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Exploring changes in recognition and stigmatisation towards individuals with schizophrenia in Singapore

Over an 8-year period, personal stigma towards schizophrenia decreased. Continued targeted education can help further strengthen public recognition of the condition (See full article, p. 516).

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Factors associated with willingness to quit smoking in a hospital-based smoking cessation programme

Recommendations for the diagnosis and management of neurofibromatosis type 1 in Singapore: A Delphi consensus

Diagnosis and management of haemophagocytic lymphohistiocytosis in adults: A narrative review and practical approach

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From teachable moment to national strategy: Acting on readiness to quit smoking

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In this issue of the *Annals*, Fong et al. note that Singapore's daily smoking prevalence has continued its long-term decline, reaching 8.4% among residents in 2024.[1] This progress reflects decades of sustained investment across Singapore's tobacco control ecosystem, spanning legislation, taxation, smoke-free public spaces, and public education.[2] Yet as prevalence falls, the remaining smokers may be harder to reach, and further gains are unlikely to come from conventional measures alone.

What comes next? Singapore has favoured a pragmatic, incremental approach to tobacco control, and it does not anticipate a sudden move towards an explicit tobacco endgame—the time-bound, structural policy approach, adopted in various forms by a growing number of countries, that aims to end the tobacco epidemic rather than simply control it.[3] If Singapore is to reduce smoking rates, it will need to think outside the box and adopt new approaches.

Fong et al. conducted a cross-sectional study of 953 hospitalised smokers referred to an inpatient cessation service between 2021 and 2025, finding that approximately half (49%) were willing to quit.[1] After adjustment, willingness was independently associated with ischaemic heart disease, cerebrovascular accident, higher symptom burden (on the chronic obstructive pulmonary disease assessment test or the modified Medical Research Council dyspnoea scale), a respiratory admission or visit in the past year, and higher educational attainment. Willingness rose progressively as these clinical features accumulated, although this composite was derived post hoc and awaits validation. Importantly, the study measured willingness, not quitting; these associations should not be read as predicting cessation.

That sicker patients are more willing to quit is intuitive, but it should prompt action. Illness, heightened perceived risks, and a smoke-free ward may together open a window of enhanced openness to change. The proportion willing to quit in this cohort exceeds the 31.3% of current smokers reporting quit intention in a national survey conducted in 2020 to 2022, although definitions and populations differ.[4] An earlier Singapore study of 7194 patients recruited into inpatient cessation programmes at 2 institutions reported 24.7% abstinence at 6 months, with the highest quit rates among those admitted with cardiovascular disease, in keeping with Fong et al.'s findings.[5]

Admission offers multiple touch points. Admission nurses already identify smokers routinely in most Singapore institutions, and the inpatient team can then deliver counselling and start nicotine replacement therapy (NRT), which also eases withdrawal once access to cigarettes is cut off. Such efforts work best when built into routine care rather than left to individual clinicians. Tobacco dependence is a treatable chronic disease, not a lifestyle choice for which patients must request help. In a randomised trial among hospitalised smokers in the US, an opt-out model, in which treatment is offered by default and patients decline if they wish, roughly doubled treatment use and increased quit attempts, regardless of stated readiness to quit.[6] Empowering nurses and other non-physician staff to initiate NRT would build on existing workflows. Because motivation during illness may be transient, the opportunity should not end at discharge—hospital and community cessation services are best viewed as parts of a single, longitudinal treatment pathway.

NRT is a well-established first-line pharmacotherapy for smoking cessation, available as patches, gum, and lozenges. Systematic review evidence shows that NRT increases quit rates by 50% to 60% regardless of setting, with no clear evidence of increased risk of myocardial infarction, and it does not need to be prescribed by a doctor.[7] Cost, however, may still deter some smokers from starting treatment.

Singapore takes a multipronged approach to tobacco control and subsidises cessation aids. The Medication Assistance Fund (MAF) subsidises clinically proven, cost-effective but high-cost drugs for eligible patients at public hospitals and polyclinics, and NRT patches,

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gum, and lozenges have been on the MAF list since 2023 for patients who are willing to quit and are enrolled in a counselling programme.[8] This has been anecdotally associated with increased NRT use. However, the subsidy is currently limited to public healthcare institutions, and eligibility criteria based on stated willingness to quit may exclude smokers who are undecided but could be engaged, as suggested by evidence on opt-out approaches. Extending subsidised NRT to general practitioner (GP) clinics and community pharmacies, coupled with pharmacist-delivered behavioural counselling at the point of sale, could reach more smokers and further increase quit rates.

Regulatory reform could widen access further. NRT is currently a Pharmacy-Only Medicine in Singapore,[9] restricting supply to hours when a pharmacist is on duty—a meaningful barrier since cravings do not keep to office hours. Reclassifying NRT as a General Sale List medicine would give smokers round-the-clock access to a safe, effective aid, potentially forestalling the single cigarette that so often precipitates relapse. Any such move should be accompanied by appropriate safeguards, including standardised product labelling and patient education on correct dosing, duration of use, and combination therapy, delivered through channels such as pharmacist helplines or printed guidance rather than only face-to-face counselling, as well as ongoing monitoring.

Fong et al.'s findings also expose a limitation in how smokers are currently reached—referral depended on patient agreement and clinical judgement, likely favouring those already inclined to quit. Since admission nurses already screen patient's smoking status, active case finding could become the default, with every smoker identified in hospital offered at least brief engagement whatever their initial stance. This first step would address the selection issue directly, at negligible extra cost, and extend the reach of cessation services to the larger group of hospitalised smokers who are undecided or not yet ready. Whether more intensive or repeated engagement for this group justifies the additional resource warrants further study in Singapore. A recent Cochrane review found only low-certainty evidence that motivational interviewing improves quit rates beyond brief advice, while the staff time and resource implications of such follow-up have yet to be formally evaluated in Singapore. Universal brief engagement at the point of admission may therefore serve as a low-cost first step for smoking cessation, with more intensive follow-up warranting pilot testing and further economic evaluation.

However, hospitals should not be the sole entry point for cessation support. Routine cessation counselling in primary and community care, at GP visits, polyclinic consultations, and pharmacy encounters, would give smokers repeated opportunities to engage, and would pair naturally with the more accessible cessation aids described above.

Education deserves particular attention. In Fong et al., educational attainment showed the strongest association with willingness to quit, although the estimates were imprecise, with wide confidence intervals and a small reference group. The national survey similarly found lower intention to quit among smokers with secondary or pre-tertiary education.[4] Generic posters and campaign messages may fail to resonate with smokers with low education attainment or health literacy, highlighting the need to tailor message content, rather than simply expand its reach. Tailored approaches built on personal engagement and relationship-based care are likely to resonate more, and Koh et al. likewise call for simpler messaging for lower-literacy groups.[4]

Finally, willingness is dynamic rather than fixed. In the Stages of Change model, smokers move through precontemplation, contemplation, action, and maintenance, often relapsing and cycling back before quitting for good.[10] Fong et al. grouped undecided smokers with those unwilling to quit, yet ambivalence provides an opportunity for engagement. Hospital admissions should therefore be viewed not merely as a means of identifying smokers ready to quit, but as an opportunity to help all smokers, regardless of readiness, progress towards cessation.

Behind every statistic in Fong et al.'s cohort is a person, embedded in a family and a community, with their own reasons for smoking and for wanting to quit smoking. Readiness to quit is not static—it can be assessed, nurtured, and advanced through timely support, one stage at a time. Longitudinal studies should now test whether the clinical features identified here relate to quit attempts and sustained abstinence, and trials should evaluate active case finding and NRT-on-discharge pathways. Meanwhile, every opportunity should be seized—whether during a hospital admission, a clinic visit, or a conversation at the pharmacy counter—to meet smokers where they are and strengthen the systems and support that make quitting easier to initiate and sustain. Do this well, and Singapore's smoking rate can fall further and faster.

Ethics statement

Not applicable, as no study participants were recruited.

Declaration

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Keywords: *nicotine dependence, public health, pulmonary medicine, respiratory tract diseases, smoking cessation, tobacco use*

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Replacing fear with familiarity: Schizophrenia, stigma, and the shared work of recovery

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World Mental Health Day, observed annually on 10 October, is an opportunity to reflect on how far Singapore has come in improving public understanding of mental illness. Public recognition of common mental illnesses in Singapore increased substantially between surveys conducted in 2014–2015 and 2022–2024, from 43.7% to 59.3%, respectively.[1] Schizophrenia, however, has not shared in this progress. In this issue of the *Annals*, Cao et al. report findings from 2 nationwide cross-sectional surveys conducted from March 2014 to April 2015 and from September 2022 to February 2024. Correct recognition of schizophrenia increased from 11.5% to 15.1%, but this difference was not statistically significant, before or after adjusting for sample differences.[2] Although fewer respondents in the later survey believed that schizophrenia reflected personal weakness rather than illness, perceptions of dangerousness and the desire for social distance remained unchanged after adjustment. This contrasts with the pooled trend from the same survey, in which Subramaniam et al. found small but statistically significant declines in perceived dangerousness and social distance across all disorders studied, although social distance remained substantial.[3] Stigma towards mental illness in general may be easing, but not measurably for schizophrenia.

The study deserves credit for addressing an important gap in the Asian literature, particularly in the Singapore context. Its strengths include the use of a nationally representative sample, oversampling of minority ethnic groups, and the use of consistent survey instruments across both study periods. However, the 2 cohorts differed substantially in educational attainment: the proportion of university graduates increased from 29% to 47%, while the proportion with 6 years of schooling or less declined from 15% to 4%. Although survey weights were post-stratified for age and ethnicity, they did not account for education, meaning that part of this shift likely reflects sampling differences rather than true population change. Regression adjustment and inverse probability weighting can mitigate, but not eliminate, confounding of this magnitude. If anything, a more highly educated sample would have been expected to demonstrate better recognition of schizophrenia, making the absence of improvement all the more striking. The study may also have been underpowered to detect a modest real improvement.

Recognition required respondents to identify the vignette as schizophrenia or psychosis. Those who instead described its defining features—such as hallucinations or delusions—were not credited, even though they had arguably recognised the core clinical syndrome. Inter-rater reliability for coding these open-ended responses was also not reported. Perhaps the most informative finding is under-emphasised. In the later survey, fewer respondents described the vignette as a vague emotional problem, while more identified it as another form of mental illness. This suggests that public understanding may have progressed from failing to recognise mental illness altogether to recognising psychiatric illness without yet distinguishing psychosis from other disorders. In addition, the personal stigma items were adapted from a depression stigma scale, and the factor structure adopted from an Australian study was applied without validation in the Singapore context.

The authors' explanations for ethnic differences also invoke religious and cultural beliefs that were not measured. Cao et al. do not report response rates, and a companion analysis of the same survey programme reported that these fell from 71% to 62%, with some residents declining because the survey concerned mental health, raising the possibility of selection bias.[1,3] Handling of missing data was not described, and the vignette was built on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria that predates current classification. Finally, the sample was limited to adults aged 65 years and below, excluding older Singaporeans in whom stigma may be the highest—an important gap in a rapidly ageing society.

Despite these limitations, the study is a stark reminder that public understanding of schizophrenia has barely

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advanced. It suggests that the relationship between knowledge and stigma is more complex than is often assumed. Recognising schizophrenia did not translate into less fear or greater social acceptance, implying that knowledge and prejudice may coexist. In Cao et al.'s data, correctly recognising schizophrenia was not associated with lower perceptions of dangerousness or less desire for social distance, only the belief that the illness reflects personal weakness was linked to poorer recognition.[2]

A more nuanced picture emerges from how respondents described the vignette. In the later survey, more respondents identified it as some form of mental disorder and fewer dismissed it as a vague emotional problem. This suggests that the public may now be better at sensing that there is a psychiatric illness, yet still struggles to specifically identify psychosis. Schizophrenia presents in complex ways that can be difficult to understand. Its negative symptoms, such as withdrawal and loss of motivation, are easily mistaken for laziness or stress. Naming the illness, however, does not by itself dispel fear. Where familiarity is absent, stereotypes readily fill the gap, and popular media often reinforce the image of the violent, unpredictable patient. Such portrayals are known to perpetuate stigma.[4] In 2025, a psychiatrist writing in *The Straits Times* warned that a Singapore television series risked reinforcing precisely this stereotype by portraying its villain as having schizophrenia.[5] Singapore is more educated and more digitally connected than ever, and awareness campaigns now reach millions through social media. Yet societal progress does not seem to have translated into better understanding one of the most stigmatised conditions. Online platforms appear to reward the sensational over the ordinary story of recovery, and broad well-being campaigns rarely mention psychosis. Moreover, digital channels are less likely to reach older and less digitally literate residents. More information has not meant less fear. Stigma, like schizophrenia itself, is socially patterned. The illness is shaped by social determinants, including childhood adversity, poverty, migration, and isolation. Those living with it often experience downward drift in employment and housing.[6] Anti-stigma work that ignores these conditions addresses attitudes while leaving intact the circumstances that sustain them.

Peer contact and support remain among the most promising approaches to reducing stigma, and the findings from Cao et al. are consistent with this view. In the later survey, respondents with a family member or close friend with similar experiences were more likely to recognise schizophrenia and expressed less desire for social distance.[2] Because these data are cross-sectional, the direction of this association is uncertain. People with less stigmatising views may also be more likely to form or disclose such relationships. A meta-analysis found that face-to-face contact outperformed education among adults, but education was more effective among adolescents, a point that is relevant to school-based programmes.[7] How such contact is organised and facilitated is equally important. A common pitfall is tokenism, in which a person with lived experience is invited to share a testimony within a campaign designed without them. This may achieve little and can feel extractive. Genuine co-creation involves peers in every step of the design, delivery, and evaluation of programmes, and ensures that peers are appropriately recognised and fairly remunerated. As the Lancet Commission on ending stigma and discrimination in mental health argues, co-created messages are more credible, culturally grounded, and ultimately more likely to change attitudes.[4]

Examples in Singapore already exist, including co-created interactive theatre and schizophrenia workshops supported by the Community Health Assessment Team (CHAT). Those of us who work alongside people living with schizophrenia see time and again that personal stories change minds in ways that clinical explanations alone cannot. Lived experience should not simply be showcased in campaigns—it should help shape them. People with lived experience deserve not only a voice, but also a seat at the table.

Public narratives that dwell on risk also obscure the hope that modern treatment can offer. An early evaluation of Singapore's Early Psychosis Intervention Programme (EPIP) published in 2005 found that the median duration of untreated psychosis fell from 12 months to 4 months after the programme was established.[8] In a Swedish nationwide cohort of nearly 30,000 patients, clozapine and long-acting injectable antipsychotics were associated with the lowest risk of rehospitalisation.[9] More recently, in a 5-week placebo-controlled trial conducted in the US, xanomeline–trospium became the first antipsychotic in decades to demonstrate efficacy without directly blocking dopamine receptors.[10] It is not yet registered for use in Singapore, and longer-term and Asian data are awaited. These advances reinforce an important point—schizophrenia is a treatable condition, and many people achieve meaningful recovery. Stating this plainly is itself an act of anti-stigma.

Yet recovery is not only a clinical or individual achievement, it is also a social one. Singapore's cultural traditions offer potential resources, rather than evidence, for this work. Confucian ideals of *ren* (humaneness and mutual obligation), Malay *gotong-royong* (mutual cooperation), and Indian *seva* (selfless service) each frame care for those who are ill as a shared responsibility. Their shadow is that concern for family face and fear of family stigma can drive concealment and delayed

help-seeking.[11] As Tan et al. writes, stigma towards a diagnosis of psychiatric illness is intertwined with a predominantly Chinese cultural concept of "face", which constitutes one's social identity and standing. A loss of face experienced by someone who receives a psychiatric diagnosis can thus extend beyond the individual and be associated with a perceived moral defect on the part of the sufferer's family.[12] The question, then, is not only whether a person with schizophrenia is ready to rejoin society, but also whether society is ready to receive them.

Several priorities follow. Future surveys should include adults over 65 years, weight samples for educational attainment, report effect sizes, and further validate psychosis-specific stigma measures. Public education should be schizophrenia-specific, address both negative and positive symptoms, and reach older and lower-income residents through non-digital channels. Campaigns should be co-created with people with lived experience, and anti-stigma initiatives should be evaluated not only by their reach, but also by their measurable impact on knowledge, attitudes, behaviour, and help-seeking.

Cao et al. have shown that the gains made in general mental health awareness have not yet extended to schizophrenia. Closing this gap will require replacing fear with familiarity and stigma with understanding. It will also require recognising that recovery is not the responsibility of the individual alone, but a shared commitment of the person, the family, and the community.

Keywords: *mental health literacy, mental illness, schizophrenia, Singapore, vignette approach*

Ethics statement

Not applicable, as no study participants were recruited.

Declaration

The authors declare that they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript. AS is employed by the Institute of Mental Health, whose Research Division conducted the Mind Matters surveys reported by Cao et al. and in references 1 and 3. AS was not involved in the design, conduct, or analysis of the surveys. AS heads EPIP, which is discussed in this editorial. CHAT sits within the wider department in which AS works, but AS has no direct role in running it.

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Tailoring neurofibromatosis type 1 care to Singapore: From consensus to implementation

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Rare diseases are easily overlooked in health systems, which are typically built around common diseases, and neurofibromatosis type 1 (NF1) is no exception. In this issue of the *Annals*, Fong et al. present one of the first Singapore-specific consensus guidelines on the diagnosis, surveillance, and management of NF1.[1] Their work deserves recognition. It cannot be stressed enough how important local guidelines are for NF1. It is not sufficient simply to adopt guidelines from other countries or continents, because referral pathways, imaging capacity, access to drugs, and possibly the ancestry-related spectrum of disease might differ, and recommendations that do not account for the local context are of little use to patients.

The authors started with a documented literature search on NF1 diagnosis, surveillance, and management using specific inclusion and exclusion criteria. They used the extracted data to draft a panel of recommendations (133 close-ended statements). A multidisciplinary panel of geneticists, dermatologists, neurologists, neurosurgeons, and oncologists rated these anonymously. Nineteen of 24 invited experts completed the first round. After a virtual meeting, 17 completed the second round. With consensus set at three-quarters agreement, 113 reached consensus after round 1. Twenty statements failed to achieve consensus, were adjusted in response to comments, and together with a new statement were submitted to a second round of the Delphi process. Nine of the 21 reached consensus after round 2. This led to the current "evidence-informed consensus-based" set of guidelines spanning genetic testing, surveillance in childhood, transition and adulthood, and management of complications. These recommendations are not evidence-based but are based on expert consensus because, for many rare diseases, such as NF1, there are very few randomised controlled trials available in the literature. The results of this endeavour are clearly presented by Fong et al. and will be particularly useful for all healthcare workers involved in the care of individuals with NF1 in Singapore.

The panel recommends surgery as an option for symptomatic plexiform neurofibromas when feasible, mirroring the international view that complete resection is seldom achievable and carries morbidity.[2] The choice between surgical and pharmacological therapy rests with a multidisciplinary board. Radiotherapy is discouraged because of the risks of secondary malignancy and vasculopathy. Mitogen-activated protein kinase kinase (MEK) inhibitors are endorsed for symptomatic, inoperable, or incompletely resected plexiform neurofibromas in children and adults. In children, an objective response, measured as a volume reduction of the plexiform neurofibroma of 20% or more, was seen in 70%.[3] In adults, the evidence shows an objective response, measured as a volume reduction of 20% or more of the plexiform neurofibroma, in about 1 in 5 patients versus 1 in 20 on placebo.[4] Pain and quality of life did not improve significantly. This is the only randomised placebo-controlled, double-blind phase 3 study of treatment with a MEK inhibitor in NF1 available at the moment. This represents a genuine but modest benefit, so patient selection, cost, and access will shape uptake. Other trials in adults were single-arm.[5,6] Selumetinib, a MEK inhibitor is covered in Singapore by the Rare Disease Fund for children with NF1 aged 2 years or older who have a symptomatic and inoperable plexiform neurofibroma. Applications for adults are not standard but are not excluded, and the fund might cover treatment of plexiform neurofibromas in adults with NF1.[7] Time will tell how many treatments in adults will be covered. The absence of consensus on tipifarnib and mechanistic target of rapamycin inhibitors honestly reflects equivocal trial results.

The stakes are high because life expectancy in NF1 is shortened by malignancy and vascular disease.[8,9,10] Malignant peripheral nerve sheath tumour (MPNST) is a leading cause of cancer-related death. However, the lifetime risk of 8–16%[8,9] is an average across a heterogeneous population in which some individuals harbour many plexiform neurofibromas and others none, and the risk carried by any single lesion remains unknown. MPNSTs typically arise in pre-existing plexiform neurofibromas, often through premalignant atypical neurofibromatous neoplasms of uncertain biological potential (ANNUBP), which carry a considerably higher risk of progression.[11] ANNUBP is diagnosed

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when at least 2 of 4 histopathological criteria are met: (1) cytological atypia, (2) loss of neurofibroma architecture, (3) hypercellularity, and (4) mitotic index > 1/50 high-power fields (HPF) and < 3/10 HPF. In the presence of a heterozygous inactivation of *CDKN2A* in the tumour, only 1 of 4 histopathological criteria is needed for diagnosis. The presence of a homozygous *CDKN2A* inactivation is sufficient for the diagnosis of ANNUBP, even in the absence of histopathological criteria.[12] The practical corollary is that imaging is valuable because it identifies which individuals and which lesions warrant closer attention, not because it can predict malignant change in a given tumour. The panel's handling of whole-body magnetic resonance imaging (MRI) at transition illustrates this reasoning. In line with the ERN GENTURIS guidelines,[2] a single whole-body scan between the ages of 16 and 20 years is suggested to map internal tumour burden. Where no internal plexiform neurofibromas are found, routine repeat whole-body imaging is not advised, whereas a high burden justifies continued surveillance. Evidence that surveillance improves outcomes is emerging. In a retrospective cohort of adolescents and adults followed with whole-body diffusion-weighted MRI and clinical review, timely nerve-sparing removal of atypical neurofibromas was associated with a lower incidence of MPNST than predicted.[13] However, reliance on historical controls limits that conclusion, and prospective validation is needed, including measurements of harm and cost. The data supports moving away from the surveillance concentrated in childhood that was customary a few decades ago, towards structured follow-up across the lifespan.

Aside from increased oncological risks, NF1 is associated with potential problems in a multitude of other areas such as growth and development, cognitive and behavioural functioning, the skeletal system, the cardiovascular system, the skin, and psychosocial well-being. The guidelines address the monitoring and management of pain, café-au-lait macules, hypertension, learning difficulties, attention-deficit/hyperactivity disorder, speech and language development, scoliosis, and osteoporosis. The guidelines recommend adding a psychologist to the multidisciplinary team, which could make an enormous difference to the quality of life of individuals with NF1.

The greatest practical challenge is retaining people in care. Many adults with NF1 drift away from specialist follow-up once paediatric services end. A recent study in Singapore of children and adults with cancer predisposition syndromes for whom whole-body MRI was recommended, showed an uptake of 57%, leaving room for improvement.[14] A formal transition programme and a national registry of individuals with NF1 and their complications would allow Singapore to measure whether recommendations are followed and whether outcomes improve. Incidence of certain complications could vary by region and/or ethnic group, as was recently reported for optic pathway glioma in children.[15,16] Region-specific incidence rates are important for building the next generation of guidelines.

Guidelines are living documents. These guidelines already address most of the unmet needs in Singapore's patients (optimised multidisciplinary NF1 care, management of neurological symptoms, management of cutaneous lesions, financial coverage for NF1, early NF1 screening, local awareness, and support groups), as was recently published.[17] The items that fell short of consensus, including surgery for bone dystrophic changes, the role of radiotherapy and targeted therapy in MPNST, and imaging for scoliosis, offer a ready research agenda. Guidelines need periodic updates, and, as Fong et al. mentioned in their publication, it might be relevant to include patient representatives in the process of updating the guidelines. Cascade testing and reproductive counselling, acknowledged by the authors as beyond the scope of this exercise, merit a consensus of their own. Fong et al. have delivered a pragmatic foundation. The task now is to implement, audit, and refine it.

Keywords: *Delphi consensus, neurofibromatosis type 1, peripheral nerve sheath tumour, surveillance*

Ethics statement

Not applicable, as no participants were recruited.

Declaration

The author declares that he has no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in this editorial. EL receives occasional consultancy fees from Alexion/AstraZeneca Rare Diseases and from Merck.

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Factors associated with willingness to quit smoking in a hospital-based smoking cessation programme

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ABSTRACT

Introduction: Hospital admissions provide an important opportunity for smoking cessation interventions. However, factors associated with willingness to quit smoking among hospitalised smokers remain underexplored, particularly in the multi-ethnic Asian population.

Methods: In this cross-sectional study of hospitalised smokers referred to an inpatient smoking cessation service between 2021 and 2025, enrolment data on willingness to quit, demographics, and clinical characteristics were analysed using multivariable logistic regression. A clinical feature score was developed to assess dose–response associations.

