ≥25 ms at 1.5T MRI and ≥15 ms at 3T MRI should be ensured. Follow-up MRI scans after treatment initiation should be performed, using the same scanner, with the same field strength and imaging parameters as the baseline scan to facilitate optimal comparison. The authors suggest a standardised MRI protocol be developed to harmonise the imaging and reporting of lecanemab candidates across all centres in Singapore.

Practical considerations for lecanemab use

Lecanemab should be stored at 2–8°C, protected from light and diluted immediately prior to use. It should not be frozen or shaken; the recommended dosage is 10 mg/kg infused intravenously over 1 hour, every 2 weeks. After dilution, immediate use is recommended. If not administered immediately, lecanemab must be stored refrigerated at 2–8°C for up to 4 hours or stored at room temperature up to 30°C for up to 4 hours. It is recommended not to freeze. If a dose is missed, the next infusion should be given as soon as possible. Infusions can be given on an outpatient basis.

Table 1. Inclusion/exclusion criteria in Clarity AD, and recommendations for lecanemab use in Singapore.

	Clarity study inclusion criteria[3]	**Recommendations for Singapore: Initiation of lecanemab treatment**
Diagnosis	• Diagnosis of MCI due to AD (global CDR 0.5) and mild AD dementia • CDR memory score 0.5−1.0 • Wechsler memory scale-IV logical memory test showing objective memory impairment below one standard deviation vs age-adjusted mean • MMSE ≥22 and ≤30 at screening and baseline	• Clinical diagnosis of MCI due to AD and mild AD dementia, based on clinicians' judgement + Singapore-validated cognitive tests, e.g. MMSE, MoCA, QDRS, CDR, others ○ MMSE score alone should not be used for identifying Singaporean patients with early dementia • Care should be taken in the evaluation of patients with lower literacy/education levels
Amyloid pathology	• Positive amyloid PET or CSF test	• Positive amyloid PET or CSF test
Age	• 50–90 years	• Based on the physician's judgement, if outside 50–90 years
BMI	• >17 and <35 kg/m^2 at screening	• Physician judgement if outside >17 and <35 kg/m^2 at screening
Concomitant medications	• If receiving an acetylcholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine, or both, participants must be on a stable dose for at least 12 weeks prior to baseline • Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to baseline	• Other AD treatments approved for use in Singapore may be used concomitantly
Patient support	• Have an identified study partner	• Ensure the patient has a carer or family member to provide support during treatment • Ensure the patients and carer/family members understand the risks and benefits of treatment
	Exclusion criteria in Clarity AD	**Recommendations for Singapore: Considerations for exclusion or additional caution**
Additional causes of cognitive impairment	• Any neurological condition that may be contributing to cognitive impairment beyond that caused by the participant's AD	• Any medical, neurological, or mental health condition that may be a primary cause of cognitive impairment or non-AD MCI or dementia
MRI contra-indications	• Patients with contraindications to MRI scan were excluded from the study	• Patients with contraindications to MRI scan or unable to tolerate repeated MRI (e.g. claustrophobia)
Brain MRI findings	• >4 microhaemorrhages (≤10 mm at the greatest diameter) • A single macrohaemorrhage (>10 mm at greatest diameter) • An area of superficial siderosis • Evidence of vasogenic oedema • Multiple lacunar infarcts or stroke involving a major vascular territory • Severe small vessel disease, or other major intracranial pathology • Other clinically significant lesions on brain MRI indicative of a dementia diagnosis other than AD	• >4 microhaemorrhages (≤10 mm at the greatest diameter) • A single macrohaemorrhage (>10 mm at greatest diameter) • An area of superficial siderosis; evidence of vasogenic oedema • >2 lacunar infarcts or stroke involving a major vascular territory. Severe small vessel disease consistent with a Fazekas score of 3, or other major intracranial pathology • Brain MRI evidence of ABRA or CAA-ri • Other major intracranial pathology that may cause cognitive impairment, including contusions or gliosis due to past traumatic injuries, aneurysms, vascular malformations, infective lesions or brain tumours • Severe enlarged perivascular spaces in the centrum semiovale are not an absolute exclusion criterion but may be a pointer to underlying cerebral a myloid angiopathy and require heightened clinical vigilance

Table 1. Inclusion/exclusion criteria in Clarity AD, and recommendations for lecanemab use in Singapore. (Cont'd)

	Clarity study inclusion criteria[3]	Recommendations for Singapore: Initiation of lecanemab treatment
CV history	• History of TIA, stroke, seizures within 12 months of screening	• History of TIA, stroke, or seizures within 12 months of treatment initiation
Other psychiatric diagnoses	• Any psychiatric diagnosis or symptoms (e.g. hallucinations, major depression, or delusions) that could interfere with study procedures in the participant • Geriatric Depression Scale-15 score ≥8 at screening	• Any mental illness that interferes with comprehension of the requirements, potential benefits, and potential harms of treatment, and is considered by the physician to render the patient unable to comply with management requirements • Major depression that will interfere with comprehension of the requirements, potential benefit, and potential harms of treatment; patients for whom disclosure of a positive biomarker may trigger suicidal ideation. • Patients with less severe depression or whose depression resolves may be treatment candidates
Immunological diseases	• Any immunological disease that is not adequately controlled, or that requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during the study	• Any immunological disease that is not adequately controlled • Patients treated with other monoclonal antibodies can be considered for lecanemab treatment, based on the treating clinician's individualised risk assessment • For patients treated with other monoclonal antibodies, consultation with the treating physician is required
Bleeding disorders	• Participants with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or INR >1.5 for participants who are not on anticoagulant treatment, for example, warfarin)	• Untreated bleeding disorder, platelet count <50,000 x 10^9/L, or INR >1.5 but not on anticoagulant
Anticoagulants	• Participants on anticoagulants should have their anticoagulant status optimised and have a stable dose for 4 weeks before screening	• Patients taking anticoagulants must be evaluated with additional caution • Consider consultation with neurologists/stroke specialists/cardiologists/ anticoagulant prescribing physicians to discuss suitability and risks of lecanemab treatment
Other medical conditions	• Any other medical conditions (e.g. cardiac, respiratory, gastrointestinal, renal disease) that are not stably and adequately controlled, or which could affect the participant's safety or interfere with the study assessments	• Any other medical condition with the potential to affect lecanemab treatment

ABRA: amyloid beta-related angiitis; AD: Alzheimer's disease; BMI: body mass index; CAA-ri: cerebral amyloid angiopathy-related inflammation; CDR: Clinical Dementia Rating; CSF: cerebrospinal fluid; CV: cardiovascular; INR: international normalised ratio; MCI: mild cognitive impairment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging; PET: positron emission tomography; QDRS: Quick Dementia Rating System; TIA: transient ischaemic attack; vs: versus

Adapted from van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2023;388:9-21.[3] Changes were made: inclusion and exclusion criteria were reorganised into a single table, and a column of recommendations for Singapore was added.

Superscript number: refer to REFERENCES

How should infusion-related adverse events be monitored and managed?

In Clarity AD, IRRs were reported in 26.4% of patients in the lecanemab group (vs 7.4% in placebo); these were predominantly mild to moderate in severity (96% grade 1 or 2), and 75% occurred with the first dose.[3] In the Asian sub-study of Clarity AD, IRR rates were lower than in the overall study population, at 12.3% of patients in the lecanemab group and 1.4% in the placebo group; all were grade 1 or 2.[15] IRRs may manifest through a range of symptoms, including fever and systemic flu-like effects such as chills, muscle aches, and joint pain.[9] Other notable symptoms may encompass gastrointestinal distress (such as nausea and vomiting), blood pressure fluctuations (hypertension or hypotension), or oxygen desaturation.[9] In Clarity AD, IRRs typically resolved within 24 hours without the need for hospitalisation. Furthermore, 63% of the study participants taking prophylactic medications did not experience subsequent IRRs.[3]

In agreement with the US Alzheimer's Disease and Related Disorders Therapeutics Work Group, the authors suggest that milder cases of IRRs can be treated with diphenhydramine and paracetamol.[10] For IRRs of grade 2 or higher severity, the infusion should be stopped, and patients should be treated with oral dexamethasone or oral prednisolone. Patients who have experienced a grade 2 or higher IRR should be prophylactically treated with oral diphenhydramine and oral paracetamol 30 minutes prior to the next infusion. Low-dose oral dexamethasone or oral prednisolone (6 hours prior to infusion) can be used for prophylaxis or treatment if diphenhydramine and paracetamol are ineffective.[10] Prophylaxis against IRRs should continue for the next 2 to 4 infusions. A summary of these recommendations is included in Table 2. For patients who experience grade 3 or higher IRRs, the infusion should be stopped immediately and lecanemab discontinued.

Monitoring and management of ARIA

ARIA are abnormal radiographic findings indicative of cerebral amyloid angiopathy-related inflammation and have been associated with various anti-amyloid

Table 2. Pharmacological recommendations for treatment and prophylaxis of IRRs of lecanemab.

Agent	Dosing recommendations	Author group's remarks
Treatment of mild IRR		
Paracetamol (oral)	500 mg to 1 g	For milder cases; dosing can be repeated every 4–6 hours until symptoms resolve.
Diphenhydramine or other antihistamines (oral)	Diphenhydramine 25–50 mg	For milder cases; dosing can be repeated every 4–6 hours until symptoms resolve. Antihistamine choice and dosage should be based on the treating physician's clinical judgement and/or hospital protocols for managing IRRs.
Dexamethasone or other corticosteroids (oral) when significant symptoms are present	Daily for 2–3 days	Corticosteroid choice and dosage should be based on the treating physician's clinical judgement and/or hospital protocols for managing IRRs.
Prophylactic treatment in patients with previous IRR		
Paracetamol (oral)	500–1000 mg	To be given 30 minutes prior to infusion. Antihistamine choice and dosage should be based on the treating physician's clinical judgement and/or hospital protocols for managing IRRs.
Diphenhydramine or other antihistamines (oral)	Diphenhydramine 25–50 mg	
Dexamethasone or other corticosteroids (oral)	Individualised	May be given as a single prophylactic dose in patients where paracetamol/ diphenhydramine is not effective. Corticosteroid choice and dosage should be based on the treating physician's clinical judgement and/or hospital protocols for managing IRRs.

IRR: infusion-related reaction

For more detailed information, refer to the Lecanemab infusion guide in Supplementary Annex S2.

Adapted from Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. J Prev Alzheimers Dis 2023;10:362-77.[10] Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Changes were made: recommendations on treatment and prophylaxis of IRRs were reorganised into tabular format; the dose recommendation of corticosteroids for the treatment of mild IRR was excluded; the dosage recommendation for corticosteroids for prophylactic treatment in patients with previous IRR was modified to "individualised"; and a remarks column reflecting the views of the author group was added.

Superscript number: refer to REFERENCES

therapies, including lecanemab.[48] Although they are most commonly reported in AD patients receiving anti-amyloid-β mABs, they are also observed in untreated AD patients.[49] In the main Clarity AD study ,[3] ARIA-E events were mostly mild-to-moderate (96%) and 78% were asymptomatic.[3] In the Asian sub-study of Clarity AD, the incidence of ARIA-E and ARIA-H was lower than in the overall study population,[15] and this difference is also reflected in emerging real-world data from Japan and China.[21,24]

All ARIA-E events in the Asian subpopulation were asymptomatic and mild-to-moderate in radiographic severity, as were almost all ARIA-H events.[15] The exact pathogenesis of ARIA is unclear, but it appears to share overlapping features with cerebral amyloid angiopathy (CAA), the deposition of amyloid-β in the vascular wall, a phenomenon observed in the majority of AD patients, with moderate-to-severe CAA in 25–50%.[50] ARIA are thought to be caused by increased blood vessel permeability and leakage induced by clearance of amyloid deposits from and alongside cerebral arteries.[50] In clinical trials, ARIA-E and ARIA-H events are usually asymptomatic, but in some cases, ARIA-E are associated with headaches, blurred vision, confusion, vomiting, or gait disturbance.[49] In rare instances, ARIA can be serious and life-threatening or fatal.[9]

The main risk factors for ARIA development are treatment with anti-amyloid-β antibodies, the presence of pre-existing microhaemorrhages, and *APOEε4* status.[48,49] The risk of ARIA development increases with drug dose and treatment duration, and patients are at the highest risk in the first few months of treatment when amyloid-β deposits are mobilised.[48] *APOEε4* status also has a dose-dependent effect, with homozygous patients at higher risk than heterozygous patients.[48,49]

Beyond established haemorrhagic markers, severe centrum semiovale enlarged perivascular spaces (CSO-ePVS) are incorporated into the Boston 2.0 criteria as a validated non-haemorrhagic marker of advanced CAA.[51] While recent data suggest a plausible link to ARIA risk, these studies rely heavily on automated quantitative techniques that are not widely available in everyday clinical practice.[52] The visual semi-quantitative scoring systems remain difficult to standardise in routine clinical practice. Consequently, ePVS is currently not utilised as an exclusion criterion in existing consensus guidelines. To ensure Singapore recommendations remain practical and easily adoptable, severe CSO-ePVS has been acknowledged in the authors' checklist not as a contraindication, but as a marker warranting heightened clinical vigilance.

In studies of various anti-amyloid treatments, including lecanemab, concomitant use of anticoagulants, antithrombotics, or antiplatelets has also been associated with increased risk of ARIA.[49] The Clarity AD trial included patients with concomitant antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) at baseline if the patient was on a stable dose, and the majority of the antithrombotic exposures were to aspirin.[9,26] Among patients receiving lecanemab alongside anticoagulants (either alone or with antiplatelet drugs or aspirin), intracerebral haemorrhage occurred in 2.5%, whereas no such cases were reported in the placebo group.[26]

The European SmPC for lecanemab recommends that it not be used in patients needing ongoing anticoagulation, and that concomitant use of thrombolytics be avoided except for life-threatening situations.[13] However, the Singapore prescribing information and USPI take a less restrictive approach, noting that lecanemab may be used in such patients, but physicians must exercise additional caution.[9,12] Additional guidance was provided by the UK guideline, which suggested that additional caution should be observed in patients receiving dual antiplatelet therapy, with such cases discussed in a multidisciplinary team to assess individual risk.[29]

Although there was no known pharmacological or immunological risk associated with lecanemab, patients undergoing treatment with other mABs were excluded from Clarity AD as a precautionary measure and to maintain scientific validity. In clinical practice, however, such an approach may be excessively restrictive and risk denying treatment to patients with clear clinical need without a corresponding safety rationale. Therefore, patients treated with other mABs can be considered for lecanemab treatment, based on individualised risk assessment, in consultation with their treating clinician.

Patients treated with lecanemab should undergo monitoring for ARIA with brain MRI scans prior to the fifth, seventh, and fourteenth infusions.[9] If a patient experiences symptoms, a clinical evaluation should be performed, including an MRI, if indicated.[9] The MRI protocol should include at least 3 sequences (T2 FLAIR, T2*GRE or SWI, and DWI) and should be done on a 1.5 T scanner at the minimum with ≤5 mm slice thickness,[53] using the same technical parameters and scanner as the baseline scan to aid the detection of ARIA. ARIA protocols for several models of MRI scanner are available from the American Society of Neuroradiology website (https://www.asnr.org/education-resources/alzheimers-webinar-series/).[54] Use of a DWI sequence is important for the identification of an acute infarct, which may be a clinical differential in a patient presenting with acute neurological symptoms. Use of T2 FLAIR and T2*GRE/SWI sequences can identify ARIA-E and ARIA-H, respectively. Both ARIA-E and ARIA-H should be graded in severity based on their clinical and MRI features to guide management

(Supplementary Annex S3, Table S1). Additionally, patients and caregivers should be informed about ARIA, their symptoms, and when to seek care, because if such patients are misdiagnosed with stroke, treatment with thrombolytics is potentially fatal (Table 3).[48]

Table 3. Critical safety point.

Critical safety point: Anticoagulants or thrombolytic agents in lecanemab recipients[9]
Intracerebral haemorrhages of 1 cm or larger have been documented in patients receiving lecanemab. Follow your institutional guidelines on the use of mechanical thrombectomy versus anticoagulants or thrombolytic agents. When evaluating whether to administer anticoagulants or thrombolytic agents (e.g. tissue plasminogen activator) to a patient already on lecanemab, additional caution should be exercised.

Superscript number: refer to REFERENCES

Based on the approach taken in Clarity AD, the authors suggest that for patients with moderate to severe ARIA-E and ARIA-H and symptomatic ARIA of any severity, lecanemab should be suspended (Supplemental Annex S3, Tables S2 and S3) until signs or symptoms resolve.[9] A follow-up MRI 2–4 months after initial identification of ARIA should be considered. Continuation of treatment after suspension and the suspension of lecanemab in patients with mild asymptomatic ARIA should be based on the clinician's judgement after resolution of ARIA-E and stabilisation of ARIA-H. The initiation of high-dose steroids (e.g. IV methylprednisolone 1 g daily for 3–5 days, and subsequent oral steroid taper over several weeks) may be considered in patients with symptomatic or severe ARIA.[55]

When should lecanemab be discontinued?

