



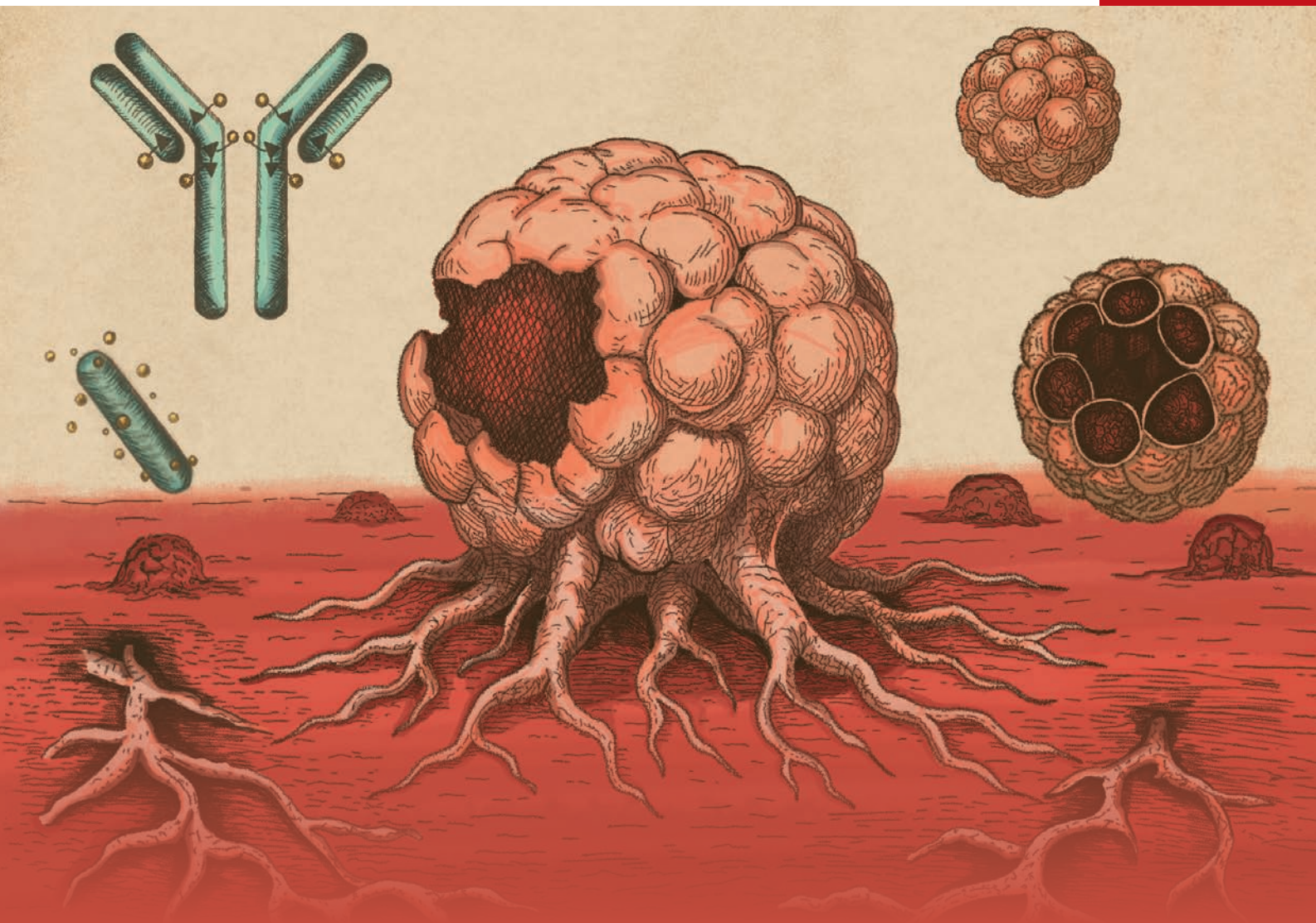
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Evaluating the impact of relative dose intensity on efficacy of trastuzumab deruxtecan for metastatic breast cancer in the real-world clinical setting

Data from the Joint Breast Cancer Registry in Singapore were used to study patients treated with T-DXd. Findings reveal that reduced dose intensity had no significant impact on real-world progression-free survival or treatment-related toxicities. (See full article, p. 458)

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Automatic brain segmentation in cognitive impairment: Validation of AI-based AQUA software in the Southeast Asian BIOCIS cohort

Advancing breast cancer and lung cancer screening: Expert perspectives to advance programmes in Singapore

Integrating traditional Chinese medicine into disease management in Singapore

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Trastuzumab-deruxtecan in breast cancer treatment: Balancing the triad of efficacy, safety and accessibility

Victor Guan Hui [Lee](#)¹ MBBS (S'pore), Joline Si Jing [Lim](#)^{1,2,3} MBBS (S'pore)

Trastuzumab deruxtecan (T-DXd), an anti-human epidermal growth receptor 2 (HER2) antibody-drug conjugate (ADC), has emerged as a transformative therapy for metastatic breast cancer (MBC), demonstrating efficacy across the full spectrum of HER2 expression including HER2 positive, HER2 low and HER2 ultralow disease.¹⁻⁴ This novel ADC consists of trastuzumab linked via an enzymatically cleavable disulfide linker to deruxtecan, a potent topoisomerase I inhibitor. Its high drug-to-antibody ratio (approximately 8) and membrane-permeable payload enable a bystander effect, contributing to its pronounced antitumour activity. The DESTINY-Breast03 trial redefined expectations in HER2-positive MBC, achieving a median overall survival of only over 50 months in the second-line setting, which far exceeds the 30-month benchmark set by previous gold standard therapy trastuzumab emtansine, underscoring a paradigm shift in the therapeutic landscape of this disease. While T-DXd is generally well-tolerated and allows most patients to preserve quality of life, its use is tempered by toxicities including alopecia, nausea and fatigue. The main long-term concern is interstitial lung disease (ILD), which requires careful monitoring. Despite its impressive clinical activity, the widespread adoption of T-DXd is constrained by its high cost and toxicity profile that can be clinically significant for some patients. These challenges underscore the need for strategies that enhance its generalisability, ensuring that more patients can benefit from its therapeutic potential without compromising safety or affordability.

In this issue of the *Annals*, a retrospective analysis of 87 patients with MBC treated with T-DXd by Lee et al. reported comparable real-world progression-free survival (rwPFS) between those receiving an initial relative dose intensity (RDI) of <85% versus ≥85%.⁵ T-DXd demonstrated favourable central nervous system (CNS) activity, with brain progression observed in only 16% of patients, and an incidence of ILD at 5%.

The study offers valuable real-world evidence (RWE) from a predominantly Asian population, demonstrating that reductions in RDI of T-DXd did

not significantly affect rwPFS. The authors should be commended for conducting this real-world analysis, which more closely mirrors routine clinical practice, where dose modifications are often made to mitigate toxicity and manage treatment costs. This study underscores the value of RWE in complementing clinical trial data. While trials often involve highly selected patient populations under controlled conditions, RWE captures outcomes in broader, more diverse groups including older patients, those with comorbidities and individuals receiving later-line therapies. Such data provide critical insights into how treatments perform in routine practice, helping to guide clinical decisions and advance patient-centred oncology care.

The patients included in this analysis were heavily pre-treated, with a median of 4 prior lines of therapy (ranging 2–15). Over 90% received T-DXd as a third-line treatment or later. The observed rwPFS was 8.1 months, which is consistent with other real-world data from Asian populations,⁶ but remains inferior compared to outcomes reported in non-Asian cohorts.⁷ In contrast, the DESTINY-Breast01 (DB-01) trial reported a median progression-free survival (PFS) of 16.4 months, despite patients receiving a median of 6 prior lines of therapy (ranging 2–27).¹ However, DB-01 enrolled only fit patients (Eastern Cooperative Oncology Group performance status 0–1) and excluded those with untreated or symptomatic brain metastases, which may account for the superior outcomes.

Lee et al. reported noteworthy findings on the intracranial activity of T-DXd. Among 11 patients with baseline CNS involvement, 9 achieved disease control following treatment with T-DXd. While the sample size is limited, these real-world results are consistent with previously reported studies and reinforce the growing body of evidence supporting the CNS efficacy of T-DXd, even in heavily pre-treated populations. Data from the DESTINY-Breast12 trial,⁸ which demonstrated a high intracranial objective response rate and prolonged CNS PFS, suggest that systemic therapy with T-DXd may complement local therapy in select patients. This is particularly relevant given

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the neurocognitive sequelae associated with local modalities such as whole-brain radiotherapy, which also fails to address extracranial disease burden. With newer agents showing good intracranial efficacy, the European Society for Medical Oncology Living Guidelines have recently recommended consideration of both T-DXd and the tucatinib–trastuzumab–capecitabine (TTC) combination as second-line options for patients with active brain metastases who do not require immediate local treatment.⁹ The selection between these regimens should be guided by patient-specific factors, toxicity profiles and accessibility. T-DXd is associated with risks such as ILD and fatigue, whereas TTC tends to cause gastrointestinal toxicities and hepatotoxicity. In the Singapore context, it may be more cost-effective to use T-DXd over TTC. Finally, there is retrospective evidence supporting the feasibility of sequencing TTC after T-DXd.¹⁰

The incidence of ILD in this study was 5.7%, notably lower than the 10–15% reported across the DESTINY-Breast trials.^{1,4} While earlier analyses have suggested that ILD rates may be higher among Asian patients—particularly within Japanese cohorts¹¹—emerging real-world data from broader Asian, non-Japanese populations indicate ILD incidences that are comparable to or even lower than those observed in the clinical trial setting.¹² This discrepancy highlights the complex interplay between ethnicity, patient selection, drug dosing and pharmacogenomic differences. Importantly, these real-world findings suggest that in routine practice, with appropriate monitoring strategies and individualised dose modifications, the risk of ILD associated with T-DXd may be effectively minimised. As we continue to integrate T-DXd into clinical practice, real-world pharmacovigilance will remain essential in optimising safety across diverse patient populations.

Although non-ILD-related toxicities such as nausea and fatigue were not explicitly captured in this study, it is reasonable to infer that their incidence and severity may be attenuated with lower RDI of T-DXd. This consideration is particularly relevant given that T-DXd-associated toxicities have been observed to be more pronounced when the drug is administered in later lines of therapy, as compared to earlier use in the DB clinical trials.¹³ These observations underscore the practical importance of dose optimisation where clinicians must balance drug efficacy with tolerability in more heavily pretreated and heterogeneous patient populations.

While this retrospective analysis suggests that reduced RDI does not compromise efficacy of T-DXd, prospective studies are needed to validate optimal

dosing strategies, with consideration of comparison for fixed versus adaptive dosing regimens, stratified by baseline patient characteristics, to better balance efficacy with tolerability. The current optimal systemic option for MBC with brain metastasis is not straightforward given the lack of head-to-head studies between T-DXd and other regimens with CNS activity like TTC; systemic collection and review of such data in diverse real-world populations are warranted. These studies should consider not only efficacy and safety but also patient-reported outcomes, quality of life and cost-effectiveness.

In Singapore, T-DXd was incorporated into the Cancer Drug List in November 2023 for HER2-positive advanced breast cancer and expanded in September 2024 to include HER2-low disease. These milestones represent a major step forward in improving access to a transformative therapy for breast cancer patients. While financial considerations remain for patients without Medisave or MediShield support, the progressive inclusion of T-DXd into national funding frameworks paves the way for broader adoption and integration of this therapy into mainstream clinical practice.

In summary, the study by Lee et al. contributes important RWE supporting the clinical utility and tolerability of T-DXd in a diverse, heavily pre-treated Asian population. The findings reinforce the notion that reduced dose intensity may preserve efficacy while potentially mitigating toxicity. Furthermore, the encouraging CNS activity of T-DXd, coupled with a manageable safety profile—particularly with regard to ILD—highlights its promise as systemic therapy for MBC patients with brain metastases. As T-DXd continues to be integrated into earlier lines of therapy and across the HER2 expression spectrum, real-world data such as these are invaluable. They complement clinical trial findings by offering nuanced insights into treatment outcomes in patient populations that are under-represented in trials, thereby guiding more personalised cancer care.

Ethics statement

Not applicable.

Declaration

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

Keywords: cancer, internal medicine, oncology, pharmacology, public health

REFERENCES

1. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med* 2020;382:610-21.
2. Cortes J, Hurvitz SA, Im SA, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial. *Nat Med* 2024;30:2208-15.
3. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med* 2022;387:9-20.
4. Bardia A, Hu X, Dent R, et al. Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer. *N Engl J Med* 2024;391:2110-22.
5. Lee HY, Shih V, Chan JJ, et al. Evaluating the impact of relative dose intensity on efficacy of trastuzumab deruxtecan for metastatic breast cancer in the real-world clinical setting. *Ann Acad Med Singap* 2025;54:458-66.
6. Wang SR, Chang KC, Shao SC, et al. RWD153 Real-World Effectiveness of Trastuzumab Deruxtecan in Patients With Metastatic Breast Cancer. *Value in Health* 2024;27:S604.
7. Botticelli A, Caputo R, Scagnoli S, et al. Real-World Outcomes of Trastuzumab Deruxtecan in Patients With HER2+ Metastatic Breast Cancer: The DE-REAL Study. *Oncologist* 2024;29:303-10.
8. Harbeck N, Ciruelos E, Jerusalem G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. *Nat Med* 2024;30:3717-27.
9. ESMO Living Guideline: HER2-positive MBC: Second-line Treatment or Progression During (Neo)Adjuvant Treatment, v1.2 - April 2025.
10. Frenel JS, Zeghondy J, Guerin C, et al. Efficacy of tucatinib, trastuzumab, and capecitabine (TTC) following trastuzumab-deruxtecan (T-DXd) in HER2-positive metastatic breast cancer (MBC): Updated results and subgroup analyses from the UNICANCER multicenter retrospective cohort. *JCO* 2025;43:1030.
11. Iwata H, Xu B, Kim SB, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in Asian patients with HER2-positive metastatic breast cancer. *Cancer Sci* 2024;115:3079-88.
12. Sang D, Su Y, Zhang Y, et al. Efficacy and safety of trastuzumab deruxtecan in Chinese patients with HER2-positive and HER2-low advanced breast cancer: a multicenter, observational, real-world study. *Ther Adv Med Oncol* 2025;17:17588359251318853.
13. Cheng A, Frank S, Baines K, et al. Real world experience of trastuzumab deruxtecan for the treatment of metastatic breast cancer in the UK. *JCO* 2024;42:1024.

Evaluating the impact of relative dose intensity on efficacy of trastuzumab deruxtecan for metastatic breast cancer in the real-world clinical setting

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ABSTRACT

Introduction: Trastuzumab deruxtecan (T-DXd) has revolutionised treatment for metastatic breast cancer (MBC). While effective, its high cost and toxicities, such as fatigue and nausea, pose challenges.

Method: Medical records from the Joint Breast Cancer Registry in Singapore were used to study MBC patients treated with T-DXd (February 2021–June 2024). This study was conducted to address whether reducing dose intensity and density may have an adverse effect on treatment outcomes.

Results: Eighty-seven MBC patients were treated with T-DXd, with a median age of 59 years. At the time of data cutoff, 32.1% of patients were still receiving T-DXd. Over half (54%) of the patients received treatment with an initial relative dose intensity (RDI) of $\geq 85\%$. Overall median real-world progression-free survival (rwPFS) was 8.1 months. rwPFS was similar between RDI groups ($<85\%$: 8.7 months, $\geq 85\%$: 8.1 months, $P=0.62$). However, human epidermal growth receptor 2 (HER2)-positive patients showed significantly better rwPFS outcomes compared to HER2-low patients (8.8 versus 2.5 months, $P<0.001$). Only 16% with central nervous system (CNS) involvement had CNS progressive disease on treatment. No significant progression-free survival (PFS) differences were found between patients with or without CNS disease, regardless of RDI groups. Five patients (5.7%) developed interstitial lung disease (ILD), with 3 (3.4%) having grade 3 events. Two required high-dose steroids and none were rechallenged after ILD. There were no fatalities.

Conclusion: Our study demonstrated that reduced dose intensity and density had no significant impact on rwPFS or treatment-related toxicities. Furthermore, only 5.7% of patients developed ILD. T-DXd provided good control of CNS disease, with 82% of patients achieving CNS disease control.

Keywords: cancer, internal medicine, oncology, pharmacology, public health

CLINICAL IMPACT

What is New

- Reduced dose intensity had no significant impact on real-world progression-free (rwPFS) survival or treatment-related toxicities.
- Trastuzumab deruxtecan provided good control of central nervous system disease.

Clinical Implications

- Similar rwPFS between different relative dose intensity groups suggests that dose reduction may be a viable option for managing toxicities.
- Better rwPFS outcomes in human epidermal growth receptor 2 (HER2)-positive patients highlight importance of HER2 status in treatment planning.
- Development of interstitial lung disease in a small percentage of patients underscores need for monitoring this potential side effect.

INTRODUCTION

Human epidermal growth receptor 2 (HER2)-positive breast cancer is recognised as a particularly aggressive subtype, associated with a poorer prognosis and a higher risk of recurrence.^{1,2} The current standard of care for first-line treatment for HER2-positive metastatic breast cancer (MBC) includes a combination of trastuzumab and pertuzumab alongside chemotherapy, which have demonstrated improvement in both progression-free survival (PFS) and overall survival (OS) in the CLEOPATRA trial.^{3,4} The treatment landscape for patients in second-line treatment and beyond has undergone a significant change with the introduction of trastuzumab deruxtecan (T-DXd), an antibody-drug

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conjugate.⁵ With its high drug-to-antibody ratio,⁶⁻⁸ T-DXd enables more efficient delivery of its highly potent microtubule inhibitor payload to tumour cells. Due to its strong ability to cross cell membranes, T-DXd exhibits a pronounced bystander effect, enabling it to spread within the tumour microenvironment and affect adjacent tumour cells, irrespective of their HER2 expression levels.⁹

Results from the pivotal DESTINY-Breast series of studies underscore its efficacy. The phase III DESTINY-Breast02¹⁰ trial (for third-line treatment and beyond in HER2-positive MBC) and DESTINY-Breast03¹¹ trial (for second-line treatment following trastuzumab and pertuzumab in HER2-positive MBC) demonstrated superior median PFS and OS compared to standard-of-care regimens. Furthermore, DESTINY-Breast04¹² and DESTINY-Breast06¹³ trials evaluated T-DXd in HER2-negative MBCs with varying levels of HER2 expression, categorised as HER2-low and HER2-ultralow, respectively. These studies also reported improved efficacy compared to chemotherapy of physician's choice.

T-DXd was first approved by Singapore's Health Sciences Authority (HSA) in October 2021 for treatment of patients with unresectable or HER2-positive MBC who have received 2 or more prior anti-HER2-based regimens in the metastatic setting.¹⁴ It was later approved in April 2023 for the use in the treatment of unresectable or metastatic HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridisation positive) breast cancer patients who have received at least 1 prior line of chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of adjuvant chemotherapy completion.¹⁵

Where accessible, medical oncologists at the National Cancer Centre Singapore (NCCS) have been prescribing T-DXd since its approval. Although efficacious, adverse events (AEs) associated with T-DXd therapy such as fatigue and nausea can be challenging.¹⁶⁻¹⁸ This can be mitigated in part with dose reduction.^{19,20} Adding to the burden of toxicities is a high drug cost associated with novel therapeutics. Singapore's healthcare financing system follows a mixed model, which combines government subsidies, mandatory savings, private insurance and out-of-pocket cost to patients.²¹ The cost of novel therapeutics is not fully reimbursed. As such, a practice has evolved to round down the prescribed dose to match the dose per vial or extend the interval between doses with the intent to ameliorate toxicities and expenses. However, there are concerns that these practices might lead to inferior outcomes compared to those reported in clinical trials.

As opposed to tightly controlled trials which mandate strict adherence to dose modification guidelines and dosing intervals, real-world settings often allow for more flexibility and extension of data to patients who may be less fit and otherwise ineligible for study inclusion.²²⁻²⁴ This variation may influence treatment outcomes.

Hence, this retrospective analysis was designed to evaluate T-DXd treatment data from NCCS. The study examines local prescription practices by medical oncologists managing MBC, such as dosing and scheduling of T-DXd. Our primary objective was to evaluate real-world PFS (rwPFS) for patients receiving upfront standard dosing versus (vs) reduced dosing of T-DXd. We also evaluated rates of disease control for patients with CNS metastases and compared the difference in AEs of special interest specifically interstitial lung disease (ILD) in patients who received standard vs attenuated dosing of T-DXd.

METHOD

The Joint Breast Cancer Registry (JBCR) was established to collect comprehensive real-world data on patients with breast cancer treated across multiple public healthcare institutions in Singapore.²⁵ Medical records from the JBCR were reviewed to identify patients aged 21 years or older who were treated with at least 1 dose of T-DXd for MBC between 1 February 2021 and 30 June 2024. T-DXd was accessible via the special access route prior to HSA approval. Patients enrolled in clinical trials evaluating T-DXd were excluded. HER2-positive disease is defined according to the American Society of Clinical Oncology-College of American Pathologists guidelines, whereas HER2-low disease refers to patients with HER2 IHC scores of 1+ or 2+ with negative fluorescent in situ hybridisation (FISH).²⁶

We calculated the relative dose intensity (RDI) of each dose of T-DXd received by patients. RDI is a measure used to describe dose delays and/or reductions occurring with a chemotherapy regimen. RDI is calculated based on the following formula:

$$\frac{\text{Dose (mg)} / (\text{Weight (kg)})}{\text{Dosing interval (weeks)}} \div 1.8 \times 100\%$$

We defined RDI <85% as clinically significant reduction as maintaining RDI has been associated with improved survival in advanced ovarian and breast cancer in both randomised clinical trials and retrospective observational studies.²⁷ We utilised the RDI from the first treatment cycle in our analysis to differentiate between patients who received upfront dose reductions and those who maintained full dosing,

aiming to demonstrate that the decision to reduce the initial dose did not adversely affect treatment outcomes.

Tumour assessment with either positron emission tomography or computed tomography (CT) scan was performed between 6-weekly to 4-monthly as per routine clinical practice. Patients who had symptoms suggestive of CNS involvement or with known CNS disease also underwent either CT or magnetic resonance imaging brain.

The primary endpoint of our study was rwPFS which is defined as the time from start of treatment to evidence of clinical or radiological progressive disease (PD) or death, whichever occurred first for patients. Secondary endpoints included first site of PD (CNS or extracranial), incidence rate and severity of ILD. The severity of ILD AEs was graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.²⁸ Patients who are alive and do not have any PD will be censored at the date of last follow-up.

Demographic and clinicopathological characteristics as well as treatment details were compared between patients with RDI $\geq 85\%$ and $<85\%$ at the first cycle using the Chi-square test for the categorical variables and Mann-Whitney U test for the continuous variables. The site of PD was also compared by RDI of the first cycle using the Chi-square test. We chose RDI for the first cycle rather than average RDI, as our study focuses on evaluating outcomes in patients who

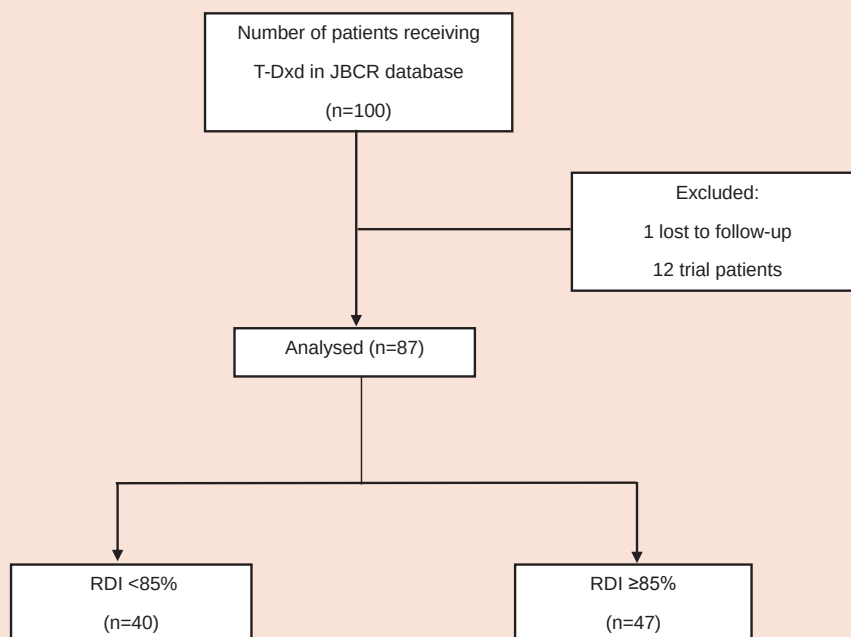
start at a lower dose rather than those who undergo dose reductions due to AEs.

rwPFS were estimated with their corresponding two-sided 95% confidence interval (CI) using Kaplan-Meier method. Difference in survival between the 2 groups was assessed using log-rank test. The reverse Kaplan-Meier method was used to estimate the median follow-up time and corresponding two-sided 95% CI. All *P* values were two-sided and those less than 0.05 were considered statistically significant. Statistical analyses were performed by using R software version 4.4.1.

RESULTS

A total of 87 female patients who received at least 1 dose of T-DXd between December 2021 and June 2024 were identified (Fig. 1). Their median age was 59.0 (range 32–91) years at the first cycle. Majority of patients had invasive ductal carcinoma (83.9%), estrogen receptor positive disease (67.8%) and HER2-positive disease (78.2%). The remaining patients had HER2-low or HER2-ultralow disease. Approximately one-third (27.6%) had brain metastasis before receiving T-DXd. Six patients (6.9%) received T-DXd as a second-line treatment, while the remaining 81 patients (93.1%) received T-DXd in the third-line or later settings. Patients received a median of 4 (range 2–15) lines of systemic treatment in the metastatic setting before receiving T-DXd. A total of 28 patients (32.1%) were still on ongoing treatment with T-DXd at the end of data collection.

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.



RDI: relative dose intensity; T-DXd: trastuzumab deruxtecan; JBCR: Joint Breast Cancer Registry

Reference: Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 Statement: updated guideline for reporting randomised trials. *BMJ*. 2025; 388:e081123.

Almost half of the patients ($n=40$, 46%) received RDI of $<85\%$ and remaining half ($n=47$, 54%) received RDI of $\geq 85\%$ in the first cycle of treatment. Among patients who received RDI $<85\%$, 22 patients had longer dosing interval while 23 patients received initial dose that was $<85\%$ of calculated dose of treatment. Fifteen patients (37.5%) in the group with RDI $<85\%$ required further dose reductions during T-DXd treatment while 31 patients (66%) in the group with RDI $\geq 85\%$ required dose reductions of at least 10% from the first dose (Table 1). Fourteen patients (16.1%) received only 1–2 doses of T-DXd before experiencing PD or succumbing to their illness—9 patients had HER2-positive disease, 2 patients had HER2 IHC2+, FISH negative disease and the remaining 3 patients had HER2 IHC1+ disease.

The median follow-up duration was 6.7 months. In the overall cohort, the median rwPFS was 8.1 months (95% CI, 5.4–10.1 months), with rwPFS rates of 60.0% at 6 months and 29.9% at 12 months (Table 2). When comparing patients with a relative dose intensity (RDI) of $<85\%$ to those with an RDI of $\geq 85\%$ in the first cycle of treatment, the median rwPFS was similar between the 2 groups, at 8.7 months for the RDI $<85\%$ group and 8.1 months for the RDI $\geq 85\%$ group ($P=0.62$), indicating no significant difference in PFS between these groups (Fig. 2). When divided into HER2-positive vs HER2 low disease, there was a significant difference between rwPFS outcomes of 8.8 months vs 2.5 months.

