



ANNALS

OFFICIAL JOURNAL OF THE ACADEMY OF MEDICINE, SINGAPORE

VOLUME 54

NUMBER 10

OCT 2025



Singapore consensus statements on the management of obstructive sleep apnoea

An expert panel developed 72 consensus statements to guide primary healthcare professionals in providing early screening, prompt diagnosis and effective treatment of obstructive sleep apnoea. (See full article, p. 627)

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ISSN 2972-4066

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From fragmented nights to unified care: Consensus directions in obstructive sleep apnoea

Zhihua Huang¹ MD, Qin Luo¹ MD, Zhihong Liu¹ MD

Obstructive sleep apnoea (OSA) has long been recognised as a highly prevalent and underdiagnosed disorder across the Asia-Pacific region, including Singapore.^{1,2} In this issue of the *Annals*, Leow et al.³ chart a major milestone by synthesising available evidence, contextualising it to the local healthcare system in Singapore, and providing clinicians with a practical framework for daily practice. This editorial seeks to situate the significance of these consensus statements within the broader global literature, highlight their implications for clinical care and public health, and outline directions for future work.

OSA is increasingly appreciated not only as a sleep disorder but also as a multisystem disease with profound cardiometabolic and neurocognitive consequences.^{4,5} The consensus process in Singapore is notable for its inclusiveness, bringing together respiratory physicians, otolaryngologists, paediatricians, dental specialists and allied health professionals.³ Such multidisciplinary collaboration is essential because OSA management spans preventive screening in primary care, complex diagnostic pathways requiring polysomnography or home-based testing, behavioural and lifestyle interventions, device-based therapies, and in select cases, surgery. By establishing 72 carefully deliberated statements—49 for adults and 23 for children—the authors provide a broad yet nuanced roadmap that extends beyond technical diagnostic thresholds to encompass feasibility, acceptability and equity considerations. This pragmatic approach ensures that recommendations are not merely aspirational but also implementable in real-world practice. Of note, strengthening engagement with primary care physicians in future updates will be essential to enhance early recognition, screening and referral of at-risk individuals in community settings.

One of the most commendable aspects of the consensus statements is the deliberate attention paid to the context of the Singapore population.³ For instance, evidence supporting a lower Epworth sleepiness cut-off score in Singapore underscores the importance

of culturally and ethnically sensitive adaptations when applying international guidelines. Similarly, the panel emphasised cost-effectiveness data, which strengthens the case for structured screening and early treatment adoption in high-risk groups. These insights resonate with prior global efforts, including the International Consensus Statement on OSA⁶ and the Asian Pacific Society of Cardiology recommendations,⁷ yet they go further in tailoring guidance for a healthcare system with constrained specialist resources and rising burden of sleep-related morbidity. In addition, recent expert consensus from China⁸ has underscored the importance of integrating OSA assessment into cardiovascular disease management, highlighting its role in risk stratification and comprehensive care pathways.

From a clinical practice perspective, the recommendations reinforce several key principles.³ First, polysomnography remains the diagnostic gold standard, but the role of home sleep apnoea testing is acknowledged for carefully selected patients. This balanced view reflects current evidence, in that outcomes are comparable in high-pretest probability populations, while safeguarding against inappropriate use in complex or comorbid patients. Second, continuous positive airway pressure remains the cornerstone therapy, with strong evidence for symptomatic relief, quality-of-life improvement, and in some subgroups, cardiovascular benefit. Yet, adherence remains the Achilles' heel. The consensus statements rightly underscore multifaceted strategies—educational, supportive, behavioural and even surgical interventions—to enhance adherence and provide alternatives for non-responders. Third, weight management, oral appliances, hypoglossal nerve stimulation and upper airway surgery are appropriately positioned as complementary or second-line therapies. The inclusion of pragmatic considerations such as nasal obstruction, humidification and dental requirements reflects a refreshing level of clinical detail that will resonate with practicing clinicians. While the consensus underscores

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Accepted: 18 October 2025

Published Online First: 22 October 2025

the importance of multidisciplinary collaboration, it does not prescribe a single preferred referral pathway, making coordinated case-based decision-making the most practical for real-world implementation. The consensus also acknowledges the limited availability of sleep-trained clinicians, underscoring the need for expanded training and capacity-building to ensure equitable access and sustainable adoption of these recommendations.

Equally important is the paediatric section, which synthesises limited but growing evidence for the screening, diagnosis and management of childhood OSA. The emphasis on adenotonsillectomy, careful diagnostic confirmation with polysomnography, and long-term follow-up highlights both the opportunities and challenges in paediatric care. The recognition of craniofacial development, orthodontic interventions and myofunctional therapy points to the importance of early, multidisciplinary engagement to mitigate lifelong consequences of untreated paediatric OSA.

While the breadth and depth of the consensus are commendable, several challenges remain. The first is implementation. The translation of statements into routine care requires primary care engagement, training of non-specialist providers and expansion of diagnostic capacity. Second, patient-centered perspectives—although considered—were not directly incorporated into the consensus process. Future efforts would benefit from the structured involvement of patient representatives to ensure that values and preferences are fully integrated. Third, the consensus statements highlight but do not expound on the rapidly evolving role of telemedicine, artificial intelligence and digital health platforms in screening and longitudinal monitoring. Singapore, with its advanced digital infrastructure, is well-placed to pilot such innovations.

Beyond Singapore, the significance of these statements lies in their potential as a model for other countries with similar healthcare landscapes. Middle-income and multicultural societies in Asia face parallel challenges: high prevalence of OSA, limited specialist manpower and variability in access to diagnostic facilities. The Singapore framework offers a template for balancing evidence-based rigour with local adaptability. In this way, the consensus statements contribute not only to national practice but also to regional and even global discourse on sleep medicine.

In summary, the Singapore consensus statements provide clinicians with a robust and contextually relevant framework for OSA management. They integrate the best available evidence with pragmatic

considerations, bridging the gap between global guidelines and local realities. Their publication should stimulate both immediate improvements in patient care and longer-term research into implementation, adherence strategies and novel technologies. As the field of sleep medicine advances, these consensus statements will serve as a living reference point, guiding clinicians while inviting continuous refinement.

Ethics statement

Not applicable as no study participants are involved.

Declaration

This work was supported by the Noncommunicable Chronic Diseases–National Science and Technology Major Project (Grant No. 2024ZD0538200), the China Postdoctoral Science Foundation (Grant No. 2024M760273), the Postdoctoral Fellowship Program (Grade C) of the China Postdoctoral Science Foundation (Grant No. GZC20251380), and the National High-Level Hospital Clinical Research Funding (Grant No. 2025-GSP-QN-21). The funders had no role in the writing of this editorial. All authors declare no conflict of interests.

Keywords: *cardiology, public health, sleep apnea, sleep disorder, unified care*

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Association of lipid accumulation product, visceral adiposity index and endometriosis: A cross-sectional study from the 1999–2006 NHANES

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ABSTRACT

Introduction: Endometriosis (EMS) is a common gynaecological disorder linked to metabolic disturbances. However, evidence on the associations between lipid accumulation product (LAP) and visceral adiposity index (VAI) with the risk of EMS remains limited. This study aimed to explore the potential associations between LAP, VAI and EMS.

Methods: Data were obtained from the 1999–2006 National Health and Nutrition Examination Survey (NHANES), including a total of 2046 samples. Weighted multivariable logistic regression models and smoothed curve fitting were used to assess the associations between LAP, VAI and EMS. Additionally, subgroup analyses and interaction tests were conducted to evaluate intergroup differences in the associations between LAP, VAI and EMS.

Results: In the fully adjusted model, higher Log₂ LAP (odds ratio [OR] 1.256, 95% confidence interval [CI] 1.102–1.431, *P*=0.0014) and Log₂ VAI (OR 1.287, 95% CI 1.105–1.498, *P*=0.0022) were significantly associated with increased EMS risk. Participants in the highest quartile of Log₂ LAP (OR 1.983, *P*=0.0029) and Log₂ VAI (OR 1.690, *P*=0.0486) had a higher risk of EMS. Subgroup analysis showed stronger associations among women with diabetes (Log₂ LAP OR 3.681, *P*=0.009; Log₂ VAI OR 4.849, *P*=0.041).

Conclusion: Elevated LAP and VAI were independently associated with an increased risk of EMS. LAP and VAI may serve as potential indicators for assessing EMS-related risk, suggesting that visceral obesity and lipid metabolic disturbances might play roles in the pathophysiological process of EMS. These findings underscore the potential of LAP and VAI as non-invasive markers for EMS risk, warranting further validation in clinical settings.

Keywords: cross-sectional study, endometriosis, lipid accumulation product, NHANES, visceral adiposity index

CLINICAL IMPACT

What is New

- This study identifies higher lipid accumulation product (LAP) and visceral adiposity index (VAI) as significant independent risk factors for endometriosis (EMS).
- Elevated LAP and VAI were found to nearly double the risk of EMS, particularly in women with metabolic conditions such as diabetes.

Clinical Implications

- LAP and VAI can serve as practical, non-invasive indicators for identifying women at higher risk of EMS, facilitating early screening and intervention.
- Lifestyle modifications, including weight management and physical activity to reduce visceral fat, may help prevent or manage EMS, especially in individuals with elevated LAP and VAI.

The global prevalence among women of reproductive age is estimated at approximately 5–10%.^{1,2} Chronic pelvic pain occurs in 50–70% of EMS cases, and about 30–50% of affected women experience infertility,³ severely impacting their quality of life and reproductive health. Therefore, identifying easily accessible and reliable indicators related to EMS is crucial for early diagnosis and effective management, helping to improve women's health outcomes and reduce disease burden.

In recent years, growing evidence has suggested that metabolic disturbances—particularly those related to obesity and abnormal lipid metabolism—may play important roles in the development and progression of EMS.^{4–6} Traditional obesity measures, such as body mass index (BMI), primarily reflect overall fat content but fail to effectively distinguish fat distribution types, especially the more health-threatening visceral fat.⁷

The LAP, an index calculated based on waist circumference (WC) and fasting triglycerides (TG), was first proposed by Kahn et al. and is considered a

INTRODUCTION

EMS is a chronic, oestrogen-dependent inflammatory disease characterised by the presence of endometrial-like glands and stroma outside the uterine cavity.¹

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Accepted: 10 September 2025

Published Online First: 15 October 2025

simple yet effective marker for assessing visceral fat dysfunction and lipid accumulation.⁸ Meanwhile, the VAI combines WC, BMI, TG and high-density lipoprotein cholesterol (HDL-C) into a composite score that closely correlates with visceral fat measured by gold-standard methods,^{9,10} providing a more comprehensive reflection of visceral adiposity and showing strong associations with insulin resistance, cardiovascular disease risk and related metabolic conditions.¹¹

Previous studies have explored the associations between individual lipid components or metabolic syndrome elements and EMS. For example, a study based on National Health and Nutrition Examination Survey (NHANES) and bidirectional Mendelian randomisation found that specific lipid levels may be associated with EMS risk.¹² Another study reported a significant association between remnant cholesterol

and EMS.¹³ However, research directly examining the associations of LAP and VAI—both indicators of visceral obesity and lipid metabolic disturbances with EMS remains limited, especially in large population-based samples.

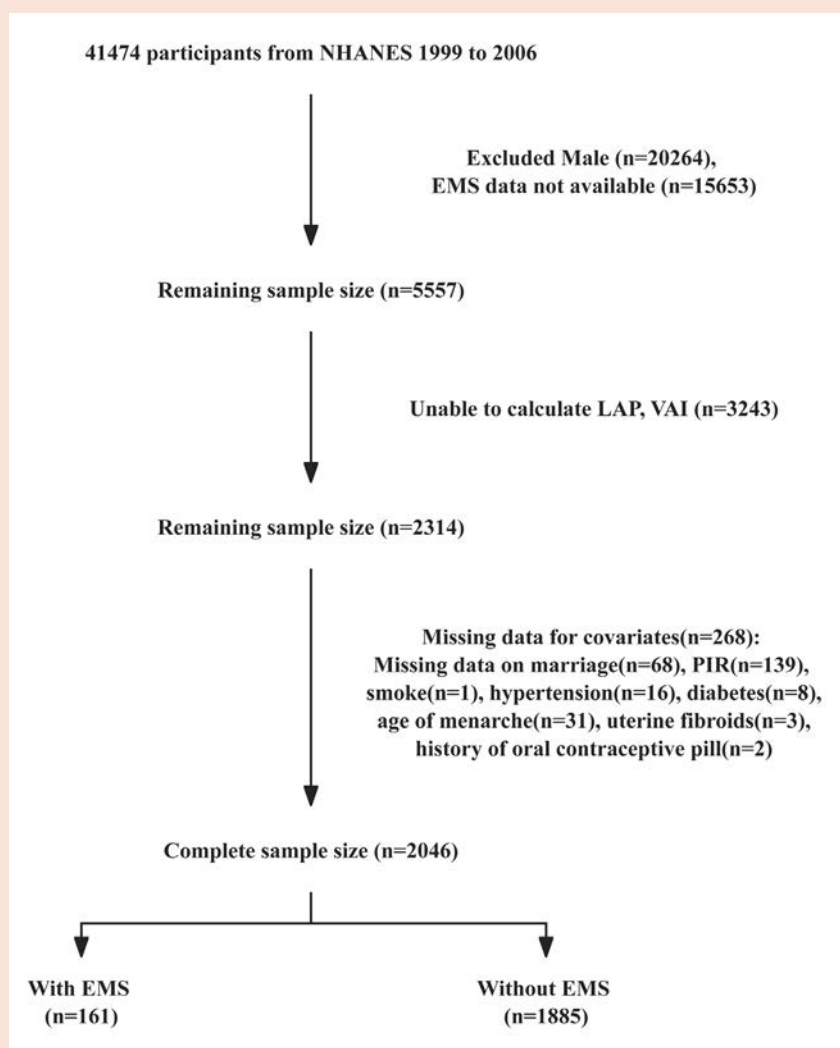
This study aims to investigate the associations between LAP, VAI and the prevalence of EMS among adult women in the US, using data from the 1999–2006 NHANES. The findings aim to provide new insights into the metabolic risk factors of EMS.

METHODS

Study dataset

This study utilised data from the NHANES 1999–2006. NHANES is a series of surveys conducted by the US National Center for Health Statistics (NCHS) using a complex, multistage probability sampling design

Fig. 1. Flowchart of participant selection from NHANES 1999–2006.



EMS: endometriosis; LAP: lipid accumulation product; NHANES: National Health and Nutrition Examination Survey; PIR: poverty income ratio; VAI: visceral adiposity index

aimed at assessing the health and nutritional status of the civilian, non-institutionalised US population (<https://www.cdc.gov/nchs/nhanes/index.htm>).

Study population

The participant selection process is detailed in Fig. 1. From an initial pool of 41,474 participants, we excluded males ($n=20,264$). Among the remaining female participants, 15,653 were excluded due to unknown EMS status, and an additional 3243 were excluded due to missing data required for LAP or VAI calculation. Participants with incomplete data on key variables were excluded to ensure analytical integrity. Finally, 268 participants were excluded because of missing covariate data. The final analytical sample included 2046 women, comprising 161 EMS cases and 1885 non-EMS controls.

Assessment of LAP and VAI

LAP and VAI were the exposure variables in this study and were calculated using the following formulas.¹⁴

$$\text{LAP} = [\text{WC}(\text{cm}) - 58] \times \text{TG}(\text{mmol/L})$$

$$\text{VAI} = \frac{\text{WC}(\text{cm})}{36.58 + 1.89 \times \text{BMI}(\text{kg/m}^2)} \times \frac{\text{TG}(\text{mmol/L})}{0.81} \times \frac{1.52}{\text{HDL-C}(\text{mmol/L})}$$

WC (cm), TG (mmol/L), HDL-C (mmol/L) and BMI (kg/m^2) were derived from NHANES measurements.

Definition of EMS

The diagnosis of EMS was based on participants' responses to the Reproductive Health Questionnaire (RHQ).¹⁵ Specifically, participants were asked, "Has a doctor ever told you that you had endometriosis?" Those who answered "yes" were classified as EMS cases, while those who answered "no" were classified as non-EMS.

Covariates

Covariates were selected based on prior literature^{3,12,13,16} and included: age, race/ethnicity, education level, poverty income ratio (PIR), smoking status, alcohol consumption, hypertension, diabetes, age at menarche, uterine fibroids and history of oral contraceptive use. Detailed definitions of covariates are provided in Supplementary Table S1.

Statistical analysis

All statistical analyses accounted for NHANES's complex sampling design, using fasting subsample weights, SDMVSTRA and SDMVPSU. Continuous variables were presented as means (95% confidence interval [CI]), and categorical variables were presented as percentages (95% CI). Because LAP and VAI were

skewed, Log_2 transformations (Log_2 LAP and Log_2 VAI) were applied to correct for data skewness. Participants were divided into 2 groups based on EMS status, and group differences were assessed using t-tests and chi-square tests. Logistic regression models were employed to evaluate the associations between Log_2 LAP, Log_2 VAI and EMS, using 3 models: Model 1 (unadjusted), Model 2 (adjusted for age, race/ethnicity, marital status and PIR) and Model 3 (adjusted for all covariates). Smoothed curve fitting and generalised additive models were used to visualise the linear relationships between Log_2 LAP, Log_2 VAI and EMS. Subgroup analyses and interaction tests were conducted to explore the potential modifying effects of age, hypertension, diabetes, smoking, alcohol consumption, age at menarche, uterine fibroids and oral contraceptive use. A 2-tailed P value was considered statistically significant if less than 0.05. All analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and Empower (X&Y Solutions Inc, MA, US).

RESULTS

Baseline characteristics of participants

This study included 2046 participants, of whom 161 were diagnosed with EMS. Table 1 presents the baseline characteristics of the study population. Compared to the non-EMS group, EMS participants were older and had higher TG levels. The EMS group also showed significantly higher Log_2 LAP and Log_2 VAI values (all $P < 0.05$). There were differences in racial/ethnic distribution, with a higher proportion of non-Hispanic, White individuals in the EMS group. Additionally, significant differences were observed between the 2 groups regarding marital status, presence of uterine fibroids, oral contraceptive use and smoking status (all $P < 0.05$). However, no significant differences were observed between the groups in PIR, BMI, WC, HDL-C, diabetes status or age at menarche (all $P > 0.05$).

Associations between Log_2 LAP, Log_2 VAI and EMS

Table 2 presents the logistic regression analysis results for the associations between Log_2 LAP, Log_2 VAI, their quartiles and the risk of EMS.

In Model 1, Log_2 LAP was significantly associated with an increased risk of EMS (OR 1.327, 95% CI 1.149–1.532). This association remained significant in Model 2 (OR 1.314, 95% CI 1.144–1.508, $P=0.0003$). Even after full adjustment in Model 3, the association between Log_2 LAP and EMS remained robust and significant (OR 1.256, 95% CI 1.102–1.431, $P=0.0014$). When analysed by quartiles, compared to the Q1 group, the ORs (95% CIs) for EMS in Q2,

Table 1. Baseline characteristics of participants according to EMS.

Characteristics	Total	Without EMS (n=1885)	With EMS (n=161)	P value
Age, years (95% CI)	37.55 (36.96–38.15)	37.25 (36.61–37.89)	40.12 (38.90–41.34)	0.0001
PIR, ratio (95% CI)	3.02 (2.92–3.13)	3.01 (2.90–3.11)	3.18 (2.86–3.51)	0.3088
BMI, kg/m ² (95% CI)	28.08 (27.67–28.48)	28.04 (27.61–28.47)	28.40 (27.41–29.39)	0.5061
WC, cm (95% CI)	92.18 (91.26–93.10)	91.98 (91.01–92.94)	93.97 (91.47–96.47)	0.1378
TG, mmol/L (95% CI)	1.38 (1.31–1.44)	1.32 (1.27–1.37)	1.91 (1.46–2.36)	0.0139
HDLC, mmol/L (95% CI)	1.48 (1.46–1.50)	1.48 (1.46–1.51)	1.45 (1.37–1.54)	0.4784
Log ₂ LAP, (95% CI)	5.14 (5.07–5.20)	5.09 (5.01–5.16)	5.54 (5.33–5.75)	0.0004
Log ₂ VAI, (95% CI)	0.64 (0.59–0.70)	0.60 (0.54–0.66)	0.99 (0.81–1.17)	0.0003
Race, % (95% CI)				<0.0001
Mexican American	7.51 (6.13–9.16)	8.21 (6.71–10.02)	1.42 (0.65–3.05)	
Other Hispanic	5.12 (3.35–7.75)	5.49 (3.53–8.43)	1.96 (0.68–5.54)	
Non-Hispanic White	70.40 (67.07–73.53)	68.75 (65.12–72.16)	84.66 (78.87–89.08)	
Non-Hispanic Black	11.84 (9.81–14.22)	12.28 (10.11–14.83)	8.05 (5.66–11.35)	
Other Race	5.13 (3.83–6.84)	5.27 (3.96–7.00)	3.90 (1.55–9.51)	
Marriage, % (95% CI)				0.0425
Married/living with a partner	68.11 (65.58–70.55)	67.32 (64.54–69.99)	74.92 (65.42–82.51)	
Divorced/separated/widowed	14.92 (13.08–16.97)	14.76 (12.84–16.91)	16.31 (9.56–26.44)	
Never married	16.97 (14.77–19.41)	17.92 (15.57–20.54)	8.77 (5.42–13.88)	
Drink, % (95% CI)				0.6160
Yes	68.14 (64.06–71.96)	67.87 (63.81–71.68)	70.46 (58.82–79.93)	
No	31.86 (28.04–35.94)	32.13 (28.32–36.19)	29.54 (20.07–41.18)	
Hypertension, % (95% CI)				0.4688
Yes	19.12 (16.85–21.61)	18.89 (16.52–21.51)	21.12 (15.54–28.04)	
No	80.88 (78.39–83.15)	81.11 (78.49–83.48)	78.88 (71.96–84.46)	

Table 1. Baseline characteristics of participants according to EMS. (Cont'd)

Characteristics	Total	Without EMS (n=1885)	With EMS (Total=161)	P value
Diabetes, % (95% CI)				0.6250
Yes	3.88 (2.89–5.19)	3.96 (2.94–5.31)	3.20 (1.29–7.73)	
No	96.12 (94.81–97.11)	96.04 (94.69–97.06)	96.80 (92.27–98.71)	
Age of menarche, % (95% CI)				0.1638
<13 years	49.53 (46.38–52.68)	48.75 (45.61–51.89)	56.28 (45.33–66.65)	
≥13 years	50.47 (47.32–53.62)	51.25 (48.11–54.39)	43.72 (33.35–54.67)	
Uterine fibroids, % (95% CI)				<0.0001
Yes	15.36 (13.45–17.49)	13.17 (11.47–15.07)	34.23 (27.08–42.18)	
No	84.64 (82.51–86.55)	86.83 (84.93–88.53)	65.77 (57.82–72.92)	
History of oral contraceptive pill use, % (95% CI)				0.0040
Yes	81.03 (78.19–83.59)	79.88 (76.70–82.72)	90.98 (84.14–95.05)	
No	18.97 (16.41–21.81)	20.12 (17.28–23.30)	9.02 (4.95–15.86)	
Smoke, % (95% CI)				<0.0001
Yes	42.48 (39.22–45.81)	40.44 (36.95–44.03)	60.01 (51.22–68.19)	
No	57.52 (54.19–60.78)	59.56 (55.97–63.05)	39.99 (31.81–48.78)	

BMI: body mass index; CI: confidence interval; EMS: endometriosis; HDL-C: high-density lipoprotein cholesterol; LAP: lipid accumulation product; PIR: poverty income ratio; TG: triglycerides; VAI: visceral adiposity index; WC: waist circumference

Q3 and Q4 were 1.397 (0.758–2.576), 1.499 (0.854–2.630) and 1.983 (1.299–3.028), respectively, with a significant dose-response trend (P for trend=0.0022).

Similarly, Log_2 VAI was positively associated with EMS in Model 1 (OR 1.403, 95% CI 1.207–1.631), Model 2 (OR 1.385, 95% CI 1.194–1.607) and Model 3 (OR 1.287, 95% CI 1.105–1.498). When analysed by quartiles in Model 3, compared to the Q1 group, the ORs (95% CIs) for EMS in Q2, Q3 and Q4 were 1.188 (0.692–2.039), 1.398 (0.832–2.348) and 1.690 (1.019–2.803), respectively. The risk in the Q4 group was significantly increased ($P=0.0486$) and a significant trend was observed (P for trend=0.0307).

The smoothed curve fitting plots further showed that, after adjusting for all covariates, Log_2 LAP and

Log_2 VAI were linearly and positively associated with EMS (Fig. 2).

Subgroup analysis

To explore heterogeneity across subgroups, we performed subgroup analyses and interaction tests (Fig. 3). Significant positive associations with EMS were observed in women aged ≥35 years, those without hypertension, smokers, drinkers, those without a history of uterine fibroids, and those with a history of oral contraceptive use. For subgroups defined by age at menarche, associations were significant in both, but no significant interaction was observed (Fig. 3A). For diabetic status, associations were significant in both diabetic and non-diabetic participants, with a statistically significant interaction

Table 2. The relationship between Log₂ LAP and Log₂ VAI and EMS.

	Model 1 OR (95% CI) P value	Model 2 OR (95% CI) P value	Model 3 OR (95% CI) P value
Log₂ LAP	1.327 (1.149–1.532) 0.0003	1.314 (1.144–1.508) 0.0003	1.256 (1.102–1.431) 0.0014
Log₂ LAP quartiles			
Q1 -2.00 to 4.44	Ref	Ref	Ref
Q2 4.44 to 5.35	1.412 (0.767–2.599) 0.2720	1.437 (0.787–2.626) 0.2440	1.397 (0.758–2.576) 0.2904
Q3 5.35 to 6.29	1.512 (0.836–2.732) 0.1766	1.519 (0.836–2.761) 0.1762	1.499 (0.854–2.630) 0.1660
Q4 6.29 to 9.52	2.374 (1.466–3.845) 0.0009	2.320 (1.451–3.709) 0.0010	1.983 (1.299–3.028) 0.0029
P for trend	0.0007	0.0006	0.0022
Log₂ VAI	1.403 (1.207–1.631) <0.0001	1.385 (1.194–1.607) 0.0001	1.287 (1.105–1.498) 0.0022
Log₂ VAI quartiles			
Q1 -2.10 to -0.04	Ref	Ref	Ref
Q2 -0.04 to 0.70	1.255 (0.744–2.118) 0.3988	1.226 (0.721–2.083) 0.4552	1.188 (0.692–2.039) 0.5352
Q3 0.70 to 1.42	1.616 (0.961–2.717) 0.0754	1.608 (0.959–2.694) 0.0778	1.398 (0.832–2.348) 0.2132
Q4 1.42 to 5.70	2.064 (1.221–3.490) 0.0090	2.001 (1.186–3.374) 0.0123	1.690 (1.019–2.803) 0.0486
P for trend	0.0040	0.0044	0.0307

Model 1: Unadjusted

Model 2: Adjusted for age, race/ethnicity, marital status and PIR

Model 3: Adjusted for age, race/ethnicity, marital status, PIR, hypertension, diabetes, smoking status, alcohol consumption, age at menarche, uterine fibroids and history of oral contraceptive use.

CI: confidence interval; EMS: endometriosis; OR: odds ratio; LAP: lipid accumulation product; OR: odds ratio; VAI: visceral adiposity index

(*P* for interaction=0.023), suggesting potential effect modification by diabetes. However, due to the smaller sample size in the diabetic subgroup, estimates should be interpreted with caution.

Significant positive associations with EMS were observed in women aged ≥35 years, those without hypertension, smokers, non-drinkers, those with age at menarche ≥13 years, those without uterine fibroids, and those with a history of oral contraceptive use (Fig. 3B). For diabetic status, associations were significant in both diabetic and non-diabetic participants; however, no significant interaction was observed (*P* for interaction=0.067).

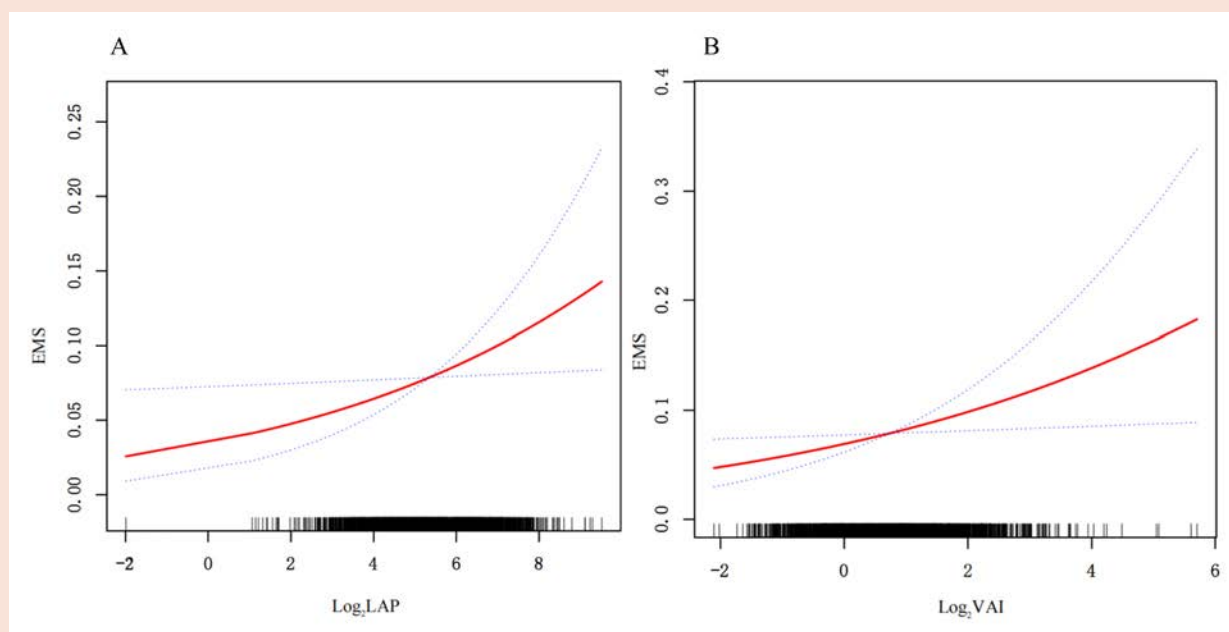
DISCUSSION

This study systematically evaluated the associations between 2 composite indicators of visceral obesity

and lipid metabolic disturbances—LAP and VAI—and the risk of EMS. Our findings showed that, after adjusting for multiple potential confounders, higher levels of both LAP and VAI were independently associated with increased prevalence of endometriosis. Women in the highest LAP quartile had nearly twice the risk of EMS compared to those in the lowest quartile, and a similar positive trend was observed across VAI quartiles.