Currently, there are no long-term data to guide the discontinuation of lecanemab. In the 18-month Clarity AD study, adverse events leading to discontinuation of lecanemab were reported in 6.9% of participants (vs 2.9% in the placebo group).[3] The authors recommend lecanemab be discontinued if patients experience severe symptomatic or radiologic ARIA, and in patients who experience grade 3 or higher IRRs. Guidance from the French Federation of Memory Clinics suggests treatment discontinuation at 18 months if a detailed cognitive examination suggests progression to moderate stages of dementia.[6] The Singapore prescribing information specifically recommends discontinuing lecanemab if the treatment is no longer expected to be effective, if patients develop intracerebral haemorrhage greater than 1 cm in diameter during treatment, or in the event of IRR, where the infusion rate may be reduced or the infusion discontinued.[9] Overall, the decision to stop lecanemab should be individualised based on the clinician's judgement and be made after consideration of the preferences of patients and caregivers, imaging evidence of amyloid clearance, and the costs and logistics of treatment.

DISCUSSION

Although their long-term impact is unclear, the introduction of lecanemab and other anti-amyloid-β antibodies marks the start of a new era for AD treatment. Because the indication for these agents is limited to early stages of AD, efforts should be made to streamline and standardise the diagnostic pathway to ensure such patients are diagnosed in a timely manner.[56,57] Patient registries will be important to provide longer-term data on the safety and efficacy of these drugs.

Shields et al. provide some practical insights into lessons learned during the introduction of lecanemab into regular clinical practice.[17] These include the establishment of a multidisciplinary team approach to lecanemab use, a standardised approach to radiology reporting, and a protocol for the identification and management of lecanemab patients in the emergency department.[17] This study also reported the use of a standardised prophylactic treatment for IRRs.[17] These approaches are consistent with the recommendations of a regional expert group promoting best practices and readiness for the introduction of anti-amyloid therapy in Asia.[57]

Early data suggest that dosing may be modified for long-term treatment. In early 2025, the US FDA approved the option of monthly IV maintenance dosing in patients who completed 18 months of bi-weekly treatment.[12] Additionally, in August 2025, the US FDA approved a subcutaneous form of lecanemab, administered using an autoinjector with a dosage of 360 mg once a week, for maintenance dosing after 18 months.[12,57] This development may reduce treatment barriers and associated costs.[59] The optimal forms of monitoring for longer-term treatment, for example, the need for repeated amyloid PET imaging for follow-up, are unclear. However, given the inconvenience and expense of imaging-based methods, plasma biomarkers may play a role in long-term monitoring.[60,61]

CONCLUSION

Lecanemab is recommended for the treatment of patients with MCI due to AD and mild AD dementia. The diagnosis of these patients should be established by CSF or PET confirmation of amyloid pathology, as well as cognitive testing using tools validated in the Singapore population. It should not be used in patients

with hypersensitivity to the drug and should be used with caution in patients at increased risk of ARIA (e.g. those who carry *APOEε4*, or MRI findings associated with increased risk). During treatment, patients should receive regular follow-up, including MRI scans and evaluation for ARIA symptoms.

To optimise the use of lecanemab in Singapore, several key priorities must be addressed. First, the development of a Singapore-specific registry will provide critical long-term data on the safety and efficacy of anti-amyloid-β antibodies and the role of plasma biomarker testing in the diagnosis and management of patients. A formal consensus process—informed by registry findings—will help resolve outstanding uncertainties and provide Singapore guidance, including concerns regarding cognitive screening protocols, co-prescription of antiplatelet agents, and discontinuation criteria (which should be anchored to objective, measurable thresholds). Localisation efforts must also extend beyond registries to include Singapore-adapted cognitive screening algorithms, explicit management strategies for discordant or borderline amyloid pathology readings, including centiloid thresholds for confirmation and plasma p-tau217 integration; clear operationalised discon-tinuation criteria to ensure standardised clinical practice; and a defined approach to *APOEε4* homozygosity, given their pivotal role in patient selection. Finally, ongoing policy discussions should integrate these clinical refinements with considerations of cost, equity, and reimbursement to facilitate access to lecanemab in Singapore.

Supplementary materials

Annex S1. A checklist summarising the recommendations for the use of lecanemab for early Alzheimer's disease in Singapore.

A. Lecanemab patient selection checklist.

B. Lecanemab diagnostic checklist.

C. Lecanemab safety monitoring checklist.

Annex S2. Lecanemab infusion guide.

Annex S3. ARIA MRI classification and dosing recommendations.

Table S1. MRI classification of radiographic severity of ARIA-E and ARIA-H.

Table S2. Dosing recommendations for patients with ARIA-E.

Table S3. Dosing recommendations for patients with ARIA-H.

Ethics statement

Not applicable, as this review did not involve the recruitment of participants or the collection of new data from human participants.

Declaration

CLC has received research funding paid to the National University Hospital, Singapore from Eisai, and has participated in advisory board meetings for Actinogen, Cerecin, Eisai, and Lilly. NK has received honoraria from Eisai for continuing medical education events. SK has received honoraria for lectures and workshops from Eisai and from DKSH. TML has provided consultation to Eisai and Lundbeck and is listed as co-inventor for the provisional patent of PENSIEVE-AI (referenced in the manuscript). KEL, ASLN, KPN, and SKST have received honorarium from Eisai. LBGT has no conflict to declare.

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Efficacy of AI in the diagnosis of oral squamous cell carcinoma from clinical images: A systematic review and meta-analysis

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ABSTRACT

Introduction: Oral squamous cell carcinoma (OSCC) is a common malignancy that is frequently diagnosed at advanced stages, partly because of limitations in conventional diagnostic approaches. This systematic review aimed to evaluate the diagnostic performance of artificial intelligence (AI) models in detecting OSCC from clinical images.

Methods: PubMed, ScienceDirect, the Cochrane Library, and Embase were searched from January 2000 to September 2024. Studies assessing the diagnostic accuracy of AI models for OSCC using clinical images were included. Studies that did not involve clinical images, were not specific to OSCC, or were not published in English were excluded. In accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, study selection was per-formed independently by 4 reviewers, with disagreements resolved through consensus. Subsequently, diagnostic accuracy data were extracted, risk of bias was assessed using Quality Assessment of Diagnostic Accuracy Studies using AI and thematic analysis was performed by 2 reviewers. Where appropriate, a random effects meta-analysis was conducted.

Results: Nine studies comprising 47,987 oral clinical images were included, with 6 studies in the meta-analysis. AI models demonstrated a pooled sensitivity of 0.94 (95% confidence interval [CI] 0.87–0.97), specificity of 0.95 (95% CI 0.86–0.98), and an area under the curve of 0.975 (95% bootstrap CI 0.911–0.986). AI systems generally achieved higher diagnostic accuracy than general practitioners and performance comparable to specialists under controlled study conditions.

Conclusion: AI models show strong diagnostic perfor-mance for OSCC detection from clinical images. However, current evidence is largely derived from retrospective and heterogeneous datasets without external validation. Prospective and blinded studies are required to deter-mine their role as decision-support tools in real-world settings.

Keywords: artificial intelligence, cancer, oral squamous cell carcinoma, otorhinolaryngology, public health

CLINICAL IMPACT

What is New

- AI demonstrates high diagnostic performance for OSCC detection in clinical images, with a pooled sensitivity of 0.94, specificity of 0.95, and strong discriminatory performance across 6 studies included in the meta-analysis.
- This review identifies the current evidence gap between promising diagnostic accuracy and clinical readiness, highlighting limited external validation, heterogeneous retrospective datasets, and concerns regarding independent data partitioning.

Clinical Implications

- AI could serve as an adjunctive screening and decision-support tool, particularly in primary care and resource-limited settings where access to specialist assessment is limited.
- Clinical implementation requires prospective, externally validated studies before routine use, with evaluation of real-world diagnostic performance, clinician adoption, and potential effects on referral and biopsy rates.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most prevalent and life-threatening malignancy of the oral cavity, representing approximately 90% of all oral malignancies.[1] Lip and oral cavity cancers accounted for an estimated 452,205 new cases and 194,108 deaths worldwide in 2024. These estimates encompass cancers of the lip and oral cavity and should not be interpreted as OSCC-specific figures.[2] Despite signifi-cant advancements in treatment modalities—such as surgery, radiotherapy, and chemotherapy—the 5-year survival rate for OSCC remains relatively low,

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particularly when the disease is diagnosed at advanced stages.[3] Early detection is therefore crucial, as patients diagnosed in the initial stages have significantly better prognoses and quality-of-life outcomes than those diagnosed later. However, current diagnostic approaches are often limited by subjective interpretation, inter-observer variability, and limited access to specialist care, especially in low-resource settings.[4]

The diagnosis of OSCC typically begins with clinical suspicion followed by histological diagnosis via tissue sampling. Clinically, it usually presents as a non-healing ulcer, an exophytic mass, or a mixed red and white patch (erythroleukoplakia), frequently affecting the lateral tongue and the floor of the mouth.[5] Imaging plays a crucial role in staging, with contrast-enhanced computed tomography (CT) assessing tumour extent and bone invasion. Magnetic resonance imaging (MRI) offers superior soft tissue resolution, especially for perineural and marrow involvement.[6] 18F-fluorodeoxyglucose positron emission tomography (PET)/CT is useful for detecting nodal and distant metastases.[7] Histologically, OSCC is characterised by invasive nests or cords of atypical squamous cells with varying degrees of keratinisation, and is graded by degree of differentiation.[8]

Recent developments in artificial intelligence (AI), particularly in machine learning and deep learning, have shown considerable promise in medical image analysis and pattern recognition, offering the potential to augment diagnostic accuracy and efficiency in OSCC detection.[9] AI models trained on histopathological images, clinical images, and radiographic data have demonstrated high sensitivity and specificity in distinguishing malignant from benign lesions.[10] Given the growing body of literature exploring the role of AI in OSCC detection, a systematic evaluation of the diagnostic accuracy of these models is both timely and necessary. Although AI has been used for various stages of OSCC investigation, this systematic review and meta-analysis aimed to critically appraise and synthesise existing evidence on the efficacy of AI-based models in diagnosing OSCC from clinical images.

METHODS

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Guided by the Population, Intervention, Comparison, Outcome and Study Design (PICOS) elements for the inclusion criteria, the primary research question was: "How efficacious is AI in the diagnosis of oral squamous cell carcinoma from clinical images?" The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD420251084762) in 2025, after the literature searches were conducted in September–October 2024. The registration was therefore retrospective in relation to the search process. No subsequent amendments were made to the registered protocol.

Search strategy and selection criteria

PubMed, ScienceDirect, the Cochrane Library, and Embase were searched to retrieve articles that evaluated the diagnostic accuracy of AI models in the diagnosis of OSCC based on clinical images.

The search combined the Boolean operators AND and OR with the search terms "deep learning", "artificial intelligence", "artificial learning", "machine learning", "machine intelligence", "neural networks", "probabilistic networks", "knowledge representation", "statistical learning", "Bayesian learning", "medical decision", "decision tool", "support tool" AND "oral cavity carcinoma", "oral cavity cancer", "oropharyngeal cancer", "oropharyngeal carcinoma", "oral cavity squamous cell carcinoma".

The searches were confined to articles published from January 2000 to September 2024. All articles were published in English or included an English translation. The search was carried out between September and October 2024. The PICOS search strategy is summarised in Supplementary Table S1.

The research team consisted of 4 reviewers who independently reviewed the titles and abstracts identified by each database to determine the final list of included articles. Disagreements were resolved through consensus discussion among the reviewers. Supplementary Table S2 summarises the studies included in the systematic review and indicates those excluded from the meta-analysis (with reasons). Although the terms "oropharyngeal cancer" and "oropharyngeal carcinoma" were included in the search strategy to increase sensitivity, only studies evaluating lesions arising within the oral cavity were eligible for inclusion.

Risk of bias and applicability were assessed independently by 2 reviewers using the Quality Assessment of Diagnostic Accuracy Studies Using AI (QUADAS-AI) framework, an extension of Quality Assessment of Diagnostic Accuracy Studies-2 developed specifically for AI-based diagnostic accuracy studies. As shown in Supplementary Table S3, each included study was evaluated across 4 core domains: patient selection, index test, reference standard, and flow and timing—with each rated for both risk of bias and applicability concerns. In addition, 3 AI-specific domains were assessed: independence of data partitioning (whether training and test datasets were drawn from separate, non-overlapping sources); model transparency (whether sufficient architectural and methodological detail was reported to enable replication); and integrity of the training/test split

(whether the test set remained fully independent from model development). Each domain was rated as low, high, or unclear risk of bias, based on prespecified signalling questions. Disagreements were resolved by consensus.

Only studies with histologically confirmed datasets were included in the meta-analysis. Supplementary Table S4 summarises the pooled models included in the meta-analysis. Supplementary Tables S5–S10 present the 2×2 data from each of the included models.

Data extraction

A standardised Excel spreadsheet with the following headings was used to extract data from all included articles.

1. Study characteristics
    a. Author
    b. Year of publication
    c. Country
    d. Sample size
    e. Study design
2. Methods of diagnosing OSCC
3. Data that the machine learning model is trained on
4. AI model characteristics
5. Diagnostic performance metrics
    a. Accuracy
    b. Precision
    c. Sensitivity
    d. Specificity
    e. Positive predictive value
    f. Negative predictive value
    g. Area under the curve (AUC) value
    h. F1

Statistical analysis

Statistical analyses were performed using R in RStudio (version 2022.12.0+353; RStudio Team, Vienna, Austria), primarily with the mada package. Individual-study sensitivity and specificity were calculated from the extracted 2×2 contingency tables, with 95% confidence intervals (CIs) estimated using the Clopper–Pearson exact binomial method. Pooled sensitivity and specificity with 95% CIs were estimated using a bivariate random-effects model (Reitsma model), fitted by restricted maximum likelihood. A summary receiver operating characteristic (SROC) curve was constructed using the Rutter–Gatsonis parameterisation, with the AUC calculated using the mada package. The AUC 95% CI was estimated using 2000 parametric bootstrap iterations.

Between-study heterogeneity was evaluated using the model's variance components, correlation, and Zhou–Dendukuri I^2 statistic. Following the benchmarks established by Higgins et al.,[11] I^2 values of 25%, 50%, and 75% were tentatively considered to represent low, moderate, and high inconsistency, respectively. These ranges were interpreted cautiously because they were not specifically developed for the Zhou–Dendukuri estimator and may be unreliable with only 6 studies.

Publication bias was explored using an effective-sample-size-weighted Deeks-type funnel plot asymmetry regression, with the log diagnostic odds ratio regressed against the inverse square root of the effective sample size. A continuity correction of 0.5 was applied to all 4 cells of the 2×2 contingency table for studies containing zero cells. Sensitivity analyses were performed using alternative continuity corrections of 0.1 and 1.0 to assess the robustness of the regression results.

RESULTS

The search from the 4 databases retrieved a total of 627 articles. After removing 114 duplicates, 513 articles remained. After reviewing the titles and abstracts, 103 articles were retrieved in full text, and 1 additional article was included from the citations. After reviewing these, 9 diagnostic articles focusing on clinical images were included in the systematic review, and 6 in the meta-analysis. The results of the search are summarised in the PRISMA flow diagram (Supplementary Fig. S1).

Characteristics of included studies

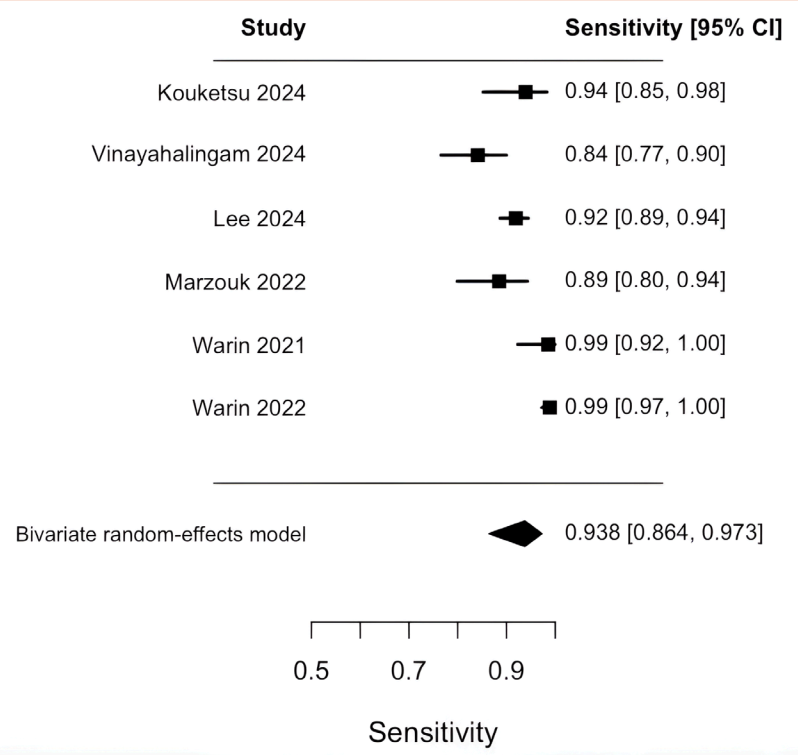
Nine eligible studies were included in the systematic review, with a total of 47,987 clinical images, of which at least 1784 were of OSCC. Six studies were included in the meta-analysis, comprising a total of 8825 clinical images. Most of the studies were from Asia, and most used convolutional neural networks (CNNs). Supplementary Table S2 summarises the characteristics of the included studies in the systematic review.