Patients were grouped by average RDI, with those $<85\%$ compared to $\geq 85\%$. The analysis showed a statistically significant difference in rwPFS: patients with average RDI $<85\%$ experienced a median rwPFS of 8.7 months, whereas patients with average RDI $\geq 85\%$ had a median rwPFS of 6.1 months ($P=0.044$).

Most patients with CNS disease at initiation of T-DXd had good control of CNS disease, only 4 out of 24 (16.7%) patients had intracranial PD at treatment failure, and 10 patients (41.7%) with CNS disease at initiation continued to receive T-DXd at the time of data analysis. Eleven (10 with HER2-positive disease and 1 with HER2 IHC2+, FISH negative disease) out of 24 patients had CNS disease that were new or progressing on initiation of T-DXd and 9 of these patients achieved control with T-DXd alone (4 patients had partial response while remaining 5 patients had stable disease). There were also no significant differences between rwPFS of patients with CNS disease and those without (8.7 months vs 7.3 months, $P=0.85$) according to RDI (Fig. 3).

Five patients (5.7%) developed ILD (one grade 1, one grade 2 and three grade 3 events). Among patients who developed grade 3 ILD (3.4%), they received an RDI of 81%, 83% and 91% of T-DXd in the first cycle. ILD occurred in 2 of the 3 patients following 2 doses

of T-DXd and the third patient after 3 doses. Only 1 patient required admission to a high dependency unit for respiratory failure but did not require intubation. All 3 patients achieved rapid resolution of ILD through high dose steroids (steroid doses equivalent to 1 mg/kg prednisolone). None of the 5 patients were rechallenged with T-DXd following ILD and there were no fatalities.

DISCUSSION

This real-world study was premised upon concerns of diminished efficacy from prescribing patterns developed in response to practical challenges in accessing novel therapeutics, such as T-DXd. Dose reduction upfront did not seem to have an impact on patients' PFS or toxicities from treatment from our experience. The observed association between lower average RDI ($<85\%$) and longer rwPFS suggests that reducing the dose does not compromise efficacy and may, in fact, reflect improved tolerability and better treatment adherence. This aligns with the DE-REAL study,²⁹ which found that dose attenuation for AEs did not impact response or survival outcomes. The TRES-Old³⁰ retrospective registry assessed T-DXd toxicity in elderly (≥ 70 years old) patients, reporting that 30% ($n=27$) initiated treatment with a reduced dose, while another 30% ($n=27$) required subsequent dose adjustments. Outcomes remained comparable regardless of dose modifications. To our knowledge, this is the first study to evaluate differences in rwPFS based on RDI at T-DXd initiation. This suggests that T-DXd may potentially be used at a lower starting dose or longer dosing interval, especially for MBC patients in resource limited settings. Further dose optimisation studies are needed to determine the optimal dosing regimen, with a broader inclusion of subjects.

This study demonstrated consistent benefits of T-DXd for patients with CNS metastases, with most achieving good control during treatment and a median progression-free survival of 8.7 months. The PFS of these patients receiving reduced RDI did not vary significantly compared to those with standard dosing. Nine out of 11 patients (81%) with new or progressing CNS disease in our cohort achieved CNS disease control with T-DXd alone; this response rate is comparable with results from TUXEDO-1³¹ and DESTINY-Breast12³² but numbers remain too small for meaningful analysis.

Despite being a heavily treated cohort, about 5.7% (5 out of 87 patients) of our patients developed ILD in contrast to the 13% in DESTINY-Breast01.³³ It is unclear if the lower rates of ILD are related to the lower dose intensity administered among these patients or because of pharmacogenetic differences between real-world and the DESTINY-Breast study populations. Careful monitoring, early recognition and timely

Table 1. Patients' characteristics by RDI of first cycle.

	Total, no. (%) (n=87)	RDI		P value ^a
		<85%, no. (%) (n=40)	≥85%, no. (%) (n=47)	
Ethnicity				0.035
Chinese	69 (79.3)	32 (80.0)	37 (78.7)	
Malay	9 (10.3)	7 (17.5)	2 (4.3)	
Indian	4 (4.6)	1 (2.5)	3 (6.4)	
Others	5 (5.7)	0 (0.0)	5 (10.6)	
Age at the first dose of T-DXd, years				0.126 ^b
Median (range)	59.0 (32.0–91.0)	60.0 (35.0–83.0)	58.0 (32.0–91.0)	
Estrogen receptor status				0.150
Positive	59 (67.8)	24 (60.0)	35 (74.5)	
Negative	28 (32.2)	16 (40.0)	12 (25.5)	
Progesterone receptor status				0.302
Positive	40 (46.0)	16 (40.0)	24 (51.1)	
Negative	47 (54.0)	24 (60.0)	23 (48.9)	
HER2 status				0.632
IHC 1+	10 (11.5)	6 (15.0)	4 (8.5)	
IHC 2+	37 (42.5)	16 (40.0)	21 (44.7)	
FISH				0.103
Positive	28 (75.7)	10 (62.5)	18 (85.7)	
Negative	9 (24.3)	6 (37.5)	3 (14.3)	
IHC 3+	40 (46.0)	18 (45.0)	22 (46.8)	
CNS metastasis				0.327
Yes	24 (27.6)	9 (22.5)	15 (31.9)	
No	63 (72.4)	31 (77.5)	32 (68.1)	
Lines of treatment (for metastatic disease)				0.573 ^b
Median (IQR)	4 (3–7)	5 (3–8)	4 (3–6)	
Range	1–15	1–14	1–15	
Reduction in RDI by >10% after first dose				0.008
Yes	46 (52.9)	15 (37.5)	31 (66.0)	
No	41 (47.1)	25 (62.5)	16 (34.0)	

CNS: central nervous system; FISH: fluorescent in situ hybridisation; HER2: human epidermal growth receptor 2; IHC: immunohistochemistry; IQR: interquartile range; RDI: relative dose intensity; T-DXd: trastuzumab deruxtecan

^a Based on chi-square test, unless otherwise specified.

^b Based on Mann-Whitney U test.

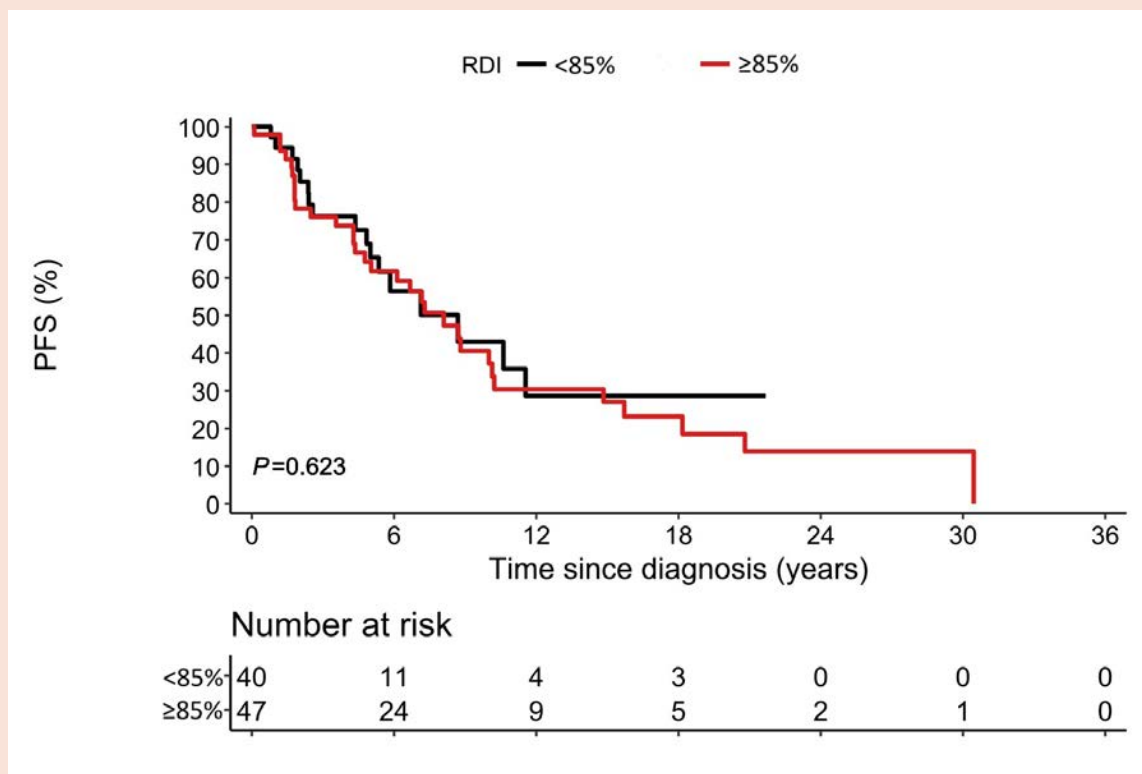
Table 2. Survival summary.

	Total (n=87)	RDI <85% (n=40)	RDI ≥85% (n=47)	P value ^a	HER2+ (n=66)	HER2- (n=21)	P value ^a
Median follow-up, months (95% CI)	6.7 (5.4–8.0)	5.7 (4.3–8.6)	7.2 (5.1–9.9)	0.345	7.2 (5.6–9.9)	5.2 (0.9–8.0)	0.035
PFS				0.623			<0.001
No. of events/patients	49/87	17/40	32/47		35/66	14/21	
Median PFS, months (95% CI)	8.1 (5.4–10.1)	8.7 (4.8–NE)	8.1 (4.8–10.1)		8.8 (6.7–14.8)	2.5 (1.4–8.7)	
6-month PFS, % (95% CI)	60.0 (47.8–70.2)	56.4 (36.0–72.5)	61.7 (45.7–74.2)		66.4 (52.3–77.2)	39.2 (17.7–60.3)	
12-month PFS, % (95% CI)	29.9 (18.0–42.7)	28.6 (10.1–50.6)	30.4 (16.0–46.1)		35.8 (21.3–50.6)	10.5 (0.7–35.4)	

CI: confidence interval; HER2: human epidermal growth receptor 2; NE: not estimable; PFS: progression-free survival; RDI: relative dose intensity

^a Based on log-rank test.

Fig. 2. Real-world progression-free survival Kaplan-Meier curve for patients with RDI <85% and RDI ≥85%.



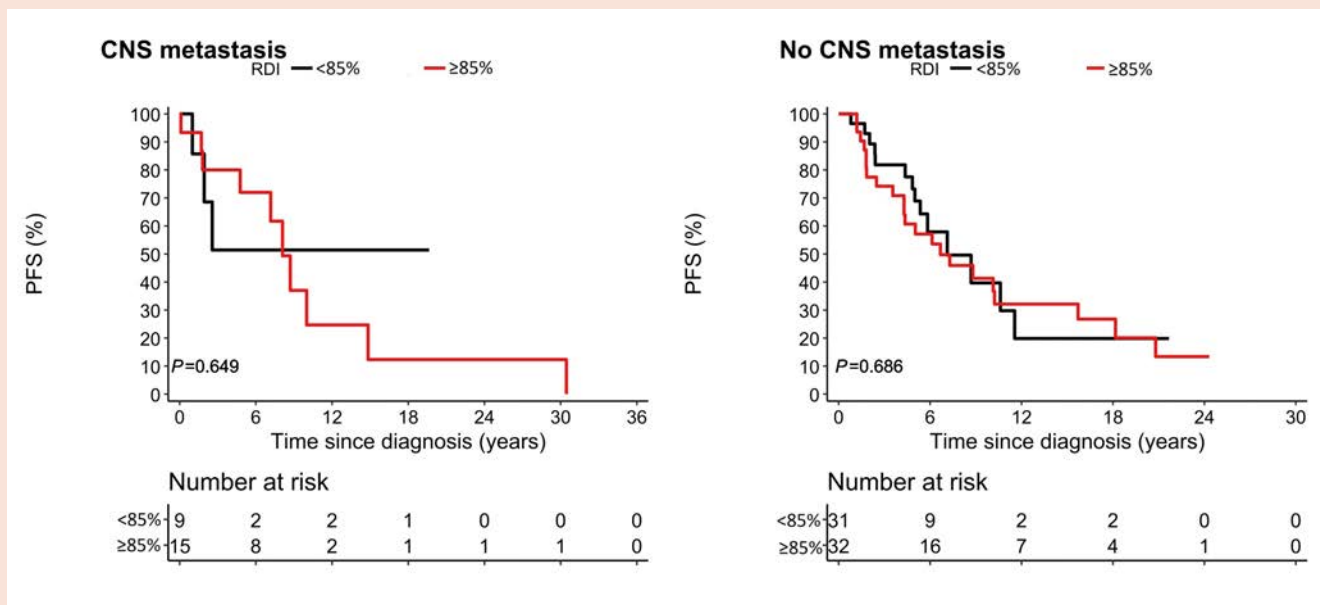
PFS: progression-free survival; RDI: relative dose intensity

glucocorticoid administration for AE management likely contributed to the avoidance of ILD fatalities in our study.^{34,35}

The rWPFS in our study population was significantly lower than that reported in DESTINY-Breast02¹⁰ and DESTINY-Breast03.¹¹ Our cohort included patients

with a median of 4 prior lines of treatment before initiating T-DXd, fewer than those in DESTINY-Breast01.³³ However, many patients in our study had a high disease burden, with several in impending or actual visceral crisis. Notably, 16.1% (14 patients) received only 1–2 doses of T-DXd before experiencing

Fig. 3. Real-world progression-free survival Kaplan-Meier curve for patients with CNS metastasis and no CNS metastasis.



CNS: central nervous system; PFS: progression-free survival; RDI: relative dose intensity

PD or succumbing to their illness. Additionally, 27.6% of patients in our study had brain metastases at T-DXd initiation, compared to 18% in DESTINY-Breast02¹⁰ and 16% in DESTINY-Breast03.¹¹ The optimal utilisation of T-DXd potentially lies in earlier treatment settings, rather than reserving it as a salvage therapy in later lines of treatment. Additionally, delaying T-DXd administration might result in an inadvertent miss in a critical window of opportunity for disease control. Implementing the use of this treatment earlier in the treatment trajectory could therefore potentially maximise its therapeutic efficacy, interrupt disease progression more effectively and improve patient outcomes.

Most real-world data have demonstrated similar PFS compared to DESTINY-Breast02¹⁰ and DESTINY-Breast03¹¹ results. The RELIEVE³⁶ study showed that median time to next treatment after T-DXd was 10.4 months, 7.6 months and 3.7 months, at median follow-up of 10.4 months for patients with HER2-positive, HER2-low and HER2-0 status, respectively. Although time to treatment failure generally results in the underestimation of PFS,³⁷ these results were comparatively more like our real-world study. Possible reasons for a lower PFS in our study include inherent differences in the multi-ethnic Singaporean population as well as higher disease burden and requires further evaluation. Relatively short follow-up and small number of patients may have also accounted for the shorter rwPFS and longer-term follow-up is warranted.

The Italian DE-REAL²⁹ study reported an rwPFS of 16 months, which is comparable to the results seen

in the DESTINY-Breast02¹⁰ and 03¹¹ studies. In the DE-REAL study, a higher proportion of patients received T-DXd in the earlier line settings with 14% receiving T-DXd in the first- or second-line treatment, 29% in the third-line treatment and 57% in fourth line and beyond. In our study, 6.8% received T-DXd in the first or second-line treatment, 13.8% in the third-line treatment and 79.4% on the fourth line and beyond. In the DE-REAL study, 26% of patients required dose reductions due to AEs, but these reductions did not appear to affect the patients' response and survival outcomes. However, this is a small group of patients who had received recommended dose of T-DXd prior to AEs and does not inform of the potential effects on patients receiving dose-reduced T-DXd from initiation of therapy.

This study supports the importance of ensuring fair and equitable trial allocation, in terms of geographical location and ethnicity.³⁸ Even within the Asian category, there are nuanced differences between different ethnic groups (e.g. South Asians, Han Chinese or Japanese).³⁹ Singapore is a multi-ethnic city-state populated by Chinese, Malays, Indians and other racial minorities.⁴⁰ Genetic variations among these ethnic groups can lead to differences in how individuals respond to pharmacotherapy, for instance drug metabolism or susceptibility to AEs.⁴¹ Therefore, it is crucial for international clinical trials to incorporate a broader representation of Asian populations to better understand drug effects and uncover pharmacogenetic issues on diverse ethnicities during clinical development of novel cancer therapeutics.

CONCLUSION

This study suggests no differences in rwPFS with upfront dose reduction of T-DXd. The relatively shorter rwPFS compared to PFS observed in contemporary pivotal clinical trials suggests that the cohort in our study consisted of heavily pre-treated patients with poorer general fitness. This likely reflects the recent access to T-DXd and the relatively short follow-up period, which may have impacted the observed outcomes. With ongoing efforts to improve access to T-DXd, future inclusion of more patients and longer follow-up will be needed to confirm the findings in our study.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Board (2019/2419).

Declaration

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

REFERENCES

- Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-82.
- Ross JS, Slodkowska EA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist* 2009;14:320-68.
- Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015;372:724-34.
- Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2020;21:519-30.
- Agostinetti E, Curigliano G, Piccart M. Emerging treatments in HER2-positive advanced breast cancer: Keep raising the bar. *Cell Rep Med* 2024;5:101575.
- Martin M, Pandiella A, Vargas-Castrillon E, et al. Trastuzumab deruxtecan in breast cancer. *Crit Rev Oncol Hematol* 2024;198:104355.
- Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. *Clin Cancer Res* 2016;22:5097-108.
- Tamura K, Tsurutani J, Takahashi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. *Lancet Oncol* 2019;20:816-26.
- Ogitani Y, Hagihara K, Oitate M, et al. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. *Cancer Sci* 2016;107:1039-46.
- Andre F, Park YH, Kim SB, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2023;401:1773-85.
- Cortes J, Hurvitz SA, Im SA, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial. *Nat Med* 2024;30:2208-15.
- Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med* 2022;387:9-20.
- Bardia A, Hu X, Dent R, et al. Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer. *N Engl J Med* 2024;391:2110-22.
- Health Sciences Authority, Singapore. New drug approvals. <https://www.hsa.gov.sg/announcements/new-drug-approval/new-drug-approvals---october-2021>, October 2021. Accessed 23 June 2025.
- Health Sciences Authority, Singapore. New drug indication approval. [https://www.hsa.gov.sg/announcements/new-drug-indication-approvals/new-drug-indication-approval---april-2023], April 2023. Accessed 23 June 2025.
- Fehm T, Cottone F, Dunton K, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): patient-reported outcomes from a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2024;25:614-25.
- Curigliano G, Dunton K, Rosenlund M, et al. Patient-reported outcomes and hospitalization data in patients with HER2-positive metastatic breast cancer receiving trastuzumab deruxtecan or trastuzumab emtansine in the phase III DESTINY-Breast03 study. *Ann Oncol* 2023;34:569-77.
- Bianchini G, Arpino G, Biganzoli L, et al. Emetogenicity of Antibody-Drug Conjugates (ADCs) in Solid Tumors with a Focus on Trastuzumab Deruxtecan: Insights from an Italian Expert Panel. *Cancers (Basel)* 2022;14:1022.
- Rugo HS, Bianchini G, Cortes J, et al. Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer. *ESMO Open* 2022;7:100553.
- Chiu JWY, Lee SC, Ho JCM, et al. Clinical Guidance on the Monitoring and Management of Trastuzumab Deruxtecan (T-DXd)-Related Adverse Events: Insights from an Asia-Pacific Multidisciplinary Panel. *Drug Saf* 2023;46:927-49.
- Tan CC, Lam CSP, Matchar DB, et al. Singapore's health-care system: key features, challenges, and shifts. *Lancet* 2021;398:1091-104.
- Rudrapatna VA, Butte AJ. Opportunities and challenges in using real-world data for health care. *J Clin Invest* 2020;130:565-74.
- Boissel JP, Cogny F, Marko N, et al. From Clinical Trial Efficacy to Real-Life Effectiveness: Why Conventional Metrics do not Work. *Drugs Real World Outcomes* 2019;6:125-32.
- Kim HS, Lee S, Kim JH. Real-world Evidence versus Randomized Controlled Trial: Clinical Research Based on Electronic Medical Records. *J Korean Med Sci* 2018;33:e213.
- Wong FY, Chua BJG, Dent R, et al. Advancing breast cancer research through real-world data from the Singapore Joint Breast Cancer Registry. *ESMO Real World Data and Digital Oncology* 2025;9:100159.
- Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update. *J Clin Oncol* 2023;41:3867-72.
- Nielson CM, Bylsma LC, Fryzek JP, et al. Relative Dose Intensity of Chemotherapy and Survival in Patients with Advanced Stage Solid Tumor Cancer: A Systematic Review and Meta-Analysis. *Oncologist* 2021;26:e1609-18.

28. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. <https://dctd.cancer.gov/research/ctep-trials/trial-development#ctcae-and-ctep-codes>, 27 November 2017. Accessed 23 June 2025.
29. Botticelli A, Caputo R, Scagnoli S, et al. Real-World Outcomes of Trastuzumab Deruxtecan in Patients With HER2+ Metastatic Breast Cancer: The DE-REAL Study. *Oncologist* 2024;29:303-10.
30. Buono G, Deleuze A, Klocker EV, et al. 237P Real-world safety and efficacy of trastuzumab-deruxtecan (T-DXd) in HER2-positive advanced breast cancer (ABC) elderly patients (pts): The TREX-Old retrospective registry. *ESMO Open* 2023;8:101425.
31. Bartsch R, Berghoff AS, Furtner J, et al. Final outcome analysis from the phase II TUXEDO-1 trial of trastuzumab-deruxtecan in HER2-positive breast cancer patients with active brain metastases. *Neuro Oncol* 2024;26:2305-15.
32. Harbeck N, Ciruelos E, Jerusalem G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. *Nat Med* 2024;30:3717-27.
33. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med* 2020;382:610-21.
34. Abuhelwa Z, Alloghbi A, Alqahtani A, et al. Trastuzumab Deruxtecan-Induced Interstitial Lung Disease/Pneumonitis in ERBB2-Positive Advanced Solid Malignancies: A Systematic Review. *Drugs* 2022;82:979-87.
35. Tarantino P, Modi S, Tolaney SM, et al. Interstitial Lung Disease Induced by Anti-ERBB2 Antibody-Drug Conjugates: A Review. *JAMA Oncol* 2021;7:1873-81.
36. Tarantino P, Hughes M, Kusmick R, et al. Abstract PS08-09: Impact of HER2 expression dynamics on the real-world activity of trastuzumab deruxtecan for metastatic breast cancer (RELIEVE). *Cancer Res* 2024;84:9_Supplement.
37. Walker B, Boyd M, Aguilar K, et al. Comparisons of Real-World Time-to-Event End Points in Oncology Research. *JCO Clin Cancer Inform* 2021;5:45-6.
38. Al Sukhun SA, Vanderpuye V, Taylor C, et al. Global Equity in Clinical Trials: An ASCO Policy Statement. *JCO Glob Oncol* 2024;10:e2400015.
39. Lo C, Nguyen S, Yang C, et al. Pharmacogenomics in Asian Subpopulations and Impacts on Commonly Prescribed Medications. *Clin Transl Sci* 2020;13:861-70.
40. National Population and Talent Division Strategy Group, Prime Minister's Office, Singapore Department of Statistics, Ministry of Home Affairs, Immigration & Checkpoints Authority, Ministry of Manpower. Population in Brief 2024. https://www.population.gov.sg/files/media-centre/publications/Population_in_Brief_2024.pdf, September 2024. Accessed 23 June 2025.
41. Ortega VE, Meyers DA. Pharmacogenetics: implications of race and ethnicity on defining genetic profiles for personalized medicine. *J Allergy Clin Immunol* 2014;133:16-26.

Automatic brain segmentation in cognitive impairment: Validation of AI-based AQUA software in the Southeast Asian BIOCIS cohort

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ABSTRACT

Introduction: Interpretation and analysis of magnetic resonance imaging (MRI) scans in clinical settings comprise time-consuming visual ratings and complex neuroimage processing that require trained professionals. To combat these challenges, artificial intelligence (AI) techniques can aid clinicians in interpreting brain MRI for accurate diagnosis of neurodegenerative diseases but they require extensive validation. Thus, the aim of this study was to validate the use of AI-based AQUA (Neurophet Inc., Seoul, Republic of Korea) segmentation software in a Southeast Asian community-based cohort with normal cognition, mild cognitive impairment (MCI) and dementia.

Method: Study participants belonged to the community-based Biomarker and Cognition Study in Singapore. Participants aged between 30 and 95 years, having cognitive concerns, with no diagnosis of major psychiatric, neurological or systemic disorders who were recruited consecutively between April 2022 and July 2023 were included. Participants underwent neuropsychological assessments and structural MRI, and were classified as cognitively normal, with MCI or with dementia. MRI pre-processing using automated pipelines, along with human-based visual ratings, were compared against AI-based automated AQUA output. Default mode network grey matter (GM) volumes were compared between cognitively normal, MCI and dementia groups.

Results: A total of 90 participants (mean age at visit was 63.32 ± 10.96 years) were included in the study (30 cognitively normal, 40 MCI and 20 dementia). Non-parametric Spearman correlation analysis indicated that AQUA-based and human-based visual ratings were correlated with total ($p=0.66$; $P<0.0001$), periventricular ($p=0.50$; $P<0.0001$) and deep ($p=0.57$; $P<0.0001$) white matter hyperintensities (WMH). Additionally, volumetric WMH obtained from AQUA and automated pipelines was also strongly correlated ($p=0.84$; $P<0.0001$) and these correlations remained after controlling for age at visit, sex and diagnosis. Linear regression analyses illustrated significantly different AQUA-derived default mode network GM volumes between cognitively normal, MCI and dementia groups. Dementia participants had

significant atrophy in the posterior cingulate cortex compared to cognitively normal participants ($P=0.021$; 95% confidence interval [CI] -1.25 to -0.08) and in the hippocampus compared to cognitively normal ($P=0.0049$; 95% CI -1.05 to -0.16) and MCI participants ($P=0.0036$; 95% CI -1.02 to -0.17).

Conclusion: Our findings demonstrate high concordance between human-based visual ratings and AQUA-based ratings of WMH. Additionally, the AQUA GM segmentation pipeline showed good differentiation in key regions between cognitively normal, MCI and dementia participants. Based on these findings, the automated AQUA software could aid clinicians in examining MRI scans of patients with cognitive impairment.

Keywords: artificial intelligence, automated brain segmentation, brain imaging, dementia

CLINICAL IMPACT

What is New

- This study aimed to validate the use of artificial intelligence (AI)-based AQUA segmentation software in a Southeast Asian community-based cohort of cognitively normal, mild cognitive impairment and dementia participants.
- There was a high correlation between human-based and AQUA-based visual ratings.
- There was a high correlation between software-based and AQUA-based disease burden quantification.
- AQUA-derived grey matter volumes distinguished between cognitive syndrome stages.