Our results align with recent studies investigating other metabolic markers and EMS. Wang et al.³ reported that a higher cardiometabolic index (CMI) was significantly associated with an increased risk of EMS. Similarly, a study on the triglyceride-glucose (TyG) index, a surrogate marker of insulin resistance, found that EMS prevalence increased with higher TyG levels.¹⁶ Multiple studies have highlighted a

Fig. 2. Smooth curve fitting of the associations between Log_2 LAP, Log_2 VAI and EMS, adjusted for covariates in Model 3. (A) Log_2 LAP and EMS; (B) Log_2 VAI and EMS.



EMS: endometriosis, LAP: lipid accumulation product; VAI: visceral adiposity index

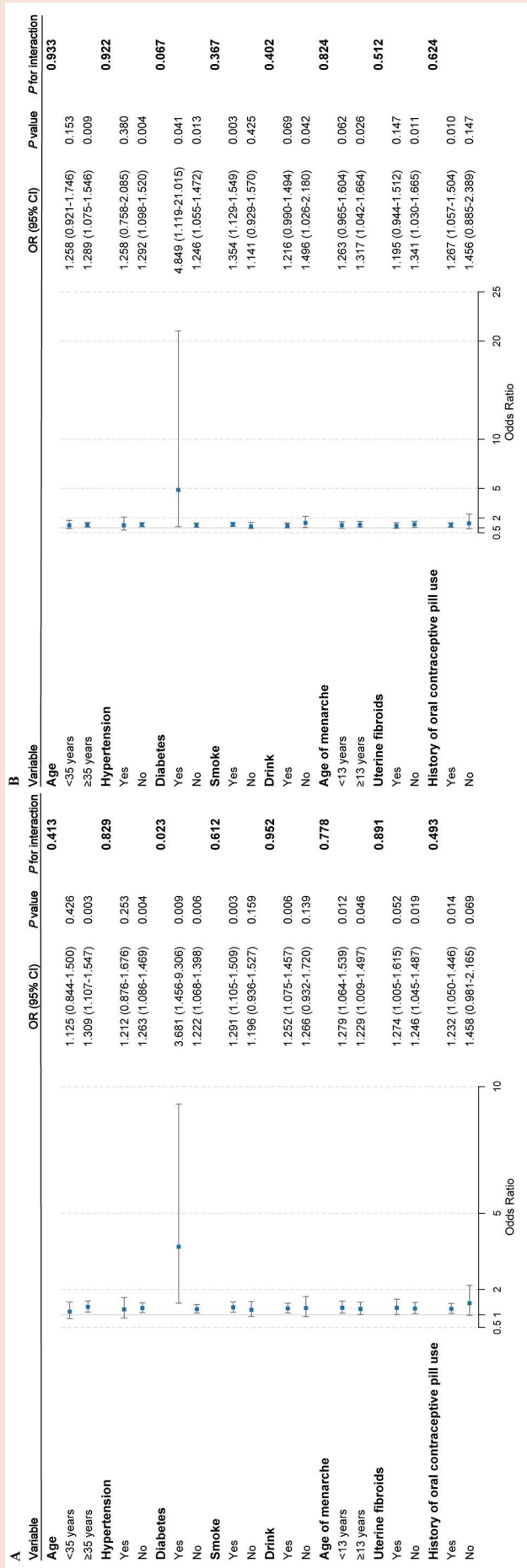
significant association between lipid metabolic abnormalities and EMS, with EMS patients more prone to lipid metabolism disorder.^{13,17,18} Unlike single biomarkers such as TyG or CMI, which primarily reflect insulin resistance or specific lipid components, LAP and VAI integrate visceral obesity and lipid dysfunction, offering a more comprehensive reflection of the metabolic networks underlying EMS. By combining anthropometric measures with lipid profiles, LAP and VAI capture the synergistic effects of visceral fat accumulation and dyslipidaemia, which may more accurately represent the multifaceted metabolic disturbances driving EMS pathogenesis.¹⁹

Our study demonstrates that elevated LAP and VAI are linked to an increased risk of EMS, which may involve several key pathophysiological mechanisms. EMS is characterised by chronic inflammation, which is not confined to the pelvic cavity but extends to systemic inflammatory responses.¹ Visceral adipose tissue is a major source of pro-inflammatory cytokines, which are significantly elevated in the peritoneal fluid of EMS patients.²⁰ As indicators of visceral fat accumulation, LAP and VAI may reflect an enhanced pro-inflammatory environment that promotes the adhesion, proliferation and angiogenesis of ectopic endometrial cells, thereby exacerbating the pathological processes of EMS.²¹ Additionally, LAP and VAI are closely related to insulin resistance, the core feature of metabolic syndrome. IR-induced hyperinsulinaemia can affect EMS development through

multiple pathways.²² IR also alters hormone levels by reducing sex hormone-binding globulin, thereby increasing circulating androgens and free oestrogens, upregulating phosphorylated forkhead box O1 in ectopic stromal cells, and enhancing the expression of Ras-related proteins and matrix metalloproteinase-9, which together increase the invasiveness of EMS.¹⁶ This insulin-driven hormonal dysregulation may amplify oestrogen-dependent growth of ectopic lesions, further linking LAP and VAI to EMS pathogenesis.

Visceral adipose tissue is also a key site for peripheral oestrogen production through aromatisation of androgens.²³ Elevated LAP and VAI may lead to increased systemic oestrogen levels, providing a favourable hormonal environment for the growth of oestrogen-dependent EMS lesions. Moreover, dyslipidaemia associated with visceral obesity may disrupt hormonal metabolic balance, further exacerbating hormonal dysregulation in EMS. Visceral fat accumulation and metabolic syndrome are also linked to increased systemic oxidative stress, which is another hallmark of EMS.²⁴ Reactive oxygen species can promote the formation and maintenance of ectopic lesions by damaging cellular components, inducing inflammation and stimulating angiogenesis.²⁵ Individuals with elevated LAP and VAI may face a higher oxidative stress burden, which, combined with the intrinsic oxidative imbalance of EMS, drives disease progression. Finally, metabolic abnormalities driven by visceral fat may impair immune surveillance,

Fig. 3. Forest plot of subgroup analysis for relationships between Log₂ LAP and Log₂ VAI and EMS. (A) Forest plot of subgroup analysis for relationships between Log₂ LAP and Log₂ VAI and EMS; (B) Forest plot of subgroup analysis for relationships between Log₂ VAI and EMS.



CI: confidence interval; EMS: endometriosis; LAP: lipid accumulation product; OR: odds ratio; VAI: visceral adiposity index

while EMS itself has been shown to involve immune dysfunction, including altered macrophage polarisation, reduced natural killer cell cytotoxicity, and shifts in T cell populations.²⁶⁻²⁸ The inflammatory environment triggered by excess visceral fat may amplify these immune defects, allowing ectopic endometrial cells to evade immune clearance and establish lesions.

Our subgroup analyses showed that the associations between LAP, VAI and EMS were statistically significant across many subgroups. As women age, oestrogen levels gradually decline, and oestrogen plays a key role in regulating fat distribution and metabolism.^{2,29} Reduced oestrogen may lead to increased visceral fat accumulation, thereby exacerbating metabolic disturbances.³⁰ A cross-sectional study based on NHANES data found a positive association between LAP and EMS prevalence, particularly in women aged 35 years and older,³¹ suggesting that age-related hormonal changes may amplify the associations between LAP, VAI and EMS. In addition, ageing is often accompanied by heightened chronic inflammation, which may further promote the development of EMS.³² Alcohol consumption may influence the association between VAI and EMS by modulating lipid metabolism and visceral fat accumulation. One study found that moderate alcohol intake was associated with improved insulin sensitivity and reduced inflammation,³³ which could weaken the impact of VAI as a metabolic abnormality indicator on EMS. Moreover, alcohol metabolism may interfere with hormonal balance (e.g. oestrogen metabolism), thereby dampening the association between VAI and EMS.³⁴ In contrast, among non-drinkers, the lack of this regulatory mechanism may make the relationship between VAI, visceral adiposity and metabolic risk more directly linked to EMS.

The subgroups without hypertension may represent metabolically healthier populations, where LAP and VAI primarily reflect visceral fat accumulation¹⁰ rather than the influence of comorbidities, thus showing a more direct association with EMS. For smokers, smoking may enhance the associations between LAP, VAI and EMS by inducing chronic inflammation or affecting hormone metabolism. Studies have shown that smoking is associated with an increased risk of EMS, which may amplify the effects of metabolic disturbances.³⁵ Later age at menarche may be related to a longer period of low oestrogen exposure, influencing fat distribution and metabolic status, thereby strengthening the associations between LAP, VAI and EMS. Additionally, the absence of uterine fibroids and a history of oral contraceptive use may reflect differences in hormonal status or reproductive health. Oral contraceptives, by modulating hormone levels, may indirectly affect metabolism and EMS

risk, though the exact mechanisms warrant further investigation.

Notably, the associations of LAP and VAI with EMS were more pronounced in the diabetes subgroup than in the non-diabetes subgroup. Diabetes and its related insulin resistance may serve as effect modifiers in the relationship between LAP and EMS, as well as between VAI and EMS. Patients with diabetes are typically characterised by systemic metabolic disturbances, hyperinsulinemia and chronic low-grade inflammation, all of which may exacerbate visceral fat accumulation, enhance the release of pro-inflammatory cytokines, and promote insulin-driven hormonal imbalances that stimulate ectopic endometrial proliferation. Together with oxidative stress and immune dysfunction, these processes may synergistically amplify the impact of LAP and VAI on EMS risk.^{36,37} Nevertheless, the relatively small sample size of the diabetes subgroup, along with the wide confidence intervals—particularly for VAI—necessitates cautious interpretation. Future large-scale prospective studies are warranted to confirm whether diabetes truly modifies the associations of LAP and VAI with EMS and to further elucidate the underlying metabolic and inflammatory mechanisms.

Clinical implications

The findings of this study have potential clinical relevance. LAP and VAI can be easily calculated using routine anthropometric measurements and lipid profiles, making them practical tools for EMS risk assessment. For women with elevated LAP or VAI, especially those with metabolic conditions such as diabetes, clinicians can incorporate these indices into routine health assessments to identify individuals at higher risk for EMS, facilitating early screening and intervention. Furthermore, lifestyle interventions, such as dietary modifications and increased physical activity to reduce visceral fat, may serve as complementary strategies to prevent or manage EMS and improve metabolic health. Given the cross-sectional design and reliance on self-reported EMS, LAP and VAI are currently best suited to identify high-risk populations for further clinical evaluation rather than as diagnostic tools.

Limitations

Despite providing valuable insights, this study has several limitations. First, the cross-sectional design precludes causal inference, and the complex pathophysiology of EMS may influence the interpretation of metabolic parameters. EMS diagnosis was based on self-reporting, which may lead to underdiagnosis or misclassification, introducing recall bias and potentially affecting the observed associations between LAP, VAI and EMS. Furthermore,

the study population was limited to women in the US, restricting the generalisability of the findings. Although multiple confounders were adjusted for, some unmeasured factors may still have influenced the results, including common hormonal treatments for EMS, dietary patterns and physical activity levels. Hormonal treatments can substantially alter metabolic parameters, such as lipid profiles, while high-fat or high-sugar diets may exacerbate visceral fat accumulation and systemic inflammation, and regular physical activity may mitigate metabolic dysfunction. These factors could collectively affect the associations between LAP, VAI and EMS, and warrant further investigation in future studies. Although subgroup analyses revealed intriguing patterns, particularly stronger associations among diabetic women, the relatively small number of EMS cases limited statistical power. Therefore, these subgroup findings should be interpreted cautiously and validated in larger, adequately powered cohorts. Future research should employ prospective cohort designs; incorporate precise clinical diagnoses; include a broader range of metabolic markers; and account for treatment interventions to validate the potential of LAP and VAI as predictive markers for EMS.

CONCLUSION

This study demonstrates a significant association between LAP, VAI and EMS prevalence, highlighting their potential as metabolic markers for risk assessment. Prospective cohort studies with clinical EMS diagnoses are needed to clarify causality and evaluate the utility of LAP and VAI in EMS management.

Supplementary material

Supplementary Table S1. Definition of covariates.

Ethics

Ethical approval was not required for this study as it used publicly available, anonymised data from the US National Health and Nutrition Examination Survey.

Declaration

This study received funding from the National Natural Science Foundation (No.82474566) and the Key Research and Development Program Project of Heilongjiang Province (No.2024ZX12C25). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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Ischaemic strokes from facial injections of dermal fillers: Clinico-radiological features and outcomes

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ABSTRACT

Introduction: Ischaemic stroke is a severe complication of dermal filler injections that remains poorly described and understood. This study aims to characterise the clinical features and outcomes of patients who experience strokes following facial dermal filler injections.

Methods: A systematic review and retrospective analysis of ischaemic strokes caused by dermal filler injections and reported over the past 3 decades, were conducted. Cases involving autologous fat were also compared against those that did not.

Results: Fifty-five cases from 45 studies were analysed. Their median age was 32 years (18–61), and most were women (49/55, 89%). Injections frequently occurred at the glabella (17/53, 32%) and temples (12/53, 23%), and autologous fat was most often used (33/55, 60%). Half (29/55, 53%) had ocular symptoms at presentation. Hemiparesis/hemiplegia (30/55, 55%) and confusion/reduced consciousness/alertness (26/55, 47%) were the predominant stroke symptoms. Most infarcts were unilateral (45/54, 83%) and large (32/48, 67%). Treatment primarily involved corticosteroids (12/41, 29%) and antiplatelet agents (11/41, 27%), while hyaluronidase injections (3/41, 7%) and hyperbaric oxygen therapy (2/41, 5%) were rarely used. Less than half (22/55, 40%) experienced good functional recovery. Those injected with autologous fat were likelier to be symptomatic from their strokes (100% versus [vs] 68%, $P=0.0012$), develop larger strokes (93% vs 24%, $P<0.0001$) and experience non-ambulatory outcomes (44% vs 73%, $P=0.0381$).

Conclusion: Strokes are rare complications of dermal fillers. Injections using autologous fat risk larger strokes and worse ambulatory outcomes. An hour of post-procedural observation appears reasonable, and those with ocular complications should undergo brain imaging even in the absence of stroke symptoms.

Keywords: autologous fat, dermal fillers, hyaluronic acid, neurology, stroke

CLINICAL IMPACT

What is New

- The glabella and temples were the 2 most common sites in strokes from dermal fillers.
- Injections with autologous fat are likelier to cause symptomatic strokes, larger strokes and poorer ambulatory outcomes.

Clinical Implications

- Caution should be practised, especially when injecting at the glabella or temples, and when using autologous fat.
- Brain imaging should be performed in patients with ocular complications, even in the absence of neurological deficits.
- As most strokes occur immediately or shortly after filler injections, an hour of post-procedural observation is a prudent measure.

INTRODUCTION

Facial injections of dermal fillers have gained prominence as a popular non-surgical method for achieving facial volumisation and contouring,

providing significant aesthetic and clinically relevant benefits, such as its non-invasiveness, enhanced convenience, reduced procedural morbidity and expedited recovery.^{1,2} Various materials have been used over the past decades, each boasting unique rheologic properties (particle size, elasticity, viscosity, cohesivity and flexibility) and advantages.² Alongside their growing popularity, complications from these procedures are increasingly recognised and reported.³ While comparatively uncommon, ischaemic strokes are concerning, given their potential for long-lasting disability and mortality.⁴ Despite these concerns, the clinico-radiological features, treatments and outcomes of affected patients remain insufficiently described in the literature, resulting in significant knowledge gaps. Therefore, a comprehensive review of literature spanning the past 30 years was conducted to better characterise the clinico-radiological features, treatment approaches and clinical outcomes of ischaemic strokes from filler injections to the facial region, with the goal

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Accepted: 13 October 2025

Published Online First: 22 October 2025

of informing current clinical practice and improving treatment outcomes.

METHODS

Search strategy

A search string was designed to identify original studies reporting the clinico-radiologic features of patients with radiologically-proven ischaemic strokes after facial injections of dermal fillers. On 1 April 2024, both authors (YJT, LHC) systematically searched PubMed and Google Scholar for relevant articles published over the past 3 decades (April 1993–March 2024). A period of 30 years was chosen to ensure that the findings remain clinically current for present-day use. MeSH terms, free text and related search terms included “facial filler or dermal filler or cerebral stroke or autologous fat or hyaluronic acid (HA)”, “collagen or poly-d,l-lactic acid or PDLLA or poly-D-lactic acid or PDLA or poly-L-lactide or PLLA” and “stroke or cerebrovascular accident”. The systematic search followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The search was performed by both authors, who reviewed the article titles and abstracts. References identified from database searches were exported to EndNote. Both authors also manually searched the references of included studies/records to identify additional articles. After removing duplicates, full-text articles were retrieved if at least 1 of the 2 authors considered the abstract potentially eligible. Each full-text article was independently assessed for final inclusion, with disagreements resolved by consensus (96% overall agreement [459 of 478 articles; $\kappa=0.815$]).

Study inclusion criteria

The following inclusion criteria were used when selecting relevant articles: (1) original articles and case reports/series involving patients with ischaemic strokes affecting their cerebrum, brainstem or cerebellum; (2) demonstrated brain magnetic resonance imaging (MRI) or computed tomography (CT) and that (3) the occurrence of stroke symptoms or the detection of ischaemic strokes on brain imaging studies in otherwise asymptomatic patients were within 7 days from the injection to regions, including the forehead, temple, glabella, periorbital area, nasal bridge/nose, nasolabial fold, cheek, lips and the chin. Despite their proximity, the glabella was considered separate from the forehead due to important differences in their arterial anatomy and propensity for vascular complications.⁵ An interval of 7 days was arbitrarily chosen to account for potential delays in the performance of brain scans, especially in cases of asymptomatic strokes. This is further supported by a recent review of dermal filler-related vascular complications, which found that most strokes occurred or were identified within a week.⁶

Laboratory-based research, animal studies, reviews, commentaries, editorials, clinical guidelines, book chapters, conference abstracts/posters and articles written entirely in languages other than English, and those without full texts or with incomplete descriptions of clinical and/or radiological features were excluded from this study. Cases of venous infarcts from cerebral venous thrombosis were also omitted, as their pathogenesis and treatment measures are different from those of ischaemic strokes. Included studies were then subjected to methodological quality assessment by both authors using the Joanna Briggs Institute Critical Appraisal Checklist for case series and case reports (Supplementary Tables S1 and S2).

Data extraction and statistical analysis

Heterogeneity among the included studies—particularly in the reporting of clinical features, diagnostic approaches and treatment outcomes—is a key concern, especially in a review composed primarily of case reports and series. To address this, clearly defined inclusion criteria (see above) were applied to enhance consistency across studies. In addition, a standardised data extraction table was used to systematically capture relevant clinico-radiologic information, including demographic data, medical history, clinical symptoms, neurological deficits, brain imaging findings, treatments administered and eventual outcomes. All data were manually extracted and entered by both authors. Filler-related data were also extracted, including the material used, the facial areas where the fillers were injected, the person injecting the filler, the volume of material used, and the methods of injection. Statistical analyses were performed using SPSS Statistics software version 30.0.0.0 (172) (IBM Corp, Armonk, NY, US). The clinical features of identified cases were retrospectively analysed together with an illustrative case described herein, after which statistical analysis was performed using Mann-Whitney U test, unpaired t-test, Pearson's chi-squared test and Fisher's Exact test as appropriate, with a two-tailed alpha of 0.05.

RESULTS

The search process is represented by a PRISMA flow diagram (Fig. 1). A total of 472 records published between April 1993 and March 2024 were identified (437 on Google Scholar and 35 on PubMed). After removing 4 duplicates, the titles and abstracts of 468 records were screened, and 416 were excluded. A total of 297 did not involve cases of ischaemic strokes of the cerebrum, cerebellum and brainstem; 113 were not primary research (86 clinical guidelines, 18 meta-analyses/systematic reviews and 9 commentaries); 2 were animal studies; 3 were written in languages other than English and 1 was a conference abstract. Full-text articles from 51 reports were

retrieved and assessed for eligibility, which, together with an additional study identified through backward citation search methods, yielded a total of 55 cases from 45 articles (6 cases series, 39 case reports) that met the inclusion criteria.⁷⁻⁵² Most articles involved patients in East Asia (43/55, 78%), while 5 cases were reported in Europe, 3 in the US and another 3 in the Middle East.

Patient characteristics, filler materials and injection sites

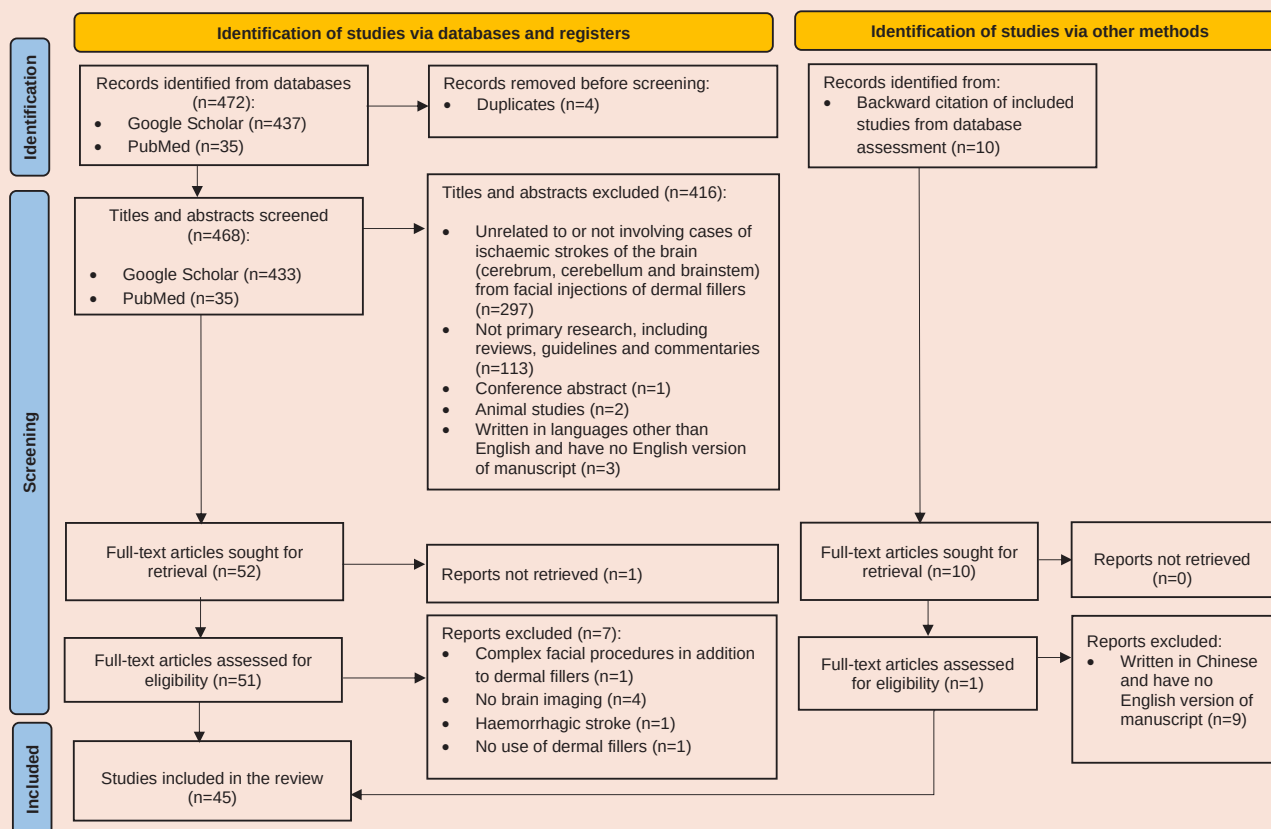
Patients' median age was 32 years (18–61 years), and most were women (49/55, 89%; female-to-male ratio 8.2:1) (Table 1 and Fig. 2). Nearly all (49/55, 89%) had no prior medical history. Of the remaining 6, 3 had pre-existing cardiovascular risk factors—1 with hypertension; another with hypertriglyceridemia and the third with hypertension, hyperlipidaemia and a history of smoking.^{20,48,49} Other clinical history included hepatitis B carrier status in one; retinoblastoma in another; and a Baker's cyst, patent foramen ovale and a previous deep vein thrombosis in 1 patient.^{34,47,50} Autologous fat was the most commonly used material (33/55, 60%), followed by HA (17/55, 31%) and poly-d,l-lactic acid (PDLLA)-containing fillers (3/55, 5%), including one case

in whom a mixture of HA and PDLLA was used.⁴⁸ Calcium hydroxylapatite was injected into 1 patient, and an unnamed collagen-based filler was used in another.^{34,45} Excluding 2 cases that did not specify the exact sites, injections were most often at the glabella (17/53, 32%) and temples (12/53, 23%).^{21,42} They were followed in decreasing frequency by the forehead (excluding the glabella; 9/53, 17%), nose and/or nose bridge (9/53, 17%), periorbital area (7/53, 13%), cheeks (5/53, 9%), nasolabial fold (4/53, 8%), chin (2/53, 4%) and the lower lip (1/53, 2%). Concurrent injections at multiple sites within a single session occurred in at least a fifth of the cases (11/53, 21%). Unfortunately, descriptions of the modes of administration such as the use of the needle or cannula, the brand and volume of the fillers used, and the professional background of the persons injecting the fillers (i.e. plastic surgeons, aestheticians or beauticians) were infrequent, precluding meaningful analysis.⁵³

Clinical features

Stroke symptoms and ocular complaints were the 2 most common features at presentation (Table 1). Around half presented with ocular complaints (29/55, 53%), of which nearly all had either monocular blurring

Fig. 1. PRISMA flow diagram.



Reference: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int J Surg* 2021;88:105906.

Table 1. Characteristics and clinico-radiological features of cases included in this study.

Characteristics	Patients	References
Median age, years (range)	32 (18–61)	[6–51]
Female sex, no. (%)	49 (89)	[6–25, 28–37, 39–45, 49–51]
With CVSRF, no. (%)	3 (5)	[19, 12, 48]
Injection site, ^a no. (%)		
• Forehead	9 (17)	[13, 16, 18, 21, 29, 36, 37, 45, 51]
• Glabella	17 (32)	[13, 15, 19, 25, 27, 30, 33, 35, 37, 39, 40, 46, 47, 49]
• Temple	12 (23)	[8, 9, 14, 16–18, 23, 24, 28, 31, 36, 42]
• Periorbital area	7 (13)	[6–8, 26, 27, 43, 46]
• Cheek	5 (9)	[10, 18, 24, 37]
• Nose or nasal bridge	9 (17)	[6, 11, 19, 22, 32, 34, 38, 44]
• Nasolabial fold	4 (8)	[7, 12, 48, 50]
• Lower lip	1 (2)	[48]
• Chin	2 (4)	[31, 48]
Multiple injection sites, ^b no. (%)	11 (20)	[7, 8, 13, 18, 19, 31, 36, 37, 46, 48]
Injection material, no. (%)		
• Autologous fat	33 (60)	[8–10, 14, 16–18, 20, 21, 23, 24, 26–28, 30, 31, 35–37, 41–43, 45–51]
• Hyaluronic acid ^c	17 (31)	[6, 11–13, 15, 19, 22, 25, 32, 34, 37–40]
• PDLA ^c	3 (5)	[7, 12, 29]
• Calcium hydroxyapatite	1 (2)	[33]
• Unspecified collagenous material	1 (2)	[44]
Stroke features		
Stroke symptoms and signs at presentation, no. (%)	43 (78)	[6–11, 13–24, 26–32, 34–36, 38, 41–43, 46–51]
• Hemiparesis/hemiplegia	23 (42)	[9, 14, 15, 17, 18, 20, 23, 24, 26–30, 36, 41, 42, 47, 48, 51]
• Confusion, reduced consciousness/alertness	19 (34)	[8–10, 14, 16, 18, 23, 24, 27, 28, 30, 31, 42, 46, 47, 49, 50]
• Giddiness/dizziness, nausea, vomiting	11 (20)	[6, 7, 10, 11, 13, 19, 21, 22, 29, 34, 38]
• Aphasia	6 (11)	[14, 23, 30, 42, 47, 48]
Stroke deficits after initial presentation, no. (%)	5 (9)	[16, 33, 37, 45]
Stroke symptoms and signs, total no. (%)	48 (87)	[6–11, 13–24, 26–38, 41–43, 45–51]
• Hemiparesis/hemiplegia	30 (55)	[6, 9, 10, 13–18, 20, 21, 23, 24, 26–31, 36, 37, 41, 42, 47–49, 51]
• Confusion, reduced consciousness/alertness	26 (47)	[8–11, 13–18, 22–24, 27–30, 31, 42, 46, 47, 49, 50]
• Giddiness/dizziness, nausea, vomiting	11 (20)	[6, 7, 10, 11, 13, 19, 21, 22, 29, 34, 38]
• Aphasia	10 (18)	[14, 23, 30, 36, 37, 42, 46–48]
• None	7 (13)	[6, 12, 25, 39, 40, 44]
Stroke onset immediately after the injection, no. (%)	14 (35)	[7, 14, 15, 19, 21, 23, 27, 29, 38, 42, 49–51]
Stroke onset within an hour of injection, ^{d,e} no. (%)	23 (58)	[7, 11, 13, 15, 19–23, 26, 27, 29, 30, 33, 38, 42, 46, 47, 50, 51]
Other features, no. (%)		
• Ocular complications	38 (69)	[6, 7, 9–15, 19, 21, 22, 25, 29–41, 43–45, 47, 49–51]
• Skin necrosis	19 (35)	[9–12, 19, 22–25, 29, 34–36, 38, 40, 43, 44, 51]
Radiological features of stroke		
Strokes in anterior circulation territory, ^f no. (%)	54 (100)	[6–26, 28–51]
Strokes in posterior circulation territory, ^e no. (%)	12 (22)	[6, 11, 14, 15, 17, 19, 22, 35, 40, 41, 50]
Unilateral strokes, ^f no. (%)	45 (83)	[6, 8–10, 12–14, 16–24, 26–33, 35–38, 40–45, 47–51]
Multifocal strokes, ^f no. (%)	32 (56)	[6, 7, 10–12, 14, 15, 19, 22, 25, 26, 29, 30, 32–35, 37–41, 44, 46, 50, 51]
Large strokes, ^g no. (%)	32 (67)	[6, 8–11, 14–18, 21–23, 26–28, 30, 31, 35, 36, 40–43, 46–50]
LVO on angiography, ^h no. (%)	16 (40)	[6, 8, 17, 20, 24, 27, 28, 30, 31, 36, 42, 46, 48]
• Intracranial LVO	12 (30)	[6, 17, 20, 24, 27, 28, 30, 36, 42, 48]
• Extracranial LVO	4 (10)	[8, 27, 31, 46]

Table 1. Characteristics and clinico-radiological features of cases included in this study. (Cont'd)

Characteristics	Patients	References
Treatmentⁱ		
• Corticosteroids, no. (%)	12 (29)	[10, 13, 15, 20, 22, 25, 29, 39, 41, 42, 45, 47]
• Antiplatelet, no. (%)	11 (27)	[10–13, 20, 25, 31, 39, 40, 42, 44]
• Anticoagulant, no. (%)	1 (2)	[10]
• Intravenous thrombolysis, no. (%)	6 (15)	[9, 14, 24, 30, 33, 38]
• Mechanical thrombectomy, no. (%)	6 (15)	[8, 24, 27]
• Hyaluronidase injections, no. (%)	3 (7)	[7, 13, 19]
• Hyperbaric oxygen, no. (%)	2 (5)	[19, 42]
• Intravenous mannitol, no. (%)	7 (17)	[13, 17, 18, 22, 36, 42, 43]
• Decompressive hemicraniectomy, no. (%)	12 (29)	[16–18, 23, 27, 28, 31, 36, 38]
Neurological outcomes		
Haemorrhagic transformation, no. (%)	5 (9)	[15, 16, 18, 37, 38]
mRS score ≤2, no. (%)	22 ^j (40)	[7, 9, 12, 13, 15, 17–20, 24, 25, 28, 29, 32, 34, 35, 39, 40, 43, 44, 49, 50]
Capable of ambulating with or without assistance, no. (%)	32 ^k (56)	[6, 7, 11–15, 17–20, 24, 25, 28–30, 32, 34, 35, 37–40, 43, 44–50]
Deaths, no. (%)	5 (9)	[8, 16, 22, 27, 47]

CVSRF: cardiovascular risk factors; LVO: large vessel occlusion; mRS: modified Rankin Scale; PDLLA: poly-D,L-lactic acid

^aUnspecified in 2 cases [20, 41].