Diagnostic test accuracy

The pooled sensitivity of AI models was 0.938 (95% CI 0.864–0.973), while the pooled specificity was 0.9543 (95% CI 0.859–0.986), indicating high diagnostic accuracy with moderate consistency across studies. The pooled sensitivity and specificity are shown in the forest plots in Figs. 1 and 2. The SROC curve yielded an AUC of 0.975 (95% bootstrap CI 0.911–0.986) (Fig. 3), indicating high discriminatory performance under controlled study conditions.

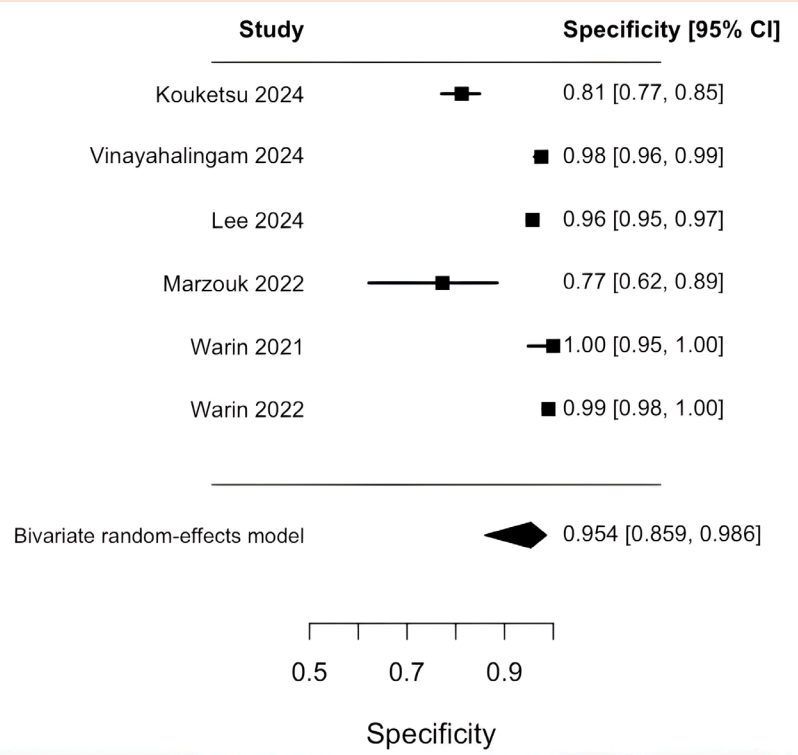
Between-study heterogeneity was observed, with a Zhou–Dendukuri I^2 of 56.7%. The estimated between-

Fig. 1. Forest plot of sensitivity.



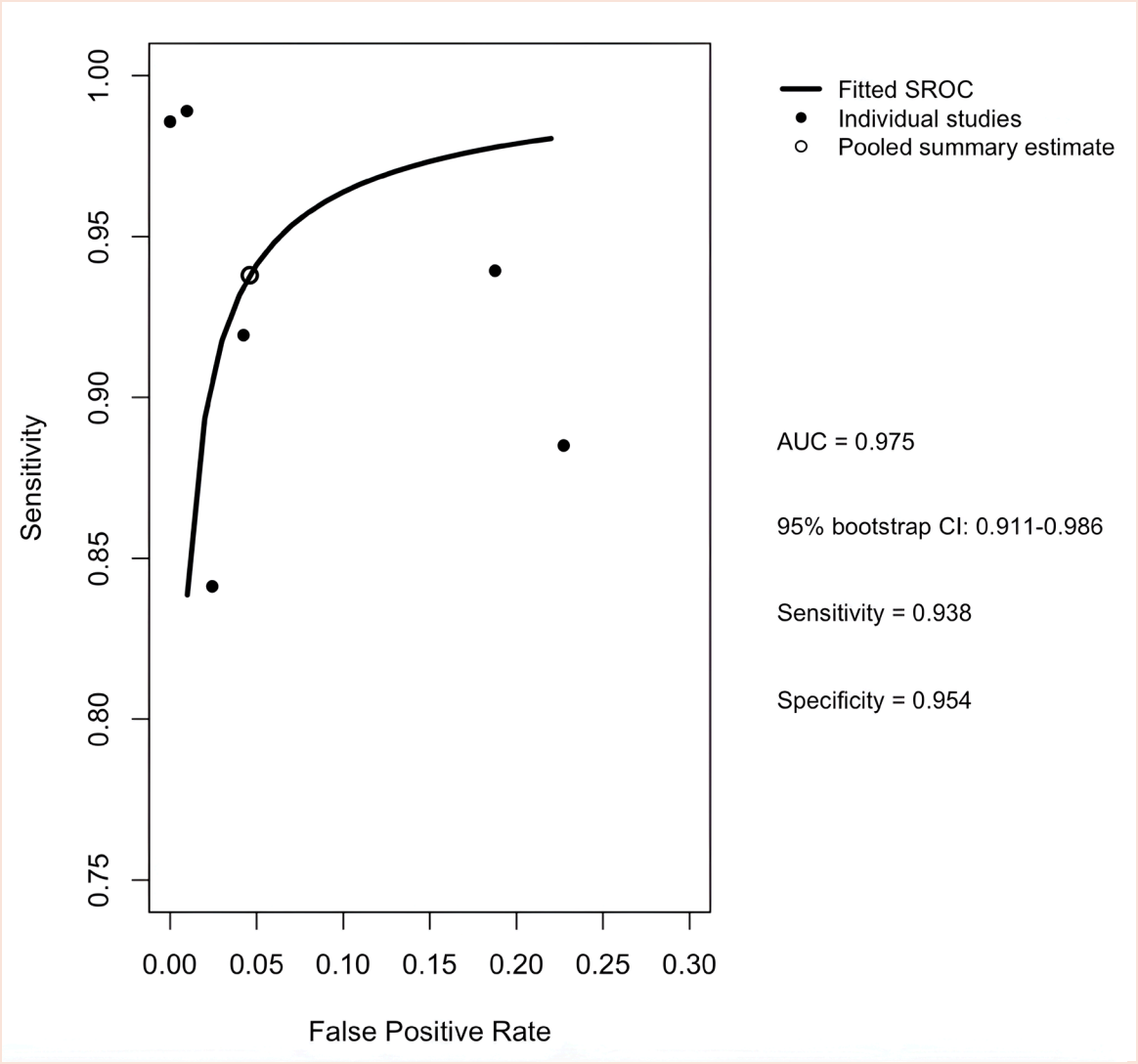
CI: confidence interval

Fig. 2. Forest plot of specificity.



CI: confidence interval

Fig. 3. Summary receiver operating characteristic curve for AI-based diagnosis of oral squamous cell carcinoma.



AI: artificial intelligence; AUC: area under the curve; CI: confidence interval; OSCC: Oral squamous cell carcinoma; SROC: summary receiver operating characteristic curve

The thick solid line represents the fitted SROC curve, the filled circles represent individual studies, and the open circle represents the pooled summary estimate. The AUC was 0.975 (95% bootstrap CI 0.911–0.986).

study variance was greater for logit false-positive rate (2.093) than for logit sensitivity (0.973), with a negative correlation between these parameters (r=-0.588). The differing variance components and negative correlation suggest heterogeneity in the relationship between sensitivity and false-positive rate, indicating that heterogeneity is primarily driven by variations in overall diagnostic accuracy across studies rather than standard threshold effects.

Risk of bias assessment

Risk of bias assessment using the QUADAS-AI framework is presented in Supplementary Table S3. The index test and reference standard domains were rated as low risk across all 9 studies. Patient selection was rated high risk in 2 studies—Marzouk et al. (2022) and Birur et al. (2022)—because of unclear case ascertainment methods, and unclear in 4 others. Among the AI-specific domains, data partitioning independence and training/test split integrity were the most frequent sources of concern, rated high risk in 2 studies and unclear in 5, reflecting limited reporting of dataset separation practices in the included literature. Model transparency was rated low risk in 4 studies and unclear in the remainder.

Publication bias

Potential publication bias was explored using a Deeks-type funnel plot asymmetry analysis (Supplementary Fig. S2). The primary analysis, using a continuity

correction of 0.5, showed no statistically significant funnel plot asymmetry (P=0.603). Sensitivity analyses using alternative continuity corrections of 0.1 and 1.0 yielded similarly non-significant results (P=0.780 and P=0.516, respectively), indicating that the findings were robust to the choice of continuity correction. However, given the small number of studies included in the meta-analysis (n=6), the analysis had limited statistical power, and publication bias cannot be excluded.

Performance of AI diagnostic models

The studies reviewed used a variety of algorithms whose accuracy varied with algorithm architecture, data preprocessing, and training strategies.

Nine studies were included in the systematic review, of which 6 provided eligible data for the quantitative meta-analysis. The meta-analysis comprised Kouketsu et al. (2024),[12] Vinayahalingam et al. (2024), Lee et al. (2024), Marzouk et al. (2022), Warin et al. (2021)[13] and Warin et al. (2022). These studies contributed paired diagnostic accuracy data from which sensitivity and specificity were estimated.

The remaining 3 studies were included in the qualitative synthesis but not in the meta-analysis because the classification was not histologically determined. Their findings are discussed separately and were not used to calculate the pooled diagnostic accuracy estimates or the SROC curve.

Across the included literature, reported diagnostic performance varied according to model architecture, preprocessing methods, dataset characteristics, and validation procedures. The following discussion distinguishes studies that contribute to the quantitative synthesis from those that provide additional qualitative evidence.

The observed between-study heterogeneity warrants consideration when interpreting these findings. The greater variance in logit false-positive rate compared with logit sensitivity suggests that false-positive rates varied more substantially across studies. The negative correlation between logit sensitivity and logit false-positive rate likely reflects differences in overall model accuracy, driven by study-specific characteristics such as AI model architecture, dataset composition, and validation procedures. These findings highlight the importance of standardised validation protocols and assessment of diagnostic performance across clinically relevant thresholds.

The included studies show that preprocessing and data augmentation were associated with improvements in diagnostic performance, although the statistical significance of these improvements was not reported. Various forms of augmentation, such as random oversampling or weight balancing, help address class imbalance and improve the efficiency of model training. Zhang et al. (2024) reported that integrating such preprocessing steps increased the model's accuracy from 95.11% to 98.34% and precision from 96.14% to 98.54%.[14] However, no P value or CI was recorded. Lee et al. (2024) introduced an innovative augmentation approach termed mosaic-based soft labelling, which achieved 94.4% accuracy, outperforming conventional over-sampling (91.1%), and weight balancing (92.8%) methods.[15] Enhancements such as normalisation and contrast adjustment help reduce inconsistencies caused by lighting and image quality, supporting the development of more generalisable models.[16] By introducing variations, these techniques improve algorithms by training them on a dataset more representative of real-world clinical circumstances. Although beneficial, these preprocessing techniques can be resource-intensive, requiring computational power and technical expertise, and may introduce data bias and limit scalability.[17]

Warin et al. (2022) conducted a comparative evaluation of several CNN models for OSCC classification, revealing that DenseNet-169 and ResNet-101 outperformed other CNNs and even oral and maxillofacial specialists in diagnostic accuracy.[18] However, because of their large architectures, these models require high-performance computing, limiting their suitability for mobile applications. In contrast, lightweight models such as SqueezeNet showed lower performance (AUC 0.71–0.88) but offered a more feasible solution for mobile deployment.

Zhang et al. (2024) explored gated recurrent units (GRUs), a type of recurrent neural network (RNN), which are less commonly used for image classification than CNNs. Traditional RNNs process sequential data by feeding the output of 1 time step as input to the next, creating a "loop".[19] However, they struggle with long-term dependencies because the gradient can vanish or explode as it propagates through many time steps. GRUs address this issue via gating mechanisms that selectively filter information, thereby improving training efficiency.[20,21] Zhang et al.'s proposed gated recurrent unit network/Northern Goshawk optimisation algorithm (GRU/NGO-LC), which incorporates Lévy flight and chaos theory, significantly outperformed CNN models such as ResNet-101 and R-CNN. It achieved accuracy, precision, and sensitivity of 98.34%, 98.54%, and 98.60%, respectively, compared with ResNet-101's 91.95%, 93.02%, and 86.71%.

The GRU/NGO-LC also surpassed the standard GRU and GRU/NGO (91.27% and 90.54% accuracy) and outperformed 5 other modern optimisation methods.[11] However, whether these differences are statistically significant cannot be determined, as neither CIs nor confusion matrix were provided.

The study suggests that the GRU/NGO-LC outperforms both the standard GRU method and other CNN models for OSCC classification. Despite its performance, the study did not assess the algorithm's computational efficiency or memory burden.

Although CNNs were the most common algorithms in these studies, some studies adopted hybrid models incorporating multiple architectures together with preprocessing and augmentation strategies. Hybrid models included in this review demonstrated higher diagnostic accuracy than conventional deep learning models, but were heterogeneous and difficult to interpret. Marzouk et al. (2022) introduced AIDTL-OCCM, a hybrid CNN incorporating contrast enhancement, DenseNet-169 feature extraction, and chimp optimisation algorithm. It achieved 90.08% accuracy, 88.6% recall, and 89.1% precision, outperforming 5 other highly optimised CNNs. The next best performing model, Inception-V4, had 85.64% accuracy, 85.7% recall, and 87.8% precision.[22] This suggests that AIDTL-OCCM has potential for the classification of OSCC in clinics. However, the study did not detail the model's processing speed or computational demands compared with other conventional models, limiting clinical applicability. Vinayahalingam et al. (2024) evaluated a hybrid combining Mask R-CNN and a Swin Transformer for multiclass lesion classification, including OSCC, leukoplakia, and oral lichen planus. This model leveraged spatial feature extraction from CNNs and transformer-based global context analysis, achieving 95.5% accuracy (CI 93.8–97.2) and 84.3% sensitivity (CI 80.4–88.2).[23] This hybrid architecture enhances pattern detection and improves the integration of information from different regions of an image. Although promising, it lacked comparison with other CNN/transformer-based models.

DISCUSSION

OSCC remains the most common and deadly malignancy of the oral cavity, with early detection playing a pivotal role in improving survival outcomes. Conventional diagnosis relies on clinical examination, histopathology, and imaging modalities such as CT, MRI, and PET/CT for staging; however, these approaches are constrained by subjectivity, cost, and limited accessibility in resource-constrained settings.

Recent advances in AI, particularly deep learning, have demonstrated growing potential to support OSCC diagnosis. This systematic review and meta-analysis demonstrates, as a proof of concept, that AI models trained on clinical images can achieve high diagnostic performance, with a pooled sensitivity of 0.94, specificity of 0.95, and AUC of 0.975. These findings suggest strong discriminatory performance across the included retrospective datasets. AI offers several theoretical advantages over traditional approaches, including objective pattern recognition, rapid image analysis, and the possibility of deployment in settings where specialist expertise or advanced imaging is unavailable. However, current evidence primarily reflects feasibility rather than readiness for routine clinical implementation.

AI versus healthcare professionals

Across the included studies, AI models demonstrated variable diagnostic performance relative to general practitioners and specialist clinicians. Some models achieved higher accuracy than clinician comparators under controlled study conditions, whereas others performed similarly or less well. These comparisons should be interpreted cautiously because of differences in study populations, model architectures, datasets, and validation methods. In Warin et al. (2022), large CNN architectures such as DenseNet-169 and ResNet-101 achieved accuracies of 98.98% (CI 98.13–99.51) and 93.27% (CI 91.51–94.75), res-pectively, compared with 89.59% (CI 87.29–91.25) for spe-cialists.[15] Although these results suggest that AI systems can achieve expert-level performance in retro-spective image-based evaluations, such large models require substantial computational resources, limiting their practicality outside tertiary care environments.