Results: Of 953 smokers (median age 57 years; 92% male), 49% reported willingness to quit smoking. In the multivariable analysis, ischaemic heart disease (odds ratio [OR] 2.20, 95% confidence interval [CI] 1.50–3.24, *P*<0.001), cerebrovascular accident (OR 2.30, 95% CI 1.30–4.12, *P*=0.005), chronic obstructive pulmonary disease assessment score ≥10 (OR 2.16, 95% CI 1.10–4.38, *P*=0.03), modified Medical Research Council dyspnoea score ≥2 (OR 1.87, 95% CI 1.06–3.31, *P*=0.03), post-secondary education (OR 13.47, 95% CI 5.51–38.75, *P*<0.001), and primary/secondary education (OR 3.49, 95% CI 1.45–9.85, *P*=0.01) relative to no formal education and respiratory admission or visit in the past year (OR 3.55, 95% CI 1.43–9.87, *P*=0.009) remained associated with willingness to quit smoking. A graded association was observed between accumulation of these clinical features and readiness to quit, with each additional feature associated with higher odds of willingness to quit (OR 2.79, 95% CI 2.18–3.57, *P*<0.001).

Conclusion: Greater clinical burden was associated with willingness to quit smoking among referred hospitalised smokers. Accumulated clinical risk factors may help identify patients with greater readiness to quit and guide targeted counselling although longitudinal studies are needed to assess clinical utility.

Keywords: nicotine dependence, public health, pulmonary medicine, respiratory diseases, smoking cessation, tobacco use

CLINICAL IMPACT

What is New

- In a multi-ethnic Asian cohort of 953 hospitalised smokers referred to an inpatient cessation service, approximately half reported willingness to quit.
- Cardiovascular comorbidities, respiratory symptoms, recent respiratory healthcare visits, and educational attainment were associated with willingness to quit.
- A graded association was observed between accumulated clinical features and greater willingness to quit, with each additional feature associated with more than twice the odds.

Clinical Implications

- Greater clinical burden may provide an opportunity to engage hospitalised smokers in cessation counselling.
- Accumulated clinical features may help identify patients with greater readiness to quit and inform personalised counselling, while cessation support should be offered universally.
- Tailoring cessation support and public health messaging to different educational backgrounds may help address potential inequalities.

INTRODUCTION

Cigarette smoking is a leading cause of preventable morbidity and mortality, and is a major contributor to premature death and cancer burden globally.[1,2] Although the prevalence of smoking has declined since the 1970s, approximately 1 billion people continue to smoke worldwide.[3] In Singapore, while the prevalence of daily smoking decreased from 12.0% in 2017 to 8.4% in 2024, smoking continues to impose substantial health and economic burden.[4,5] The 2021

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Global Burden of Disease Study revealed that the percentage of disability-adjusted life years caused by smoking was 1.80% for women and 8.80% for men in Singapore.[6] Smoking-related cost in Singapore has been estimated at approximately USD500 million, with USD14.9 million attributed to direct healthcare expenditure.[7]

Smoking cessation significantly reduces the adverse health consequences of tobacco use. A significant reduction in total mortality has been associated with quitting smoking among older Chinese adults in Singapore.[8] The World Health Organization identified smoking cessation support as a core tobacco control measure and strongly recommends offering intensive cessation support to smokers interested in quitting smoking in the forms of behavioural counselling and pharmacotherapy.[9]

Various factors have been identified as improving the success of smoking cessation, one of which is an individual's motivation and intention to quit smoking.[10-13] Higher motivation to quit has been shown to predict quit attempts and cessation success in both primary care and specialist settings.[14,15] Identifying factors associated with willingness to quit smoking may help healthcare providers recognise individuals who are more receptive to smoking cessation interventions.

Hospitalisation provides a critical opportunity for smoking cessation. Acute illness, increased perceived health risk, and a smoke-free hospital environment may enhance engagement with cessation services and influence readiness to quit. In Singapore, a 2024 national health survey has identified sociodemographic correlates of intention to quit smoking, and prior inpatients studies have focused primarily on cessation outcomes rather than readiness to quit.[10,11] However, factors associated with willingness to quit smoking among hospitalised smokers have not been well characterised in multi-ethnic Asian population.

This study aimed to assess factors associated with willingness to quit smoking among hospitalised smokers referred to an inpatient smoking cessation service, and to determine the proportion of symptomatic smokers and airflow obstruction.

METHODS

Study population

Current smokers (n=953) admitted to Singapore General Hospital and referred to the inpatient smoking cessation service between 2021 and 2025 were consecutively recruited. Current smokers were defined as persons who have smoked at least 100 cigarettes and now smoke either every day or some days. Smoking status was routinely assessed at each inpatient admission by the admission nurse. Patients identified as current smokers were offered referral to the inpatient smoking cessation service, and referrals were generated if the patient agreed. For patients who initially decline referral, the inpatient team could generate a referral following further clinical assessment and discussion. At recruitment, demographic characteristics, comorbidities, and clinical data were collected through a medical record review and supplemented by patient interview. Willingness to quit smoking, chronic obstructive pulmonary disease (COPD) Assessment Test (CAT) score; COPD Diagnostic Questionnaire (CDQ); and the presence and duration of respiratory symptoms (cough, sputum production, dyspnoea) and chronic bronchitis were assessed at recruitment. Willingness to quit smoking was assessed using a standardised clinical question and categorised as "yes", "undecided", or "no". For analysis, this was dichotomised into "willing" (yes) and "not willing" (undecided/no). High symptom burden was categorised as CAT≥10 and modified Medical Research Council (mMRC) dyspnoea score ≥2.

Portable spirometry (Spirolab, MIR, Rome, Italy) was performed when clinically appropriate and in the absence of contraindications, to identify smokers with airflow limitation that do not have chronic respiratory disease. Patients with known chronic respiratory diseases—including COPD, asthma, bronchiectasis, and interstitial lung disease—were excluded. Spirometry was therefore performed in a subset of patients and was not systematically conducted for all patients.

Ischaemic heart disease (IHD) was defined as history of acute coronary syndrome, coronary artery disease, myocardial infarction, coronary bypass surgery, percutaneous coronary intervention, or ischaemic aetiology of heart failure. Cerebrovascular accident (CVA) was defined as history of rapid onset of focal or global neurological deficit lasting more than 24 hours and attributable to vascular cause.[16] All other comorbidities were recorded as per electronic medical record.

Respiratory admission or visit in the past year was defined as inpatient, emergency department, or specialist outpatient visit for respiratory-related causes including upper and lower respiratory tract infection, bronchitis, and pneumonia within the preceding year. Upper respiratory tract infection (URTI) in the past year was defined as patient-reported acute self-limiting illness with nasal congestions, throat irritation, or cough symptoms without healthcare utilisation.[17] Chronic bronchitis was defined as presence of chronic cough and sputum production for most days in at least 3 months over 2 consecutive years.[18] Prior smoking cessation counselling was defined based on patients' self-report of having previously participated in a formal

smoking cessation counselling session prior to the index hospitalisation. All study data were entered into REDCap electronic data capture tools hosted at Singapore General Hospital.[19,20]

Spirometry

Spirometry was performed in accordance with American Thoracic Society/European Respiratory Society standards, with reference values derived from the Global Lung Function Initiative 2012.[21]

Statistical analysis

All analyses were performed using RStudio version 4.4. (R Foundation for Statistical Computing, Vienna, Austria) within the RStudio integrated development environment (Posit Software, Boston, MA, US). Continuous variables were assessed for normality using the Shapiro–Wilk test. All continuous data that were not normally distributed were presented as median (interquartile range, IQR). Between-group comparisons were performed using the Mann–Whitney U test for continuous variables, and the chi-square test for categorical variables. Variables that demonstrated statistical significance in univariate analyses (P<0.05) and were clinically relevant were entered into a multivariable logistic regression model to identify factors associated with willingness to quit smoking using "glm" function in R. Model performance was assessed using the likelihood ratio test, area under the receiver operating characteristic curve (AUC), Hosmer–Lemeshow goodness-of-fit test, and pseudo-R^2 measures. Multicollinearity was assessed using variance inflation factors, with values <2 indicating low collinearity. Clinical features demonstrating a statistically significant association with willingness to quit smoking in the multivariable model were selected for dose–response analysis. The relationship between the number of such features present and willingness to quit smoking was assessed using chi-square tests and multivariable logistic regression. Missing data for CAT score (n=263 missing) was handled using a complete-case approach, and patients with missing CAT scores were excluded from the multivariable analysis. For the sensitivity analysis, multiple imputation using chained equations (m=5) with predictive mean matching was performed to account for missing CAT values using the mice package. The imputation model included all variables from the multivariable model, including the outcome variable, and estimates were pooled using Rubin's rules. Statistical significance was defined as P<0.05.

RESULTS

Clinical characteristics

A total of 953 patients referred to the inpatient smoking cessation service were included in the analysis. The study population was predominantly male (92%) and of Chinese ethnicity (60%), with 49% having post-secondary education. The median age was 57 years (IQR 49–65), and the median smoking exposure was 23 pack-years (IQR 13–40). The most common comorbidities were hypertension (45%), hyperlipidaemia (45%), and IHD (31%).

Factors associated with willingness to quit smoking

Overall, 49% of the patients reported willingness to quit smoking at recruitment. Willingness to quit smoking was significantly associated with having post-secondary education (61% versus [vs] 38%, P<0.001). Clinical factors associated with willingness to quit included higher symptom burden (CAT score ≥10 and mMRC dyspnoea scale score ≥2), respiratory admission or visit in the past year (6.9% vs 2.0%, P<0.001), and prior smoking cessation counselling (48% vs 37%, P<0.001) compared with those who were undecided or not willing to quit smoking. A higher proportion of patients expressing willingness to quit smoking had IHD (40% vs 23%, P<0.001), CVA (13% vs 8.4%, P=0.038), chronic bronchitis (18% vs 10%, P<0.001), or ≥2 URTI in the preceding year (11% vs 6.5% , P=0.035) There were no significant differences between groups with respect to age, sex, ethnicity, and number of smoking pack-years (Table 1). Supplementary Table S1 outlines additional baseline characteristics.

The authors evaluated factors associated with willingness to quit smoking using multivariable logistic regression. Variables that were statistically significant in the univariate analysis and clinically relevant were included in the multivariable model: IHD, CVA, highest education level attained, CAT score ≥10, and mMRC dyspnoea scale score ≥2, respiratory admission or visit in the past year, ≥2 URTI in the past year, chronic bronchitis, prior smoking cessation counselling, age, sex, and smoking pack-years. In the multivariable analysis of 667 patients (excluding those with missing CAT score and education level), IHD (odds ratio [OR] 2.20, 95% confidence interval [CI] 1.50–3.24, P<0.001), CVA (OR 2.30, 95% CI 1.30–4.12, P=0.005), CAT score ≥10 (OR 2.16, 95% CI 1.10–4.38, P=0.03), mMRC dyspnoea scale score ≥2 (OR 1.87, 95% CI 1.06–3.31, P=0.03), patients with post-secondary education (OR 13.47, 95% CI 5.51–38.75, P<0.001), and primary/secondary education (OR 3.49, 95% CI 1.45–9.85, P=0.01) relative to no formal education and respiratory admission or visit in the past year (OR 3.55, 95% CI 1.43–9.87, P=0.009) remained associated with willingness to quit smoking (Fig. 1). The multivariable model demonstrated good overall fit (likelihood ratio $\chi^2(13)=160.82$, P<0.001), with good discrimination (AUC=0.77) and acceptable calibration (Hosmer–Lemeshow P=0.49). The model explained a moderate proportion of variance (Nagelkerke R^2=0.29). In

Table 1. Baseline characteristics of smokers referred to an inpatient smoking cessation service stratified by willingness to quit smoking at enrolment.

Characteristics	Overall n=953	Undecided/no n=489	Yes n=464	*P* value
[a]Age, median (Q1, Q3), years	57.00 (49.00, 65.00)	58.00 (49.00, 66.00)	57.00 (48.00, 64.50)	0.6
[b]Sex, no. (%)				0.4
Female	81 (8.5)	46 (9.4)	35 (7.5)	
Male	872 (91.5)	443 (90.6)	429 (92.5)	
[b]Ethnicity, no. (%)				0.2
Chinese	576 (60)	310 (63)	266 (57)	
Indian	135 (14)	62 (13)	73 (16)	
Malay	196 (21)	98 (20)	98 (21)	
Others	46 (4.8)	19 (3.9)	27 (5.8)	
[b]Marital status, no. (%)				0.2
Married	637 (67)	316 (65)	321 (69)	
Single/separated/widowed/divorced	316 (33)	173 (35)	143 (31)	
[b]Highest education attained, no. (%)				<0.001
Missing	85 (8.9)	29 (5.9)	56 (12.0)	
No formal education	55 (5.8)	48 (9.8)	7 (1.5)	
Primary/secondary	343 (36)	225 (46.1)	118 (25.5)	
Post-secondary	470 (49.3)	187 (38.2)	283 (61.0)	
[a]BMI, median (Q1, Q3), kg/m^2	24.60 (21.80, 28.31)	24.40 (21.80, 28.40)	24.80 (21.80, 28.20)	0.5
[a]Smoking pack-years, median (Q1, Q3)	23.00 (13.00, 40.00)	23.00 (13.00, 41.00)	23.00 (13.00, 40.00)	0.9
[b]CAT score ≥10, n=690, no. (%)	69 (7.2)	19 (4.9)	50 (17)	**<0.001**
[b]mMRC dyspnoea scale score ≥2, no. (%)	135 (14)	42 (8.6)	93 (20)	**<0.001**
[b]Respiratory admission/visit (past year), no. (%)	42 (4.4)	10 (2.0)	32 (6.9)	**<0.001**
[b]Prior smoking cessation counselling, no. (%)	406 (43)	181 (37)	225 (48)	**<0.001**
[b]Hyperlipidaemia, no. (%)	430 (45)	226 (46)	204 (44)	0.5
[b]Hypertension, no. (%)	426 (45)	219 (45)	207 (45)	1.0
[b]IHD, no. (%)	295 (31)	111 (23)	184 (40)	**<0.001**
[b]CVA, no. (%)	100 (10)	41 (8.4)	59 (13)	**0.038**
[b]Chronic bronchitis, no. (%)	133 (14)	50 (10)	83 (18)	**<0.001**
[b]≥2 URTI (past year)	81 (8.5)	32 (6.5)	49 (11)	**0.035**

BMI: body mass index; CAT: COPD Assessment Test; CVA: cerebrovascular accident; IHD: ischaemic heart disease; mMRC: modified Medical Research Council; URTI: upper respiratory tract infection

[a] Mann-Whitney U test; [b] Pearson's chi-squared test

P<0.05 in bold indicate statistical significance.

sensitivity analyses using multiple imputation for missing CAT score, the associations observed in the primary complete-case analysis remained largely consistent (Supplementary Table S2).

Dose–response relationship

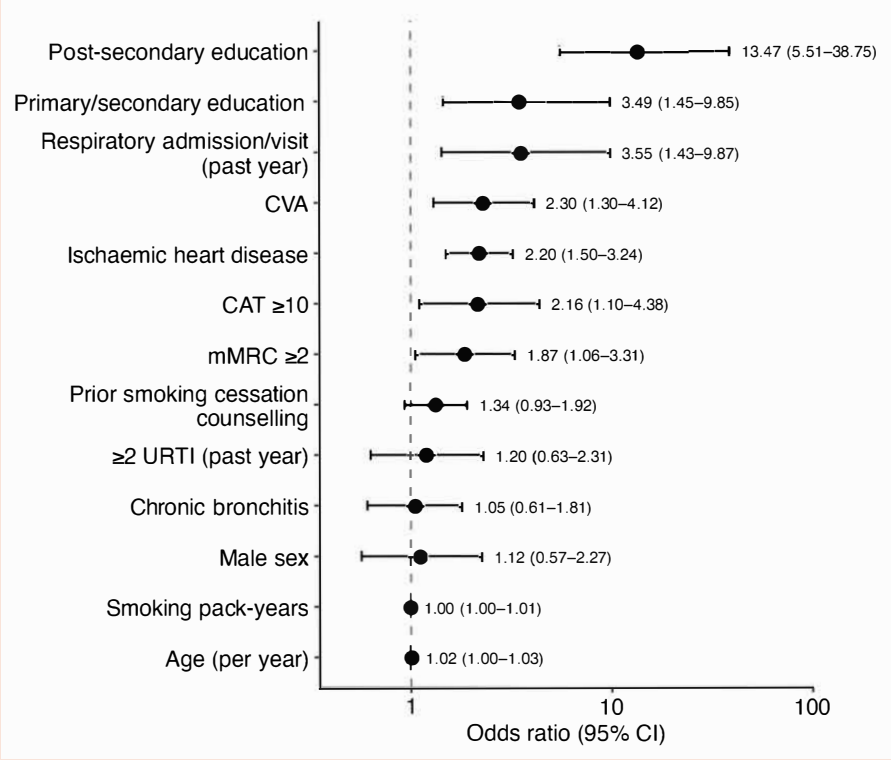
The authors examined the dose–response relationship of the 5 clinical features that remained significant in the multivariable model (IHD, CVA, CAT ≥10, mMRC≥2, and respiratory admission or visit in the past year). The presence of each feature was coded as 1, and a composite feature score (range 0–5) was calculated by summing the number of features present for each patient. Individuals with missing CAT scores were excluded. The proportion of patients expressing willingness to quit smoking increased progressively with the number of features present: 27.6% among those with no features, 58.4% with 1 feature, 66.7% with 2 features, and 87.5% with 3 features. None of the patients in this study population had more than 3 features. This demonstrates a graded, dose–response relationship between the number of clinical features and willingness to quit (Fig. 2).

In multivariable logistic regression adjusted for age and sex, the composite feature score was significantly associated with willingness to quit smoking, demonstrating a graded dose–response association. Each additional clinical feature was associated with more than a 2-fold increase in the odds of expressing willingness to quit smoking (OR 2.79, 95% CI 2.18–3.57, $P<0.001$).

Spirometry characteristics in a subgroup of smokers

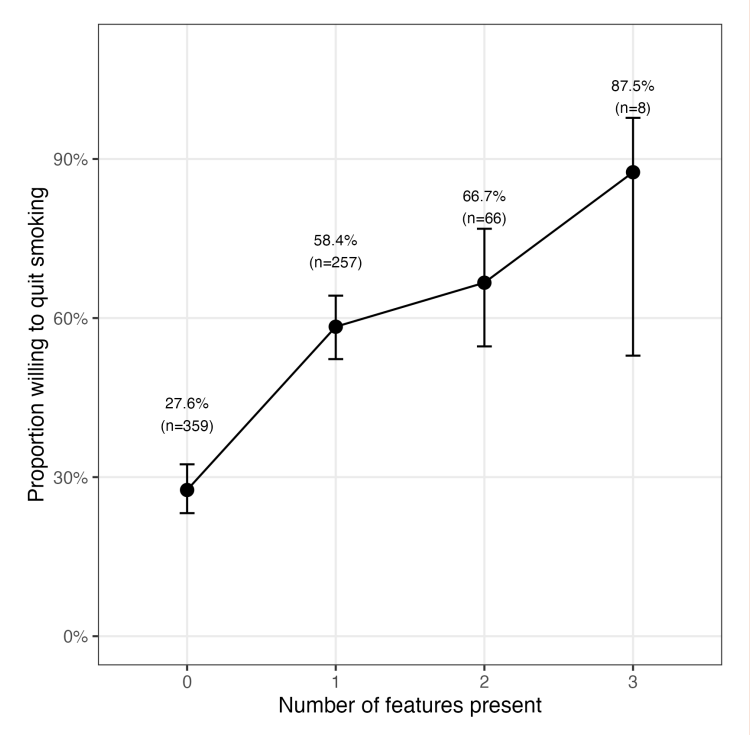
The median CDQ score for the overall study population was 17 (IQR 12–22), with 340 patients (36%) having a CDQ score ≥20, which indicates a high likelihood of COPD.[22,23] However, only 68 patients underwent inpatient spirometry, with a median FEV_1/FVC ratio of 77.6% (IQR 72.3–82.6). Among them, 11 patients (16.2%) demonstrated airflow obstruction, defined as $FEV_1/FVC<0.70$. The CDQ score was significantly higher in patients with obstructive spirometry compared with those without obstruction (median 25 vs 21, $P=0.014$). In contrast, there was no significant difference in CAT scores between the 2 groups (median 7 [IQR 5–7] vs 4.5 [IQR 2–12], $P=0.50$). Neither

Fig. 1. Multivariate analysis of factors associated with willingness to quit smoking at enrolment.



CAT: chronic obstructive pulmonary disease assessment test; CI: confidence interval; CVA: cerebrovascular accident; mMRC: modified Medical Research Council dyspnoea scale; URTI: upper respiratory tract infection
Forest plot illustrates the adjusted odds ratio of willingness to quit smoking. Dot indicates odds ratio and error bar indicates 95% confidence interval. Odds ratio for post-secondary education and primary/secondary education are shown relative to the reference category of no formal education. For binary variables, absence of the characteristic was used as the reference category unless otherwise stated.

Fig. 2. Dot plot illustrates the dose–response relationship between number of features present and willingness to quit smoking.



Points represent observed proportions, and error bars indicate 95% confidence intervals.

CDQ score nor the presence of airflow obstruction was significantly associated with willingness to quit smoking. As spirometry was performed in a minority of patients, these findings should be interpreted as exploratory.

DISCUSSION

In this study, the authors identified several clinical factors associated with willingness to quit smoking among smokers who were referred to an inpatient smoking cessation service during a hospitalisation episode. High symptom burden, recurrent URTIs, respiratory admission or visit in the past year, comorbid IHD, and CVAs were associated with readiness to quit. Importantly, the authors observed a graded association between the accumulation of these clinical factors and willingness to quit, with each additional factor associated with more than a 2-fold increase in the odds of expressing a willingness to quit.

The findings suggest that greater clinical burden may coincide with increased receptiveness to smoking cessation during hospitalisation, consistent with prior studies.[24-26] Cardiovascular comorbidities have been associated with higher smoking cessation success rate compared to those without, particularly among older adults.[27] However, substantial variations in cessation rates among individuals with cardiovascular comorbidities have been reported across countries, likely reflecting differences in socioeconomic factors, tobacco control policies, and the smoking cessation programmes.[28] The association between IHD/CVA and willingness to quit may reflect greater perceived health risk and disease burden. However, recent hospitalisation for an acute cardiovascular or cerebrovascular event may have also served as a teachable moment that increased patients' motivation to quit smoking.

Presence of respiratory symptoms had previously been associated with greater intention to quit smoking, whereas associations with objective measures of lung function severity have been inconsistent.[29] Results of this study were similar, where higher symptom burden was associated with willingness to quit smoking, while the presence of airflow obstruction was not. CDQ scores were higher among patients with obstructive spirometry, but objective airflow limitation did not appear to influence readiness to quit. This may reflect the fact that spirometry abnormalities are often asymptomatic or less perceptible to patients compared to overt cardiovascular events or symptomatic respiratory illness. However, as spirometry was performed in a minority of patients in this study, these findings should be interpreted cautiously.

The association between lower educational attainment and reduced willingness to quit smoking is consistent with previous Singapore and international data.[11,30,31] These findings have broader implications

for public health strategy and health literacy, and may highlight an issue of inequality in health campaigns. Messaging about the harms of smoking may be disproportionately directed towards individuals with higher health literacy, inadvertently neglecting those with lower educational attainment. Tailoring public awareness campaigns and cessation support strategies to individuals with varying educational backgrounds may help address these inequities.

While prior studies have demonstrated ethnic differences in smoking cessation outcomes in Western populations, the authors did not observe a significant association between ethnicity and willingness to quit smoking in the study population.[32] This discrepancy may reflect differences in study populations, the distinction between readiness to quit and actual cessation outcomes, and potential limitations in statistical power. Further studies are needed to explore these relationships in diverse populations.

Singapore's Health Promotion Board has a comprehensive smoking cessation strategy spanning primary care and hospital settings, incorporating behavioural counselling and pharmacotherapy, both of which are key to successful cessation.[33,34] Nevertheless, smoking cessation programme quit rates in Singapore remain comparable to global outcomes, at approximate 25%.[35,36]

Smoking cessation is a process of dynamic behavioural change, and willingness to quit smoking is only 1 component of motivational readiness. While willingness to quit assessed at a single time point is not equivalent to sustained cessation behaviour, it may represent an important intermediate transitional state associated with subsequent quit attempts and treatment engagement.[14,15] Although smoking cessation support should be offered universally, the findings suggest that cumulative clinical burden may represent a transient period of enhanced motivation, potentially providing an opportunity for more targeted smoking cessation engagement.