^bMultiple injection sites refer to the injection of dermal filler at multiple areas on the ipsilateral face.

^cIncludes a case that involves a mixture of 25% hyaluronic and 75% PDLLA.

^dExcludes 7 cases without stroke symptoms [6, 12, 25, 39, 40, 44].

^eExcludes 8 cases in whom the time of onset was undescribed [6, 9, 17, 18, 28, 37].

^fExcludes patient 3 from Huo et al.'s series [27].

^gExcludes 7 cases in whom the size of infarcts was undescribed [13, 20, 24, 27, 38, 45, 51].

^hAngiographies were unperformed/unreported in 15 cases [13, 21, 23, 25, 26, 32, 34, 35, 37–40, 43, 45, 47].

ⁱMissing data in 14 cases [6, 16, 26, 32, 34, 37, 46, 48, 49, 51].

^jAt least 22 cases [7, 9, 12, 13, 15, 17–20, 24, 25, 28, 29, 32, 34, 35, 39, 40, 43, 44, 49, 50].

^kAt least 31 cases [6, 7, 11–15, 17–20, 24, 25, 28–30, 32, 34, 35, 37–40, 43, 44, 46, 48–50].

or loss of vision (27/29, 93%), and more than a third experienced ocular or peri-ocular pain (11/29, 38%). Stroke symptoms were the presenting features in most cases (43/55, 78%). Among these symptoms, hemiparesis/hemiplegia occurred in at least 23 (42%); confusion or reduced consciousness/alertness in 19 (34%); giddiness/dizziness, nausea and/or vomiting in 9 (16%) and aphasia in 6 (11%). After the onset of their initial symptoms, 5 cases (9%) subsequently developed new neurological deficits, while 9 (16%) experienced additional ocular symptoms, resulting in a total of 48 (87%) and 38 cases (69%) with stroke-like symptoms and ocular complaints, respectively. However, the interval from their presentation to the development of new neurologic/ocular symptoms was undescribed by most authors. Overall, hemiparesis/hemiplegia remained the most common stroke feature during their initial period of hospitalisation (30/55, 55%), followed by confusion or reduced consciousness/alertness (26/55, 47%); giddiness/dizziness, nausea and/or vomiting (11/55, 20%) and aphasia (10/55, 18%). A significant portion of patients (7/55, 13%) continued to exhibit/experience no stroke-like deficits, with ischaemic strokes being incidentally detected by brain imaging.^{7,13,26,40,41,45}

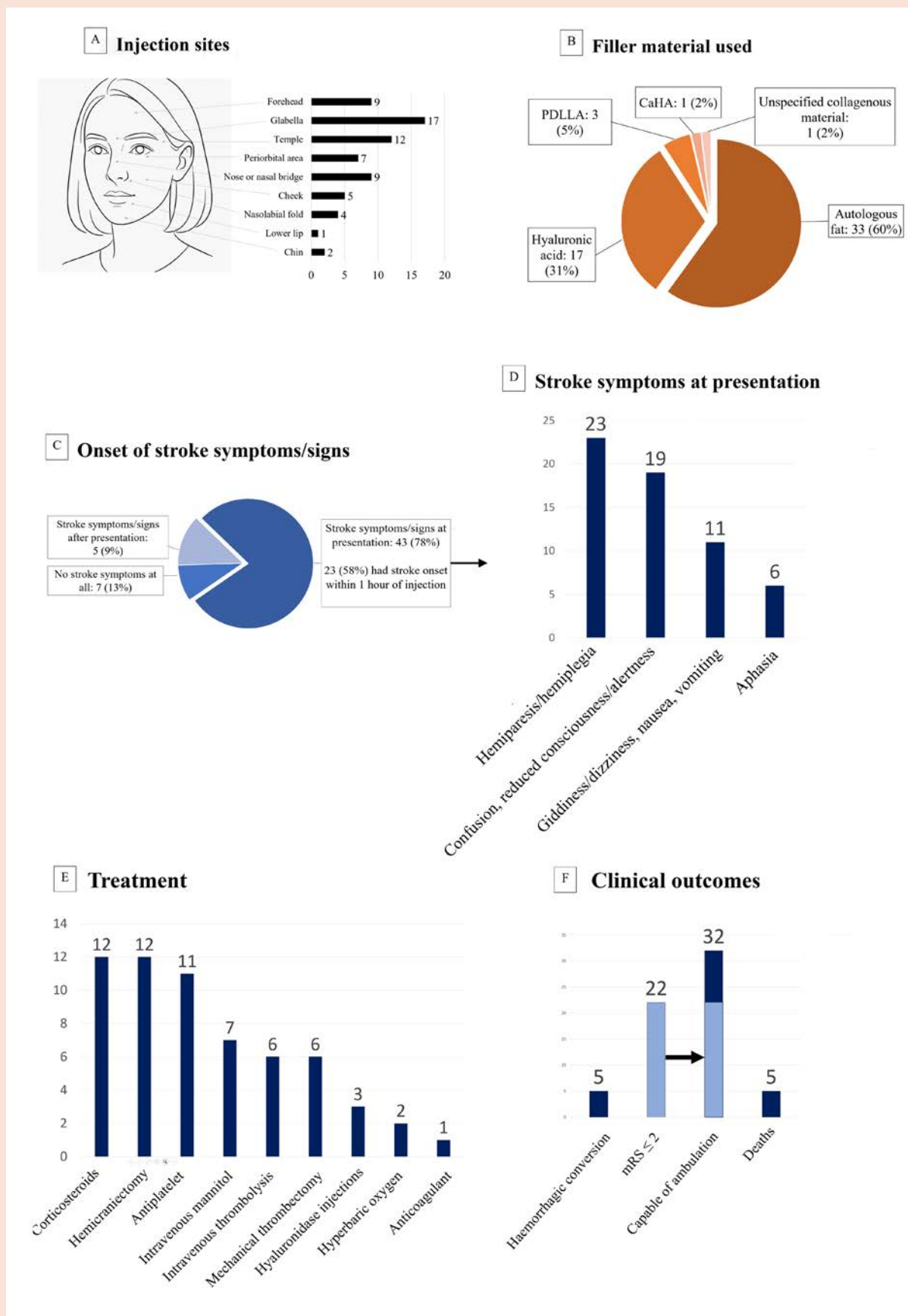
The interval between their injections and stroke onset is another area of interest. Excluding 7 patients who had no stroke symptoms and 8 with unknown

stroke onset time, more than half (23/40, 58%) developed neurological deficits soon after receiving their injections—immediate in 14, shortly after in 3, within 10 minutes in 2 patients, within 30 minutes in another 2, and within an hour in 1 patient. Longer intervals of more than an hour were reported in 16, including 4 who developed stroke symptoms around a day after their injections.^{17,38,46}

Radiological features

Brain imaging in the form of CTs and/or MRIs was performed in all cases (Table 1). Excluding Huo et al.'s patient 3 whose infarcts were not well-detailed, all cases (54/54, 100%) had infarcts in regions supplied by the anterior circulation, of which a fifth (12/54, 22%) had concurrent infarcts in areas supplied by the posterior circulation.²⁸ Majority of the infarcts were unilateral (45/54, 83%) and were evenly split between both hemispheres (left versus [vs] right hemisphere = 1.1:1), while bilateral infarctions occurred in only a few (9/54, 17%). Multifocal strokes occurred in slightly more than half (30/54, 56%), and at least 32 patients (32/48, 67%; excluding 7 cases without descriptions of stroke size) had sizeable territorial infarcts. Other radiological findings include co-existing right occipital lobe subarachnoid haemorrhages in 1 case, and in the left frontal and parietal lobes in another.^{7,13} Vascular imaging of the intracranial and/or cervical arteries

Fig. 2. Summary of study findings.



CaHA: calcium hydroxylapatite; mRS: modified Rankin Scale; PDLA: poly-d,l-lactic acid
 Note: Refer to Table 1 for details.

was performed in nearly three-quarters of the cases (73%, 40/55). Among these, magnetic resonance angiography was performed in 18 patients (18/55, 33%), CT angiography in 13 patients (13/55, 24%), digital subtraction angiography in 12 patients (12/55, 22%), transcranial Doppler sonography in 2 patients (2/55, 0.03%), and carotid ultrasound in another 2 patients (2/55, 0.03%). Among them, large vessel occlusions were identified in 16 (40%), involving the intracranial arteries in 12 and extracranial arteries in 4.

Treatment and outcome

Treatment was documented in only 41 (75%) patients, including corticosteroids in 12 (12/41, 29%), antiplatelet agents in 11 (27%), intravenous mannitol in 7 (17%), intravenous thrombolysis in 6 (15%), mechanical thrombectomy in 6 (15%), hyaluronidase injections in 3 (7%; retrobulbar and forehead in 1 case, peribulbar in another, and the glabella and forehead in a third), hyperbaric oxygen therapy in 2 patients (5%), an unspecified anticoagulant in 1 patient, and decompressive hemicraniectomies in 12 (29%) (Table 1). Sixteen patients (39%) received at least 2 of these aforementioned treatment modalities. Excluding 1 patient whose infarct size was unknown, all who underwent decompressive hemicraniectomy had large infarcts.³⁹ Haemorrhagic transformations were uncommon, occurring in only 5 (5/55, 9%).^{16,17,19,38,39} Notably, only 1 in 6 patients who received intravenous thrombolysis and none of those who underwent thrombectomy developed haemorrhagic transformation.³⁹

Clinical outcomes were inconsistently reported, and the evolution of neurological deficits, in most cases, was either left undescribed or incompletely detailed. Based on the available data, 5 patients died (5/55; 9%) at different time points (the 4th, 6th and 16th day from presentation; unknown in 2), and all except 1 (patient 3 from Huo et al.'s series whose radiological features were inadequately detailed) had large unilateral anterior circulation infarcts.^{9,17,23,28,48} Less than half who survived (22/55, 40%) achieved good functional recovery, with modified Rankin Scale (mRS) scores of ≤ 2 over periods of up to 5 years. However, most (32/55, 58%) were capable of ambulating, whether independently or with assistance.

Differences in stroke features and outcomes in patients who received autologous fat vs HA and/or PDLLA.

The stroke features and outcomes of patients who received autologous fat were then compared against those injected with HA and/or PDLLA (Table 2).^{54,55} While there were no differences in their median age, sex or mortality events, those injected with HA and/or PDLLA had higher incidences of cutaneous (53% vs 26%, $P=0.0037$) and ocular complications (100% vs

48%, $P=0.0001$), while those who received autologous fat tended to be symptomatic from their strokes (100% vs 68%, $P=0.0012$), have large strokes (93% vs 24%, $P<0.00001$), and were likelier to end up incapable of walking (41% vs 84%, $P=0.0024$). The latter group was also likelier to have received injections at their temples (41% vs 0%, $P=0.0008$).

DISCUSSION

Over the past 30 years, the landscape of filler injections has transformed significantly with advances in both materials and technology.^{2,58,59} The introduction of hyaluronic acid revolutionised the field, offering safer, reversible and more versatile options. Since then, the industry has expanded to include biostimulatory fillers like poly-L-lactic acid and PDLLA, which promote collagen regeneration for longer-lasting, natural-looking results. Alongside synthetic fillers, autologous fat grafting has experienced a resurgence, appealing to patients seeking natural, long-term volume restoration using their own tissue. Improvements in procedural techniques and anatomical understanding have since enhanced safety and precision, marking a shift from simple wrinkle correction to full facial rejuvenation and contouring.^{2,58,59} This research on filler-related strokes is therefore timely, as facial injections of dermal fillers become increasingly popular and accessible.

This study reaffirms the rarity of derma filler-related strokes and depicts affected patients as typically young women in their thirties. While this female predominance aligns with both previous and current trends in dermal filler use, these patients were notably younger than those reported in the literature.^{56,57} Unsurprisingly, cardiovascular risk factors were exceedingly rare. Most strokes, especially in older reports, involved the use of autologous fat, perhaps reflecting its well-established role as a dermal filler and a more recent shift towards the use of other materials, such as HA and PDLLA.^{58,59} The findings also reveal important features and characteristics of strokes from dermal fillers. First, the glabella and temples were the 2 most common injection sites leading to strokes when compared to other facial regions. The underlying pathomechanism likely involves the inadvertent injection of filler material into an extracranial artery, which then enters the ophthalmic and intracranial arterial systems due to (1) anastomoses between these vessels and intracranial arteries, (2) the application of positive pressure during these injections and (3) Poiseuille's law favouring retrograde flow in narrow distal arteries.⁷ Injections to the glabella are well-associated with higher risks of ocular and skin complications.⁶⁰ These were ascribed to the intricate arterial network (central and paracentral arteries, and supratrochlear arterial branches) at varying skin depths

Table 2. Comparison of clinical features in patients with strokes from dermal filler injections with autologous fat against hyaluronic acid and/or PDLLA.

	Autologous fat (n=34)	HA and/or PDLLA ^a (n=19)	P value
Median age, years (range)	30.5 (18–50)	34 (20–61)	NS
Female sex, no. (%)	29 (85)	17 (89)	NS
Sites of injections, ^b no. (%)			
• Temple	13 (41)	0 (0)	0.0008
• Nose or nasal bridge	0 (0)	8 (42)	0.0001
• Glabella	9 (28)	7 (37)	NS
• Nasolabial fold	3 (9)	2 (11)	NS
• Periorbital	5 (16)	2 (11)	NS
• Forehead	7 (22)	2 (11)	NS
• Multiple ^c	8 (25)	4 (36)	NS
Stroke symptoms, no. (%)	34 (100)	13 (68)	0.0012
Skin necrosis, no. (%)	7 (21)	10 (53)	0.0037
Ocular complications, no. (%)	16 (48)	19 (100)	0.0001
Large strokes, ^d no. (%)	27 (93)	4 (24)	<0.00001
Death	4 (12)	1 (5)	NS
Ambulatory, with or without assistance ^e	14 (41)	16 (84)	0.0024

HA: hyaluronic acid; NS: not specified; PDLLA: poly-d,l-lactic acid

^aIncludes the use of HA and P-DLLA, or both concurrently as a mixture.^bUnspecified in 2 cases [20, 41].^cMultiple injection sites refer to the injection of dermal filler at multiple areas on the ipsilateral face.^dMissing data in 7 cases in whom the size of infarcts was undescribed [13, 20, 24, 27, 38, 45, 51].^eData from 30 cases who were injected with autologous fat, HA and/or PDLLA [6, 7, 11–15, 17–20, 24, 25, 28–30, 32, 37–40, 43, 46, 48–50].Numbers in boldface indicate statistically significant *P* values.

in that region, and their short retrograde distance to the ophthalmic arteries (OAs), thereby increasing the risk of retrograde movement of material into intracranial arteries.⁵ Strokes from temporal injections can similarly be attributed to the entry of material into the intracranial arteries through the anastomotic connections between the superficial temporal artery and the OA.^{61–63}

Second, strokes invariably involved areas supplied by the anterior circulation, were often unilateral and large, and mostly occurred immediately or shortly after their injections. These are unsurprising, given that the inadvertent entry of injected material into the intracranial arteries was thought to occur via anastomotic connections with the ipsilateral OA, an explanation further supported by the frequent occurrence of ischemic ocular complications.^{5,8,61–63} In several cases, there was a notable delay between the time of injection and the onset of stroke and/or ocular symptoms, and it remains uncertain whether this reflects the delayed entry of filler material into the intracranial arterial system, or a failure to recognise stroke symptoms early, particularly those with mild neurological deficits. Regardless, a short period of

post-procedural observation appears prudent, as most strokes occurred within an hour after injection.

Third, several patients who presented with ocular symptoms had no neurological deficits, and strokes were incidentally discovered only by brain imaging. Nearly all had small strokes, which explains the absence of noticeable neurological deficits. However, given the risk of stroke progression, recurrence and disability, those presenting with ocular symptoms should therefore also undergo brain imaging even in the absence of neurological deficits. Last, the findings highlight important differences in the clinical features between different filler materials. Individuals who received autologous fat injections were at a greater risk of larger strokes and worse functional outcomes than those injected with HA and/or PDLLA. This may be due to the larger size and lower solubility of fat particles (400–1000 µm) compared to HA and PDLLA (30–70 µm), thereby increasing their likelihood of occluding the larger intracranial arteries and leading to larger strokes, more pronounced stroke symptoms, and poorer clinical recovery and outcomes.^{64–67} Taken together, the findings support the need for post-procedural observation (of an hour) after facial filler

injections, particularly when involving high-risk areas such as the glabella or temples, and when using autologous fat. While it is well-established that those with ocular complications require urgent work-up and treatment, the findings further underscore the need for early neuroimaging in the initial assessment of these patients to evaluate for strokes, even in the absence of cardiovascular risk factors or overt neurological deficits.

This study has important limitations. Its retrospective nature, small size, the inconsistent descriptions of clinico-radiological features, and the preponderance of Asian reports can limit the findings' applicability to the broader population. Key details, such as who performed the injections (e.g. doctors, nurses, unlicensed practitioners), their injection methods (cannula or needle), and the volume and brand of the fillers used, were often missing, precluding deeper analysis of the impact of these factors on the risk of stroke, clinico-radiological features and treatment outcomes. Furthermore, clinical outcomes were described at different time points, often without standardised assessments (i.e. mRS), rendering it difficult to analyse the trajectory and extent of recovery. Reporting bias was also a concern, as adverse events may be underreported due to potential commercial interests and influences. Asymptomatic strokes following filler injections could also go undetected, and the actual number of strokes is likely larger. Similarly, publication bias—where studies reporting higher incidences of adverse events such as strokes, are less likely to be published compared to those with lower rates—may contribute to a systematic underestimation of the true incidence and prevalence of strokes following filler injections. This potentially skews the perceived safety of facial fillers and confounds the findings from the comparative analysis of stroke features and outcomes between the use of autologous fat vs HA and/or PDLLA. The preponderance of Asian reports and the potential for geographical bias are also difficult to explain. Whether this reflects their greater susceptibility to dermal filler-related strokes, greater scientific interest on this issue in East Asia, differences in injection methods, or rheological differences of various filler formulations/brands used across different regions cannot be conclusively determined by the study's design.⁶⁸ While potentially relevant to Asian populations, the findings should therefore be interpreted and applied with caution in other regions of practice. Furthermore, methodological limitations also hindered the authors' attempt to study the differences in stroke risks between these materials, a question best addressed by randomised controlled trials.

Despite these limitations, the findings reinforce existing knowledge of dermal filler-related strokes,

such as the young age of affected patients, their lack of cardiovascular risk factors, the risks associated with glabellar injections, and that up to 10% of patients may have no stroke symptoms.¹⁹ These findings further add to existing descriptions of dermal filler-related strokes, including the important differences in the clinical features and treatment outcomes between autologous fat and HA and/or PDLLA injections. With dermal fillers set to stay in high demand, larger prospective studies with longer follow-up periods will be required in the future to address the aforementioned limitations and challenges.

CONCLUSION

Dermal filler-related strokes are rare but severe complications with a high risk of lasting neurological deficits and disability. Prompt recognition and intervention are therefore essential. Those injected with autologous fat tend to have larger strokes and experience non-ambulatory outcomes than those injected with HA and/or PDLLA. As most strokes occur shortly after facial injections, an hour of post-procedural observation appears reasonable, particularly when autologous fat is used, or when injecting at high-risk areas such as the glabella and temples. Given that a significant portion of cases had asymptomatic strokes, brain imaging is therefore recommended for those presenting with ocular complications after filler injections, even in the absence of obvious neurological symptoms or deficits.

Supplementary materials

Table S1. JBI risk of bias quality assessment for case series.

Table S2. JBI risk of bias quality assessment for case reports.

Ethics statement

Not applicable. This is a study on cases of dermal filler-related strokes reported in medical literature over the past 30 years. The data are publicly available. Institutional approval was therefore not needed.

Declarations

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. All authors have no conflict of interest to declare. This study did not receive funding.

Acknowledgements

The authors would like to acknowledge and thank Dr Nara Sugianto (Department of Neurology, Singapore General Hospital, Singapore) for her help in the early stages of literature search and review.

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Singapore consensus statements on the management of obstructive sleep apnoea

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ABSTRACT

Introduction: Obstructive sleep apnoea (OSA) is common in Singapore, with moderate to severe OSA affecting around 30% of residents. These consensus statements aim to provide scientifically grounded recommendations for the management of OSA, standardise the management of OSA in Singapore and promote multidisciplinary collaboration.

Methods: An expert panel, which was convened in 2024, identified several areas of OSA management that require guidance. The expert panel reviewed the current literature and developed consensus statements, which were later independently voted on using a 3-point Likert scale (agree, neutral or disagree). Consensus (total ratings of agree and neutral) was set a priori at $\geq 80\%$ agreement. Any statement not reaching consensus was excluded.

Results: The final consensus included 49 statements that provide guidance on the screening, diagnosis

and management of adults with OSA. Additionally, 23 statements on the screening, diagnosis and management of paediatric OSA achieved consensus. These 72 consensus statements considered not only the latest clinical evidence but also the benefits and harms, resource implications, feasibility, acceptability and equity impact of the recommendations.

Conclusion: The statements presented in this paper aim to guide clinicians based on the most updated evidence and collective expert opinion from sleep specialists in Singapore. These recommendations should augment clinical judgement rather than replace it. Management decisions should be individualised, taking into account the patient's clinical characteristics, as well as patient and caregiver concerns and preferences.

Keywords: adult, consensus, obstructive sleep apnoea, paediatrics, polysomnography, sleep apnoea

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Accepted: 9 September 2025

Published Online First: 16 October 2025

CLINICAL IMPACT

What is New

- This paper provides comprehensive guidance on the diagnosis and management of adult and paediatric obstructive sleep apnoea.
- This guidance has taken into consideration the applicability of the recommendations on the healthcare environment in Singapore.

Clinical Implications

- The recommendations in this paper may guide primary care professionals in providing early screening, prompt diagnosis and effective treatment.
- It also provides guidance on the appropriateness of referral to specialty care.
- These recommendations may optimise care by ensuring only the best care, based on the latest available evidence, is given to patients in Singapore.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a condition characterised by repeated episodes of upper-airway obstruction during sleep associated with desaturations or arousal from sleep.¹ This results in fragmented, non-restorative sleep as well as the classic symptoms of OSA (including loud snoring, gasping or choking, and excessive daytime sleepiness), which define OSA syndrome (OSAS).² Untreated OSA is associated with hypertension, increased rates of myocardial infarction, stroke, depression, accidents and impaired quality of life.¹

The Singapore Health Study 2012, a cross-sectional population study that included adults aged 21–79 years, found that 30.5% of Singaporeans had moderate to severe OSA, defined as an apnoea-hypopnoea index (AHI) of ≥ 15 events/hour. The prevalence of OSAS—defined as an AHI of ≥ 5 events/hour and an Epworth sleepiness score (ESS) of ≥ 10 —was 18.1%.³ Treatment for OSA, with continuous positive airway pressure (CPAP), has been shown to be cost-effective from the Singapore health system perspective.⁴

While most diagnostic and therapeutic interventions for OSA are available in Singapore, the complexity and multifactorial nature of OSA, and the potentially high level of resources required in its management necessitate multidisciplinary collaboration and evidence-based clinical guidance. These consensus statements aim to provide scientifically grounded recommendations for the management of OSA, standardise the management of OSA in Singapore,

promote multidisciplinary collaboration and elevate clinical decision-making.

METHODS

The panel was convened in January 2024, led by a steering committee formed by members of the Chapter of Sleep Medicine Physicians, Academy of Medicine, Singapore. Workgroup members, representing respiratory physicians, otolaryngologists, paediatricians and dentists in both private and public institutions were nominated by the steering committee. The College of Physicians, College of Pediatrics and Child Health, College of Dental Surgeons and Chapter of Otolaryngologists from the Academy of Medicine, Singapore were invited to nominate experts involved in the care of adult or paediatric patients with sleep-disordered breathing for participation in this panel. The College of Family Physicians Singapore was invited but did not nominate any participants. In addition, the consensus voting panel comprised sleep technologists, an internal medicine physician, a public health physician and a sleep scientist.

The expert panel identified several areas of management that require guidance, including the screening, diagnosis, management and long-term care of adult and paediatric patients with OSA.

The expert panel performed an online literature search on PubMed, Cochrane and Google Scholar, using the keywords “obstructive sleep apnea”, “screening”, “diagnosis”, “treatment” and “management.” Evidence summaries were developed based on the results of the literature search and were presented to the expert panel. The evidence was reviewed and appraised using the Grading of Recommendations Assessment, Development, and Evaluation, otherwise known as GRADE system.⁵ Based on this system, the level of evidence was designated as follows: (1) high (authors have high confidence that the true effect is similar to the estimated effect); (2) moderate (authors believe that the true effect is probably close to the estimated effect); (3) low (true effect might be markedly different from the estimated effect); and (4) very low (low confidence in the effect estimate). The authors adjusted the level of evidence if the estimated effect, when applied in Singapore, may differ from the published evidence due to various factors such as ethnicity, cultural differences, healthcare systems and resources and accepted practice.

Consensus recommendations were developed based on the retrieved evidence and modified using a modified Delphi-based approach facilitated by email voting (in October 2024). The strength of recommendation was classified as “strong” if the panel identified that the desirable effects of an intervention clearly outweigh the undesirable effects and that most

informed patients would choose the recommended management; “weak” if the trade-offs are less certain, either because of low-quality evidence, where evidence suggests that desirable and undesirable effects are closely balanced, or where alternative interventions are available; or good practice statement if the recommendation is based on the clinical experience of the expert panel. The experts also independently rated statements on a 3-point Likert scale (agree, neutral or disagree) with an option to submit their comments for further optimisation. Consensus (total ratings of “agree” and “neutral”) was

set a priori at $\geq 80\%$ agreement. Any statement not reaching consensus was excluded.

RESULTS

The expert panel developed 72 consensus statements: 49 statements covered the management of OSA in adults and 23 statements on OSA in children. The 21 statements on the screening and diagnosis of OSA in adults are shown in Table 1. The 28 statements on the treatment and follow-up of OSA in adults are enumerated in Table 2. Lastly, the 23 statements on paediatric OSA are outlined in Table 3.

Table 1. Summary of the recommendations on the screening and diagnosis of OSA in adults.