Smaller, lightweight models such as SqueezeNet and Swin-S demonstrated lower diagnostic accuracy—84.59% (CI 82.2–86.8) and 79.18% (CI 76.5–81.69%), respectively—but offer greater feasibility for mobile and point-of-care applications. SqueezeNet achieved an accuracy of 84.59%, marginally exceeding the 83.27% (CI 80.78–85.55)[18] reported for GPs, whereas Swin-S achieved a slightly lower accuracy. However, Birur et al. reported that MobileNet and VGG19 achieved higher sensitivities (82% and 87%) and accuracies (79% and 87%) than GPs, who demonstrated a sensitivity of 60% and an accuracy of 70%.[24] These findings suggest that diagnostic performance varies across lightweight architectures, and that computational efficiency should be evaluated alongside accuracy. Overall, these findings support the feasibility of AI as an assistive screening tool in primary care.

Potential clinical applications

AI holds promise as a decision-support tool that may reduce diagnostic error and assist clinicians, particularly in resource-limited settings.[22,23] Lightweight models such as MobileNet enable near real-time lesion assessment from smartphone images, while larger models may complement diagnostic workflows in specialist centres.[24] AI-based tools could also lower barriers by facilitating preliminary self-screening and prompting earlier clinical consultation. AI models with high diagnostic sensitivity may help

identify suspicious lesions that warrant further clinical assessment, reducing the likelihood of missed OSCC. Models with high specificity may help reduce false-positive assessments and unnecessary referrals or biopsies. The practical effects of these approaches require evaluation in prospective clinical studies.

Limitations

This review has several important limitations. Only 6 studies were eligible for meta-analysis, with 3 additional studies included qualitatively, limiting statistical power and generalisability. Substantial heterogeneity in datasets, preprocessing techniques, and model architectures hindered direct comparison across studies. Most models were CNN-based, introducing potential architectural bias, and many lacked external validation. Diagnostic overlap between early OSCC and oral potentially malignant disorders (OPMDs) further complicates model performance and remains a challenge for both AI systems and clinicians. Publication bias could not be excluded, as the small number of studies limited the power to detect funnel plot asymmetry.

Although the pooled AUC of 0.975 (95% bootstrap CI 0.911–0.986) indicates high discriminatory performance, these findings should be interpreted in the context of the predominantly retrospective and controlled study settings. Curated image datasets may not adequately represent the variability encountered in routine clinical practice, including differences in image quality, lighting conditions, lesion presentation, and disease prevalence. Furthermore, models evaluated using clearly distinguishable malignant and nonmalignant lesions may demonstrate inflated diagnostic performance compared with more challenging real-world presentations, particularly early OSCC and oral potentially malignant disorders. The lower bound of the bootstrap CI highlights uncertainty in the pooled AUC estimate but should not be interpreted as a prediction of real-world performance. Prospective external validation using representative clinical populations is therefore neces-sary to establish the generalisability and clinical utility of these models.

Future research directions

Future studies could stratify by oral cavity subsite (e.g. tongue versus buccal mucosa versus floor of mouth). Future studies could also benchmark AI systems against clinicians with clearly defined levels of training and experience. Such analyses may identify anatomical locations or clinical scenarios where AI provides the greatest incremental benefit.

Future studies should also focus on multiclass models capable of differentiating OSCC from benign lesions and diagnostically complex OPMDs. In Vinayahalingam's 2024 study, OSCC was classified with high accuracy using their hybrid deep learning model, whereas the detection of oral lichen planus and leukoplakia was only moderately effective.[23]

Further expansion of lesion segmentation would be particularly useful for hard-to-visualise oropharyngeal/nasopharyngeal regions to aid clinicians in surgical planning, biopsy targeting, or radiotherapy planning.

Other imaging modalities could also benefit from further study. AI is increasingly applied in advanced imaging such as CT, MRI, and histopathology. In CT and MRI, AI can support tumour segmentation, staging, and prediction of treatment response, aiding preoperative planning and personalised therapy. In histopathology, AI models facilitate automated classification, grading, and prognosis, providing reproducible and quantitative insights that assist pathologists.

Multimodal integration of clinical, radiographic, histological, and molecular data may improve staging, personalised treatment, and prognostication by enhancing diagnostic accuracy, reducing interobserver variability, and supporting comprehensive patient management. Transformer-based architectures are particularly suited for such complex data integration.

Finally, in real-world deployment, many high-performing models require substantial computational resources, depend on network availability, and may face language barriers. They should be tested in clinical environments, with future trials focusing on practical outcomes such as diagnostic speed, clinician adoption, and reduction in unnecessary biopsies.

Regulation, reliability, and outlook

Despite promising accuracy in controlled settings, widespread clinical adoption of AI remains constrained by limited external validation, dataset bias, and regulatory challenges. These findings should be interpreted as proof of concept rather than evidence of clinical readiness. Additionally, issues of transparency, accountability, data privacy, and medicolegal responsibility must be addressed. Explainable AI techniques may improve clinician trust by providing interpretable outputs.[28] Ultimately, AI is unlikely to replace clinicians in the near future. Instead, it can be positioned as an adjunct that augments clinical judgment. Although AI excels at processing large datasets and identifying subtle patterns, it lacks the contextual reasoning, empathy, and ethical judgment intrinsic to clinical care. At this point, its optimal role may lie in supporting—not supplanting—the human elements of medicine. However, it is prudent to note that current performance estimates reflect early-stage implementations and are likely to be surpassed as model architectures mature, datasets diversify, and validation extends into real-world clinical environments.

CONCLUSION

As a proof of concept, AI models demonstrate strong potential for OSCC detection from clinical images and can achieve diagnostic performance comparable to clinicians in retrospective settings. AI has the potential to improve early detection and streamline diagnostics. However, translation into routine practice requires rigorous prospective validation, explainability, and assessment within real-world clinical workflows. AI can be a complementary decision-support tool that enhances, rather than replaces, clinical expertise in OSCC diagnosis.

Supplementary materials

Table S1. PICOS search strategy.

Table S2. Summary of characteristics of included studies in the systematic review.

Table S3. Risk of bias and applicability assessment of included studies using the QUADAS-AI framework.

Table S4. Summary of pooled models included in meta-analysis.

Table S5. Kouketsu et al. 2024—2×2 contingency table.

Table S6. Vinayahalingam et al. 2024—2×2 contingency table.

Table S7. Lee et al. 2024—2×2 contingency table.

Table S8. Marzouk et al. 2022—2×2 contingency table.

Table S9. Warin et al. 2021—2×2 contingency table.

Table S10. Warin et al. 2022—2×2 contingency table.

Fig. S1. PRISMA flow diagram.

Fig. S2. Deeks' funnel plot.

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Ethics statement

Not applicable; this was a systematic review with no direct patient involvement and no identifying information.

Declaration

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Case studies and expert opinion on the management of complement-mediated and secondary thrombotic microangiopathy in Singapore

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ABSTRACT

Complement-mediated thrombotic microangiopathy (C-TMA), previously referred to as atypical haemolytic uraemic syndrome, is a rare cause of thrombotic microangiopathy (TMA). Secondary TMAs are heterogeneous conditions associated with established triggers (e.g. drugs, infection, pregnancy), some of which may be driven by complement activation. Differentiating between C-TMA and secondary TMA can be difficult, as there may be considerable overlap between the conditions. The authors describe 3 cases of TMA potentially involving complement activation as examples of a multidisciplinary approach to diagnosis and management in Singapore. Complement component 5 (C5) inhibition is central to the treatment of C-TMA, but lack of access to therapy remains a major challenge in the region, as illustrated by Case 1 (probable C-TMA). Case 2 (gemcitabine-associated TMA) and Case 3 (lupus nephritis-associated TMA) explore the emerging role of C5 inhibitors in secondary TMAs. Short-duration C5 inhibitor treatment is feasible for some patients without pathogenic gene variants but should be undertaken only with appropriate monitoring.

Keywords: atypical haemolytic uraemic syndrome, complement-mediated thrombotic microangiopathy, complement inhibition, C5 inhibitor, microangiopathic haemolytic anaemia, secondary thrombotic microangiopathy

INTRODUCTION

Complement-mediated thrombotic microangiopathy (C-TMA)—also known as atypical haemolytic uraemic syndrome[1]—refers to the primary form of the syndrome, which arises from genetic abnormalities that result in uncontrolled complement pathway activation.[2,3] C-TMA is a rare cause of TMA and has a varied clinical presentation. The diagnosis is one of exclusion, made after ruling out other causes of TMA, particularly immune thrombotic thrombocytopenic purpura (iTTP) and Shiga toxin-producing *Escherichia coli* haemolytic-uraemic syndrome (STEC-HUS).[2] Secondary TMAs are heterogeneous conditions associated with established and clear triggers (e.g. drugs, infection, pregnancy).[1] Complement activation has been implicated in some cases of secondary TMA, with a multi-hit process resulting in TMA.[4,5]

Available guidance regards early recognition and prompt treatment of primary C-TMA with complement component 5 (C5) inhibitors as being vital to limiting adverse outcomes, such as end-stage kidney disease (ESKD).[4,6-10] C5 inhibitor therapy may also benefit cases of secondary TMA that have not responded to conventional therapy and may have an element of complement activation.[4,5]

Although international guidelines provide general recommendations for the diagnosis and management of C-TMA,[9-12] no Singapore-specific guidance exists. The challenges in Singapore include the rarity of cases, limited physician experience with the condition, restricted availability of specialised investigations, and the high cost of C5 inhibitors. These factors complicate the management of C-TMA and complement-associated secondary TMA.

This article uses illustrative case studies from Singapore to explore the recognition, diagnosis, and management of patients with probable C-TMA (Case 1), gemcitabine-associated TMA (Case 2), and lupus nephritis (LN)-associated TMA (Case 3). The aim is to equip clinicians with practical insights to support early diagnosis, guide appropriate therapy, and optimise outcomes despite practice limitations in Singapore.

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PATIENT CASE STUDIES

Case 1: Probable C-TMA

A 53-year-old woman presented with generalised tonic-clonic seizures and oliguric acute kidney injury (AKI), following an acute respiratory tract infection and fever. On admission, she had a normal coagulation screen but elevated lactate dehydrogenase (LDH), thrombocytopenia, schistocytes, and low C3 (Table 1). As her ADAMTS13 activity of 23% (i.e. not <10%) was inconsistent with iTTP,[13] a diagnosis of TMA precipitated by sepsis, or C-TMA, was considered instead. Kidney biopsy showed chronic TMA. A C-TMA genetic panel was negative for pathogenic variants.

Table 1. Clinical features, investigations, treatments, and outcomes of cases of C-TMA and secondary TMA with presumed complement activation.[a]

	Case 1 (probable C-TMA)[a]	Case 2 (gemcitabine-associated TMA)[a]	Case 3 (LN-associated secondary TMA)[a] (paediatric)[b]
Age, years	53	54	16
Sex	Female	Female	Female
Medical history	Menorrhagia due to fibroids; no family history of kidney disease	Pancreatic adenocarcinoma treated with surgery and chemotherapy (capecitabine and gemcitabine); no family history of kidney disease	No significant medical history; no family history of kidney disease or SLE
Initial symptoms/presentation	Generalised tonic-clonic seizures and acute kidney failure after acute respiratory tract infection with fever and headache	TMA after receiving 6 cycles of capecitabine and gemcitabine (cumulative dose 12,400 mg/m^2), followed by mixed nephritic–nephrotic syndrome and AKI 2 months later	History of pallor for 20 days and generalised oedema for 10 days
Initial laboratory results			
Haematology	At presentation: Hb 11.8 g/dL, WBC 25.8 × 10^9/L, platelets 57 × 10^9/L, schistocytes 1+	At presentation: Hb 7.6 g/dL, WBC 13.8 × 10^9/L, platelets 264 × 10^9/L, schistocytes 5–10 per hpf After 1 month of steroids: Hb 8.3 g/dL, WBC 11.1 × 10^9/L, platelets 83 × 10^9/L, schistocytes 10–15 per hpf	Initial presentation: Hb 7.1 g/dL, WBC 4.2 × 10^9/L, platelets 128 × 10^9/L After 1 month of treatment for LN: Hb 8.2 g/dL, WBC 5.64 × 10^9/L, platelets 10 × 10^9/L, reticulocytes 1.02%; blood film suggestive of MAHA (microcytic hypochromic RBC, schistocytes 2+, crenated cells 2+)
Renal	Baseline Cr: 38 μmol/L Cr at presentation: 300 μmol/L Peak Cr: 578 μmol/L	Baseline Cr: 77 μmol/L Cr at presentation: 107 μmol/L Peak Cr: 233 μmol/L Urinalysis: RBC 76, WBC 30, granular casts 1/μL, hyaline casts 7/μL, waxy casts 6/μL Urine protein/creatinine ratio: 658 mg/mmol	Initial presentation: Cr 112 μmol/L, eGFR 52 mL/min/1.73 m^2 (Schwartz), urine protein 2+, and RBC 2+ After 1 month of treatment for LN: Cr 486 μmol/L, urine RBC >1000/hpf, urine protein: Cr ratio 1603 mg/mmol
ADAMTS13 activity	23%	86%	31%
Immunology	*ADAMTS13* Ab negative; ANA, ANCA IIF, dsDNA, anti-MPO, anti-PR3, and anti-GBM negative; C3 low (0.57 [normal 0.9–1.8 g/L]); C4 normal; anti-factor H not tested, as PLEX and rituximab had already been started (which can interfere with the result)	ANA, ANCA, and anti-dsDNA negative; direct agglutination test negative; anti-factor H antibodies not tested because (1) there was a clear cause for TMA (gemcitabine); (2) heterozygous CFHR3-CFHR1 deletion (see below) is a common CNV in the general population; (3) cost limitations	Initial presentation: ANA positive, anti-dsDNA >800 U/mL,[c] C3 0.17 g/L, C4 6 mg/dL. After 1 month of treatment for LN: ANA 1:320 (by immunofluorescence, normal <1:80),[c] anti-dsDNA 220 IU/mL,[c] C3 0.4 g/L, C4 0.15 g/L, lupus anticoagulant negative, anticardiolipin IgM and IgG negative, anti-β2-glycoprotein I IgM and IgG negative, ENA negative; direct Coombs test positive; anti-factor H antibodies not tested

Table 1. Clinical features, investigations, treatments, and outcomes of cases of C-TMA and secondary TMA with presumed complement activation.[a] (Cont'd)

	Case 1 (probable C-TMA)[a]	Case 2 (gemcitabine-associated TMA)[a]	Case 3 (LN-associated secondary TMA)[a] (paediatric)[b]
Other	At presentation: LDH 5428 U/L, bilirubin and AST normal, procalcitonin 12 µg/L	At AKI diagnosis: LDH 1808 U/L; haptoglobin <0.3 g/L; PT, APTT, and fibrinogen levels normal	Initial presentation: albumin 18 g/L After 1 month of treatment for LN: haptoglobin <0.08 g/L, LDH 497 U/L, albumin 23 g/L, ESR 41 mm/hr, CRP 15.5 mg/L
Kidney biopsy	Kidney biopsy was performed 1 month after initial presentation; focal segmental and global glomerulosclerosis with features suggesting chronic TMA.	Kidney biopsy not performed	Kidney biopsy not performed
Other investigations	Lumbar puncture: unremarkable PET-CT: bilateral pleural effusions, no occult malignancy or sepsis Kidney U/S: unremarkable	PET-CT: no recurrence of pancreatic cancer; CA19-9 and CEA normal.	Initial presentation: Kidney U/S: mild swelling; no hydronephrosis or focal cortical lesions; echocardiography: bilateral pleural effusions and mild pericardial effusion
C-TMA genetic testing	Mayo Clinic C-TMA NGS panel negative (*ADAMTS13, C3, C5, CD46, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI, DGKE, MMACHC, THBD*)	Invitae C-TMA NGS panel NGS panel negative (*ADAMTS13, C3, CD46, CD55, CD59, CFB, CFH, CFI, DGKE, INF2, MMACHC, PLG, THBD)* Multiplex probe identified a non-pathogenic *CFHR3-CFHR1* gene variant (University of Iowa)	Not performed
Time from initial presentation to final diagnosis	<1 month	2 months	1 month
Final diagnosis	Probable C-TMA	Gemcitabine-associated TMA (with presumed complement activation)	LN with RPGN, nephrotic syndrome, and LN-associated (secondary) TMA (with presumed complement activation)
Differential diagnoses considered	Disseminated meningococcal infection with septic acute tubular necrosis (ruled out by negative blood, urine, and CSF cultures); iTTP (ruled out as ADAMTS13 activity was not <10%); SLE with multi-organ involvement (ruled out because of negative autoimmune screen and kidney biopsy not suggestive of LN)	Malignancy-related TMA (ruled out due to no evidence of malignancy recurrence); iTTP (ruled out as ADAMTS13 activity was not <10%); C-TMA (less likely because another diagnosis was made, there was no family history of C-TMA, and no pathogenic genetic variants were found)	iTTP (ruled out because ADAMTS13 activity was not <10%); catastrophic antiphospholipid syndrome (ruled out because antiphospholipid antibody negative)
Treatment	Dialysis (1 month); PLEX, rituximab, steroids (11 months); relapsed after 11 months; eculizumab started after 13 months (given for 9 months); meningococcal vaccination 2 weeks before start of eculizumab; oral penicillin V tablets for antibiotic prophylaxis throughout the course of eculizumab	Discontinuation of gemcitabine, plus corticosteroids for 1 month (no response); eculizumab (900 mg weekly for 4 weeks, then 1200 mg every 2 weeks) for a total of 6 doses; meningococcal ACYW135, pneumococcal, and *Haemophilus influenzae* vaccinations 9 months earlier (before distal pancreatectomy and splenectomy); meningococcal serogroup B vaccination at eculizumab initiation; oral penicillin V tablets for antibiotic prophylaxis throughout the treatment duration	For LN and RPGN: intravenous pulse corticosteroids (total of 7 cycles), mycophenolate mofetil, cyclophosphamide, hydroxychloroquine, furosemide, antihypertensives For TMA: PLEX (2 cycles of 5 sessions) with FFP as replacement fluid, eculizumab (900/1200 mg) for a total of 7 doses, FFP infusion (without PLEX) before eculizumab dose 4. Antibiotic prophylaxis (e.g. penicillin V) throughout the duration of C5 inhibition, as the patient was unlikely to respond to meningococcal vaccination due to concomitant immunosuppression for LN