Key strengths of this study include the prospective recruitment of hospitalised smokers referred to the inpatient smoking cessation service, systematic clinical assessment, and the use of validated questionnaires to evaluate symptom burden in a large, multi-ethnic inpatient group. The programme-based study population reflects real-world referral patterns within an inpatient care setting, enhancing the practical relevance of the findings.

Several limitations should be acknowledged. First, as the study population comprised hospitalised smokers referred to the inpatient smoking cessation service, selection bias may have been present. Although smoking status was systematically assessed on admission, referral depended on patient agreement and clinician judgement, potentially favouring individuals who were more motivated to quit or clinically prioritised. Therefore, the findings may not be generalisable to all hospitalised smokers.

Second, subsequent smoking cessation outcomes could not be ascertained. Although willingness to quit is an important component of behaviour change, it does not necessarily translate into sustained smoking cessation. As such, the clinical implications of the findings should be interpreted with caution. Future longitudinal studies are needed to determine whether the identified clinical factors and composite risk scores are associated with quit attempts, treatment engagement, and long-term abstinence. Third, willingness to quit was self-reported and assessed at a single time point, which may represent a transient state that does not necessarily translate into quit attempts or sustained abstinence. Additionally, a validated scale was not used, as a pragmatic assessment approach was adopted within a real-world clinical programme.

Fourth, the composite clinical feature score was constructed post hoc based on variables identified in the multivariable model and should therefore be interpreted as exploratory. The observed dose–response relationship may be subject to overfitting, and no formal validation was performed. As such, this finding should be considered hypothesis-generating and requires confirmation in independent cohorts. Fifth, spirometry was performed in a minority of patients, which limits any conclusions regarding airflow obstruction, and fixed ratio rather than lower limit of normal was used which may yield different prevalence.

Finally, data on nicotine dependence (e.g. Fagerstrom score) and prior quit attempts, socioeconomic status and psychological state were not assessed—these could not be included in the analysis, which may result in residual confounding. Despite these limitations, this study provides valuable insight into the factors associated with willingness to quit smoking and highlights the cumulative effect of multiple clinical features on willingness to quit in a group of smokers enrolled in the inpatient smoking cessation service.

CONCLUSION

Greater clinical burden was associated with willingness to quit smoking among referred hospitalised smokers. Accumulated clinical risk factors may help identify patients with greater readiness to quit and guide targeted counselling. However, longitudinal studies are needed to determine whether willingness to quit translates into sustained smoking cessation and to evaluate the clinical utility of these findings in guiding smoking cessation interventions.

Supplementary materials

Table S1. Additional baseline characteristics of smokers referred to an inpatient smoking cessation service stratified by willingness to quit smoking at enrolment.

Table S2. Factors associated with willingness to quit smoking in multivariable logistic regression.

Annex S1. STROBE checklist for cross-sectional studies.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (CIRB 2020/2584). Written informed consent was obtained from all participants at recruitment.

Declaration

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

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Exploring changes in recognition and stigmatisation towards individuals with schizophrenia in Singapore

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ABSTRACT

Introduction: Schizophrenia is a debilitating illness that causes long-term impairment in individuals and imposes an economic burden on society. Early recognition is essential for successful treatment outcomes. Mental health literacy—including recognition of and stigma towards mental illnesses—is crucial for guiding policy and informing targeted interventions. This study examined changes in schizophrenia recognition and stigma in Singapore over an 8-year period (2015–2023), as well as current trends in their sociodemographic correlates.

Methods: The study used data from 2 nationwide cross-sectional studies on mental health literacy using a vignette approach. Singapore residents aged 18–65 years were recruited via disproportionate stratified sampling. Respondents were presented with a vignette of a person with schizophrenia, and recognition was assessed using an open-ended question. Stigmatising attitudes were assessed using the Personal Stigma Scale and the Social Distance Scale.

Results: Correct recognition of schizophrenia increased from 11.5% to 15.1%, though the difference was not statistically significant. A lower "weak-not-sick" stigma score in the 2023 survey persisted after adjusting for sociodemographic differences between survey cohorts. Younger age and social contact with individuals with schizophrenia were associated with better recognition and less stigma. Individuals of Malay and Indian ethnicities attributed schizophrenia to a personal weakness but showed less social distancing.

Conclusion: The lack of significant improvement in recognition may reflect the continued need for schizophrenia-specific public education. The lower personal stigma score observed in the 2023 survey may also reflect broader changes in mental health awareness. Future initiatives should focus on culturally tailored anti-stigma interventions for schizophrenia that are accessible to older individuals and leverage social contact.

Keywords: ethnicity, mental health literacy, population-based survey, social stigma, socioeconomic

CLINICAL IMPACT

What is New

- This nationwide study examined changes in schizophrenia recognition and stigma in Singapore over 8 years.
- Personal stigma decreased, but public recognition of schizophrenia remained limited.

Clinical Implications

- Poor recognition of schizophrenia may delay help-seeking and access to early intervention.
- Schizophrenia-specific public education and culturally tailored, contact-based anti-stigma initiatives may improve mental health literacy, facilitate earlier detection, and encourage timely treatment.

INTRODUCTION

Schizophrenia is a common yet debilitating illness that affects 1% of the global population and is associated with a reduction in life expectancy of about 15 years compared with the general population.[1] With a typical onset in early adulthood, schizophrenia causes long-term social and occupational impairment and a substantial economic burden, with an annual cost ranging from USD94 million in Puerto Rico to USD102 billion in the US.[2] Schizophrenia is usually characterised by positive symptoms (hallucinations, delusions, disorganised speech and behaviour) and negative symptoms (diminished expression or avolition).[1] The duration of untreated psychosis is associated with poorer treatment response and other adverse long-term outcomes.[3] The relapse rate within the first year of schizophrenia onset is estimated to be up to 37%. Patients' impaired insight into their illness

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is associated with medication non-adherence, and increased relapse risk.[4,5] Early recognition is therefore critical for timely help-seeking and improved treatment outcomes.

Mental health literacy refers to knowledge and beliefs about mental disorders that aid their recognition, management, or prevention.[6] More recently, mental health literacy has been defined as understanding mental disorders, decreasing stigma, and promoting help-seeking efficacy.[7] Social stigma occurs when mental illness cues lead to stereotypes, prejudices, and discrimination, affecting not only individuals with mental illness but also their families, treatment institutions, and mental health professionals.

Mental health literacy has been studied widely in Western countries, but fewer studies have been conducted in Asian countries.[8] In Asia, mental illness is generally perceived as less socially acceptable and associated with personal weakness. A systematic review of stigma towards mental illnesses in Asian countries revealed that individuals with mental illness were considered dangerous and aggressive, especially those with schizophrenia and bipolar disorder.[9] Studies on mental health literacy are even scarcer in Singapore, a multi-ethnic country in Southeast Asia. The first Singapore population-based study on mental health literacy was conducted in 2015, and reported schizophrenia as the least recognised and the most stigmatised condition.[10, 11]

Public attitudes towards mental illness may evolve over time in response to awareness campaigns and policy initiatives. Reassessing schizophrenia recognition and stigma over time provides an opportunity to evaluate whether such efforts have translated into measurable improvements in mental health literacy.

The current study aimed to (1) examine changes in schizophrenia recognition, personal stigma, and social stigma in Singapore over an 8-year period, and (2) explore sociodemographic factors associated with recognition and stigmatising attitudes.

METHODS

Study design and sample

This study used data from 2 nationwide cross-sectional studies on mental health literacy, employing a vignette approach: one from March 2014 to April 2015 and the other from September 2022 to February 2024. The 2022–2024 study served as a follow-up to examine changes in mental health literacy among Singapore residents over time. Both studies employed the same survey design, sampling strategy, and eligibility criteria to enable meaningful comparison. Ethical approval was obtained from the Institutional Research Review Committee of the Institute of Mental Health and the National Healthcare Group Domain Specific Review Board (2021/00695). The study population comprised Singapore citizens and permanent residents aged 18–65 years who were literate in English, Chinese, Malay, or Tamil and residing in Singapore during the study period. Informed consent was obtained from study respondents and legally acceptable representatives for respondents below 21 years, as the age of majority in Singapore is 21.

Participants were randomly selected from a regularly updated national population registry of Singapore citizens and permanent residents using a disproportionate stratified sampling design with 12 strata defined by ethnicity (Chinese, Malay, Indian, and Others) and age group (18–34, 35–49, and 50–65 years). Malay and Indian residents and those aged 50–65 years were over-sampled to ensure an adequate sample size for subgroup analyses. Data were collected through interviewer-administered face-to-face structured interviews that were conducted in the respondents' preferred language. Interviewers from the contracted survey company underwent centralised training on recruitment procedures, informed consent, and standardised questionnaire administration. The target sample size was determined based on the study objectives, accounting for subgroup analyses, the complex survey design, and anticipated non-response.

Questionnaires (sociodemographic information, vignette-related questions, Personal Stigma Scale [PSS], and Social Distance Scale [SDS])

Sociodemographic information, including age, sex, ethnicity, marital status, education, employment, and income, was collected. Subsequently, respondents were presented with a vignette describing a person with schizophrenia, developed by research psychiatrists and reviewed by a panel of senior clinical psychiatrists to ensure it met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria[12] for schizophrenia. The vignette character's name was matched to the respondent's sex and ethnicity to facilitate identification. The terms "schizophrenia" and "psychosis" were not used within vignette descriptions or questionnaires to avoid variations in interpretation of clinical terminology. The vignettes and questionnaires underwent standardised forward- and back-translation and cognitive testing across all language versions to ensure conceptual equivalence and cultural appropriateness.

Respondents were asked what they believed the character in the vignette was suffering from. Responses were recorded in an open-ended format and categorised by the study team. Responses mentioning schizophrenia or psychosis were classified as correct recognition. Delusions, hallucinations, and other schizophrenia-specific symptoms described in DSM-IV were categorised as schizophrenia-specific

symptoms. General terms, such as "mental health issues", "problems", "mental", and "crazy", were classified as psychological/mental/emotional problems. Responses reflecting themes of loneliness, stress, or "not a problem" were categorised accordingly. All other responses were classified as "others".

Stigmatising attitudes towards schizophrenia were assessed using PSS and SDS. PSS is a 9-item subscale of the Depression Stigma Scale, validated for assessing stigma towards mental disorders. For this study, the 8-item PSS subscale was administered ("I would not vote for a politician if I knew they had a mental illness" was excluded) in order to maintain methodological consistency with previous Singapore studies.[11] Responses were recorded on a 5-point Likert scale (1 = strongly agree to 5 = strongly disagree). Responses were reverse-coded, and the mean score was calculated by summing up the item scores, with higher scores indicating higher personal stigma.[13,14] SDS includes 5 items measuring willingness to interact with the person described in the vignette. Responses were recorded on a 4-point Likert scale (1 = definitely willing to 4 = definitely unwilling), and mean scores were calculated, with higher scores indicating greater social distancing.[15] To describe item endorsement, for each item of the PSS, "strongly agree" and "agree" responses were combined, as were "disagree" and "strongly disagree" responses for analysis.

Statistical analyses

All estimates were weighted to adjust for oversampling and post-stratified for age and ethnicity to reflect the Singapore resident population. Descriptive statistics were used to describe the sociodemographic characteristics of the sample, the recognition of the schizophrenia vignette, and the stigma scale scores. Frequencies and percentages were calculated for categorical variables, whereas weighted mean and standard error of the mean were calculated for continuous variables. Differences in sociodemographic variables between surveys were assessed by cross-tabulation using the chi-square test. Multiple logistic regression analysis was performed to determine sociodemographic correlates of correct recognition of schizophrenia. All analyses were conducted using Stata software version 18.0 (StataCorp, College Station, TX, US), with statistical significance set at $P<0.05$ (2-sided).

For stigma analysis, the stigma items were grouped based on the previously established factor structure reported by Yap et al.[16] Prior exploratory structural equation modelling has revealed 2 distinct dimensions within PSS ("weak-not-sick" and "dangerous-unpredictable") and 1 "social distance" dimension within SDS. That validation study evaluated a 3-factor model using polychoric correlation matrices and demonstrated improved model fit compared with an equivalent confirmatory factor analysis solution. These validated stigma dimensions were applied in the present analysis. Separate multivariable linear regressions were conducted to examine sociodemographic correlates of each stigma dimension score.

To account for sociodemographic differences between survey cohorts, additional pooled survey-weighted regression analyses were conducted, combining data from both survey years. Survey year was included as the primary predictor of interest. Sociodemographic characteristics were entered as covariates to assess whether differences in recognition and stigma persisted after adjustment for changes in sample composition. Sensitivity analyses using doubly robust inverse probability-weighted regression models were additionally performed to evaluate the robustness of findings after balancing baseline sociodemographic characteristics between survey cohorts.

RESULTS

Sociodemographic characteristics of the sample

Table 1 presents the sociodemographic characteristics of the respondents receiving the schizophrenia vignette in the Mind Matters 2015 (MM15) study and Mind Matters 2023 (MM23) study. Sample characteristics differed significantly in education and personal income. In both cohorts, most respondents were male, Chinese, married, employed, with a monthly income of less than SGD2000, without personal experience similar to the vignette, and without family or close friends with an experience similar to the vignette. In MM15, the largest proportion of respondents (35.1%) were from the 18–34 age group, whereas in MM23, the largest proportion (36.9%) were from the 50–65 age group. University graduates formed the largest group (46.9%) in MM23, while A-level, polytechnic, and other diploma holders formed the largest group (29.7%) in MM15.

Recognition of schizophrenia vignette and sociodemographic correlates of recognition

Table 2a presents the correct recognition of schizophrenia in both cohorts. Only 11.5% of the respondents correctly recognised the vignette in MM15 and 15.1% correctly recognised it in MM23. However, the difference in correct recognition was not statistically significant. Table 2b presents the categorisation of recognition responses for both surveys. There was a significant difference in how respondents categorised the problem described in the vignette. In MM23, a higher proportion of respondents categorised the vignette as another mental disorder (32.4%) than in MM15 (20.9%). Additionally, fewer

Table 1. Sociodemographic characteristics of the schizophrenia cohort sample of the Mind Matters 2015 study and Mind Matters 2023 study.

		Mind Matters 2015		Mind Matters 2023			
		No.	**Weighted %**	**No.**	**Weighted %**	**Chi-square test**	***P* value**
Age group	18–34 years	231	35.1	201	32.0	0.46	0.634
	35–49 years	167	31.3	188	31.1		
	50–65 years	197	33.6	213	36.9		
Sex	Female	276	46.4	308	48.5	0.27	0.601
	Male	319	53.6	294	51.5		
Ethnicity	Chinese	203	74.6	166	74.2	0.02	0.992
	Malay	191	12.9	191	13.0		
	Indian	192	9.2	193	9.3		
	Others	9	3.2	52	3.4		
Marital status	Never married	178	29.7	181	29.9	0.04	0.962
	Married	384	64.2	375	63.5		
	Divorced, widowed, separated	33	6.1	46	6.6		
Education	6 years of education and below	95	15.0	28	4.0	9.42	**<0.001**
	Secondary education	163	25.9	135	20.3		
	A level, polytechnic, and other diploma	190	29.7	198	28.8		
	University	147	29.3	224	46.9		
Employment	Employed	448	80.1	494	85.2	1.53	0.217
	Unemployed	21	4.0	22	3.6		
	Economically inactive	126	15.9	86	11.2		
Personal income	<SGD2000	268	39.6	202	29.3	6.73	**<0.001**
	SGD2000–3999	175	33.0	165	24.5		
	SGD4000–5999	66	15.9	103	22.4		
	SGD6000–9999	41	8.5	78	14.7		
	Above SGD10,000	18	3.1	45	9.1		
Personal experience similar to the vignette	No	566	93.8	572	95.6	0.79	0.374
	Yes	29	6.2	28	4.4		
Family or close friends with experience similar to the vignette	No	489	85.8	499	81.2	2.49	0.115
	Yes	106	14.2	102	18.8		

SGD: Singapore dollars

respondents described the vignette as a general psychological, mental, or emotional problem in MM23 (20.6%) than in MM15 (29.4%).

Pooled survey-weighted regression analysis was conducted, with survey year as the key predictor and sociodemographic variables as covariates (Supplementary Table S1). After adjustment, survey year was not significantly associated with correct recognition of schizophrenia (odds ratio [OR]=0.97, 95% confidence interval [CI] 0.54–1.74, *P*=0.911).

Table 3 describes the sociodemographic correlates of correct recognition. Sex and marital status were not significantly associated with correct recognition in either survey. In MM15, respondents with incomes between SGD6000 and SGD9999 had significantly higher odds of correct recognition. In MM23, unemployment and having family or friends with an experience similar to the vignette yielded higher odds of correct recognition. Conversely, in both surveys, respondents with personal experiences similar to the vignette had significantly lower odds of correct recognition. In MM23, respondents aged 35–49 years, with 6 years or less of education, and with income between SGD2000 and SGD5999 also had lower odds of recognising the vignette.

Table 2a. Correct and incorrect recognition of the schizophrenia vignette for the Mind Matters 2015 study and Mind Matters 2023 study.

	Mind Matters 2015 Schizophrenia		Mind Matters 2023 Schizophrenia			
	No.	**Weighted percentage [95% CI]**	**No.**	**Weighted percentage [95% CI]**	**Chi-square test**	***P* value**
Correct recognition	60	11.45 [8.36–15.50]	82	15.08 [11.36–19.75]	1.71	0.192
Incorrect recognition	535	88.55 [84.50–91.64]	520	84.92 [80.25–88.64]		

CI: confidence interval

Table 2b. Distributions of categories describing the problem in the schizophrenia vignette for the Mind Matters 2015 study and Mind Matters 2023 study.

	Mind Matters 2015 Schizophrenia		Mind Matters 2023 Schizophrenia			
	No.	**Weighted percentage [95% CI]**	**No.**	**Weighted percentage [95% CI]**	**Chi-square**	***P* value**
Schizophrenia	60	11.5 [8.4–15.5]	82	15.1 [11.4–19.7]	2.734	0.0109
Schizophrenia-specific symptoms	92	16.2 [12.6–20.6]	66	13.2 [9.7–17.7]		
Recognised as other mental disorder	129	20.9 [16.9–25.7]	222	32.4 [27.3–37.9]		
Psychological/mental/emotional problems	184	29.4 [24.8–34.5]	114	20.6 [16.2–25.9]		
Psychological stress	41	6.3 [4.1–9.6]	29	5.5 [3.3–9.1]		
Loneliness	53	8.8 [6.2–12.5]	57	7.3 [4.9–10.7]		
Others	32	6.7 [4.4–10.2]	28	4.5 [2.7–7.5]		
Not a problem	4	0.2 [0.1–0.5]	4	1.4 [0.5–4.2]		

CI: confidence interval

Table 3. Sociodemographic correlates of correct recognition of schizophrenia vignette.

		Mind Matters 2015		Mind Matters 2023	
		OR [95% CI]	*P* value	OR [95% CI]	*P* value
Age group	18–34 years	Ref		Ref	
	35–49 years	1.04 [0.39–2.79]	0.939	0.37 [0.16–0.85]	**0.020**
	50–65 years	0.96 [0.34–2.70]	0.933	0.31 [0.09–1.05]	0.059
Sex	Female	1.43 [0.66–3.08]	0.364	1.74 [0.82–3.72]	0.151
	Male	Ref		Ref	
Ethnicity	Chinese	Ref		Ref	
	Malay	0.54 [0.24–1.22]	0.138	0.87 [0.38–1.98]	0.743
	Indian	0.78 [0.38–1.58]	0.490	0.85 [0.43–1.69]	0.647
	Others	1.09 [0.11–11.03]	0.939	0.40 [0.10–1.53]	0.179
Marital status	Never married	0.95 [0.39–2.28]	0.902	1.31 [0.57–2.98]	0.524
	Married	Ref		Ref	
	Separated/divorced/widowed	1.03 [0.15–6.94]	0.977	3.95 [0.72–21.52]	0.112
Education	6 years of education and below	0.36 [0.04–3.49]	0.375	0.04 [0.00–0.73]	**0.030**
	Secondary education	0.72 [0.24–2.14]	0.553	0.49 [0.10–2.39]	0.380
	A level, polytechnic, and other diploma	1.14 [0.41–3.15]	0.796	0.89 [0.28–2.84]	0.848
	University	Ref		Ref	
Employment status	Employed	Ref		Ref	
	Unemployed	2.88 [0.55–15.18]	0.211	7.86 [1.54–40.15]	**0.013**
	Economically inactive	0.90 [0.29–2.83]	0.861	1.59 [0.38–6.63]	0.522
Income	<SGD2000	4.10 [0.60–27.82]	0.149	0.27 [0.05–1.53]	0.139
	SGD2000–3999	2.60 [0.46–14.68]	0.278	0.10 [0.02–0.45]	**0.002**
	SGD4000–5999	3.55 [0.54–23.51]	0.189	0.14 [0.03–0.56]	**0.006**
	SGD6000–9999	11.16 [1.91–65.22]	0.008	0.34 [0.09–1.24]	0.102
	Above SGD10,000	Ref		Ref	
Personal experience similar to the vignette	No	Ref		Ref	
	Yes	0.03 [0.00–0.36]	0.005	0.03 [0.00–0.42]	**0.009**
Family or close friends with experience similar to the vignette	No	Ref		Ref	
	Yes	2.04 [0.76–5.46]	0.157	3.54 [1.31–9.57]	**0.013**

CI: confidence interval; OR: odds ratio; SGD: Singapore dollars
Ref: reference categories
Values in bold represent statistically significant results ($P<0.05$)

Stigma towards schizophrenia and sociodemographic correlates of stigma dimensions

Table 4 reports descriptive statistics of stigma scores in terms of "weak-not-sick", "dangerous-unpredictable", and "social distance." There was a statistically significant reduction in "weak-not-sick" and "dangerous-unpredictable" scores between the 2 periods. Supplementary Tables S2–S4 show pooled survey-weighted regression analyses on stigma dimensions. MM23 remained significantly associated with lower "weak-not-sick" stigma scores (β=–0.65, 95% CI –0.99 to –0.31, *P*<0.001). Differences in "dangerous-unpredictable" (β=–0.35, 95% CI –0.77 to 0.06, *P*=0.096) and "social distance" stigma (β=0.03, 95% CI –0.56 to 0.61, *P*=0.933) were not statistically significant after adjustment. Sensitivity analyses using doubly robust inverse probability weighting demonstrated largely consistent findings (Supplementary Tables S5–S9).

Table 5 presents the linear regression analyses of factors associated with stigma dimensions. For the "weak-not-sick" dimension, respondents in the 35–49 and 50–65 age groups consistently had significantly higher scores in both periods. In MM15, Malay ethnicity was associated with a higher score, while income of SGD6000–9999 was associated with a lower score. In MM23, secondary education, SGD2000–5999 income, and personal experience similar to the vignette were associated with higher scores, whereas unemployed individuals exhibited lower scores in this dimension.

For the "dangerous-unpredictable" dimension, in MM15, being in the 35–49 age group and having 6 years of education or less were associated with higher scores. In contrast, in MM23, income emerged as a significant factor. Compared with respondents in the highest income bracket (>SGD10,000), all other income groups had higher stigma scores in the "dangerous-unpredictable" dimension, with the strongest associations in the <SGD2000 and SGD4000–5999 groups

For the "social distance" dimension, Malay and Indian ethnicities were consistently associated with lower stigma scores across both periods. In MM23, having family or close friends with an experience similar to the vignette was associated with significantly lower stigma scores.

Relationship between stigma and recognition

Table 6 illustrates the relationship between stigma and recognition by survey year. Across both time periods, a higher "weak-not-sick" dimension score was associated with significantly lower odds of recognition of schizophrenia.

OR was derived from multivariable logistic regression after adjusting for sociodemographic factors (i.e. age, sex, ethnicity, marital status, education, employment, income), personal experience similar to the vignette and family or close friends with an experience similar to the vignette.

DISCUSSION

Despite a slight increase from 11.5% to 15.1%, there was no significant improvement in schizophrenia recognition between the 2 time periods. This finding remained consistent in pooled regression analyses adjusting for sociodemographic differences between survey cohorts, suggesting that differences in sample composition did not account for the lack of significant improvement in recognition. This finding is consistent with recognition rates reported in other Asian countries.[17-21]

Lower stigma scores observed in MM23 may reflect broader changes in public attitudes towards mental health, potentially associated with recent anti-stigma initiatives in Singapore. Several national initiatives including the "Beyond the Label" movement, the Health Promotion Board's "It's OKAY to Reach Out" campaign, and the Mind SG portal have aimed to improve mental health awareness in Singapore.[22,23]

Furthermore, higher scores on the "weak-not-sick" stigma dimension, which reflects the belief that schizophrenia arises from personal weakness rather than a medical condition, were consistently associated with lower odds of schizophrenia recognition. This suggests that individuals endorsing such beliefs may

Table 4. Descriptive statistics of stigma dimension score.