Statement	Level of evidence	Strength of recommendation
Screening		
Screening for OSA is recommended in patients with hypertension, cardiovascular disease, diabetes mellitus or obesity, or preoperative patients.	Low	Strong
The use of validated screening tools is recommended for OSA screening.	Moderate	Strong
Screening for OSA is recommended in pregnant individuals with obesity (BMI 30 kg/m ² or higher).	Moderate	Strong
Diagnosis		
Sleep testing is recommended in patients with symptoms of OSA or those found to have elevated risk based on validated screening tools.	Moderate	Strong
Sleep testing is recommended in patients with young/resistant hypertension, AF requiring cardioversion/ablation, unexplained pulmonary hypertension or unexplained nocturia.	Moderate	Strong
Sleep testing may be considered in post-stroke patients with OSA symptoms and who are likely to be able to use CPAP.	Low	Weak
Clinical tools, questionnaires and prediction algorithms SHOULD NOT be used in isolation to diagnose OSA in adults.	Moderate	Strong
PSG or home sleep tests should only be ordered under the guidance of medical or dental professionals with appropriate training in sleep medicine.	Very low	Strong
PSG (Level I) is recommended as the gold standard in the diagnosis of OSA.	Moderate	Strong
In-laboratory PSG performed by personnel qualified in sleep medicine is recommended as the gold standard and reference diagnostic sleep test.	Moderate	Strong
PSG should include sleep electroencephalogram, electrooculogram, electromyogram, electrocardiogram, respiratory flow, snoring, respiratory effort, oxygen saturation, body position and video monitoring.	Moderate	Strong
PSG is recommended in patients with clinical suspicion of OSA with discordant HSAT findings.	Low	Strong
Level III or Level IV sleep studies are NOT recommended to diagnose OSA in patients with significant cardiac, respiratory or neuromuscular comorbidities.	Moderate	Strong
A split-night diagnostic protocol, rather than a full-night diagnostic protocol for PSG may be considered for the diagnosis of OSA.	Low	Weak
All sleep studies (Level I to IV) must be interpreted and reported by a specialist trained and certified in sleep medicine.	Very low	Strong

Table 1. Summary of the recommendations on the screening and diagnosis of OSA in adults. (Cont'd)

Statement	Level of evidence	Strength of recommendation
HSAT		
An HSAT is recommended for patients with a high pretest probability for moderate to severe OSA and without significant cardio-respiratory comorbidities.	Moderate	Strong
The need for, and appropriateness of, an HSAT must be based on the patient's medical history and a face-to-face examination by a physician, either in person or via telemedicine.	Very low	GPS
An HSAT to diagnose OSA or assess treatment efficacy must be ordered by a physician.	Very low	Strong
HSAT should NOT be used for general screening of asymptomatic populations.	Very low	GPS
Diagnosis, assessment of treatment efficacy, and treatment decisions must NOT be based solely on automatically scored HSAT data.	Very low	GPS
The raw data from the home sleep apnoea test device must be reviewed and interpreted by a physician who is trained and certified in the management of OSA.	Very low	GPS
BMI: body mass index; CPAP: continuous positive airway pressure; GPS: good or best practice statement; HSAT: home sleep apnoea test; OSA: obstructive sleep apnoea; PSG: polysomnography		

Table 2. Summary of recommendations on the treatment and follow-up of OSA in adults.

Statement	Level of evidence	Strength of recommendation
CPAP		
CPAP treatment is recommended in symptomatic patients with OSA of any severity.	High	Strong
CPAP therapy is recommended in the treatment of moderate-severe OSA in patients with hypertension.	Moderate	Strong
In OSA patients who do not fulfil the conventional criteria for treatment, symptomatic improvement after a short trial of CPAP may help determine if long-term CPAP is beneficial.	Low	Weak
CPAP therapy should be considered in patients with moderate-severe OSA and AF undergoing rhythm control.	Moderate	Strong
CPAP therapy should be considered in patients with OSA and heart failure.	Moderate	Strong
OSA treatment should be considered in asymptomatic patients with moderate-severe OSA.	Moderate	Strong
OSA treatment may NOT be indicated in elderly patients who are minimally symptomatic.	Low	Weak
CPAP should be prescribed by and used under the guidance of a medical professional appropriately trained and certified in the management of OSA.	Very low	GPS
A change in PAP mode should be prescribed by and used under the guidance of medical professionals appropriately trained and certified in the management of OSA.	Very low	GPS
Initiation of CPAP therapy		
Home auto-titrating PAP is recommended for CPAP initiation in adults with OSA and no significant comorbidities.	Moderate	Strong
In adult OSA patients not using auto-PAP, home or in-laboratory PAP titration are recommended for CPAP initiation.	Moderate	Strong
In-laboratory PAP titration is recommended in adults with OSA with significant comorbidities or who fail home auto-PAP titration.	Moderate	Strong
Split-night titration may be considered when moderate to severe OSA is observed during a minimum recording time of 2 hours and wherein at least 3 hours are available for CPAP titration.	Low	Weak

Table 2. Summary of recommendations on the treatment and follow-up of OSA in adults. (Cont'd)

Statement	Level of evidence	Strength of recommendation
Improving CPAP adherence		
Patient education by professionals trained to provide CPAP therapy is recommended to increase PAP adherence.	Moderate	Strong
Supportive interventions and behavioural therapies by professionals trained to provide CPAP therapy may be considered to increase CPAP adherence.	Moderate	Weak
Heated humidification may be considered in OSA patients who report nasal congestion, dry nose or mouth, and sore throat.	Moderate	Weak
Treatment of nasal obstruction should be considered to improve CPAP adherence.	Moderate	Strong
Other non-surgical treatments		
In patients with OSA who are overweight or obese, weight management is recommended.	Moderate	Strong
Oral appliances should be considered in adjunctive treatment of mild to moderate OSA in patients with craniofacial and dentofacial anomalies.	Moderate	Strong
Hypoglossal nerve stimulation may be considered in selected patients with moderate to severe OSA who are CPAP intolerant.	Moderate	Strong
Surgical treatment		
Upper-airway surgery should be considered in selected patients with suitable upper-airway anatomy who fail non-surgical treatment.	Moderate	Strong
Upper-airway surgery should be considered as an adjunct in selected patients to improve adherence to and/or efficacy of other treatment modalities.	Moderate	Strong
Long-term management and follow-up		
Follow-up PSG or HSAT is recommended to assess response to treatment with non-PAP interventions.	Low	Strong
Follow-up PSG or HSAT may be considered in patients on OSA treatment with clinically significant weight gain or loss since the initial diagnosis of OSA or the initiation of treatment.	Low	Weak
OSA patients should be followed up within the initial weeks after CPAP initiation to assess treatment efficacy and adherence.	Low	Strong
Subsequent yearly evaluation may be considered after CPAP efficacy and adherence are ensured. Longer intervals may be appropriate for selected patients who are highly adherent to PAP therapy, have sustained resolution of OSA-related symptoms, and have no concerns regarding their PAP therapy.	Very low	GPS
OSA patients with persistent or recurrent sleep-related complaints or persistent difficulties with CPAP use should receive more frequent follow-ups.	Very low	GPS
Routine sleep testing is NOT recommended to re-evaluate OSA status in patients on CPAP therapy with good symptom control and no change in clinical status (e.g. significant weight loss or upper-airway surgery).	Very low	GPS

AF: atrial fibrillation; CPAP: continuous positive airway pressure; GPS: good or best practice statement; HSAT: home sleep apnoea test; OSA: obstructive sleep apnoea; PAP: positive airway pressure; PSG: polysomnography

DISCUSSION

OSA in adults

Screening

In asymptomatic patients, there is little evidence that screening or testing for OSA in adults without comorbidities is beneficial. Screening for OSA is

aimed at identifying asymptomatic patients with high pretest probability of OSA who should be referred for sleep testing, as they are likely to benefit from potential OSA treatment. Current evidence suggests that OSA screening should be performed in patients with hypertension, cardiovascular disease, diabetes mellitus or obesity, or in preoperative patients (Fig. 1).^{1,6-9} The Society of Anesthesia and Sleep Medicine

Table 3. Summary of recommendations on the management of OSA in children.

Statement	Level of evidence	Strength of recommendation
Screening		
Children of all ages should be screened by their family physicians or paediatricians for the presence of snoring as well as symptoms and signs suggestive of OSAS during routine health visits.	Moderate	Strong
Diagnosis of OSA should be considered in children with adenoid hypertrophy, tonsil hypertrophy, obesity, allergic rhinitis, structural abnormalities of the airways, Down syndrome, Prader-Willi syndrome, achondroplasia, neuromuscular disease and other at-risk comorbidities.	Moderate	Strong
For children with prematurity, family history of OSA, genetic, craniofacial or neuromuscular conditions that increase the risk of OSA, a lower threshold to screen and evaluate is recommended.	Low	Strong
Diagnosis		
Clinical evaluation including history, physical examination, audio/video recordings and standardised questionnaires have insufficient sensitivity and specificity for the diagnosis of OSA in children.	Moderate	Strong
In-laboratory overnight attended PSG with video recording and CO ₂ monitoring is recommended as the gold standard and reference diagnostic sleep test for the diagnosis of OSA in children.	Moderate	Strong
In selected children with high pretest probability, sleep oximetry may be considered when PSG is not feasible.	Low	Weak
Sleep studies including Levels I to IV studies should be ordered under the guidance of medical professionals appropriately trained and certified in sleep medicine or the management of OSA.	Very low	GPS
Sleep studies including Levels I to IV studies should be interpreted and reported by a paediatric sleep specialist with clinical review.	Very low	GPS
PSG definition for OSA applies to children 1 to 18 years old.	Low	Strong
Using PSG, an AHI ≥ 1 /hour or a pattern of obstructive hypoventilation, defined as hypercapnia (i.e. PaCO ₂ TcCO ₂ > 50 mmHg) in at least 25% of total sleep time, indicates OSA in children.	Low	Strong
The severity of OSA is recommended to be graded on PSG findings as follows: mild (AHI ≥ 1 /hour and < 5 /hour); moderate (≥ 5 /hour and < 10 /hour); and severe (≥ 10 /hour).	Low	Strong
Treatment		
A trial of nasal corticosteroids with or without montelukast may be considered in children with mild OSA with adenoid and/or tonsil hypertrophy. Regular follow-up is recommended to evaluate efficacy and adverse reactions.	Moderate	Weak
If resources permit, a sleep study is recommended for patients being considered for surgery indicated for the treatment of OSA.	Low	Strong
For children with OSA with clinical findings discordant with adenoid and/or tonsil hypertrophy, assessment of other risk factors of OSA (e.g. obesity or atopy, dentofacial anomalies, hypotonia) and targeted intervention is recommended.	Low	Strong
Clinicians should counsel patients and caregivers and explain that obstructive sleep-disordered breathing may persist or recur after adenotonsillectomy and may require further management.	Low	Strong
Follow-up sleep study is recommended post-surgical intervention for those with comorbidity, severe OSA and persistent or recurrent symptoms.	Low	Strong
PAP should be considered in children with moderate to severe OSA without adenoid and/or tonsil hypertrophy, persistence after surgery, or those who refuse or are not suitable for surgery. Other treatments may also be considered in developing a treatment plan for these patients.	Moderate	Strong
In-laboratory PAP titration is recommended for all children with OSA who are prescribed CPAP for optimal PAP settings.	Moderate	Strong
Follow-up PSG with or without CPAP titration in children on chronic PAP support is indicated to determine whether pressure requirements have changed as a result of the child's growth and development, if symptoms recur while on PAP, or if additional or alternate treatment is instituted.	Low	Strong
If PAP is implemented, regular evaluation is recommended to monitor for efficacy and adverse effects.	Low	GPS

Table 3. Summary of recommendations on the management of OSA in children. (Cont'd)

Statement	Level of evidence	Strength of recommendation
Dentofacial orthopaedics (growth modification orthodontic treatment) may be considered in children with primary snoring, upper airway resistance syndrome or OSA who exhibit craniofacial or dentofacial anomalies with hypoplastic and/or retrognathic maxilla and mandible.	Moderate	Weak
Myofunctional therapy may be considered as a treatment modality or an adjunctive treatment for mild to moderate OSA.	Low	Weak
For overweight or obese children with OSA, behavioural and dietary interventions to control weight are recommended.	Low	Strong

AHI: apnoea-hypopnoea index; OSA: obstructive sleep apnoea; OSAS: obstructive sleep apnoea syndrome; PSG: polysomnography

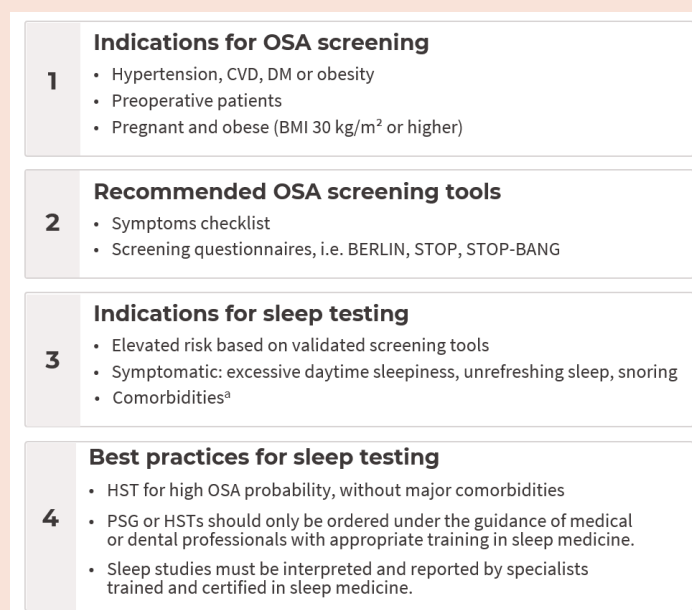
(SASM) and the Society for Obstetric Anesthesia and Perinatology (SOAP) also recommend screening for OSA for pregnant individuals with obesity (body mass index [BMI] of 30 kg/m² or higher), due to their high pretest probability.¹⁰

There are several validated screening tools available, including the Berlin questionnaire; snoring, tiredness, observed apnoea, high blood pressure (STOP) questionnaire; and STOP-BMI, age, neck circumference and gender (BANG) questionnaire.¹¹⁻¹³ The ESS, an assessment tool for subjective sleepiness, has also been used to screen for symptoms of OSA.¹⁴ These 4 aforementioned questionnaires are the most widely used screening tools in primary care and have all been validated across a wide range of patient-types. STOP-BANG, in particular, has been validated in

a Singapore population. Identification of OSA symptoms is the foundation of OSA screening tools, as the identification of symptoms substantially improves the diagnostic yield of polysomnography.¹⁵ An ESS score of 8 or above predicted a mean sleep latency on the multiple sleep latency test of less than 10 minutes in a Singapore cohort, suggesting that a lower cut-off for excessive daytime sleepiness may be appropriate in Singapore.¹⁶ A study that included patients in Singapore with OSA symptoms found that polysomnography (PSG) was able to detect abnormal AHI in 71.8% patients (AHI 5–15: 22.3%; AHI >15–30: 18.3%; AHI >30: 31.2%).¹⁷

In the primary care setting, a screening test with higher sensitivity may be preferred to ensure adequate diagnostic investigation. Of the 4 questionnaires

Fig. 1. Obstructive sleep apnoea screening and testing guidelines.



BMI: body mass index; CVD: cardiovascular disease; DM: diabetes mellitus; HST: home sleep test; OSA: obstructive sleep apnoea; PSG: polysomnography; STOP: snoring, tiredness, observed apnoea, high blood pressure; STOP-BANG: STOP-BMI, age, neck circumference and gender

^a Young/resistant hypertension, atrial fibrillation requiring cardioversion/ablation, unexplained pulmonary hypertension, unexplained nocturia, post-stroke patients with OSA symptoms who are likely able to use continuous positive airway pressure.

mentioned, STOP-BANG possessed the greatest pooled sensitivity.¹² The evidence is unclear as to which questionnaire is the most specific. Furthermore, the SASM/SOAP guidelines do not recommend the Berlin questionnaire, the STOP-BANG questionnaire and the ESS for screening in pregnant women;¹⁸ screening for OSA symptoms may be considered instead.

While the evidence on the harms and costs of screening are limited, the expert panel opines that the harms, financial and workforce burden and disruption to the clinical workflow are minimal. Nonetheless, the real-world cost-utility tradeoff of screening in the primary care setting has yet to be assessed.

Diagnosis

Misdiagnosing patients with OSA can lead to significant harm as a result of over or under treatment. Supervised PSG is the current gold standard for the diagnosis of OSA in adults.^{1,19} This test involves the recording of multiple physiological signals required for a quantitative assessment of sleep and sleep disorder. This involves sleep electroencephalography, electrooculography, electromyography, respiratory flow and effort, oxygen saturation and carbon dioxide measurement, and video and audio recording.

Given the significant time, effort and cost associated with PSG, it should only be performed in patients that would benefit from testing and eventual treatment, such as those with symptoms of OSA or those found to have elevated risk based on validated screening tools, those at elevated cardiovascular risk, those with conditions that may be aggravated by OSA, such as patients with young/resistant hypertension, atrial fibrillation (AF) requiring cardioversion/ablation, unexplained pulmonary hypertension or unexplained nocturia (Fig. 1).^{1,6,19,20} Due to the high prevalence of OSA in stroke patients (up to 70%) and a number of studies showing improved recovery in these patients using CPAP, sleep testing may also be considered in post-stroke patients with OSA symptoms and who are likely to be able to use CPAP.^{1,19}

Clinical tools, questionnaires and prediction algorithms do not have sufficient accuracy to diagnose OSA and should, therefore, not be used as the sole test for diagnosing OSA.¹¹⁻¹⁴ While PSG (Level I) remains the gold standard in the diagnosis of OS, Levels II to IV sleep studies may be considered to diagnose OSA in patients with high pre-test probability.^{1,21} However, Level III or Level IV sleep studies should not be used in patients with significant cardiac, respiratory or neuromuscular comorbidities, as these conditions may affect the accuracy of the sleep test results. PSG is also the preferred diagnostic test in patients with discordant home sleep apnoea test (HSAT), as well as those with persistent suspicion of OSA despite normal or inconclusive respiratory polygraphy.¹

As OSA is just one of the various medical conditions that may cause OSA symptoms (e.g. daytime sleepiness, loud snoring, waking up gasping or choking, morning headaches, dry mouth or sore throat, mood changes, and memory and concentration problems), knowledge of sleep medicine is important prior to requesting a sleep test. Hence, guidance from medical or dental professionals with appropriate training in sleep medicine should be sought before ordering a sleep test (Fig. 1). Guidance from trained sleep professionals would also aid in determining the appropriateness of a split-night diagnostic protocol rather than a full-night diagnostic protocol when ordering PSG for the diagnosis of OSA.²² Finally, the expert panel reiterates that sleep studies, regardless of level, must be interpreted and reported by a specialist trained and certified in sleep medicine.

Home sleep apnoea testing (HSAT)

An HSAT is a well-validated alternative to PSG for the diagnosis of OSA in selected populations.²³ These devices monitor only selected physiologic variables, which may include peripheral arterial tonometry, electrocardiography, cardiopulmonary coupling, respiratory effort, and airflow and oxygen saturation. Some devices may even include limited electroencephalography channels. Due to their lower resolution and accuracy, these devices are currently recommended only for patients with a high pretest probability of moderate-to-severe OSA with no significant comorbidities, which may affect the accuracy of the HSAT results.^{1,21} These include significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular conditions, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke, or severe insomnia. In appropriately selected patients, treatment outcomes are similar to those diagnosed with PSG or HSAT.^{24,25}

Given the importance of patient selection for the success of HSAT, the expert panel underscores the performance of a medical history and a face-to-face examination (in person or virtually) by a physician prior to ordering an HSAT. The expert panel also does not recommend the use of HSAT for general screening of asymptomatic populations, as the benefit of an OSA diagnosis and treatment in asymptomatic individuals without associated comorbidities is not established, and may lead to unnecessary discomfort and associated costs. The expert panel also recommends the review and interpretation of raw data from HSAT by a trained physician and suggests to avoid over-reliance on the automatic scoring of HSAT data. Lastly, in-laboratory PSG should be considered in negative, inconclusive, or technically inadequate HSATs in patients with high suspicion for OSA.^{1,26,27}

Continuous positive airway pressure (CPAP)

CPAP is the gold standard treatment for symptomatic OSA, regardless of severity. CPAP acts as a pneumatic splint to maintain the patency of the upper airways during sleep. There is robust evidence that CPAP is associated with improvements in AHI, daytime sleepiness and sleep-related quality of life.^{28,29} Several studies have also shown that CPAP is associated with a reduction in blood pressure in patients with hypertension, although heterogeneity between studies is high.^{30–35} Furthermore, a systematic review found that even in non-sleepy OSA patients, CPAP was associated with improved health-related quality of life scores.³⁶ Hence, OSA treatment with CPAP should also be considered in patients with moderate to severe OSA, even if they are asymptomatic. That said, shared decision-making is imperative to discuss the expected benefits of treatment relative to the patient's baseline risk level, and against the cost of CPAP and the low adherence rates documented in patients with little or no symptoms.³⁷

Due to cardiovascular risks associated with OSA, research has also explored the benefits of CPAP in patients with OSA and various cardiovascular conditions. For example, a meta-analysis found that in patients with both OSA and AF who were on anti-arrhythmic therapy, CPAP use was associated with a 49% reduction in the risk of AF recurrence.³⁸

CPAP therapy should also be considered in patients with OSA and heart failure (HF). The association between OSA and HF is well established. Patients with HF and untreated OSA have heightened risk due to systemic and pulmonary hypertension, risk of arrhythmias, reduced response to HF treatment and lower quality of life. CPAP should be considered in these patients to slow down the progression of HF, improve response to HF treatment, reduce the risk of hospitalisation due to HF and improve quality of life.³⁹

Disadvantages of CPAP include high cost, discomfort and inconvenience associated with the use of the CPAP device, which has led to low adherence and frequent treatment discontinuation as reported in the literature. While the benefits of CPAP typically outweigh its harms and cost, it should still be used judiciously and may not be appropriate in patients who are likely to receive only minimal benefit, such as elderly patients who are minimally symptomatic. Importantly, the expert panel recommends that CPAP be prescribed by and used under the guidance of medical professionals who are appropriately trained and certified in the management of OSA. Changes in CPAP mode should also be made by appropriately trained and certified professionals.

Initiation of CPAP therapy

The initiation of CPAP requires titration of pressures to eliminate apnoeas and hypopnoeas (or at least

reduce AHI to <5 events/hour) in all sleep positions and sleep stages while preventing arousal and central apnoea events. Titration may be done manually or automatically, in-laboratory or at home, and via split-night or full-night titration. Manual in-laboratory titration with continuous monitoring of airflow, leak and arterial oxygen saturation during sleep is the gold standard for positive airway pressure (PAP) titration.¹ However, automatic PAP (auto-PAP) devices, including automatic CPAP devices, can identify a therapeutic pressure where 90% or 95% of all titration pressures fall regardless of sleep stage or position.⁴⁰ Furthermore, meta-analyses have been able to demonstrate that in patients with moderate to severe OSA without significant comorbidities, home auto-PAP titration was as effective as in-laboratory PAP titration in reducing OSA severity and daytime sleepiness in improving quality of life.³⁰ In patients with significant comorbidities or those who fail home auto-PAP titration, in-laboratory titration is recommended.

Split-night titration, which involves using the initial hours of the PSG for diagnostic evaluation and the remaining time for PAP titration, has shown comparable outcomes to full-night titration in terms of long-term adherence and subjective sleepiness.^{41,42} However, specific conditions must be satisfied to conduct a split-night PSG, such as the presence of moderate to severe OSA, a minimum of 2 hours of diagnostic recording and at least 3 hours available for CPAP titration.¹

Lastly, the choice of titration strategy should consider other factors, such as patient preferences and the availability of resources, while being guided by the clinical judgement of the sleep medicine specialist.

Improving CPAP adherence

The benefits of CPAP are strongly correlated with treatment adherence; however, non-adherence to CPAP may be as high as 80%.⁴³ Hence, effort should be made to improve CPAP adherence.

Educational interventions aim to enhance awareness of OSA, its implications and the advantages of treatment, on the primary assumption that providing knowledge can influence personal beliefs and attitudes, potentially driving behavioural changes. The nature and delivery of educational approaches varied across studies, encompassing printed materials, video presentations, online education, phone consultations, one-on-one counselling, tailored feedback, and reviews of individual PSG results. The impact of educational interventions on CPAP adherence is varied, with most studies indicating some level of improved compliance with treatment.^{30,44} These interventions pose minimal risks and are relatively inexpensive, with costs ranging from low to moderate depending on the approach. As a result, the benefits generally outweigh the potential risks.

Supportive interventions provide additional encouragement and reinforcement through various strategies such as telemonitoring (e.g. telephone calls, texting), personalised support platforms and peer buddy systems. These interventions engage patients, increase support and reinforce strategies to increase CPAP adherence. Most studies on supportive interventions report a modest improvement in adherence although some report no benefit.^{1,44}

Behavioural interventions focus on modifying behavioural constructs to improve adherence to CPAP. Unlike educational interventions that provide passive knowledge transfer, these interventions require participant engagement and behavioural changes. Such interventions include motivational enhancement therapy, cognitive behavioural therapy and progressive muscle relaxation training. There is low-quality evidence suggesting that these interventions may increase CPAP adherence, which is associated with improvement in symptoms.^{30,44} These interventions may be combined with educational and supportive interventions for greater improvement in adherence. While the potential harm of these interventions is negligible, the associated costs may be high, depending on the resources needed to implement specific interventions.

Heated humidification may improve CPAP adherence by relieving upper-airway symptoms such as nasal congestion, dry nose and mouth, and sore throat, which are common adverse effects of PAP.⁴⁵ Most CPAP machines have built-in humidification systems. However, systematic reviews have failed to show improvement in adherence or symptom scores, while only 1 cohort study showed greater adherence with humidification.^{30,46,47} Furthermore, water may condense into the PAP circuit or the user's face. Hence, heated humidification should be used only after careful consideration of the specific adverse effects of CPAP on the patient, being most appropriate in those with nasal congestion, dry nose or mouth or sore throat.

As nasal PAP interfaces require airway patency, the presence of pre-existing nasal obstruction or the development of new nasal obstruction due to CPAP use may lead to low CPAP adherence. Strategies to resolve nasal obstruction may include conservative, medical, or rarely, surgical options. Conservative strategies include the use of nasal pillows or an oronasal/full-face mask as second-line interfaces; however it should be emphasised that studies show that patients with nasal obstruction have better efficacy and compliance outcomes with nasal masks compared to oronasal masks, which should only be used as a last resort.⁴⁸ Medical interventions include the use of sodium hyaluronate nasal spray, saline nasal spray or intranasal corticosteroid sprays; however, the clinical evidence supporting these interventions is weak and

of poor quality.^{49,50} On the other hand, nasal surgery has been shown to significantly improve adherence in up to 90% of PAP-intolerant users due to nasal obstruction.^{51,52} Given the variable benefits and risks of these 3 types of intervention, clinicians should combine best clinical judgement, careful patient selection and shared decision-making when deciding the most appropriate strategy to improve CPAP adherence in patients with nasal obstruction.

Other non-surgical treatments

The role of weight loss on the severity of OSA is well established. Meta-analyses of randomised and non-randomised studies employing a variety of weight loss methods resulting in weight changes ranging from -5 to -19 kg also found AHI reductions of 4 to 25 episodes/hour.⁵³⁻⁵⁶ The expert panel recognised the benefits of weight loss in individuals who are overweight or obese, regardless of the presence of OSA, and underscored its additional benefit in patients with OSA. Furthermore, weight loss through dietary modification and exercise is not associated with serious adverse effects, and costs may be modest—hence, the strong recommendation given by the expert panel. Additionally, adjunctive weight loss therapies such as pharmacotherapy may be considered in carefully selected patients with OSA.⁵⁷ The choice of specific intervention should consider the patient's overall clinical condition, including the severity of obesity and the presence of comorbidities, as well as individual values and preferences. For instance, while GLP-1 receptor antagonists are known to have cardiovascular benefits, phentermine and topiramate may cause insomnia, which may worsen daytime sleepiness.⁵⁷

Oral appliances, such as mandibular repositioning/advancement devices, relocate the mandible, hyoid, and the attached muscles and soft tissues into a forward position. This increases the pharyngeal airway space and activates the tongue, soft palate, masseter and submental muscles during sleep to minimise pharyngeal collapsibility. Clinical guidelines of the American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine recommend oral appliances over no therapy in adult patients with OSA who refuse or cannot tolerate CPAP.⁵⁸ Clinical trials have shown that customised oral appliances are effective in reducing AHI; improving daytime sleepiness, quality of life and hypertension in patients with mild to moderate OSA; and have high acceptability and self-reported adherence.^{59,60} A Singapore study also found that mandibular advancement was noninferior to CPAP for reducing 24-hour mean arterial BP in participants with hypertension and increased cardiovascular risk.⁶¹ However, only patients with suitable dentition (i.e. sufficient healthy teeth and

periodontium to retain the device), adequate protrusive jaw function, and without temporomandibular disorders may use oral appliances. Patients should also be aware of the impact of long-term use of oral appliances, such as minor tooth movements, occlusion changes, and possible temporomandibular joint-related symptomology.⁶² Regular follow-up and the management of side-effects are essential to maximise the treatment adherence and clinical effectiveness of oral appliance therapy.⁶³ Hypoglossal nerve stimulation (HNS) is an emerging treatment for OSA and may be considered in carefully selected patients with moderate to severe OSA who cannot tolerate CPAP. The Phase III trial STAR cohort demonstrated that HNS is associated with a 68% reduction in AHI as well as improvements in oxygen desaturation index, oxygen saturation during sleep, snoring, ESS and quality of life.^{64,65} However, the impact of HNS on cardiovascular health is still currently unknown.

Despite data supporting its efficacy in selected patients, HNS may be associated with surgical risk during implantation, device malfunction and potential for nonresponse, all of which should be discussed with the patient.¹ Furthermore, the upfront cost of HNS is high.

Surgical treatment

Soft tissue surgery or maxillomandibular advancement (MMA) surgery for OSA is typically regarded as a secondary treatment option, reserved for patients who do not respond to or cannot tolerate CPAP therapy or other non-surgical approaches. Given the high non-adherence rate to CPAP, alternative treatments, including upper-airway surgery, may be appropriate for a notable proportion of OSA patients. Evidence shows that, for individuals unable or unwilling to use CPAP, surgical intervention can lead to significant improvements in excessive daytime sleepiness, snoring, blood pressure and AHI or respiratory disturbance index (i.e. number of apnoeas, hypopnoeas and respiratory effort-related arousals per hour of sleep) in carefully selected patients with suitable anatomy.⁶⁶⁻⁶⁸ Additionally, surgery has shown clinically meaningful benefits for sleep-related and overall quality of life, with minimal risk of lasting swallowing difficulties. A Singapore study also found that anterior palatoplasty was associated with reduced snoring, improved oxygen saturation and subjective improvement in tiredness.⁶⁹ The expert panel also recommends surgery as a complementary treatment in select cases to enhance the efficacy of or adherence to other therapies. Ideal candidates for such an approach include those with favourable anatomical features, such as tonsillar hypertrophy, lack of palatal or lateral pharyngeal obstruction, or individuals without a high BMI or severe OSA.