Table 1. Clinical features, investigations, treatments, and outcomes of cases of C-TMA and secondary TMA with presumed complement activation.[a] (Cont'd)

	Case 1 (probable C-TMA)[a]	Case 2 (gemcitabine-associated TMA)[a]	Case 3 (LN-associated secondary TMA)[a] (paediatric)[b]
Outcome	Progression to ESKD; eculizumab started after funding was secured; platelets and Hb normalised on eculizumab At 3-year follow-up after starting eculizumab, no recurrence of TMA	Within 4 weeks of starting eculizumab, TMA resolved, and there was partial recovery from AKI At 10-month follow-up, still in cancer remission; no recurrence of TMA	Slow response of LN and TMA Discharged home after 4th eculizumab dose Currently, SLE in remission, RPGN resolved, MAHA resolved
Subsequent follow-up planned	Every 6 months (full blood count, Cr, LDH, C3, C4)	Every 3 months (blood and urine evaluations)	Every 2 months
Duration of follow-up (since initial presentation)	5 years	10 months	8 months

Ab: antibody; ADAMTS13: A Disintegrin and Metalloproteinase with Thrombospondin type 1 motif, member 13; AKI: acute kidney injury; ANA: antinuclear antibodies; ANCA: antineutrophil cytoplasmic antibodies; anti-GBM: anti-glomerular basement membrane; APTT: activated partial thromboplastin time; AST: aspartate transaminase; CA19-9: cancer antigen 19-9; CEA: carcinoembryonic antigen; CNV: copy number variation; Cr: creatinine; CRP: C-reactive protein; CSF: cerebrospinal fluid; C-TMA: complement-mediated TMA; dsDNA: double-stranded DNA; eGFR: estimated glomerular filtration rate; ENA: extractable nuclear antigens; ESKD: end-stage kidney disease; ESR: erythrocyte sedimentation rate; FFP: fresh frozen plasma; Hb: haemoglobin; hpf: high-power field; IgG: immunoglobulin G; IgM: immunoglobulin M; IIF: indirect immunofluorescence; iTTP: immune thrombotic thrombocytopenic purpura; LDH: lactate dehydrogenase; LN: lupus nephritis; MAHA: microangiopathic haemolytic anaemia; MPO: myeloperoxidase; NGS: next-generation sequencing; PET-CT: positron emission tomography-computed tomography; PLEX: plasma exchange; PR3: proteinase 3; PT: prothrombin time; RBC: red blood cells; RPGN: rapidly progressive glomerulonephritis; SLE: systemic lupus erythematosus; TMA: thrombotic microangiopathy; U/S: ultrasound; WBC: total white blood cell count

[a] The cases presented were managed at different centres in Singapore.

[b] Considerations unique to paediatric cases are included in Fig. 1.

[c] Different assays (and therefore units) were used at centres overseas and in Singapore.

Because of funding limitations for C5 inhibitors, initial treatment was plasma exchange (PLEX), pulsed methylprednisolone, rituximab, and dialysis. Anti-factor H antibodies were not tested, as PLEX and rituximab had been started (which can interfere with the result). Her initial response to PLEX was good, and she was weaned off dialysis 1 month later. Over the next 8 months, PLEX was tapered to once a week. Two months later, she had a relapse of TMA and AKI requiring reinitiation of dialysis. Despite re-intensification of PLEX, kidney function could not be salvaged.

A cost analysis indicated that 6 months of eculizumab, which would provide a 2-year relapse rate of <5%,[14] would cost less than SGD200,000 compared with annual, lifelong costs of SGD210,000–355,000 for PLEX with fresh frozen plasma (FFP) and haemodialysis for patients who developed ESKD.

Funding for eculizumab was secured, and the patient received treatment for a total of 9 months. Her platelet count normalised within a month, and her haemoglobin stabilised. She had no further recurrence of C-TMA at 3-year follow-up after starting eculizumab.

The final diagnosis was probable C-TMA despite a negative genetic panel. The initial episode was triggered by sepsis, but no clear trigger was identified at the time of relapse. The unprovoked relapse and low C3 were suggestive of underlying complement dysregulation.

Case 2: Gemcitabine-associated TMA

A 54-year-old woman presented with TMA 14 days after receiving 6 cycles of adjuvant chemotherapy (capecitabine and gemcitabine) for pancreatic adenocarcinoma. Laboratory results showed microangiopathic haemolytic anaemia (MAHA), mild thrombocytopenia, and AKI (Table 1). Chemotherapy had been administered on day 15 of cycle 6, as TMA onset was not yet recognised. The cumulative dose of gemcitabine was 12,400 mg/m^2, with TMA onset 162 days after first exposure. Following haematology consultation, gemcitabine was discontinued and the patient received a 4-week trial of corticosteroids, without significant improvement.

Two months later, she presented with mixed nephritic–nephrotic syndrome and worsening MAHA and thrombocytopenia. ADAMTS13 activity was 86%. There was no evidence of autoimmune disease or recurrence of malignancy. Genetic testing indicated a non-pathogenic heterozygous deletion of *CFHR3-CFHR1* (multiplex probe, University of Iowa). As there was a clear drug cause for TMA and this *CFHR3-CFHR1* deletion is a common copy number variation seen in the general population,[15] anti-factor H antibodies were not tested.

Gemcitabine-associated TMA was clinically suspected. As short-duration eculizumab can be appropriate in such patients,[16-20] she was treated with 6 doses of eculizumab. TMA resolved, and there was

partial recovery from AKI within 4 weeks (Supplementary Fig. S1), suggesting that complement activation was a contributing mechanism to the TMA. A later rise in creatinine, attributed to overdiuresis, gradually improved. Ten months later, she remained in cancer remission with no recurrence of TMA.

Case 3: LN-associated (secondary) TMA

A 16-year-old girl presented at a centre outside Singapore with pallor and generalised oedema, anaemia, thrombocytopenia, and AKI (Table 1). Following investigation, she was diagnosed with systemic lupus erythematosus (SLE) with LN, and received methylprednisolone, mycophenolate mofetil, and cyclophosphamide.

The patient was transferred to Singapore 1 month after initial presentation. Her creatinine level had increased further, and she had progressive thrombocytopenia associated with elevated LDH and MAHA on blood film (Table 1). Her ADAMTS13 activity level was 31%. The diagnosis was LN with rapidly progressive glomerulonephritis (RPGN) and LN-associated TMA.

Treatment for proliferative LN and RPGN continued. PLEX was started for LN-associated TMA but produced no early improvement, and the patient continued to have high transfusion requirements. Based on the literature[21-23] and local experience, the prognosis was considered poor, warranting more aggressive therapy. Given that complement is implicated in the pathogenesis of LN, and eculizumab can be beneficial in some cases of LN-associated TMA,[24-26] eculizumab was initiated.

A gradual response was observed for both LN and TMA (Supplementary Fig. S1). In total, she received 7 cycles of pulse intravenous methylprednisolone, 10 sessions of PLEX with FFP as replacement fluid, 7 doses of eculizumab, and an infusion of FFP (without PLEX) before the fourth eculizumab dose. One month after starting eculizumab, she no longer required transfusions and her condition had improved enough for her to be discharged home, suggesting that complement activation was a contributing mechanism to the TMA. Five months later, SLE was in remission, and RPGN and MAHA had resolved.

DISCUSSION

Prompt management of C-TMA and secondary TMA with presumed complement activation is important to prevent complications.[7,10,11,27] In Singapore, where such cases are rare, physicians need to be aware of the different causes of TMA and their underlying triggers, as early diagnosis and treatment are essential to prevent kidney function deterioration.

Given the heterogeneous clinical manifestations of C-TMA, the possible presence of associated conditions, and the occurrence of complement activation in some cases of secondary TMA, diagnosis and management require a multidisciplinary approach.[6] Not all tests/assays relevant to C-TMA are available in Singapore. ADAMTS13 activity testing (to rule out iTTP) is performed centrally at a reference laboratory in Singapore using fluorescence resonance energy transfer–VWF73 and enzyme-linked immunosorbent assay methodologies.[28] STEC-HUS can be ruled out based on clinical and microbiological findings. However, functional testing of complement activities and screening of pathological complement gene variants are not available in Singapore. Where genetic testing was deemed necessary in the example cases, samples were sent to laboratories in the US (Mayo Clinic in Case 1, Invitae and University of Iowa in Case 2). Heterogeneity exists between centres because of the rarity of cases and absence of a standardised pathway. The time required to obtain genetic test results, or the absence of pathogenic gene variants, should not preclude making a clinical diagnosis of C-TMA and prompt treatment initiation.

C5 inhibitors are the cornerstone of C-TMA treatment.[6-8,29,30] Eculizumab and ravulizumab are both approved for use in Singapore.[31,32] Early initiation of C5 inhibitor treatment can help prevent progression to ESKD.[7,27] In addition, without specific treatment of C-TMA, the risk of TMA recurrence is high (Case 1).[4] As C5 blockade increases the risk of infections, patients should receive meningococcal vaccination before treatment starts and prophylactic antibiotics during C5 inhibitor treatment.[4,29]

Since April 2026, eculizumab has been included in the Medication Assistance Fund in Singapore, allowing MediSave, the national medical savings scheme, to be used for payment.[31] This further reduces patients' out-of-pocket payments. Case 1 highlights that, in appropriate patients, eculizumab is cost-saving in the long run compared with a lifetime of dialysis and PLEX.

Case 1 also illustrates the clinical consequences of a funding-related treatment delay. Treatment duration for C5 inhibitors should be considered on a case-by-case basis and guided by genetic testing results if available. Although long-term eculizumab may be required in patients with pathogenic variations, it can be discontinued safely after a short duration of treatment in patients with C-TMA without pathogenic variants (Case 1), although with certain caveats.[14,33] A study assessing eculizumab discontinuation after achieving remission reported an overall relapse rate of 23% (13/55 patients), which was highest (50%) in patients carrying rare complement gene variants and lowest (4%) in those without a variant.[14] Investigators implemented structured monitoring after treatment cessation, and eculizumab was resumed within 7 days of relapse in all but 1 case. If eculizumab discontinua-

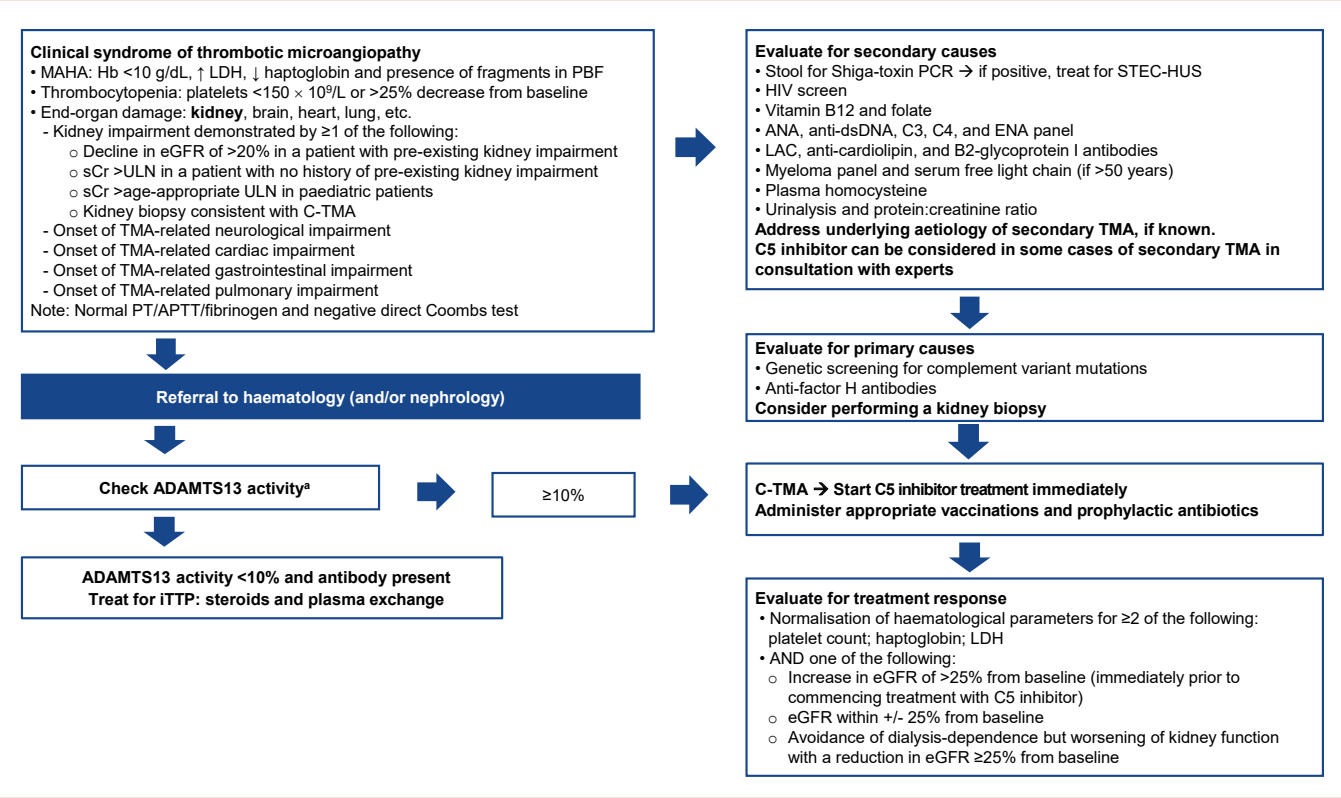
tion is considered in a routine practice setting, the patient should be monitored closely, and early restart of treatment must be guaranteed in the event of relapse. Data from France and the US indicate that prompt initiation of eculizumab and a genetics-based discontinuation strategy can reduce overall healthcare costs.[14,34]

PLEX may be used in patients with TMA until iTTP has been ruled out, in patients with factor H antibodies, or when C5 inhibitors are not available.[6,9] However, PLEX is not a preferred long-term solution and is associated with eventual renal deterioration, mortality, and other transfusion-related complications.[4] Case 1 illustrates the limitations of PLEX for achieving a durable response, and the importance of prompt C5 inhibitor therapy for salvaging kidney function.

The primary therapeutic strategy for drug-induced TMA is drug cessation.[9,12] The pathophysiology of gemcitabine-associated TMA appears to relate in part to complement activation.[20,35] Eculizumab may be beneficial in some patients.[18-20] It can be considered particularly for severe cases or cases that do not resolve after drug cessation and supportive measures (Case 2).[10,17,18,29] Short-duration eculizumab may be safe and feasible in such patients after removal of the culprit drug.[14,16,20]

Autoimmune diseases, such as SLE, can trigger TMA or occur concurrently.[21,22,25,26] Complement overactivation by both classical and alternative pathways is often found in patients with LN.[21,23] Given the increased incidence and severity of SLE in Asian populations,[36-38] physicians in Singapore should be aware of the possibility of SLE-associated TMA. The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 LN guideline recommends managing LN-associated TMA according to its underlying aetiology and lists eculizumab as a treatment to consider once iTTP and other causes have been excluded.[39] Eculizumab can provide a favourable response in such patients, including Asian patients.[24-26] Case 3 illustrates that, in appropriate patients, short-duration eculizumab induction therapy can improve thrombocytopenia and kidney function.