Clinical Implications

- AI techniques show a high correspondence with existing, established automated pipelines and can aid clinicians in interpreting brain MRI for diagnoses

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INTRODUCTION

Dementia is a heterogeneous disorder that is accompanied by brain alterations, such as grey matter (GM) loss and cerebral small vessel disease burden, including white matter hyperintensities (WMH).^{1,2} Studies show a high prevalence of cerebral small vessel disease in Singapore and the region.³ Notably, WMH have been correlated with poor cognitive outcomes, and predict incident dementia and death as well as higher risk of progression to dementia.⁴⁻⁷ These structurally complex and diverse changes that occur to the brain are significant indicators that can be observed through neuroimaging techniques like magnetic resonance imaging (MRI). The diagnosis of dementia encompasses a spectrum of individuals ranging from those who are cognitively normal, those with mild cognitive impairment (MCI) and lastly, those diagnosed with dementia. The prevalence of dementia in Asia varies, with estimates ranging from 1% to 15% with higher small vessel disease load being associated with faster cognitive decline.⁸⁻¹⁰ Importantly, dementia is on the rise in the region with numbers expected to triple by the year 2050.¹¹ In the Singapore context, the most recent estimates indicate a dementia prevalence of 8.8% in older adults aged 60 years and above.¹²

In clinical settings, the diagnosis of dementia is usually carried out through comprehensive neuropsychological assessments alongside a few basic structural MRI scans. MRI is a key diagnostic tool that helps with the understanding of dementia staging and diagnosis. It allows for a better understanding of the structural condition of the brain, given its ability to provide detailed images that can highlight areas of atrophy, abnormal tissue or vascular changes within the brain.

Current methods of interpretation and analysis of brain MRI scans include visual ratings that require trained professionals to visually examine and rate the scans. Given that this is done manually, it can be time-consuming and subjective as ratings can differ depending on the rater.¹³⁻¹⁵ Although there are software-based neuroimage processing alternatives available, such as the Computational Anatomy Toolbox (CAT12)¹⁶ and the Lesion Segmentation Toolbox (LST),¹⁷ these still require some form of expertise in neuroimaging. Given the recent estimates indicating a significant rise in the prevalence of dementia, especially in Asia, recent efforts have established artificial intelligence (AI) techniques to aid clinicians in interpreting brain MRI scans for the accurate diagnosis of neurodegenerative diseases.¹⁸⁻²⁴

Some advantages of AI-based automated brain segmentation pipelines include AI-based software for brain MRI volumetric analysis, which is accurate

in detecting subtle structural brain changes. This provides clinicians with valuable information for early diagnosis and monitoring disease progression. AI software such as AQUA^{24,25} (Neurophet Inc., Seoul, Republic of Korea) can provide quantitative information based on brain MRI segmentation, particularly in degenerative brain disorders, which include MCI and dementia. Prior validation studies using the AQUA pipeline have demonstrated a high association between total intracranial volume and years of education, as well as a good association between regional brain volume and the risk of cognitive decline.^{26,27} However, no prior validation studies using AQUA have examined the effectiveness of its derived GM segmentation in differentiating between cognitive syndromes along the dementia spectrum.

Conducting volumetric analyses and visual ratings of brain MRI scans allows us to measure changes in brain regions associated with Alzheimer's disease, such as the hippocampus and entorhinal cortex, which are known to undergo significant atrophy in patients with Alzheimer's disease dementia, with regional volume reduction linked to cognitive decline. Recently, automated methods of detecting WMH have been increasingly popular due to their ability to provide an objective evaluation of WMH, which includes precise volumes and locations of these WMH.^{24,25} This automated approach is highly beneficial to clinicians and radiologists, as it aids in efficient and informed decision-making, without the hassle of time-consuming visual inspection. In addition, the objective measurements of WMH from automated tools could improve intra- and inter-rater consistency.²⁸ The AQUA pipeline for WMH quantification has illustrated good performance in prior studies compared to traditional methods.²⁴ However, the use of automated pipelines to provide WMH ratings comparable to visual WMH ratings has not been carried out and will need extensive validation prior to their use in clinical settings. This is especially important to enable timely intervention and management of patient symptoms.

To address these gaps, the main aim of this study was to validate the AI-based AQUA segmentation and WMH quantification software against traditional pipelines in a Southeast Asian community-based cohort of cognitively normal, MCI and dementia participants. Given the past validation studies of the AQUA pipeline, we hypothesised that WMH quantification obtained from AQUA would be similar to that obtained from other automated pipelines. Additionally, we hypothesised that there would be a good correlation between human-based visual reads and AQUA-based WMH ratings. We also hypothesised that GM volumes obtained from AQUA would distinguish between syndromes along the dementia spectrum.

METHOD

Participants

Participants were recruited as part of a community-based research cohort from the Dementia Research Centre (Singapore), Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore. All participants had cross-sectional neuroimaging and neuropsychological assessments carried out as part of their visit. Data from April 2022 to July 2023 were considered for this study. Inclusion criteria comprised the presence of a cognitive concern among individuals from the community aged between 30 and 95 years, inclusive of the specified limits. Key exclusion criteria included illiteracy, diagnosis of major psychotic, psychiatric and neurological disorders, and serious systemic disease. Participants recruited into the Biomarker and Cognition Study, Singapore (also known as BIOCIS) cohort, with a diagnosis of cognitively normal, MCI or dementia were selected based on chronological order. A research diagnosis was assigned to each participant based on existing criteria and guided by their performance on the Montreal Cognitive Assessment (MoCA).^{29–31} Participants with a MoCA score of 27 to 30, inclusive, were classified as cognitively normal. Next, participants who were diagnosed with MCI had scores of 22 to 26, inclusive, on their MoCA test. Lastly, participants who scored less than 22 on their MoCA test were diagnosed with dementia.

Neuropsychological assessments

Neuropsychological assessments through MoCA³² were administered to the participants and rated by trained raters. The MoCA test is a widely used assessment tool by healthcare professionals to monitor cognitive impairment in adults. The MoCA test is deemed as one of the most sensitive neuropsychological tests available for dementia detection. It measures several domains, including executive function as well as memory.

Neuroimaging acquisition

Brain MRI scans for all participants were conducted using the 3T Siemens Prisma Fit scanner (Siemens Healthineers, Erlangen, Germany). The T1-weighted magnetisation-prepared rapid gradient-echo sequence comprised the following parameters: repetition time of 2000 ms, echo time of 2.26 ms, inversion time of 800 ms, flip angle of 8°, matrix size of 256×256 pixels and voxel size of 1.0×1.0×1.0 mm³. The Fluid Attenuated Inversion Recovery (FLAIR) sequence comprised the following parameters: 192 continuous sagittal slices, repetition time/echo time/inversion time = 7000/394/2100 ms, flip angle of 120°, field of view of 320×320 mm², matrix of 320×320 pixels,

isotropic voxel size of 0.8×0.8×1.0 mm³ and bandwidth of 650 Hz/pixel.

All scanned images were reviewed during acquisition, and participants with severe motion artifacts and overt pathological findings were excluded from analysis.

AQUA-based pre-processing of T1-weighted and T2 FLAIR MRI

In T1-weighted MRI brain segmentation of AQUA, brain image pre-processing tasks included min-max intensity normalisation, and histogram matching-based intensity regularisation. Based on cropped local patch images extracted from the whole image, AI algorithms used a three-dimensional convolutional neural network technique to segment brain MRI scans. The proposed architecture employed a variety of AI techniques that enhanced individual brain regions for memory efficiency and robust performance. For efficient training, we performed pre-training and fine-tuning with auxiliary and radiologists-confirmed labels, respectively. This learning strategy enabled heterogeneous neuroimaging data to be used in training without manual annotations. For T2 FLAIR MRI lesion segmentation of AQUA, we developed a spatial augmentation technique that allowed AI algorithms to encompass various pre-defined thicknesses within an iso-cubic dimension (Supplementary Fig. S1). Secondly, leveraging the spatially augmented information, we developed the AI algorithms, which underwent training with the individual characteristics of image slice thickness.^{28,33,34}

White matter hyperintensity visual ratings

MRI neuroimaging assessments were conducted by visually inspecting T1-weighted and FLAIR images obtained. WMH of periventricular and deep white matter lesions were quantified using the Fazekas scale,³⁵ by trained raters with established experience. Specifically, periventricular WMH and deep subcortical WMH were separately rated on a 0 to 3-point scale for both hemispheres. The scoring criteria were as follows: for periventricular WMH, the absence of any WMH = 0; the presence of caps or pencil-thin lining = 1; a smooth halo along the edges of the lateral ventricle = 2; and irregular hyperintensities extending into deep white matter = 3. For deep subcortical WMH, the absence of any WMH = 0; the presence of non-confluent foci of WMH in the deep subcortical region = 1; beginning confluence of WMH foci = 2; and the presence of large confluent areas = 3. The modified Fazekas scale allowed for quantification of white matter lesions in 4 brain regions, namely right periventricular, left periventricular, right deep subcortical and left deep subcortical, to provide a score range of 0–12.⁹ All visual ratings were performed

by 2 independent raters, and any significant discordance in scores was resolved by consensus.

WMH volume derivation

MRI scans were pre-processed using the CAT12 protocol within the Statistical Parametric Mapping 12 toolbox (Wellcome Trust Centre for Neuroimaging, University College London, London, UK; <http://dbm.neuro.uni-jena.de/cat12/>) in MATLAB 2022b software (The MathWorks Inc, Natick, MA, US). First, T1-weighted scans were spatially normalised to template space, registered and corrected for image inhomogeneities.^{36,37} The images were then segmented to estimate GM, white matter and cerebrospinal fluid volumes based on voxel intensities. White matter volume was calculated by summing white matter voxels.

CAT12 then applied a low resolution-specific registration technique to align the tissue probability map and CAT12 atlas to individual scans, followed by fine local tissue corrections.³⁸⁻⁴⁰ WMH were defined as GM-like voxels near the ventricles with high white matter probability or isolated GM islands within white matter.

Next, WMH were identified using the LST protocol in the Statistical Parametric Mapping toolbox, generating binary WMH lesion probability maps.^{17,41} First, T2 FLAIR images were co-registered with T1-weighted scans, and T1-weighted images were segmented into GM, white matter and cerebrospinal fluid.⁴² These segmentations were combined with FLAIR images to estimate WMH probability. A binary lesion map was then grown along voxels that appeared hyperintense on the T2 FLAIR image. T1-weighted and FLAIR images of 10 randomly chosen participants with mild to severe WMH load were segmented at $\kappa = 0.30$, $\kappa = 0.20$, and $\kappa = 0.10$, to define this threshold. $\kappa = 0.10$ was selected as the optimal threshold. Finally, the total lesion volume for each participant was extracted using the LST toolbox.

Statistical analysis

Participant demographics

Chi-square or Fisher's Exact test (where appropriate) were carried out for categorical variables, and an independent samples t-test was used for continuous variables to determine group differences between cognitively normal, MCI and dementia participants (Table 1).

Correlation analyses

We used non-parametric Spearman correlation to assess the association between AQUA-derived Fazekas ratings and human-derived Fazekas ratings for total, periventricular and deep WMH in separate

correlation tests. We also used Spearman rank correlation to assess the correlation between AQUA-derived WMH volumes with LST-derived and CAT12-derived WMH volumes. Non-parametric testing was used since WMH ratings and volumes did not show a normal distribution.

Multiple regression analyses

We carried out additional regression analyses to assess the association between AQUA-derived, LST-derived and CAT12-derived WMH volumes after controlling for age at visit, sex and diagnosis as covariates.

Subsequently, using regression analyses, we examined differences in GM volumes between the cognitively normal, MCI and dementia diagnostic groups in key default mode network GM regions. These regions included the hippocampus, posterior cingulate cortex, precuneus and medial orbitofrontal cortex between the diagnostic groups. These default mode network regions were selected since early atrophy in these regions is specifically associated with dementia.⁴³ For this set of analyses, we first carried out an analysis of variance to examine differences in GM between the 3 diagnostic groups. Subsequently, Tukey's post hoc analysis was carried out to examine pair-wise differences in GM volumes in all regions. Following this, in regions that showed group differences in GM volume in the analysis of variance, we carried out a multiple regression analysis to examine GM volume differences between diagnostic groups, where age at visit and sex were included as covariates.

RESULTS

A total of 90 participants were included in the study, comprising 30 cognitively normal, 40 MCI and 20 dementia participants. The study cohort had an average age at visit of 63.32 ± 10.96 years. Participant demographics are detailed in Table 1. Dementia participants were significantly older compared to both cognitively normal and MCI participants. There were no differences in sex, total intracranial volume and total GM volume between the groups.

AQUA-based WMH ratings are closely associated with human-based visual ratings

When assessing the association between human-based and AQUA-derived WMH ratings, the Spearman correlation analysis indicated that there was a high correlation for total ($\rho=0.66$; $P<0.0001$), periventricular ($\rho=0.50$; $P<0.0001$) and deep ($\rho=0.57$; $P<0.0001$) WMH.

High correlation between AQUA-based volumes and standard automated pipeline based white matter hyperintensity volumes

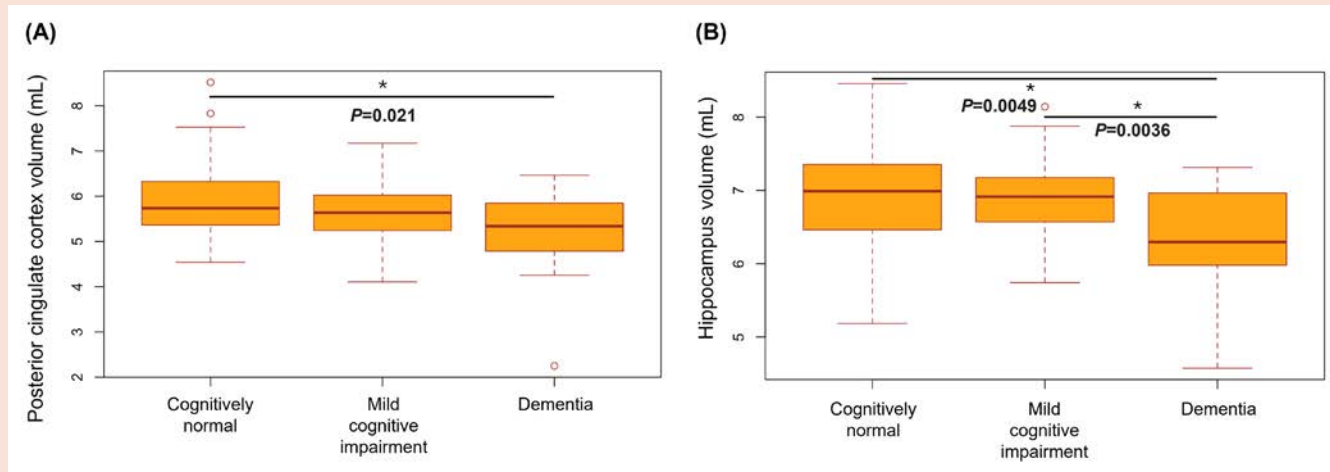
The association between volumetric WMH obtained from AQUA, LST and CAT12 software was assessed

Table 1. Participant demographics: Continuous variables are reported as mean (SD) and the categorical variables are reported as frequency (percentage).

	Cognitively normal (n=30)	Mild cognitive impairment (n=40)	Dementia (n=20)	P value
Age at visit, years, mean (SD)	57.56 (10.89)	63.82 (8.82)	70.95 (10.40)	<0.001
Sex, female, no. (%)	22 (73.3)	27 (67.5)	14 (70)	0.87
Total intracranial volume in mL, mean (SD)	1462.57 (119.99)	1456.48 (146.24)	1443.19 (117.12)	0.87
Total grey matter, volume in mL, mean (SD)	474.32 (40.00)	468.52 (42.46)	447.80 (42.38)	0.08

SD: standard deviation

Fig. 1. High correlation between AQUA-based volumes and standard automated pipeline-based white matter hyperintensity volumes. Spearman rank correlation analyses showed a strong association between AQUA-derived WMH volumes and (A) LST-based as well as (B) CAT12-based WMH volumes. Spearman rank correlation values are indicated as ρ as well as their associated P values. Additional linear regression analyses showed that these associations remained after controlling for age at visit, sex and diagnosis (data in Results section).



WMH: white matter hyperintensities; LST: Lesion Segmentation Toolbox; CAT12: Computational Anatomy Toolbox

* Indicates significance at the $P<0.05$ threshold.

using non-parametric Spearman's rank correlation. Here, AQUA-derived WMH volume was highly correlated with both LST-derived ($\rho=0.84$; $P<0.0001$; Fig. 1A) and CAT12-derived ($\rho=0.85$; $P<0.0001$; Fig. 1B) WMH volumes.

Additional linear regression analysis showed a strong association between AQUA-derived WMH and both LST- ($\beta=0.40$; $P<0.0001$; 95% CI 0.31–0.49) and CAT12-derived ($\beta=1.10$; $P<0.0001$; 95% CI 1.02–1.16) WMH volumes after controlling for age at visit, sex and diagnosis.

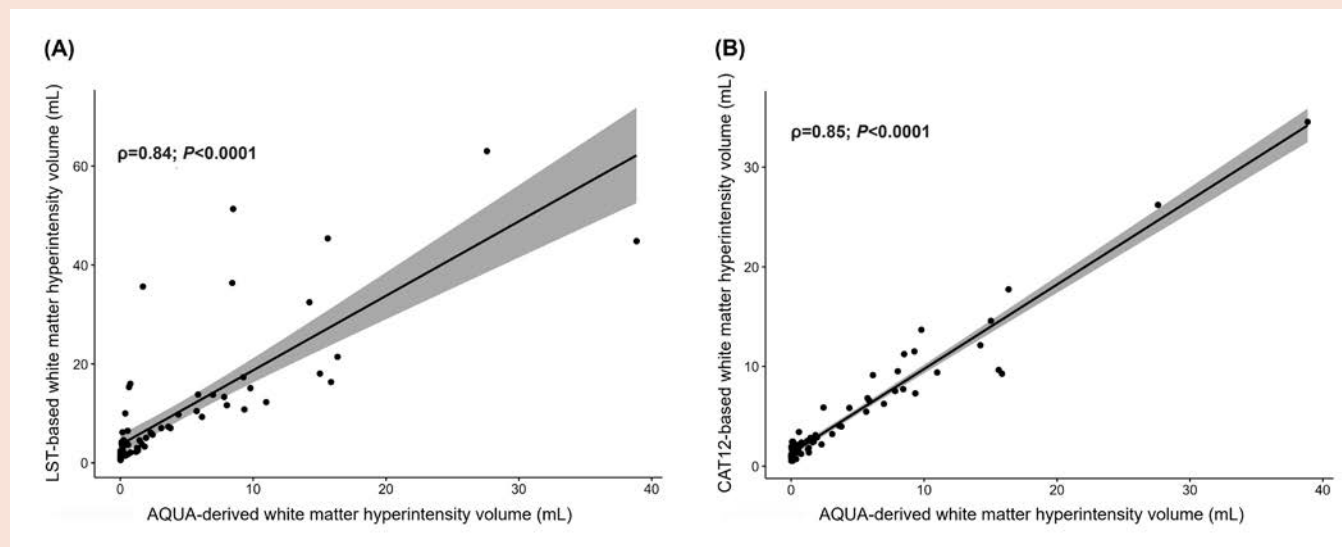
Group differences in AQUA derived GM volumes in default mode network regions between cognitively normal, mild cognitive impairment and dementia groups

Analysis of variance assessed group differences in GM volumes between cognitively normal, MCI and dementia participants. GM volume decreased further along the dementia spectrum, especially in the

posterior cingulate cortex ($P=0.0279$; Fig. 2A) and hippocampus ($P=0.0021$; Fig. 2B). Tukey post hoc pairwise analyses showed that dementia participants had greater posterior cingulate cortex atrophy compared to cognitively normal participants ($P=0.021$; 95% CI -1.25 to -0.08) and greater hippocampal atrophy compared to cognitively normal ($P=0.0049$; 95% CI -1.05 to -0.16) and MCI ($P=0.0036$; 95% CI -1.02 to -0.17) participants.

Subsequent multiple regression analysis indicated a significant reduction in hippocampus volume ($\beta=-0.477$; $P=0.023$; 95% CI -0.88 to -0.06) in dementia participants compared to cognitively normal participants even after controlling for age at visit and sex. A marginal reduction in posterior cingulate cortex volume ($\beta=-0.467$; $P=0.065$; 95% CI -0.96 to 0.03) was observed in dementia participants compared to cognitively normal participants even after controlling for age at visit and sex. There were no differences in precuneus and medial orbitofrontal cortex volume

Fig. 2. Group differences in AQUA-derived grey matter volumes in default mode network regions between cognitively normal, mild cognitive impairment and dementia participants. Grey matter volume decreased further along the dementia spectrum especially in the posterior cingulate cortex and hippocampus regions. Tukey post hoc analyses showed that dementia participants had greater posterior cingulate cortex atrophy compared to cognitively normal participants, and greater hippocampal atrophy compared to cognitively normal and mild cognitive impairment participants. Tukey post hoc analyses results are indicated as $P < 0.05$.



CAT12: Computational Anatomy Toolbox; LST: Lesion Segmentation Toolbox

between the diagnostic groups in the multiple regression analyses.

DISCUSSION

In this study, we examined the usefulness of AI-based software for the automated segmentation of both T1-weighted and FLAIR images in individuals along the continuum of cognitive impairment. WMH ratings and volumes, as well as GM volumes were obtained from AQUA software and compared against human-based and standard neuroimage processing protocols at the Dementia Research Centre (Singapore). In this validation study of 90 participants with a research diagnosis of cognitively normal, MCI and dementia, we illustrated high concordance between human-based and AQUA-based visual ratings of WMH, as well as between existing automated WMH processing pipelines and AQUA. Furthermore, AQUA-based GM volumes in the default mode network showed differences between the diagnostic groups, especially in the hippocampus and posterior cingulate cortex.

Our results demonstrate a high correlation between human-based semi-quantitative visual ratings and AQUA-based ratings of WMH. This would represent the first cohort study to validate the robustness of the WMH ratings pipeline from AQUA. We also observed a high correlation between LST/CAT12 and AQUA-based WMH quantification across the syndrome stages, providing important evidence on the utility of AI-based software for the automated

rating and quantification of WMH. Additionally, the time taken to carry out the WMH image processing and segmentation to determine both the rating and volume outputs was less than 20 minutes, compared to significantly longer times for human-based visual ratings, as well as LST/CAT12-based WMH quantification. Determination of visual rating scores using AQUA software also removed the subjectivity of visual ratings. Indeed, manual ratings are tedious and time-consuming and also have significant disadvantages, including large intra- and inter-observer variabilities, often ranging from 10% to 68%.¹³⁻¹⁵ Moreover, the segmentation performance of AQUA using FLAIR imaging has been developed and validated with strong correlation with human-based visual ratings across various MRI resolutions, ranging from 1 mm to 5 mm slice thickness. In this manner, an automated and quick approach such as AQUA is highly beneficial to clinicians, allowing them to make informed decisions swiftly and efficiently, without the need for time-consuming visual inspection.

When assessing the need for an automated WMH segmentation tool, there are several factors that need to be considered, including the type of scans required, the time taken for segmentation, as well as the availability of the software. In this regard, AQUA uses only the FLAIR scans to obtain WMH ratings and volume, whereas LST requires both T1-weighted and FLAIR, and CAT12 requires only the T1-weighted images. Keeping this in mind, the use of FLAIR scans only, which are the best image type for the detection

of WMH, and the simplified software user experience make AQUA an alternative for the efficient rating and quantification of WMH. Indeed, recently published findings have demonstrated AQUA to have good generalisability and robustness across different datasets.^{24,25} In addition to this, findings from this study validate the robustness of the WMH ratings pipeline from AQUA through the high correlation between human-based visual ratings and AQUA-based ratings of WMH. Given the high prevalence of WMH in Singapore and the region, as well as its relevance in predicting the progression of dementia and cognitive impairment, accurate and timely identification of WMH is imperative for clinical outcomes and therapeutic intervention.^{9,10}

Our findings illustrated that AQUA-based segmentation can distinguish between diagnostic groups based on their GM volumes. Specifically, GM volumes from default mode network regions of interest obtained from AQUA showed greater atrophy in dementia participants compared to cognitively normal and MCI participants. In particular, the posterior cingulate cortex and hippocampus showed significant atrophy even after controlling for age at visit and sex. Since the difference in volume of the default mode network between cognitively normal, MCI and dementia was significant, GM volumes derived from AQUA are a good representation of the neurodegenerative process seen in conditions such as Alzheimer's disease. Notably, the segmentation of T1-weighted structural images to derive GM volume information took less than 5 minutes using the AQUA pipeline, compared to processing times of up to a few hours using other automated neuroimage processing software such as Freesurfer (Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, MA, US).²² AQUA also requires minimum technical know-how. Thus, the use of AQUA in clinical settings could assist clinicians in quantifying WMH volumes in a simple and accurate manner. In particular, development and deployment of patient- and clinician-friendly segmentation methods could enable fast and accurate diagnosis, as well as provide meaningful information on brain structure to aid the diagnosis of neurodegenerative diseases. AI algorithms could also help radiologists as a first line of screening for abnormalities, thus saving time that can be dedicated to more complex abnormalities.

Notably, the AQUA pipeline for T1-weighted MRI conducts sub-regional analysis on a larger scale (>100 regions) in a shorter processing time (<5 min) compared to that of existing tools.⁴⁴ Moreover, its segmentation capabilities have been developed and validated for both East Asian and Caucasian

populations, which are likely to improve applicability and generalisability. Additionally, the AQUA pipeline for T2 FLAIR also has high robustness with low-quality images or participants with severe atrophy.²⁴ This pipeline yields automatic scoring outcomes based on the objective measurements from imaging, validated across multiple studies.^{24,26,27,45} Clinical cases employing these pipelines underscore their alignment with clinical manifestation, emphasising their clinical relevance and reliability.^{25,46} Shorter processing times would enable clinicians to examine greater number of patients more efficiently, effectively and accurately, without the need for tiresome manual visual assessments by trained raters. This would, in turn, lead to potential reduction in healthcare cost, in addition to time savings, as well as help tackle the shortage of qualified radiologists.^{23,47}

Limitations

Our study has some limitations. Our analyses were based on cross-sectional data with a moderate sample size. Due to the moderate sample size of some of our diagnostic groups, potential type II errors in subgroup comparisons are a likely limitation of this study. Thus, these findings need to be further validated using a larger and longitudinal dataset to further examine the suitability of AI-based software such as AQUA for patient-related outcomes. This must be taken into consideration prior to clinical implementation. Additionally, a research diagnosis was used to categorise participants along the dementia spectrum. In this regard, future biomarker-supported studies will provide greater insights into the association between AQUA-based brain changes and more comprehensive diagnosis. We also did not control for the presence of vascular risk factors in our analyses. Future analyses can take into consideration the impact of vascular risk factors, especially on the detection and quantification of WMH.

CONCLUSION

In summary, this validation study indicated the usefulness of AQUA in a community-based research cohort for cognitive impairment and its ability to efficiently quantify WMH burden and GM atrophy changes in cognitively normal, MCI and dementia participants. The AQUA software showed a high correspondence with existing automated pipelines but was much faster and simpler in execution, thus making it a good candidate for clinical settings. Larger longitudinal studies using AQUA segmentation will enable the validation of baseline AQUA-based brain measures, such as GM and WMH volume, for predicting the progression of cognitive decline and conversion from MCI to dementia, which will be imperative for its clinical implementation.

Supplementary material (available online)

Fig. S1. Example of Neurophet AQUA T1 segmentation results.

Ethics statement

The study was approved by Nanyang Technological University Institutional Review Board (2021-1036).

Declaration

All participants provided informed consent in accordance with the Declaration of Helsinki. Nagaendran Kandiah received honoraria and research funding from Neurophet Inc. All other authors declare that they have no competing interests. Individuals from Neurophet Inc. are co-authors on this manuscript and helped install the software as well as provide input on software specifications for the manuscript. They did not have any role in study design, data analysis or reporting of results.

Availability of data and materials

Anonymised data will be shared by request from any qualified investigator.