	Mind Matters 2015			Mind Matters 2023			t-test	*P* value
	Mean	SD	CI	Mean	SD	CI		
Weak-not-sick	10.14	2.09	9.94–10.35	9.25	2.20	9.02–9.49	5.24	**0.001**
Dangerous-unpredictable	12.69	2.47	12.44–12.93	12.18	2.33	11.91–12.45	2.71	**0.007**
Social distance	13.24	3.26	12.86–13.59	13.07	2.86	12.75–13.39	0.70	0.481

CI: confidence interval; SD: standard deviation
Values in bold represent statistically significant results (*P*<0.05)

Table 5. Survey-weighted linear regression analysis for factors predicting stigma dimension by survey year.

		Mind Matters 2015						Mind Matters 2023					
		Weak-not-sick		Dangerous-unpredictable		Social distance		Weak-not-sick		Dangerous-unpredictable		Social distance	
		Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value
Age group	18–34 years	Ref		Ref		Ref		Ref		Ref		Ref	
	35–49 years	0.96 [0.31–1.62]	**0.004**	0.70 [–0.01 to 1.41]	0.053	0.04 [–0.90 to 0.97]	0.940	0.74 [0.12–1.36]	**0.020**	0.02 [–0.74 to 0.78]	0.955	0.69 [–0.18 to 1.56]	0.121
	50–65 years	1.15 [0.48–1.83]	**0.001**	1.50 [0.75–2.25]	**<0.001**	1.14 [0.00–2.29]	**0.050**	1.42 [0.74–2.11]	**<0.001**	0.10 [–0.76 to 0.95]	0.821	0.02 [–0.97 to 1.02]	0.964
Sex	Female	–0.13 [–0.55 to 0.30]	0.558	–0.16 [–0.66 to 0.34]	0.535	0.07 [–0.68 to 0.81]	0.863	–0.31 [–0.77 to 0.15]	0.186	–0.48 [–0.97 to 0.01]	0.057	–0.23 [–0.88 to 0.42]	0.487
	Male	Ref		Ref		Ref		Ref		Ref		Ref	
Ethnicity	Chinese	Ref		Ref		Ref		Ref		Ref		Ref	
	Malay	0.93 [0.49–1.36]	**<0.001**	–0.31 [–0.84 to 0.21]	0.240	–1.70 [–2.36 to –1.03]	**<0.001**	0.37 [–0.08 to 0.83]	0.110	–0.13 [–0.69 to 0.43]	0.645	–1.55 [–2.28 to –0.83]	**<0.001**
	Indian	0.19 [–0.28 to 0.65]	0.435	–0.05 [–0.58 to 0.48]	0.841	–0.88 [–1.57 to –0.19]	**0.012**	0.35 [–0.09 to 0.78]	0.116	–0.39 [–0.87 to 0.09]	0.113	–1.30 [–1.92 to –0.68]	**<0.001**
	Others	0.53 [–0.59 to 1.65]	0.355	–0.71 [–1.68 to 0.25]	0.147	–0.49 [–2.97 to 1.99]	0.700	–0.68 [–1.38 to 0.03]	0.062	–0.40 [–1.19 to 0.40]	0.328	–1.08 [–1.95 to –0.21]	**0.015**
Marital status	Never married	–0.11 [–0.68 to 0.46]	0.706	–0.09 [–0.69 to 0.51]	0.756	–0.13 [–1.01 to 0.75]	0.772	–0.31 [–0.94 to 0.32]	0.337	–0.38 [–1.07 to 0.31]	0.281	–0.03 [–0.86 to 0.81]	0.951
	Married	Ref		Ref		Ref		Ref		Ref		Ref	
	Separated/ divorced/ widowed	0.17 [–1.10 to 1.45]	0.789	0.51 [–0.72 to 1.74]	**0.414**	0.23 [–1.64 to 2.10]	0.811	–0.12 [–0.93–0.69]	0.766	–0.78 [–1.80 to 0.25]	0.137	–1.03 [–2.52 to 0.47]	0.179
Education	6 years of education and below	0.70 [–0.31 to 1.72]	0.175	1.15 [0.05–2.26]	0.041	0.00 [–1.58 to 1.58]	1.000	0.90 [–0.13 to 1.93]	0.086	0.53 [–0.87 to 1.93]	0.459	0.58 [–1.69 to 2.85]	0.615
	Secondary education	0.21 [–0.60 to 1.02]	0.609	0.05 [–0.93 to 1.03]	0.922	–0.40 [–1.62 to 0.83]	0.526	0.66 [0.04–1.29]	**0.038**	0.04 [–0.80 to 0.88]	0.931	–1.00 [–2.15 to 0.15]	0.089

Table 5. Survey-weighted linear regression analysis for factors predicting stigma dimension by survey year. (Cont'd)

		Mind Matters 2015						Mind Matters 2023					
		Weak-not-sick		Dangerous-unpredictable		Social distance		Weak-not-sick		Dangerous-unpredictable		Social distance	
		Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value
	A level, polytechnic, and other diploma	0.34 [–0.34 to 1.01]	0.326	–0.05 [–0.83 to 0.74]	0.907	–0.34 [–1.20 to 0.52]	0.439	0.19 [–0.42 to 0.80]	0.541	–0.44 [–1.09 to 0.22]	0.193	–0.63 [–1.45 to 0.19]	0.134
	University	Ref		Ref		Ref		Ref		Ref		Ref	
Employment status	Employed	Ref		Ref		Ref		Ref		Ref		Ref	
	Unemployed	–0.94 [–1.95 to 0.07]	0.068	–0.13 [–1.41 to 1.15]	0.841	0.16 [–2.34 to 2.67]	0.897	–1.35 [–2.61 to –0.09]	**0.035**	–0.79 [–1.89 to 0.31]	0.156	0.61 [–1.63 to 2.86]	0.592
	Economically inactive	0.17 [–0.53 to 0.86]	0.634	0.31 [–0.49 to 1.10]	0.452	0.75 [–0.48 to 1.98]	0.229	0.01 [–0.74 to 0.75]	0.988	–0.68 [–1.51 to 0.16]	0.112	–0.92 [–2.39 to 0.56]	0.222
Income	<SGD2000	–0.19 [–1.40 to 1.02]	0.755	0.29 [–1.35 to 1.94]	0.726	1.73 [–0.39 to 3.85]	0.110	1.35 [0.32–2.37]	**0.010**	2.29 [1.09–3.49]	**<0.001**	1.04 [–0.69 to 2.78]	0.239
	SGD2000–3999	–0.42 [–1.54 to 0.69]	0.456	0.57 [–1.04 to 2.18]	0.490	1.86 [–0.05 to 3.77]	0.057	1.48 [0.40–2.55]	**0.007**	1.27 [0.13–2.42]	**0.030**	0.28 [–1.22 to 1.77]	0.717
	SGD4000–5999	–0.69 [–1.83 to 0.46]	0.242	0.84 [–0.73 to 2.41]	0.294	1.51 [–0.41 to 3.42]	0.122	1.23 [0.24–2.22]	**0.015**	2.09 [1.02–3.17]	**<0.001**	0.17 [–1.18 to 1.52]	0.804
	SGD6000–9999	–1.22 [–2.42 to –0.01]	**0.048**	0.13 [–1.64 to 1.91]	0.883	2.98 [0.91–5.06]	0.005	0.80 [–0.17 to 1.77]	0.106	1.28 [0.09–2.47]	**0.035**	0.15 [–1.34 to 1.63]	0.847
	Above SGD10,000	Ref		Ref		Ref		Ref		Ref		Ref	
Personal experience similar to the vignette	No	Ref		Ref		Ref		Ref		Ref		Ref	
	Yes	0.32 [–0.42 to 1.07]	0.397	–0.96 [–2.30 to 0.39]	0.163	–1.24 [–2.82 to 0.35]	0.127	0.95 [0.12–1.79]	**0.025**	1.27 [–0.04 to 2.59]	0.057	0.03 [–1.69 to 1.74]	0.974
Family or close friends with experience similar to the vignette	No	Ref		Ref		Ref		Ref		Ref		Ref	
	Yes	0.51 [–0.10 to 1.12]	0.104	0.52 [–0.13 to 1.17]	0.116	0.09 [–0.89 to 1.07]	0.853	–0.36 [–0.86 to 0.15]	0.165	–0.35 [–0.96 to 0.25]	0.255	–1.40 [–2.12 to –0.68]	**<0.001**

Ref = reference categories
Values in bold represent statistically significant results ($P<0.05$)

Table 6. Relationship between stigma dimensions and recognition by survey year.

Stigma dimension	Mind Matters 2015		Mind Matters 2023	
	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Weak-not-sick	0.58 [0.46–0.73]	<0.001	0.61 [0.50–0.74]	<0.001
Dangerous-unpredictable	0.94 [0.79–1.11]	0.461	1.15 [0.96–1.38]	0.122
Social distance	0.95 [0.82–1.09]	0.449	0.93 [0.81–1.07]	0.340

CI: confidence interval; OR: odds ratio

be less likely to recognise schizophrenia as a mental health condition requiring professional care. While increasing public awareness of the biological basis of schizophrenia may improve recognition and encourage treatment-seeking, biological explanations alone may not be sufficient to reduce stigma and may reinforce perceptions of dangerousness or unpredictability.[24] Future interventions should therefore adopt a multifaceted approach that addresses both mental health literacy and stigmatising beliefs.

The absence of substantial improvement in recognition may reflect limited schizophrenia-specific public education, as existing campaigns emphasise broader mental well-being topics. Currently, schizophrenia-focused outreach is mainly conducted through the Early Psychosis Intervention Programme (EPIP).[25] Early evaluations of EPIP showed that the median duration of untreated psychosis decreased from 12 months to 4 months.[26] These findings highlight the importance of community-wide interventions to enhance early detection and treatment.

The complexity of schizophrenia symptoms may hinder recognition. Compared with those of depression and anxiety, schizophrenia symptoms are more multifaceted, making it more difficult to educate the public. Studies have found that laypeople are better at recognising positive symptoms than negative symptoms.[27,28] The current study also found that hallucinations and delusions accounted for the majority of schizophrenia-specific symptoms recognised by the respondents. Future interventions should increase awareness of negative symptoms and their clinical significance.

This study found that age and ethnicity are associated with mental health literacy. Both surveys revealed that people who were aged 50 years and above were less likely to recognise schizophrenia and more likely to attribute it to personal weakness, consistent with previous research.[29,30] In the Singapore context, many anti-stigma mental health campaigns use digital platforms. However, older adults, particularly those of lower socioeconomic status, often face digital literacy barriers that limit engagement with such initiatives.[31,32]

Across the 2 time periods, Malay and Indian respondents consistently had a higher "weak-not-sick" stigma score and lower "dangerous-unpredictable" and "social distance" stigma scores. This suggests that they are more likely to attribute schizophrenia to personal weakness but have a higher tolerance towards individuals with the illness. Cultural and religious beliefs may partly explain these patterns. In Islamic teachings, life adversities, including the experience of mental illness, are often regarded as a test from God.[33] Individuals with severe mental illnesses are considered less accountable for their actions, as the illness is understood to impair reasoning and judgement.[34] Moreover, the emphasis placed on familial and community responsibility for support and inclusion may partly account for the lower levels of social distancing observed among Malay respondents.[35,36] Among Indians, the perception of mental disorders is largely influenced by folk, Ayurvedic, or classic Indian medicine traditions. Ayurvedic practitioners treat people with mental illness humanely and sympathetically, which might explain the more tolerant view towards individuals with schizophrenia.[35,37]

Social contact is another factor associated with mental health literacy. Respondents with family members or friends with similar experiences were better able to recognise schizophrenia and reported lower stigma. A prior local study has shown that caregivers experience stigmatising attitudes and emotional distress by association with their care recipients.[38] Shared experience may thus foster empathy and understanding, contributing to more supportive attitudes towards people with mental illness.

Strengths and limitations

The current study has several strengths. It used 2 nationwide cross-sectional surveys conducted using the same methodology to identify changes in, and factors associated with, schizophrenia literacy over time. The disproportionate stratified sampling and oversampling of minority groups ensured a representative sample. Vignette and questionnaire development by psychiatrists and researchers, with professional translation, ensured cultural relevance and reduced language biases. However, the study is limited in certain aspects. As the study was conducted in Singapore, the findings might not be generalisable to other countries. A cross-sectional design limits causal inference, and interview-based responses may be subject to social desirability bias. Despite efforts to ensure conceptual equivalence, cultural and linguistic differences may have influenced interpretation of the vignette and stigma-related items. Differences in education and income between the 2 survey cohorts may reflect changes in the sociodemographic profile of the Singapore resident population over time, potentially introducing sampling heterogeneity and affecting comparability. Pooled regression analyses and doubly robust inverse probability-weighted sensitivity analyses were conducted to account for differences in sample composition. Nevertheless, given the repeated cross-sectional design, findings should be interpreted as adjusted differences between survey periods rather than individual-level longitudinal changes, and residual confounding cannot be fully excluded.

CONCLUSION

There was no significant improvement in schizophrenia recognition from 2015 to 2023, possibly reflecting limited schizophrenia-specific public education. A lower personal stigma score, particularly within the "weak-not-sick" dimension, was observed in 2023 and persisted after adjustment for sociodemographic differences between survey cohorts.

This study provides valuable insights into schizophrenia recognition and stigma in the context of Singapore. Although relatively uncommon, schizophrenia has a long-term impact and imposes an economic burden. Future initiatives should consider targeted schizophrenia-specific education and contact-based approaches involving individuals with lived experience to improve recognition, reduce stigma, and promote greater community acceptance.

Supplementary materials

Appendix S1. Schizophrenia vignette.

Table S1. Pooled survey-weighted logistic regression on changes of correct schizophrenia recognition over time with survey year as the key predictor and all sociodemographic variables as covariates.

Table S2. Pooled survey-weighted linear regression on "weak-not-sick" stigma with survey year as the key predictor and all sociodemographic variables as covariates.

Table S3. Pooled survey-weighted linear regression on "dangerous-unpredictable" stigma with survey year as the key predictor and all sociodemographic variables as covariates.

Table S4. Pooled survey-weighted linear regression on social distance stigma with survey year as the key predictor and all sociodemographic variables as covariates.

Table S5. Doubly robust IPW logistic regression on correct schizophrenia recognition.

Table S6. Doubly robust IPW linear regression on "weak-not-sick" stigma.

Table S7. Doubly robust IPW linear regression on "dangerous-unpredictable" stigma.

Table S8. Doubly robust IPW linear regression on social distance stigma.

Table S9. Covariate balance before and after IPW.

Ethics statement

The study was approved by the National Healthcare Group Domain Specific Review Board (2021/00695).

Declaration

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Recommendations for the diagnosis and management of neurofibromatosis type 1 in Singapore: A Delphi consensus

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ABSTRACT

Introduction: Neurofibromatosis type 1 (NF1) is a multisystem genetic disorder with wide phenotypic variability, necessitating coordinated multidisciplinary care and Singapore-relevant guidance. This study aimed to develop Singapore-specific, consensus-based recommendations for NF1 diagnosis, surveillance, and management.

Methods: The study involved 2 rounds of online surveys and a participant meeting with 24 experts from Singapore. Following a literature review, a 151-statement questionnaire was developed (133 Likert-style statements, 13 open-ended questions, 5 single-select questions). Statements were rated on a 9-point Likert scale with a predefined consensus threshold of ≥75%; analyses were performed after each round.

Results: Surveys 1 and 2 involved 19 and 17 participants, respectively, with 14 attending the meeting. Consensus was reached for 113/133 statements in Survey 1 and 9/21 in Survey 2. Experts reached consensus on genetic testing across diagnostic scenarios, including Sprouty-related EVH1 domain-containing protein 1 analysis and ribonucleic acid testing. Agreed surveillance incorporated examinations twice a year until the age of 5 years, at least annually thereafter in childhood, annual symptom checks in adults with triennial specialist review, and targeted MRI-based imaging, including whole-body magnetic resonance imaging around transition. Management recommendations favoured multidisciplinary review and surgical resection when feasible.

Conclusion: This Delphi consensus provides unified recommendations to support consistent NF1 care across paediatric and adult services in Singapore, while highlighting areas without consensus and priorities for implementation and further research.

Keywords: Delphi consensus, MPNST, NF1, plexiform neurofibroma, recommendation

CLINICAL IMPACT

What is New

- To the authors' knowledge, this is the first Singapore-specific Delphi consensus providing comprehensive, multidisciplinary recommendations for the diagnosis, surveillance, and management of neurofibromatosis type 1 (NF1).
- The consensus integrates expert practice in Singapore with international evidence and highlights areas where Singapore-specific data remain limited.

Clinical Implications

- Provides unified, practical guidance to support consistent NF1 care across paediatric and adult services in Singapore.
- Identifies implementation priorities, such as surveillance pathways, access to imaging, and use of mitogen-activated protein kinase kinase inhibitors for symptomatic plexiform neurofibromas.

INTRODUCTION

Neurofibromatosis type 1 (NF1), previously referred to as von Recklinghausen's disease, is an autosomal dominant genetic disorder characterised by the presence of tumours affecting the skin and central and peripheral nervous systems.[1] It is estimated that NF1 has an incidence of approximately 1 in every 2500–3000 live births, with a global prevalence of approximately 1 in 3000 individuals.[2,3] Accurately determining the prevalence of NF1 is challenging due to its highly variable clinical presentation, differences among studied populations, and variations in case identification methods.[2,3]

NF1 is characterised by distinct clinical features, including café-au-lait macules, axillary and inguinal freckling, neurofibromas, and Lisch nodules.[4] Cutaneous neurofibromas (CNFs) are the most characteristic feature of NF1. They appear on the skin and develop in more than 90% of patients with NF1. Plexiform neurofibromas (PNs) are another classical feature of NF1. They are slow-growing peripheral nerve sheath tumours arising from deep nerves, with up to

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50% of patients developing NF1-PNs.[5,6] NF1-PNs can be symptomatic, depending on their size and location.

In addition to CNFs and NF1-PNs, NF1 is associated with an increased risk of malignant tumours, including malignant peripheral nerve sheath tumours (MPNSTs), gliomas, gastrointestinal stromal tumours (GISTs), breast cancer, and others.[7-9] Patients have a 2.7- to 4-fold higher risk of malignancy and can have a life expectancy 8–20 years shorter than that of the general population.[10] Specifically, NF1-PNs are clinically important because they carry a risk of malignant transformation to MPNSTs, either directly or through premalignant intermediate lesions, such as atypical neurofibromas or atypical neurofibromatous neoplasms of uncertain biological potential. MPNSTs have a poor prognosis despite the availability of aggressive treatments, severely affecting patients' quality of life and imposing substantial psychological and financial burdens.[11] However, the risk of malignant transformation for an individual lesion is not well defined. Individuals with NF1 have an estimated lifetime risk of developing MPNST of approximately 10–15%. NF1 is also associated with neurocognitive complications, such as attention-deficit hyperactivity disorder and learning difficulties.[7,8] In summary, NF1 exhibits highly variable clinical presentations and has lifelong ramifications for patients, making diagnosis, treatment, follow-up, and overall management particularly challenging.

Effective care necessitates a coordinated, multidisciplinary approach integrating diagnosis, surveillance, and treatment. While targeted therapies, such as mitogen-activated protein kinase kinase (MEK) inhibitors, have improved outcomes, many aspects of NF1 management remain inadequately defined, underscoring the need for structured, consensus-driven care.

Existing frameworks, including the Chinese Expert Consensus (2021 and 2025),[12,13] emphasise multidisciplinary care, structured surveillance, and coordinated, patient-centred management, although their applicability varies by healthcare setting.

Compared with China's more heterogeneous healthcare system, Singapore benefits from a more centralised healthcare structure with streamlined referrals and greater access to advanced diagnostics and targeted therapies, enabling earlier integration of precision medicine.

From an epidemiological and genetic perspective, NF1 incidence appears broadly comparable between Chinese and Singaporean populations; however, emerging evidence suggests potential differences in mutation spectra and phenotypic expression across Asian populations. These variations, together with differences in healthcare accessibility and resource allocation, underscore the importance of adapting global and national guidelines to local contexts.

Within Singapore, NF1 represents a rare but clinically significant condition, with an estimated 800–1800 affected individuals based on current prevalence data. The disease imposes a substantial and sustained burden on the healthcare system, requiring lifelong surveillance, repeated imaging studies, multidisciplinary consultations, and, in selected cases, high-cost targeted therapies.[14] Complications such as malignant transformation, complex NF1-PN, and neurocognitive impairment further increase healthcare utilisation and associated costs, as well as indirect socioeconomic burden through reduced productivity and educational challenges. Although international and Chinese guidelines provide important guidance, they do not fully address Singapore's healthcare and resource considerations.

In this context, the present consensus complements existing Chinese and international guidelines by providing a regionally relevant framework for NF1 diagnosis and management. It highlights both shared principles and context-specific adaptations, thereby offering a scalable model that can inform clinical practice not only in Singapore but also across Southeast Asia.

METHODS

Study design

This study employed a modified Delphi technique, comprising 2 rounds of electronic surveys and a virtual expert meeting to develop consensus recommendations for NF1 management in Singapore.

Surveys were conducted between May 2025 and December 2025, with an interim meeting in August 2025. The questionnaire was developed by the research team, administered via an independent vendor using Decipher software version 153 (Decipher Media LLC, San Francisco, US). Responses were analysed with descriptive statistics using Microsoft Excel, with consensus defined as ≥75% agreement after each survey round. Since this was a non-interventional physician survey, no formal ethical approval was required.

Participants

Twenty-four expert clinicians (geneticists, oncologists, neurologists, dermatologists, and surgeons [specialising in neurosurgery and surgical oncology]) from Singapore with recognised expertise in NF1 management were invited to participate. Participants for the study were selected using specific criteria rather than through a random sampling process. Participants meeting the pre-defined eligibility criteria were

invited to participate in the study via individual emails. Participants who completed Survey 1 were invited to join a virtual participant meeting and participate in Survey 2. Participation in Survey 2 was independent of attendance at the meeting. A 2-member steering committee endorsed the questionnaire, moderated the participant meeting, and approved the outcomes of the study. The steering committee was supported by delegated representatives in the conduct of the study.

Informed consent was obtained electronically from all participating experts prior to survey participation. Participants were provided with detailed information regarding the objectives of the study, the voluntary nature of participation, and the intended use and publication of aggregated results. Participants could withdraw consent at any time without consequences.

All data were collected through a secure survey platform and de-identified prior to analysis. Personal information was collected only for descriptive purposes and was not linked to individual responses. Data were reported in an anonymised and aggregated form to ensure confidentiality. Access to data was restricted to the research team, and no personally identifiable information was disclosed in analysis or publication.

Study stages

Development of the survey questionnaire

Survey 1 was developed from key statements drawn from a targeted literature review focused on the objectives of this Delphi study. The objectives included understanding the current practices followed in Singapore and recommending appropriate modifications to optimise outcomes in patients with NF1.

A comprehensive literature search was conducted in the PubMed database using different objective-specific search terms. Additional relevant literature was identified using a grey literature search.

The literature search was conducted in PubMed using combinations of keywords including "neurofibromatosis type 1", "NF1", "plexiform neurofibroma", "MPNST", "guidelines", "consensus", "surveillance", and "management". The search was supplemented by grey literature and existing international guidelines (e.g. ERN GENTURIS, Chinese consensus).

The search was not limited by time, and all applicable literature was screened. All the retrieved articles were screened for population and objectives. A total of approximately 1082 records were retrieved. After screening titles and abstracts, studies were included if they addressed NF1 diagnosis, surveillance, or management in human populations and were published in English. Case reports, non-relevant mechanistic studies, and non-human studies were excluded. Key references were selected based on relevance and used to generate Delphi statements. A detailed search strategy is included in Supplementary Table S1.

A questionnaire with 151 statements consisting of 133 Likert-style statements, 13 open-ended questions, and 5 single-select questions was developed to address the following themes:

- Genetic testing (n=8)
- Adult management (n=50)
- Childhood management (n=31)
- Surveillance (n=62)
    - All ages (n=15)
    - Adults aged >18 years (n=16)
    - Children aged 0–16 years (n=22)
    - Transition age from 16 to 18 years (n=9)

Survey 1 and participant meeting

The first round of the Delphi survey was shared electronically through individual emails to the participants and completed online between May 2025 and July 2025. Participants from the first round of the survey were invited to a virtual meeting to review the survey results and to share their expert views, focusing primarily on statements that did not achieve consensus in Survey 1. The scientific workshop was non-compulsory, and all participants received the follow-up minutes from these discussions before the initiation of Survey 2. This participant meeting was moderated by the steering committee. The sponsor and the members of the steering committee did not participate in the surveys.

Survey 2 and final data analysis

Statements that did not reach consensus in Survey 1 and any additional statements deemed appropriate from the participant meeting were included in Survey 2 (n=21). Survey 2 was shared electronically through individual emails to the participants and was completed between October 2025 and December 2025.