Fig. 1. Workflow for suspected C-TMA.



ADAMTS13: A Disintegrin and Metalloproteinase with Thrombospondin type 1 motif, member 13; ANA: antinuclear antibodies; APTT: activated partial thromboplastin time; C3: complement component 3; C4: complement component 4; C5: complement component 5; C-TMA: complement-mediated TMA; dsDNA: double-stranded DNA; eGFR: estimated glomerular filtration rate; ENA: extractable nuclear antigens; Hb: haemoglobin; HIV: human immunodeficiency virus; iTTP: immune thrombotic thrombocytopenic purpura; LAC: lupus anticoagulant; LDH: lactate dehydrogenase; MAHA: microangiopathic haemolytic anaemia; PBF: peripheral blood film; PCR: polymerase chain reaction; PT: prothrombin time; sCr: serum creatinine; STEC-HUS: Shiga toxin-producing *Escherichia coli* haemolytic-uraemic syndrome; TMA: thrombotic microangiopathy; ULN: upper limit of normal

[a] Paediatric cases: iTTP is very rare in children. Treatment for C-TMA can start before the results of tests to rule out iTTP become available.[40]
Note: The workflow is based on expert opinion and has been adapted from existing consensus guidance[10,40] for applicability in Singapore.

Guidelines on the management of patients with C-TMA, including those with secondary TMA associated with complement activation, are available in several Asian countries, including Taiwan, Korea, and Japan,[4,9,12] as well as from international organisations.[11] The authors' recommended approach for healthcare providers in Singapore involves recognising the signs and symptoms of C-TMA, identifying secondary TMA involving complement activation, and ensuring a timely diagnosis and prompt treatment initiation (Fig. 1). The proposed workflow is based on expert opinion and adapts available consensus guidance[10,40] for applicability in Singapore.

Uncontrolled case observations cannot establish efficacy or causation and are subject to selection and reporting bias. In Cases 1 and 2, the temporal coincidence of eculizumab with recovery cannot exclude a role for concurrent immunosuppression, removal of the offending drug, or the natural history of a resolving trigger. C5 inhibitor treatment was associated with haematological recovery, but its independent contribution to renal outcomes cannot be determined from uncontrolled observations.

CONCLUSION

Physicians need to be aware of C-TMA and secondary TMA associated with complement activation as potential causes of TMA. Early recognition and treatment of TMA are essential to prevent kidney function deterioration. The authors propose a multidisciplinary diagnostic approach to guide healthcare providers in Singapore, based on expert opinion and adapted from international guidance for applicability in Singapore. C5 inhibition is central to the treatment of C-TMA, but lack of access to therapy remains a major problem in this region. There is an emerging role for C5 inhibitors in secondary TMAs postulated to be driven by complement activation. Short-duration treatment is feasible in some patients without pathogenic gene variants but should be undertaken only with appropriate monitoring.

Ethics statement

The patients have provided their informed consents for the use of their de-identified data as case examples for the purpose of this publication. These case vignettes are used to illustrate specific scenarios with regard to the management of C-TMA followed by accompanying commentary from the authors' perspectives.

Declaration

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Lessons learned from real-world implementation of entrustable professional activities in an internal medicine residency programme

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ABSTRACT

The competency-based medical education framework has driven the adoption of entrustable professional activities (EPAs) for workplace-based assessment, yet real-world implementation experience from Southeast Asian settings remains scarce. In this commentary, the authors describe the transition to an EPA-based assessment model in an internal medicine residency programme in Singapore, drawing on perspectives from the programme director, core faculty members, programme coordinator, and graduates who participated in a roundtable discussion. Six key lessons emerged. First, explicit and repeated dialogue about trust is needed to secure buy-in from learners and assessors. Second, EPA tasks and standards must be clearly linked to core professional competencies while balancing assessment burden through simplified, distributed workplace-based assessments. Third, informal feedback from supervisors, though often undocumented, carries valuable performance information that should be systematically captured. Fourth, overall entrustment decisions require holistic synthesis of quantitative and qualitative data rather than simple score aggregation. Fifth, mapping entrustment gaps back to underlying competency domains enables targeted remediation. Sixth, there continues to be a need to address the key limitations of current EPA models, which include inter-rater variability and misalignment with fixed-length residency training structures. These practical insights offer guidance for programmes navigating similar transitions and highlight the need for further qualitative research to refine EPA implementation strategies in comparable training contexts.

Keywords: entrustable professional activities, internal medicine, medical education, postgraduate medical training, residency

INTRODUCTION

In the early 2000s, the competency-based medical education (CBME) framework became the gold standard for clinical training and assessment of physicians in postgraduate subspecialty programmes. These physicians were regularly assessed on Accreditation Council for Graduate Medical Education (ACGME) core competencies (patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and systems-based practice) to determine their eligibility for training progression. Subsequently, workplace-based assessments (WBAs) of entrustable professional activities (EPAs)[1,2] became popularised, where desirable core competencies are mapped to practical work descriptors, such that entrustment decisions can be made by preceptors based on the assessed level of supervision required by the trainees to carry out professional tasks.[1] While the application of EPAs has been described extensively in Western healthcare systems from which it was first developed,[3,4] there is a relative paucity of literature exploring its real-world implementation in Asian contexts,[5] where there could be unique sociocultural and practice-specific nuances and challenges.

In this article, the authors, comprising the programme director (PD), 2 core faculty members (CFMs), a residency programme coordinator, and 2 graduates of an internal medicine (IM) residency programme in Singapore, came together for a roundtable discussion of their experiences on the ground holding different roles within the EPA training system, and distilled key lessons learned and challenges in real-world EPA implementation.

In 2010, Singapore first launched its ACGME-accredited residency programmes for postgraduate specialist training.[6] By 2023, residency programmes in Singapore started to transition to a revised training model designed to translate broad competencies into EPAs.[2,7] Likewise, in the National University Health System (NUHS), the residency programmes gradually

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transitioned to an EPA-based assessment model between 2023 and 2025.

The NUHS IM residency programme is a 3-year postgraduate specialty training programme that hosts, on average, 100–125 junior residents across training sites within the cluster (National University Hospital, Ng Teng Fong General Hospital, and Alexandra Hospital). The programme is supported by 29 CFMs who provide longitudinal supervision, mentorship, and performance review to their assigned resident mentees. WBAs are regularly conducted, including the mini-clinical evaluation exercise, chart-stimulated recall, direct observation of procedural skills, multi-source feedback, monthly end-of-rotation evaluations, and ambulatory care assessments. Unlike older WBAs that involved evaluation of generic competency domains, the current EPA framework rates trainees' performance in relation to practical units of work under 4 core IM EPAs (inpatient care, ambulatory care, acutely ill patient, and bedside procedures). The level of entrustment for each assessment item is accorded based on observed clinical performance and entrustment-based discussion, with higher entrustment levels corresponding to a reduced need for supervision.

Every 6 months, residents will consolidate their portfolio comprising an aggregate of WBAs and extra-clinical achievements before meeting their assigned CFM for a joint review and discussion. The number of WBAs required in relation to the respective EPAs for each resident is outlined in Table 1. Where additional context is required, CFMs may seek qualitative feedback from supervising physicians. Thereafter, the CFM proposes an overall entrustment level for their assigned resident at a central clinical competency committee (CCC) meeting. CCC faculty members will deliberate on the final entrustment levels for the 4 core IM EPAs after rounds of robust discussion grounded in the data and feedback provided within the WBAs, in alignment with the best practices advocated for programmatic assessments in CBME.[8] Advancement to subsequent phases of training is contingent on the attainment of pre-defined minimum entrustment thresholds appropriate for the level of training (Fig. 1).

Lessons learned from real-world EPA implementation

Communicate a shared understanding of trust explicitly with stakeholders (learners and assessors)

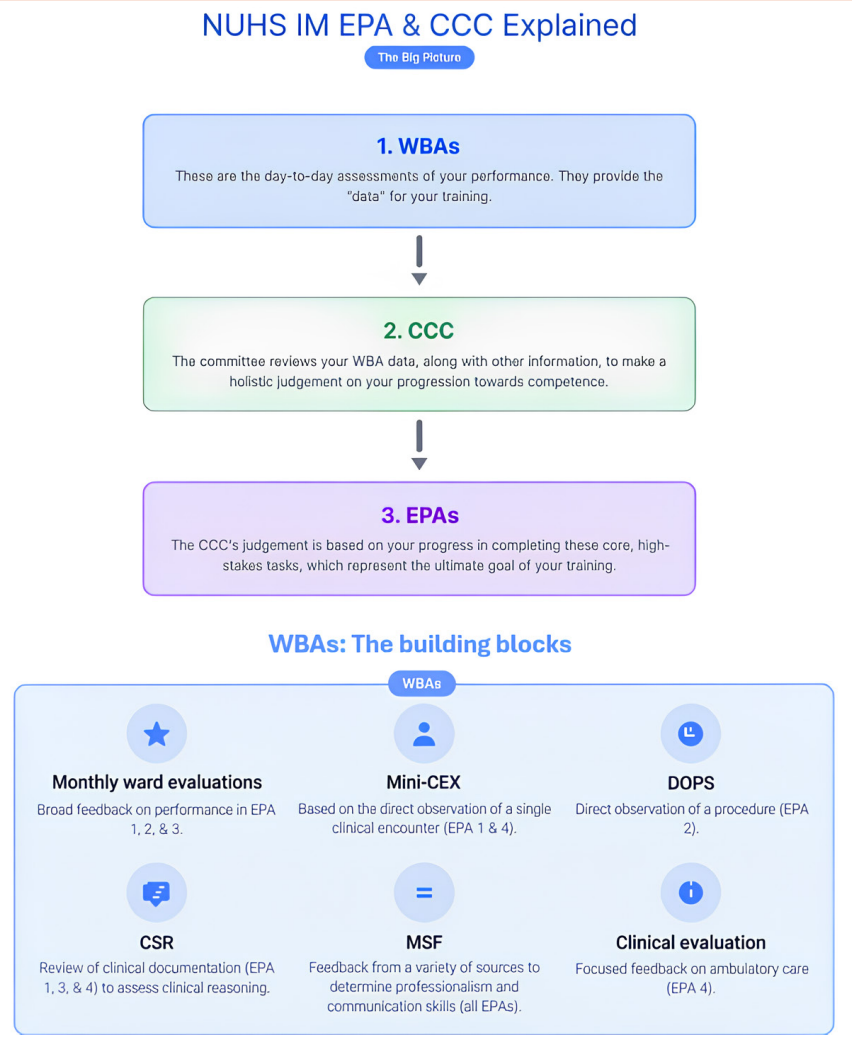
The introduction of EPAs necessitates deliberate and transparent conversations about trust,[1] which is the guiding principle that links observed performance to graded autonomy, in order to secure buy-in from

Table 1. Tabulation of the required WBAs mapped to EPAs in the internal medicine residency programme at NUHS.

S/N	Learning outcomes	Formative assessments							
		In-training examinations	Mini-clinical evaluation exercise	Chart-stimulated recall	Direct observation of procedure skills	Monthly performance evaluation	Multisource feedback	Procedure logs	Portfolio reflection
1	EPA 1: Managing patients in the medical inpatient ward	X	X	X		X	X		X
2	EPA 2: Performing medical bedside procedures				X	X	X	X	X
3	EPA 3: Managing acutely ill patients			X		X	X		X
4	EPA 4: Managing medical patients in ambulatory care setting	X	X	X		X			X

EPA: entrustable professional activities; NUHS: National University Health System; WBAs: workplace-based assessments

Fig. 1. Visual guide on EPA-based competency appraisal model in the internal medicine residency programme at NUHS.



CCC: clinical competency committee; CRS: chart-stimulated recall; DOPS: direct observation of procedural skills; EPAs: entrustable professional activities; IM: internal medicine; Mini-CEX: mini-clinical evaluation exercise; MSF: multisource feedback; NUHS: National University Health System; WBAs: workplace-based assessments

stakeholders (i.e. learners and assessors) to this model of competency appraisal.

At a broader level, entrustment in medical care relates to the fiduciary principle of the patient–physician relationship.[7] In tertiary hospital settings, specialist consultants bear the ultimate responsibility for patient care, but are supported by a team of junior physicians and residents-in-training to whom they entrust various clinical duties in executing decisions and patient management.

Additionally, an entrustment-based model more appropriately appraises the longitudinal progress of attaining entrustment milestones in professional tasks than older frameworks, which focus on assessing absolute competency that could be unrealistic, especially for advanced skill sets.[7] Sustaining this shared understanding requires repeated and structured engagement with stakeholders through faculty development workshops, dialogue, and periodic review of on-the-ground EPA implementation.

Within the Singapore context, training was conducted at various specialty departments across all sites and reached approximately 250–300 physician faculty members prior to the transition to EPAs in July 2023. These sessions presented opportunities for regular conversation between the residency programme and clinical departments across training sites to sustain a shared understanding of what contributes to grounded trust. Both assessors and residents were reminded of specific tasks tied to EPAs while the degree of supervision related to varying levels of entrustment were reiterated. Given the limited ability to achieve a clear understanding of EPA and the related entrustment concepts in a single sitting, constant engage-

ment was delivered repeatedly in bite-sized content (e.g. short presentations, reminders via messaging platforms, and emails) 2–3 times a year. These methods created and sustained a shared understanding of grounded trust.

Relating EPA tasks and standards to core professional competencies: Practical execution of WBAs

In general, EPAs must form part of standard professional work in a given context and represent a recognisable clinical work output that can be assessed in an observable and measurable manner. This work is performed via a demonstration of knowledge, skill sets, and attitudes that can be acquired through training and is executed within a stipulated timeframe under varying degrees of supervision.[2] Importantly, they must relate to 1 or more underlying core professional competencies.[2] Within an IM residency programme, EPAs such as "taking a history from a newly admitted patient from the emergency department" or "managing an acutely deteriorating patient" may relate to multiple ACGME core competencies, such as patient care, medical knowledge, and interpersonal/communication skills.

Additionally, the need for comprehensive EPA assessments must be carefully balanced against assessment fatigue that can lead to inaccurate appraisals. Therefore, EPA forms with simplified descriptors (and illustrated examples) were employed, with each evaluation encounter assessing only a limited aspect of clinical work (e.g. 1 assessment form allowing a maximum of 3 EPAs to be assessed). Assessment burden can also be split among a larger pool of assessors to allow for diversity of opinions and reduce the risk of bias. For example, inpatient and ambulatory care EPAs on clinical skills are assessed by covering consultants, while competency domains such as professionalism and communication are evaluated by nurses and allied health colleagues. Importantly, conduct of assessments can be flexible based on the clinical supervisors' discretion—for instance, an EPA form might be filled out retrospectively if the preceptor has opportunistically observed a resident performing certain clinical tasks during regular ward work.[9] To balance the risk of heterogeneity of opinions and EPA scale utilisation by a larger pool of assessors, the authors limit the assessor group for specific assessments, such as the chart-stimulated recall, to appointed CFMs to improve the reliability of EPA grading.[10]

Harnessing valuable performance datapoints outside of structured assessments

In practice, some of the most consequential information about trainee performance emerges outside formal assessment tools. Unsolicited, spontaneous feedback from clinical supervisors is frequently received informally by the PD, CFMs, or programme coordinators to highlight concerns of suboptimal clinical practice or professional conduct. The tendency of faculty supervisors refraining from formally documenting negative observations in writing is driven by their fear of limiting trainees' progression and desire to avoid potentially awkward interactions with junior staff whom they may work with again in future. There is also a risk that informal feedback becomes perceived as gossip, which can then damage the institutional feedback culture. However, from the authors' experience, informal feedback often contains rich information, which can become valuable in driving performance improvement if leveraged in a constructive manner.[11]

To harness this important source of data while maintaining fairness and reliability, programme directors and CCC chairpersons must engage supervisors in understanding the principles of programmatic assessment.[12] Faculty members need clarity on how individual data points over a longitudinal period contribute to overall entrustment decisions and how timely, direct feedback can benefit trainee development. When supervisors appreciate that entrustment determinations rely on aggregated evidence rather than isolated comments, the barrier to feedback may be reduced as they feel more assured that raising concerns is constructive rather than punitive.

Trainees will also benefit from opportunities to learn from direct and real-time feedback and have the chance to provide contextual information to account for their observed performance; factors such as fatigue, multitasking, and distractions, and varying institutional practices and norms can have significant impact on trainees' abilities to perform in the real world.[13] Such valuable information may be lost if trainees do not have the chance to provide clarification. Data obtained from informal sources must be clarified and triangulated via the described measures and clearly documented within portfolios before they can be used in the determination of entrustment levels for the respective EPAs. In NUHS, CFM supervisors are responsible for such data verification and triangulation work before portfolios are presented at CCC to help ensure that the entrustment decision-making process is grounded in robust datapoints.