REFERENCES

- Karas GB, Scheltens P, Rombouts SAR, et al. Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 2004;23:708-16.
- Campbell NL, Unverzagt F, LaMantia MA, et al. Risk Factors for the Progression of Mild Cognitive Impairment to Dementia. *Clin Geriatr Med* 2013;29:873-93.
- Lam BYK, Yiu B, Ampil E, et al. High burden of cerebral white matter lesion in 9 Asian cities. *Scientific Reports* 2021;11:1-12.
- Kloppenborg RP, Nederkoorn PJ, Geerlings MI, et al. Presence and progression of white matter hyperintensities and cognition: a meta-analysis. *Neurology* 2014;82:2127-38.
- Prins ND, Scheltens P. White matter hyperintensities, cognitive impairment and dementia: an update. *Nat Rev Neurol* 2015;11:157-65.
- Prasad K, Wiryasaputra L, Ng A, et al. White matter disease independently predicts progression from mild cognitive impairment to Alzheimer's disease in a clinic cohort. *Dement Geriatr Cogn Disord* 2011;31:431-4.
- Kumar D, Yatawara C, Wang B, et al. APOE4 and Confluent White Matter Hyperintensities Have a Synergistic Effect on Episodic Memory Impairment in Prodromal Dementia. *J Alzheimers Dis* 2022;8:1103-14.
- Catindig JAS, Venketasubramanian N, Ikram MK, et al. Epidemiology of dementia in Asia: insights on prevalence, trends and novel risk factors. *J Neurol Sci* 2012;321:11-6.
- Vipin A, Satish V, Saffari SE, et al. Dementia in Southeast Asia: influence of onset-type, education, and cerebrovascular disease. *Alzheimers Res Ther* 2021;13:195.
- Heng LC, Lim SH, Foo H, et al. Confluent white matter in progression to Alzheimer dementia. *Alzheimer Dis Assoc Disord* 2021;35:8-13.
- Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health* 2022;7:e105-25.
- Subramaniam M, Abidin E, Asharani PV, et al. Prevalence of dementia in Singapore: Changes across a decade. *Alzheimers Dement* 2025;21:e14485.
- Grimaud J, Lai M, Thorpe J, et al. Quantification of MRI lesion load in multiple sclerosis: A comparison of three computer-assisted techniques. *Magn Reson Imaging* 1996;14:495-505.
- Zijdenbos AP, Forghani R, Evans AC. Automatic "pipeline" analysis of 3-D MRI data for clinical trials: Application to multiple sclerosis. *IEEE Trans Med Imaging* 2002;21:1280-91.
- Styner M, Lee J, Chin B, et al. 3D Segmentation in the Clinic: A Grand Challenge II: MS lesion segmentation. *The MIDAS Journal* 2022.
- Gaser C, Dahnke R, Thompson PM, et al. CAT – A Computational Anatomy Toolbox for the Analysis of Structural MRI Data. *Gigascience* 2024;13:giae049.
- Schmidt P, Gaser C, Arsic M, et al. An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *Neuroimage* 2012;59:3774-83.
- Zhu W, Huang H, Zhou Y, et al. Automatic segmentation of white matter hyperintensities in routine clinical brain MRI by 2D VB-Net: A large-scale study. *Front Aging Neurosci* 2022;14:915009.
- Barnett M, Wang D, Beadnall H, et al. A real-world clinical validation for AI-based MRI monitoring in multiple sclerosis. *NPJ Digit Med* 2023;6:196.
- Buchner JA, Kofler F, Etzel L, et al. Development and external validation of an MRI-based neural network for brain metastasis segmentation in the AURORA multicenter study. *Radiother Oncol* 2023;178:109425.
- Song J, Hahn J, Lee J, et al. Comparative validation of AI and non-AI methods in MRI volumetry to diagnose Parkinsonian syndromes. *Sci Rep* 2023;13:3439.
- Lee H, Kim HW, Lee M, et al. Evaluating brain volume segmentation accuracy and reliability of FreeSurfer and Neurophet AQUA at variations in MRI magnetic field strengths. *Sci Rep* 2024;14:24513.
- Lu SL, Xiao FR, Cheng JCH, et al. Randomized multi-reader evaluation of automated detection and segmentation of brain tumors in stereotactic radiosurgery with deep neural networks. *Neuro Oncol* 2021;23:15600-8.
- Lee S, Rieu ZH, Kim RE, et al. Automatic segmentation of white matter hyperintensities in T2-FLAIR with AQUA: A comparative validation study against conventional methods. *Brain Res Bull* 2023;205:110825.
- Kim HW, Rieu Z, Kim D, et al. Clinical Utilization of Brain Magnetic Resonance Imaging-Based Artificial Intelligence Software in the Spectrum of Alzheimer's Disease: Case Series. *J Korean Neuropsychiatr Assoc* 2023;62:86-94.
- Kim REY, Lee M, Kang DW, et al. Increased Likelihood of Dementia with Coexisting Atrophy of Multiple Regions of Interest. *J Alzheimers Dis* 2024;97:259-71.
- Kim RE, Lee M, Kang DW, et al. Effects of education mediated by brain size on regional brain volume in adults. *Psychiatry Res Neuroimaging* 2023;330:111600.
- Rieu ZH, Kim REY, Lee M, et al. A Fully Automated Visual Grading System for White Matter Hyperintensities of T2-Fluid Attenuated Inversion Recovery Magnetic Resonance Imaging. *J Integr Neurosci* 2023;22:57.
- Tan JP, Li N, Gao J, et al. Optimal cutoff scores for dementia and mild cognitive impairment of the Montreal Cognitive Assessment among elderly and oldest-old Chinese population. *J Alzheimers Dis* 2015;43:1403-12.
- Ng A, Chew I, Narasimhalu K, et al. Effectiveness of Montreal Cognitive Assessment for the diagnosis of mild cognitive

- impairment and mild Alzheimer's disease in Singapore. *Singapore Med J* 2013;54:616-9.
31. Kandiah N, Zhang A, Cenina AR, et al. Montreal Cognitive Assessment for the screening and prediction of cognitive decline in early Parkinson's disease. *Parkinsonism Relat Disord* 2014;20:1145-8.
 32. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695-9.
 33. Lee M, Kim J, Kim REY, et al. Split-Attention U-Net: A Fully Convolutional Network for Robust Multi-Label Segmentation from Brain MRI. *Brain Sci* 2020;10:974.
 34. Rieu ZH, Kim JY, Kim REY, et al. Semi-Supervised Learning in Medical MRI Segmentation: Brain Tissue with White Matter Hyperintensity Segmentation Using FLAIR MRI. *Brain Sci* 2021;11:720.
 35. Fazekas F, Chawluk JB, Alavi A. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol* 1987;149:351-6.
 36. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage* 2005;26:839-51.
 37. Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage* 2007;38:95-113.
 38. Mangin JF, Regis J, Frouin V. Shape bottlenecks and conservative flow systems [medical image analysis]. *Proceedings of the Workshop on Mathematical Methods in Biomedical Image Analysis*, San Francisco, CA, US 1996;319-28.
 39. Dahnke R, Yotter RA, Gaser C. Cortical thickness and central surface estimation. *Neuroimage* 2013;65:336-48.
 40. Ashburner J, Friston KJ. Diffeomorphic registration using geodesic shooting and Gauss-Newton optimisation. *Neuroimage* 2011;55:954-67.
 41. Penny W, Friston K, Ashburner J, et al. *Statistical Parametric Mapping: The Analysis of Functional Brain Images*. 1st Ed. Amsterdam/Boston: Elsevier/Academic Press; 2007.
 42. De Marco M, Manca R, Mitolo M, et al. White Matter Hyperintensity Load Modulates Brain Morphometry and Brain Connectivity in Healthy Adults: A Neuroplastic Mechanism? *Neural Plast* 2017;40505.
 43. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008;1124:1-38.
 44. Pemberton HG, Zaki LAM, Goodkin O, et al. Technical and clinical validation of commercial automated volumetric MRI tools for dementia diagnosis-a systematic review. *Neuroradiology* 2021;63:1773-89.
 45. Kim HW, Rieu Z, Lee H, et al. White Matter Lesion Asymmetry: A Potential Indicator of Amyloid Positivity in Patients with Mild Cognitive Impairment. *Alzheimer's & Dementia* 2023;19:e082908.
 46. Kim HW, Kim HJ, Lee H, et al. Magnetic resonance image-based brain age as a discriminator of dementia conversion in patients with amyloid-negative amnesic mild cognitive impairment. *Sci Rep* 2023;13:1-10.
 47. Allyn J, Radiological Society of North America. International Radiology Societies Tackle Radiologist Shortage. 19 February 2020. <https://www.rsna.org/news/2020/february/international-radiology-societies-and-shortage>. Accessed 5 August 2025.

Factors associated with persistent high healthcare service utilisers in Singapore: A population health analysis

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ABSTRACT

Introduction: Albeit comprising a small portion of the hospital population, persistent high utilisers (PHUs) contribute disproportionately to healthcare expenditures. Amid rising healthcare costs and an ageing population, this study examines factors associated with PHUs among residents in eastern Singapore.

Method: This is a retrospective study of eligible patients at Changi General Hospital in Singapore between 1 January 2020 and 31 December 2022. The study included Singapore citizens who utilised any services offered by CGH. Patients were classified as PHUs if their annual healthcare expenditure exceeded SGD3700 for 3 consecutive years. Demographics, healthcare utilisation patterns and clinical profiles were compared, and multivariable analyses were conducted to identify factors associated with PHUs.

Results: There were 267,838 eligible patients identified, with 5316 (2%) classified as PHUs. PHUs accounted for 18.4% of the total healthcare expenditure, with the highest costs attributed to inpatient services, followed by outpatient services. PHUs were more likely to be older, male, non-Chinese and of lower socioeconomic status. Conditions with the strongest association with PHUs were mental health disorders, chronic obstructive pulmonary disease, osteoporosis, asthma and renal diseases. Inpatient discharges from renal medicine, psychological medicine and general/geriatric medicine wards had the strongest association with PHUs. Utilisation of allied health services had the highest odds of being a PHU in outpatient care.

Conclusion: This study identified key factors associated with PHUs, providing invaluable insights into the planning of population health services within the hospital's geographical region. Targeted service development and process improvements of medical care can help mitigate persistent high utilisation.

Keywords: epidemiology, healthcare cost, healthcare utilisation, population health, public health

CLINICAL IMPACT

What is New

- This is the first study in Singapore to identify persistent high healthcare service utilisers from the lens of national-level healthcare utilisation.
- The findings identified key factors associated with persistent high healthcare utilisation.

Clinical Implications

- This study further underscored the importance of advancing integrated care between hospitals, community and primary care in the management of patients with complex care to manage persistent high utilisation of healthcare services for conditions beyond diabetes, hypertension and dyslipidaemia.

INTRODUCTION

Singapore's healthcare system comprises private and public sector providers,¹ financed through a

combination of government subvention and subsidies, personal medical savings and funds, health insurance and a government endowment fund.² Public sector primary care, intermediate and long-term care (ILTC) facilities, and hospitals are grouped and managed by 3 healthcare clusters that receive annual subvention and subsidies from the government for the provision of medical services. In 2023, Singapore's Ministry of Health (MOH) launched the multi-year Healthier SG (a national initiative to focus on preventive healthcare) strategy,³ with 1 key feature to support the 3 healthcare clusters in managing primary care, ILTC and hospitals to care for the residents within their catchment areas. Supported by capitation funding based on the residential population, the strategy focuses on right-siting, service efficiency and preventive care.³ Patients may seek care from private or public providers island-wide, where transfer payments will be made between clusters.³ To optimise the use of capitation funds,⁴ the healthcare clusters would need to identify and implement targeted interventions for high utilisers (HU), reduce healthcare costs and allow resource reallocation. Addressing HUs minimises cost

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variability and stabilises resource allocation under the capitation funding model.

Patients with complex needs are often HUs of healthcare services,^{5,6} with various definitions used to identify them.⁷ Studies showed that most HUs reduce their utilisation over time,^{8,9} but a subgroup of them termed persistent HUs (PHUs),^{10–12} continue high utilisation for more than 2 years.^{10,13} Although PHUs represent a small proportion of the population, they incur disproportionate healthcare expenditures.^{10,11,14,15,24,25} Early identification of PHUs through various definitions aims to reduce future utilisation.^{16,17} However, heterogeneity in definitions, study populations and healthcare financing models makes direct comparisons and application to the Singapore context difficult.

Although some studies in Singapore have characterised PHUs, they focused on either inpatient settings¹⁸ or specific conditions,¹⁹ defining high utilisation based on expenditures, a minimum length of stay or a minimum number of emergency department (ED) visits. While effective for capturing PHUs with high inpatient costs, these approaches may miss other healthcare utilisation patterns such as high outpatient clinic visits or medication costs without inpatient admissions. Moreover, with residents given the flexibility to seek care across multiple institutions nationwide, such a method may not adequately identify PHUs with dispersed utilisation patterns.

With these in mind, this study aimed to examine factors associated with PHUs among residents in eastern Singapore by adopting a different approach to identify PHUs from the lens of national-level healthcare utilisation. Findings from this study could offer potential insights on possible early identification of PHUs, targeted interventions for PHUs and strategic healthcare resource reallocation to reduce their healthcare utilisation. Overall, this study comprised 2 main components. First, it identified PHUs residing within the catchment area of Changi General Hospital (CGH)—a public tertiary hospital in eastern Singapore—from 2017 to 2019, from the national registry. Thereafter, the annual gross bill threshold incurred by these PHUs in CGH was derived and applied to identify PHUs who had visited CGH in 2020–2022.

METHOD

Study design, settings and participants

This retrospective cohort study included all CGH patients who utilised the hospital's services (i.e. ED, inpatient, day surgery, specialist outpatient clinics and community health services—referred to as outpatient services) between 1 January 2020 and 31

December 2022, excluding non-Singapore citizens and those deceased before 1 January 2023.

Definitions of PHUs

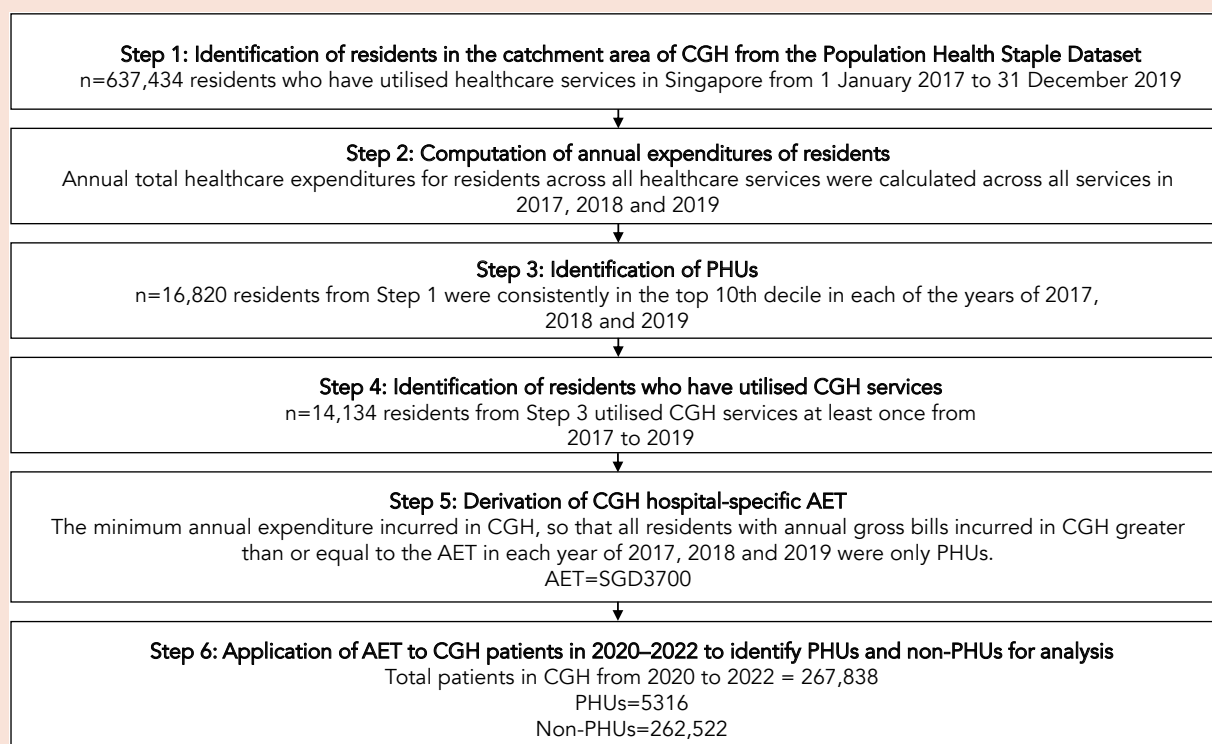
Although utilisation and cost are both common approaches, used either in combination or separately in defining PHUs,²⁰ an expenditure-based approach (surrogate for cost) was employed instead of a utilisation-based approach, basing the expenditure on a patient's gross healthcare bills, for a few reasons. First, a utilisation-based approach may not accurately capture instances of costly healthcare use, such as short inpatient stays that result in disproportionately high bills. Second, in the absence of cost data reflecting the actual expenses incurred by the healthcare system in delivering services, expenditure serves as the most appropriate proxy for assessing patients' healthcare utilisation.²¹

This study classified Singapore citizens as HUs in a year if their annual gross healthcare bills were within the 10th decile of the Singapore population in the same year. These gross healthcare bills referred to gross bills (inclusive of any government subsidies or third-party payments) captured in MOH's Population Health Staple Dataset (PHSD), which recorded all healthcare services utilised by residents at all public healthcare institutions and care settings in Singapore, subsidised primary care and step-down care services (offered by ILTC facilities), inpatient, day surgery and selected outpatient services in private hospitals.

First, PHSD was used to identify PHUs who resided within the catchment area of CGH from 2017 to 2019. Then, the threshold of annual gross bills—which were incurred by these PHUs in CGH—was estimated at SGD3700; this was used to identify PHUs among patients who had visited CGH in 2020–2022. Details of how the threshold was derived from PHSD are described in Supplementary Appendix S2 and Fig. S1. Therefore, a patient was classified as an HU that year if he/she had an annual expenditure of at least SGD3700 in CGH. PHUs were then defined as patients who were HUs for 3 consecutive years from 2020 to 2022 and non-PHUs otherwise. A flowchart of this methodology is summarised in Fig. 1.

In this study, CGH data (instead of the national registry) were used for a few reasons. First, institutional data can be timely accessed with minimal delays and administrative barriers. Second, internal data autonomy enables further qualitative exploration, such as case note reviews, to identify care gaps and understand PHU profiles. Last, institutional data offered higher granularity, capturing details like inpatient discharge specialities, outpatient visit characters and a detailed breakdown of bills by

Fig. 1. Flowchart for PHU determination.



AET: annual expenditure threshold; CGH: Changi General Hospital; PHUs: persistent high utilisers

service type. This allowed deeper insights often missed in the national registry.

Data sources and variables

All datasets were obtained from CGH's administrative databases. Visit-level data were extracted for inpatient admissions, ED visits, outpatient specialist visits and day surgery admissions. Bills data were extracted by service types (e.g. gross bill for specific ward types during inpatient admissions). Patient-level variables were aggregated annually (2020–2022) for variables such as (1) demographics, (2) healthcare service utilisation (i.e. total gross bills, number of visits/admissions and visit/admission details by service type) and (3) disease conditions.

Patients' age, sex, ethnicity, resident status and housing type (based on the housing type with the largest proportion in the block via patients' postal code data²²) were studied. To estimate the density of PHU in each geographic location, a population-related census by geographical location was obtained from the website by a government agency in Singapore and referenced to the 2020 data.²² All healthcare expenditures were adjusted to 2022 Singapore dollars.²³

Dates of expenditures for emergency and outpatient services were based on attendance dates, while those for inpatient services were based on

admission dates. Annual healthcare expenditure (gross bills and number of visits/admissions) was estimated by summing gross bills, including subsidies and third-party payments, by year. Patients' disease conditions were identified based on inpatient discharge diagnosis codes (International Classification of Diseases, Tenth Revision), broadly categorised as detailed in Supplementary Table S3. Inpatient discharge specialities and outpatient specialities were collated to assess associations with PHU status.

Statistical methods

Categorical variables were summarised as frequencies and percentages, while continuous variables as mean and standard deviation (SD). Comparisons between PHUs and non-PHUs were tested with chi-square tests and two-sample t-test for categorical and continuous variables, respectively. For healthcare utilisation-related data, the mean with SD and median with interquartile range of the total healthcare expenditures (2020–2022) were presented, and differences were tested with the Mann-Whitney U-test. Multi-variable logistic regressions were conducted to study the association between PHU status with different disease conditions, healthcare utilisation patterns and demographic characteristics. Statistical significance was set at 5% and analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient population

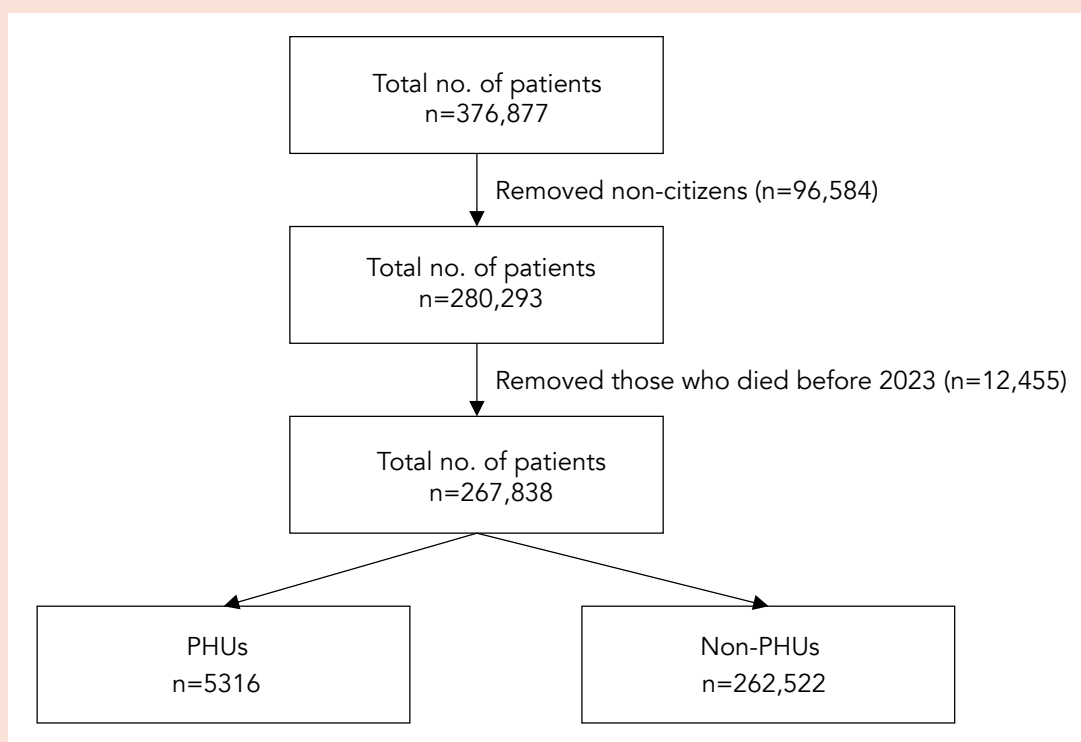
From 1 January 2020 to 31 December 2022, 376,877 patients visited CGH. After excluding non-Singapore citizens (25.6%) and those who passed away before 1 January 2023 (3.3%), 267,838 patients remained in the study cohort. Of these, 5316 were identified as PHUs (1.98%) and 262,522 as non-PHUs (98.0%) (Fig. 2). Fig. 3 illustrates expenditure differences over 3 years for PHUs and non-PHUs, and their distribution across service types. Across the 3 years, despite

comprising only 1.98% of the study cohort, PHUs incurred disproportionately higher total healthcare expenditure at SGD298.8 million (18.4% of CGH's total expenditure), compared to the 99.1% of non-PHUs at SGD1329.5 million. The mean total expenditure for PHUs was SGD56,200 per patient, 11 times that of non-PHUs, at SGD5064.

Patient population characteristics

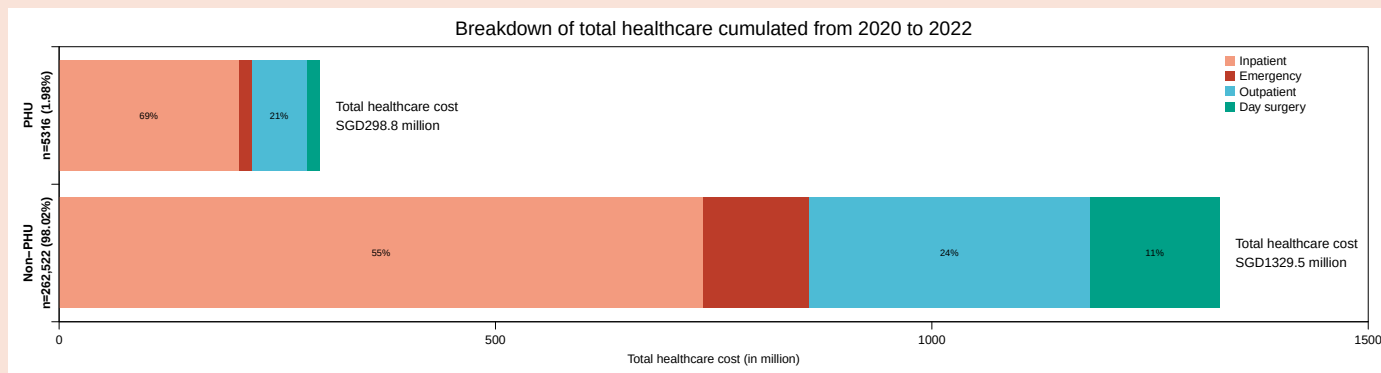
Table 1 compares the demographic profiles of PHUs and non-PHUs. The mean age of PHUs was statistically higher than non-PHUs at 66.3 (SD=14.6) and 48.9

Fig. 2. Flowchart of patients included in the study cohort.



PHUs: persistent high utilisers

Fig. 3. Breakdown of total bill cumulated from 2020 to 2022 for services utilised by PHUs versus non-PHUs.



PHUs: persistent high utilisers

(SD=19.7), respectively ($P<0.001$). The proportion of males was higher in PHUs (58%) compared to non-PHUs (56%). The ethnic distribution of patients was different between PHUs and non-PHUs ($P<0.001$) with more non-Chinese (Indian, Malay and other ethnic groups) in the PHU group (39%) as compared to the non-PHU group (33%). The distribution of housing types was statistically different ($P<0.01$); PHUs (34%)

lived in 1- to 3-room flats (a proxy for lower socioeconomic status [SES]), which was statistically higher compared to non-PHUs (23%).

Table 2 summarises differences in healthcare service utilisation between PHUs and non-PHUs. Among the cohort, 27% had inpatient admissions (89% of PHUs and 26% non-PHUs). PHUs had 3.5 times more admissions and a mean inpatient expenditure of 4.6 times

Table 1. Demographic comparison of PHUs and non-PHUs.