Data analysis

A 9-point Likert scale was used to rate responses to the statements, in line with best practice. Participants rated their level of agreement with each statement anonymously, ranging from 1 (disagreement) to 9 (agreement). These scores were divided into 3 groups: agree (7–9 points), neither agree nor disagree (4–6 points), and disagree (1–3 points). Responses to open-ended and single-/multiple-select questions were quantified. Consensus was deemed to have been reached in either round of the survey when ≥75%

of the respondents allotted either the highest or the lowest range of scores. This threshold was selected based on recommendations from previous Delphi studies and systematic reviews, which commonly report consensus levels between 70% and 80%. A 75% cut-off provides a balance between ensuring strong agreement among experts and maintaining feasibility for achieving consensus without being overly restrictive. Each question also had a "Do not know" option for Survey 1, enabling the respondent to skip questions that were not related to their experience and ensuring that every question was viewed at least once by each respondent.

RESULTS

Participants

Of the 24 invited participants, 19 (response rate: 79.2%) completed Survey 1; these included clinical geneticists (n=4), dermatologists (n=3), neurologists (n=5), neurosurgery specialists (n=3), oncologists (n=2), and surgical oncologists (n=2). These participants were subsequently invited to a virtual participants meeting. In the meeting, 14/19 participants (73.7% attendance) were present. Following the discussion, a revised second survey was circulated to 18/19 participants. One participant withdrew consent to participate further in the study, and Survey 2 was therefore not sent to this participant. Survey 2 was completed by 94.4% (n=17/18) of the expert participants.

Theme-wise consensus

Table 1 summarises the consensus recommendations reached during the study. In Survey 1, participants reached consensus on 113/133 closed-ended statements. The statements that did not reach consensus in Survey 1 were taken forward for further consideration. Following discussion and refinement during the scientific workshop, Survey 2 comprised 21 closed-ended statements, of which 9 reached consensus. All statements rated by the participants are summarised in the Supplementary Materials (consensus in Survey 1 [Table S2]; statements from Survey 2 [Table S3]; open-ended questions [Figs. S1–S6]).

For the genetic testing theme, all the statements achieved consensus during Survey 1 (Survey 1: 8/8; Survey 2: none, as all statements achieved consensus in Survey 1). For the adult management theme, 40/49 statements achieved consensus during the 2 surveys (Survey 1: 34/49; Survey 2: 6/14). For the childhood management theme, all the statements achieved consensus during Survey 1 (Survey 1: 31/31; Survey 2: none, as all statements achieved consensus in Survey 1). For the surveillance theme (including age-specific statements for all ages, adults aged >18 years, children aged 0–16 years, and transition age from 16 to 18 years), 40/47 statements achieved consensus during the 2 surveys (Survey 1: 40/45; Survey 2: 4/7).

DISCUSSION

The expert panel in this Delphi consensus deliberated on various aspects of NF1 management, including genetic testing; disease management in childhood and adulthood; and surveillance protocols for various stages, subtypes, and complications of the disease, such as NF1-PN, breast cancer, and optic pathway glioma.

Genetic testing

Distinguishing NF1 from other syndromes, such as Legius syndrome, in young children who present only with pigmented skin lesions can be difficult, especially in the absence of a family history or additional clinical features. Genetic testing, when available, is a valuable tool for accurate diagnosis. Experts broadly agreed that genetic testing benefits patients having NF1 who do not meet clinical criteria, those with a confirmed clinical diagnosis, and those with suspected NF1 microdeletions or complex presentations.[15] International consensus guidelines for the diagnosis of NF1 set forth by Legius et al. emphasise the importance of distinguishing NF1 from other genetic disorders, including Legius syndrome, Noonan syndrome, and constitutional mismatch repair deficiency.[4] To distinguish between these disorders, techniques such as multigene panel testing should be considered to establish the exact diagnosis. This aligns with the opinions of the experts participating in this study. Given the complexity of NF1 molecular testing, genotype–phenotype variability, and the potential for mosaic disease, genetic testing should ideally be ordered and interpreted by clinicians with expertise in clinical genetics or in collaboration with genetics services. Appropriate pre- and post-test genetic counselling is important to support informed decision-making and accurate interpretation of test results.

Given the autosomal dominant inheritance of NF1, genetic counselling plays an important role in discussing familial implications, including cascade testing of at-risk relatives and reproductive options. Cascade testing can facilitate the identification of affected family members who may benefit from surveillance and clinical management. Similarly, reproductive counselling may include discussion of prenatal diagnosis and preimplantation genetic testing where available and appropriate. These topics were

Table 1. Recommendations based on consensus reached during the study.

Genetic testing for NF1

• Genetic testing would be valuable for patients suspected of having NF1 in the following scenarios:
  ○ Patients who do not meet the clinical diagnostic criteria;
  ○ When cost is not a limiting factor.
• There is value in genetic testing for patients who have a clinical diagnosis of NF1.

• Genetic testing is considered helpful for patients with suspected NF1 microdeletion or those presenting with complex NF1 presentations, such as malignancy.
• If an *NF1* variant is not detected, sequence analysis and deletion/duplication analysis of *SPRED1* are considered in individuals with only pigmentary features.
• If a variant in *NF1* or *SPRED1* is not detected through DNA analysis, it is advisable to consider RNA analysis.
• If the phenotype cannot be distinguished from those of other disorders, a multigene panel that includes *NF1*, *SPRED1*, mismatch repair, and other genes of interest should be considered.
NF1 surveillance in childhood
• Systematic clinical assessment by NF1 specialists, including skin and neurological examinations, blood pressure measurement, height, weight, and evaluation of pubertal development, should be performed at least annually for children up to 10 years, every 2 years for children over 10 years, yearly for those up to 18 years during transition, and once every 3 years in adults.
• Pain assessment for NF1 symptoms should be conducted during clinic visits.
Children with NF1 are recommended to follow a surveillance protocol that includes: • Physical examinations at least twice a year until the age of 5 years, and at least annually thereafter. • Monitoring growth and overall development. • Annual neurological examinations to detect possible nerve tumours, headaches, or seizures. • Regular measurement of head circumference. • Annual ophthalmological evaluations throughout childhood to screen for optic pathway gliomas. • Screening for learning disorders and attention deficit hyperactivity disorder when the child starts school. • Annual pain score assessment. • Annual cardiac assessment should include blood pressure monitoring, with echocardiography performed based on clinical indication or in patients receiving treatments for which cardiac monitoring is recommended, such as MEK inhibitors.
• Clinical evaluation of children with NF1 who are suspected of having orbital or periorbital PN should include a physical examination for signs such as blepharoptosis, proptosis, eyelid oedema, orbital dysplasia or dystopia, distortion of the (peri)orbital skeleton, eye pulsation, and strabismus; clinical testing of vision, refractive error, visual fields, ocular motility and alignment, and optic disc evaluation to rule out glaucoma or optic neuropathy; and MRI of the brain and orbits for all suspected cases.
Childhood management of NF1
Treatment of NF1 • Treatment for NF1 in children depends on their needs and may include surgical intervention for PNs, pharmacotherapy for headaches or seizures, educational assessment with school support, pharmacological or non-pharmacological approaches for pain management, therapeutic counselling to address low self-esteem and negative body image, and early intervention through speech, physical, or occupational therapy.
Development • Children with NF1 should be monitored for cognitive and behavioural difficulties, including developmental milestones (ideally before school), academic progress, sleep patterns, ability to maintain focus on an activity, distractibility, social interaction, and motor skills. • Management of cognitive and behavioural difficulties in children with NF1 may require early involvement of a special educational needs coordinator, close collaboration among teachers, educational psychologists, occupational therapists, and community paediatricians, cognitive behavioural therapy, and the use of methylphenidate under experienced supervision. • Addressing the effects of NF1 on psychosocial and neuropsychological functioning may involve assessing psychosocial well-being and neuropsychological functioning at every clinic visit, including a psychologist in the multidisciplinary team, providing counselling interventions, and addressing issues such as childhood bullying. • Children diagnosed with NF1 should undergo a speech and language assessment, followed by appropriate intervention if necessary.
Treatment of PNs • Surgical resection is a preferred treatment option for children with NF1-PN when it is feasible. • MEK inhibitors may be considered as a treatment option for children with NF1 who have symptomatic PNs, including cases that are inoperable or remain symptomatic after partial resection.

Table 1. Recommendations based on consensus reached during the study. (Cont'd)

Management of vascular symptoms
- Assessment of hypertension in children with NF1 should include Doppler ultrasonography of the aorta and renal arteries, renal arteriography, and magnetic resonance angiography.

Surveillance of adult NF1

Surveillance in adulthood
- For adults (over 18 years) with NF1, a symptom check should be conducted at least annually by a primary care physician and every 3 years by an NF1 specialist.
- In adults, routine screening for optic pathway gliomas is not recommended. Clinical evaluation should be symptom-driven, including assessment of visual acuity and visual disturbances where clinically indicated.

PNs
- NF1 patients with PNs may undergo WB-MRI, regional MRI, or FDG PET scan by the age of 21 years or prior to transition to adult care.

Pheochromocytoma screening
- In NF1, biochemical or imaging screening for pheochromocytoma in asymptomatic, non-hypertensive individuals is not recommended.
- In NF1, measurement of plasma free metanephrines as a single test is more sensitive and specific in an individual clinically suspected to have pheochromocytoma. Surveillance for pheochromocytoma in patients with NF1 should include an annual blood pressure check starting at the age of 10 years.
- For NF1 patients with hypertension and vasculopathy, management should include MRI as the preferred imaging modality for evaluating renovascular hypertension, spiral CT, and CT angiography for individuals with impaired renal function (GFR <30 mL/min), and selective imaging such as ultrasound for those clinically suspected to have a vascular lesion.

Breast cancer screening

Breast cancer surveillance should consider the following:
- Screening with annual breast MRI should be the primary approach.
- Mammography is the second-best alternative when MRI is not available.
- Annual screening in NF1 should begin at the age of 30 years.
- Breast cancer screening in NF1 should be performed once every 2 years after the age of 50 years.
- Risk-reducing bilateral mastectomy should not be performed in patients with NF1.

Malignancy screening
- WB-MRI may be considered between the ages of 16 and 20 years to assess internal tumour burden, particularly PNs.
- If no internal PNs are detected, routine follow-up with WB-MRI is not recommended.
- Patients with a high internal tumour burden may require ongoing imaging surveillance due to the increased risk of malignant transformation.

Adult management of NF1

General
- Laser treatment for café-au-lait macules and freckles may be considered for patients with NF1.
- Patients with NF1 usually do not exhibit KIT or PDGFRA overexpression in GISTs, limiting the use of imatinib in this population.
- For maintaining the health of patients with NF1, considerations include vitamin D supplementation, monitoring curve progression for scoliosis management, treating osteoporosis as in the general population, and performing annual clinical back evaluations using the Adam's forward bend test.
- Osteoporosis in patients with NF1 is generally managed according to standard clinical guidelines, similar to patients without NF1, provided there are no NF1-specific complications.
- The initial step in pain management is to use age-appropriate pain intensity assessment tools to determine the level of pain.
- Treatment options for adult patients with NF1 may include surgical intervention for PNs, pharmacotherapy for headaches or seizures, therapeutic counselling for pain management and addressing low self-esteem or negative body image, as well as psychosocial counselling.

Benign and malignant tumours
- For patients with CNFs, clinical assessment comprising physical examination and palpation should be repeated at least annually.
- Radiotherapy is not recommended for optic pathway gliomas due to the increased risks of late-onset cerebrovascular complications and secondary malignancy.
- Pheochromocytoma screening is recommended for hypertensive NF1 patients who are over 30 years of age, are pregnant, have paroxysmal hypertension, or experience hypertension-associated symptoms such as headache, palpitations, or sweating.
- Current treatment options for CNFs include surgical excision, laser removal, and electrodesiccation.
- Surgical resection is the preferred treatment for patients with NF1 for specific conditions, including NF1-PN, malignant peripheral nerve sheath tumours, optic pathway glioma with proptosis or hypertensive hydrocephalus, CNFs, and GISTs.
- Risk-reducing bilateral mastectomy is not routinely recommended for NF1 patients without breast cancer; however, it may be considered in individuals with additional significant risk factors (e.g. pathogenic variants in other breast cancer predisposition genes or strong family history), in accordance with established risk thresholds.

Table 1. Recommendations based on consensus reached during the study. (Cont'd)

NF1-PNs

- Radiotherapy is not recommended for NF1-PNs due to the increased risk of secondary malignancy and moyamoya syndrome.
- The following therapies may be considered for treating patients with NF1-PNs, based on clinical and safety outcomes: surgery, chemotherapy, and MEK inhibitors.
- NF1-PN with rapid growth (>20% increase in volume per year) and impending morbidity is likely a candidate for intervention.
- A slowly growing NF1-PN (<5% increase in volume per year) without actual or impending morbidity may be suitable for observation.
- Surgical resection can be a treatment option, if feasible, for symptomatic NF1-PN.
- MEK inhibitors may be considered as a treatment option for adult NF1 patients with symptomatic PNs, including cases that are inoperable or remain symptomatic after partial resection.
- MRI is preferred over CT to assess NF1-PNs.
- Among different types of neurofibromas, NF1-PNs exhibit the highest tendency to evolve into malignant peripheral nerve sheath tumours.

CT: computed tomography; CNF: cutaneous neurofibroma; DNA: deoxyribose nucleic acid; FDG PET: fluorodeoxyglucose positron emission tomography; GFR: glomerular filtration rate; GISTs: gastrointestinal stromal tumours; KIT: KIT proto-oncogene receptor tyrosine kinase; MEK: mitogen-activated protein kinase; MRI: magnetic resonance imaging; NF1: neurofibromatosis type 1; PDGFRA: platelet-derived growth factor receptor alpha; PNs: plexiform neurofibromas; RNA: ribonucleic acid; *SPRED1*: Sprouty-related EVH1 domain-containing protein 1; WB-MRI: whole-body magnetic resonance imaging

not specifically evaluated as part of the Delphi process and therefore fall outside the scope of the present consensus recommendations.

In addition, mosaic NF1 should be considered in individuals with segmental or atypical presentations, as lower variant allele fractions may reduce the sensitivity of standard genetic testing and complicate clinical diagnosis. Recognition of mosaicism is also important during genetic counselling, as it has implications for the interpretation of genetic test results, recurrence risk assessment, and family counselling.

Surveillance

Experts agreed that systematic clinical assessment for individuals with NF1, including skin and neurological examinations along with monitoring of blood pressure, height, weight, and pubertal development, should be performed annually in children up to 10 years of age, once every 2 years in children older than 10 years, yearly for adolescents up to 18 years during transition, and once every 3 years in adults. Experts also supported the established guideline recommendation of twice-yearly screening until the age of 5 years and yearly surveillance thereafter. These intervals ensure ongoing surveillance tailored to age and developmental stage.

For patients with NF1-PN, whole-body MRI (WB-MRI) and localised MRI are preferred by the participating experts for initial assessment, while localised MRI is preferred for routine surveillance and assessment of treatment response. Factors considered by the study participants included symptoms, change in tumour size, age, timing (prior to transition to adult services), pain, and PN location. The practices recommended by the expert group differ from those set forth by the ERN GENTURIS consensus group, which recommends performing WB-MRI during the transition from childhood to adulthood. If no internal PNs are detected on this scan, routine follow-up with WB-MRI is not advised. However, more frequent WB-MRI assessments may be considered for patients identified as having a high risk of developing MPNST.[7]

In Singapore, breast cancer is the most common malignancy among women and is most frequently diagnosed after the age of 40 years, although it is already the leading cancer in women aged 30–39 years. Singapore data on NF1-associated breast cancer are limited; however, an institutional cohort analysis from Singapore reported a mean age at breast cancer diagnosis of approximately 48 years, with cases occurring as early as 30 years. This observation is consistent with international evidence demonstrating that more than 50% of breast cancers in NF1 occur before the age of 50 years, with a peak incidence between 34 and 44 years. These findings support the recommendation for earlier initiation of screening at the age of 30 years, compared with general population screening programmes in Singapore.[13,16,17] Experts in this study recommended initiating annual breast cancer screening for patients with NF1 at the age of 30 years using breast MRI as the preferred method, with mammography as an alternative. This is consistent with ERN GENTURIS guidelines. In contrast, the transition to biennial screening after the age of 50 years reflects Singapore expert consensus and adaptation to regional clinical practice. Risk-reducing bilateral mastectomy is not advised for NF1 patients without breast cancer, as current evidence does not support its benefit.[7] The Chinese expert consensus similarly supports earlier screening initiation, although exact age thresholds may vary. This alignment suggests a shared recognition across Asian populations of increased early risk, while differences likely reflect variations in Singapore epidemiological data, healthcare system structure, and resource availability.

Osteoporosis represents a clinically relevant condition in the ageing population in Singapore, with studies

reporting a prevalence of approximately 9.3–19.4% among postmenopausal women and around 0.7% among men aged over 50 years.[18]

Available international data suggest that NF1 is associated with impaired bone health, with osteopenia reported in up to 50% of patients and osteoporosis in approximately 20–50%, indicating a higher burden of reduced bone mineral density compared with the general population.[19,20] Nevertheless, these findings are derived from heterogeneous cohorts and may not be directly generalisable to the Singapore population due to differences in genetic background, environmental factors, and healthcare systems.

In the absence of robust Singapore-specific epidemiological data and NF1-specific clinical management guidelines for osteoporosis, the expert panel recommended managing osteoporosis in patients with NF1 according to general population guidelines. This approach represents a pragmatic and evidence-consistent strategy, ensuring that patients receive standard-of-care management while acknowledging the need for future regional studies to better define disease burden and optimise NF1-specific management strategies.

Childhood management

Experts agreed on a structured approach to the management of NF1 in children. Key components include early speech and language assessment, prompt evaluation of persistent headaches, and supportive interventions such as counselling for self-esteem and body image, alongside speech, physical, and occupational therapy.

Management should be individualised, incorporating surgical resection for PNs when feasible, pharmacological treatment for neurological symptoms, and educational support. Additionally, MEK inhibitors were recognised as an option for symptomatic, inoperable, or partially resected PNs.

Experts agreed that the assessment of hypertension in children with NF1 should include Doppler ultrasonography of both the aorta and renal arteries, with additional imaging as clinically indicated.

Experts also agreed that children with NF1 should be monitored for cognitive and behavioural issues, including developmental progress before school, academic performance, sleep patterns, ability to concentrate, distractibility, social interaction, and motor skills. Strong consensus across these areas highlights the importance of comprehensive and ongoing developmental assessment in childhood NF1 management.

Moreover, experts agreed that managing cognitive and behavioural difficulties in children with NF1 may require early involvement of a special educational needs coordinator, close collaboration among teachers, educational psychologists, occupational therapists, and community paediatricians, as well as cognitive behavioural therapy. Additionally, methylphenidate under experienced supervision was considered an appropriate option when necessary. Strong consensus across these strategies highlights the importance of a multidisciplinary approach to support affected children.

Experts recommended routine assessment of psychosocial well-being and involvement of psychological services, highlighting the need for a holistic, multidisciplinary approach to paediatric NF1 care.

Adult management

Management of NF1-PN across paediatric and adult populations reflects a continuum of care consistent with a coordinated, patient-centred approach.

CNFs are histologically benign, multicellular tumours that occur in the majority of individuals with NF1. Despite their high prevalence and significant impact on patients, CNF management remains challenging.[21] For patients with CNFs, clinical assessment including physical examination and palpation should be performed at least annually. Surgical resection is considered the treatment of choice, with current options including surgical excision, laser removal, and electrodesiccation. The participating experts in this study reached consensus on the recommended approach to CNF management.

According to the ERN GENTURIS guidelines, surgery is considered when feasible, although complete resection is often challenging and associated with morbidity.[7] Participating experts in this study did not endorse surgery as the sole primary treatment for NF1-PN, but agreed it should be a treatment option, considered within a multidisciplinary framework, alongside pharmacological options. Additionally, for unresectable or inoperable NF1-PN, radiotherapy is generally avoided, primarily because of the increased baseline risk of radiation-induced neoplasms in patients with NF1 and the potential for NF1-PNs to undergo malignant transformation into MPNSTs.[5] Aligned with the evidence, the experts in this study did not reach consensus on using these treatment methods during Survey 1.

Management of tumours in NF1

Upon deliberation, the panel of experts agreed that surgery and chemotherapy may be used in patients with NF1-MPNST, based on their clinical and safety outcomes. The majority of the experts in the study opined that the decision on whether NF1-PN should be treated surgically or pharmacologically should be made by a multidisciplinary board on a regular basis.

Patients with NF1-associated GISTs typically lack KIT proto-oncogene receptor tyrosine kinase and platelet-derived growth factor receptor alpha mutations, limiting the therapeutic utility of imatinib in this population. NF1-associated GISTs are often characterised by multiple small tumours arising predominantly in the small intestine and differ biologically from sporadic GISTs.[22] In this study, only 50% of the experts agreed with this statement during Survey 1; however, unanimous consensus was reached in Survey 2. The initial lack of consensus likely reflects the specialised nature of this topic and variations in familiarity with the molecular characteristics of NF1-associated GISTs. The absence of consensus may result from either insufficient knowledge among respondents or genuine differences in interpretation, which is understandable given the complexity of the subject matter.

Interestingly, in Survey 1, the participants agreed on using MEK inhibitors for the treatment of NF1-PN. These inhibitors have been shown to shrink NF1-PNs and improve pain in the paediatric population. Selumetinib is approved in Singapore for the treatment of patients aged 3 years and above with symptomatic and inoperable NF1-PNs.[23] MEK inhibitors have also demonstrated promising efficacy in adult patients, supported by clinical trial data. In the KOMET trial in adults with symptomatic and inoperable NF1-PNs, selumetinib demonstrated an objective response rate of 20% (n=14/71; 95% confidence interval [CI] 11.2–30.9) by cycle 16, compared with 5% (n=4/74; 95% CI 1.5–13.3) with placebo (P=0.011).[24] In addition to tumour response, studies have reported reductions in tumour volume and improvements in patient-reported out-comes, including pain and quality of life, highlighting the broader clinical benefits of treatment.[25-27] Considering the growing evidence for the use of MEK inhibitors in adult patients with NF1, the participants reached consensus on using these agents for the treatment of symptomatic NF1-PNs; inoperable, symptomatic NF1-PNs; and NF1-PNs that remain symptomatic following partial resection.

Although tipifarnib and mechanistic Target of Rapamycin (mTOR) inhibitors, such as sirolimus, are approved for NF1 in Singapore, consensus on their use for NF1-PNs or NF1-MPNSTs was not achieved. Tipifarnib, a farnesyltransferase inhibitor, although well tolerated, did not significantly prolong time to progression in patients with NF1-PN in a phase 2 trial.[28] Another phase 2 study assessed sirolimus in non-progressive NF1-PNs and found that sirolimus did not meaningfully shrink NF1-PNs.[29]

The divergence in expert opinion is likely due to limited and inconsistent efficacy in clinical trials. The observed variability reflects clinical equipoise, differences in expert experience, and ongoing safety concerns. Similar patterns are noted in the Chinese consensus, where these agents are not routinely recommended. Overall, the lack of consensus reflects broader uncer-tainty in the global evidence base, rather than practice variation specific to Singapore.

Strengths and limitations

This study offers several strengths, including a focused design and a multidisciplinary expert panel representing key specialties involved in NF1 management. To the authors' knowledge, this is the first and largest study of its kind in Singapore to examine multiple aspects of NF1 diagnosis and management, achieving a high response rate that reflects strong engagement from the expert community. The use of independent facilitators and anonymous feedback enhanced the rigour and reliability of the process.

However, certain limitations should be acknowledged. First, the purposive, non-random sampling and a relatively small sample size (n=24) may limit generalisability and introduce selection bias. Although experts were selected based on recognised involvement in NF1 management, formal quantitative criteria were not uniformly applied. Second, the absence of patient representatives and primary care physicians may restrict the consideration of patient-centred and real-world perspectives. Third, the analysis was based primarily on agreement proportions without detailed statistical measures, and responses may have been influenced by the interim discussion between survey rounds. In addition, the questionnaire was not formally validated. Finally, the recommendations are based on expert opinion without long-term outcome validation, and their applicability to other settings may require adaptation.

The recommendations were not formally graded by strength (e.g. strong/moderate/weak) as is done in frameworks such as ERN GENTURIS, due to the consensus-based Delphi methodology and lack of systematic evidence synthesis. Future work could incorporate formal evidence grading systems to enhance interpretability and clinical applicability.

CONCLUSION

In this study, consensus was achieved on the key aspects of NF1 diagnosis and management in Singapore. Experts agreed on the role of genetic testing and the importance of multidisciplinary team-guided decision-making for individualised treatment. Surgical resection remains central for NF1-PNs and MPNSTs, with treatment strategies tailored through multidisciplinary team review. Among pharmacological therapies, only MEK inhibitors achieved consensus, supported by evidence demonstrating meaningful tumour reduction and clinical benefit, whereas no consensus was reached for other agents, such as mTOR inhibitors or tipifarnib.