Currently accepted practice favours the use of surgery as a second-line treatment for OSA.^{1,70,71} Primary surgical intervention may be considered for patients with specific anatomical abnormalities (e.g. craniofacial structural issues or significant tonsillar enlargement) as treatment for these conditions, but not only for the treatment of OSA itself. Nonetheless, improvement in OSA parameters, such as AHI, may be expected when these abnormalities are surgically corrected. MMA is a well-established surgical strategy to improve multi-level upper-airway patency. Surgical success in mitigating the severity of AHI and the cure rate (achieving AHI of less than 5) were 85.5% and 38.5%, respectively.^{72,73}

Patients considering surgical treatment for OSA should be informed of potential risks and challenges, such as postoperative pain, the possibility of surgical failure and perioperative complications.

Additionally, bariatric surgery may be considered in Asian patients with OSA and obesity-related complications, and a BMI of 32.5 kg/m² or higher (lower than the 35.0 kg/m² indicated for Westerners) or >37.5 kg/m² without complications, as Asians have a higher risk of obesity-related complications at lower BMIs.⁵⁷

Long-term management and follow-up

Follow-up PSG or HSAT play a role in the assessment of response to non-PAP interventions for OSA. Literature supports the use of follow-up PSG or HSAT after acclimatisation and optimisation of oral appliances. This is usually done when mandibular protrusion and symptom alleviation have been judged as adequate by a qualified dentist and/or sleep medicine specialist.²² The expert panel also recommends the use of follow-up PSG or HSAT following surgical therapy after an appropriate period of healing to evaluate treatment efficacy.^{74,75} Patients treated with HNS should undergo follow-up PSG or HSAT to aid in HNS system optimisation.^{22,76} The decision for whether to use PSG or HSAT may be guided by several factors, such as the presence of comorbidities, the ability to wear or operate the HSAT equipment, and the cost and availability of tests.

Follow-up PSG or HSAT may also be considered in patients on OSA therapy who experience significant changes in body weight.²² The Sleep Heart Health Study suggests that a 10% to 20% increase in body weight could lead to a significant increase in AHI even while on therapy, which may lead to inadequate therapy and recurrence of symptoms.⁷⁷ Hence, a 10% to 20% change in body weight should prompt the clinician to consider follow-up testing.

The expert panel recognised the importance of follow-up visits in OSA patients initiated on CPAP

therapy to assess treatment efficacy and adherence. Such visits provide the opportunity to make further adjustments and provide advice on CPAP adherence, as previously discussed. Once CPAP efficacy has been established and adherence is ensured, follow-up visits may be conducted yearly. However, longer intervals may be appropriate for selected patients, such as those who are highly adherent to PAP therapy, have sustained resolution of OSA-related symptoms, and have no concerns regarding their PAP therapy. In contrast, patients with persistent or recurrent sleep-related complaints or persistent difficulties with CPAP use should receive more frequent follow-up to identify issues with therapy and discuss alternative options.

OSA in children

The exact prevalence of OSA in Singapore children is unknown; however, studies from other countries estimate a prevalence rate of 1% to 6%.^{78,79} One Singapore study did note that in children with obesity, the prevalence was 13.3%.⁸⁰ If left undiagnosed or untreated, OSA can lead to serious complications in children. These include stunted growth, maxillofacial growth issues, neurocognitive impairments, behavioural and learning difficulties, metabolic disorders, hypertension, and increased cardiovascular risks in adulthood.^{81,82} Hence, early diagnosis and intervention are crucial in improving the outcomes of affected children. These paediatric consensus statements aim to guide the management of children with OSA up to 18 years of age.

Screening

The screening for OSA in children involves screening for snoring as well as other signs and symptoms suggestive of OSAS. Aside from snoring, symptoms of OSAS in children include pauses or gasps in breathing during sleep, mouth breathing, restlessness during sleep, waking up in different positions or unusual positions, daytime sleepiness, bedwetting, headaches especially in the mornings, poor school performance, or behavioural problems such as irritability, crankiness, hyperactivity, or difficulty paying attention.⁸³⁻⁸⁵ A few screening questionnaires for children, such as the OSA score, paediatric sleep questionnaire and OSA-18, have been developed but the diagnostic accuracy of these tools is low and vary widely depending on the target population and the cutoff score, which significantly limit their utility in real-world practice.⁸⁶⁻⁸⁸

Signs of OSAS in children include signs of tiredness or fatigue, "allergic shiners," swollen nasal mucosa, micrognathia, macroglossia, high arched palate, adenoidal facies, hypertrophied tonsils and hyponasal speech. A standard head and neck examination, including assessment of the tonsils, should be conducted and described according to the Brodsky

scale.⁸⁹ The presence of nasal obstruction, turbinate hypertrophy or septal hypertrophy should be noted. The examination should also include general muscle tone and neurologic status.⁸³⁻⁸⁵

Children with adenoid hypertrophy, tonsil hypertrophy, obesity, allergic rhinitis, structural abnormalities of the airways, Down syndrome, Prader-Willi syndrome, achondroplasia, neuromuscular disease and craniofacial abnormalities should all raise suspicion of OSA. The presence of other risk factors, such as a history of prematurity or a family history of OSA, should also prompt primary care providers to screen and evaluate children for OSA.⁸²

Diagnosis

While history and physical examination are essential parts of care for a child suspected of OSA, these procedures alone, as well as the use of audio/video recording or standardised questionnaires, do not have adequate specificity or sensitivity to establish a diagnosis of OSA in children.⁸³⁻⁸⁵ In this population, an in-laboratory overnight attended PSG with video recording and carbon dioxide monitoring is recommended as the gold standard and reference diagnostic sleep test.^{78,84,90}

Regarding the use of HSAT in the diagnosis of OSA in children, a task force found that this test is not reliable or valid for routine use in children.⁹¹ While some studies compared HSATs with PSG in children, the risk of bias and the heterogeneity between studies were both high. Literature on the use of HSAT to monitor carbon dioxide levels or identify arousals was absent. The task force also noted that the technical feasibility of HSAT in real-world conditions was low when used in children.

The expert panel recognises the limitations of the gold standard diagnostic sleep test for children, such as the lack of availability, high cost and poor tolerance by the patient. Hence, sleep oximetry and other HSAT may be considered when PSG is not feasible in selected children with high pretest probability.⁹¹⁻⁹³ The expert panel also recommends that the order, review and interpretation of raw data from HSAT to be done by a trained paediatric sleep physician. An in-laboratory overnight attended PSG with video recording and carbon dioxide monitoring should be considered in negative, inconclusive or technically inadequate HSATs in patients with high suspicion for OSA.

OSA is diagnosed in children with an abnormal PSG with an obstructive AHI >1. Although there is no universal consensus on cutoffs for OSA severity in children, several studies have used an AHI of 1 to <5 for mild, 5 to <10 for moderate, and ≥10 for severe OSA⁹²⁻⁹⁴; the expert panel agreed to adopt this classification.

Treatment

The treatment of paediatric OSA should consider the severity of the disease, the underlying cause of airway obstruction, the benefits and risks of each intervention, and the long-term effect of the treatment on the child throughout growth and development, including the likelihood of recurrence.

A trial of nasal corticosteroids with or without montelukast may be considered in children with mild OSA with adenoid and/or tonsil hypertrophy. Meta-analyses have found that medical therapy using nasal corticosteroids with or without montelukast may significantly improve AHI in children with mild OSA.^{95,96} However, follow-up of the studies included in this meta-analysis was short; hence, the long-term impact of nasal corticosteroids with montelukast in paediatric OSA is unclear. Therefore, the expert panel recommends regular follow-up in children with mild OSA treated with medical therapy to assess efficacy and monitor for side effects.

With adenotonsillar hypertrophy being the main contributor to OSA in the majority of otherwise healthy children, tonsillectomy and adenoidectomy (T&A) may be considered in children with moderate to severe OSA with adenotonsillar hypertrophy.⁷⁸ There is robust evidence that T&A results in improvements in PSG parameters, daytime and night-time symptoms, behaviour and quality of life.⁹⁷⁻⁹⁹ However, the expert panel underscores the importance of a sleep study in children being considered for surgery,⁹⁷ as children with severe OSA at baseline derive the greatest benefit from surgery whereas those with milder disease may experience an improvement or resolution of OSA even with conservative therapy or watchful waiting. Older children (>7 years), and those with chronic asthma or obesity were also more likely to have persistent OSA—in many of these patients, OSA improved but did not completely resolve, even with T&A.¹⁰⁰ Other risk factors of persistence or recurrence of OSA after T&A include severe OSA, Down syndrome and craniofacial, and genetic and neuromuscular disorders.

PAP is the standard therapy for moderate to severe OSA in children without adenoid and/or tonsil hypertrophy, those with persistence of OSA after surgery, or those who refuse or are not suitable for surgery.^{101,102} For children receiving PAP, adjustment and regular evaluation of ventilator parameters under PSG are recommended, as the necessary pressures may change as the child grows. During follow-up, adverse effects such as nasal symptoms, optic irritation or skin irritation should be addressed. Clinicians should also be aware that PAP may lead to craniofacial abnormalities; hence, regular reassessment is encouraged.

Dentofacial orthopaedics (growth modification orthodontic treatment) is recommended in children with OSA who exhibit dentofacial development problems with hypoplastic and/or retrognathic maxilla and mandible.¹⁰³⁻¹⁰⁸ Those with primary snoring or upper-airway resistance syndrome (increased upper-airway resistance leading to repeated arousals without meeting the criteria for apnoea or hypopnoea) may also benefit from this intervention. Maxillary expansion and/or protraction, with or without mandibular anterior growth guidance, depending on the type of dentofacial deformity, may be implemented in appropriately selected children with mild to moderate OSA by trained dental specialists in conjunction with interdisciplinary management. Maxillary arch expansion and dentofacial growth modification should be considered in children at or before puberty.¹⁰⁸ Long-term therapy is associated with better outcomes and regular follow-up is recommended with sleep monitoring.

Myofunctional therapy has emerged as a useful adjunct treatment modality for the management of OSA in children, especially those with non-severe OSA. A meta-analysis found that despite significant heterogeneity in the exercises used in trials, myofunctional therapy decreased AHI by over 40% and increased oxygen saturations in children with mild to moderate OSA.¹⁰⁹

Obesity is an independent risk factor for OSA. Children with obesity are likely to be associated with persistent OSA.^{110,111} Clinicians should recommend weight control in children with OSA who are overweight or obese. Systematic reviews have shown that various types of weight loss interventions improve AHI in paediatric OSA.^{112,113}

Limitations

Given the varied clinical situations and healthcare resources present, these recommendations should augment clinical judgement rather than replace it. Clinicians should be aware of the challenges that may limit the applicability of these consensus recommendations in different ethnic groups within their populations, access to specific technologies, availability of resources, and the availability of sleep-trained clinicians working in multidisciplinary teams.

While the perspectives of patients and their caregivers were widely considered during the development of the consensus statements, the expert panel did not include patient advocates or representatives of patient groups. Their inclusion should be considered in future work.

Lastly, as digital technologies advance, several opportunities on the use of telemedicine and artificial intelligence in the diagnosis and monitoring of

patients with OSA are emerging.¹¹⁴ As the expert panel was unable to find sufficient literature to develop recommendations regarding this aspect of OSA management, we recommend well-designed Singapore studies to aid the development of future guidance.

CONCLUSION

The 72 consensus statements presented in this paper aim to guide clinicians based on the most updated evidence and collective expert opinion from sleep specialists in Singapore. These consensus statements strive to provide guidance on important clinical questions and create an interdisciplinary framework for the appropriate management of OSA, thus potentially improving patient outcomes. These recommendations should augment clinical judgement rather than replace it. Management decisions should be individualised, taking into account the patient's clinical characteristics as well as patient and caregiver concerns and preferences.

Ethics statement

Not applicable as this is a systematic review.

Declaration

This study was funded in full by an unrestricted grant from the Lee Foundation. The funder did not have any role in study design, data analysis or reporting of results. The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Acknowledgements

The authors thank the Lee foundation for their generous philanthropy.

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Risk-based screening programmes for cancer diagnosis: A systematic review with narrative synthesis

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ABSTRACT

Introduction: Risk-based screening (RBS) has emerged as a promising alternative to age-based cancer screening. However, evidence regarding real-world implementation outcomes remains fragmented. Thus, a systematic review was conducted to evaluate the implementation methodologies and outcomes of RBS programmes across different cancer types.

Methods: MEDLINE, Embase, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials and Scopus were systematically searched from their respective dates of inception up to 8 July 2024. Prospective and randomised controlled trials (RCTs), which implement the RBS of cancer in an asymptomatic population, or studies retrospectively evaluating the outcomes of the same were included. Geographic distribution, population characteristics, RBS methodology, diagnostic accuracy and clinical outcomes were narratively synthesised.

Results: Among the 33 included studies (i.e. 21 prospective cohort, 8 RCTs, 3 retrospective and 1 non-RCT), sample sizes ranged from 102 to 1,429,890 participants. Most RBS trials were conducted in China (n=7, 21.2%), followed by the Netherlands (n=4, 12.1%) then the US, Australia and Sweden (n=3, 9.8%). Studies predominantly examined colorectal (27.3%), breast (21.2%) and prostate cancer (18.2%). Three main stratification approaches emerged: algorithmic (48.5%), validated risk models (39.4%) and physician assessment (9.1%). Implementation outcomes showed higher uptake in moderate-risk (75.4%) compared to high-risk (71.3%) and low-risk groups (67.9%). Five studies demonstrated cost-effectiveness with increased quality-adjusted life years, while 12 studies showed superior or non-inferior cancer detection rates compared to traditional screening.

Conclusion: The RBS of cancer has the potential to optimise healthcare resource allocation while minimising harm and increasing receptiveness for patients. More work is needed to evaluate long-term outcomes prior to the scaling of RBS programmes.

Keywords: early detection of cancer, health services and outcomes, preventive medicine, risk-based screening, systematic review

CLINICAL IMPACT

What is New

- Risk-based screening (RBS), an emerging approach for the early detection of cancer, can lead to superior or non-inferior cancer detection rates compared to traditional screening with better cost-effectiveness and patient acceptability.
- Effective programmes were documented for common cancers, such as breast and cervical cancer, across different geographical regions.

Clinical Implications

- RBS can potentially optimise healthcare resource allocation while minimising harms from unnecessary screening.
- Long-term outcomes from large-scale programmes and participant experiences need to be evaluated before widespread RBS implementation.

INTRODUCTION

Cancer remains one of the most significant public health burdens, with almost 20 million new cases and 9.7 million deaths attributable to cancer in 2022.¹ The detection and diagnosis of cancer remain a challenge for clinicians, as approximately half of recorded cancers are only detected at the advanced stage.^{2,3} Late cancer diagnoses often translate to poor patient prognosis and limited therapeutic options with low curative potential.^{4,5} Thus, there is much interest in methods for the early detection of cancer to achieve better survivorship outcomes.

The objective of early detection is to confirm the presence of cancer or precancerous lesions in an individual at the earliest time to inform management. One approach is screening, where investigations are

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Accepted: 2 September 2025

Published Online First: 7 October 2025

done proactively for an asymptomatic population to identify individuals with high-risk cancers for further evaluation, such as biopsy or prophylactic therapy.⁶ Organised cancer screening programmes at the state or national levels are often age-based, where all asymptomatic individuals are recommended for an investigation for a particular cancer at a specific frequency once they reach a certain age.⁷ However, recent studies have found that cancer incidence is rising among younger age groups,⁸⁻⁹ which precludes this increasingly at-risk population from current early detection strategies. Furthermore, age-based screening is agnostic to inter-individual risk profiles, which potentially reduce its diagnostic accuracy¹⁰ and increase screening harms associated with false positive results or overdiagnosis.^{11,12} Investigations with higher specificity or sensitivity are often associated with higher cost or invasiveness, such as colonoscopy for colorectal cancer and magnetic resonance imaging (MRI) for prostate cancer, which complicates population-wide adoption. Yet, lower-cost and non-invasive modalities, which may be easily implemented at a population level, are associated with lower sensitivity and/or specificity, such as urine prostate-specific antigen, which can lead to false positives and negatives.

One emerging solution is risk-based screening (RBS), where a detailed cancer risk profile of an individual is used to tailor screening recommendations, such as age of screening, screening modalities and frequency. Risk profiles can include indices, such as family history of malignancy, cancer-related biomarker levels, lifestyle, past medical history and socioeconomic status.^{13,14} Recent advances in genomic medicine have also incorporated polygenic risk scores (PRS) or single-nucleotide polymorphisms into these risk profiles. One example is the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), which predicts the chances of a woman carrying breast or ovarian cancer susceptibility genes (e.g. BRCA1, BRCA2) and risk of developing such malignancies.¹⁵ The algorithm computes these probabilities by considering the family history of related cancers, the presence of high-risk gene variants, and associated lifestyle factors such as contraceptive use and mammographic density.¹⁵

Studies have shown that the implementation of BOADICEA and similar breast cancer risk models for RBS is cost-effective¹⁶ and acceptable¹⁷ among females. Although many *in silico* studies have been published on cancer risk prediction models, the evidence on the practical implementation of RBS remains limited. There have been RBS trials exploring the implementation of risk-based cancer screening, such as the Colorectal cancer RiSk Prediction¹⁸ trial in Australia and the Stockholm Model 3 - Magnetic Resonance Imaging trial¹⁹ in Sweden for prostate

cancer. Yet to date, no systematic review has been conducted to evaluate the effectiveness of RBS programmes beyond those for breast cancer²⁰ and lung cancer.²¹ As such, the efficacy of RBS across different cancers and the range of methodologies employed have not been summarised. Thus, a systematic review was conducted to (1) summarise current RBS methodologies for each cancer among pragmatic trials; (2) evaluate the effectiveness in terms of accuracy, cost and patient acceptability of implemented RBS programmes; and (3) highlight potential equity gaps in such programmes.

METHODS

The systematic review was conducted with reference to the Cochrane Handbook for Systematic Reviews of Intervention²² and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).²³ The review was prospectively registered in the International Prospective Register of Systematic Reviews (CRD42024542831).

Search strategy

A systematic search was conducted on Embase and MEDLINE on the Ovid platform, PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL from their respective dates of inception to 8 July 2024. The search strategy comprised controlled search terms, such as “early detection of cancer”, “neoplasms” and “diagnostic screening programs.” Text terms relating to risk stratification, screening programmes and cancer were also incorporated. The strategy was piloted on PubMed, and further reviewed and refined by a medical information specialist. The strategy was then translated to other databases as befitting their native search syntax. The full search strategies can be found in Supplementary Table S1. A bibliometric search of the references of included studies was conducted for completeness.

Study selection and data extraction

Studies investigating the uptake and effectiveness of implemented RBS programmes among asymptomatic participants without a current diagnosis of the cancer being screened were included. The exclusion criteria included studies of paediatric patients, studies of *in silico* modelling of RBS outcomes, reviews of any kind, conference abstracts, letters and editorials. Title-abstracts retrieved with the aforementioned search strategies were uploaded to Covidence, a collaborative systematic review management platform. Two investigators (YYT and MFBF) independently screened the title-abstracts against the inclusion and exclusion criteria. Full-text papers were then retrieved and independently screened for inclusion by the investigators.

Data extraction was performed with data entered into a collaborative spreadsheet that was piloted on the first 3 studies. The extraction sheet was further refined after discussions among the investigators and deployed for the rest of the articles. Similar to study selection, data extraction was performed independently by the 2 investigators for each article (YYT and FF). Primary endpoints were the uptake of the initial risk stratification test and subsequent risk-informed procedures, and the diagnostic accuracy of RBS. Secondary endpoints included the participant acceptability of RBS, cost-effectiveness metrics and long-term mortality and morbidity outcomes.

Any disagreements at the study selection, data extraction and quality assessment stages were resolved via discussions between the investigators (YYT and MFBF). A third review author (ST) was consulted if no consensus was reached.

Quality assessment

The risk of bias of included studies was assessed independently by 2 investigators for each study (YYT and MFBF). Specifically, the Cochrane Risk-of-Bias 2 (RoB2) tool²⁴ was used to assess randomised controlled trials (RCTs), while the Cochrane Risk Of Bias In Non-randomised Studies of Intervention (ROBINS-I) tool²⁵ was used for prospective and retrospective cohort studies. Risk of bias was then visualised using the Risk-

of-Bias VISualisation tool²⁶ as traffic-light plots and summary plots.

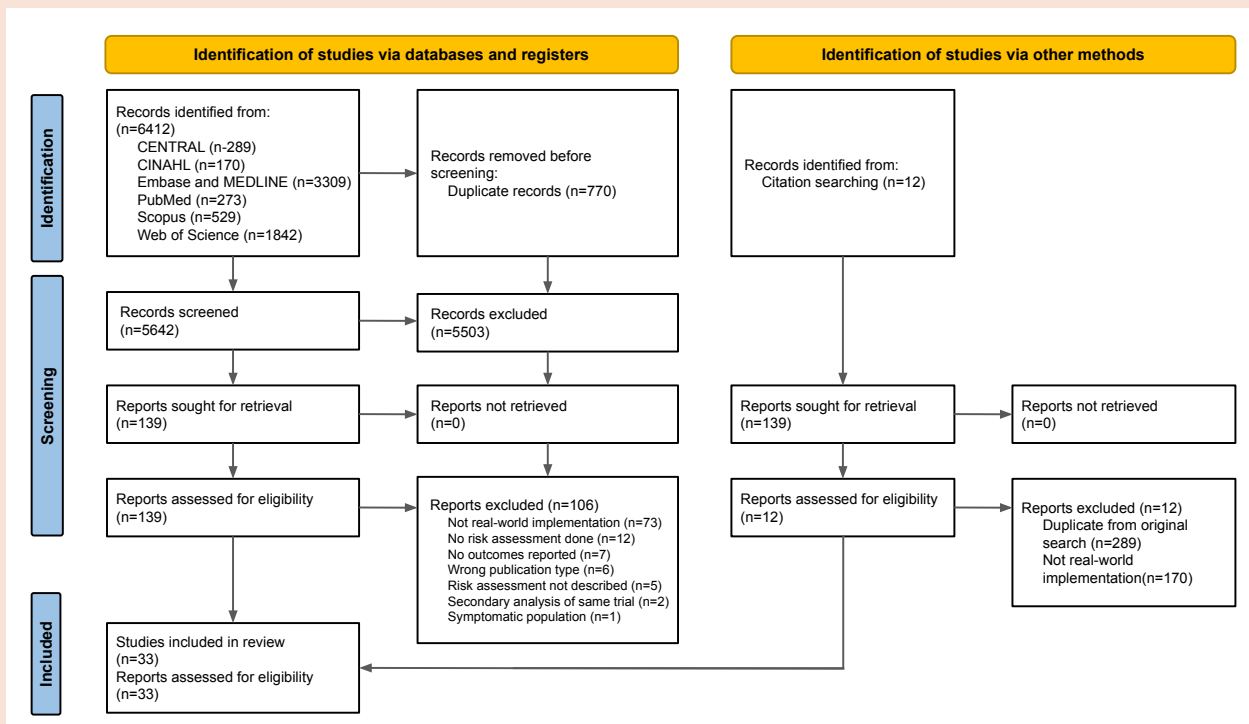
Data synthesis

Due to the heterogeneous methods and outcomes reported as expected of implementation studies, a quantitative meta-analysis was not conducted. Instead, the outcomes were summarised with descriptive statistics, such as median, interquartile range (IQR) and mean proportions where appropriate. Narrative synthesis was conducted to summarise qualitative aspects of the study characteristics, risk stratification methodologies, follow-up interventions and evaluated outcomes.

RESULTS

The systematic database search for primary studies yielded 6412 citations, of which 770 were duplicates. Among the 5503 citations excluded, primary reasons for exclusion include the absence of implementation of real-world RBS programmes, RBS programmes that did not focus on cancer and inappropriate study designs. The full-texts of 139 citations were retrieved following the title-abstract sieve, of which 106 were excluded for reasons such as lacking real-world implementation of risk stratification or not reporting any outcomes. On searching the bibliography of the included articles, the full-text papers of 12 additional

Fig. 1. PRISMA flowchart of study selection.



Source: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int J Surg* 2021;88:105906.

citations were retrieved, of which all were excluded from the review (Fig. 1).

Hence, 33 studies satisfied the inclusion criteria, and their data were extracted for evidence synthesis,^{18,19,27-57} and their characteristics are summarised in Table 1. Of the 33 studies, 21 studies were prospective cohort studies (63.6%),^{19,27,28,30-32,34-37,40,43,45,47,50-52,54-57} 8 were RCTs (24.2%),^{18,33,38,39,41,46,49,53} 3 were retrospective studies of previous or ongoing RBS programmes (9.1%),^{29,42,44} and 1 was a non-RCT (3.0%).⁴⁸ The studies were published within a year range of 2008–2024. Most studies (n=22, 66.7%) were multicentre trials at a national level embedded within primary to tertiary care settings,^{18,19,27-29,31,34,36,41-44,46,48-51,53-56} while the remainder were single-centre screening trials (n=11, 33.3%).^{30,32,35,37-40,45,47,52,57} The sample size ranged from 102 participants in a single-centre trial⁵⁰ to 1,429,890 participants in a nationwide cancer screening trial.²⁹

The most common cancer to be evaluated for RBS was colorectal (n=9, 27.3%),^{18,33,38,43,45-47,51,53} followed by breast (n=7, 21.2%),^{29,31,32,35,36,40,48} then prostate (n=6, 18.2%).^{19,37,41,42,52,56} By region, most studies were conducted in Europe (n=16, 48.5%), followed by the Asia-Pacific (n=12, 36.4%) then North America (n=5, 15.2%). By country, most studies were conducted in China (n=7, 21.2%),^{27,30,45,51-54} followed by the Netherlands (n=4, 12.1%),^{28,37,44,46} Sweden,^{19,41,56} Australia^{18,33,50} and the US^{36,42,47} (both n=3, 9.1%, respectively) (Fig. 2). Of the studies with a comparator arm, 9 compared against standard care protocols,^{18,33,35,38,44,48,49,53,55} 3 studies compared against a universal screening protocol,^{29,41,46} 2 studies compared against no screening^{28,39} and 1 study compared against the population with average cancer risk.³⁶

Risk-of-bias outcomes are presented in Figs. 3A–D. Among the RCTs, 4 were rated as low risk of bias,^{18,46,49,53} 1 with some concerns³⁹ and 3 with high risk of bias.^{33,38,41} The domains with significant methodological issues were mainly that of outcome measurement, due to the implementation of participant self-report of screening as the main measurement method. Among the non-randomised studies of intervention, 5 were rated as low risk of bias,^{31,32,40,44,52} 12 had some concerns^{19,29,30,34,43,45,47,48,50,51,54,57} and 8 were rated as high risk of bias.^{27,28,35-37,42,55,56} Significant methodological issues were raised with regard to deviations from the intended intervention due to the lack of compliance reporting and measures to ensure compliance. There were also issues with confounding due to the insufficient reporting of baseline characteristics and absence of confounder adjustment, as well as the selection of outcomes due to the absence of a protocol existing prior to the study publication.

RBS methods

A summary of risk stratification methods by cancer type is presented in Table 2. Across the 33 studies, 23

utilised some form of imaging or clinical investigation that was specific to the cancer evaluated. These tests include mammogram for breast cancer, prostate serum antigen test for prostate cancer, fecal immunochemistry test for colorectal cancer and high-risk human papillomavirus types testing for cervical cancer. One study conducted Epstein-Barr virus serology testing for the risk stratification of nasopharyngeal carcinoma.⁵⁴ Twenty-three studies assessed the level of genetic risk of the participant, mostly via family history of cancer, while 4 studies conducted genetic testing on recruited participants to assess for high-risk cancer genetic polymorphisms to calculate a polygenic risk score.^{19,31,40,41} Otherwise, cancer risk score was calculated with previously validated risk models incorporating participant characteristics, relevant family and personal history and symptoms, such as the Gail model³² and Tyrer-Cuzick model⁴⁸ for breast cancer. Clinical questionnaires were deployed in 24 studies for risk assessment, of which 20 studies^{18,29,32-35,37,38,41-43,45-48,50,51,53,54,57} assessed the family history of cancer or related pathologies, such as polyps in colorectal cancer.⁴⁵ Eleven studies assessed lifestyle factors that were associated with the cancer risk evaluated in the questionnaire,^{18,31,32,34,38,39,46,49,51,53,57} the most common of which was smoking history. Thirteen studies assessed the previous medical history that was associated with the cancer risk evaluated,^{18,19,31,32,34,38,39,41,43,47,49,51,57} such as a previous diagnosis of inflammatory bowel disease in colorectal cancer⁴³ or a prescription of contraceptives in breast cancer.^{31,32} Seven studies assessed self-reported cancer-specific symptomatology among the participants.^{18,37,38,43,45,49,57}

After collecting information on risk factors, stratification was done primarily via 3 approaches. Most studies stratified interventions by the presence or absence of a singular or combination of risk factors through an algorithmic approach (n=16, 48.5%),^{27-30,32,35,36,39,41,44,45,49,52,53,56} while 13 studies calculated a risk score using a previously validated model to stratify participants.^{18,19,31,34,37,38,40,46-48,51,54,57} Validated models include the Stockholm-3 model for prostate cancer¹⁹ and the PLCO_{m2012} model for lung cancer.³⁴ The remaining 3 studies involved a risk assessment by the physician to personalise a risk-stratified intervention for the participant.^{42,43,50} Across the studies, participants would be stratified between 2 and 3 risk strata, each with a set of strata-specific interventions. One study further personalised these interventions to the individual risk profile of the participants in addition to strata-specific interventions, specifically personalising the initiation age of mammography and MRI of the breast.⁴⁰

A summary of risk-stratified interventions by cancer type is presented in Table 3. Participants within the high-risk strata were often recommended invasive procedures or biopsies, such as colonoscopy in

Table 1. Summary of study characteristics.