Categories	Overall (n=267,838)	PHUs (n=5316)	Non-PHUs (n=262,522)	P value ^a
Age in 2020, no. (%)				
Mean (SD)	49.3 (19.7)	66.3 (14.6)	48.9 (19.7)	<0.001
40 and below	95,284 (36)	297 (6)	94,987 (36)	<0.001
41–50	35,916 (13)	370 (7)	35,546 (14)	
51–60	48,163 (18)	1001 (19)	47,162 (18)	
61–70	48,521 (18)	1419 (27)	47,102 (18)	
71–80	26,560 (10)	1354 (25)	25,206 (10)	
Above 80	13,394 (5)	875 (16)	12,519 (5)	
Sex, no. (%)				
Female	118,509 (44)	2256 (42)	116,253 (44)	0.008
Male	149,329 (56)	3060 (58)	146,269 (56)	
Ethnicity, no. (%)				
Chinese	177,427 (66)	3232 (61)	174,195 (66)	<0.001
Indian	21,795 (8)	482 (9)	21,313 (8)	
Malay	48,533 (18)	1055 (20)	47,478 (18)	
Others	20,083 (7)	547 (10)	19,536 (7)	
Resident status, no. (%)				
Citizens	18,276 (7)	111 (2)	18,165 (7)	<0.001
Permanent residents	249,562 (93)	5205 (98)	244,357 (93)	
Housing type, no. (%)				
1–2 rooms	15,081 (6)	581 (11)	14,500 (6)	<0.001
3 rooms	45,799 (17)	1244 (23)	44,555 (17)	
4 rooms	79,342 (30)	1536 (29)	77,806 (30)	
5 rooms or executive	63,502 (24)	1100 (21)	62,402 (24)	
Private	53,720 (20)	691 (13)	53,029 (20)	
Missing	10,394 (3.9)	164 (3.1)	10,230 (3.9)	

PHUs: persistent high utilisers; SD: standard deviation

^aP value estimated from Chi-square test.

higher than non-PHUs. The proportion of urgent admissions was similar between groups despite statistical significance. Still, PHUs had an average length of stay 4.0 times longer than non-PHUs, with higher usage across all ward types. Regarding ED utilisation, 60% of the study cohort visited the ED (90% of PHUs and 59% of non-PHUs). PHUs had 4.0 times higher mean ED expenditures and 3.76 times more visits than non-PHUs. Self-referred ED visits were higher among PHUs (73.9%) than non-PHUs (64.9%), but the difference was not statistically significant. For outpatient services, 80% of the cohort utilised them, including all PHUs and 80% of

non-PHUs. PHUs had 7.5 times higher mean outpatient expenditures and 6.2 times more visits than non-PHUs. The mean number of no-show visits was 3.1 times higher in PHUs than in non-PHUs. Last, 21% of the study cohort underwent day surgery (58% of PHUs and 21% of non-PHUs). PHUs had 1.8 times higher mean day surgery expenditure and 1.7 times more day surgery than non-PHUs.

Among those with inpatient admission, all diseases were significantly associated with being a PHU, except dyslipidaemia and myocardial infarction (MI) (Table 3 [item A]). Specifically, mental health disorders (presence of either schizophrenia, major depressive

Table 2. Service utilisation and bill size comparison of PHU and non-PHUs.

	Overall (n=267,838)	PHUs (n=5316)	Non-PHUs (n=262,522)	P value
Total gross bill from 2020 to 2022				
Mean (SD)	6140 (15,800)	56,200 (54,500)	5120 (11900)	<0.001
Median [Q1, Q3]	1430 [440, 5250]	41,100 [25,900, 68,200]	1360 [430, 4820]	
Inpatient admissions, no. (%)	71,931 (27)	4737 (89)	67,194 (26 %)	<0.001
Total inpatient gross bill from 2020 to 2022				
Mean (SD)	14,300 (24,900)	43,800 (54,800)	12,000 (19,200)	<0.001
Median [Q1, Q3]	6720 [2850, 16,400]	29,600 [13,700, 56,100]	6100 [2710, 14,600]	
Total no. of inpatient admissions from 2020 to 2022				
Mean (SD)	1.78 (2.02)	5.34 (5.12)	1.53 (1.25)	<0.001
Median [Q1, Q3]	1.00 [1.00, 2.00]	4.00 [2.00, 7.00]	1.00 [1.00, 2.00]	
Urgent admissions from 2020 to 2022				
Mean (SD) of total no.	1.40 (1.71)	4.28 (4.29)	1.19 (1.09)	<0.001
Mean (SD) of proportion	79.4 (37.4)	80.3 (29.8)	79.4 (37.9)	<0.001
Total no. of inpatient admissions with surgery encounter from 2020 to 2022				
Mean (SD)	0.491 (0.822)	1.36 (1.86)	0.429 (0.650)	<0.001
Total no. of inpatient LOS from 2020 to 2022				
Mean (SD)	10.3 (20.1)	34.3 (39.8)	8.49 (16.4)	<0.001
Median [Q1, Q3]	4.00 [2.00, 10.0]	21.0 [9.00, 45.0]	4.00 [2.00, 8.00]	
Patients who stayed in A ward ¹ , no. (%)	495 (0)	67 (1)	428 (0)	<0.001
Total no. of inpatient LOS in class A from 2020 to 2022				
Mean (SD)	2.74 (3.20)	4.18 (4.94)	2.51 (2.77)	0.0121
Median [Q1, Q3]	1.00 [1.00, 3.00]	2.00 [1.00, 4.50]	1.00 [1.00, 3.00]	
Patients who stayed in B ward ² , no. (%)	7348 (3)	945 (18)	6403 (2 %)	<0.001

Table 2. Service utilisation and bill size comparison of PHU and non-PHUs. (Cont'd)

	Overall (n=267,838)	PHUs (n=5316)	Non-PHUs (n=262,522)	P value
Total no. of inpatient LOS in class B from 2020 to 2022				
Mean (SD)	3.60 (6.87)	7.00 (12.6)	3.09 (5.37)	<0.001
Median [Q1, Q3]	1.00 [1.00, 3.00]	3.00 [1.00, 7.00]	1.00 [1.00, 3.00]	
Patients who stayed in C ward ³ , no. (%)	57,752 (22)	4430 (83)	53,322 (20)	<0.001
Total no. of inpatient LOS in class C from 2020 to 2022				
Mean (SD)	10.6 (20.1)	32.5 (38.0)	8.77 (16.5)	<0.001
Median [Q1, Q3]	4.00 [2.00, 10.0]	20.0 [8.00, 43.0]	4.00 [2.00, 9.00]	
Patients who stayed in ICU ⁴ or HD ⁵ ward, no. (%)	3308 (1)	466 (9)	2842 (1)	<0.001
Total no. of inpatient LOS in ICU or HD from 2020 to 2022				
Mean (SD)	12.2 (19.1)	17.4 (25.0)	11.3 (17.8)	<0.001
Median [Q1, Q3]	6.00 [3.00, 12.0]	9.00 [5.00, 18.8]	5.00 [3.00, 11.0]	
ED visits, no. (%)	159,736 (60)	4782 (90)	154,954 (59)	<0.001
Total ED gross bill from 2020 to 2022				
Mean (SD)	855 (1320)	3170 (4590)	784 (990)	<0.001
Median [Q1, Q3]	533 [354, 922]	2180 [1140, 3830]	524 [350, 875]	
Total no. of ED visits from 2020 to 2022				
Mean (SD)	1.79 (2.83)	6.20 (12.3)	1.65 (1.74)	<0.001
Median [Q1, Q3]	1.00 [1.00, 2.00]	4.00 [2.00, 7.00]	1.00 [1.00, 2.00]	
Total no. of self-referred visits from 2020 to 2022				
Mean (SD)	1.22 (2.68)	4.82 (11.9)	1.11 (1.62)	<0.001
Median [Q1, Q3]	1.00 [0, 1.00]	3.00 [1.00, 6.00]	1.00 [0, 1.00]	
Percentage of self-referred visits from 2020 to 2022				
Mean (SD)	65.2 (44.3)	73.9 (31.4)	64.9 (44.6)	0.689
Outpatient visits, no. (%)	214,142 (80)	5295 (100)	208,847 (80)	<0.001
Total outpatient gross bill from 2020 to 2022				
Mean (SD)	1840 (3050)	11,900 (8850)	1580 (2200)	<0.001
Median [Q1, Q3]	801 [261, 2100]	10,800 [6040, 15,400]	761 [253, 1940]	
Total outpatient from 2020 to 2022				
Mean (SD)	10.9 (16.1)	60.3 (42.9)	9.65 (12.4)	<0.001
Median [Q1, Q3]	5.00 [2.00, 13.0]	51.0 [32.0, 77.0]	5.00 [2.00, 12.0]	
Specialist outpatient clinics, no. (%)	214,142 (80)	5295 (100)	208,847 (80)	<0.001

Table 2. Service utilisation and bill size comparison of PHU and non-PHUs. (Cont'd)

	Overall (n=267,838)	PHUs (n=5316)	Non-PHUs (n=262,522)	P value
Actualised visits				
Mean (SD) of total no.	8.40 (11.5)	40.1 (32.2)	7.57 (9.07)	<0.001
Mean (SD) of percentage	84.7 (19.7)	67.7 (16.6)	85.1 (19.6)	<0.001
Walk-in visits				
Mean (SD) of total no.	5.24 (7.67)	20.1 (17.7)	4.52 (5.94)	<0.001
Mean (SD) of percentage	36.3 (25.5)	33.4 (16.7)	36.4 (25.8)	0.0026
No-show visits (denominator: actualised + no show)				
Mean (SD) of total no.	2.95 (3.62)	8.37 (9.39)	2.73 (2.97)	<0.001
Day surgery, no. (%)	56,923 (21)	3062 (58)	53,861 (21)	<0.001
Total day surgery gross bill from 2020 to 2022				
Mean (SD)	3070 (3250)	5300 (4910)	2950 (3080)	<0.001
Median [Q1, Q3]	2130 [935, 3770]	3770 [1860, 7480]	2080 [915, 3690]	
No. of day surgery				
Mean (SD)	1.61 (1.11)	2.58 (1.96)	1.55 (1.01)	<0.001
Median [Q1, Q3]	1.00 [1.00, 2.00]	2.00 [1.00, 3.00]	1.00 [1.00, 2.00]	

HD: high dependency; ICU: intensive care unit; LOS: length of stay; SD: standard deviation; PHUs: persistent high utilities

^aA ward: most expensive option—private room with no government subsidy.

^bB ward: moderately priced—shared room (4–6 beds) with partial subsidy.

^cC ward: most affordable—basic shared room (8–10 beds) without air-conditioning and with the highest subsidy.

^dICU ward: specialised unit providing close monitoring and life support for critically ill patients, with the highest level of care and staffing.

^eHD ward: provides a higher level of care than general wards for patients who are stable but still require close monitoring and medical support.

disorder, anxiety disorder or bipolar disorder) showed the strongest association (odds ratio [OR]=3.48; 95% confidence interval [CI]=[2.97, 4.08]), followed by chronic obstructive pulmonary disease (COPD) (OR=2.69; 95% CI=[2.29, 3.17]) and osteoporosis (OR=2.64; 95% CI=[2.36, 2.94]). Table 3 (item B) shows that renal medicine or nephrology department (OR=14.1; 95% CI=[12.2, 16.2]) had the strongest association with being a PHU, followed by the psychological medicine (OR=11; 95% CI=[7.86, 15.3]), general medicine or geriatric medicine (OR=4.9; 95% CI=[4.55, 5.28]). Table 3 (item C) highlights that visits to allied health services had the highest odds of being a PHU (OR=23.2; 95% CI=[20, 27]). Across the 3 logistic regression models, older age, male sex, non-Chinese and lower socioeconomic status had significantly higher odds of being a PHU.

Table 4 details the mean bills for each service type and services within the service types by PHUs and non-PHUs, while Supplementary Fig. S2 details the proportion of services spent for each service type by groups. For inpatient admission, ward services and

investigations constitute the largest portion of bills, with PHUs spending 4.13 and 3.69 times more, respectively, compared to non-PHUs. In the ED, attendance fees and investigation dominated costs, with PHUs spending 4.77 and 3.75 times, respectively than non-PHUs. In outpatient care, PHUs primarily spent on medications, investigations and consultations, whereas non-PHUs spent most on investigations. PHU medication bills were 14.8 times higher than non-PHUs. For day surgery, facility fees accounted for the largest share, with PHUs spending 1.7 times more than non-PHUs. The heat map in Supplementary Fig. S3 shows the density of PHUs per 1000 residents in subzones with over 3000 residents. Bedok North (7.83), Tampines East (7.16) and Kembangan (7.12) had the highest PHU densities.

DISCUSSION

Key results

This study identified factors significantly associated with being a PHU, including older age, male sex,

Table 3. Distribution of (A) disease profile, (B) inpatient discharge specialties, (C) outpatient specialties by groups and adjusted OR from respective logistic regression models with 95% CI for diseases associated with being a PHU.

	Overall	PHUs	Non-PHUs	P value ^a	Adjusted OR ^b [95% CI] ^c
(A) Disease profile^{c, d}					
No. of patients	71,817	4735	67,082	-	-
No. of conditions					
Mean (SD)	1.44 (1.81)	3.17 (2.30)	1.32 (1.71)	<0.001	
Median [Q1, Q3]	1.00 [0, 3.00]	3.00 [1.00, 5.00]	0 [0, 3.00]		
Conditions, no. (%)					
Diabetes	18,868 (26)	2338 (49)	16,530 (25)	<0.001	1.47 [1.33–1.62] ^e
Hypertension	24,373 (34)	3005 (63)	21,368 (32)	<0.001	1.28 [1.17–1.41] ^e
Dyslipidaemia	19,076 (27)	2271 (48)	16,805 (25)	<0.001	0.939 [0.85–1.04]
Stroke	3544 (5)	381 (8)	3163 (5)	<0.001	1.1 [0.973–1.24]
Atrial fibrillation	3429 (5)	689 (15)	2740 (4)	<0.001	1.88 [1.7–2.09] ^e
Asthma	1223 (2)	193 (4)	1030 (2)	<0.001	2.41 [2.02–2.88] ^e
Chronic obstructive pulmonary disease	1165 (2)	238 (5)	927 (1)	<0.001	2.69 [2.29–3.17] ^e
Myocardial infarction	3596 (5)	530 (11)	3066 (5)	<0.001	0.986 [0.879–1.11]
Ischaemic heart disease	8744 (12)	1496 (32)	7248 (11)	<0.001	1.81 [1.67–1.97] ^e
Heart failure	2988 (4)	688 (15)	2300 (3)	<0.001	1.67 [1.5–1.86] ^e
Renal	8767 (12)	1730 (37)	7037 (10)	<0.001	2.4 [2.22–2.6] ^e
Osteoporosis	2996 (4)	547 (12)	2449 (4)	<0.001	2.64 [2.36–2.94] ^e
Dementia	2701 (4)	479 (10)	2222 (3)	<0.001	1.89 [1.67–2.13] ^e
Mental health disorders ^e	1334 (2)	259 (5)	1075 (2)	<0.001	3.48 [2.97–4.08] ^e
(B) Inpatient discharge specialty^c					
No. of patients	71,817	4735	67,082		
Patients who had admissions to, no. (%)					
Cardiovascular medicine/cardiology	10,079 (14)	1235 (26)	8844 (13)	<0.001	4.45 [4.08–4.84] ^e
Dermatology	141 (0)	19 (0)	122 (0)	0.00177	4.17 [2.31–7.53] ^e
Endocrinology	872 (1)	116 (2)	756 (1)	<0.001	3.25 [2.53–4.17] ^e
Otolaryngology	1717 (2)	138 (3)	1579 (2)	0.0168	3.59 [2.87–4.49] ^e

Table 3. Distribution of (A) disease profile, (B) inpatient discharge specialties by groups and adjusted OR from respective logistic regression models with 95% CI for diseases associated with being a PHU. (Cont'd)

	Overall	PHUs	Non-PHUs	P value ^a	Adjusted OR ^b [95% CI] ^c
Ophthalmology	436 (1)	47 (1)	389 (1)	<0.001	3.77 [2.57–5.52] ^g
Gastroenterology	4000 (6)	588 (12)	3412 (5)	<0.001	3.92 [3.49–4.41] ^g
General/geriatric medicine	28,349 (39)	3073 (65)	25,276 (38)	<0.001	4.9 [4.55–5.28] ^g
Infectious disease	2454 (3)	317 (7)	2137 (3)	<0.001	2.93 [2.5–3.43] ^g
Neurology	2325 (3)	205 (4)	2120 (3)	<0.001	2.81 [2.35–3.35] ^g
Neurosurgery	590 (1)	41 (1)	549 (1)	0.79	2.03 [1.4–2.95] ^g
Oral and maxillofacial surgery	141 (0)	4 (0)	137 (0)	0.103	2.62 [0.821–8.38]
Orthopaedic surgery	10,521 (15)	873 (18)	9648 (14)	<0.001	3.31 [3.01–3.63] ^g
Psychological medicine	345 (0)	67 (1)	278 (0)	<0.001	11 [7.86–15.3] ^g
Renal medicine/nephrology	1381 (2)	558 (12)	823 (1)	<0.001	14.1 [12.2–16.2] ^g
Respiratory medicine	3663 (5)	564 (12)	3099 (5)	<0.001	4.1 [3.64–4.63] ^g
Rehabilitation medicine	2706 (4)	379 (8)	2327 (3)	<0.001	3.07 [2.66–3.53] ^g
Sleep medicine surgery science	1586 (2)	127 (3)	1459 (2)	0.0248	3.24 [2.58–4.07] ^g
General surgery	12,924 (18)	1562 (33)	11,362 (17)	<0.001	4.61 [4.26–5] ^g
Urology	2349 (3)	258 (5)	2091 (3)	<0.001	3.58 [3.04–4.23] ^g
(C) Outpatient specialty^f					
No. of patients	226,895	5308	221,587	-	
Patients who ever visited, no. (%)					
Allied health services	18,138 (8)	1313 (25)	16,825 (8)	<0.001	23.2 [20–27] ^g
Medical discipline services	113,458 (50)	5119 (96)	108,339 (49)	<0.001	4.34 [4.07–4.62] ^g
Nursing related clinic services	2786 (1)	368 (7)	2418 (1)	<0.001	5.55 [4.92–6.26] ^g
Surgical discipline services	153,258 (68)	4999 (94)	148,259 (67)	<0.001	2.3 [2.14–2.47] ^g
Other services	74,236 (33)	3737 (70)	70,499 (32)	<0.001	1.82 [1.6–2.07] ^g

CI: confidence interval; OR: odds ratio; PHUs: persistent high utilisers; SD: standard deviation

^aP value estimated from Chi-square test.^bAdjusted OR from a logistic regression with adjustments for age, sex, ethnicity and housing type where all the reference groups presented are “No” or absence of the mentioned items.^cA total of 63,430 patients were considered for the analysis after excluding 2681 (4.1%) of patients with missing housing type data.^dLimited to patients who were admitted to inpatient at least once during the study period.^eMental health disorders represented patients diagnosed with either schizophrenia, major depression, anxiety or bipolar disorder.^fA total of 218,090 patients were considered for the analysis after excluding 8805 (3.8%) of patients with missing housing type data.^gRepresents statistical significance at 5% level.

Table 4. Mean bills breakdown by service types and different services (in SGD).

Service type	Services	PHU (SGD)	Non-PHU (SGD)	Ratio ^a
Inpatient	Emergency visit attendance fees	485.38	146.08	3.32
	Consumables	3378.37	932.97	3.62
	Dialysis	1208.07	54.19	22.29
	Facility fees	2922.6	1019.33	2.87
	Implants	1430.94	592.24	2.42
	Investigations	8817.26	2386.4	3.69
	Medications	3202.07	481.35	6.65
	Others	8.98	2.67	3.36
	Procedures	4485.15	1005.32	4.46
	Professional fees	2197.71	713.04	3.08
	Rehabilitation services	1113.54	280.52	3.97
	Ward services	15167.08	3673.49	4.13
Emergency department	Attendance fees	1599.76	426.98	3.75
	Investigations	1292.79	270.89	4.77
	Medications	52.56	17.71	2.97
	Others	5.35	1.77	3.02
	Procedures	55.18	18.49	2.98
	Professional fees	0.06	0.03	2
Outpatient	Consultation	1795.29	381.76	4.7
	Consumables	0.01	0.01	1
	Investigations	3904.91	696.86	5.6
	Medications	4973.36	335.7	14.81
	Miscellaneous	136.88	27.06	5.06
	Miscellaneous treatment	0.17	0.02	8.5
	Other procedures	0.11	0.65	0.17
	Others	223.01	11.91	18.72
	Procedures	642.14	65.53	9.8
	Rehabilitation services	349.98	49.34	7.09
	Services	19.73	1.04	18.97
Day surgery	Consultation	42.61	34.54	1.23
	Consumables	869.86	371.48	2.34
	Facility fees	2131.85	1256.36	1.7
	Implants	84.56	50.96	1.66
	Investigations	594.47	334.64	1.78
	Medications	108.56	52.74	2.06
	Others	136.75	78.71	1.74
	Procedures	124.55	59.09	2.11
	Professional fees	978.97	559.8	1.75

PHUs: persistent high utilisers; SGD: Singapore dollars

^aRepresents the ratio of the mean value from PHUs and the mean value from non-PHUs.

non-Chinese and lower SES. Despite only comprising 2% of the study cohort, they accounted for nearly 20% of the total healthcare expenditure. PHUs spent 4.6, 4.0, 7.5 and 1.8 times more on inpatient, ED, outpatient and day surgery services respectively, compared to non-PHUs. Mental health disorders had the strongest association with being a PHU, followed by COPD and osteoporosis. Renal medicine was the inpatient specialty most strongly associated with PHUs, while utilisation of allied health services in outpatient settings had the strongest association.

Interpretation

This study's analysis reflected the high prevalence of cardiovascular and other chronic medical conditions in PHUs, which was commonly observed across studies.^{5,10,11,18} While diseases such as diabetes, hypertension and dyslipidaemia are more prevalent in this study's population settings, the analysis saw specifically that mental health issues, COPD and osteoporosis had the highest odds of being a PHU, highlighting that prioritisation of the needs of these conditions to address high utilisation would be useful. While the prevalence of mental health disorders (5.0%) among PHUs was lower than other chronic medical conditions, its strong association (OR 3.48) was observed, in line with many studies in US Medicaid and total population studies.^{7,24}

Renal conditions were the most prevalent among the diseases with the highest odds of association with being a PHU. This was aligned with the findings of other studies given that patients often had worsening symptoms with progression of chronic kidney disease, with other possible complications such as acute kidney injury, heart failure, MI, stroke and anaemia requiring outpatient, ED visits and inpatient admissions.²⁵⁻²⁷ Utilisation of allied health services in outpatient settings was strongly associated with PHU status, which was unsurprising given that PHUs usually have functional impairments or psychosocial challenges, requiring intervention by allied health professionals. This study further underscored the importance of advancing integrated care between hospitals, community and primary care, e.g. via patient-centred care models^{12,30-33} in the management of patients with complex care. Integrated care models through community sited services can reduce reliance on hospital-based allied health intervention and address persistent high utilisation more effectively. Future studies could benefit from cross-jurisdictional comparisons to understand how differences in healthcare systems, social practices and cultural structures influence healthcare utilisation.

Similar to other studies, PHUs in this study were older, lived in smaller flat sizes and have a higher prevalence of chronic diseases as well as mental health

disorders. While the OR for being a PHU was higher in those above the age of 41, the OR was lower for those above 80 years compared to those aged between 41 and 80 years. While a previous study in the US²⁸ attributed similar findings to mortality effects, this explanation was not applicable to this study as patients who were deceased prior to 2023 were excluded. The mechanism underlying this observation warrants further investigation by future studies. The study's findings also align with a previous study in Singapore²⁹, which identified total length of stay in the last 12 months and days following the last non-elective admission as key predictors of frequent hospital use. This reinforces the value of historical inpatient utilisation in identifying high-needs patients. Last, useful insights on the distribution of PHUs across the catchment area of CGH were provided to aid regional health management. The identification of the subzones with a higher density of PHUs would facilitate the assessment and development of service needs in these areas with stakeholders in medical care as well as social services.

Strength

Defining PHU in this study presented methodological challenge due to substantial heterogeneity in existing literature on study population selection criteria, PHU definitions and healthcare expenditure metrics.³ To the authors' knowledge, only 1 other study from Singapore conducted analysis on PHUs in a 1000-bed academic medical centre,¹⁸ using the annual threshold of the top 10% of inpatient expenditure (SGD8150) to define a PHU (if they were HUs for 3 consecutive years). A novel threshold-setting approach, which considered the residents' total healthcare expenditure and those who had significant hospital service utilisations, was undertaken. In this study, the threshold for an HU in the hospital was established at SGD3700, taking reference from the healthcare expenditure of the resident population across all healthcare services in hospitals and the community. While the derived threshold was lower, this reflects a larger denominator with further lower-cost users. Additionally, policy shifts between the 2 periods (2005–2013 and 2020–2022) such as the expansion of Community Health Assist Scheme³⁰ in 2019, a Singapore government programme that provides subsidies for Singapore citizens at participating clinics, may have expanded subsidies and shifted care towards the community, reducing hospital-centric expenditures and lowering top-decile thresholds in this analysis. Further, this study considered all healthcare services within CGH apart from just inpatient admission, although inpatient admissions were the main contributor to the healthcare expenditures. This approach revealed that high outpatient service

utilisation contributed substantially to total expenditure, with some patients classified as PHU based on outpatient service utilisation alone. This approach, which expanded the study population beyond a focus on specific chronic conditions,¹⁹ captured patient groups who might otherwise slip through the gaps in care, particularly those with high healthcare needs that do not fit neatly into specific disease categories. Last, the analysis of visit-level and billing-item-level data provided granular insights into utilisation patterns that may not be discernible in national-level datasets.

This study identified key factors associated with PHUs. These factors can inform clinical interventions and system-level strategies to address PHUs. Once these interventions and strategies are identified, relevant resources can be scoped and set aside so that the interventions and strategies can be implemented efficiently to address PHUs. These resources may include (1) manpower and information technology (IT) infrastructure needed for the development of predictive tools for early identification of at-risk PHU patients using predictive tools; (2) manpower, workflow and IT integration to enhance coordination between hospital, community and primary care, particularly in managing mental health, renal care and rehabilitation, so that the fragmentation of care can be reduced and unnecessary utilisation can be prevented. Additionally, the geospatial insights on PHU concentration across subzones offer a basis for prioritising service development and outreach efforts within the catchment area in Singapore. Admittedly, the findings may not be generalisable to other countries due to underlying differences in healthcare practices and policies. Nevertheless, the reported methodology offers a systematic framework for studying PHUs, and this framework can be readily employed by other researchers in other countries who also aim to develop clinical interventions and system-level strategies that address PHUs.

Limitations

This study is not without its limitations. First, the analysis was restricted to PHUs who utilised CGH's services, excluding those residing in CGH's catchment area but sought care elsewhere. Second, while many CGH patients were discharged to community hospitals for continued care, expenditure data from these facilities were unavailable for a comprehensive analysis. Third, healthcare utilisation patterns would usually fluctuate with patient, policy and environmental factors, which should be considered when the results from the analysis is generalised. Also, the cross-sectional design of this study using calendar year cut-offs may have resulted in patients who were ill and consumed a series of sequential services spanning the

year-end to fall below the HU threshold, compared to a patient with similar care journey beginning earlier in the year.

Additionally, the derivation of the annual expenditure threshold did not account for expenditures incurred in private services due to data limitations. This could partly explain the association of low SES with PHU as higher SES residents may tend to seek care in private institutions. The macro-costing approach used, although suitable for estimating overall healthcare utilisation, unfortunately does not allow attribution of expenditure to specific conditions. As such, observed associations with individual chronic diseases, may reflect the cumulative cost burden of multimorbidity rather than isolated disease effects. The study period was also affected by the COVID-19 pandemic, which may have influenced healthcare utilisation patterns. However, the recency of the data for this study context (requiring 3 years of data) ensures relevance despite this limitation. Additionally, findings from these patients identified during the pandemic are likely to offer more valuable and relevant insights, as they are more likely to be clinically complex (given that many avoided healthcare services during the pandemic).