Consensus was also established on age- and risk-adapted surveillance protocols across the lifespan. Overall, these findings align with Chinese and international frameworks in emphasising multidisciplinary team care and lifelong management, while reflecting region-specific adaptations. This consensus provides a pragmatic, context-specific guide for NF1 management in Singapore.

Supplementary materials

Table S1. Search strategy.
Table S2. Statements that achieved consensus in Survey 1.
Table S3. Statements that did not achieve consensus in Survey 1 and achieved/did not achieve consensus in Survey 2.
Fig. S1. Open-ended question 1.
Fig. S2. Open-ended question 2.
Fig. S3. Open-ended question 3.
Fig. S4. Open-ended question 4.
Fig. S5. Open-ended question 5.
Fig. S6. Open-ended question 6.

Ethics statement

This work synthesised expert insights and publicly available literature and did not include patient-level data; therefore, institutional ethics approval was not needed. All experts provided consent to participate in the advisory discussions.

Declaration

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All data generated or analysed during this study are included in this published article and its supplementary information files. Further information is available from the corresponding author upon request.

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Diagnosis and management of haemophagocytic lymphohistiocytosis in adults: A narrative review and practical approach

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ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory state characterised by inappropriate survival of immune cells, cytokine storm, profound cytopenias, and rapidly progressive multi-organ failure. In adults with secondary HLH, the most common triggers include haematological malignancy, autoimmune/autoinflammatory conditions, and infections. In Asian contexts, both malignancy-induced (with higher rates of NK/T-cell lymphoma than B-cell lymphoma) and Epstein-Barr virus-induced HLH are particularly common. Additionally, there is a distinct "Asian" variant of intravascular B-cell lymphoma with no cutaneous manifestations that tends to manifest with HLH and may require random skin biopsies to diagnose. Diagnosis can be supported by the HLH-2004 diagnostic and therapeutic guidelines for haemophagocytic lymphohistiocytosis or the H-score in adult HLH, and subsequent management involves high-dose corticosteroids with targeted immunomodulatory treatments or chemotherapy directed at the underlying condition. In this narrative review article, the authors provide a comprehensive overview of HLH epidemiology, diagnosis, and management strategies with a practical approach for frontline clinicians practising in Asian contexts.

Keywords: Asia, haematology, hyperinflammation, immunosuppressive agents, macrophage activation syndrome, multi-organ failure, rheumatology

CLINICAL IMPACT

What is New

- This review provides a practical clinical approach to patients with suspected haemophagocytic lymphohistiocytosis (HLH) based on clinical assessments, laboratory and bone marrow findings.
- Evidence-based management options based on aetiological classification of HLH are discussed.

Clinical Implications

- Management options for HLH include high-dose corticosteroids, intravenous immunoglobulin, interleukin-1 receptor antagonists, and etoposide.

Vignette:

A 55-year-old Chinese lady was admitted for pyrexia of unknown origin for 3 weeks, associated with a 5 kg weight loss. She had no rashes and no infective, autoimmune, or other systemic symptoms. On admission, she had fluid-refractory hypotension requiring inotropic support in the intensive care unit. Her physical examination was otherwise unremarkable. Laboratory investigations revealed severe pancytopenia (white blood cell 0.9 x 10^9/L, haemoglobin 6.5 g/dL, platelet 16 x 10^9/L), transaminitis (aspartate transaminase 500 U/L, alanine transaminase 720 U/L, alkaline phosphatase 875 IU/L), hyperferritinaemia (ferritin 55,000 ng/mL), hypertriglyceridaemia (4.1 mmol/L) and hypofibrinogenaemia (1.1 g/L). The coagulation panel was normal. The peripheral blood film did not show early cells or features of haemolysis. A whole-body positron-emission tomography-computed tomography scan did not reveal suspicious masses or significant lymphadenopathy. Bone marrow trephine biopsy revealed haemophagocytosis, with no evidence of haematological malignancy. The patient was diagnosed with idiopathic haemophagocytic lymphohistiocytosis (HLH) and treated with intravenous pulsed methylprednisolone. However, in the following days, the patient deteriorated, requiring dual inotropic support and intubation for mechanical ventilation.

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The deterioration was attributed to a systemic hyperinflammatory state, with possible nosocomial pneumonia. Despite supportive and broad-spectrum antimicrobial treatment, she eventually succumbed to her illness. A post-mortem examination was performed, revealing that the patient had intravascular B-cell lymphoma. The case was subsequently presented at a mortality and morbidity meeting, and the team reviewed the literature, which showed an elevated incidence of malignancy-associated HLH in Asian populations (with NK/T-cell more than B-cell lymphoma). Notably, the haemophagocytic subtype of intravascular large B-cell lymphoma, historically termed the "Asian variant", is particularly relevant in Asian populations; it may present without cutaneous involvement and tends to manifest with HLH, which was consistent with the patient's case. In such cases, random skin biopsies could have been helpful for diagnosis. The team also reflected that continued aggressive pursuit of the rare causes of HLH remains necessary even if the standard infective/autoimmune/malignancy workup is unyielding, while being mindful of the potential for immunosuppressive treatment to mask the underlying disease process.

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterised by inappropriate survival and proliferation of cytotoxic T-cells and macrophages/histiocytes, leading to cytokine storm (uncontrolled systemic inflammatory response), haemophagocytosis, and end-organ damage.[1] With the rare exception of familial HLH that is typically seen in the paediatric population, adult patients usually develop HLH in response to underlying infective triggers, occult or known malignancies, or autoimmune conditions. Macrophage activation syndrome (MAS) is considered a subset of secondary HLH that is triggered by underlying autoimmune conditions such as systemic juvenile idiopathic arthritis (sJIA), adult-onset Still's disease (AOSD), or systemic lupus erythematosus (SLE).

Patients with HLH often present clinically with haemodynamic instability, fevers, and even multi-organ failure requiring intensive care. Laboratory investigations may reveal characteristic features of severe hyperferritinaemia, hypofibrinogenaemia, fasting hypertriglyceridaemia, and a hepatocellular pattern of transaminitis. These manifestations of HLH can mimic those of other systemic inflammatory states such as sepsis and systemic inflammatory response syndrome, resulting in HLH being frequently misdiagnosed or diagnosed late. This delay can lead to severe consequences, as timely treatment is crucial to improving patient outcomes.[2] The use of criteria that rely on laboratory tests, many of which have significant overlap with other diseases, poses additional challenges.[3]

In this narrative review article, the authors focus on a practical approach for the diagnosis and management of HLH in the adult population for frontline clinicians (Fig. 1).

METHODS

For the purposes of this narrative review article, the authors performed an updated PubMed search for articles from January 2000 to December 2025 using the following terms in title and abstract searches: "haemophagocytic lymphohistiocytosis" or "hemophagocytic lymphohistiocytosis" or "macrophage activation syndrome" and "adult", and included only articles with full-text availability and article types that were original research, guidelines, or review articles. This yielded 296 articles, which were reviewed alongside the authors' personal libraries of relevant articles on this topic.

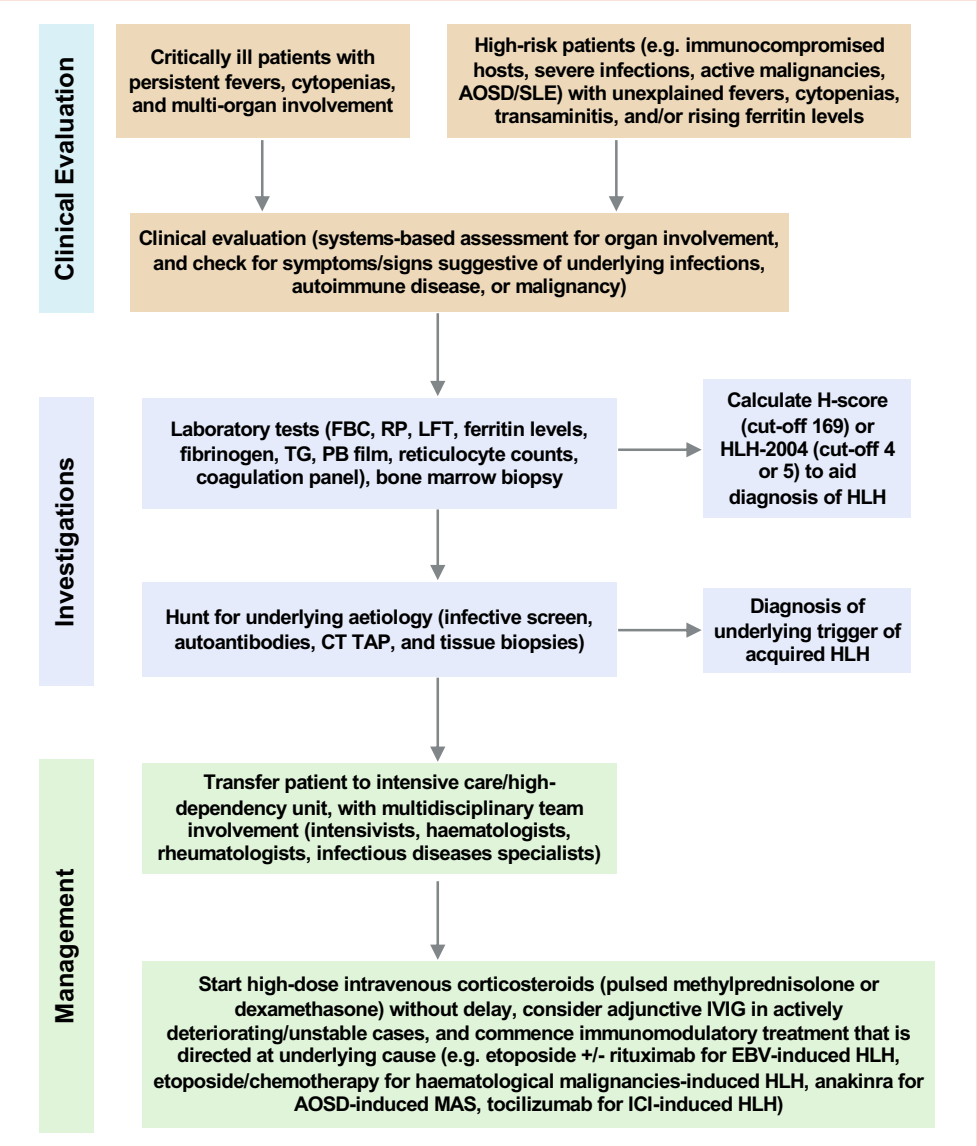
RESULTS

Aetiology and disease pathophysiology

From molecular studies, the current postulation of HLH pathophysiology involves a probable underlying genetic predisposition to cytolytic pathway dysfunction or disruption, such that immune cell apoptosis (immune downregulation) is impaired, culminating in a vicious cycle of CD8+ T-lymphocyte and macrophage activation with cytokine release an overall sustained systemic hyperinflammatory state.[1,4]

HLH can occur in both the paediatric (<18 years) and adult populations, and can be primary or secondary. Primary HLH typically manifests in early childhood due to mutations in genes such as *PRF1, UNC13D, STX11,* and *STXBP2* that disrupt the interactions among natural killer (NK) cells, CD8+ cytotoxic T-cells, and antigen-presenting cells.[1] Consequently, these dysfunctional and deregulated cells produce increased levels of proinflammatory cytokines, causing systemic activation of macrophages and a systemic inflammatory state.[5] Primary HLH can be further classified based on the inheritability of the genetic mutations involved (X-linked, recessive, or dominant), or the clinical syndrome it occurs in, such as Griscelli syndrome.[5] Evidence has emerged of heterozygous mutations causing HLH as well. While most primary forms of HLH require 2 mutated copies (homozygous), a single heterozygous mutation in genes like *RAB27A* can increase the risk of developing secondary HLH or trigger a less common presentation of

Fig. 1. Diagnostic and management algorithm for suspected cases of HLH.



AOSD: adult-onset Still's disease; CT TAP: computed tomography scan of the thorax, abdomen, and pelvis: EBV: Epstein-Barr virus; FBC: full blood count; HLH: haemophagocytic lymphohistiocytosis; ICI: immune checkpoint inhibitor; IVIG: intravenous immuno-globulin; LFT: liver function test; MAS: macrophage activation syndrome; PB film: peripheral blood film; RP: renal panel; SLE: systemic lupus erythematosus Created in BioRender. NG, I. (2025) https://BioRender.com/6qoz30z

primary HLH, especially when combined with other mutations or factors.[6,7] In the absence of a characterised genetic syndrome, such cases of primary HLH are commonly termed familial HLH.

Unlike its paediatric counterpart, adult-onset HLH is secondary to an acquired pathology. From epidemiological studies across the world (the US, Europe, and Asia) of secondary HLH cases in adults, the 3 major causes of HLH are haematological malignancies (29–73%), infections (18–38%), and autoimmune/autoinflammatory conditions (0–21%) (Table 1).[8-15] In Ramos-Casals et al.'s 2014 review of 2197 reported cases of HLH worldwide, it appears that Asian settings (China, South Korea, Japan, and Taiwan) had higher rates of malignancy-triggered HLH than the West (the US and European countries), at approxi-mately 50% versus (vs) 33%.[16] In 2 cohort studies in China, malignancy-induced HLH was the predominant cause (42–46%), and T/NK-cell non-Hodgkin lymphoma outnumbered B-cell lymphoma.[14,15] On the other hand, the proportion of autoimmune-related HLH was similar in both Asian and Caucasian cohorts.[16] Infection remains a common trigger in most developed countries, with Epstein-Barr virus (EBV) being the predominant causative virus in Asia and the US, whereas human immunodeficiency virus (HIV) is more commonly the infective trigger in

European countries.[16] In 2 cohort studies in China, EBV infection was the most commonly identified infective trigger.[14,15] Besides geographical location, there is also heterogeneity in the distribution of adult HLH aetiologies depending on the clinical setting (e.g. acute and critical care, specialist centres).

Iatrogenic causes of HLH are rare but increasingly recognised, ranging from post-transplant (solid organ or haematopoietic stem cell transplant) to drug reaction with eosinophilia and systemic symptoms (DRESS) and, most recently, chimeric antigen receptor T-cell (CAR-T)/bispecific T-cell engager (BiTE)/immune checkpoint inhibitor (ICI)-associated HLH.[4,16-19] In the absence of known primary HLH-associated genetic mutations that can, by themselves, lead to HLH manifestations, an acquired "trigger" (infection, malignancy, autoimmune disease, and/or drugs) is often required to set off this hyperinflammatory state.[1,4] Additionally, it is not uncommon to have patients with no identifiable cause of secondary HLH, with nearly 1 in 5 cases labelled as "idiopathic".[20]

In adult HLH, a third of cases have more than 1 identified aetiology, for example, haematological malignancy or autoimmune disease with superimposed infection.[16] Brisse's threshold model best illustrates the current understanding of adult secondary HLH, which posits that endogenous components (genetic predisposition) and exogenous components (e.g. immunocompromised state, infective triggers, malignancy) are required to collectively tip the patient over a "threshold" beyond which fulminant HLH occurs.[1,17]

Clinical approach to identifying and diagnosing HLH

Clinicians should have a low threshold to evaluate for HLH in patients with pyrexia of unknown origin, as well as critically ill patients with fever, cytopenias involving 2 or more cell lines, and evidence of multi-organ involvement. Patients with HLH may present insidiously[4]; therefore, close monitoring for evolving HLH is warranted in high-risk patients, such as those with a known immunosuppressed state, severe infections, active malignancies, or associated auto-immune conditions (AOSD or SLE), who develop unexplained fevers, cytopenias, transaminitis, or rising ferritin levels, even if they appear clinically "well" or stable.

Patients with HLH can present with a myriad of multisystemic clinical manifestations related to the hyperinflammatory state/sequelae and/or underlying condition. These may include persistent unremitting fevers; haemodynamic instability (e.g. due to third-

Table 1. Aetiologies of secondary HLH in adults.

Categories	Description
Infections	• Viruses: human herpes viruses (EBV [predominant in Asia and US[16]], CMV, HSV, VZV), HIV (predominant in Europe[16]), parvovirus B19, hepatitis viruses, HHV-6/8, influenza, dengue, COVID-19, Ebola virus • Bacterial: *S. aureus, S. pneumoniae, H. influenzae, E. coli, Salmonella spp., Klebsiella spp.,* mycoplasma, *Mycobacterium spp.* (both tuberculous [predominant[16]] and non-tuberculous), *Rickettsia spp.* • Fungal: *Candida, Histoplasma, Cryptococcus* • Parasitic: *Leishmania spp., Plasmodium spp., Toxoplasma spp., Babesia spp., Pneumocystis jirovecii*
Malignancy	• Haematological malignancies (most common): lymphoma (especially non-Hodgkin lymphoma), leukaemia • Solid organ malignancies
Autoimmune/autoinflammatory	• Adult-onset Still's disease • Systemic lupus erythematosus • Rheumatoid arthritis (rare) • Systemic vasculitides (rare) • Inflammatory bowel disease
Iatrogenic (drugs/therapy-related)	• Immune-checkpoint inhibitor therapy (e.g. anti-programmed cell death receptor 1 [PD-1], programmed cell death ligand 1 [PD-L1], and cytotoxic T lymphocyte-associated antigen 4 [CTLA-4] inhibitors) • CAR-T therapy • Drug reaction with eosinophilia and systemic symptoms (DRESS) (commonly implicated drugs include antibiotics, aspirin and other non-steroidal anti-inflammatory drugs, anticonvulsants [e.g. carbamazepine, lamotrigine], allopurinol) • Post-transplant (solid organ, haematopoietic stem cell transplant)

CAR-T: chimeric antigen receptor T-cell; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HIV: human immunodeficiency virus; HLH: haemophagocytic lymphohistiocytosis; HSV: herpes simplex virus; VZV: varicella-zoster virus

Malignancy-associated HLH (especially aggressive T/NK-cell lymphomas) and EBV-associated HLH are particularly common in Asian contexts.

spacing from vasodilatory state or hypoalbuminaemia); neurological symptoms (e.g. confusion, ataxia, seizures, headaches, irritability); non-specific gastrointestinal symptoms (e.g. nausea/vomiting, abdominal pain, diarrhoea); hepatosplenomegaly; lymphadenopathy; as well as evidence of underlying cytopenias (manifesting as symptoms/signs of anaemia, bleeding diatheses from thrombocytopenia); liver dysfunction (manifesting as jaundice, altered mentation due to hepatic encephalopathy, and coagulopathy); renal dysfunction (with acute kidney injury potentially requiring renal replacement therapy); and/or acute respiratory distress syndrome (manifesting as respiratory failure).[4,17]

In patients with clinical manifestations suggestive of HLH, it is important to evaluate for clinical clues that may suggest underlying infections, rheumatic conditions, malignancy, and iatrogenic causes. For instance, clinicians should elicit infectious symptoms/signs such as respiratory symptoms (cough, rhinorrhoea, sore throat, breathlessness or pleuritic chest pain); gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhoea); urinary tract symptoms (dysuria, urinary frequency and urgency, foul-smelling urine, haematuria); and skin rashes. Predisposing history and risk factors should also be elicited, including the presence of a known immunocompromised state (e.g. history of human immunodeficiency virus infection, or use of immunosuppressants); positive sick contacts; travel history; and high-risk sexual behaviours and exposures. In addition, to evaluate for associated autoimmune conditions, clinicians should assess for quotidian fevers, salmon-pink evanescent rashes and/or arthralgias/arthritis that wax and wane with fever, sore throat, clinical evidence of serositis (pleuritic chest pains, pleural effusions), hepatosplenomegaly, and/or lymphadenopathy, which may be seen in AOSD, and evaluate for symptoms/signs of connective tissue disease including inflammatory arthritis, alopecia, eye pain/redness, oral ulcers, malar rash or photosensitivity, sicca symptoms, Raynaud's phenomenon, vasculitic rashes or cutaneous manifestations of SLE. Likewise, assess for B-symptoms (fever, night sweats, significant loss of appetite/weight) and generalised lymphadenopathy, which may be seen in lymphomas. It is equally important to review patients' medication records to look for potential drug triggers associated with DRESS (these patients may also have eosinophilia and rashes). It is crucial to perform a review of drug history, and for patients with known cancers, the recent treatment history of immune checkpoint inhibitors or CAR-T therapies.

In all suspected cases of HLH, laboratory tests including full blood count, liver and renal function tests, serum ferritin levels, fibrinogen, fasting triglyceride (TG), peripheral blood film and reticulocyte counts, haemolytic screen (haptoglobin, lactate dehydrogenase [LDH], and indirect bilirubin), coagulation panel, and/or specialised biomarkers (soluble CD25, CD163, NK cell activity, cytokine panel) should be performed (Table 2).[24] Although measurement of fasting triglyceride levels is suggested in conventional HLH criteria,[21] it may not be practical in acutely ill patients. Non-fasting lipids are increasingly accepted in guidelines on routine cholesterol screening and cardiovascular risk prediction[25]; however, the accuracy of non-fasting lipids in HLH criteria remains to be established. As with other biochemical markers, TG should not be interpreted in isolation and is neither specific nor sensitive on its own to predict HLH. For instance, a recent study found that hypertriglyceridaemia was a common metabolic sequela that persisted in 1 in 5 intensive care unit patients even 3 months after their discharge.[26] Although immune biomarkers such as those assessing T/NK-cell activity have increasingly been described, their use in routine clinical practice remains limited by cost considerations and lack of widespread test availability.[24] Serum ferritin is an excellent screening biomarker: levels <500 μg/L have a 94% sensitivity in ruling out HLH,[22] and very high levels (>10,000 μg/L) are highly suggestive of the diagnosis in paediatric HLH.[23] However, extreme elevation of ferritin levels has lower diagnostic specificity in adults, in whom sepsis, liver failure, adult-onset Still's disease and malignancy can also produce extreme hyperferritinaemia. Of note, C-reactive protein is typically elevated but lacks diagnostic specificity and can be blunted when interleukin (IL)-6 inhibitor therapy is used, whereas erythrocyte sedimentation rate (ESR) can be spuriously normal due to hypofibrinogenaemia in HLH.[4,20]

Bone marrow aspirate and trephine biopsy were traditionally considered to be important in the diagnostic evaluation of suspected HLH, in part due to their stated role in the original HLH diagnostic criteria. The utility of bone marrow evaluation is primarily to look for histopathological evidence of haemophagocytosis. However, bone marrow haemophagocytosis has poor sensitivity and specificity: it is absent in up to 40% of HLH patients because it appears late, and it can also occur secondary to infection, autoimmune disease, marrow failure, and transfusion.[4,21,27]

To facilitate the diagnosis of HLH, 3 sets of main criteria can be used: the HLH-2004 criteria[22] (originally developed for diagnosis of primary/familial HLH, revised in 2024[1,28]), H-score[8] (developed for use in adult patients with secondary HLH), and European Alliance of Associations for Rheumatology/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation 2016 MAS classification criteria[30] (originally developed for use in MAS secondary to sJIA, and subsequently validated in

Table 2. Key investigations in suspected cases of secondary HLH in adults.