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Stojadinovic 2008 ³²	US	NRSI (prospective)	Multicentre, international screening trial in a tertiary care setting	Intervention: 1751 Control: 390	Breast	Point-of-care electrical impedance scan of breast tissue	High: Informed findings and given risk-appropriate follow-up Low: Routine screening
Venturini 2013 ³⁶	Italy	NRSI (prospective)	Single-centre in a primary care setting	Intervention: 1666 Control: NA	Breast	Point-of-care mammogram results Clinical questionnaire calculating Gail model score	High: Referred for both ultrasound and contrasted MRI Moderate: Mammography and ultrasound Low: Mammography only
Budal 2014 ⁵⁵	Norway	NRSI (prospective)	Multicentre, national screening programme	Intervention: 1744 Control: NA	Cervical	Point-of-care high-risk HPV testing	High: Immediate colposcopy Low: Routine screening
Grönberg 2015 ¹⁹	Sweden	NRSI (prospective)	Multicentre, national screening trial in a primary care setting	Intervention: 47,688 Control: NA	Prostate	Utilised STHLM3 model Plasma protein biomarkers related to PCa Genetic testing for high-risk polymorphisms Prostate examination results Clinical questionnaire eliciting age, family history of cancer and recent prostate biopsy findings	High: Prostate biopsy and urologist referral Low: No biopsy
Pedersen 2015 ³⁹	Denmark	RCT	Single-centre screening trial in a primary care setting	Intervention: 2052 Control: 2052	Lung	Low-dose CT scan Self-reported age, smoking history and previous COPD diagnosis	High: Annual screening by low-dose CT scans Low: Return to routine screening
Field 2016 ⁴⁹	UK	RCT	Multicentre, national screening trial in a cancer specialist centre setting	Intervention: 2028 Control: 2027	Lung	Self-reported age, smoking history and previous medical record	High: Immediate referral to multidisciplinary team Moderate: Follow-up CT at 3 and 12 months

Table 1. Summary of study characteristics. (Cont'd)

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Yen 2016 ²⁹	Taiwan	NRSI (retrospective)	Multicentre, national breast cancer screening programme	Intervention: 1,429,890 Control: NA	Breast	Clinical questionnaire eliciting family history of cancer, menstrual and reproductive history	Average: Follow-up CT at 12 months Low: No follow-up
Yousaf-Khan 2016 ²⁸	Netherlands	NRSI (prospective)	Multicentre, international screening trial in a community setting	Intervention: 5297 Control: NA	Lung	Point-of-care CT imaging	High: Biennial mammography Low: Return to routine screening
Guivathian 2017 ⁴⁷	US	NRSI (prospective)	Single-centre screening trial in a tertiary care setting	Intervention: 700 Control: NA	Colorectal	Clinical questionnaire eliciting past personal history of cancer, polyp history and family history of polyps	High: Genomic evaluation Moderate: Low-dose follow-up CT and VDT Low: Next regular screening
Swenen 2017 ³⁵	Belgium	NRSI (prospective)	Single-centre screening trial in a cancer specialist centre setting	Intervention: 11,123 Control: 2008	Breast	Clinical breast examination Clinical questionnaire eliciting family and personal history of cancer	High: Ultrasound Low: Biennial mammogram
Li 2018 ⁴⁵	China	NRSI (prospective)	Single-centre, community mass screening programme	Intervention: 891,199 Control: NA	Colorectal	FIT test results Clinical questionnaire eliciting biodata, CRC-related symptoms and family history of CRC	High: Colonoscopy Low: FIT
Dwarte 2019 ⁵⁰	Australia	NRSI (prospective)	Multicentre, national in a cancer specialist centre setting	Intervention: 102 Control: NA	Pancreatic	Endoscopic ultrasound results Blood test results Genetic risk assessment using PancPRO, a questionnaire eliciting family history of cancer	High: Close surveillance or treatment Average: Yearly endoscopic ultrasound for 5 years

Table 1. Summary of study characteristics. (Cont'd)

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Chen 2021 ⁵⁴	China	NRSI (prospective)	Multicentre, national screening programme in a community setting	Intervention: 53,382 Control: NA	Nasopharyngeal	Epstein-Barr virus serology results	High: Endoscopy Moderate: Annual blood testing Low: 5-yearly visit
Loopik 2021 ⁴⁴	Netherlands	NRSI (retrospective)	Multicentre, national screening programme in a primary care setting	Intervention: 619,253 Control: 769,442	Cervical	Point-of-care high-risk HPV test	High: Cytologic assessment on physician-sampled material and colposcopy Low: Return to routine screening
Nordström 2021 ⁴¹	Sweden	RCT	Multicentre, national screening trial in a community setting	Intervention: 1372 Control: 921	Prostate	Utilised STHLM3 model Plasma protein biomarkers related to PCa Genetic testing for high-risk polymorphisms Prostate examination results Clinical questionnaire eliciting age, family history of cancer and recent prostate biopsy findings	High: Sytematic and MRI-guided biopsy Low: Return to routine screening
Reesink 2021 ³⁷	Netherlands	NRSI (prospective)	Single-centre screening trial in a primary care setting	Intervention: 496 Control: NA	Prostate	MRI-imaging of prostate with PI-RADS staging European Randomized Study of Screening for Prostate Cancer risk calculation, utilising age, family history of PCa, related symptoms and PSA levels	High: Targeted and systematic biopsy Moderate: Sytematic biopsy Low: No biopsy
Xu 2021 ³⁰	China	NRSI (prospective)	Single-centre screening trial in a tertiary care setting	Intervention: 2444 Control: NA	Cervical	Cytology with reference to Bethesda grading Point-of-care DH3 HPV test assay	High: Colposcopy and biopsies Moderate: Rescreening by cytology every 12 months

Table 1. Summary of study characteristics. (Cont'd)

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Adeoye 2022 ⁵⁷	Hong Kong	NRSI (prospective)	Single-centre screening trial in a community setting	Intervention: 100 Control: 881	Oral	Visual oral examination Clinical questionnaire assessing family history, biodata, lifestyle factors, past medical history and related symptoms	High: Screening required Moderate: Screening on availability Low: Routine opportunistic screening
Kortlever 2022 ⁴⁶	Netherlands	RCT	Multicentre, national screening programme in a primary care setting	Intervention: 11,364 Control: 11,384	Colorectal	Clinical questionnaire eliciting smoking history, recent FIT results, family history of cancer and biodata	High: Colonoscopy Low: Return to routine screening
Michael 2022 ⁴²	US	NRSI (retrospective)	Multicentre, national screening trial in a primary care setting	Intervention: 564 Control: NA	Prostate	PSA test results Clinical questionnaire eliciting age, race and family history of cancer	High: Urology referral
Trevena 2022 ³³	Australia	RCT	Multicentre, national in a primary care setting	Intervention: 12,420 Control: 12,880	Colorectal	Clinical questionnaire eliciting family history of cancer	High: Assessment by familial cancer service or colonoscopy Moderate: Colonoscopy every 5 years Low: FOBT every 2 years
Chen 2023 ⁵³	China	RCT	Multicentre, national community screening programme	Intervention: 3937 Control: 7858	Colorectal	Clinical questionnaire to calculate Asia-Pacific Colorectal Screening Score	High: Colonoscopy Low: FIT screening and routine screening
Chiu 2023 ⁵²	China	NRSI (prospective)	Single-centre screening trial in a primary care setting	Intervention: 1536 Control: NA	Prostate	PSA test scores Prostate Health Index scores MRI prostate findings	High: MRI-guided and systematic prostate biopsy Moderate: Systematic prostate biopsy Average: No biopsy
Emery 2023 ¹⁸	Australia	RCT	Multicentre, national screening trial in a primary care setting	Intervention: 369 Control: 365	Colorectal	Clinical questionnaire assessing family history, biodata, lifestyle factors, past medical history and related symptoms	High: Referral to familial cancer centre for formal assessment Moderate: Colonoscopy every 5 years

Table 1. Summary of study characteristics. (Cont'd)

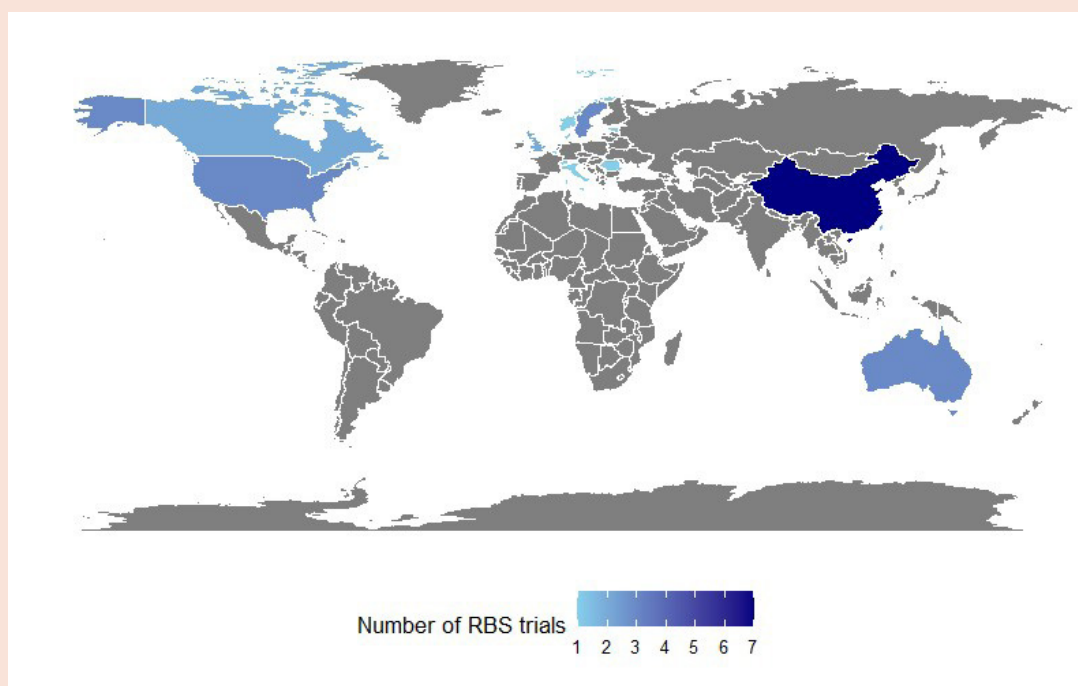
Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Gareth Evans 2023 ⁴⁸	UK	NRCT	Multicentre, national screening programme in a primary care setting	Intervention: 2472 Control: NA	Breast	Breast density scores from mammogram Clinical questionnaire to calculate Tyrer-Cuzick score	Average: iFOBT every 2 years High: Appointment with relevant medication Moderate: Appointment with relevant medication
Padrik 2023 ⁴⁰	Estonia	NRSI (prospective)	Single-centre screening trial in a cancer specialist center setting	Intervention: 2637 Control: NA	Breast	Polygenic risk score of 2803 single-nucleotide polymorphisms derived from gene testing	High: Earlier initiation of mammography and MRI-breast with discussion of chemoprevention therapy Moderate: Earlier initiation of mammography and discussion of chemoprevention therapy Slightly raised: Earlier initiation of mammography Low: Mammography from 50 years old onwards
Alterbeck 2024 ⁵⁶	Sweden	NRSI (prospective)	Multicentre, national screening trial in a primary care setting	Intervention: 999 Control: NA	Prostate	PSA test results	High: Referral to urologist with targeted and systematic biopsies Average: Invitation to screen in 2 years Low: Invitation to screen in 5 years
Dong 2024 ⁵¹	China	NRSI (prospective)	Multicentre, national screening programme in a tertiary care setting	Intervention: 946,706 Control: NA	Colorectal	FIT test results Clinical questionnaire eliciting biodata, family history of cancer, biodata, lifestyle factors, past medical history and CRC-related symptoms	High: Colonoscopy Low: Return to routine screening

Table 1. Summary of study characteristics. (Cont'd)

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Manuc 2024 ⁴³	Romania	NRSI (prospective)	Multicentre, national screening trial in a primary care setting	Intervention: 170,413 Control: NA	Colorectal	Clinical questionnaire eliciting family history of CRC and cancer syndromes, past medical history and CRC-related symptoms	High: Colonoscopy Average: FIT
Plys 2024 ³⁸	Switzerland	RCT	Single-centre screening trial in a primary care setting	Intervention: 258 Control: 257	Colorectal	Clinical questionnaire eliciting input for QCancer-Colorectal risk calculator, such as family history of cancer, biodata, CRC-related lifestyle factors, past medical history and CRC-related symptoms	High: Colonoscopy Moderate: Choice between FIT or colonoscopy Low: FIT
Tammemagi 2024 ³⁴	Canada	NRSI (prospective)	Multicentre, national screening programme in a community setting	Intervention: 7329 Control: NA	Lung	Utilised PLCO _{n2012} risk model Biodata (e.g. age, ethnicity) Family history of lung cancer Smoking history Past medical history	High: Low-dose CT scan Average: Return to routine screening
Walker 2024 ³¹	Canada	NRSI (prospective)	Multicentre, national screening programme in a primary care setting	Intervention: 4246 Control: NA	Breast	Polygenic risk score calculated from oral saliva samples Clinical questionnaire based on BOADICEA model that factors in family history of cancer, biodata, lifestyle factors and past medical history	High: Mammogram and MRI-breast Moderate: Earlier initiation of mammogram Average: Mammogram every 2 years from age 50 onwards
Yu 2024 ²⁷	China	NRSI (prospective)	Multicentre national screening programme in a primary care setting	Intervention: 9218 Control: NA	Cervical	Cytology with reference to Bethesda grading Point-of-care high-risk HPV test	High: Colposcopy and biopsy as appropriate Low: Follow-up with cytology after 3 years

BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; COPD: chronic obstructive pulmonary disease; CRC: colorectal cancer; CT: computed tomography; FIT: fecal immunochemistry test; FOBT: fecal occult blood test; HPV: human papillomavirus; iFOBT: immunochemical fecal occult blood test; MRI: magnetic resonance imaging; NA: not applicable; NRCT: non-randomised controlled trial; NRSI: non-randomised studies of intervention; PCa: prostate cancer; PLCO_{n2012}: Prostate, Lung, Colorectal, and Ovarian Model 2012; PSA: prostate serum antigen; RCT: randomised controlled trial; STHLM3: Stockholm-3 model; VDT: volume doubling time

Fig. 2. Distribution of completed RBS programmes worldwide.



RBS: risk-based screening

Figs. 3. Traffic-light plots describing the risk of bias as assessed by (A, C) Cochrane Risk-of-Bias 2 tool and (B, D) Cochrane Risk Of Bias In Non-randomised Studies of Interventions stratified by studies and risk-of-bias domains, respectively.

(A)

		Risk of bias					
		D1	D2	D3	D4	D5	Overall
Study	Pedersen 2015	-	+	+	+	+	-
	Field 2016	+	+	+	+	+	+
	Nordström 2021	+	-	-	-	+	X
	Kortlever 2022	+	+	+	+	+	+
	Trevena 2022	+	+	X	-	-	X
	Chen 2023	+	+	+	+	+	+
	Emery 2023	+	+	+	+	+	+
	Plys 2024	+	X	+	-	+	X

D1: Randomisation process
D2: Deviations from intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Judgement
X High
- Unclear
+ Low

Figs. 3. Traffic-light plots describing the risk of bias as assessed by (A, C) Cochrane Risk-of-Bias 2 tool and (B, D) Cochrane Risk Of Bias In Non-randomised Studies of Interventions stratified by studies and risk-of-bias domains, respectively. (Cont'd)

(B)

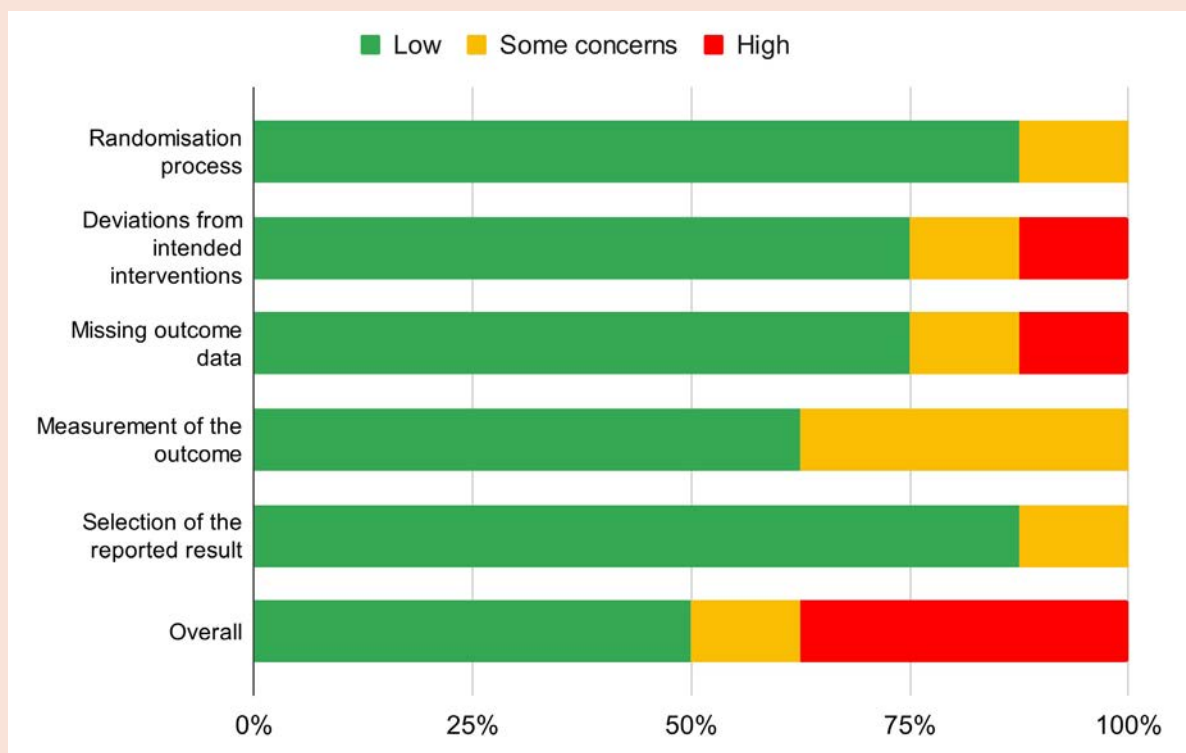
	Risk of bias							Overall
	D1	D2	D3	D4	D5	D6	D7	
Stojadinovic 2008	+	-	+	X	+	+	-	X
Venturini 2013	+	+	+	+	+	+	+	+
Budal 2014	-	+	+	-	+	-	-	X
Gronberg 2015	+	+	+	-	+	+	+	-
Yen 2016	+	+	+	X	+	+	+	-
Yousaf-Khan 2016	-	-	+	-	X	+	+	X
Guivatchian 2017	+	-	+	+	+	+	+	-
Swenen 2017	-	+	+	-	-	+	-	X
Li 2018	+	+	-	-	+	+	-	-
Dwarte 2019	+	-	+	+	+	+	-	-
Chen 2021	+	+	+	-	+	+	-	-
Loopik 2021	+	+	+	+	+	+	+	+
Reesink 2021	-	-	+	-	X	+	-	X
Xu 2021	-	+	+	+	+	+	-	-
Adeoye 2022	+	-	+	+	+	-	-	-
Michael 2022	-	+	+	-	X	+	+	X
Chiu 2023	+	+	+	+	+	+	+	+
Gareth Evans 2023	-	+	+	+	-	+	+	-
Padrik 2023	+	+	+	+	+	+	+	+
Alterbeck 2024	-	-	+	+	X	+	+	X
Dong 2024	+	+	+	-	-	+	+	-
Manuc 2024	+	+	-	-	+	+	-	-
Tammemagi 2024	+	-	+	+	+	+	+	-
Walker 2024	+	+	+	+	+	+	+	+
Yu 2024	-	-	+	-	-	+	-	X

D1: Bias due to confounding
 D2: Bias in the selection of participants into the study
 D3: Bias in the classification of interventions
 D4: Bias due to deviations from intended interventions
 D5: Bias due to missing data
 D6: Bias in the measurement of outcomes
 D7: Bias in the selection of the reported result

Judgement
 X High
 - Unclear
 + Low

Figs. 3. Traffic-light plots describing the risk of bias as assessed by (A, C) Cochrane Risk-of-Bias 2 tool and (B, D) Cochrane Risk Of Bias In Non-randomised Studies of Interventions stratified by studies and risk-of-bias domains, respectively. (Cont'd)

(C)



(D)

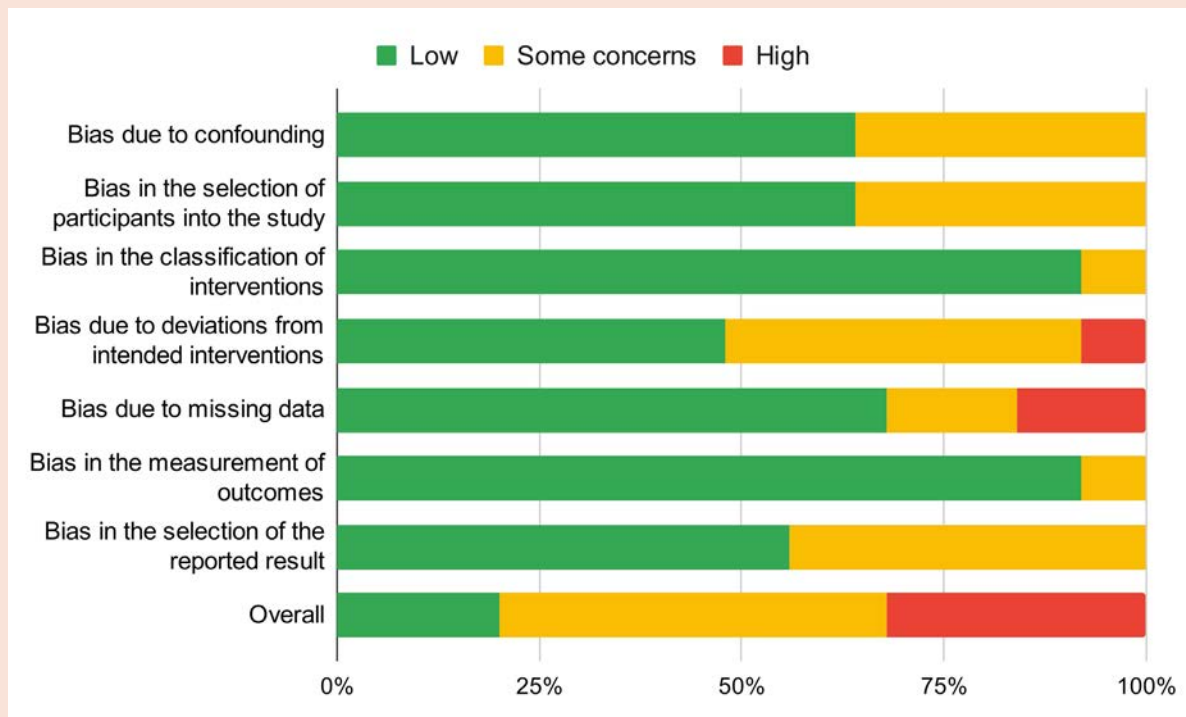


Table 2. Summary of risk stratification methods reported across included studies.

Cancer type	Risk stratification methods	Validated risk models
Breast	- Clinical breast examination - Gene testing for polygenic risk scoring - Point-of-care mammogram - Point-of-care electrical impedance scanning - Self-report or clinic-administered risk questionnaires	BOADICEA Gail model Tyrer-Cuzick model
	- Cervical cytology - Point-of-care human papillomavirus testing	None
Colorectal	- Fecal immunochemical test - Self-report or clinic-administered risk questionnaires	Asia Pacific Colorectal Screening Score
Lung	- Computed tomography imaging - Self-report or clinic-administered risk questionnaires	Liverpool Lung Model PLCO _{m2012}
Nasopharyngeal	Epstein-Barr virus serology	None
Oral	- Visual oral examination - Self-report or clinic-administered risk questionnaires	None
Pancreatic	- Blood test - Endoscopic ultrasound of pancreas - Self-report or clinic-administered risk questionnaires	PancPRO
Prostate	- Blood test - Gene testing for high-risk polymorphisms - Manual prostate examination - Magnetic resonance imaging results - Prostate serum antigen test - Self-report or clinic-administered risk questionnaires	STHLM3 European Randomized Study of Screening for Prostate Cancer

BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; PLCO_{m2012}: Prostate, Lung, Colorectal, and Ovarian; STHLM3: Stockholm - Model 3

colorectal cancer screening^{33,38,43,45,46,51,53} and referral to a specialist or an oncology clinic for follow-up.^{18,19,28,33,42,56} One study further recommended discussion with a clinician for the initiation of chemoprevention therapy of breast cancer.⁴⁰ Participants within the moderate-risk strata were recommended non-invasive tests instead or returned to routine screening with a higher frequency than average participants.

RBS outcomes

Cancer risk and survivorship outcomes

Of the 33 studies, 10 studies did not record cancer diagnoses as an outcome measure among the risk-stratified participants.^{18,31,33,38,40,41,43,44,48,50} Seven studies found that higher risk-strata participants had a statistically significant higher rate of cancer diagnosis than lower risk-strata participants,^{28,30,39,42,44,50,54} which concurred with the theoretical risk model findings of the respective studies. In the remaining studies that reported cancer diagnosis endpoints, 4 studies reported a follow-up duration of less than a year,^{35,37,46,47} 14 studies reported a follow-up duration between 1 and 5 years,^{27,30,32,36,42,45,49,52,53,55-57,70,72} while 5 studies

followed up with patients for 5 years or more.^{28,29,39,51,54} In terms of outcomes, 2 studies found that RBS participants had a statistically significant higher rate of cancer diagnosis than control participants,^{36,41} while 3 studies found that RBS was non-inferior to the control paradigm in diagnosing cancer.^{29,46,53} Only one study, the Danish Lung Cancer Screening Trial, reported on the mortality outcomes of participants, specifically that there was no significant differences in lung cancer mortality between the participants that underwent RBS and those that did not undergo screening.³⁹

Only 12 studies reported at least one measure of diagnostic test accuracy of the implemented RBS programme,^{28,30,34,36,40,44-46,54,55,57} such as sensitivity or area under the receiver operating characteristic curve.

Participant uptake and acceptability

Nine studies reported on the extent of uptake of strata-specific interventions.^{18,19,29,30,33,34,37,38,43,44,46-49,51,53,56,57} The median proportion of high-risk participants that received their strata-specific intervention was 71.3% (IQR 38.8%), 75.4% (IQR 38.3%) for moderate-risk participants and 67.9% (IQR 55.0%) for low-risk participants. One study found that risk-stratified

Table 3. Summary of follow-up interventions for each cancer type stratified by risk level.

Cancer type	Risk		
	Low	Moderate	High
Breast	Routine screening	Early initiation of mammogram Higher frequency of mammogram	Referral for mammogram and magnetic resonance imaging Discussion for chemoprevention therapy
Cervical	Routine screening Follow-up cytology	Not applicable	Immediate colposcopy with or without biopsy
Colorectal	Fecal occult blood test/fecal immunochemical test Routine screening	Higher frequency of colonoscopy	Genomic evaluation Immediate colonoscopy Referral to cancer specialist centre
Lung	Routine screening	Follow-up computed tomography	Immediate computed tomography imaging Referral to multidisciplinary oncology team Referral to pulmonologist
Nasopharyngeal	Routine follow-up	Blood test	Nasoendoscopy
Oral	Routine opportunistic screening	Scheduled screening on availability	Screening required
Pancreatic	Not applicable	Regular endoscopic ultrasound for a duration	Close surveillance
Prostate	Routine screening	Systematic prostate biopsy	Magnetic resonance imaging-guided and systematic prostate biopsy Referral to urology

participants who were made aware of their cancer risk assessment were significantly more likely to undergo risk-appropriate screening than those who did not.¹⁸ Three studies reported significant positive changes in patient-reported outcomes, such as decreased anxiety towards cancer, high satisfaction with the screening process or increased perceived risk of cancer.^{18,34,50} One study further reported qualitative findings, following an in-depth interview of the participants, which concluded that participants found genetic counselling useful as they gained knowledge of their own risk factors for cancer and were empowered to proactively self-monitor or act upon their cancer risk profile.⁵⁰

Cost-effectiveness and healthcare utilisation

Seven studies analysed the comprehensive health services and outcomes of RBS programmes, yielding promising results.^{18,19,32,34,49,51,53} The majority of these studies^{18,32,49,51,53} concluded that RBS can lead to potential cost savings and a significant increase in quality-adjusted life years compared to existing screening guidelines. Additionally, one study found that RBS resulted in substantially reduced rates of

unnecessary biopsies,¹⁹ while another study revealed that RBS programmes did not lead to increased waiting times for computed tomography scans, despite the increased scan volume.³⁴

DISCUSSION

Significant developments have facilitated the translation of cancer risk prediction models into the real-world implementation of RBS programmes to stratify asymptomatic individuals for risk-appropriate screening. To the authors' knowledge, this is the first systematic review to consolidate the evidence base for the real-world implementation of RBS programmes. A majority of the studies explored screening for colorectal cancer, followed by breast and prostate cancer with most RBS programmes employing algorithm-driven risk stratification or validated risk scoring equation based on the presence of risk factors. Although few studies have recorded cancer diagnoses among participants, available data indicate RBS programmes either outperform or demonstrate non-inferiority to standard screening guidelines. Furthermore, studies assessing participant acceptability found that those enrolled in RBS viewed such

programmes positively, citing improvements in education towards cancer risk and their options with respect to their individual propensities for cancer.