CONCLUSION

This study highlighted PHUs as a small but distinct patient group with disproportionately high healthcare utilisation across all service types. Their profile (i.e. older age, male sex, lower socioeconomic status, chronic disease burden and strong associations with mental health disorders, renal conditions and allied health services used) highlighted the complexity of their needs. These findings can inform clinical interventions and system-level strategies to address PHUs. Early identification of at-risk patients using predictive tools can support timely care planning. Enhanced coordination between hospital, community and primary care, particularly in managing mental health, renal care and rehabilitation, may reduce the fragmentation of care and prevent unnecessary utilisation.

Supplementary materials

Appendix S1. Population Health Staple Dataset (PHSD): The Singapore National Healthcare Expenditure Registry dataset.

Appendix S2. Threshold estimation.

Fig. S1. Breakdown of eligible residents from the study cohort in DS1.

Fig. S2. Bills breakdown by PHUs and non-PHUs for the different services for (A) inpatient admission, (B) emergency department, (C) outpatient and (D) day surgery.

Fig. S3. Heat map for the no. of resident PHUs per 1000 residential population in the respective subzones.

Table S1. Comparison of catchment area demographics with study population demographics.

Table S2. Determination of AET in DS1.

Table S3. ICD-10 codes for broad disease conditions.

Table S4. Fully adjusted logistic regression models with 95% CI for (A) diseases, (B) inpatient discharge specialty and (C) outpatient specialty.

Table S5. Subgroup analysis: PHUs versus non-PHUs by sex (female and male), age group (above 60 and 60 and below) and ethnicity (Chinese, Malay, Indian and Others).

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2023/2314) and deemed it not to require ethical deliberation, as this is a service evaluation project using deidentified data.

Declaration

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

REFERENCES

- Ministry of Health, Singapore. Upcoming Healthcare Facilities from 2025 onwards. <https://www.moh.gov.sg/seeking-healthcare/find-a-facility-or-service/types-of-medical-facilities-and-services/find-a-medical-facility/facilities-from-2025-onwards/>. Accessed 18 August 2025.
- Ministry of Health, Singapore. Government Health Expenditure and Healthcare Financing. <https://www.moh.gov.sg/others/resources-and-statistics/government-health-expenditure-and-healthcare-financing>. Accessed 18 August 2025.
- Ministry of Health, Singapore. The White Paper on Healthier SG, 21 September 2022. <https://www.healthiersg.gov.sg/resources/white-paper/>. Accessed 1 March 2024.
- Ministry of Health, Singapore. Capitation, 10 May 2023. <https://www.moh.gov.sg/newsroom/capitation>. Accessed 30 December 2024.
- Zook CJ, Moore FD. High-cost users of medical care. *N Engl J Med* 1980;302:996-1002.
- Reid R, Evans R, Barer M, et al. Conspicuous consumption: characterizing high users of physician services in one Canadian province. *J Health Serv Res Policy* 2003;8:215-24.
- Wammes JJG, van der Wees PJ, Tanke MAC, et al. Systematic review of high-cost patients' characteristics and healthcare utilisation. *BMJ Open* 2018;8:e023113.
- Chakravarty S, Cantor JC. Informing the Design and Evaluation of Superuser Care Management Initiatives: Accounting for Regression-to-the-Mean. *Med Care* 2016;54:860-7.
- Johnson TL, Rinehart DJ, Durfee J, et al. For many patients who use large amounts of health care services, the need is intense yet temporary. *Health Aff (Millwood)* 2015;34:1312-9.
- Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. *CMAJ* 2016;188:182-8.
- Figueroa JF, Zhou X, Jha AK. Characteristics And Spending Patterns of Persistently High-Cost Medicare patients. *Health Aff (Millwood)* 2019;38:107-14.
- Longden T, Wong CY, Haywood P, et al. The prevalence of persistence and related health status: An analysis of persistently high healthcare costs in the short term and medium term. *Soc Sci Med* 2018;211:147-56.
- Chang HY, Boyd CM, Leff B, et al. Identifying Consistent High-cost Users in a Health Plan: Comparison of Alternative Prediction Models. *Med Care* 2016;54:852-9.
- Cohen SB. The Concentration and Persistence in the Level of Health Expenditures over Time: Estimates for the U.S. Population, 2012–2013. September 2015. In: Statistical Brief (Medical Expenditure Panel Survey (US)) [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2001.
- Jiang L, Qiu Q, Zhu L, et al. Identifying Characteristics Associated with the Concentration and Persistence of Medical Expenses among Middle-Aged and Elderly Adults: Findings from the China Health and Retirement Longitudinal Survey. *Int J Environ Res and Public Health* 2022;19:12843.
- Lee JY, Muratov S, Tarride JE, et al. Managing High-Cost Healthcare Users: The International Search for Effective Evidence-Supported Strategies. *J Am Geriatr Soc* 2018;66:1002-8.
- Howson SN, McShea MJ, Ramachandran R, et al. Improving the Prediction of Persistent High Health Care Utilizers: Retrospective Analysis Using Ensemble Methodology. *JMIR Med Inform* 2022;10:e33212.
- Ng SHX, Rahman N, Ang IYH, et al. Characterising and predicting persistent high-cost utilisers in healthcare: a retrospective cohort study in Singapore. *BMJ Open* 2020;10:e031622.
- Tan JK, Quan L, Salim NNM, et al. Machine Learning–Based Prediction for High Health Care Utilizers by Using a Multi-Institutional Diabetes Registry: Model Training and Evaluation. *JMIR AI* 2024;3:e58463.
- Berkman ND, Chang E, Seibert J, et al. Management of High-Need, High-Cost Patients: A “Best Fit” Framework Synthesis, Realist Review, and Systematic Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2021.
- Schousboe JT, Paudel ML, Taylor BC, et al. Estimating True Resource Costs of Outpatient Care for Medicare Beneficiaries: Standardized Costs versus Medicare Payments and Charges. *Health Services Research* 2016;51:205-19.
- Gov.sg. Sold and Rented HDB Properties and Facilities. Updated 15 July 2015. <https://data.gov.sg/datasets?topics=housing&page=3&resultId=187>. Accessed 10 June 2022.
- Ministry of Health, Singapore. Consumer Price Indices (CPI). <https://www.healthhub.sg/a-z/health-statistics/consumer-price-indices-cpi>. Accessed 10 June 2022.
- Banerjee S, Alabaster A, Kipnis P, et al. Factors associated with persistent high health care utilization in managed Medicaid. *Am J Manag Care* 2021;27:340-4.
- Sanchez JJG, James G, Carrero JJ, et al. Health Care Resource Utilization and Related Costs of Patients With CKD From the United States: A Report From the DISCOVER CKD Retrospective Cohort. *Kidney Int Rep* 2023;8:785-95.
- Jha V, Al-Ghamdi SMG, Li G, et al. Global Economic Burden Associated with Chronic Kidney Disease: A Pragmatic Review of Medical Costs for the Inside CKD Research Programme. *Adv Ther* 2023;40:4405-20.
- Chen W, Howard K, Gorham G, et al. Costs and healthcare use of patients with chronic kidney disease in the Northern Territory, Australia. *BMC Health Serv Res* 2024;24:791.

28. Yoon J, Chee CP, Su P, et al. Persistence of High Health Care Costs among VA Patients. *Health Serv Res* 2018; 53:3898-916.
29. Ta A, Goh HL, Tan CS, et al. Identifying prospective frequent readmitters for hospital to home intervention using machine learning. *Int J Integr Care* 2019;19:228.
30. Ministry of Health, Singapore. Speech by Mr Gan Kim Yong, Minister for Health, at the Community Health Assist Scheme (CHAS) Carnival, 27 July 2019. [https://www.moh.gov.sg/newsroom/speech-by-mr-gan-kim-yong-minister-for-health-at-the-community-health-assist-scheme-\(chas\)-carnival-27-july-2019](https://www.moh.gov.sg/newsroom/speech-by-mr-gan-kim-yong-minister-for-health-at-the-community-health-assist-scheme-(chas)-carnival-27-july-2019). Accessed 30 June 2025.
31. gov.sg. Master Plan 2019 Planning Area Boundary (No Sea). <https://data.gov.sg/collections/2104/view>. Accessed 1 May 2022.
32. Singapore Department of Statistics. Population Trends, 2024. <https://www.singstat.gov.sg/publications/population/population-trends>. Accessed 18 August 2025.
33. OneMap Singapore. Population Query. <https://www.onemap.gov.sg/apidocs/populationquery>. Accessed 15 May 2025.

Integrating traditional Chinese medicine into disease management in Singapore

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ABSTRACT

Introduction: While traditional Chinese medicine (TCM) has a long history and continues to be widely practised, its overall clinical efficacy according to conventional scientific standards remains the topic of ongoing research and exploration. This review focuses on the potential use of acupuncture and Chinese herbal medicine (CHM) in combination with Western medicine in Singapore, based on recently published data on the clinical effectiveness and cost-effectiveness of these TCM treatments.

Method: We collated and summarised 71 research papers published in the past decade, focusing on randomised controlled trials, systematic reviews and population-based cohort studies that had a total sample size (treatment and control arms) exceeding 60. English-language articles published between 2015 and 2025 were identified by searching PubMed/MEDLINE, the Cochrane Library and the China National Knowledge Infrastructure. The search strategy included intervention terms like "acupuncture", "Chinese medicine", "TCM", "traditional Chinese medicine", "RCT" and "randomized controlled trial"; economic evaluation terms like "cost" and "cost-effectiveness"; and disease conditions of concern. We narrowed our research to the clinical effectiveness and cost-effectiveness of CHM in which either the individual ingredients or the products were listed as Chinese Proprietary Medicines (CPMs).

Results: The summary tables demonstrate that the integration of acupuncture and/or CPMs with conventional Western medicine can enhance treatment outcomes across various chronic and non-chronic diseases. Their affordability and preventive focus can contribute to long-term healthcare cost savings, benefiting both patients and the healthcare system as a whole.

Conclusion: With a robust regulatory framework, scientific validation and government support, acupuncture and CPMs have an important role in the

management of various diseases, especially chronic ones, in Singapore.

Keywords: acupuncture, Chinese Proprietary Medicines, chronic diseases, clinical effectiveness, cost-effectiveness

CLINICAL IMPACT

What is New

- High-quality clinical trials and cohort studies demonstrate the efficacy and cost-effectiveness of traditional Chinese medicine treatments using acupuncture and Chinese Proprietary Medicines (CPMs) for chronic and non-chronic diseases in Singapore.

Clinical Implications

- Acupuncture can be a valuable stand-alone or adjunctive treatment that complements conventional treatments for managing chronic and non-chronic diseases, particularly for patients who experience adverse effects from medications or who seek non-pharmaceutical options.
- Integrating acupuncture and/or CPMs into Singapore's Chronic Disease Management Programme could provide a patient-centred approach, enhancing symptom management and potentially reducing the healthcare burden associated with chronic diseases.

INTRODUCTION

Traditional Chinese medicine (TCM) was introduced to the Singapore population by early Chinese

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immigrants from China.¹ During Singapore's colonial era, particularly between 1819 to 1959, Chinese medicine physicians offered their services as community service as well.¹ By employing a proactive strategy towards preventive care for health maintenance and providing efficacious remedies for illnesses for over 2 centuries, TCM has gained the trust and support of the public as complementary medical therapy.²

According to the 2022 National Population Health Survey, 8081 adults (aged 18–79 years) from 11,771 eligible households participated in the interviews.³ The survey also collected information on the timing of the most recent TCM visit, health conditions treated through either Western medicine or TCM (or both), the types of TCM prescriptions received and the primary reasons for seeking consultation. This information provided valuable insights into healthcare-seeking behaviours and the integration of different treatment approaches in the population. One in 5 adults reported using TCM within 1 year of the survey.² Of these, nearly 40% also used Western medicine for the same condition, suggesting that many view TCM as having an integral role in their illness and health.²

The importance of TCM in Singapore led to the enactment of the Traditional Chinese Medicine Practitioners Act in 2000, followed by the establishment of the Traditional Chinese Medicine Practitioners' Board to formally recognise, register and regulate TCM practitioners and acupuncturists.⁴ To enhance the role of TCM in Singapore, the Ministry of Health (MOH) established the Traditional Chinese Medicine Research Grant (TCMRG) in 2014, to encourage collaborative research between Singapore's public health and TCM institutions. The goal is to harness TCM principles together with scientific research methodologies and expertise to promote the integration of TCM into Western medicine practice, so as to provide better healthcare and achieve improved health outcomes in a sustainable manner.⁵ The 6th TCMRG Grant Call was open from 8 January 2025 to 31 March 2025.

Management of chronic diseases (CDs) in Singapore

The increasing prevalence of coexisting 2 or more CDs in individuals (i.e. multimorbidity) is a major public health concern. According to a retrospective cohort study of 254,377 patients, the prevalence of multimorbidity was 62.4%, which led to significant healthcare costs.⁶ Another study in Singapore on the healthcare and societal cost of multimorbidity among elderly residents found that the prevalence of multimorbidity was significantly associated with age.⁷ The healthcare cost burden is associated with the prevalence of multimorbidity.⁶ In Singapore, the healthcare expenditure increased from SGD3.8

billion in 2010 to SGD11.1 billion in 2019, and is expected to rise to SGD27 billion by 2030, excluding the impact of COVID-19.⁸

This high rate of multimorbidity not only correlates with the utilisation of healthcare resources but also highlights the urgent need for effective management strategies to alleviate its impact on the healthcare system. Consequently, the national initiative Healthier SG was implemented in July 2023.⁹ The main objective of this programme is to nurture an ecosystem that promotes better health by leveraging the primary healthcare system and collaborating with community partners.¹⁰ As of February 2024, the Healthier SG Chronic Tier subsidy framework includes subsidised pricing comparable to polyclinics for selected chronic medications at Healthier SG General Practitioner clinics to enhance affordability for enrolled residents.¹¹ There are currently 23 chronic diseases in the Chronic Disease Management Programme (CDMP) that are generally progressive, require long-term care, and have their medications covered and subsidised under the Singapore Community Health Assist Scheme (CHAS). They are: (1) chronic conditions that require submission of clinical data to assess the effectiveness of disease management: diabetes mellitus and pre-diabetes, hypertension, lipid disorders, asthma, chronic obstructive pulmonary disease and chronic kidney disease (nephritis/nephrosis); (2) mental illnesses: anxiety disorders, major depressive disorder, bipolar disorder and schizophrenia; (3) other chronic conditions including stroke, major neurocognitive disorder (dementia), osteoarthritis, Parkinson's disease, benign prostatic hyperplasia, epilepsy, osteoporosis, psoriasis, rheumatoid arthritis, ischaemic heart disease, allergic rhinitis, gout and chronic hepatitis B.¹²

In 2020, MOH initiated a pilot study to extend subsidy and MediSave coverage for acupuncture treatments of neck pain and lower backache in public healthcare institutions (PHIs).¹³ Following formal diagnosis and referral by the treating medical specialist at a PHI, patients aged 18 years and older can receive acupuncture, including electroacupuncture for these 2 conditions.¹⁴

In January 2025, MOH encouraged PHIs to engage in a regulatory sandbox effort focused on the combination of Western medicine and TCM in the treatment of CDs, using acupuncture and/or Chinese Proprietary Medicines (CPMs), for a designated duration. The MOH's vision includes creating "TCM Integrative sandboxes" within PHIs.² The sandbox initiative allows the execution of evidence-based TCM treatments alongside standard healthcare practices under controlled procedures with the goals of enhancing treatment outcomes while managing potential risks. The initiative also includes the rigorous cost-effectiveness evaluation of the applied TCM treatments.²

Acupuncture

Acupuncture is one of the primary therapeutic approaches within the framework of TCM, which involves the insertion of fine needles into specific acupoints. The underlying treatment mechanisms can be explained through both TCM theory and insights from modern biomedical research.¹⁵

While acupuncture's clinical application covers a broad range of diseases, its multi-targeted treatment effects are significantly beneficial in addressing the growing burden of multimorbidity in Singapore. The non-pharmaceutical nature of acupuncture provides an alternative for patients who did not achieve desired outcomes from drug treatments or experienced adverse effects from medications. Additionally, acupuncture holds promise in alleviating CD symptoms, which can fit within the integrated patient-centred care setting.

Chinese herbal medicine (CHM)

CHMs are classified into raw CHMs and CPMs.¹⁶ Due to the low toxicity of most raw herbs and the existing regulation of herbs with hazardous chemicals already regulated under the Poisons Act, the Health Sciences Authority (HSA) applies light-touch controls to the import, export, sale and distribution of raw herbal medicines.¹⁶ The supplier must comply with the regulatory requirements to ensure the absence of prohibited ingredients and potent medicinal substances; labelling requirements; and limits on heavy metal content. HSA will perform ad hoc testing when severe adverse events are reported.

According to the Medicines Act of Singapore, CPMs are defined as finished products (capsules, tablets, pills, mixtures, powders, etc.) that contain raw Chinese medicinal materials used in TCM practice. Injections and products containing any chemically defined isolated constituents as an active ingredient are excluded.¹⁷ The regulation was initiated in 1999 to promote safety and quality of CPMs and remove substandard, fake imitation and adulterated products. This includes establishing and identifying ingredients that should be prohibited; setting limits for naturally occurring substances, toxic heavy metals and microbial limits; establishing requirements in labelling; avoiding transmissible spongiform encephalopathy in animal-derived ingredients; prohibiting substances from endangered species; and setting standards for advertisements and promotions. The regulatory control for CPMs is tighter than that of health supplements but less stringent than for pharmaceuticals. As of July 2025, there are 13,687 CPMs listed as compared with 7943 listings in 2001. However, not all the listed CPMs are marketed.

Review of the clinical effectiveness and cost-effectiveness of acupuncture and CPMs in the management of chronic and non-chronic diseases

The clinical effectiveness of TCM has been a subject of interest in both TCM and modern medicine research. The body of clinical research on acupuncture and CHMs for CD management has expanded considerably over the past 2 decades.

This review focuses on the utilisation of acupuncture and CPMs in Singapore and aims to comprehend their clinical effectiveness and cost-effectiveness as evidenced by clinical studies. We analysed research papers according to the following inclusion criteria: (1) published within the last decade, with a focus on randomised controlled trials (RCTs), systematic reviews and population-based cohort studies involving sample sizes larger than 60 participants; and (2) either the individual ingredients or the products were listed as CPMs (excluding decoctions) in Singapore. To broaden the application of acupuncture and CPMs, our review included studies on 38 diseases both covered and not covered under the CDMP (Table 1). This comprehensive approach enables an evidence-based evaluation to guide and prioritise current potential projects of the MOH's TCM Integrative Sandbox initiative.

A literature search was conducted in PubMed/MEDLINE, Cochrane Library and China National Knowledge Infrastructure (CNKI) for English-language articles published from 2015 to 2025. The search strategy incorporated the following keywords and their combinations including (1) intervention terms such as "acupuncture", "Chinese medicine", "TCM", "traditional Chinese medicine", "RCT" and "randomized controlled trial"; (2) economic evaluation terms including "cost" and "cost-effectiveness"; (3) condition and disease of interest terms including specific standardised names such as "hypertension", "diabetes mellitus", "neoplasia", "cerebrovascular accident", etc.

Supplementary Table S1 provides a comprehensive summary of 71 clinical studies (48 on acupuncture and 23 on CPMs) that demonstrated favourable clinical outcomes in managing the chronic and non-chronic diseases (CNCD) through acupuncture and CPMs. The application of acupuncture and/or CPMs in the management of 38 CNCD offer significant clinical effectiveness ($P < 0.05$).

Supplementary Table S2 shows 4 studies that examined the cost-effectiveness of CPMs relative to conventional medicine or placebo in the management of hypertension, heart failure, knee osteoarthritis and chronic obstructive pulmonary disease. Another study assessed the cost-effectiveness of acupuncture for migraine. These studies demonstrated that

Table 1. Chronic and non-chronic diseases recommended for acupuncture and/or Chinese Proprietary Medicines in the studies reviewed.

Type of disorder	Chronic and non-chronic diseases (CNCD)	Clinical effectiveness studies		Cost-effectiveness studies	
		ACU	CPM	ACU	CPM
Circulatory disorder	Hypertension (CNCD1) ^a	2	1		1
	Ischaemic heart disease (CNCD2) ^a	1	1		1
Dermatological disorder	Atopic dermatitis (CNCD3)	1			
	Chronic spontaneous urticaria (CNCD4)	1			
Endocrine/metabolic disorder	Diabetes mellitus/pre-diabetes (CNCD5) ^a	1	2		
	Hyperlipidaemia (lipid disorders) (CNCD6) ^a		1		
	Obesity/overweight (CNCD7)	2	1		
Gastrointestinal disorder	Functional constipation (CNCD8)	2			
	Functional dyspepsia (CNCD9)	1			
	Irritable bowel syndrome (CNCD10)	2			
Genitourinary disorder	Benign prostatic hyperplasia (CNCD11) ^a	1	1		
	Chronic kidney disease (nephrosis/nephritis) (CNCD12) ^a		1		
	Chronic pelvic pain syndrome (CNCD13)	1			
	Stress urinary incontinence (CNCD14)	1			
Hepatic disorder	Chronic hepatitis B (CNCD15) ^a		1		
Nervous system disorder	Bell's palsy (CNCD16)	2			
	Dementia (CNCD17) ^a	2	1		
	Epilepsy (CNCD18) ^a	2			
	Migraines (CNCD19)	2		1	
	Parkinson's disease (CNCD20) ^a		1		
	Stroke (CNCD21) ^a	4	2		
	Trigeminal/post-herpetic neuralgia (CNCD22)	1			
Musculoskeletal disorder	Chronic lower back pain (CNCD23)	1			
	Chronic neck pain (CNCD24)	1			
	Gout (CNCD25) ^a		1		
	Osteoarthritis (CNCD26) ^a	2	2		1
	Rheumatoid arthritis (CNCD27) ^a	1	1		
Respiratory disorder	Allergic rhinitis (CNCD28) ^a	1			
	Asthma (CNCD29) ^a	1	1		
	Chronic obstructive pulmonary disease (CNCD30) ^a		1		1
Reproductive health disorder	Infertility (CNCD31)	1			
	Uterine fibroid (CNCD32)	1			
Oncological disorder	Cancer (CNCD33)	4	1		

Table 1. Chronic and non-chronic diseases recommended for acupuncture and/or Chinese Proprietary Medicines in the studies reviewed. (Cont'd)

Type of disorder	Chronic and non-chronic diseases (CNCD)	Clinical effectiveness studies		Cost-effectiveness studies	
		ACU	CPM	ACU	CPM
Ophthalmological disorder	Dry eye (CNCD34)	1			
Psychiatric disorders	Anxiety (CNCD35) ^a	1	1		
	Insomnia (CNCD36)	2			
	Major depression (CNCD37) ^a	1	1		
	Schizophrenia (CNCD38) ^a	1	1		
Total studies		48	23	1	4

ACU: acupuncture; CNCD: chronic and non-chronic diseases; CPMs: Chinese Proprietary Medicines

^a Included in the Chronic Disease Management Programme (CDMP) in Singapore.

Psoriasis, osteoporosis and bipolar disease in the CDMP were not included in the analysis due to a lack of suitable studies based on the study's eligibility criteria.

acupuncture and/or CPMs, alone or in combination with Western medicines, could potentially reduce healthcare costs by improving outcomes, decreasing hospitalisation rates or duration, and lowering re-admissions.

Limitation of this review

This review highlights key findings on the role of acupuncture and CPMs in the management of CNCD. However, several limitations should be noted. First, while the included studies suggest potential clinical benefits and cost-effectiveness of acupuncture and CPMs in CNCD management, extensive local epidemiological data and cost-effectiveness analyses, including TCM usage associated with lower medication burden or reduced hospital admission are lacking. The evidence was obtained mainly from studies (69 out of 71) conducted outside Singapore, and the findings may have limited direct applicability to other non-Chinese populations (Malays, Indians and other ethnic groups) due to potential genetic, dietary, constitutional and lifestyle differences. Genetic variations, such as polymorphisms in drug-metabolising enzymes, could influence treatment responses and outcomes. For instance, the frequency of the A2455G polymorphism variant of *CYP1A1* in Singapore was 31% in Malays, 28% in Chinese and 18% in Indians.¹⁸ Moreover, a local study reported that “damp heat”, “phlegm-dampness” and “qi deficiency” were the most prevalent among the diverse population in Singapore.¹⁹ In contrast, balanced “yang deficiency” and “qi deficiency” constitutions were the most prevalent within the general population in China.²⁰ Therefore, caution should be exercised when generalising the TCM efficacy results to ethnically distinct populations from different geographies, which warrants further in-depth studies in multiracial Singaporean cohorts.

In addition, several systematic reviews and meta-analyses of RCTs have indicated that the majority of the studies used CHM decoctions rather than CPMs in the intervention. In this study, we excluded RCTs and population-based cohort studies using CHM decoctions, as well as non-English articles. To ensure that most internationally published CNCD studies could be included, we included multicentre cohort studies and non-double-blind studies. Consequently, to our knowledge and review criteria, clinical studies of the 3 chronic diseases—psoriasis, osteoporosis and bipolar disorder—could not be included in Supplementary Table S1 due to a lack of suitable studies based on our eligibility criteria.

To our knowledge, this is the first Singapore study that has comprehensively searched, reviewed and evaluated articles on TCM clinical efficacy and cost-effectiveness in the management of CNCD using focused inclusion and exclusion criteria. The articles included in the review carry risks of bias and a lack of higher levels of evidence, for example, the inclusion of 5 single-blind clinical studies. While this analysis includes data from systematic reviews, meta-analyses and RCTs, it is important to recognise that methodological limitations exist in many TCM trials. For instance, a study evaluating the risk of bias in 4175 RCTs revealed that significant concerns persist about allocation concealment and blinding despite demonstrated improvements concerning uncertain risk regarding random sequence generation and selective reporting.²¹ Some of the included systematic reviews of acupuncture studies also reported the inclusion of studies that did not follow standard tools, such as Cochrane's risk-of-bias tool, resulting in lower methodological quality, a higher possibility of publication bias and low-certainty evidence.

Nevertheless, most of the articles included that involved RCTs have relatively large sample sizes, ranging from a hundred to several thousands. For studies involving population-based cohort designs, sample sizes were large, ranging from thousands to tens of thousands, and were conducted nationwide or in multiple centres. The majority of studies were conducted in China and Taiwan; hence, it is essential for more TCM studies to be conducted in localised regions in Southeast Asia so that the findings can be better applied to Singapore. Clinical heterogeneity may be present due to the diversity in conventional TCM treatments and their varying courses. The key sources of heterogeneity are: (1) acupuncture techniques including manual manipulation and electroacupuncture, and stimulation intensity; (2) selection of acupoints such as standardised versus (vs) individualised protocols, and varied philosophies; (3) treatment duration, intervals, frequency and practitioner experience; (4) CPMs' variability including formulation differences, for example, fixed doses in research studies vs individualised regimens in clinical practice. Future Singapore-tailored research could include large, pragmatic multicentre trials to assess real-world clinical effectiveness and cost-effectiveness, as well as ethnically stratified analyses to determine the differential responses among Chinese, Malay, Indian and other populations within the integrative care model.