Test	Description
Full blood count	• To evaluate for cytopenias (typically 2 or more cell lines involved; due to cytokine storm-mediated bone marrow suppression and haemophagocytosis) ◦ Laboratory reference ranges for full blood count in National University Hospital, Singapore: white blood cell 4.3–10.4x10^9/L (males and females); haemoglobin 13.1–16.8 g/dL (males)/11.5–14.9 g/dL (females); platelets 150–410x10^9/L (males and females) ◦ Cytopenias defined in HLH-2004 criteria[22] as such: haemoglobin <9 g/dL, platelets <100x10^9/L, neutrophils <1x10^9/L ◦ Severe cytopenias defined as such: white blood cell <1.5x10^9/L, absolute neutrophil count <0.5x10^9/L, haemoglobin <7 g/dL, platelets <50x10^9/L • To look for eosinophilia (which may suggest DRESS, connective tissue disorder or certain haematological neoplasms)
C-reactive protein/erythrocyte sedimentation rate	• Typically elevated CRP (but not specific for HLH), may have paradoxically low/normal ESR (due to low fibrinogen)
Renal panel	• To assess for elevated serum creatinine (acute kidney injury)
Liver panel	• To assess for hepatocellular pattern of transaminitis (due to cytokine-mediated hepatocellular injury), hypoalbuminaemia (negative acute phase reactant)
Ferritin levels	• Typically elevated (due to increased liver production and macrophage activation) ◦ <500 µg/L has a 94% sensitivity in ruling out HLH[25] ◦ Very high levels (>10,000 µg/L) are highly suggestive of the diagnosis in paediatric HLH[26]
Fibrinogen	• Hypofibrinogenaemia is common (due to pro-coagulant processes that consume fibrinogen, and cytokine-mediated fibrinogen breakdown) ◦ Laboratory reference range in National University Hospital, Singapore: 2.18–4.6 g/L ◦ Cut-off <2.5 g/L used in H-score[8] and ≤1.5 g/L used in HLH-2004 criteria[22] ◦ Severe hypofibrinogenaemia <0.5 g/L
Lactate dehydrogenase	• Usually elevated (due to cytotoxic sequelae)[8]
Coagulation panel	• To assess for coagulopathy (which could be related to liver dysfunction or concurrent disseminated intravascular coagulation; if present, should warrant sending off D-dimer as well)
Triglycerides	• Usually elevated, cut-off ≥1.5 mmol/L used in H-score[8], 3 mmol/L used in HLH-2004 criteria[22]
Hepatitis B/C/HIV, EBV/CMV/VZV/HSV, HHV-6/8, parvovirus B19, dengue serology, mycoplasma serology, respiratory viral swab, blood cultures, urine cultures	• Evaluation of common infections that are reported to be associated with HLH/MAS
Autoantibodies (antinuclear antibodies, anti-double-stranded DNA, complement C3/C4, rheumatoid factor, anti-cyclic citrullinated peptide, antineutrophil cytoplasmic antibodies)	• Evaluation of rheumatic conditions associated with HLH/MAS
CT scan of the neck, thorax, abdomen and pelvis or positron-emission tomography-CT whole body	• To look for suspicious masses/collections (that may suggest occult malignancy/infections), hepatosplenomegaly, lymphadenopathy (which may be amenable to biopsy), vascular abnormalities (e.g. in vasculitis or intravascular lymphoma)
Magnetic resonance imaging of the brain	• In patients with neurological symptoms/signs, may reveal white/grey matter inflammation, or leptomeningeal enhancement
Lumbar puncture	• In patients with neurological symptoms/signs, may reveal cerebrospinal fluid pleocytosis and high protein (suggesting central nervous system inflammation)
Bone marrow aspirate and trephine biopsy	• To evaluate for histopathological evidence of haemophagocytosis, as well as assess for evidence of myelo/lymphoproliferative disease
Biopsy of affected tissue (e.g. lymph node, liver, spleen, lung, skin)	• For diagnostic evaluation – both to identify histopathological evidence of haemophagocytosis (in liver, spleen, lymph nodes), and to assess for occult malignancies (e.g. random skin biopsies to detect intravascular large B-cell lymphoma in Asian patients)

CMV: cytomegalovirus; CRP: C-reactive protein; CT: computed tomography; DNA: deoxyribonucleic acid; DRESS: drug reaction with eosinophilia and systemic symptoms; EBV: Epstein-Barr virus; ESR: erythrocyte sedimentation rate; HIV: human immunodeficiency virus; HLH: haemophagocytic lymphohistiocytosis; HLH-2004: HLH-2004 diagnostic and therapeutic guidelines for haemophagocytic lymphohistiocytosis; HSV: herpes simplex virus; MAS: macrophage activation syndrome; VZV: varicella-zoster virus

adult patients with AOSD[30]) (Table 3). While the HLH-2004[22] and HLH-2024[28] criteria are often extrapolated for use in adult HLH, it must be recognised that their reportedly high sensitivity/specificity were derived from their performance in the original derivation cohort of paediatric familial HLH, and when the HLH-2004 criteria were applied to adult validation cohorts, their diagnostic accuracy was lower.[31,32] Recently, Lachmann et al. performed a multicentre validation study of the HLH-2004 criteria, HLH-2024 criteria, and the H-score across 13 international secondary-HLH cohorts comprising both adult and paediatric patients. They found that the best-performing diagnostic criteria were the original HLH-2004 criteria (using decreased cut-off ≥4) (mean sensitivity 87%, mean specificity 86%), followed by HLH-2024 criteria (using decreased cut-off ≥4) (mean sensitivity 84%, mean specificity 88%), and then H-score (using cut-off ≥169) (mean sensitivity 82%, mean specificity 88%).[25] On subgroup analysis of only intensive care unit patients, all 3 models demonstrated good diagnostic performance.[25] For screening purposes, the authors found that a ferritin cut-off of 500 µg/L had 94% mean sensitivity in all cohorts to rule out secondary HLH.[25] Bilston et al.'s 2022 multicentre study of adult HLH patients found that the HLH-2004 criteria (using cut-off ≥5) were more specific (93% versus [vs] 71%), but less sensitive (91% vs 96%) than H-score (using cut-off ≥169).[31] In general, HLH-2004 performed better than the H-score for most aetiologies, with the exception of autoimmune and inflammatory aetiologies, for which the H-score had better sensitivity.[31] In post-haematopoietic stem cell transplant recipients, a higher optimal H-score cut-off ≥233 was reported, due to a higher probability of presenting with post-transplant manifestations of fever, cytopenias, splenomegaly and systemic inflammatory response syndrome, which overlap with HLH criteria.[31]

In recent years, there have also been various criteria developed to assess for immune effector cell-associated haemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), a severe form of haemotoxicity post-CAR T-cell therapy, including the MD Anderson 2018 criteria,[33] the European Society for Blood and Marrow Transplantation (EBMT)/Joint Accreditation Committee of the International Society for Cell and Gene Therapy (ISCT) and EBMT/European Hematology Association 2022 best practice recommendations,[34] and the IEC-HS 2023 criteria.[35]

In adults with undifferentiated HLH, the H-score offers a convenient, calculator-supported estimate of probability for clinicians, but it should be interpreted alongside the HLH-2004/HLH-2024 criteria; of note, its specificity is lower and diagnostic performance varies based on the cohort profile and underlying aetiology, so no single tool replaces clinical judgement and an active search for the trigger. The H-score (conventional cut-off ≥169) comprises important constituent items including underlying immunosuppressed state, fever, presence of hepatosplenomegaly, cytopenias, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, and elevated aspartate transaminase levels, as well as bone marrow evidence of haemophagocytosis.[8]

The extent and sequence of aetiological workup should be based on clinical suspicion of underlying aetiology, patients' preferences and goals of care, and resource availability or cost considerations. In general, an infective workup could include serologies for EBV, herpes simplex virus, varicella-zoster virus, and human immunodeficiency virus, as well as a dengue screen, COVID-19/respiratory viral swabs, mycoplasma serology, and other specific microbiological or serological tests for bacterial, fungal, and/or parasitic infections, depending on the index of clinical suspicion. Antinuclear antibodies, anti-double-stranded DNA, complement C3/C4, and/or rheumatoid factor/anti-cyclic citrullinated peptide, or antineutrophil cytoplasmic antibodies could be evaluated for the possibility of connective tissue diseases. A computed tomography (CT) scan of the neck, thorax, abdomen, and pelvis, or even a positron-emission tomography-CT scan, could be performed to look for evidence of occult malignancies, organomegaly, lymphadenopathy, infected collections, or even vessel wall abnormalities, which may suggest intravascular lymphoma or vasculitis. Bone marrow evaluation is also helpful to look for signs of haematological malignancies (lymphoma, leukaemia). Besides bone marrow evaluation, biopsy of affected/abnormal tissues (identified clinically or on imaging modalities) may help with the diagnosis of the underlying condition,[4] such as excisional lymph node biopsy to evaluate for underlying lymphoma, or bronchoalveolar lavage/transbronchial lung biopsy or liver biopsy to exclude infections and malignancies. In particular, there is a highly fatal yet highly elusive form of lymphoma known as intravascular large B-cell lymphoma, which can present with a haemophagocytic variant in Asian populations characterised by fevers, hepatosplenomegaly, thrombocytopenia, and bone marrow involvement with non-neoplastic haemophagocytic histiocytes.[36] If left undiagnosed or untreated, it is highly aggressive with a median survival time of 2–8 months.[36] Although this subtype of intravascular lymphoma often has no obvious cutaneous involvement, limited evidence has shown that random skin biopsies (RSBs) may be helpful to diagnose this insidious entity, especially in Asian patients with a high-risk phenotype (pyrexia of unknown origin, diagnosed HLH, thrombocytopenia, and markedly elevated LDH).[37] RSBs (either incisional or telescopic punch biopsies) should be performed over 3 or 4 different anatomical sites, usually over the

Table 3. Key HLH diagnostic criteria.

	HLH-2004 criteria[22]	HLH-2024 criteria[28]	H-score for secondary adult HLH (2014)[8]	EULAR/ACR/PRINTO (2016) MAS criteria[29]
Diagnostic criteria	Presence of either (A) Molecular diagnosis consistent with familial HLH; or (B) ≥4–5 of the following: - Fever ≥38.5°C - Splenomegaly (≥2 cm below the costal margin) - Cytopenias of ≥2 peripheral blood lineages (haemoglobin <9 g/dL, platelets <100x10^9/L, neutrophils <1x10^9/L) - Fasting triglycerides ≥3 mmol/L and/or fibrinogen ≤1.5 g/L - Ferritin levels ≥500 µg/L - Low/absent natural killer cell activity - Soluble CD25 levels ≥2400 U/mL - Haemophagocytosis in bone marrow, spleen, lymph node, or liver	Presence of either (A) Molecular diagnosis consistent with familial HLH in a patient with suggestive clinical symptoms/signs; or (B) Functional cellular findings consistent with familial HLH in a patient with suggestive clinical symptoms/signs; or (C) ≥4–5 of the following: - Fever ≥38.5°C - Splenomegaly (≥2 cm below the costal margin) - Cytopenias of ≥2 peripheral blood lineages (Hb <9 g/dL, platelets <100x109/L, neutrophils <1x109/L) - Fasting triglycerides ≥3 mmol/L and/or fibrinogen ≤1.5 g/L - Ferritin levels ≥500 µg/L - Soluble CD25 levels ≥2400 U/mL - Haemophagocytosis in bone marrow, spleen, lymph node, or liver Removal of NK cell activity from HLH-2004 criteria	Calculate H-score (proposed cut-off value of 169) based on the following parameters: - Underlying immunosuppressed state (e.g. HIV, or long-term immunosuppressant therapy such as glucocorticoid, cyclosporine, azathioprine): absent or present - Fever (°C): <38.4, 38.4–39.4, or >39.4 - Organomegaly: none, hepatomegaly OR splenomegaly, or hepatomegaly and splenomegaly - Cytopenias: 1 lineage, 2 lineages, or 3 lineages - Ferritin (µg/L): <2000, 2000–6000, or >6000 - Fasting triglycerides (mmol/L): <1.5, 1.5–4, >4 - Fibrinogen (g/L): ≥2.5 or <2.5 - Aspartate transaminase (IU/L): ≥30 or <30 - Haemophagocytosis in bone marrow: absent or present	In a patient with known or suspected systemic juvenile idiopathic arthritis, diagnosis can be made if there is fever, ferritin level >684 µg/L, and ≥2 of the following: - Platelet ≤181x109/L - Aspartate transaminase >48 U/L - Fasting triglycerides >1.76 mmol/L - Fibrinogen ≤3.6 g/L
Usage	Originally developed for use in patients with primary familial HLH, but with extended usage in secondary adult HLH based on external validation studies		Developed for use in adult patients with secondary HLH	Developed for use in MAS secondary to systemic juvenile idiopathic arthritis, but subsequently validated in MAS secondary to adult-onset Still's disease
Efficacy (in specific derivation cohorts)	Familial HLH: 99% sensitivity, 97.1% specificity (for cut-off ≥5)[28] Adult HLH: 91% sensitivity, 93% specificity (for cut-off ≥5)[31] Critically ill adult HLH: 73–93% sensitivity, 95–99% specificity (for cut-off ≥5)[31,32] Secondary HLH patients (both adults and children): 87% sensitivity, 86% specificity (for cut-off ≥4)[25]	Familial HLH: 96.2% sensitivity, 99.5% specificity (for cut-off ≥5)[28] Critically ill HLH patients (both adults and children): 84% sensitivity, 88% specificity (for cut-off ≥4)[25]	Adult HLH: 93–96% sensitivity, 71–86% specificity (for H-score ≥169)[8,31] Critically ill adult HLH: 98% sensitivity, 83% specificity (for H-score ≥169)[8,31] Secondary HLH patients (both adults and children): 82% sensitivity, 88% specificity (for H-score ≥169)[25]	Systemic juvenile idiopathic arthritis (paediatric): 73% sensitivity, 99% specificity[30] Adult-onset Still's disease: 100% sensitivity, 70% specificity[44]

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; HLH: haemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome; PRINTO: Paediatric Rheumatology International Trials Organisation

Performance figures for HLH-2004/HLH-2024 were derived from paediatric familial-HLH case-control databases tested against severe infection and systemic juvenile idiopathic arthritis; accuracy in adult secondary HLH is likely to be lower.

thigh, posterior arm, and abdominal wall, as well as cherry angiomas if they are present.[38] While life-saving immunosuppressive treatment should not be unduly delayed, when possible, it is preferable for PET-CT scans and tissue biopsies to be performed prior to initiation of high-dose glucocorticoids, which have the potential to reduce diagnostic yield, especially in the context of steroid-sensitive lymphomas.

Management strategies for HLH

Management of patients with HLH involves supportive care in a high-dependency or intensive care unit, with multidisciplinary team involvement usually comprising intensivists, haematologists, rheumatologists, and infectious disease specialists.

Initial immunomodulatory treatment for all HLH cases (Table 4) typically involves high-dose glucocorticoids in the form of either intravenous "pulsed" methylprednisolone (500 mg–1 g/day for 3–5 days) followed by maintenance prednisolone (1 mg/kg/day) on a tapering regimen, or a dexamethasone regimen based on the HLH-94 regimen (10 mg/m^2 for 2 weeks, 5 mg/m^2 for 2 weeks, 2.5 mg/m^2 for 2 weeks, 1.25 mg/m^2 for 1 week, then taper off by week 8).[39] Of note, dexamethasone may be the preferred option in patients with central nervous system (CNS) involvement due to better CNS penetration.[27] Intravenous immunoglobulin (1 g/kg/day for 2 days, which can be repeated after 2 weeks) may be considered as an adjunctive "bridging" treatment option for deteriorating or unstable patients.[19,21]

The choice of treatment depends on the suspected underlying trigger. Infection-associated HLH requires prompt initiation of antimicrobial treatment. Speci-

Table 4. Common treatment options for HLH.

Treatment	Mechanism of action	Indication	Common dosage	Important adverse effects/ monitoring required
IV "pulsed" methylprednisolone	Glucocorticoids	MAS	Up to 1 g/day for 3–5 days[1]	Hyperglycaemia/diabetes, metabolic side effects, weight gain, osteoporosis (long-term), avascular necrosis (long-term), cataracts/glaucoma (long-term), adrenal insufficiency (long-term), mood/behaviour changes (e.g. hyperactivity, insomnia), consider PJP (cotrimoxazole) prophylaxis and hepatitis B (entecavir) prophylaxis (anti-HBc positivity) if using equivalent to prednisolone ≥20 mg/day for ≥1 month
IV/PO dexamethasone		Secondary HLH other than MAS	10 mg/m^2 for 2 weeks, 5 mg/m^2 for 2 weeks, 2.5 mg/m^2 for 2 weeks, 1.25 mg/m^2 for 1 week, then taper off by week 8 (HLH-94 regimen)[39]	
Intravenous immunoglobulin (IVIG)	Multimodal immunomodulatory effects	As initial bridging therapy in actively deteriorating/unstable patients	1 g/kg/day for 2 days[27] (can repeat after 14 days)	Allergy, anaphylaxis (IgA-deficient patients may be predisposed to anaphylaxis in older IgA-containing IVIG preparations), or infusion reactions, caution in renal impairment (avoid sucrose-containing IVIG preparations), beware of pseudohyponatraemia, transient cytopenias (rarely haemolysis), fluid overload (in heart failure or renally impaired patients), increased thromboembolic risk, risk of blood-borne infections
SC anakinra (IV route can be used off-label; limited availability in public hospitals)	IL-1 receptor antagonist	MAS	2–6 mg/kg/day, up to 10 mg/kg/day in divided doses[19] (maximum 100 mg per dose[27])	Injection site reaction, infection risk (bacterial)
IV etoposide	DNA topoisomerase II inhibitor	Malignancy-associated HLH, EBV-associated HLH, and for refractory MAS and other secondary HLH	Either 150 mg/m^2 HLH-94 regimen[39] or 100 mg/m^2 when combined with doxorubicin and methylprednisolone in the DEP regimen[40,41] (Renal/liver dose adjustment is required.)	Infusion reactions, gastrointestinal side effects, alopecia, myelosuppression, secondary malignancies (e.g. leukaemia)

IV/PO cyclosporine	Calcineurin inhibitor	MAS	3–7 mg/kg/day in 2 divided doses (IV) or 3–5 mg/kg/day in 2 divided doses (PO)[27]	Hirsutism (cyclosporine), gingival hypertrophy (cyclosporine), gastrointestinal side effects, neurotoxicity (headache/seizures, tremors, neuropathy), acute tubular nephropathy, metabolic side effects (diabetes, hyperlipidaemia, gout), increased infection risk (viral—e.g. CMV, EBV, bacterial, fungal infections); consider checking trough levels (pre-third dose cyclosporine trough 50–100 ng/ml, tacrolimus trough <20 ng/mL[27])
PO tacrolimus	Calcineurin inhibitor	Alternative to cyclosporine for MAS	0.1 mg/kg/day in 2 divided doses[27]	
IV emapalumab (Limited availability in public hospitals)	IFN-γ antagonist	Refractory or recurrent primary HLH, and MAS secondary to AOSD/sJIA	6 mg/kg/day for day 1, then 3 mg/kg/day every 3–4 days (can increase up to 10 mg/kg per 3 days for inadequate response)[27]	Infusion reactions, increased infection risk (especially TB, CMV, VZV, bacterial, PJP), consider antiviral (valacyclovir), PJP (cotrimoxazole), antifungal (fluconazole) prophylaxis[27]; can monitor CXCL9 to confirm functional IFN-γ blockade[27]
IV rituximab	Anti-CD20 monoclonal antibody	Adjunctive treatment in EBV-associated HLH, core component of immunochemotherapy in lymphoma-associated HLH, possible role as salvage therapy in MAS	375 mg/m^2/dose, weekly, for 2–4 weeks[27]	Infusion reactions, gastrointestinal side effects, cytopenias/neutropenia, hypogammaglobulinaemia, increased infection risk (especially hepatitis B virus, CMV, HSV, JC virus, COVID, bacterial, PJP) [consider PJP (cotrimoxazole) prophylaxis and hepatitis B (entecavir) prophylaxis for all anti-HBc positive patients]
PO ruxolitinib	JAK-1/2 inhibitor	Salvage therapy	Start at 10 mg BD, uptitrate to maximum 25 mg BD[27]	Gastrointestinal side effects, flu-like symptoms, hyperlipidaemia, increased risk of venous thromboembolism, increased risk of infections (especially VZV)

AOSD: adult-onset Still's disease; CMV: cytomegalovirus; DNA: deoxyribonucleic acid; EBV: Epstein-Barr virus; HLH: haemophagocytic lymphohistiocytosis; HSV: herpes simplex virus; IFN: interferon; IV: intravenous; IVIG: intravenous immunoglobulin; JAK: Janus kinase; JC: John Cunningham; MAS: macrophage activation syndrome; PO: per os (by mouth); PJP: *Pneumocystis jirovecii*; SC: subcutaneous; sJIA: systemic juvenile idiopathic arthritis; TB: tuberculosis; VZV: varicella-zoster virus

Etoposide requires dose reduction for renal/hepatic impairment and cytopenias (frequently present in HLH) and carries infection and secondary-malignancy risk.

fically, in patients with EBV-associated HLH, rituximab can reduce the EBV-infected B-cell reservoir and is a useful adjunct, but etoposide-based therapy remains the backbone for high-risk or refractory disease, especially as EBV typically resides in T/NK compartments.[40,41] For patients with MAS secondary to AOSD, IL-1 receptor antagonist (anakinra), calcineurin inhibitor (cyclosporine), and/or interferon (IFN)-γ inhibitor (emapalumab) should be considered.[42] For MAS secondary to other rheumatic diseases, guideline-directed therapeutic options for severe/life-threatening manifestations can be considered, for instance, cyclophosphamide or rituximab, on top of hydroxychloroquine in SLE.[43] Refractory MAS may be treated with etoposide.[19] For patients with malignancy, definitive chemotherapeutic or other forms of treatment should be commenced as soon as the patient is stabilised, as malignancy-associated HLH will continue to recur if the underlying malignancy remains active. Nonetheless, the exact timing at which cancer treatment (which is also highly immunosuppressive) should be commenced depends on the clinician's experience and patient contextual factors. In general, the prognosis of malignancy-associated HLH is the worst across all HLH aetiological subtypes, associated with all-cause mortality exceeding 50%.[27] Lastly, for CAR-T/BiTE/ICI-induced HLH, IL-6 receptor antagonist (tocilizumab) and etoposide can be used.[19]

In terms of salvage therapies for refractory HLH, multiple agents have been described, ranging from Janus kinase inhibitors (ruxolitinib), anti-CD52 (alemtuzumab), IFN-γ antagonist (emapalumab), to combination chemo-therapy regimens, plasmapheresis, and splenectomy, with allogeneic haematopoietic stem cell transplantation considered for high-risk haematological malignancies or relapsed disease following salvage treatment.[19,27]

CONCLUSION

HLH is a life-threatening hyperinflammatory syndrome that can complicate infections, autoimmune conditions, and malignancies in adult patients. Diagnosis is often challenging due to non-specific symptoms and laboratory results. Timely diagnosis requires a high index of clinical suspicion and a practical approach for evaluating suspected cases to identify the underlying triggering condition and to promptly initiate immunomodulatory treatment.

Ethics statement

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

Declaration

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Fear of cancer recurrence in caregivers of paediatric cancer survivors in Singapore

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Dear Editor,

More children now survive cancer, and their parents often continue to fear that the disease will return.[1] Fear of cancer recurrence (FCR) is a common unmet need in survivorship, but most studies measure it in survivors rather than caregivers. In a recent meta-analysis, caregivers reported similar levels of FCR to those of survivors, with about half of the caregivers experiencing clinically significant FCR, which was associated with depression and anxiety.[2] In paediatric cancer, these caregivers are usually parents. About half of the caregivers also reported dysfunctional fear of progression years after treatment ends,[3] and about one-third of adult childhood-cancer survivors still reported clinically significant FCR decades after the end of treatment.[4] Separate parent and child versions of the FCR Inventory now exist to evaluate the multidimensional aspects of fear, worry, and preoccupation regarding cancer recurrence or progression, reflecting its clinical relevance.[5]

In Singapore, FCR has been documented in adult survivors (43.6% clinical, 32.1% severe).[6] The authors are not aware of any study describing FCR in caregivers of paediatric cancer survivors in Singapore or elsewhere in Southeast Asia.[7] In this community-based Singapore sample, the authors aimed primarily to describe the magnitude and content of FCR among caregivers of paediatric cancer survivors. As a secondary, exploratory observation, the authors also examined whether FCR appeared to differ by time elapsed since the child completed treatment, while recognising that the cross-sectional design cannot establish how fear evolves over time within an individual caregiver.

This was a cross-sectional survey of caregivers of paediatric cancer survivors, carried out between March and April 2023 through Ain Society's Young Heroes Cancer Care, a community-based organisation in Singapore. Eligible participants were parents of children treated for cancer. The authors invited all eligible caregivers reachable during this period. Among 50 caregivers approached, 30 (60%) took part. Researchers with no conflict of interest administered the survey in person, clarified items, and checked each form to ensure there were no missing data. The survey covered demographics, the Fear of Cancer Recurrence Inventory-caregiver version (FCRI-c), and a self-developed risk-factor questionnaire.

The authors scored the 42-item FCRI-c using its original 7-factor structure,[8] with item 13 reverse-scored and total scores ranging from 0 to 172. The Severity subscale also serves as the FCRI Short Form, where a score of ≥13 indicates clinically significant FCR and ≥22 indicates high-specificity clinical FCR.[9] Caregivers were grouped according to the time since the child's last treatment, using a 5-year long-term-survivor threshold: ≤5 years (Group 1: n=18; 3.1 ± 1.6 years) and >5 years (Group 2: n=12; 9.3 ± 3.1 years; range, 5.1–17.0 years) (Table 1). Caregivers reported this in various formats, which the authors converted to elapsed years. Data were analysed using independent-samples t-tests. No a priori sample-size calculation was performed; the sample was simply the caregivers reachable through 1 organisation. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary Annex S1).

The 2 groups did not differ significantly on age, sex, or educational qualification (all $P>0.05$). No clinical data on the child's cancer (e.g. malignancy type, stage, treatment, complications, or secondary malignancy) were collected.

FCR was common among the caregivers. Overall, 96.7% of caregivers scored above the FCRI Short

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Table 1. Demographic characteristics and between-group FCRI-c comparisons (n=30).