Pooling data for overall entrustment appraisal: More than the sum of its parts

There is an inherent risk that residency programmes may default to summing or averaging individual EPA scores to derive overall entrustment levels. This approach is unsound given that individual entrustment scales are ordinal and non-continuous in nature,[14] such that the overall entrustment decisions cannot be a summation of individual assessments. Additionally,

qualitative feedback provided in each entrustment assessment encounter must be considered, as it offers rich contextual information on how the entrustment decision was made and provides insights into possible contributing factors to trainees' demonstrated performance.

Meaningful entrustment decisions therefore require deliberate and thoughtful synthesis by CFMs. Prior to CCC meetings, faculty supervisors must review the full portfolio, integrate numerical ratings with narrative comments, and consider the breadth of clinical exposure represented. Examination of case mix and contextual factors is particularly important, as entrustment in 1 domain may not be generalisable to all clinical situations.

Eventually, each CFM should present an interpretive narrative of the resident's developmental trajectory, proposing entrustment levels grounded in the holistic appraisal of the evidence (based on the previously described methods). Central CCC deliberations then serve as a forum for further calibration and peer scrutiny. Technology can support this process through information systems that tabulate assessments, visualise trends, and aggregate qualitative comments to enhance clarity and efficiency.[15]

Analysing competency deficiencies from entrustment decisions to guide feedback and remediation

Entrustment levels describe degrees of supervision required in performing professional tasks, but do not specify the underlying causes of underperformance. When residents fail to achieve expected EPA levels, it is essential to analyse the contributory competency gaps. Low entrustment in inpatient care, for instance, may stem from deficiencies in foundational medical knowledge, inappropriate clinical judgement within the practice context, or poor communication skills. Mapping entrustment outcomes back to ACGME core competency domains is therefore necessary for targeted feedback and structured remediation.

Going a step further, specific frameworks help provide granular analysis of performance by looking for qualities or the lack thereof, which influence entrustment decisions. CFMs look for behaviours related to attributes such as agency, reliability, integrity, and humility, which may not be completely captured within the traditional competency models.[16] This helps to address the core question of why the trainee in question cannot be entrusted to perform specific tasks (defined within EPAs) at a stated level of supervision (e.g. direct or remote). It will also help the programme articulate the desired behaviours and attitudes that must be demonstrated to help trainees become trustworthy.

Furthermore, supervisors should examine whether identified competency gaps are pervasive across multiple EPAs or confined to specific contexts. A resident who performs competently in scheduled ambulatory clinics but struggles in acute emergency settings may require focused support in managing time pressure, prioritisation, or crisis communication. Conversely, cross-cutting concerns across several EPAs may indicate a more foundational deficiency. Specific remediation strategies can then be planned to close these gaps in the appropriate work environment context defined by the corresponding EPAs.

Limitations of EPA models in present residency constructs

First, EPAs may be subject to bias (e.g. pre-conceived notions about certain trainees) and inter-rater variability (e.g. assessor idiosyncrasies, "hawk"/"dove" assessors, differing levels of expertise in task appraisals, and variable frame of reference).[17] Moreover, after migrating the assessment construct from traditional competency scales to EPA-based scoring, the authors recognised that faculty members may have differing interpretations of how grading should be done. For example, while 1 might appraise a high-performing junior resident at an entrustment level of a registrar (indirect/remote supervision), others may accord this individual with an entrustment grade that simply matches the current level of training, thereby under-appraising the individual's entrustment level. Strategies to mitigate these drawbacks include faculty development programmes, objective deliberation by a central assessment committee not directly involved in supervisory roles, and regular audits of the grading patterns of individual assessors. Specifically, assessors must be reminded to go beyond vague adjectival qualifiers (e.g. diligent, astute, careless, incompetent, etc.) and instead provide thick description of observed performance and behaviour to aid the CCC in grading the overall performance in relation to the pre-defined entrustment levels.

In addition, when Professor Olle ten Cate conceived the EPA model, he envisioned the concurrent need to evolve medical training from "fixed-length variable-outcome programmes" to "fixed-outcome variable-length programmes".[2] Yet, in reality, residency programmes operate within a time-bound model where residents can only progress to the next phase of training after completing a stipulated duration of clinical postings. Therefore, while some residents who fail to meet entrustment cut-offs may require remediation post-ings and extension of residency training, it remains impossible within the present structure for high-achieving residents who attain higher levels of entrustment to "fast-track" their training. How the residency structure can be adjusted to arrive at a fixed-outcome variablelength model commensurate with the ethos of an EPA assessment framework warrants further discourse.

CONCLUSION

The authors shared their key takeaways from on-the-ground experiences with the implementation of an EPA model of professional assessment in an IM residency programme in Singapore. Moving forward, formal qualitative studies involving interviews and focus group discussions with key stakeholders of EPA implementation in Singapore residency programmes would be helpful to iron out the common challenges and implementation strategies that can optimise the EPA model of competency assessment.

Ethics statement

Not applicable, as no study participants were recruited.

Declarations

The authors 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. There is no conflict of interest to declare. ChatGPT was used in the process of text drafting for language editing, to refine and strengthen the coherence of the points originally generated by the authors. Microsoft Copilot and Gemini were used to generate the figure. The authors declare that all AI-generated content were thoroughly reviewed for accuracy and assessed to be free from plagiarism with appropriate citations/attributions as required. The authors take full responsibility for the content within the manuscript.

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ASCITES: A framework supporting gastroenterologists to deliver primary palliative care for patients with decompensated cirrhosis

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Dear Editor,

Decompensated cirrhosis is a life-limiting condition with a high symptom burden and poor prognosis, with median survival often <2 years,[1] and symptom severity comparable to cancer, chronic obstructive pulmonary disease, and heart failure.[2] Yet palliative care uptake remains low and is typically introduced too late.[3] In Singapore, decompensated cirrhosis affects an estimated 175–200 per 100,000 population and contributes substantially to life-years lost.[4] Although recognition of palliative care needs has increased, workforce and resource constraints limit specialist involvement, highlighting the need to integrate palliative care into routine hepatology practice.

Primary palliative care, defined as core palliative competencies delivered by non-specialist clinicians,[5] represents such an approach. Gastroenterologists are well positioned to provide this care given their longitudinal relationships with patients and caregivers across clinic visits, hospitalisations, and disease transitions. However, barriers to integration include prognostic uncertainty, limited patient and caregiver understanding of palliative care, clinician discomfort with advance care planning, and competing priorities such as transplant evaluation.[5] The absence of a clear, practical structure for incorporating these elements may further limit clinician confidence and consistency.

These challenges do not reflect a lack of recognition of palliative care's value among gastroenterologists. Preliminary findings from a qualitative study of gastroenterologists' perspectives on palliative care integration (authors' unpublished data) suggest that they broadly value specialist palliative care and its benefits for symptom management, psychosocial support, and caregiver burden, often citing a professional responsibility to address these needs. Nevertheless, translating this recognition into practice remains challenging: gastroenterologists describe the cognitive effort of shifting from a curative, problem-solving orientation to goals-of-care discussions, alongside lower self-efficacy in addressing psychosocial needs and navigating family resistance. This suggests a role for approaches that provide greater structure and support.

To provide such structure, the authors propose **ASCITES**: **A**dvance care planning, **S**ymptom control, **C**aregiver support, **I**nformation sharing, **T**reatment rationalisation, **E**ngagement of a multidisciplinary team, and **S**pecialist palliative care referral. ASCITES is intended to help gastroenterologists systematically incorporate palliative principles into routine practice. The framework was developed by synthesising American Association for the Study of Liver Diseases,[5] European Association for the Study of the Liver,[6] and American Gastroenterological Association[7] guidance with consensus discussion among the author group, who have clinical experience in hepatology and palliative care. Rather than being derived through a

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Table 1. The ASCITES framework — domains and triggers.

Letter	Domain	Trigger/focus
A	Advance care planning	Initiate early, led by the primary gastroenterologist; revisit as disease progresses or capacity changes.
S	Symptom control	Actively screen for physical and psychological symptoms (e.g. pain, pruritus, fatigue, anxiety) using validated tools such as the Edmonton Symptom Assessment Scale.
C	Caregiver support	Routinely assess caregiver burden; connect caregivers to counselling, peer support and respite care.
I	Information sharing	Communicate disease trajectory and prognosis clearly, sensitive to family-centred decision-making norms.
T	Treatment rationalisation	Review and deprescribe medications in line with goals of care and the evolving benefit-harm balance.
E	Engagement of multidisciplinary team	Coordinate nursing, allied health and case-management input; hold regular multidisciplinary review.
S	Specialist palliative care referral	Escalate to specialist or home-based palliative care for refractory symptoms, complex decision-making, or difficult family dynamics.

formal Delphi process, ASCITES maps core palliative principles onto the familiar structure of a clinical consultation, designed for busy settings. The 7 domains are interconnected rather than sequential or standalone, forming a checklist to be adapted to each patient and family. Among patients with decompensated cirrhosis identified as having palliative care needs using tools such as the Supportive and Palliative Care Indicators Tool, the surprise question, or the Bristol Prognostic Score,[6] a systematic symptom assessment and early serious illness conversation should be triggered. These discussions inform advance care planning and alignment of care with patient goals, which guide treatment rationalisation and timely multidisciplinary involvement, while specialist referral provides an additional layer of support for patients with increasing complexity (Table 1). Where available, a dedicated cirrhosis hotline may further support timely intervention and reduce unnecessary hospital presentations.

Symptom assessment should extend beyond commonly recognised complications such as ascites, variceal bleeding, and hepatic encephalopathy to include less visible symptoms including fatigue, pruritus, sleep disturbances, anxiety, and depression, which are frequently overlooked despite their impact on quality of life. Caregiver support is similarly integral: caregivers of patients with cirrhosis experience substantial, often under-recognised burden, which may be compounded by alcohol or substance use issues and can affect their own health over time.[8] Routine assessment of caregiver burden and access to counselling, peer support, and respite care should be an integral component of care rather than an optional adjunct. Information sharing on prognosis must also be handled with cultural sensitivity: in many Asian societies, including Singapore, norms favouring family-centred decision-making should be navigated carefully, balancing patient autonomy with family dynamics.[9]

ASCITES has not yet been formally piloted. Potential implementation strategies include an electronic medical record smart phrase to prompt and document its use, dissemination through gastroenterologist training and clinical champions, incorporation into fellowship teaching, and periodic audit and feedback. Prospective evaluation should examine feasibility alongside clinical outcomes, including advance care planning completion, symptom burden, caregiver well-being, clinician self-efficacy, and healthcare utilisation. Implementation science frameworks may further help determine how this approach works, for whom and under what conditions, informing sustainable adoption across diverse hepatology settings.

In Singapore, where specialist palliative care capacity remains limited, patients with decompensated cirrhosis and identified palliative care needs should first receive gastroenterologist-delivered primary palliative care. Substantial palliative care needs may exist even among patients who remain ambulant and relatively independent, underscoring the need for routine needs-based assessment rather than reliance on functional decline alone. Specialist palliative care should complement rather than replace primary palliative care, directing expertise towards patients with greater complexity. Home-based palliative care may represent a subsequent step for selected patients, particularly those with limited mobility, increasing care needs, or a preference for community-based care; a Singapore feasibility study of home-based palliative care for end-stage liver disease is underway and may clarify this landscape.[10]

Beyond ASCITES itself, wider adoption of primary palliative care within hepatology will require system-level enablers: validated needs-based screening tools, institutional support for multidisciplinary collaboration, and appropriate funding mechanisms, alongside dedicated resources such as specialist nurse support, care coordinators, and access to community and home-based services. Collaborative models integrating hepatology and specialist palliative care may further enhance quality of life and reduce unnecessary healthcare utilisation.

In summary, the persistent gap in quality end-of-life care for patients with decompensated cirrhosis underscores the need for gastroenterologists to develop skill sets to deliver primary palliative care earlier in the disease trajectory. Care should be grounded in the bio-psycho-social-spiritual model, which extends beyond patients' physical symptoms. ASCITES provides a practical framework to support this shift by embedding core palliative care principles within routine hepatology practice. High-quality palliative care should be a shared responsibility, initiated early by the gastroenterologist, supported by multidisciplinary care, and complemented by specialist, community, and home-based palliative care as patients' needs become more complex.

Ethics statement

Not applicable as no patient data were used.

Declaration

No funding was received for this study. The authors declare that 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. Generative artificial intelligence (AI) tools were used solely to assist with language refinement, editing and improvement of readability. AI technologies were not used to generate scientific content, formulate arguments, analyse data, interpret findings, or draw conclusions.

Keywords: *gastroenterology, internal medicine, palliative medicine, quality of life, sarcopenia*

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Preliminary clinician usability and acceptability evaluation of an AI-powered toxicology clinical decision support tool

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Dear Editor,

Acute toxicological presentations are complex and time-critical, requiring clinicians to integrate toxicokinetics, evolving clinical manifestations, and antidote recommendations under marked time pressure. This complexity increases cognitive load and contributes to variability in decision-making, particularly where specialist toxicology expertise is not immediately available.

Artificial intelligence (AI)-enabled clinical decision support systems (CDSS) aim to augment clinician performance through evidence-informed recommendations. Such systems may standardise care and improve workflow efficiency. However, successful integration into routine practice depends on clinician acceptance, usability, and trust in system outputs.[1] Even technically robust systems often fail to achieve sustained adoption when perceived as cumbersome, poorly integrated, or misaligned with clinical reasoning.[2]

The System Usability Scale (SUS) is a widely validated measure of perceived usability and provides a standardised benchmark for user experience.[3] Beyond usability, both clinician trust and perceived usefulness are recognised as important factors associated with AI-driven decision-support adoption, particularly in high-risk clinical settings. Despite expanding interest in AI applications in healthcare, evidence evaluating clinician-centred outcomes, including usability, trust, and perceived usefulness within toxicology remains limited. Existing evaluations have focused primarily on technical performance rather than clinician interaction and usability.[4,5]

An AI-powered toxicology clinical decision support tool (ToxC) was implemented using Google's NotebookLM platform with a manually curated corpus of 19 sources selected for authority, currency, and relevance to acute toxicology, including toxicology textbooks, clinical guidelines, journal literature, and local protocols. This study evaluated clinician-reported usability and acceptability of ToxC and examined subgroup differences and associations among usability, the study-specific trust score, perceived usefulness, and satisfaction.

This was a cross-sectional evaluation of clinician interaction with ToxC using convenience sampling. Healthcare professionals managing acute toxicological presentations received instructions on using ToxC before personally entering poisoning scenarios or questions based on clinical experience or hypothetical situations, reviewing the generated responses, and asking follow-up questions as desired. They subsequently completed a structured electronic questionnaire comprising the 10-item SUS; a 5-item study-specific trust scale assessing (1) recommendation relevance, (2) cognitive-load reduction, (3) real-life trust, (4) clinical alignment, and (5) willingness to recommend the tool; and global ratings of usefulness and satisfaction. Data were analysed using descriptive statistics, subgroup analyses, correlations, and univariable linear regression. Descriptive usability and acceptability findings were the main focus of the evaluation; correlations and univariable regressions were treated as exploratory analyses of relationships among clinician-reported measures. The study was approved by the National Healthcare Group Domain Specific Review Board (2025-1761).

A total of 95 clinicians completed the evaluation. Most respondents were aged 31–40 years, practised in emergency medicine, and were junior doctors. The mean SUS score was 75.3 (95% confidence interval [CI] 71.6–79.0), corresponding to a "Good" grade on the Bangor adjective scale and significantly exceeding the conventional acceptability threshold of 68.[6,8] The composite trust score was 4.39 (95% CI 4.27–4.51), while mean usefulness and satisfaction scores were both 4.43. More than 90% of respondents rated usefulness and satisfaction highly. Recommendation relevance, alignment with clinical reasoning, and willingness to recommend the tool were also rated highly. No statistically significant subgroup differences were

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Table 1. Summary of clinician characteristics, usability, trust, and acceptability outcomes of the AI-powered toxicology clinical decision support tool (n=95).