While TCM modalities are relatively safe when properly administered, adverse events have been reported. For instance, a meta-analysis of 11 acupuncture studies including 845,637 participants reported that the overall risk of at least 1 adverse event was approximately 9.31 per 100 patients treated.²² Mild and transient adverse events, including local bleeding, pain or flare around needling site may be regarded as part of the acupuncture treatment or therapeutically intended reactions.²² Severe adverse events, such as pneumothorax, significant cardiovascular or syncope, and fall or trauma are rare; they occur in 1 to 3 cases out of 1 million treatments.²² A Singapore survey of 1028 participants indicated that patients who ingested CHM and Western prescription medicines were 3.65 times more likely to encounter an adverse event compared with those who took CHM alone.²³ Among 18 adverse event reports adjudicated for patients who consumed CHM and Western prescription medicines concurrently, gastrointestinal discomfort, such as churning, mild pain, diarrhoea, nausea, fatigue and skin rash were recorded.²³ The primary safety issue with CPMs is the potential drug-herb interaction (DHI), which could be mitigated by encouraging disclosure of CPM and Western prescription medicines during patients' medication reconciliation, and establishing

evidence-based interaction databases and DHI knowledge sharing among both conventional and TCM healthcare providers.

Despite the shortcomings, this is the first compilation of articles with extensive evidence-based TCM clinical efficacy and cost-effectiveness results, which may provide a relevant basis for the integration of conventional medicine with acupuncture and/or CPMs in the treatment of CNCD of interest in Singapore.

We hope this review will guide policymaking and the development of strategies for integrating acupuncture and/or CPMs into CNCD management as a new model of care moving forward. Many feasible options can be explored and pursued, including: (1) structured cross-referral system that allows formalised, transparent referral pathways between physicians and accredited TCM providers, ensuring patient safety via shared records and avoiding unintentional duplication of therapies; (2) introduction of evidence-based TCM modalities in hospital care to shorten recovery times, improve symptom control and reduce length of stay of inpatients; (3) expansion of cross-disciplinary education, such as through a TCM practitioners-pharmacists partnership for the joint development of a DHI database and review of reported cases of adverse events resulting from DHI; (4) co-location of clinics that enable accredited TCM practitioners to provide coordinated care with conventional healthcare clinicians in polyclinics or specialised outpatient facilities.

CONCLUSION

In providing holistic and patient-centric care, acupuncture and CPMs may effectively manage symptoms and control the underlying complications of CNCD. Its integration with conventional medicine can enhance treatment outcomes, while its affordability and preventive focus can contribute to long-term healthcare cost savings, benefiting both patients and the healthcare system as a whole. With a robust regulatory framework, scientific validation and government support, acupuncture and CPMs have an important role in CNCD management in Singapore.

While acupuncture and CPMs offer potential scientifically efficacious and cost-saving benefits, such as complementing conventional medicine to lower healthcare costs and reduce the occurrence of adverse events, challenges such as quality control and the continuous need for high-quality research to validate these conclusions remain.

Addressing these challenges is crucial to maximising the potential and inclusion of acupuncture and CPMs in Singapore's integrated CNCD healthcare management system.

Supplementary materials

Table S1. Clinical effectiveness of acupuncture and/or Chinese Proprietary Medicines registered in Singapore in the management of chronic and non-chronic diseases.

Table S2. Cost-effectiveness of acupuncture and Chinese Proprietary Medicines registered in Singapore in the management of chronic and non-chronic diseases.

Ethics statement

Not applicable as this is a systematic review and meta-analysis of literature.

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. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

- Smith AA. Capturing Quicksilver: The Position, Power, and Plasticity of Chinese Medicine in Singapore. New York: Berghahn Books; 2018.
- Ministry of Health, Singapore. Speech By Mr Ong Ye Kung, Minister For Health, At the forum on the use of evidence-based traditional Chinese medicine in Western medicine practice. <https://www.moh.gov.sg/newsroom/speech-by-mr-ong-ye-kung--minister-for-health--at-the-forum-on-the-use-of-evidence-based-traditional-chinese-medicine-in-western-medicine-practice>. Accessed 27 July 2025.
- Epidemiology & Disease Control Division, Ministry of Health, Singapore. National Population Health Survey 2022 (Household Interview and Health Examination). <https://www.moh.gov.sg/others/resources-and-statistics/nphs-2022>. Accessed 27 July 2025.
- Ministry of Health, Singapore. Public Consultation On Proposed Amendments to the Traditional Chinese Medicine Practitioners Act Singapore. <https://www.moh.gov.sg/newsroom/public-consultation-on-proposed-amendments-to-the-traditional-chinese-medicine-practitioners-act>. Accessed 27 July 2025.
- Ministry of Health, Singapore. Traditional Chinese Medicine Research Grant (TCMRG). <https://www.moh.gov.sg/policies-and-guidelines/research-grants/traditional-chinese-medicine-research-grant>. Accessed 1 February 2025.
- Tan SY, Lew KJ, Xie Y, et al. Healthcare cost of patients with multiple chronic diseases in Singapore public primary care setting. *Ann Acad Med Singap* 2021;50:809-17.
- Picco L, Achilla E, Abdin E, et al. Economic burden of multimorbidity among older adults: impact on healthcare and societal costs. *BMC Health Serv Res* 2016;16:173.
- Tan V, Lim J, Akksilp K, et al. The societal cost of modifiable risk factors in Singapore. *BMC Public Health* 2023;23:1285.
- Ministry of Health, Singapore. Healthier SG Enrolment Programme to Commence on 5 July. <https://www.moh.gov.sg/newsroom/healthier-sg-enrolment-programme-to-commence-on-5-july>. Accessed 27 July 2025.
- Foo C, Chia HX, Teo KW, et al. Healthier SG: Singapore's multi-year strategy to transform primary healthcare. *Lancet Reg Health West Pac* 2023;37:100861.
- Ministry of Health, Singapore. Healthier SG Chronic Tier. <https://www.healthiersg.gov.sg/enrolment/healthier-sg-chronic-tier/about/>. Accessed 10 July 2025.
- Ministry of Health, Singapore. Chronic Disease Management Program: Handbook for Healthcare Professionals. [https://www.primarycarepages.sg/schemes-and-programmes/Documents/Chronic%20Disease%20Management%20Programme%20\(CDMP\)%20Handbook%20for%20Healthcare%20Professionals%202024.pdf](https://www.primarycarepages.sg/schemes-and-programmes/Documents/Chronic%20Disease%20Management%20Programme%20(CDMP)%20Handbook%20for%20Healthcare%20Professionals%202024.pdf). Accessed 27 July 2025.
- Ministry of Health, Singapore. Pilot for Extension of Subsidy and Medisave for Acupuncture At Public Specialist Outpatient Clinics. <https://www.moh.gov.sg/newsroom/pilot-for-extension-of-subsidy-and-medisave-for-acupuncture-at-public-specialist-outpatient-clinics>. Accessed 27 July 2025.
- Agency for Care Effectiveness. Acupuncture for adults with low back pain and neck pain. <https://www.ace-hta.gov.sg/healthcare-professionals/ace-technology-guidances/medical-technology-guidance/acupuncture-for-adults-with-low-back-pain-and-neck-pain>. Accessed 27 July 2025.
- Liu S, Wang ZF, Su YS, et al. Somatotopic Organization and Intensity Dependence in Driving Distinct NPY-Expressing Sympathetic Pathways by Electroacupuncture. *Neuron* 2020;108:436-50.e7.
- Yee SK, Chu SS, Xu YM, et al. Regulatory control of Chinese Proprietary Medicines in Singapore. *Health Policy* 2005;71:133-49.
- Hu M, Ding P, Ma J, et al. Cost-Effectiveness Analysis of the TCM "Yupingfeng Granules" in the Treatment of Acute Exacerbations of COPD Based on a Randomized Clinical Trial. *Int J Chron Obstruct Pulmon Dis* 2022;17:2369-79.
- Chowbay B, Zhou S, Lee EJ. An interethnic comparison of polymorphisms of the genes encoding drug-metabolizing enzymes and drug transporters: experience in Singapore. *Drug metabolism reviews* 2005;37:327-78.
- Ng HP, Chong SY, Li YH, et al. Objective Analysis of Traditional Chinese Medicine Syndrome Differentiation of Patients With Diabetes and Prediabetes: Protocol for a Nonrandomized, Exploratory, Observational Case-Control Study Using Digitalized Traditional Chinese Medicine Diagnostic Tools. *JMIR research protocols* 2024;13:e56024.
- Yaqi W, Weibo Z, Yixing W, et al. Traditional Chinese Medicine constitution among patients with allergic rhinitis and its correlation with anxiety and depression. *J Tradit Chin Med* 2023;43:1252-58.
- Long Y, Chen R, Guo Q, et al. Do acupuncture trials have lower risk of bias over the last five decades? A methodological study of 4 715 randomized controlled trials. *PLoS One* 2020;15:e0234491.
- Bäumler P, Zhang W, Stübinger T, et al. Acupuncture-related adverse events: systematic review and meta-analyses of prospective clinical studies. *BMJ open* 2021;11:e045961.
- Ng CYJ, Zhao Y, Wang N, et al. A multi-center cross-sectional study of Chinese Herbal Medicine-Drug adverse reactions using active surveillance in Singapore's Traditional Chinese Medicine clinics. *Chin Med* 2024;19:44.

Advancing breast cancer and lung cancer screening: Expert perspectives to advance programmes in Singapore

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ABSTRACT

Introduction: The high prevalence and mortality rates of breast cancer and lung cancer in Singapore necessitate robust screening programmes to enable early detection and intervention for improved patient outcomes, yet 2024 uptake and coverage remain suboptimal. This narrative review synthesises expert perspectives from a recent roundtable discussion and proposes strategies to advance breast cancer and lung cancer screening programmes.

Method: A 2024 roundtable convened clinical practitioners, health policymakers, researchers and patient advocates discussed current challenges and opportunities for improving cancer screening in Singapore. Perspectives and insights were analysed to identify themes related to existing programme gaps, opportunities for innovation and implementation challenges.

Discussion: Singapore's national breast cancer screening programme has been in place for over 2 decades, yet screening uptake remains suboptimal. A national lung cancer screening programme, in contrast, is still in its early stages of implementation. Regardless, employment of risk stratification approaches that integrate genetic, demographic and lifestyle factors could enhance screening effectiveness by identifying high-risk individuals, while also taking local epidemiological trends into consideration. Integration of digital health technologies, artificial intelligence and behavioural change models can enhance cancer screening uptake and accuracy to overcome barriers such as low awareness, cultural beliefs and socioeconomic factors that contribute to low participation rates.

Conclusion: Key recommendations include enhancing public awareness, refining screening guidelines, expanding access and applying innovative technologies. A coordinated effort among stakeholders is crucial to continually assess and enhance screening programmes to narrow the practice-policy gap and ultimately reduce breast cancer and lung cancer burden in Singapore.

Keywords: Breast cancer, lung cancer, preventive medicine, public health, screening

CLINICAL IMPACT

What is New

- This narrative review highlights the breast cancer and lung cancer burden in Singapore and underscores the need for improved uptake and coverage for cancer screening programmes.
- Strategies are proposed to improve cancer screening programmes.

Clinical Implications

- Risk stratification approaches and the adoption of innovative technology in screening protocols are strategies to improve screening coverage and diagnostic accuracy.
- Coordinated efforts beyond the clinic are necessary to improve public perception and acceptance of cancer screening programmes.

INTRODUCTION

The high disease burden of both breast cancer and lung cancer in Singapore has necessitated the rapid evolution and advancement of breast and lung health management in Singapore.¹ A 2024 roundtable in Singapore brought together clinical practitioners, health policymakers, researchers and patient advocates to discuss the current landscape of breast cancer and lung cancer in Singapore, identify unmet needs and put forward strategies to address these gaps.² A key topic of discussion was the current state of cancer screening programmes in Singapore, alongside potential technologies and approaches to advance these programmes. Cancer screening programmes serve to enable early cancer detection and treatment, which has been associated with significant improvements in survival, reductions in morbidity and amelioration of

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disease burdens for breast cancer and lung cancer.³ However, the importance of screening needs to be continually publicised and emphasised at the societal level, otherwise screening rates can decline over time. This is seen in the case of cervical cancer screening in Singapore, where there was an alarming decline in cervical cancer screening rates from 57.9% in 2007 to 43.1% in 2022.⁴ Furthermore, when there is better understanding of certain barriers to cervical cancer screening such as fear and discomfort, new approaches such as self-sampling can be adopted, which can offer new ways to improve the acceptability and uptake of these screening tests.⁵

Comparing across various cancer screening programmes in Singapore, the national breast cancer screening programme was established over 2 decades ago, while a national screening programme for lung cancer is still in nascent stages of implementation.^{6,7} Regardless of when a screening programme is established, technological and research advancements should be continually assessed for application to screening programmes to improve patient outcomes and overall population health. This review aims to summarise expert perspectives that were discussed, bring together relevant insights to help shape a framework to facilitate screening coverage and uptake, improve access and advance cancer screening programmes for earlier detection of breast cancer and lung cancer in Singapore.

METHOD

The roundtable was held in October 2024 and convened clinical practitioners, health policymakers, researchers and patient advocates discussed current challenges and opportunities for improving cancer screening in Singapore. Perspectives and insights were analysed to identify themes related to existing programme gaps, opportunities for innovation and implementation challenges.

RESULTS

Breast cancer screening in Singapore

In Singapore, the age-standardised incidence rate (ASIR) for breast cancer has risen from 20.1/100,000 population in 1968–1972 to 76.2/100,000 population in 2018–2022, with approximately 25% of breast cancer diagnoses in younger women under 50 years of age as of 2018–2022.⁸ Similarly, the age-standardised mortality rates (ASMR) reported for breast cancer in Singapore has also increased from 5.7/100,000 population to 11.6/100,000 population.⁸ While diagnoses at advanced stage III or later breast cancer has remained constant, an increase in the incidence in ductal carcinoma in situ and stage I breast cancer cases has been observed over the past

decade, with 58% of breast cancer diagnoses being in stage I.⁸

In 2002, the national breast cancer screening programme was started to enable early detection of breast cancer to reduce mortality. Current screening guidelines recommend breast cancer screening starting at 50 years of age, with screening recommended for women 40–49 years at physician's discretion, dependent on an individual's risk-factor profile.⁹ With the rising and significant proportion (20.1%) of breast cancer diagnoses in younger women 40–49 years, current screening programmes may overlook this high-risk population, as genetic risk factors are typically not tested for.^{8,9}

Since the inception of the national breast cancer screening programme, screening rates have improved from 29.7% before 2002 to 39.6% in 2010¹⁰; however, current local screening programmes for breast cancer have stagnated and report low screening rates of about 40% in 2019, which is much lower than in other high-income countries, with screening rates of 72% in New Zealand, 75% in both Norway and the United Kingdom, and 90% in Sweden.¹¹ In multicultural Singapore, Malay ethnicity and low socioeconomic status have been significantly associated with poorer cancer screening uptake,¹² presenting unique challenges in screening relating to Singapore's ethnic and cultural diversity. The Singapore Breast Cancer Cohort, established in 2010 as an ongoing multi-ethnic cohort study, aims to help better evaluate the phenotypic and genetic risk factors for breast cancer in Singapore, so that more people who are at higher risk of breast cancer are identified and better informed to take the necessary precautionary and early screening measures.¹³

Low awareness, misconceptions about personal risk factors and poor understanding of screening eligibility have been cited as contributors to lower screening uptake.¹¹ As many people in Singapore are time-poor, the time required for screening, alongside their low perceived susceptibility to breast cancer also serve as barriers to preventive care.^{14,15}

Lung cancer screening in Singapore

With lung cancer remaining a leading cause of mortality worldwide, its late diagnosis has been identified as a contributing factor to high mortality rates and poor patient outcomes.^{16,17} Although the decreasing trend of ASIR for lung cancer in men in Singapore has been encouraging, at 30.0/100,000 population in 2018–2022, many of the patients diagnosed with lung cancer are diagnosed at advanced stages of the disease, with 60% of diagnoses at stage IV.⁸ The ASMR for lung cancer in men in Singapore was 20.1/100,000 population in the

same period, with one of the lowest survival rates of 21.9% among common cancers in Singapore.⁸ Similar to men, the ASIR and ASMR of lung cancers in women have gradually declined over the past decade.⁸ However, there is a notable increase in lung cancers among female non-smokers (60–80% of all female lung cancers) and most cases were diagnosed at late stages (70.5%).^{18–21} The unique epidemiology of lung cancer in Singapore, where there are trends of rising cases of lung cancer in female non-smokers, and the relatively higher rates of lung cancer being first diagnosed at the late stages, may warrant targeted risk-based lung cancer screening guidelines and recommendations that take into account Singapore data and trends.

The current lung cancer screening guidelines adopted both in Singapore and globally recommend lung cancer screening in individuals aged 50–80 years with a 20 pack-year smoking history, and who currently smoke or have quit in the past 15 years.²² However, a local study showed that implementation of these criteria in Singapore could miss about 42% of lung cancer patients, as the criteria do not account for risk factors associated with females and/or never-smokers.²¹

With a national lung cancer screening programme in its nascent stages of implementation, updates to screening eligibility criteria are necessary to reflect local disease epidemiology and improve sensitivity of the programme in identifying those with high-risk.²³ In addition, the use of low-dose computed tomography (LDCT) scans to enable earlier diagnosis has been recommended for lung cancer screening, and should be considered when a national lung cancer screening programme is established.^{7,23} Nevertheless, LDCT is unable to reliably differentiate between malignant nodules from incidental tuberculosis findings, which may necessitate additional testing to confirm a diagnosis alongside additional psychological and cost implications.²⁴ While systematic reviews have showed cost-effectiveness of lung cancer screening with LDCT, further evaluation on the impact and feasibility of a national screening programme is needed, to take into account Singapore's healthcare landscape, infrastructure readiness and funding model, especially when planning to screen more people in the higher risk groups and subpopulations.^{23,25}

Risk stratification approach for cancer screening

The changing epidemiological trends of both breast cancer and lung cancer highlight the need for more precision and higher resolution in identifying those at high risk of cancer for targeted screening. A risk stratification approach would enable the consideration of multiple genetic, demographic and behavioural risk factors to assign cancer risk, and identify

those who are at high cancer risk. With growing understanding on genetic risk factors and hereditary components for breast cancer and lung cancer, there is strong evidence to employ a risk-based stratified approach for breast cancer and lung cancer screening, ensuring coverage of populations that are under-represented, at high risk and unique to the epidemiology of Singapore.^{26–29} A wider and risk-based cancer screening approach would mean higher rates of detection of cancer at the earlier stages, where treatment is less costly and survival rates are better, to reduce the overall cancer burden in Singapore.

Risk stratification for breast cancer

In breast cancer, a risk stratification approach that considers ethnic background and other polygenic factors, alongside traditional risk factors such as age and family history, would enable more precise identification of those at high risk of breast cancer over age-based screening criteria.^{26,27} Breast cancer risk varies across ethnicities in Singapore, with the Malay population in Singapore being at higher risk compared to the other populations.¹³ Breast cancer in Malay women typically presents at a younger age, at more advanced stages and with more aggressive tumour biology.^{30–32} More specifically, mutations in the breast cancer genes (BRCA) have been established to confer significantly higher oncogenic risk for breast cancer.²⁷ Although BRCA testing is internationally recognised, uptake of BRCA testing is still low in Singapore, even when recommended to patients based on their risk profiles.³³

Risk stratification for lung cancer

Emerging evidence indicate family history of lung cancer as being a significant risk factor for lung cancer in Asian populations.³⁴ In addition, oncogenic factors, such as epidermal growth factor receptor gene (EGFR) mutations, have been found to have a major role in the pathogenesis of lung cancer in females and never-smokers, a seemingly unique phenomenon in Asia.^{28,29,35} Family history, alongside genetic factors, should be considered when determining risk of lung cancer to ensure that this high-risk population is identified for screening. Using a risk stratification approach would also help guide conversations and promote understanding of cancer risk, and in turn facilitate screening acceptance.³⁶

Integrating digital health for improved detection and care

In today's digitised and data-rich society, risk stratification in the screening for breast cancer and lung cancer is more feasible than before and would, at the same time, enable more convenient and robust data collection across the population.³⁷ Using artificial

intelligence, models may be trained on this population health dataset to identify high-risk patients and provide personalised health and screening advice to facilitate screening adherence and uptake.^{38,39} A comprehensive population health dataset would also allow timely and informed formulation of public health policies, cancer screening protocols and healthcare resource allocation to improve access of high-risk populations to screening programmes.

In diagnostic radiology, machine learning-based radiomics may augment LDCT for better detection of small nodules, which will aid radiologists and patients in the earlier detection of lung cancer.⁴⁰ However, members of the roundtable acknowledge that optimisation is still required on the interpretation of small and subsolid nodules to differentiate between early cancer and tuberculosis, and as technology evolves, this will be less of an issue over time.⁴⁰

Behavioural health science in promoting preventive care

Identification of high-risk populations, improvement of screening protocols and increased subsidised cancer screening do not automatically lead to increased uptake in screening.⁴¹ A deeper understanding of the underlying factors that drive compliance and application towards effecting health behavioural changes is necessary to lead reductions in certain behaviours, increase compliance to cancer screening guidelines and drive improvement in screening uptake rates.⁴² The use of behavioural change models to encourage preventive care seeking behaviours should be leveraged, as it has been shown to ameliorate the uptake of cancer screening.⁴³ Motivational interviewing by healthcare professionals has been shown to be helpful in engaging with patients more meaningfully in their decision-making for cancer screening, ensuring awareness and understanding of the importance and value of cancer screening.⁴⁴

The cost of screening and genetic testing, lack of perceived value, and spiritual and religious beliefs have been cited as barriers to both routine breast cancer screening and BRCA testing in Singapore.^{11,33,45} Raising public awareness of risk factors for breast cancer and lung cancer is crucial for patients to better understand their cancer risk and the importance of cancer screening, so as to facilitate discussions on cancer screening with their physician.³⁶ For lung health, public awareness campaigns should focus on smoking cessation, mitigating risk factors that affect lung health and improving awareness of comorbidities associated with lung cancer development, such as chronic obstructive pulmonary disorder.⁴⁶ These lung cancer campaigns should of course target smokers and ex-smokers, providing a platform that encourages them

to reduce their risk factors, seek preventive care and participate in general health screening programmes.

Community activities also play a role in raising awareness and improving cancer screening uptake. Patient- and community-led initiatives, such as the Mammo-bus, a mobile mammography unit, can drive engagement and participation in community breast cancer screening programmes.¹¹ In Singapore, the Lung Cancer Consortium was established to unify clinical, research and community efforts, bringing together programmes such as “I Quit” by the Health Promotion Board and other awareness campaigns to combat tobacco use.

DISCUSSION

It is normal that practice runs ahead of policy—what differentiates an exceptional healthcare system from a good one is its ability to keep the practice-policy gap as small as possible. This ensures that the healthcare system is able to push evidence synthesis to be as near the edge as possible, while ramping up health technology assessments to keep up with the latest science, technology and evidence; so that health policy keeps pace with the rate of change in clinical practice.

Successful cancer screening programmes require concerted national efforts with support from across clinical practitioners, researchers and health policy-makers. Overall, the key priorities for cancer screening programmes in Singapore are to improve screening uptake, to improve screening coverage for at-risk populations, to detect cancer earlier and at earlier stages, and to provide patients with timely medical advice and treatment. For breast cancer, one of the key thrusts is to support research to better understand the attitudes and behaviours towards breast cancer screening, and discern effective strategies to change behaviours and improve screening uptake. Another focus should be on updating breast cancer screening guidelines to include more definitive guidance on screening in those aged 40–49 years of age, employing a risk stratification approach to improve coverage and access to screening for those at risk.

For lung cancer, policy and practice updates should focus on the implementation of a risk-based national screening programme. This requires development of an evidence-based protocol for lung cancer screening, which includes updates to the screening criteria in a way that is progressive and offers flexibility to account for unique phenotypes that present in Asia, while also using LDCT as a screening tool. Further research is required on the use of artificial intelligence to improve specificity of LDCT in identifying lung cancer, as well as to investigate cost and resource

implications with employing LDCT in a national lung cancer screening programme.

To evaluate the effectiveness and impact of population- and risk-based cancer screening programmes, experts from the roundtable had suggested several metrics to be measured and tracked (Table 1), which can be used for assessing against set benchmarks and targets. Setting of targets and benchmarks should be policy- and evidence-based, and done in close consultation with clinicians, researchers and policymakers.

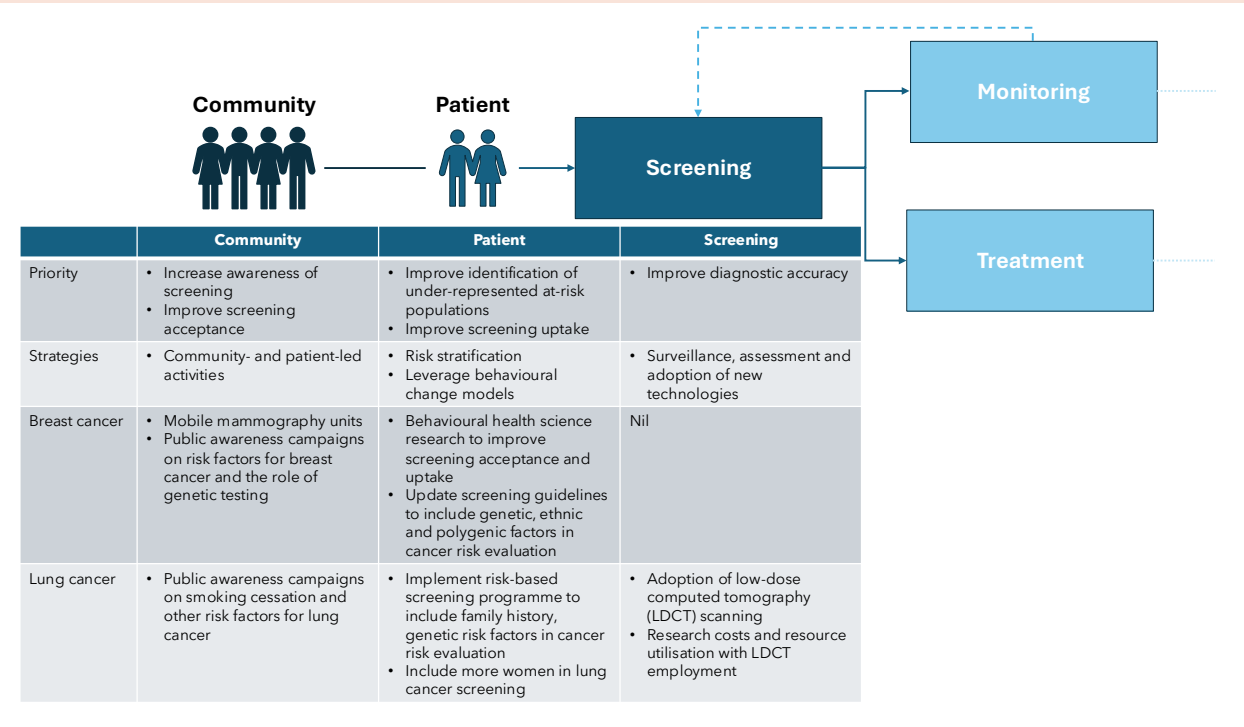
CONCLUSION

The expert roundtable discussions provided insights on gaps in current screening programmes for both breast cancer and lung cancer and helped put forth strategies to bridge these gaps, facilitate earlier detection and reduce morbidity of cancer in Singapore (Fig. 1). These strategies include integration of a risk stratification approach that would underpin cancer screening criteria to improve screening coverage in under-represented, high-risk populations; the adoption of new technologies to enhance diagnostic

Table 1. Proposed metrics to evaluate performance of cancer screening programmes.