Variables	Group 1: ≤5 years (n=18)	Group 2: >5 years (n=12)	*P* value
Age, mean ± SD, years	45.50 ± 8.43	46.92 ± 8.41	0.655
Female, no. (%)	11 (61%)	9 (75%)	-
Male, no. (%)	7 (39%)	3 (25%)	-
Tertiary education, no. (%)	6 (33%)	5 (42%)	0.712
Time since treatment, mean ± SD, years	3.1 ± 1.6	9.3 ± 3.1	-
Triggers, mean ± SD (maximum 32)	23.33 ± 4.13	19.00 ± 4.97	0.039
Severity, mean ± SD (maximum 36)	22.14 ± 4.34	19.22 ± 6.00	0.212
Psychological distress, mean ± SD (maximum 16)	9.76 ± 3.74	8.33 ± 4.42	0.411
Functioning impairments, mean ± SD (maximum 24)	13.90 ± 6.33	12.00 ± 7.31	0.508
Insight, mean ± SD (maximum 12)	7.14 ± 2.69	4.89 ± 3.72	0.127
Reassurance, mean ± SD (maximum 12)	8.81 ± 2.91	7.22 ± 4.21	0.323
Coping strategies, mean ± SD (maximum 40)	26.43 ± 7.37	23.78 ± 7.79	0.400
FCRI-c total, mean ± SD (maximum 172)	111.52 ± 14.29	94.44 ± 24.01	0.073

FCRI-c: Fear of Cancer Recurrence Inventory-caregiver; SD: standard deviation
FCRI-c subscale and total scores are presented as mean ± SD.
Group comparisons were conducted using independent-samples t-tests.
P<0.05 in bold was considered statistically significant.
The Triggers subscale result should be interpreted with caution given the modest and unequal group sizes as well as the number of comparisons performed. Replication in a larger sample is warranted. Effect sizes were not computed here but are recommended for future work.

Form cut-off score (≥13) and 50.0% scored above the high-specificity cut-off score (≥22). These proportions are higher than the survivor benchmarks of 53.9%/30.0%[9] and the 58.8%/19.2% for the FCRI Short Form cut-off score and high-specificity cut-off score, respectively, as reported in the largest known meta-analysis (n=9311),[10] although caregiver-specific norms are still scarce. The most endorsed fears were those that concerned the child, namely, sparing the child further treatment stress (96.7%) and losing the child (86.7%), followed by long-term medical problems (93.3%) and financial concerns (money as a source of fear, family financial worry, and loss of income; 86.7–90.0%).

In the exploratory comparison, Group 1 (≤5 years) had higher scores than Group 2 on every subscale and in the total (111.52 ± 14.29 versus [vs] 94.44 ± 24.01; *P*=0.073). The Triggers subscale, which assesses cues and situations that may prompt or intensify FCR, reached statistical significance (23.33 ± 4.13 vs 19.00 ± 4.97; *P*=0.039). The remaining subscales, including Severity, Insight, and Reassurance, did not reach statistical significance (ranging from *P*=0127 to *P*=0.508).

To the authors' knowledge, this is the first study to describe caregiver FCR in Singapore, a setting where caregiver-focused data have been lacking, even though the persistence of parental FCR after treatment is well documented in Western populations.[2-4] This study's data add to the understanding of caregiver FCR by showing that concerns extend beyond cancer recurrence to encompass potential long-term health consequences. Worry about long-term medical problems (93.3%) fits the documented burden of late effects among childhood cancer survivors treated in Singapore.[11] Fear of a second cancer, itself a late effect,[4] was not asked about separately and should be studied in future work.

Financial concerns, such as out-of-pocket treatment costs and loss of household income during a child's cancer treatment, may also influence caregiver FCR in Singapore. As these factors were not assessed in this study, the authors cannot determine whether they would help explain differences in caregiver FCR between Singapore and Western cohorts. The higher Triggers score in Group 1 may reflect greater early reactivity to cancer-related reminders such as routine body scans, which occur more often soon after treatment, though this study cannot confirm this. As these are between-group comparisons rather than repeated measures, and some Group 1 caregivers may still have been in active follow-up (clinical status was not recorded), the authors cannot separate recent

treatment from ongoing surveillance and treat these as preliminary signals for longitudinal work. In informal interactions with researchers, caregivers who seemed to be coping often mentioned "scanxiety" (a term that has come to refer to anxiety related to scanning procedures), though only when asked. They further described the pressure to be "strong and hoping for the best." While this is an informal observation and not a study measure, it shows how easily caregiver FCR can be missed without a simple screening approach.

The study has clear limitations. It is a convenience sample of 30 caregivers from 1 organisation. Caregivers engaged with a community support organisation may differ systematically from caregivers who do not seek support services, thus introducing self-selection bias. As such, the findings should be considered preliminary and hypothesis-generating. The sample size was too small (n=18 vs 12) to detect even large effects reliably; self-report is subject to recall and social-desirability bias; no clinical data were collected; and the cross-sectional design cannot show how FCR changes within an individual caregiver.

Clinically significant FCR was common in this community-based Singapore sample, extended beyond recurrence into concerns about long-term effects, and appeared higher earlier after treatment, although only Triggers reached significance. Larger, multi-site longitudinal studies in Singapore and the region are needed to map how caregiver FCR develops. Brief FCR screening within existing follow-up services (e.g. late effects clinics and community-based cancer organisations), with referral pathways, is a reasonable next step. However, its feasibility, outcomes, timing, costs, and acceptability to caregivers and clinicians should first be formally evaluated.

Supplementary material

Annex S1. STROBE checklist for cross-sectional studies.

Ethics statement

Ethics approval was obtained prior to data collection (NERC/002/2023). All participants provided written informed consent.

Declarations

The authors declare that they have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors had full responsibility for the study design, data collection, analysis, interpretation, and manuscript preparation.

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Keywords: *anxiety, cancer survivors, caregivers, child, fear of cancer recurrence, oncology, paediatric, Singapore, survivorship*

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Closing the gender gap in human papillomavirus protection: A survey of healthcare workers

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Dear Editor,

Infection with human papillomavirus (HPV) remains one of the most common sexually transmitted infections globally and is a leading cause of anogenital and oropharyngeal cancers.[1] Although traditionally regarded as a women's health issue because of its well-established association with cervical cancer and cervical screening programmes, HPV also contributes substantially to disease burden in men.[2] Highly effective vaccines are available to prevent HPV infection and associated malignancies in both sexes.[3] Many countries have therefore expanded vaccination programmes for HPV to include males.[4] However, vaccine uptake among men remains suboptimal, and this disparity is often attributed to factors such as knowledge, perceived risk, cost, and healthcare provider recommendation.[5,6]

In Singapore, there are limited data on HPV-related knowledge and vaccination attitudes among adults, particularly men. Understanding the sociocultural and structural barriers is important to improve vaccine uptake. Therefore, this study aimed to evaluate factors influencing HPV vaccine uptake in men.

The authors conducted a cross-sectional mixed-methods study among staff aged 21 years and above at Sengkang General Hospital, a 1000-bed public acute care hospital in northeast Singapore. Quantitative and qualitative data were collected and analysed using a convergent approach to assess awareness, knowledge, attitudes, and behavioural drivers related to HPV vaccination in males.

The survey (see Supplementary Appendix S1) was informed by the study objectives, relevant literature on HPV vaccine acceptance, and Singapore's vaccination recommendations. The study team reviewed the questions for content relevance, clarity, and appropriateness for the Singapore healthcare context.

Prior awareness of HPV was assessed using a screening question (question 5 of the survey, "Before today, had you heard of human papillomavirus [HPV]?"). Participants who reported no prior awareness did not proceed to subsequent sections.

Knowledge was assessed by questions 6–11, including HPV transmission, disease burden, and vaccine eligibility in males. The knowledge score was calculated by adding the number of correct responses. The score was categorised as adequate (≥4) or low (<4). Attitudes were assessed by questions 12–17, including perceptions of disease severity, vaccine safety, cost-effectiveness, and physician influence. A composite score was calculated as the mean of all items and categorised as positive (≥4), neutral (3–3.99), or negative (<3). HPV vaccine acceptance was assessed using self-reported vaccination status and willingness to receive the HPV vaccine for themselves and their sons in questions 18–21. Question 22 was a qualitative open-ended question exploring barriers and facilitators to vaccination.

This study was approved by the SingHealth Centralised Institutional Review Board with a waiver of informed consent. The questionnaire was disseminated via institutional email, using a QR code that linked to an online FormSg survey. The survey was conducted over a 2-week period from 24 February to 10 March 2026.

Descriptive statistics were used to summarise quantitative data. Categorical variables were reported as frequencies and percentages, while Likert-scale items were summarised using means and standard deviations (SDs). Group comparisons were performed using chi-square tests for categorical variables and independent-sample t-tests for continuous variables.

Open-ended responses were analysed using qualitative content analysis by 2 researchers, with themes refined through discussion. Quantitative and qualitative findings were integrated during interpretation.

A total of 306 participants completed the questionnaire. The largest age group was aged 30–39 years (45.1%); participants were predominantly female (69.3%), and highly educated, with 54.3% holding a university degree and 43.5% holding postgraduate qualifications.

Overall, 266 respondents (86.9%) had previously heard of HPV. Most recognised that HPV can be

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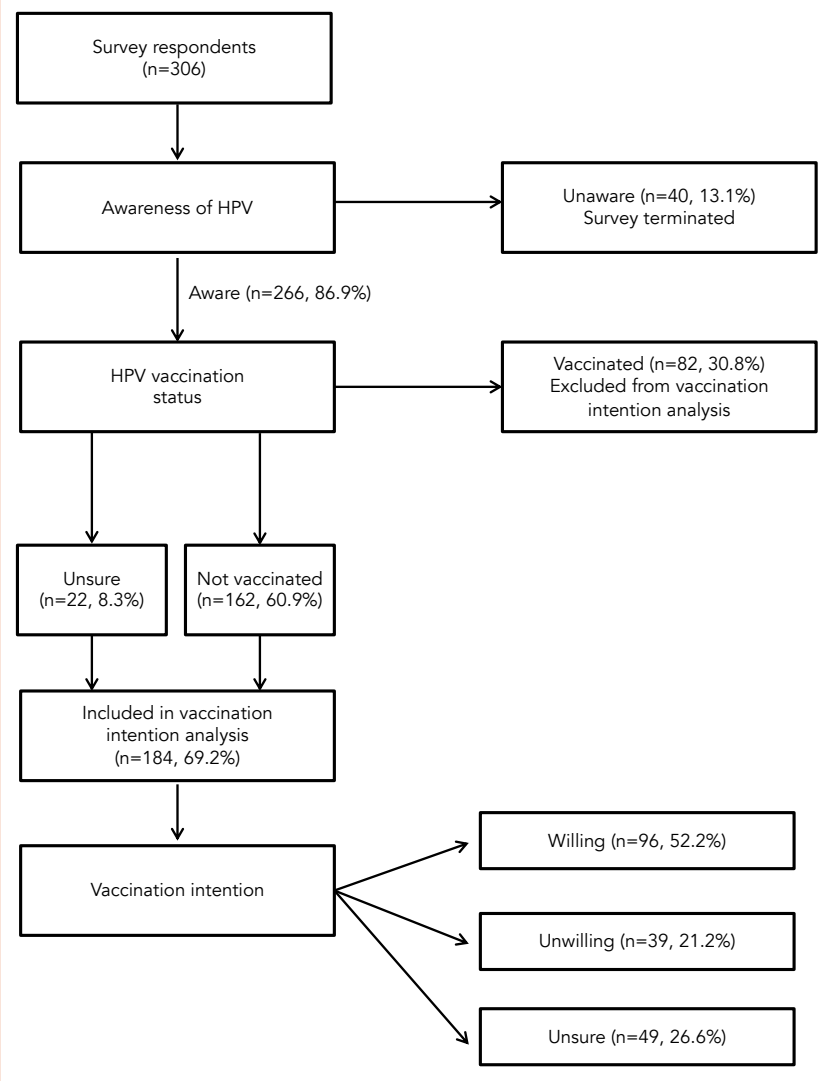
transmitted through sexual contact (n=252, 94.7%) and that HPV infection can occur in men (n=213, 80.1%). However, awareness of HPV-related cancers in men was lower: 165 (62.0%) identified HPV as a cause of anal cancer, 165 (62.0%) of penile cancer, and 141 (53.0%) of throat cancer in men. Among the respondents, 129 (48.5%) knew that the Gardasil-9 vaccine is approved for men. The mean knowledge score was 4.00 (SD 2.01), with 170 (63.9%) demonstrating adequate knowledge (score ≥4).

Attitudes towards male HPV vaccination were generally favourable, with 182 respondents (68.4%) showing a positive attitude (mean score ≥4.0 on the 5-point Likert scale; overall mean score 4.20, SD 0.60). There were 234 respondents (88.0%) who agreed that HPV vaccination could help protect a person's sexual partner, while 221 (83.1%) felt that vaccination for men should be more widely publicised. A total of 241 respondents (90.6%) reported they would be more likely to accept vaccination if recommended by a doctor. However, only 103 (38.8%) agreed that HPV vaccination in men was cost-effective at the prevailing out-of-pocket price, while 103 (38.7%) were neutral about it.

There were 82 respondents (30.8%) who reported having previously received the HPV vaccine, while 162 (60.9%) had not been vaccinated, and 22 (8.3%) were unsure of their vaccination status. Among the 184 respondents without confirmed prior vaccination, 96 (52.2%) indicated willingness to receive the HPV vaccine, whereas 39 (21.2%) would not, and 49 (26.6%) were unsure.

Among those with sons eligible for HPV vaccination, 13 (44.8%) indicated willingness to vaccinate their son against HPV, whereas 15 (51.7%) were unsure, and only 1 respondent (3.5%) was unwilling.

Fig. 1. Flow diagram of participant selection and vaccination intent analysis.



HPV: human papillomavirus

This study provides a detailed assessment of knowledge, attitudes, and determinants of HPV vaccination in men, revealing several insights. Although overall awareness of HPV was relatively high, modest knowledge gaps remained regarding HPV-related disease burden and vaccine eligibility in men. The observation that superficial awareness does not translate into a meaningful understanding of the cancer implications of HPV in men is highly consistent with findings from prior studies.[6,7]

The observed positive attitude rate (68.4%) falls within the upper range reported in prior systematic reviews.[6,8] However, positive attitudes do not always translate into vaccination behaviour, suggesting the influence of additional barriers beyond individual perceptions.

Despite generally positive attitudes, actual vaccine uptake remained low. Although only 30.8% of respondents reported prior HPV vaccination, 52.2% of those without confirmed prior vaccination expressed willingness to receive the vaccine, highlighting an "intention–behaviour gap" described in the vaccination literature, whereby expressed willingness does not always translate into vaccination behaviour because of structural or logistical barriers.[9] The strong influence of healthcare provider recommendation observed in this study underscores the important role that clinicians can play in shaping vaccination decisions through proactive recommendation and counselling, thereby improving HPV vaccine uptake.

Additionally, this study highlighted the potential influence of perceived cost-effectiveness on vaccine uptake. Indeed, previous studies have consistently established financial costs and the perceived value of HPV vaccination as key determinants of HPV uptake across different populations.[6,9]

Willingness and indecision regarding HPV vaccination of eligible sons were similarly common, highlighting parents as an important target for educational interventions.

Lastly, it is reassuring to note that confidence in vaccine safety was generally high, with 71.8% of respondents perceiving the vaccine to be safe. This is consistent with the extensive evidence demonstrating the favourable safety profile of HPV vaccination.[10] The focus of interventions can be redirected from stressing safety concerns to closing the intention–behaviour gap as mentioned above.

In conclusion, knowledge gaps, uncertainty, and cost concerns remain important barriers to HPV vaccination. Targeted education and clinician-led discussions may help translate willingness into greater HPV vaccine uptake among men in Singapore.

Supplementary material

Appendix S1. Survey questions.

Ethics statement

The study was approved by the SingHealth Centralised Institutional Review Board with a waiver of informed consent (2026-0173). Due to the anonymous nature of the online survey, no identifiable personal data were collected. Participation was voluntary and implied consent was provided by proceeding to complete the survey.

Declaration

No funding was received for this study. The authors declare that they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript. The authors used ChatGPT (OpenAI) for language editing, and the authors take full responsibility for its contents. No generative AI tools were used for data collection, data analysis, or interpretation of results.

Keywords: *attitudes, health knowledge, papillomaviridae, papillomavirus infections, men's health, prevention and control, vaccination coverage*

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Hospitalisation at home for bariatric patients in Singapore: A safe and cost-effective postoperative care model

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Dear Editor,

Hospital-at-Home (HaH) provides acute, hospital-level care in patients' homes and is an emerging model of perioperative surgical care. Early applications, including ileostomy dysfunction and bariatric surgery,[1] have demonstrated improved patient satisfaction, reduced length of stay, and non-inferior safety profiles.[2] While HaH has shown effectiveness in non-surgical populations, its clinical outcomes and cost-effectiveness in surgical settings remain under-explored.

With obesity projected to affect over 1.5 billion adults by 2035, demand for bariatric surgery is rising particularly in Asia,[3] including Singapore.[4] Conventional postoperative care relies on inpatient admission, placing significant strain on physical bed capacity. Enhanced Recovery After Surgery (ERAS) has been shown in meta-analyses to reduce length of stay and healthcare costs, without increasing post-operative complications.[5] These protocols have enabled same-day discharge. However, eligibility criteria remain stringent as patients are typically under 60 years old, have a body mass index (BMI) of <45 kg/m², ≤2 comorbidities, reside close to hospital, and have no perioperative complications.[6]

Despite same-day discharge pathways, many programmes still require structured post-discharge support, including home visits by nurses for up to 5.7 days or continuous remote monitoring for up to 7 days.[6,7] While ERAS facilitates early discharge in low-risk patients, it does not eliminate the need for ongoing clinical oversight. HaH, enabled by technology-supported remote monitoring and multidisciplinary care, offers a scalable approach to extend perioperative care to higher-risk bariatric patients who would otherwise require prolonged hospitalisation in a brick-and-mortar model.

A retrospective observational study was conducted to compare clinical and cost outcomes between bariatric patients managed under the HaH service and eligible patients receiving usual inpatient care at the National University Health System in Singapore. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (2023/00245).

The types of primary bariatric surgery included sleeve gastrectomy, Roux-en-Y gastric bypass, and one-anastomosis gastric bypass. With co-management between surgeons and physicians in HaH, patients were cared for by a multidisciplinary team of nurses and allied health professionals. They received teleconsultations and compulsory wound inspection during in-person physician home visits. Dieticians were also involved in the escalation of diets, and glucose levels were closely monitored in patients with a pre-operative history of diabetes mellitus. There were no complications of hyperglycaemia or hypoglycaemia. Patients could also participate in one-on-one rehabilitation by physiotherapists for functional decline. There was also a 24/7 medical service for patients to escalate their concerns to the HaH physicians with expedited investigations, home visits, or transfer to the hospital in the event of emergencies. All patients were required to remain in hospital for 1 night before being transferred to HaH the following day.

Continuous variables were summarised as mean ± standard deviation or median (interquartile range [IQR]), depending on distribution, and compared using independent-samples t-tests or Mann–Whitney U tests, respectively. Categorical variables were summarised as no. (%) and compared using chi-square or Fisher's exact tests, as appropriate. Exploratory adjusted linear regression analyses were performed for length of stay and gross hospitalisation bill, adjusting for age, sex, procedure type, pre-operative BMI, and comorbidity count.

Among the patients eligible for HaH who were under 60 years old with no immediate postoperative complications, 39 bariatric surgery patients were

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Table 1. Patient characteristics, clinical, and cost outcomes.

	HaH cohort (n=39)	Inpatient cohort (n=36)	*P* value
Patient characteristics			
Age in years, mean ± SD	38 ± 8.9	40 ± 11.5	0.27
Male sex, no. (%)	13 (33.3)	14 (38.9)	0.64
Ethnicity, no. (%)			0.07
Chinese	5 (12.8)	12 (33.3)	
Malay	24 (61.5)	14 (38.9)	
Indian	10 (25.6)	9 (25.0)	
Others	0	1 (2.8)	
Bariatric procedure, n(%)			1.00
Gastric bypass	27 (69.2)	25 (69.4)	
Sleeve gastrectomy	12 (30.8)	11 (30.6)	
Pre-operative comorbidity count, median [IQR]	1 [0–2]	1.5 [0–3]	0.21
Pre-operative comorbidities, no. (%)			
Type 2 diabetes	10 (25.6)	12 (33.3)	0.61
Hypertension	11 (28.2)	14 (38.9)	0.34
Hyperlipidaemia	10 (25.6)	15 (41.7)	0.15
Ischaemic heart disease	0 (0)	3 (8.3)	0.11
Chronic kidney disease	1 (2.6)	1 (2.8)	1.00
Pre-operative BMI, kg/m², median [IQR]	43.2 [37.7–46.5]	43.0 [37.0–46.8]	0.92
Clinical and cost outcomes			
Total length of stay,[a] days, median [IQR]	3 [3–4]	2 [2–3]	<.001
Mortality within episode of care, no. (%)	1 (2.6)	0 (0)	1.00
30-day readmission,[b] no. (%)	1 (2.6)	2 (5.6)	0.60
30-day emergency department attendance,[b] no. (%)	3 (7.7)	3 (8.3)	1.00
Gross hospitalisation bill,[a] SGD, median [IQR]	17,876 [16,551–20,183]	20,156 [17,562–21,275]	0.02

BMI: body mass index; HaH: Hospital at Home; IQR: interquartile range; SD: standard deviation; SGD: Singapore dollar

[a] For HaH cohort, defined as the sum of conventional inpatient stay and HaH stay

[b] Defined as 30-day post discharge from either HaH (HaH cohort) or inpatient ward (inpatient cohort)

enrolled in HaH while 36 patients opted for the usual inpatient care during the period from August 2023 to April 2025. The mean age of the HaH cohort was 38 years, 2 years younger than the inpatient cohort. There were more female patients than male patients in both cohorts. Over two-thirds of the patients in both cohorts underwent primary gastric bypass procedures. HaH patients had a lower 30-day readmission rate (2.6% versus 5.6%) than those receiving inpatient care. No major postoperative complications were recorded. There was 1 death in the HaH cohort after returning to hospital for a sleeve gastrectomy leak on postoperative day (POD) 3. However, a review of the case during a multidisciplinary mortality did not reveal any failure in care, as most sleeve gastrectomy patients were discharged on POD 2 and the outcome would not have been different in usual inpatient care. The escalation of care to the hospital for emergency

reoperation was expedient. Six-month postoperative BMI was also analysed among patients with available follow-up data (n=58), with a median [IQR] BMI of 30.7 [28.4–34.0] kg/m² in the HaH cohort and 32.4 [29.5–37.7] kg/m² in the inpatient cohort, with no statistically significant difference between groups (*P*=0.208). Overall, HaH saved 90 inpatient bed-days during the study period. The main reason for rejecting HaH was personal preference for conventional inpatient care.

In exploratory adjusted linear regression analyses accounting for age, sex, ethnicity, bariatric procedure type, pre-operative BMI, and comorbidity count, HaH was associated with a longer total length of stay compared with inpatient care (adjusted difference: 1.2 days; 95% confidence interval [CI] 0.90–1.56; *P*<0.001). HaH was associated with a lower gross hospitalisation bill, although the difference was not statistically significant (adjusted difference: –SGD853; 95% CI –2119 to 412; *P*=0.183). Additional baseline health indicators, including EQ-5D-5L and STOP-Bang scores, were available only for a subset of patients and were not included in the adjusted models to avoid substantial loss of sample size and unstable estimates.

To the authors' knowledge, this is the first Asian study evaluating HaH for post-bariatric surgery recovery. The findings on feasibility and safety are consistent with existing studies on HaH. A French study of patients undergoing sleeve gastrectomy or Roux-en-Y gastric bypass discharged to HaH after 1 postoperative night reported no significant differences in early complications or readmissions. Effective outcomes were supported by close coordination between surgical teams and HaH providers.[8] Similarly, a Spanish study demonstrated shorter total length of stay in the HaH cohort compared with inpatient care, with no mortality reported.[9]

This study is limited by its retrospective design, small sample from a single health system, and potential self-selection, as patients who chose HaH may have differed in motivation, health literacy, or perceived behavioural control. The eligibility criteria may also limit generalisability to older or clinically unstable patients.

The findings support HaH as a viable, psychologically acceptable alternative to inpatient recovery following bariatric surgery in younger, tech-savvy patients. Future work will evaluate early metabolic disease control. By maintaining safety while reducing costs and inpatient bed-days, HaH offers a solution to the rising demand for metabolic surgery. Wider implementation across Singapore, and its extension to other procedures, such as cholecystectomy, should be considered with agreed surgical–HaH protocols.

Ethics statement

This study was approved by the National Healthcare Group Domain Specific Review Board (2023/00245).

Declaration

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

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