Although many risk models for various cancer types have been elucidated, the implementation of such models to inform risk-appropriate screening in the real-world setting remains poorly studied. Various *in silico* studies have demonstrated the potential cost-effectiveness of RBS over age-based screening paradigms,⁵⁸⁻⁶⁰ yet such cost-savings may be erroneously high as modelling studies often overestimate the real-world compliance rate to risk-appropriate screening among the participants. Hence, future studies on cancer screening can consider reporting health services outcomes, such as cost-savings incurred or disability-adjusted life-years, so as to quantify the cost-effectiveness of RBS in relation to the upfront costs of risk stratification. Factors impacting the attendance of RBS and subsequent follow-up visits are similar to that of traditional screening,⁶¹ including perceived lack of self-efficacy, fear of cancer diagnosis, cultural beliefs towards cancer and inconvenience.^{17,62,63} Recent work has shown that one way to overcome these barriers is through timely and reassuring communication of results and their implications to patients, as well as centring the discussion of cancer risk management around autonomy and self-efficacy.⁶² Our review found that participants in the higher risk strata had higher adherence to follow-up, which implies that differing sets of facilitators and barriers to RBS and follow-up exist between participants of different risk-strata. Thus, future research should focus on understanding these stratum-specific barriers to RBS attendance and follow-up adherence, thus enabling the development of targeted interventions that can be implemented alongside RBS programmes. Such studies can be part of a broader implementation framework, which can include approaches such as but not limited to (1) stratum-specific barrier assessment studies, (2) development of targeted interventions and (3) research into comparative effectiveness across different implementation strategies.

There may be public and provider resistance against the de-implementation of screening among supposedly low-risk participants if RBS were to be effectuated,⁶⁴ as it contradicts pre-existing age-based screening guidelines as recognised in the public consciousness.^{65,66} RBS may expose high-risk individuals to discrimination by insurers and employers. Furthermore, RBS that implements PRS derived from genomic testing may face even more significant challenges, such as high costs⁶⁷ and the ethico-legal consequences following genomic testing, including data privacy, test result uncertainty and conflict with personal and religious values.^{68,69} Thus, healthcare

system administrators and policymakers may consider consulting public opinion and work closely with private insurers to design fair and reasonable risk-stratification screening programmes. Subsequently, extensive public communication might be required to address the complexity underlying RBS programmes and to reconcile pre-existing sociocultural beliefs and ideas towards cancer screening, so as to enhance the public enthusiasm and uptake of such programmes. There is a role for healthcare professionals (HCPs) in the promotion of RBS as well, especially general practitioners and family medicine specialists, as they are often the first healthcare encounter that most patients have. A recent review reported that HCPs are more likely to accept and promote RBS if presented with robust evidence of its efficacy and cost-effectiveness that outweighs the need for more resources and patient-facing work.⁷⁰ Thus, healthcare administrators and policymakers can also consider providing more support to HCPs on-the-ground in the implementation of such programmes, by having guideline update sessions, providing more administrative support or streamlining care pathways for referrals.

Even if RBS were to be implemented in spite of the aforementioned barriers, consideration must be given to underserved populations and the applicability of models to non-Caucasian populations. In this systematic review and among other studies, most risk-prediction models were derived from the case-control studies of majority-Caucasian cohorts, such as the Stockholm-3 model,⁷¹ BOADICEA model⁷² and PLCO_{m2012}⁷³ model. Thus, the transferability of these models to non-Caucasian populations is limited, which explains the observed lack of RBS studies in the Asia-Pacific, South American and Middle Eastern–North African (MENA) regions. Yet, it is precisely these same countries that may benefit the most from RBS due to the potential cost-savings and patient harm reduction observed in successful programmes, suggesting its suitability for adoption in low-resource regions within those geographies. As such, there exist ethnic disparities in early cancer detection tools, which are further compounded by existing socioeconomic inequalities that already complicate healthcare access among underserved populations.^{74,75} Of note, China is an exception as researchers were able to utilise the China Kadoorie Biobank to derive risk-prediction models representative of their population,⁷⁶⁻⁷⁸ although no real-world implementation of these models has been recorded to our knowledge. One study⁵³ also utilised the Asia-Pacific Colorectal Screening Score⁷⁹ in the implementation of RBS, which is more representative of Asian populations.

Despite the above problems, RBS remains a promising way forward for cancer screening based on the findings of this review. First, RBS was able to

reduce costs and excessive patient harm by reducing the number of unnecessary investigations while maintaining good accuracy in diagnosing true cancers. This was achieved when RBS programmes were able to match the appropriately powered investigation to the risk level of the individual. Furthermore, the participants viewed genomic testing for cancer screening positively, and the newfound knowledge empowered them to manage their cancer risk levels appropriately. Hence, such factors underlying the acceptability or refusal of an individual to RBS must be better studied to inform the real-world implementation of RBS, such that it can achieve high uptake in both screening and follow-up across all demographics.

In terms of quality assessment, study quality was poor among the non-randomised studies of intervention, as only 5 studies were rated with a low overall risk of bias. One significant factor was the absence of measures to account for deviations from the risk-stratified interventions among the participants. Studies either reported a low compliance rate of risk-stratified interventions among the participants or did not consider the capacity of participants to seek care and opinions extraneous to the study paradigm. This bias further translated to the high rates of lost-to-follow-up among some of the studies as well, since participants who did not comply with the risk-stratified intervention may drop out from the study altogether. Study quality was higher but could be improved among the RCTs, especially in terms of outcome measurement. This was so as among trials that assessed the initial compliance of RBS, outcomes were measured via participant self-reporting, which is less accurate than medical record linkage. Otherwise, the RCTs were generally well-designed and likely to report unbiased findings. In addition to risk of bias assessed by RoB2 and ROBINS-I, the authors further identified the potential for both differential verification bias and lead-time bias in these studies. Differential verification biases may arise because low-risk participants often received less rigorous or no follow-up investigations compared to high-risk participants, leading to the inconsistent verification of outcomes between groups. This could impact the assessment of diagnostic accuracy by inflating the detection rates among high-risk participants who received more intensive evaluations. Additionally, lead-time bias may influence survival outcomes, as high-risk participants are likely diagnosed earlier due to expedited diagnostic testing, which may appear to extend survival compared to low-risk individuals. Studies evaluating treatment, morbidity and mortality outcomes among these cohorts should therefore account for both differential verification bias and lead-time bias to provide a more accurate interpretation of RBS effectiveness.

The primary strength of our review was the comprehensiveness of the search done across 7

databases. Furthermore, our review focused on implementation trials to address the translation gap of cancer risk prediction models with a comprehensive synthesis of outcomes beyond that of usual clinical indicators, such as diagnostic test accuracy measures or mortality estimates. However, there are some limitations. The main limitation is that of the significant heterogeneity in study designs and outcomes reported across the included studies. As such, meta-analysis was precluded from our review as well as limiting the comparability of results between trials. However, as RBS is a complex public health intervention, such heterogeneity is expected especially in a real-world implementation setting. Thus, the authors attempted to improve the interpretability of results by using a systematic approach in narrative synthesis and summarising key risk stratification methodologies by cancer types.

CONCLUSION

The RBS of cancer is being implemented worldwide, following the *in silico* development and validation of various cancer risk prediction models. A majority of real-world-implemented RBS programmes screened for colorectal cancer, followed by breast and prostate cancer. Most studies were conducted in either the North American or European region, with most Asian studies conducted in China. More risk prediction models need to be developed primarily from non-Caucasian cohorts to facilitate the translation of RBS to Asian, South American and MENA settings. This review also suggests concerns regarding the uptake of risk-appropriate screening in real-world settings, necessitating qualitative studies to elucidate the facilitators and barriers of RBS among patients and clinicians alike. As RBS becomes increasingly mainstream, subsequent studies must take care in adjusting for potential lead time and verification bias when assessing survivorship outcomes, while also evaluating the cost-effectiveness and ethico-legal considerations of personalised screening strategies.

Supplementary material

Table S1. Complete search strategies used for retrieval of articles in this systematic review in the following databases: (A) CENTRAL, (B) CINAHL, (C) Embase and MEDLINE on OvidSP, (D) PubMed, (E) SCOPUS and (F) Web of Science.

Ethics statement

Not applicable, as no new data were collected from human or animal subjects.

Declaration

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

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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When is it ethically defensible for a medical practitioner to deviate from clinical practice guidelines?

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ABSTRACT

In modern medical practice, clinical practice guidelines (CPGs) have supported physicians with the development of treatment plans through concise recommendations based on evidence from medical research. Yet, the growing demographics of older patients with complexities and comorbidities mean that there is a group of real-world patients which CPGs may not adequately cover. These guidelines, which are primarily based on randomised controlled trials (RCTs), often have restrictive inclusion criteria and hence exclude such patients in their studies, resulting in recommendations that may not be in the patient's best interests. Hence, when treating such patients, physicians may be required to deviate from CPGs' recommendation to ensure the best patient outcome. This puts doctors in a difficult ethical dilemma: whether to follow the CPGs, deviate and risk being complained of, or not treat and refer the patient for palliative care. This article explores the ethical principles and considerations involved when physicians choose to deviate from CPGs in the interest of individualised patient care. The guiding philosophy when using CPGs should be that CPGs can guide the development of treatment plans, but are not meant to direct, dictate or restrict doctors in clinical decision-making.

Keywords: clinical practice guidelines, deviation from guidelines, ethics, evidence-based medicine, medical education, physician

INTRODUCTION

In today's world of rising average life expectancy, the world is populated by a significant number of older patients with complex illnesses and multiple comorbidities, such as chronic conditions like hypertension, diabetes, and cardiac and pulmonary diseases.¹ In a 2019 US study, the Agency for Healthcare Research and Quality found that 84.1% of all inpatient stays were complicated by 1 or more comorbidities, and half of these stays included 3 or more comorbidities.²

These growing demographics of older patients, individuals with comorbidities and persons with complex illnesses present a significant challenge to the use of clinical protocols based on clinical practice guidelines (CPGs). CPGs are heavily reliant on randomised controlled trials (RCTs), which tend to exclude individuals over a specified age and those with comorbidities.³ Hence, for these groups of patients who are left out of RCTs, adherence to CPGs' recommendations may not be in their best interests. This puts doctors in a difficult dilemma when facing such patients: whether to follow the CPGs, deviate and risk being complained of, or not treat and refer the patient for palliative care.

When doctors do deviate from CPGs, they may be called upon to justify the deviation before disciplinary tribunals or the courts, because society expects them to be accountable for their actions and decisions.⁴ In such situations, the justification for deviation may be grounded in well-established ethical principles that support the primacy of patient welfare in the face of guideline limitations.

At the same time, medical practitioners and users of CPGs must recognise the guiding principles of using CPGs. CPGs are defined as clinical recommendations derived from a systematic review of research evidence to assist clinical decision-making.⁵ While they serve as valuable tools to support the development of treatment plans, they are intended to guide, and not dictate, restrict or mandate clinical decision-making. When applying recommendations derived from CPGs, doctors are expected to exercise clinical judgement to tailor treatment modalities to the specific needs and circumstances of each patient.⁶ Hence, in complex or atypical clinical scenarios not adequately covered by CPGs, it is ethically permissible for doctors to deviate from CPGs, provided it is grounded in ethical principles, and supported by sound clinical reasoning and contextual factors beyond mere adherence to standardised protocols. Let us first understand the

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Accepted: 1 September 2025

Published Online First: 1 October 2025

ethical principles and reasoning supporting deviation from CPGs.

Ethical principles to apply when considering deviation

(1) Principle of medical beneficence

The principle of medical beneficence refers to the physician's obligation to act in the patient's best interests, and this may at times require deviation from CPGs. This is particularly relevant for categories of patients for whom CPGs may not adequately cover: older patients, patients with comorbidities and persons with complex illnesses.⁶ The patient may not be responding to the recommended treatment, or has developed adverse reactions, allergies or hypersensitivity to the treatment.⁷ The patient may also have a comorbidity that does not support the use of recommended treatment, or have an uncommon variant of the condition such that there is a lack of experience with and expertise on the variant to be included in CPGs.⁸ In these situations, beneficence is compromised if the physician chooses to persist in following the CPG's recommendations when it is not clinically indicated to do so.

At the same time, a good physician who recommends a deviation needs to have balanced the potential benefit and risk of deviations through a careful risk-benefit analysis. Doctors can make use of clinical experience, evidence of benefit from anecdotal reports, or specific deviations that are accepted and practised by clinical colleagues with good evolving evidence of benefit to minimise risks and enable early mitigation. Consulting a colleague also precludes the possibility of personal bias. In other words, deviation from CPGs should be made in the patient's best interests.

(2) Respect for patient autonomy

Respecting the patient's autonomy involves prioritising the patient's wishes, preferences, specific needs and any special considerations. When a patient's wishes cannot be adequately fulfilled by CPGs, it becomes ethically justifiable to deviate from CPGs. Tailoring treatment plans to accommodate patient-specific factors not only upholds their right to participate meaningfully in healthcare decisions but also promotes patient-centred care.

Obtaining informed consent is a fundamental aspect of respecting the patient's autonomy, because physicians must be honest with their patients and empower them to make their own informed decisions about their health. In obtaining informed consent, information that should be shared with the patient includes anything that the patient is reasonably likely to have attached significance to, when arriving at the decision to give consent. This legal principle was

also established in the landmark case of *Montgomery v Lanarkshire Health Board* [2015], which established that a physician has a duty of care to warn patients of material risks and share information that a reasonable patient would find relevant and material.⁹ Information sharing, when the patient wants to or needs to know include the proposed treatment plan, deviations from established clinical guidelines, along with an explanation of the reasons for such deviations and any associated risks.

(3) Primacy of patient welfare

The principle of primacy of patient welfare is based on a fundamental obligation of the physician to prioritise the patient's well-being and interests above all other considerations.¹⁰ This includes providing patient-centred care that prioritises specific needs and any special considerations. To uphold this principle, the physician needs to have discretionary space, time, support and resources to enable the exercise of good clinical and ethical decisions. When patients' clinical situations are not adequately covered under CPGs, the physician exercises this discretion by deviating in order to uphold the primacy of the patient's welfare. In the absence of this discretionary space, the physician may not be able to treat the patient appropriately and may be forced to abandon the patient and refer the patient elsewhere.

The principle of primacy of patient welfare also requires the physician to uphold the principle of fidelity and non-abandonment. The principle of fidelity and non-abandonment obliges the doctor to continue to care for the patient despite the difficulties and complexity of the work, and to not abandon the patient because of potential medicolegal risks. Rigidly adhering to CPGs purely to avoid legal repercussions (defensive medicine) undermines the ethical responsibility to prioritise the patient's well-being as the first and paramount consideration.

Guiding principles when using CPGs

The guiding principle when using CPGs is that CPGs are supposed to guide doctors in developing treatment plans, but they are not supposed to dictate, direct or restrict doctors in their clinical judgement, or in deciding the treatment modality. CPGs were never intended to provide comprehensive management, supersede professional judgement, or serve as legal precedents.¹¹ Rather, CPGs simply reflect the best judgement of a multidisciplinary team of expert physicians and allied health professionals who have systematically reviewed and synthesised the best available scientific evidence for a specific clinical scenario.¹¹ Hence, physicians should use their professional judgement when applying guidelines in

individualised patient care because good, evidence-based medical practice is a sum of the best research evidence, the patient's values and preferences, and the physician's clinical experience and expertise.¹² Physicians applying CPGs should remain flexible and adaptable to accommodate individual patient circumstances, comorbidities and preferences, because CPGs should be used to support patient-centred care that prioritises their needs, values and preferences.

Limitation of CPGs

The first limitation of CPGs is that recommendations may be unsuitable or erroneous, because different CPGs are developed using different methodologies and rely on evidence of differing quality. In some cases, the quality of the underlying evidence may be misrepresented, particularly since few CPGs have their full methodology published or have their guidelines submitted for external review.¹³ For example, in a US study pertaining to neurosurgical guidelines, researchers found that only 8.9% of evidence used were from well-designed RCTs or meta-analysis of RCTs, even though 24.4% of CPGs were graded as having been based on such Level 1 evidence.¹⁴ Hence, physicians may use the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument to evaluate the quality of guidelines. AGREE II characterises the quality of guidelines by evaluating the explicit scope and purpose (having clear objectives and target audience), stakeholder involvement (inclusion of individuals from all relevant professional groups), rigour of development, clarity of presentation, applicability and editorial independence (free from bias).¹⁵

Second, authors of CPGs who have financial ties to pharmaceutical companies may have undue bias due to a conflict of interest. In Japan, a study of urological guidelines found that 88.6% of authors had received financial incentives.¹⁶ Such incentives can influence guideline development and lead authors to recommend products or treatments they are affiliated with, rather than basing recommendations strictly on the best available research evidence.

Third, CPG's recommendations may be inaccurate if they are outdated and do not reflect the best current practices. To remain relevant and reliable, CPGs should be regularly reviewed and updated with new research evidence. At the same time, physicians have a professional responsibility to maintain clinical competence by staying up to date with the latest advancement in their field.¹³

CONCLUSION

Modern medical practice invariably involves elderly patients with multiple comorbidities and persons with complicated illnesses that make standard CPG recommendations unsuitable. When managing such

cases, clinicians are often required to deviate from CPGs' recommendations in order to uphold the principle of primacy of the patient's welfare. While such deviations may later be scrutinised in disciplinary proceedings or the court, they are not inherently unethical, provided that they are grounded in careful consideration of the patient's unique clinical circumstances with appropriate clinical judgement. The physician's commitment to the primacy of patient welfare is the fundamental ethical basis for all clinical decisions including deviations from standardised guidelines.

The guiding philosophy when using CPGs is that they are intended to guide, not dictate or restrict decision-making. Their primary purpose is to offer medical recommendations based on the best available research evidence. However, good medical practice must go beyond evidence and guidelines alone. It must integrate the patient's unique clinical characteristics and circumstances with the physician's professional experience, expertise and judgement to deliver patient-centred care.

Ethics statement

Not applicable given no participant involvement.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. The authors declare that generative AI (ChatGPT) was used to correct grammar and spelling. All sentences checked using generative AI have been edited by the authors before submission.

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Trichophyton indotineae isolated in 2 migrant workers: An emerging fungal pathogen of global importance

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Dear Editor,

The emergence of *Trichophyton (T.) indotineae*—a drug-resistant dermatophyte—has raised international public health concerns. First identified as a new species in 2020 with origins in South Asia, it has since spread elsewhere. The first case was reported in the US in 2023, and in the UK in 2024.¹ We report 2 cases of *T. indotineae* in migrant workers in Singapore, illustrating the clinical challenges and public health concerns with this emerging pathogen.

A 32-year-old Bangladeshi welder presented with a pruritic rash of 6 months affecting his trunk and buttocks. He had no medical history and had been working in Singapore for 11 years, residing in a dormitory. Examination showed annular plaques with scales and a rim of erythema. Scattered follicular papules with small abscesses were present on the lower abdomen (Fig. 1A). Prior treatments included over-the-counter creams, fixed-dose antifungal-corticosteroid creams and antifungal tablets (unspecified) from Bangladesh, itraconazole 200 mg once daily (OD) for 2 weeks and terbinafine 250 mg OD for 2 weeks. Fungal culture yielded *Trichophyton* species, later confirmed as *T. indotineae* on Internal Transcribed Spacer (ITS) sequencing. The patient was subsequently treated with itraconazole 200 mg OD for 6 weeks with improvement.

The second case, a 25-year-old Indian construction worker with no medical history, presented with a pruritic groin rash for 6 months. A dormitory resident, he reported that over half his roommates had symptoms but could not afford treatment. He sought care incidentally during management of an unrelated fracture. Examination showed a large hyperpigmented region over the buttocks without central clearing (Fig. 1B). Prior treatments included steroid-antibiotic combination creams for 3 months. Skin scrapings demonstrated hyphae, and tinea corporis was diagnosed. Topical and oral terbinafine 250 mg OD were administered for 2 weeks with no improvement. Fungal culture grew *T. mentagrophytes* complex (Figs. 1C and 1D), later confirmed as *T. indotineae* on

ITS sequencing. He was given ketoconazole wash, miconazole cream and itraconazole 200 mg OD for 6 weeks with improvement. Mild transaminase derangement developed, which subsequently resolved. Both patients were compliant to treatment.

T. indotineae, a part of the *T. mentagrophytes* complex, is also known as *T. mentagrophytes* ITS Genotype VIII. Its rapid emergence has seen it overtake *T. rubrum* as the predominant dermatophyte. *T. indotineae* is now identified in 40% of samples sent to the UK's National Reference Mycology Laboratory.² It is anthropophilic and predominantly spread via direct contact, although sexual and zoonotic transmission have been suggested.^{1,3} The global concern is its high resistance rate to firstline systemic antifungals (terbinafine). Resistance arises from squalene epoxidase (SQLE) gene mutations and is believed to stem from unregulated widespread use of corticosteroid and combination creams in India, Nepal and Bangladesh. More worrying is the emergence of itraconazole resistance, leading to multi-drug-resistant tinea.⁴

Our cases describe the local emergence and clinical features of *T. indotineae* while highlighting several key challenges:

Delayed recognition/diagnosis. Tinea typically affects covered body areas. Despite the disease burden and psychological distress from pruritus, providers may downplay its impact. Misdiagnosis is common: up to 70% of tinea, particularly those pre-treated with topical corticosteroids (tinea incognito), were diagnosed as eczema. Tinea is the most common cause of topical steroid misuse.⁵ Widespread indiscriminate use of over-the-counter creams, topical corticosteroids and corticosteroid-antifungal-antibacterial combination creams temporarily masks the rash and symptoms, further delaying diagnosis. The estimated diagnostic delay of *T. indotineae* is 10 months.⁶ These issues are compounded in the migrant population where costs and access to care are barriers to early diagnosis.

Diagnostic difficulties. Unlike conventional tinea, *T. indotineae* is more extensive, facial involvement is

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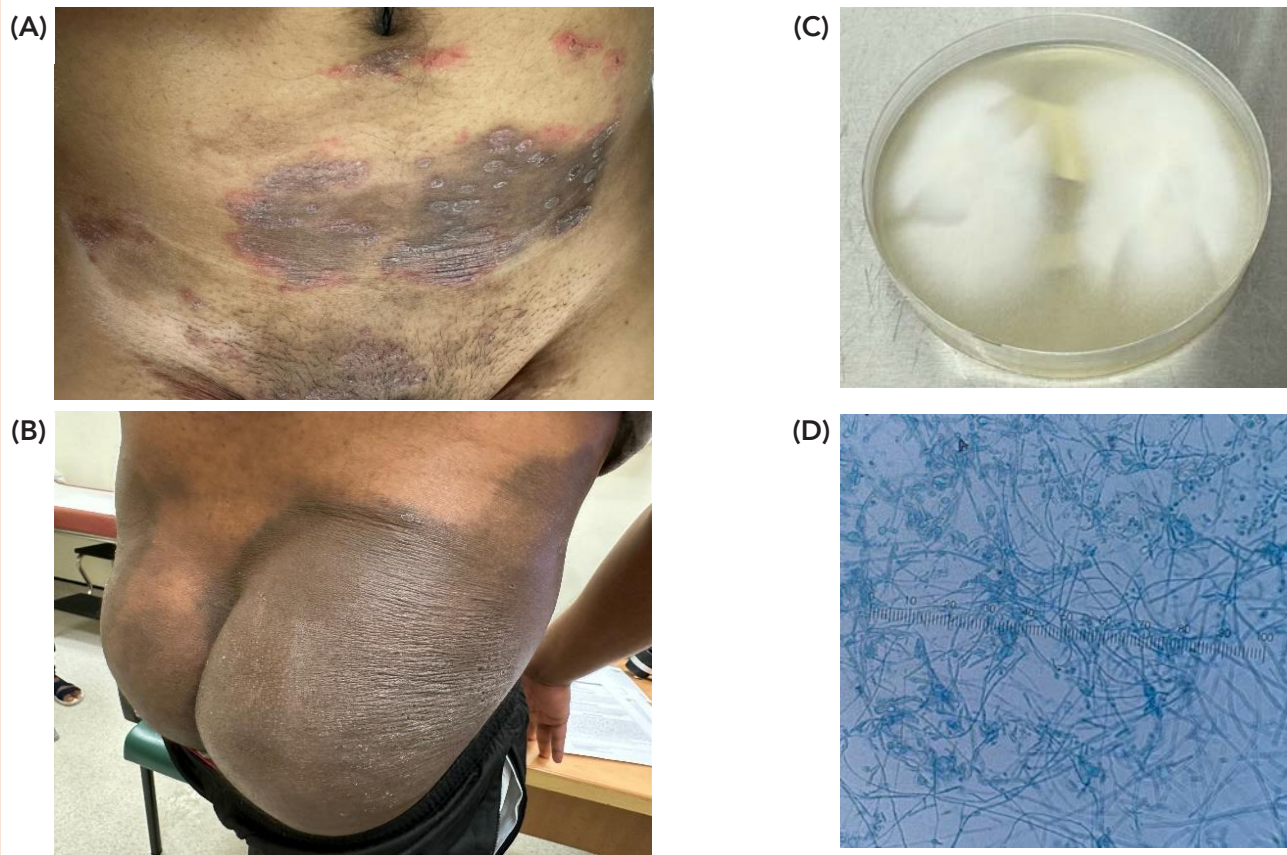
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Accepted: 18 July 2025

Published Online First: 15 October 2025

Fig. 1. Two cases of *T. indotineae* in migrant workers in Singapore.

(A) Hyperpigmented plaques with annular erythema, scattered follicular papules and pustules on the lower abdomen of Case 1; (B) Hyperpigmented patch without erythema or central clearing over the gluteal region of Case 2, despite 1 month of oral itraconazole; (C) *T. indotineae* grown on potato dextrose agar; (D) Microscopic morphology of *T. indotineae* using lactophenol cotton blue stain.

more common, and 14% lack hallmark features like scaling and central clearing.⁴ Similar microbiological challenges exist. Microscopic morphology cannot distinguish *T. indotineae* from *T. mentagrophytes* complex, causing misdiagnosis as *T. mentagrophytes/interdigitale*. Confirmatory diagnosis requires DNA sequencing, which is not routinely available in clinical diagnostic laboratories.³ Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) is a potential tool to identify *T. indotineae* with some in-house or publicly available databases, but this may not be practised widely in clinical diagnostic laboratories.⁷

Treatment resistance. Terbinafine resistance was reported in up to 85% of samples.⁵ Although itraconazole is recommended as the treatment of choice, resistance was reported in 27% of cases, and 15% are resistant to both terbinafine and itraconazole. Prolonged higher doses of itraconazole (200mg/day for 6–12 weeks) may be needed to achieve cure. Alternatives include newer triazoles posaconazole and

voriconazole. Fluconazole may not be helpful due to high minimum inhibitory concentrations.⁴

Several strategies are important in response to the looming *T. indotineae* epidemic. First, having an index of suspicion of *T. indotineae* is key. The unique morphology, extensiveness, along with epidemiological risk factors of ethnicity, contact history and recent travel to South Asia are important clues.¹ A pragmatic low-cost indicator is poor response despite standard therapy. Second, initial evaluation of suspected dermatophyte infection with microscopy is essential. Fungal cultures, although non-diagnostic of *T. indotineae*, may suggest *T. indotineae* if *T. mentagrophytes* complex is cultured. Sequence-based identification and antifungal testing are confirmatory, thus healthcare investment and access to such technologies is essential. Third, antifungal-corticosteroid or triple combination creams (corticosteroid-antifungal-antibacterial) should be discouraged and topical steroid regulation strengthened. In India, 80% of dermatophyte infections received prior

combination creams.⁸ In the US, 15% of prescribed topical medications for fungal infections contained corticosteroids.⁹

The burden of *T. indotineae* in Singapore's 450,000 migrant workers in the construction, marine and process industries and the larger Singapore context remains unclear.¹⁰ These 2 cases are likely the tip of the iceberg, given its endemicity in South Asia coupled with high-density living, costs and barriers to healthcare in Singapore. Local transmission of *T. indotineae* may already be occurring, as seen in other communities with similar socio-economic conditions.²

Our report highlights the importance of recognising *T. indotineae*, an evolving global epidemic with diagnostic and treatment challenges. Its local burden in migrant workers and the wider community is potentially significant and could be worsened by combination cream use. Accordingly, access and optimal treatment for migrant workers must be a public health priority to prevent widespread community emergence and ensure health equity.

Ethics statement

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Declaration

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

Keywords: *dermatophytosis, fungal, Indotineae, Itraconazole, migrant worker, public health, Terbinafine, Trichophyton*

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Fragility fractures of the lower limb beyond the hip: A descriptive prospective cohort study

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Dear Editor,

There is an increased recognition that geriatric low-energy lower-limb fragility fractures may have comparatively significant morbidity and mortality as do geriatric hip fractures. Existing literature suggests that these patients may be at least as frail as the geriatric hip fracture population. Recent expansions in orthogeriatric team capabilities have enabled orthogeriatric co-management of these non-hip non-vertebral (NHNV) geriatric lower-limb fragility fractures. Our objective is to characterise this group of NHNV lower-limb fragility fractures, elucidate the benefit of orthogeriatric co-management, and identify predictors of poor outcomes and increased mortality in these patients.

We conducted a prospective cohort study of all NHNV lower-limb fragility fractures in Tan Tock Seng Hospital, Singapore from January 2021 to December 2022. This coincided with the implementation of orthogeriatric co-management of NHNV lower-limb fragility fractures in our institution. The data were obtained from our institutional lower-limb fragility fracture registry that includes patients who meet the following criteria: (1) minimum 60 years of age, (2) admission for an NHNV lower-limb fracture and (3) fall from standing height. Fracture types included femur, tibia, pelvic, acetabular, peri-implant and peri-prosthetic fractures. Baseline demographics including age, sex, fracture location, management modality (surgical or conservative), preoperative Clinical Frailty Scale (CFS), as well as premorbid ambulatory status and aids were collected from clinical charts.

The primary outcome of the study was the 1-year mortality. Secondary outcomes included the rates of acute inpatient medical complications, and the length of acute hospital stay.

The study has obtained institutional ethics approval from the National Healthcare Group Institutional Review Board (2024-3152).