Domain	Outcome	Result
Study participants	Total participants	95 clinicians
	Age distribution	21–30 years: 16 (16.8%) 31–40 years: 43 (45.3%) >40 years: 36 (37.9%)
	Clinical discipline	Emergency medicine: 76 (80.0%) Internal medicine: 3 (3.2%) Intensive care: 1 (1.1%) Other specialties: 15 (15.8%)
	Professional role	Junior doctors (MO/CA/RP): 50 (52.6%) Residents: 9 (9.5%) Senior doctors: 36 (37.9%)
System usability (SUS)	Mean composite SUS score	75.3 (95% CI 71.6–79.0)
	Interpretation	"Good" usability (Bangor adjective scale); exceeded the conventional acceptability threshold of 68
	Distribution of SUS scores	≥68 (acceptable): 65/95 (68.4%) ≥80 (good–excellent): 45/95 (47.4%) ≥90 (excellent): 27/95 (28.4%)
Individual usability perceptions (SUS)	Highest-rated positive items	Would like to use the system frequently (4.62) Most people would learn to use it quickly (4.54) Easy to use (4.49) Functions well integrated (4.47) Confident using the system (4.15)
	Lowest-rated negative items[a]	Need support to use the system (2.94); needed to learn a lot before getting started (2.51); unnecessarily complex (2.37); too much inconsistency (2.19); cumbersome to use (2.17)
Study-specific trust evaluation[b]	Composite trust score	4.39 (95% CI 4.27–4.51)
	Relevant recommendations	Mean 4.56; 93/95 (97.9%) rated ≥4
	Reduced cognitive load	Mean 4.31; 84/95 (88.4%) rated ≥4
	Trust recommendations in real-life scenarios	Mean 4.24; 81/95 (85.3%) rated ≥4
	Recommendations aligned with clinical reasoning	Mean 4.32; 80/95 (84.2%) rated ≥4
	Would recommend the tool to colleagues	Mean 4.55; 89/95 (93.7%) rated ≥4
Overall evaluation	Perceived usefulness	Mean 4.43 (95% CI 4.30–4.56); 89/95 (93.7%) rated ≥4
	Overall satisfaction	Mean 4.43 (95% CI 4.28–4.58); 87/95 (91.6%) rated ≥4
Relationships between study outcomes	Pearson correlations	Positive correlations were observed among SUS, the study-specific trust score, usefulness, and satisfaction (r=0.684–0.812; all P<0.001)
Exploratory univariable associations with clinician-reported outcomes	Trust score–satisfaction association	β=0.694 (95% CI 0.580–0.808); R^2=0.659; P<0.001
	Trust score–perceived usefulness association	β=0.625 (95% CI 0.526–0.724); R^2=0.626; P<0.001
	SUS–satisfaction association	β=0.040 (95% CI 0.032–0.048); R^2=0.530; P<0.001
	SUS–perceived usefulness association	β=0.036 (95% CI 0.028–0.044); R^2=0.468; P<0.001

Table 1. Summary of clinician characteristics, usability, trust, and acceptability outcomes of the AI-powered toxicology clinical decision support tool (n=95). (Cont'd)

Domain	Outcome	Result
Subgroup analyses	Professional role	Senior doctors demonstrated numerically higher SUS scores than junior clinicians; differences were not statistically significant (P>0.70)
	Clinical discipline	No statistically significant differences in SUS scores across emergency medicine, internal medicine, or other specialties (P>0.64)
	Overall findings	No statistically significant subgroup differences were detected; small subgroup sizes limited inference.

β: unstandardised regression coefficient; CA: clinical associate; CI: confidence interval; MO: medical officer; R^2: coefficient of determination; RP: resident physician; SUS: System Usability Scale

[a] Negative SUS items are reverse-scored within the composite SUS score; lower raw values on these negatively worded items indicate more favourable usability.

[b] The study-specific trust score comprised items assessing recommendation relevance, cognitive-load reduction, trust in real-life scenarios, alignment with clinical reasoning, and willingness to recommend ToxC. These items represent related clinician-reported perceptions and overlap conceptually with concurrently assessed usefulness and satisfaction.

detected, although small subgroup sizes limited inference. Exploratory analyses showed positive correlations among SUS, the study-specific trust score, usefulness, and satisfaction (r=0.684–0.812; all P<0.001). In exploratory univariable linear regression, the trust score was associated with satisfaction (R^2=0.659, P<0.001) and perceived usefulness (R^2=0.626, P<0.001); SUS was also associated with satisfaction (R^2=0.530, P<0.001) and perceived usefulness (R^2=0.468, P<0.001) (Table 1).

The principal contribution of this preliminary evaluation is the description of clinician reported usability and acceptability of ToxC. Associations among the questionnaire measures were exploratory. The study-specific trust score incorporates recommendation relevance, cognitive-load reduction, real-life trust, clinical alignment, and willingness to recommend, several of which overlap conceptually with perceived usefulness and satisfaction. This overlap, together with collection of all measures through the same self-report questionnaire at the same time, may inflate the observed associations. These results therefore do not establish trust as an independent factor influencing acceptance or demonstrate predictive or causal relationships.

These findings support previous evidence that usability and clinician perceptions are important considerations in AI-enabled clinical decision support.[8,9] High ratings for recommendations relevance, clinical alignment, usefulness, and satisfaction reflect favourable clinician perceptions following interaction with ToxC but do not establish clinical effectiveness.

This study has several limitations. The evaluation was conducted in a simulated rather than live clinical environment, and behavioural outcomes such as decision change, time-to-decision, and patient outcomes were not assessed. All outcomes were self-reported and may not reflect actual usage behaviour. The study-specific trust score incorporates several clinician-reported perceptions that are conceptually related to usefulness and satisfaction, which should be considered when interpreting the observed associations. The cross-sectional design does not capture longitudinal adoption or changes in clinician perceptions with repeated use. Convenience sampling and the predominance of emergency medicine clinicians may limit generalisability to other disciplines and healthcare settings, while small subgroup sizes for non-emergency medicine disciplines limit inference from subgroup analyses. Accuracy, completeness, and safety of ToxC-generated responses were not evaluated in this study. Accordingly, the present findings alone do not establish readiness for clinical deployment, and these dimensions require separate evaluation to complement the present usability and acceptability findings. Finally, the absence of an active comparator precludes assessment of the relative benefit of ToxC over existing clinical resources.

In conclusion, this preliminary evaluation demonstrated favourable clinician-reported usability and acceptability of ToxC, with good system usability and high ratings of trust, perceived usefulness, and satisfaction. Accuracy, completeness, and safety of ToxC-generated responses were not evaluated. Therefore, these findings do not support clinical deployment. Further evaluation of these dimensions is required before considering clinical use.

Ethics statement

The study was approved by the National Healthcare Group Domain Specific Review Board (2025-1761).

Declaration

No funding was received for this study. The authors declare that 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. The authors used ChatGPT (OpenAI) to assist with language editing, improving clarity and grammar during the preparation of this manuscript. All content was reviewed, verified, and approved by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

Keywords: *artificial intelligence; clinical decision support; clinical toxicology; digital health; emergency medicine*

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Emergency department management of primary spontaneous pneumothorax in Singapore: A nationwide survey of practice and attitudes

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Dear Editor,

Primary spontaneous pneumothorax (PSP) is a common emergency department (ED) presentation, typically affecting young, thin, and healthy individuals.[1] While recent evidence increasingly supports conservative management for clinically stable patients with moderate-to-large PSP, practice variation persists internationally. The landmark randomised trial by Brown et al. demonstrated non-inferiority of conservative care compared with interventional treatment for radiographic resolution at 8 weeks, with fewer adverse events.[2] Updated guidelines from the British Thoracic Society (BTS) and the European Respiratory Society (ERS) now reflect this shift.[3,4] However, no study has examined PSP management preferences among ED physicians in Singapore. The authors conducted a nationwide survey to address this gap.

The authors administered a nationwide anonymous online cross-sectional survey targeting physicians practising in adult EDs across Singapore's 3 public healthcare clusters: Singapore Health Services, National Healthcare Group (NHG), and National University Health System (NUHS). The survey was hosted on FormSG, a secure self-service web application provided by the Government Technology Agency of Singapore.

The survey instrument was informed by current international guidelines (BTS 2023 and American College of Chest Physicians [ACCP] 2001) and recent randomised trials supporting conservative management of PSP. It was adapted from the questionnaire developed by Kelly et al.[5] for Australian and New Zealand clinicians, and was modified for the Singapore context. Three clinical scenarios were designed to represent realistic ED presentations of moderate-to-large PSP with increasing radiological severity while maintaining clinical stability across cases: moderate-to-large PSP without collapse (Scenario 1), large PSP with lung collapse (Scenario 2), and large PSP with mediastinal shift (Scenario 3). Scenarios depicted young patients (aged 19–28 years) who were haemodynamically stable and minimally dyspnoeic, with well-controlled pain and no social vulnerability factors. Two symptom-duration variants were tested per scenario: >24 hours versus (vs) 6–8 hours from onset. Response options included conservative management (observation with or without supplemental oxygen), needle aspiration, small-bore intercostal catheter (≤14 French), and large-bore intercostal catheter (≥16 French). Respondents also used 5-point Likert scales to rate the factors influencing their management decisions and their self-reported awareness of guidelines.

A total of 122 physicians responded (with an estimated response rate of 25–30%, based on the approximate number of practising ED physicians), comprising specialists (51.6%, 63/122), registrars (21.3%, 26/122), and junior doctors (27.0%, 33/122), distributed across all 3 healthcare clusters and both tertiary referral centres (52.5%) and general hospitals (47.5%). Most respondents reported that their institution had a PSP protocol (84.4%, 103/122), typically developed by a multidisciplinary team (65.6%, 80/122).

Vital signs were the most influential factor prompting intervention (99.2%, 121/122), followed by guideline recommendations (95.9%, 117/122), radiological features other than size (95.1%, 116/122), patient-reported dyspnoea (89.3%, 109/122), pneumothorax size on chest X-ray (82.8%, 101/122), and follow-up availability (82.0%, 100/122). The mean patient age above which respondents favoured intervention was 52.9 years (standard deviation 16.9 years). Preference for conservative management decreased markedly with increasing radiological severity, from 65% in Scenario 1 to 15% in Scenario 2, and only 3% in Scenario 3, even though all patients were clinically stable. This suggests that conspicuous imaging abnormalities, such as lung collapse or mediastinal shift, continue to drive clinicians towards drainage, even when physiological parameters are reassuring.[6,7] These findings

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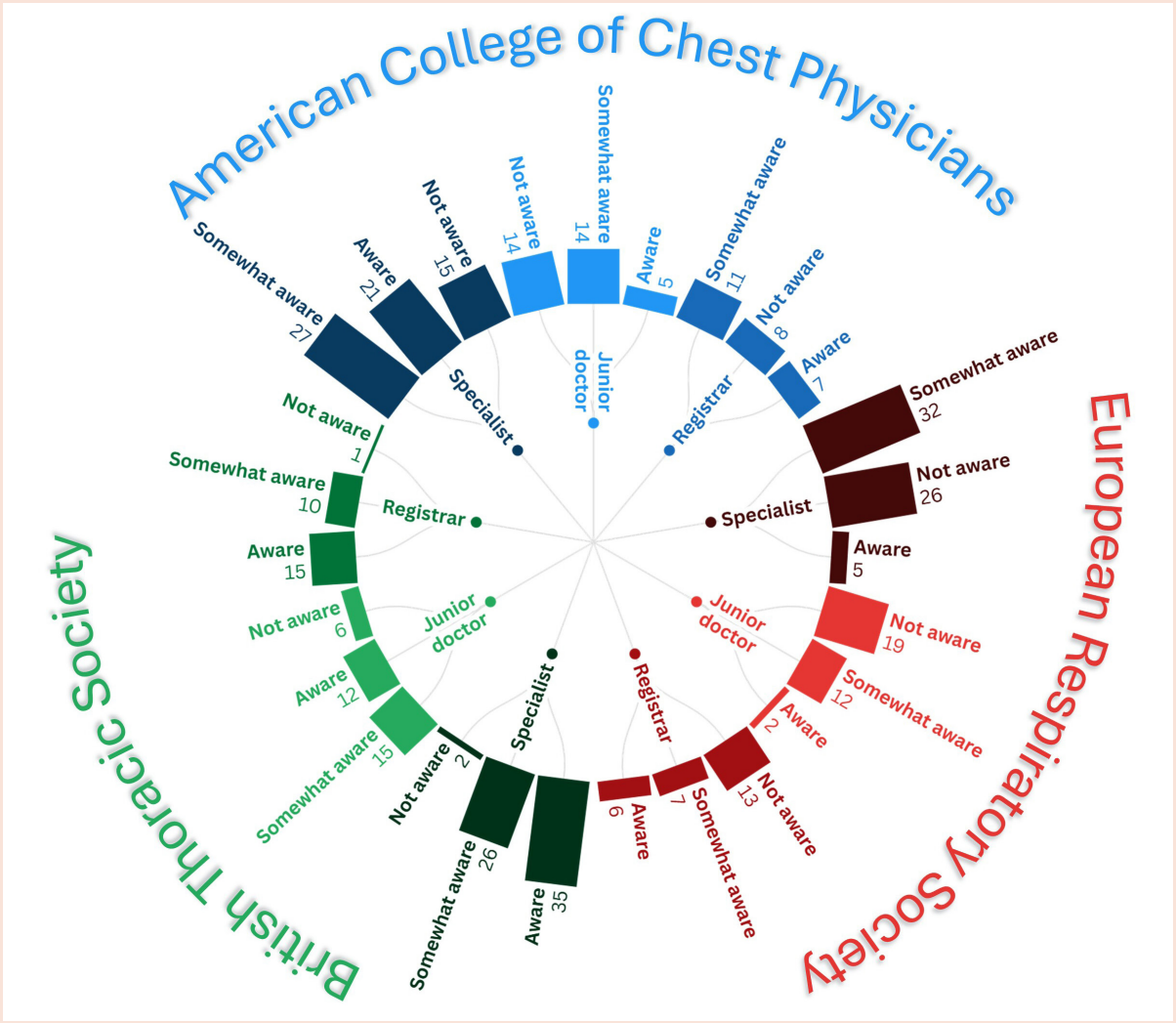
support the need for clearer Singapore guidance on how radiological severity should be interpreted alongside clinical stability.[3,4]

Important differences emerged by physician seniority. Specialists were significantly less likely to cite medicolegal risk as an important factor in decision-making (34.9% vs 66.7% of junior doctors, *P*=0.002), possibly reflecting greater confidence in evidence-based approaches. In Scenario 3, specialists were more likely to choose small-bore catheters, while a significantly higher proportion of those selecting large-bore drains were non-specialists (71.4% vs 28.6%, *P*=0.045). Overall, medicolegal concern was prominent, with 46.7% reporting worry about non-intervention in stable large PSP, rising to 72.1% with mediastinal shift (difference of 25.4 percentage points, 95% confidence interval 13.5–37.3, *P*<0.001).

Self-rated guideline awareness was high for the BTS guidelines (92.6% at least somewhat aware) but notably poor for the ERS 2024 guidance, with 47.5% reporting no awareness even though it is the most recently published guidance assessed in the survey.[4] Crucially, awareness alone did not translate into a preference for conservative management, particularly for scenarios with more pronounced radiological findings. By physician grade, specialists were more aware of the ACCP and BTS guidelines than non-specialists (*P*=0.028 and 0.049, respectively) (Fig. 1).

Healthcare cluster-level analysis revealed that physicians from NUHS, which has an established institutional PSP pathway, reported the highest awareness of local protocols (92%) and the lowest preference for interventional management.[6] The cluster's tertiary hospital has operated a multidisciplinary conservative management pathway since April 2021, offering eligible patients outpatient observation rather than routine chest tube insertion. These

Fig. 1. Awareness of guidelines by physician grade.



findings suggest that structured institutional pathways, rather than guideline knowledge alone, may be key drivers of practice alignment with contemporary evidence.

This study and that of Kelly et al.[5] identified vital signs as the most important factor influencing clinicians' decisions to intervene, suggesting that reliance on physiological stability as a decisive threshold may be consistent across emergency medicine practice internationally. However, Singapore respondents were notably more likely to select large-bore intercostal catheters for PSP with mediastinal shift (>16% vs 1.6%), even though existing evidence suggests that small-bore catheters are associated with fewer complications and shorter hospital stays.[8] This highlights an area where Singapore practice could better align with current evidence.

This study has limitations. Self-reported preferences may not fully reflect actual clinical behaviour, and the simplified scenarios could not capture the full complexity of ED encounters, including patient preferences and shared decision-making. The estimated response rate of 25–30% may limit generalisability, although representation across all clusters, physician grades, and hospital types supports the breadth of perspectives captured. The anonymous, voluntary design also precluded characterisation of non-responders.

In conclusion, Singapore ED physicians demonstrate considerable variation in PSP management preferences, associated with radiological severity, physician seniority, and institutional factors. Standardised multidisciplinary pathways, targeted education for junior clinicians on small-bore catheter use, improved dissemination of contemporary guidelines (particularly ERS 2024), and shared decision-making resources may help reduce unwarranted variation and promote evidence-aligned care.

Ethics statement

Ethics approval with waiver of documented informed consent was obtained from the NHG Domain Specific Review Board (2024/4345).

Declaration

The authors declare that 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. The study did not receive funding.

Keywords: *conservative management, emergency department, pleural disease, pneumothorax, respiratory medicine*

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