A total of 252 patients with NHNV lower-limb fragility fractures were included in the 2-year prospec-

tive study. Of these, 81.0% of the cohort were females, with a mean age of 77.7 years on admission. Femoral and lower-limb peri-implant/peri-prosthetic fractures were the most common fracture locations (30.6% and 22.2%, respectively). Moreover, 78.2% of patients had a CFS (4 and higher) suggesting frailty. Surgical intervention was the predominant management modality (57.1%). Only 35.2% of the cohort was allowed to fully weight bear as tolerated after intervention, regardless of intervention modality (Table 1).

The mean length of stay for the operated patients was 10.9 days, versus 8.6 days for conservatively treated patients. Time to surgery was short at 2.5 days. The incidence of inpatient medical complications was 17.9%, with the majority being urinary tract infection (UTI). One-year mortality was 11.1% (Table 1).

After excluding 2 outliers, multiple regression modelling of length of stay, complications and 12-month mortality proceeded against age and sex, given significant between-group differences on admission ($P < 0.05$). The model was improved when further regressed against mobility status, CFS group on admission and management modality. Management modality was significantly correlated to length of stay and complications ($P < 0.001$ for both). Surgical management improved the odds of survival at 12 months (odds ratio [OR] 2.06, 95% confidence interval [CI] 0.65–6.53, $P = 0.22$). Allowing weight-bearing as tolerated reduced the length of stay by 3.01 days (95% CI -4.91 to -1.11, $P < 0.001$). Post-operative delirium (OR 9.61 [95% CI 4.38–14.84], $P < 0.001$), stroke (OR 8.63 [95% CI 1.54–15.72], $P = 0.02$) and UTI (OR 3.56 [95% CI 0.41–6.72], $P = 0.03$) were significantly correlated to length of stay. However, none of the complications were correlated to survival at 12 months.

We therefore present the largest-known prospective cohort study on NHNV lower-limb fragility fractures co-managed by an orthogeriatric team. This cohort had high rates of frailty and was skewed towards females, consistent with large prospective cohort

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Accepted: 10 July 2025

Published Online First: 22 August 2025

Table 1. Demographics and 1-year outcomes of non-hip non-vertebral lower-limb fragility fractures.

Demographics	Orthogeriatric care cohort (n=252)
Age, mean (SD)	77.7 (10.0)
Female, no. (%)	204 (81.0)
CFS group, no. (%)	
1–3	55 (21.8)
4–9	197 (78.2)
Location of fracture, no. (%)	
Femur	77 (30.6)
Patella	30 (11.9)
Tibia	33 (13.1)
Ankle	36 (14.3)
Acetabulum	20 (7.9)
Periprosthetic, peri-implant	56 (22.2)
Mobility on admission, no. (%)	
Community ambulant	147 (58.3)
Homebound	105 (41.7)
Level of assisted mobility, no. (%)	
Independent of aid	133 (52.8)
Single arm aid	45 (17.9)
Double arm aid	15 (5.9)
Personal assistance	32 (12.7)
Wheelchair/bedbound	27 (10.7)
Treatment type, no. (%)	
Conservative	108 (42.9)
Operated	144 (57.1)
Weight-bearing status post-intervention, no. (%)	
Non-weight bearing	143 (56.7)
Partial weight bearing (i.e. 50% of weight bearing on affected limb)	23 (9.1)
Weight bearing as tolerated	89 (35.3)
Outcomes	
Length of stay, days; mean (SD)	
Conservative	8.6 (9.9)

Table 1. Demographics and 1-year outcomes of non-hip non-vertebral lower-limb fragility fractures. (Cont'd)

Demographics	Orthogeriatric care cohort (n=252)
Operative	10.9 (7.7)
Total	9.4 (6.5)
Time to surgery, days; mean (SD)	2.9 (2.5)
Inpatient medical complications, no. (%)	
Urinary tract infection	18 (7.1)
Pneumonia	6 (2.4)
Delirium	13 (5.2)
DVT/PE	7 (2.8)
Stroke	3 (1.2)
Acute myocardial infarction	0 (0)
Gastrointestinal bleeding	3 (1.2)
Total incidence	50 (17.9)
Inpatient mortality, no. (%)	5 (2.0)
One-year mortality, no. (%)	28 (11.1)

CFS: Clinical Frailty Score; DVT: deep vein thrombosis; PE: pulmonary embolism; SD: standard deviation

studies including the Canadian Multicentre Osteoporosis Study (CMOS) and Tromsø Study, reporting incidences in females 2–3 times more than that of males.^{1,2} The CMOS also showed that the selectivity of females over males extended to mortality rates. Over the 19-year follow-up, 1 in 15 deaths in women was attributable to an NHNV fracture, compared to 1 in 40 deaths in women attributable to a hip or vertebral fracture. More data are required on the anatomical predilection of NHNV lower-limb fractures. The Global Longitudinal study of Osteoporosis in Women suggests that NHNV lower-limb fractures tend to be more proximal (femur, leg, pelvis and knee).³ The Australian cohort study 45 and up suggests that pelvic and proximal femur fractures are age-dependent, but not ankle and proximal tibia/fibula fractures, where the incidence remained relatively constant with age.⁴

Our study shows that orthogeriatric intervention for these patients is beneficial. Compared with unpublished institutional data before the commencement of orthogeriatric intervention for this cohort,

operated patients had seen an improved length of stay with orthogeriatric co-management from a mean of 12.1 days to 10.9 days, attributable to pre-operative optimisation for anaesthetic fitness, aggressive post-operative delirium care protocol, early mobilisation and removal of urinary catheters. Conservatively managed patients in our study saw a slight increase in their mean length of stay from 5.5 to 8.6 days; this may be confounded by the much more significant proportion of frail patients in our intervention cohort that would have required a longer period of medical optimisation as a result of the injury. In all, despite an intervention cohort that is older and frailer, there was no increase in inpatient or 1-year mortality, while pneumonia rates were quartered. It is a testament to the benefit of orthogeriatric co-management in this cohort. The ultimatum is to validate the orthogeriatric management of lower-limb fragility fractures^{8,9} to have non-inferior mortality and cost benefits compared to hip fractures.⁵⁻⁷

Surgical management of these NHNV lower-limb fragility fractures should be encouraged, having improved the odds of survival at 12 months by 2.06 times in our cohort. Likewise, early and full mobilisation should be encouraged to reduce their length of stay. It is also encouraging that 1-year mortality in this NHNV lower-limb fragility fracture cohort is lower than our local 1-year all-cause mortality of hip fractures, most recently quoted to be 14.5% in a sister institution.¹⁰

In conclusion, this is the largest-known prospective cohort that characterised NHNV lower-limb fragility fractures. This unique cohort is frailer and predominantly female. Orthogeriatric care should be encouraged as standard care in this cohort, and surgical intervention is encouraged for its mortality benefit.

Ethics statement

This study was approved by the National Healthcare Group Institutional Review Board (2024-3152). Waiver of consent was granted as only de-identified data were obtained in a retrospective manner for which patient's confidentiality was not compromised, and no patient was harmed in the process.

Declaration

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

Keywords: femur, fragility fracture, frailty, orthogeriatric, osteoporosis, pelvis

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Medicolegal implications of advice for surgical treatment of breast cancer

Mona P Tan¹ FRCS

Dear Editor,

I read with interest a letter by Ngaserin et al. published in the *Annals*.¹ The acknowledgement that breast conservation treatment (BCT) for eligible women with breast cancer results in higher survival than mastectomy is heartening. There has been data since 2007 reporting that women who underwent BCT had better survival outcomes.² This early data was subsequently supported by such a significant body of evidence in the ensuing years that in 2016, Johns et al. recommended that all eligible patients should undergo BCT.³ It was also suggested that it may no longer be appropriate for such patients to be offered the choice of mastectomy, as the latter did not provide an equivalent survival outcome.³ In 2021, this treatment approach was reinforced by further cumulative data of close to 1 million patients providing robust evidence that there is a consistent benefit of overall survival in favour of breast-conserving surgery.⁴ There are more recent studies that demonstrate a survival benefit of 56–70% with BCT compared with mastectomy.⁵ Based on their findings, de Boniface et al. echoed the sentiment of Johns & Dixon,³ and stated that for breast cancer patients who are eligible for BCT, mastectomy cannot be considered to offer equivalent outcomes.⁵ A Singapore study by Leong et al. published in 2022 compared the survival outcomes of breast conserving surgery (BCS) with radiotherapy (BCT) and mastectomy.⁶ While the degree of survival advantage may not be directly comparable to that observed by de Boniface et al., an improved survival outcome with BCT was also reported in Singapore.^{5,6}

In spite of the large volume of data available to date and broad agreement among numerous researchers that BCT offers improved survival prior to 2022, it was reported in 2023 that endoscopic mastectomy was offered to women at a Singapore hospital without clear indications as to why these patients were not considered eligible candidates for BCT.⁷ It is also unclear if the patients were counselled about the chances of survival that BCT confers when they consented to endoscopic mastectomy; the ethical implications associated with this study are also unclear.

The chronology of these studies uncovers and identifies an area of possible mismatch in scientific evidence, treatment philosophy and real-life practices among Singapore surgeons. This has ramifications for patient care.

The 2022 study by Leong et al. reported a BCT rate of 53% among women with Stage I and II breast cancer, with 3% undergoing only BCS without radiation.⁶ It is worthwhile noting that these 3% of patients who did not complete radiotherapy had a significantly poorer overall survival than those who underwent BCS with radiotherapy and mastectomy. Hence, while Ngaserin et al. reported the BCS rate of 56% as low-normal,¹ the true rate of BCT for this cohort was in fact lower at 53%. In 2016, it was suggested that an ideal BCT rate should be 70%.⁸ Earlier, it was reported by Brooks et al. that 1% increase in mastectomy rate is estimated to reduce survival rate by 0.1% on a population basis.⁹ In a cohort of 3655 patients,⁶ this could mean that about 62 women would potentially have had compromised survival as a result of having undergone mastectomy. With recent data to show a 56–70% relative survival advantage with BCT,⁵ it is now suggested that a suboptimal BCT rate may compromise population survival to an even greater extent.

BCT need not be confined to women with Stage I and II breast cancer. There is ample data reporting that selected women with larger tumours (>5 cm) and those with locally advanced breast cancer (LABC) can undergo BCT without survival detriment.¹⁰ However, there is a paucity of Singapore data on a large scale to understand BCT rates for LABC, as women with these tumours were not included in the initial randomised controlled trials comparing BCT with mastectomy. In the context of current robust data that demonstrate favourable outcomes with BCT, it would be extremely useful to know the BCT rates for this group of women with large tumours and LABC, and how this new data would contribute further to BCT rates and patient survival outcomes.

The survey performed by Ngaserin et al. is commendable.¹ However, it does raise medicolegal

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Accepted: 10 July 2025

Published Online First: 1 October 2025

issues. In light of available data dating back to 2007, suggesting better survival outcomes with BCT, together with large volume of data allowing strong conclusive statements supporting BCT in 2021,³⁻⁵ it is of considerable concern that in a survey performed in 2023, none of the 22 surgeons surveyed in this study would advise their patients that BCT offers better survival than mastectomy. With such a large body of evidence providing ample support of BCT, the medicolegal implications for this manner of patient communication and education are highly worrying, to the point of being alarming. This is especially so with the introduction of legal tests requiring doctors to detail available treatment options. While patient autonomy is important, Johns & Dixon suggested that surgeons may be abrogating their duty by offering mastectomy as an option to BCT-eligible patients.³ There is therefore now a pressing need for further research to identify and understand firstly, the reasons why surgeons who treat women with breast cancer, surveyed in 2023, do not inform patients of the fact that in the majority of cases, BCT leads to better survival. Second, in light of such robust evidence in existence for several years in favour of BCT, why merely half of Singapore surgeons would choose BCT for patients who are BCT-eligible candidates. This raises the possibility of apparent lapses and gaps in Singapore physician acknowledgement and acceptance of robust clinical evidence.

Perhaps it is time that we, as a surgical community, evaluate how we can be educated to recognise best practices and adopt them expeditiously and safely. Having done a survey among Singapore surgeons, the best physician group to spearhead positive change would be Ngaserin et al. Only then can the gap between current evidence and clinical practice be rectified and addressed, so that we will be able to do our patients the justice of offering appropriate surgical intervention and treatment for optimum survival.

Ethics statement

Not applicable given no participant involvement.

Declaration

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

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Transcatheter mitral valve repair with the PASCAL precision system: First case in Singapore

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Dear Editor,

Severe mitral regurgitation (MR) is associated with significant mortality and morbidity when left untreated.¹ In patients who are not suitable for surgery, transcatheter edge-to-edge repair (TEER) provides a minimally-invasive therapeutic option. The MitraClip (Abbott Cardiovascular) is the most widely used TEER device globally, with the first human implantation performed in 2003 and the first case in Singapore and Asia in 2011.^{2,3} The underlying concept of the TEER technique involves grasping the anterior and posterior mitral valve leaflets and approximating them to reduce MR. Since then, other TEER devices with their own unique features have emerged, with PASCAL (Edwards Lifesciences) being the next to receive commercial approval in Europe and the US. The authors herein report the first case of TEER using the PASCAL system in Singapore and Southeast Asia at the National Heart Centre Singapore (NHCS).

A 77-year-old female was managed in NHCS for symptomatic severe degenerative MR. She had New York Heart Association (NYHA) functional class II dyspnoea on exertion and a prior heart failure admission. Her comorbidities included hypertension, dyslipidaemia, lumbar spondylosis and a history of falls with bilateral hip fractures requiring hip replacements. A transthoracic echocardiogram (TTE) showed severe MR, a dilated left ventricle (LV) with normal LV systolic function, and an elevated pulmonary artery systolic pressure of 58 mmHg. Transoesophageal echocardiogram (TEE) demonstrated posterior mitral valve prolapse at the P2 segment with a flail tip resulting in severe MR (Figs. 1A and 1B). Coronary angiography showed moderate coronary artery disease. She was evaluated for mitral valve surgery but declined. Following a Heart Team discussion, she was deemed an appropriate candidate for TEER due to her age, comorbidities and suitable mitral valve anatomy.

The procedure was performed in the cardiac catheterisation laboratory under general anaesthesia

with TEE guidance. Vascular access was obtained through the right femoral vein and left atrial (LA) access was secured through a transseptal puncture. The guide sheath was then introduced into the LA, through which the steerable and implant catheters were manoeuvred to the mitral valve (Fig. 1C). Two PASCAL Ace implants were placed centrally at the site of P2 prolapse. TEE imaging was used to confirm adequate leaflet grasping between the implant's paddles and clasps before deployment (Fig. 1D). MR severity was reduced to trivial with a satisfactory mitral inflow gradient of 3 mmHg (Figs. 1E and 1F). The delivery system was removed, and the right femoral vein access site was closed with 2 Perclose ProGlide (Abbott Cardiovascular) vascular closure devices. The patient was extubated immediately after the procedure and monitored overnight in the high-dependency unit. She ambulated well and was discharged the next day in stable condition. At 1 month, her symptoms improved to NYHA functional class I, with only trivial MR on TTE.

The MitraClip device, as the pioneer in TEER, has demonstrated its safety and efficacy through robust clinical trials with EVEREST II for degenerative MR and COAPT for functional MR.^{4,5} The PASCAL device was subsequently introduced and evaluated in the CLASP IID trial, which randomised patients with moderate-to-severe or severe symptomatic degenerative MR at prohibitive surgical risk to undergo TEER with either MitraClip or PASCAL.⁶ The trial demonstrated that PASCAL was comparable to MitraClip in terms of safety and efficacy, with no differences in all-cause mortality, heart failure hospitalisations, major adverse events and MR reduction at 1 year.

The PASCAL implant features broad-contoured paddles (compared to MitraClip's narrower arms) and clasps armed with a single row of retention elements (as opposed to MitraClip's gripper with multiple rows) (Supplementary Table S1). These design differences aim to reduce stress and potential leaflet injury. Additionally, the PASCAL implant incorporates a central spacer to bridge the coaptation gap and

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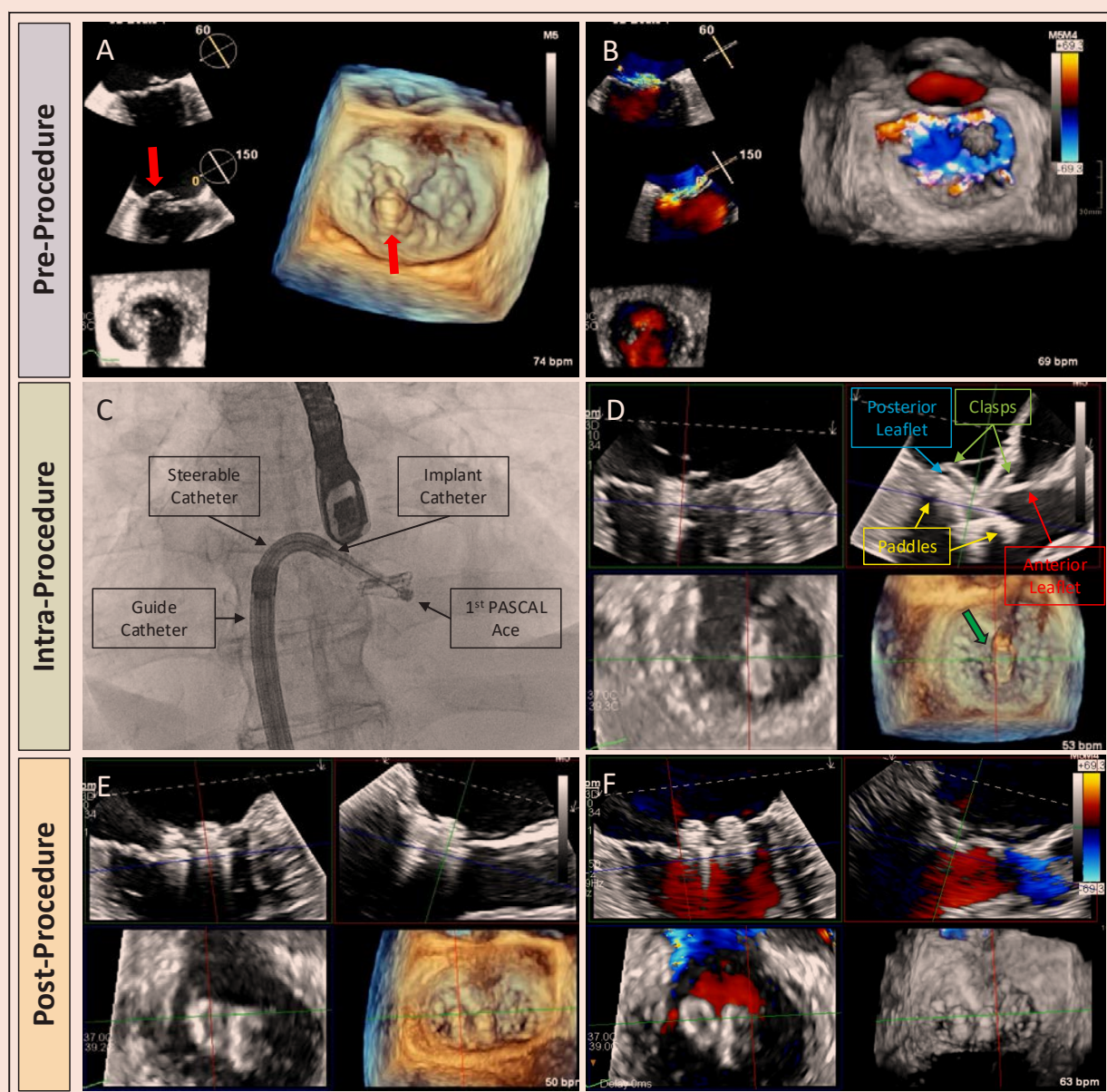
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Accepted: 15 August 2025

Published Online First: 8 October 2025

Fig. 1 Mitral valve transcatheter edge-to-edge repair with PASCAL system.



Pre-procedure. Transesophageal echocardiographic (TEE) images showing (1A) posterior leaflet prolapse with flail at the P2 segment (red arrows) resulting in (B) severe mitral regurgitation (MR). Intra-procedure. (C) Fluoroscopic image showing the guide sheath, steerable catheter and implant catheter delivering the first PASCAL Ace implant to the mitral valve. (D) TEE 3D multi-planar reconstruction (MPR) imaging showing the first PASCAL Ace implant positioned centrally between the A2/P2 segments (green arrow) with the posterior mitral valve leaflet grasped between the paddle and clasp while the anterior leaflet is in position before the clasp was lowered. Post-Procedure. TEE 3D MPR images showing (E) both PASCAL Ace implants deployed with (F) trivial MR.

features a flexible nitinol structure with passive closure, allowing the implant to flex and extend with leaflet motion (whereas MitraClip employs a rigid mechanical active closure). Its ability to elongate and slenderise makes it easier to navigate around the subvalvular apparatus, reducing the risk of chordal entanglement. The PASCAL is available in 2 sizes: the original PASCAL, or "P10", with a 10 mm width and a larger spacer; and the PASCAL Ace, which is narrower at 6mm with a smaller spacer. In contrast, the MitraClip

device offers 4 clip sizes with varying widths (4 mm and 6 mm) and lengths (9 mm and 12 mm), designated as NT, NTW, XT and XTW ("W" indicating a wider clip and "X" a longer clip). The PASCAL Precision delivery system consists of 3 components (guide sheath, steerable catheter and implant catheter) that allow for independent movements, enhancing flexibility and manoeuvrability, while the MitraClip delivery system comes in 2 components (steerable guide catheter and clip delivery system).

The introduction of the PASCAL system marks a significant advancement in transcatheter mitral valve repair in Singapore, offering an additional TEER option for patients unsuitable for open-heart surgery. Alongside the MitraClip, the availability of 2 distinct TEER devices, each with their unique designs, enables treatment for a broader range of mitral valve anatomies.

Supplementary Material

Supplementary Table S1. Comparison between MitraClip and PASCAL.

Ethics statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Declaration

Ningyan Wong and See Hooi Ewe have received honoraria fees from Abbott Vascular. Khung Keong Yeo has received research funding from Abbott Vascular, consulting or honoraria from Abbott Vascular and Peijia Medical and speaker or proctor fees from Abbott Vascular and Peijia Medical. Wei Chieh Jack Tan has received educational grants from Abbott Vascular and Edwards Lifesciences. Ignasius Aditya Jappar

declares no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: cardiology, mitral regurgitation, mitral valve prolapse, structural heart intervention, transcatheter mitral valve repair, transesophageal echocardiography

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Prognostic factors and outcomes of extremity necrotising fasciitis in Singapore

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Dear Editor,

Necrotising fasciitis (NF) is a rapidly progressive infection that spreads across the fascial planes, leading to tissue necrosis and severe systemic toxicity.¹ In Singapore, Wong et al. conducted a retrospective study on a cohort of 89 patients in 2004 and found that the misdiagnosis rate was 85%, amputation rate was 23% and mortality rate was 21%.^{2,3} However, since these early studies, there has been a paucity of data on NF in the Singapore context, despite changing antimicrobial resistance patterns and evolving management approaches.^{2,3} To address this gap, a 17-year retrospective cohort study was conducted in the National University Hospital (NUH) in Singapore. The aim was to report an update of the clinical/microbiological profile, adverse outcomes (amputation/mortality) rates and identify predictive factors for adverse outcomes in patients with extremity NF.

A total of 167 patients with surgically confirmed NF of the extremities (upper or/and lower limbs) from January 2005 to December 2021 were reviewed. The diagnosis of NF was confirmed intraoperatively by the presence of friable necrotic fascia and “dishwater fluid”, with further confirmatory histopathology performed when in doubt. Tissue cultures were taken in all patients. All patients received empirical antibiotics (i.e. benzylpenicillin, ceftazidime, clindamycin) based on institutional guidelines followed by culture sensitivity-directed antibiotics. Patient demographic variables, comorbidities, clinical presentation, laboratory and microbiological investigation results were recorded. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was calculated. The primary outcomes were amputation and mortality rates during index hospitalisation. Logistic regression was performed to identify independent predictors of amputation/mortality.

The mean age of patients was 57 years, with majority being male (62.3%) and of Chinese (45.5%) or Malay

(39.5%) ethnicity. Diabetes mellitus (56.9%) was the most common comorbidity. Most NF cases involved the lower limbs only (80.2%, 134/167), while 17.3% (29/167) involved upper limbs only and 2.4% (4/167) involved both upper and lower limbs. Only 74.8% (122/167) of patients in the cohort had LRINEC scores of ≥ 6 . Monomicrobial gram-positive NF (56.9%, 95/167) was the most common, followed by polymicrobial (27.5%, 46/167), monomicrobial gram-negative (10.8%, 18/167) and vibrio (3.6%, 6/167) infections. Moreover, 22.2% of patients in this cohort had infections which were not sensitive to empirical antibiotics.

Amputation and mortality rates of patients were 30.5% (51/167) and 25.1% (42/167), respectively. Accurate initial diagnosis of NF was made in 80 (47%) patients, and 55.8% (92/167) of patients were operated within 24 hours. Multivariate logistic regression showed that advanced age, positive blood cultures, bacterial infections not sensitive to empirical antibiotics and hyperlipidaemia (HLD) were significantly associated with amputation (Table 1). Multivariate logistic regression also showed that advanced age, multifocal involvement and end-stage renal failure (ESRF) were significantly associated with mortality (Table 1). The odds ratio (OR) and 95% confidence interval (CI) for all variables mentioned are detailed in Table 1.

Despite increased awareness and the adoption of the LRINEC score, the amputation and mortality rates of patients with NF remain high at 31% and 25%, respectively.^{2,3} While the numbers still lie within global norms, it is still higher than that reported by previous Singapore studies, highlighting the need for improved management strategies.^{2,4}

Wong et al. recommended surgical treatment within 24 hours, however only 55.8% of the patients underwent surgery within 24 hours. Increasingly surgery within 6 hours is recommended, and delayed surgery is associated with poorer outcomes.⁵ Surgical

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Accepted: 26 August 2025

Published Online First: 30 September 2025

Table 1. Multivariate analysis of risk factors for mortality and amputation.

	Variable	Death/amputation, no. (%)	Survival/salvaged, no. (%)	Multivariate analysis ^a	
				OR (95% CI)	P value
Mortality	Age, years (mean ± SD)	62 ± 11	55 ± 14	1.05 (1.01–1.09)	0.021
	Glucose ≥10 mmol/L	23/70 (32.9)	47/70 (67.1)	2.91 (1.17–7.21)	0.021
	Involvement (multifocal)	8/17 (47.1)	9/17 (52.9)	4.80 (1.49–15.50)	0.027
	ESRF (GFR <15 mL/min/1.73 m ²)	9/18 (50.0)	9/18 (50.0)	4.43 (1.19–16.50)	0.09
Amputation	Age, years (mean ± SD)	62 ± 11	54 ± 14	1.04 (1.01–1.08)	0.012
	Positive blood cultures	23/51 (45.1)	28/51 (54.9)	2.53 (1.11–5.79)	0.028
	Sensitivity ^b	18/37 (48.6)	19/37 (51.4)	0.21 (0.078–0.56)	0.020
	Hyperlipidaemia	29/58 (50.0)	29/58 (50.0)	3.68 (1.57–8.60)	0.030

CI: confidence interval; ESRF: end-stage renal failure; GFR: glomerular filtration rate; OR: odds ratio; SD: standard deviation

^aAnalysis used backwards model selection.

^bBacteria were not sensitive to empirical antibiotics used.

Values are expressed in no. (%) unless indicated otherwise.

exploration is recommended even when the diagnosis is not confirmed. While this may result in negative explorations, the benefit of early surgical intervention outweighs the risks associated with delayed surgery.

This study suggests an evolving microbiological landscape for extremity NF in Singapore, with decreasing polymicrobial and increasing gram-positive monomicrobial NF.

Findings reveal that 22% of bacterial isolates were resistant to NUH's empirical antibiotic regime, and methicillin-resistant *Staphylococcus aureus* (MRSA) was the most common resistant organism isolated. Notably, all cases of MRSA in this study occurred in patients with recent hospital admissions (within 3 months).

The Infectious Disease Society of America recommends broader empirical coverage for NF, including vancomycin or linezolid plus piperacillin-tazobactam, a carbapenem or ceftriaxone and metronidazole.⁶ Given that a lack of sensitivity to empirical antibiotics was a significant predictor of amputation, there may be a need to re-evaluate antimicrobial protocols. It may be beneficial to start high-risk patients such as those with recent hospital admission on empirical antibiotics that cover MRSA and resistant gram-negative bacteria.^{6–9} However, these considerations must be balanced with the goals of antimicrobial stewardship.

Advanced age, bacteraemia, lack of microbial sensitivity to empirical antibiotics and HLD were significantly associated with amputation. Advanced age, hyperglycaemia, ESRF and multifocal NF were associated with mortality.

Reported prognostic factors of NF have been largely heterogenous, and this study aims to provide further

clarity to the prognostic factors of NF specific to the Singapore cohort. The factors identified in this study will help clinicians in Singapore to better identify and promptly escalate care for more vulnerable NF patients (e.g. older/bacteraemia/HLD/ESRF). Of note, the LRINEC scores were not predictive of amputation or mortality after multivariate analysis and should be used with caution as a prognostic tool. Sex and ethnicity were also not found to be independent predictive factors for amputation or death.

In conclusion, extremity NF continues to pose a major clinical challenge in Singapore, with persistently high rates of amputation and mortality. Based on the findings, the following recommendations are proposed: (1) identification, appropriate counselling and treatment of patients with identified risk factors for amputation and mortality; (2) early surgical intervention within 6 hours of diagnosis; (3) broadening empirical antimicrobial coverage to include MRSA-active agents (e.g. vancomycin) and carbapenems for gram-negative organisms in patients with recent healthcare exposure of less than 3 months; (4) early engagement of a multidisciplinary team for comprehensive management.

Ethics statement

This study was approved by the National University of Singapore Institutional Review Board (NUS-IRB-2022-00956).

Declaration

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

Keywords: *necrotising fasciitis, orthopaedics, outcomes, prognostic factors, Singapore*

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