Proposed metric	Objective	Relevant screening programme
Screening recommendation rates	Assess identification of at-risk populations	Breast cancer Lung cancer
Screening uptake rates	Assess screening participation	
Equity of access to screening	Assess screening coverage	
Screening interval adherence and follow-up timelines	Assess screening protocols	
Diagnostic accuracy		
Patient experience		
Cost effectiveness	Assess economic impact of new technologies	Lung cancer

Fig. 1. Proposed strategies for advancing breast cancer and lung cancer screening programmes in Singapore.



accuracy of screening protocols; and change behaviour strategies to improve acceptance, normalise evidence-based cancer screening and improve participation rates. Acknowledging that utilisation of these strategies to inform and update health policies requires time, investment and training. Changes in screening programmes, thresholds for cancer screening and the use of new technology should be evidence-based and take into consideration Singapore data and epidemiological trends, cultural sensitivities, and healthcare system capacity and complexities.

Ethics statement

No patient data were used in the development of the manuscript.

Declaration

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REFERENCES

- Dee EC, Laversanne M, Bhoo-Pathy N, et al. Cancer incidence and mortality estimates in 2022 in southeast Asia: a comparative analysis. *Lancet Oncol* 2025;26:516-28.
- Digital Health Society of South East Asia, Precision Public Health Asia Society & Society of Behavioural Health, Singapore. The Policy & Practice Roundtable Series - New Perspectives on Breast Health & Lung Health in the Healthier SG Era. 2024. <https://www.dhs-sea.com/post/policy-and-practice-roundtable-on-breast-and-lung-health-1-october-2024>. Accessed 6 August 2025.
- Crosby D, Bhatia S, Brindle KM, et al. Early detection of cancer. *Science* 2022;18:375:eaay9040.
- Chin FHX. Evaluating the effectiveness of cervical cancer screening and prevention in Singapore. *Ann Acad Med Singap* 2024;28:53:338-9.
- Chan GMF, Ong LSD, Shen L, et al. High acceptability of HPV self-sampling in a Singapore primary care setting. *Ann Acad Med Singap* 2025;54:319-21.
- Wang SC. The Singapore National Breast Screening Programme: Principles and Implementation. *Ann Acad Med Singap* 2003;466-76.
- Aggarwal, B, Coughlan, D. Low-dose computerised tomography screening for lung cancer in Singapore: Practical challenges of identifying participants. *Ann Acad Med Singap* 2022;51:648-50.
- National Registry of Diseases Office. Singapore Cancer Registry Annual Report 2022. https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/scr-ar-2022_web-report6c6e8522-cf39-416f-9390-5fe903065927.pdf. Accessed 6 August 2025.
- Chootipongchaivat S, Wong XY, Ten Haaf KS. et al. Cost-effectiveness analysis of breast cancer screening using mammography in Singapore: A modeling study. *Cancer Epidemiol Biomarkers Prev* 2021;30:653-60.
- Loy EY, Molinar D, Chow KY, et al. National breast cancer screening programme, Singapore: Evaluation of participation and performance indicators. *J Med Screen* 2015;22:194-200.
- Rajendram P, Singh P, Han KT, et al. Barriers to breast cancer screening in Singapore: A literature review. *Ann Acad Med Singap* 2022;51:493-501.
- Chan TK, Tan LWL, van Dam RM, et al. Cancer Screening Knowledge and Behavior in a Multi-Ethnic Asian Population: The Singapore Community Health Study. *Front Oncol* 2021; 11:684917.
- Ho PJ, Yeoh YS, Miao H, et al. Cohort profile: The Singapore Breast Cancer Cohort (SGBCC), a multi-center breast cancer cohort for evaluation of phenotypic risk factors and genetic markers. *PLoS One* 2021;16:e0250102.
- Surendran S, Foo C, Tan DHY, et al. Understanding Barriers and Facilitators of Breast and Cervical Cancer Screening among Singapore Women: A Qualitative Approach. *Asia Pac J Cancer Prev* 2023;24:889-95.
- Lim SK, Teo XL, Ng JL, et al. A Survey on Singaporean Women's Knowledge, Perception and Practices of Mammogram Screening. *Ann Acad Med Singap* 2015;44:317-25.
- Woodard GA, Jones KD, Jablons DM. Lung Cancer Staging and Prognosis. In: Reckamp, KL (Ed), *Lung Cancer Treatment and Research*. Cham: Springer;2016.
- GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2024;403:2100-32.
- Toh CK, Ong WS, Lim WT, et al. A Decade of Never-smokers Among Lung Cancer Patients-Increasing Trend and Improved Survival. *Clin Lung Cancer* 2018;5:e539-50.
- Toh CK, Gao F, Lim WT, et al. Never-Smokers With Lung Cancer: Epidemiologic Evidence of a Distinct Disease Entity. *J Clin Oncol* 2006;24:2245-51.
- Chang GC, Chiu CH, Yu CJ, et al. Low-dose CT screening among never-smokers with or without a family history of lung cancer in Taiwan: a prospective cohort study. *Lancet Respir Med* 2024;12:141-52.
- Loh CH, Koh PW, Ang DJM, et al. Characteristics of Singapore lung cancer patients who miss out on lung cancer screening recommendations. *Singapore Med J* 2022;65:279-87.
- Chapter of Respiratory Physicians. Lung Cancer Screening in Singapore. January 2025. https://www.ams.edu.sg/view-pdf.aspx?file=media%5C7406_fi_190.pdf Accessed 6 August 2025.
- Liew CJY, Leong LCH, Teo LLS, et al. A practical and adaptive approach to lung cancer screening: A review of international evidence and position on CT lung cancer screening in the Singaporean population by the College of Radiologists Singapore. *Singapore Med J* 2019;60:554-9.

24. Ang YLE, Chia PL, Chua KLM, et al. Lung Cancer in Singapore. *J Thorac Oncol* 2021;16:906-11.
25. Grover H, King W, Bhattarai N, et al. Systematic review of the cost-effectiveness of screening for lung cancer with low dose computed tomography. *Lung Cancer* 2022;170:20-33.
26. Gierach GL, Choudhury PP, García-Closas M. Toward Risk-Stratified Breast Cancer Screening: Considerations for Changes in Screening Guidelines. *JAMA Oncol* 2020;6:31-3.
27. Obeagu EI, Obeagu GU. Breast cancer: A review of risk factors and diagnosis. *Medicine (Baltimore)* 2024;103:E36905.
28. Ha SY, Choi SJ, Cho JH, et al. Lung cancer in never-smoker Asian females is driven by oncogenic mutations, most often involving EGFR. *Oncotarget* 2015;6:5465-74.
29. Moorthi S, Paguirigan A, Itagi P, et al. The genomic landscape of lung cancer in never-smokers from the Women's Health Initiative. *JCI Insight* 2024;9e174643.
30. Bhoo-Pathy N, Hartman M, Yip CH, et al. Ethnic differences in survival after breast cancer in South East Asia. *PLoS One* 2012;7:e30995.
31. Tan EY, Wong HB, Ang BK, et al. Locally Advanced and Metastatic Breast Cancer in a Tertiary Hospital. *Ann Acad Med Singap* 2005;34:595-601.
32. Pek CH, Tan EY, Chen JJ, et al. Advanced Breast Cancer—Are We Doing Enough? *Breast J* 2012;18:644-6.
33. Chiang J, Ngeow J. The management of BRCA1 and BRCA2 carriers in Singapore. *Chin Clin Oncol* 2020; 9:62.
34. Ang L, Chan CPY, Yau WP, et al. Association between family history of lung cancer and lung cancer risk: a systematic review and meta-analysis. *Lung Cancer* 2020;148:129-37.
35. Zhou F, Zhou C. Lung cancer in never smokers-the East Asian experience. *Transl Lung Cancer Res* 2018;7:450-63.
36. Taylor LC, Hutchinson A, Law K, et al. Acceptability of risk stratification within population-based cancer screening from the perspective of the general public: A mixed-methods systematic review. *Health Expect* 2023;26:989-1008.
37. Powell D. Walk, talk, think, see and feel: harnessing the power of digital biomarkers in healthcare. *NPJ Digit Med* 2025;7:45.
38. Chandran U, Reps J, Yang R, et al. Machine Learning and Real-World Data to Predict Lung Cancer Risk in Routine Care. *Cancer Epidemiol Biomarkers Prev* 2023;32:337-43.
39. Zhang B, Shi H, Wang H. Machine Learning and AI in Cancer Prognosis, Prediction, and Treatment Selection: A Critical Approach. *J Multidiscip Healthc* 2023;26:1779-91.
40. Geppert J, Asgharzadeh A, Brown A, et al. Software using artificial intelligence for nodule and cancer detection in CT lung cancer screening: systematic review of test accuracy studies. *Thorax* 2024;79:1040-9.
41. Institute of Medicine (US) and National Research Council (US) National Cancer Policy Board. Fulfilling the Potential of Cancer Prevention and Early Detection. In Curry SJ, Byers T, Hewitt M (Eds.). Washington, DC: National Academies Press; 2003.
42. A report of an Expert Group. Research in the behavioural and social sciences to improve cancer control and care: a strategy for development. *Eur J Cancer* 2004;40:316-25.
43. Dsouza JP, Broucke SVD, Pattanshetty S, et al. A comparison of behavioural models explaining cervical cancer screening uptake. *BMC Womens Health* 2022;22:235.
44. Chan DNS, So WKW. Effectiveness of motivational interviewing in enhancing cancer screening uptake amongst average-risk individuals: A systematic review. *Int J Nurs Stud* 2021; 113:103786.
45. Moey SF, Sowtali SN, Mohamad Ismail MF, et al. Cultural, Religious and Socio, Ethical Misconceptions among Muslim Women towards Breast Cancer Screening: A Systematic Review. *Asian Pacific Journal of Cancer Prevention* 2022;23:3971-82.
46. Durham AL, Adcock IM. The relationship between COPD and lung cancer. *Lung Cancer* 2015;90:121-7.

Upper limb fragility fractures: A missed opportunity

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Dear Editor,

Global ageing has led to a rise in osteoporosis¹ and fragility fractures, which are fractures that occur due to low-energy trauma. Upper limb fragility fractures, particularly proximal humerus and distal radius fractures, are known risk factors for future hip fractures.² Clinical guidelines recommend secondary preventive assessments and interventions after any fragility fracture. These include fall risk evaluation, lifestyle modifications, calcium and vitamin D supplementation, and bone mineral density (BMD) testing to detect and guide osteoporosis treatment.³ However, implementation rates of secondary prevention after upper limb fractures remain poorly studied.

Our study primarily aimed to investigate the prevalence of prior upper limb fragility fractures in a hip fracture cohort. Our secondary aims were to analyse implementation rates of secondary prevention measures after the upper limb fracture, and compare the function of hip fracture patients with and without prior upper limb fractures.

We conducted a retrospective cohort study of patients in a prospective hip fracture registry admitted between January 2012 and June 2020 to Tan Tock Seng Hospital, a major trauma centre in Singapore. Patients with pathological fractures or high-energy trauma were excluded. For patients with multiple hip fractures, only the first was included. We identified patients who had an upper limb fragility fracture of the proximal humerus, distal humerus or distal radius prior to the hip fracture.

Among 5003 hip fracture patients (Fig. 1), 245 (4.9%) had a previous upper limb fragility fracture. The upper limb fracture was sustained at a mean age of 77 (standard deviation [SD] 8.9), and the hip fracture at 82 (SD 8.6). The upper limb fracture occurred a mean of 52 months (SD 41.2) before the hip fracture. Patients were mostly female (206/245, 84.1%) and ambulant independently without aid (227/245, 75.9%). Distal radius (150/245, 61.2%) and proximal

humerus (86/245, 35.1%) fractures were most common. Regarding risk factors for falls, 28.2% (69/245) had a previous hospital encounter for a fall, and 61.2% (150/245) had comorbidities predisposing them to falls, most frequently diabetes (73/245, 29.8%), lower limb arthritis (61/245, 24.9%), cardiovascular disease (41/245, 16.7%) or stroke (31/245, 12.7%).

Despite these risk factors, 80.8% (198/245) did not undergo BMD testing after their upper limb fracture. Among those tested, 86.7% (39/47) were osteoporotic and the rest were osteopaenic. The mean Singapore fracture risk assessment tool 10-year risk was 29.1% (SD 12.1%) for a major osteoporotic fracture and 15.7% (SD 8.6%) for a hip fracture. The majority (192/245, 78.4%) were not prescribed osteoporosis medications. Additionally, most were not subjected to fall prevention interventions; 49.4% (121/245) had no fall risk assessment, 64.9% (159/245) had no vision assessment, and 51.4% (126/245) had no physiotherapy.

Of the 245 patients, 80 (32.7%) had at least 1 new fall or fracture before their hip fracture. Among them, 60.0% (48/80) sustained a new fracture. Most of these (42/80, 52.5%) were fragility fractures, most commonly of the distal radius (20/80, 25.0%), humerus (11/80, 13.8%), vertebra (10/80, 12.5%) or pubic ramus (7/80, 8.8%). Even after these events, 72.5% (58/80) did not undergo BMD testing and 81.3% (65/80) were not prescribed osteoporosis medications. Among patients with new fragility fractures, 69.0% (29/42) did not undergo BMD testing and 83.3% (35/42) were not prescribed osteoporosis medications.

Patients with prior upper limb fractures were more likely to be homebound (adjusted odds ratio 1.55, 95% confidence interval 1.07–2.23, $P=0.020$). While they had lower abbreviated mental test (mean 5.92, SD 3.43 versus [vs] mean 6.96, SD 6.57, $P=0.057$) and Modified Barthel Index scores (median 90, interquartile range [IQR] 79–98 vs median 90, IQR 83–100, $P=0.132$), these differences were not significant after

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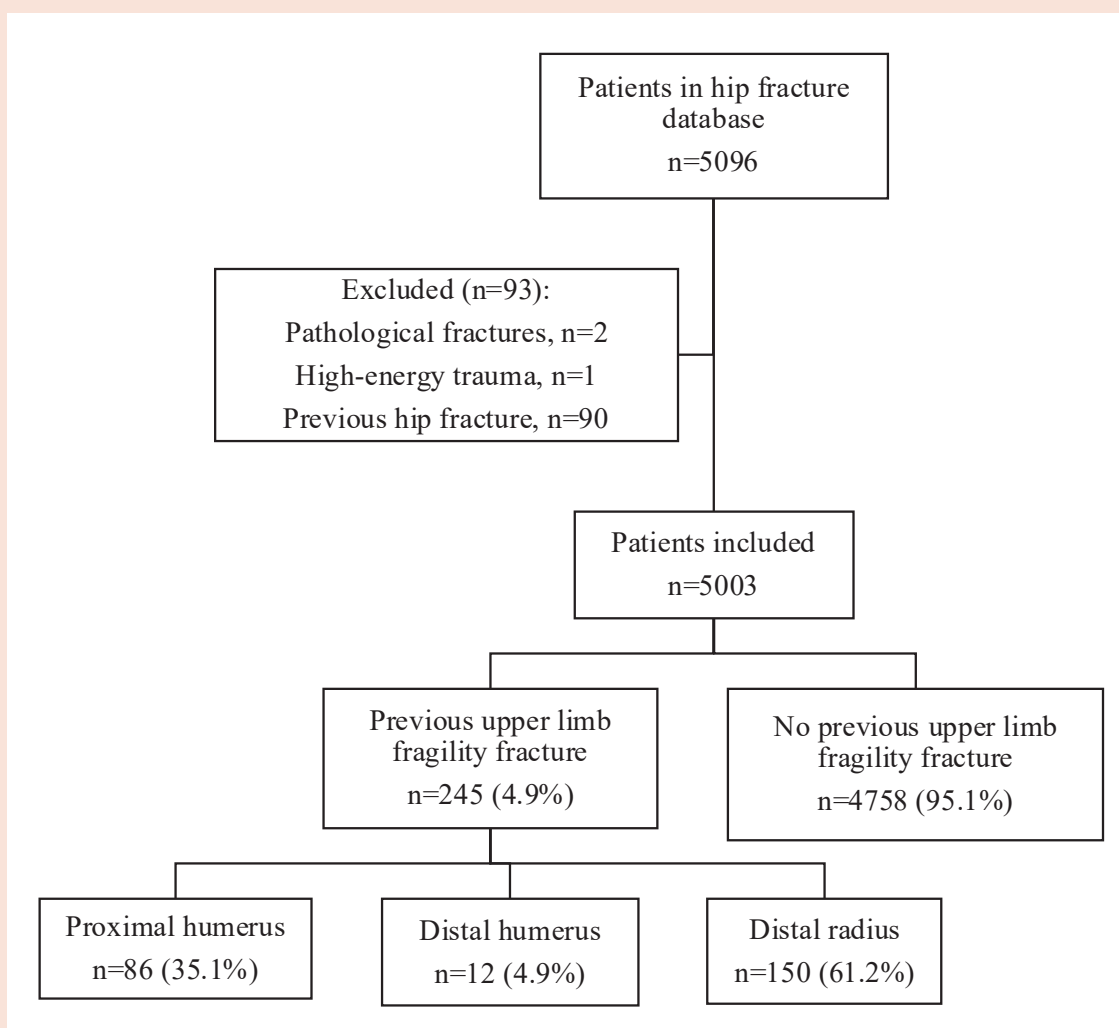
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Fig. 1. Flowchart of study cohort derivation



adjusting for age and gender. Age-adjusted Charlson Comorbidity Index was similar between the 2 groups (mean 5.53, SD 3.48 vs mean 6.96, SD 6.57, $P=0.242$).

Our findings highlight a significant prevalence of prior upper limb fragility fractures in a hip fracture cohort. The “osteoporotic career” has been described in which patients have a sequence of fragility fractures, starting with wrist fractures and leading up to hip fractures.⁴ Despite this, rates of secondary prevention after the upper limb fracture were low, and remained inadequate even after a second fall or fracture. All patients who underwent BMD testing after the upper limb fracture were osteoporotic or osteopaenic, suggesting underdiagnosis in the majority who were not screened.

Possible barriers to secondary prevention include low physician awareness that certain types of upper limb fractures are osteoporotic fractures,⁵ lack of willingness from orthopaedic surgeons to manage

osteoporosis,⁶ and inadequate interdisciplinary communication.⁷ Patients may also underestimate their fracture risk, resulting in reduced adherence to follow-up and treatment.⁸

Concerningly, rates of fall prevention interventions such as fall risk assessment, vision assessment and physiotherapy were inadequate. This is despite many patients having risk factors for future falls such as a previous fall or comorbidities that predispose them to falls. Fall risk assessment and prevention are key aspects of secondary fracture prevention.⁹ International guidelines recommend a multicomponent fall risk assessment to identify modifiable risk factors, including mobility issues, vision and hearing problems, diseases and medications, nutrition and environmental factors.¹⁰ The failure to implement fall prevention represented opportunities to prevent future fractures and their associated morbidity.

Our study’s strengths include its large sample size and the use of a well-established hip fracture registry

with prospectively collected data. The study also had limitations. As a retrospective study, causal relationships could not be established. While the electronic medical records system captured most medical records from public healthcare institutions, some records, especially those from private institutions or from the years prior to widespread adoption of the electronic records system, could not be accessed. Finally, our study was not scoped to identify reasons for the low rates of secondary prevention.

In conclusion, this study underscores the urgent need to improve fall risk interventions and osteoporosis screening and treatment in patients with upper limb fragility fractures. In view of the rapidly ageing population and rising burden of osteoporosis in Asia, stakeholders—including orthopaedic surgeons, geriatricians, policymakers and insurers—must urgently implement structured programmes to ensure that every fragility fracture event leads to appropriate osteoporosis and fall risk assessments.

Ethics statement

Ethics approval was granted by the National Healthcare Group Domain Specific Review Board (2022/00402).

Declaration

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

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Keywords: *fractures, fragility fractures, frailty, hip fractures, orthopaedic surgery*

REFERENCES

1. Salari N, Ghasemi H, Mohammadi L, et al. The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis. *J Orthop Surg Res* 2021;16:609.
2. Shoji MM, Ingall EM, Rozental TD. Upper Extremity Fragility Fractures. *J Hand Surg Am* 2021;46:126-32.
3. Mitchell P, Magaziner J, Costa M, et al. FFN Clinical Toolkit. Zurich: Fragility Fracture Network 2020. https://www.fragilityfracturenetwork.org/wp-content/uploads/2020/10/FFNClinicalToolkit_English_v1_web.pdf. Accessed 13 March 2024.
4. Akesson K, Mitchell P. Capture the Fracture: A Global Campaign to Break the Fragility Fracture Cycle. Nyon: International Osteoporosis Foundation; 2012. <https://share.osteoporosis.foundation/WOD/2012/report/WOD12-Report.pdf>. Accessed 28 March 2024.
5. Kim TI, Choi JH, Kim SH, et al. The Adequacy of Diagnosis and Treatment for Osteoporosis in Patients with Proximal Humeral Fractures. *Clin Orthop Surg* 2016;8:274-9.
6. Barton DW, Griffin DC, Carmouche JJ. Orthopedic surgeons' views on the osteoporosis care gap and potential solutions: survey results. *J Orthop Surg Res* 2019;14:72.
7. Benzvi L, Gershon A, Lavi I, et al. Secondary prevention of osteoporosis following fragility fractures of the distal radius in a large health maintenance organization. *Arch Osteoporos* 2016;11:20.
8. Langer FW, da Silveira Codevilla AA, Bringhenti R, et al. Low self-awareness of osteoporosis and fracture risk among postmenopausal women. *Arch Osteoporos* 2016;11:27.
9. Ambrose AF, Cruz L, Paul G. Falls and Fractures: A systematic approach to screening and prevention. *Maturitas* 2015;82:85-93.
10. Montero-Odasso M, van der Velde N, Martin FC, et al. World guidelines for falls prevention and management for older adults: a global initiative. *Age Ageing* 2022;51:afac205. Erratum in: *Age Ageing* 2023;52:afad188. Erratum in *Age Ageing* 2023;52:afad199.

Patients' preferences for nutrition care from health professionals in public primary care setting: A cross-sectional study in Singapore

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Dear Editor,

The Burden of Disease in Singapore 1990–2017 report by the Ministry of Health, Singapore and Institute for Health Metrics and Evaluation highlighted that the largest contributors to Singapore's disease burden were non-communicable diseases (e.g. chronic diseases such as hypertension, diabetes mellitus and hyperlipidaemia), which comprised 80.3% of the total burden in 2017. Of these, the largest burdens were from cardiovascular diseases, making up 14.2% of total disability-adjusted life years (DALYs).¹

The Global Burden of Diseases, Injuries, and Risk Factors Study 2019 reported 8% to less than 10% of DALYs in Singapore are attributable to dietary risks,² which meant that the burden caused by metabolic diseases could potentially be reduced by early intervention of modifiable risk factors, such as diet and nutrition. Nutrition care, which is the provision of nutrition-related advice and counselling by a health-care professional (HCP), to improve the nutrition behaviour of patients,³ can be provided by different HCPs, such as doctors, dietitians and nurses. An Australian qualitative study found that primary care physicians were preferred by patients to be the providers of nutrition care as they were considered to provide personalised and professional nutrition care.³

To our knowledge, no studies have explored preferences and their associated factors as well as perceptions towards nutrition care among patients with chronic conditions in Asia. This is a knowledge gap that our study sought to address.

We conducted a facility-based cross-sectional survey of patients aged 21 years and above with at least 1 chronic condition (diabetes mellitus, hypertension, hyperlipidaemia) in a polyclinic situated in the northern part of Singapore from 22 July 2023 to 8 May 2024. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (DSRB Reference: 2022/00855).

As there is no existing relevant validated questionnaire suited to answer our research question, the study team designed a self-administered research

questionnaire with 22 questions in English by adapting 3 overseas qualitative studies^{3,4,5} to the Singapore context (Supplementary materials, Appendix S1).

Patients were recruited via convenience sampling and invited to complete this questionnaire. They were approached by trained study team members who were care coordinators with a nursing background and managed the care of patients with chronic conditions. Informed consent was obtained from patients by study team members.

We approached 482 eligible patients and 14 declined to participate; 468 patients were recruited and 30 with incomplete data were removed via case-wise omission, yielding 438 patients with complete responses with approximately 4.5% margin of error. A summary of the sociodemographic data of the patients is presented in Supplementary Table S1.

We developed two binary logistic regression models to examine the patients' preferred source of nutrition care between doctors and dietitians, and their reasons for their preference. The first model examined the patients' preference for doctors, and the model examined their preference for dietitians; both models controlled for age and sociodemographic factors, using R studio version 2023.09.1+494 (RStudio Corporation, Massachusetts, US) running R-Base (4.2.2). Presence of multicollinearity was tested by examining the variance inflation factor (VIF) of each predictor variable. All predictor variables showed a VIF of less than 5, indicating low concern of multicollinearity.

In the two binary logistic regression models, the dependent variables were the patients' preference for doctors or dietitians as their source of nutrition care; the independent variables were the patients' age, sex, ethnicity, types of chronic conditions, education level and household income, with odds ratio (OR) and 95% confidence interval (CI) for each variable. *P* values <0.05 were considered statistically significant.

Among the 438 patients included in the study, the majority were Chinese (248/438, 56.6%) and the

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most common chronic disease was hyperlipidaemia (311/438, 71.0%), similar to findings from the Singapore National Health Survey 2022.⁶ The majority of patients indicated doctors as their preferred provider of nutritional care (198/438, 45.2%), followed by dietitians (161/438, 36.8%) and nurses (79/438, 18.0%). For those who chose doctors, the top reasons were reliability (141/198, 71.2%), comfort (114/198, 57.6%) and convenience (99/198, 50.0%). These findings are similar to the findings of the Australian study by Ball et al. 2014.³

From our survey, a vast majority of patients 77.6% (340/438) had received nutritional care from an HCP previously, with 47.6% (162/340) from doctors, 25.9% (88/340) from nurses and 26.5% (90/340) from dietitians.

A summary of the factors influencing the patients' preferences as well as their perceptions towards the nutritional care provided by the HCPs is presented in Supplementary Fig. S1. Across the 3 HCPs, a significantly lower percentage of patients who received nutritional care from doctors felt that doctors had spent sufficient time with them (137/162, 84.6%), compared with those who received nutritional care from nurses (83/88, 94.3%) and dietitians (85/90, 94.4%). Also, a significantly lower percentage of patients who received nutritional care from doctors (111/162, 68.5%) felt that the recommendations given were easy to follow compared with those who received nutritional care from nurses (75/88, 85.2%) and dietitians (67/90, 74.4%).

A vast majority of patients felt that nutritional care was useful (385/438, 87.9%), important (383/438, 87.4%) and accessible (354/438, 80.8%). The most common area requiring improvement for HCPs chosen by patients was more counselling time, with 62.1% (272/438), indicating this for doctors, 34.2% (150/438) for dietitians and 33.1% (145/438) for nurses, similar to the study by Lepre et al. 2023.⁵

In our first binary regression model, age was the only independent variable that was significantly associated with preference for doctors (Table 1A). Older age of patients increased the odds of preferring a doctor as the source of nutrition care, with OR 1.03 (95% CI 1.01–1.06).

In our second model on factors associated with preference for dietitian (Table 1B), age and Malay ethnicity were negatively associated with preference for dietitians. Older patients were less likely to prefer dietitians, with adjusted OR 0.95 (95% CI 0.93–0.98), and Malay patients were also less likely to prefer dietitian, with adjusted OR 0.60 (95% CI 0.37–0.98). However, patients with a monthly income of more than SGD6000 were also more likely to prefer dietitians (adjusted OR 1.69, 95% CI 1.27–4.44).

These findings highlight a potential gap between patients' preference and quality of care received—in that although the patients preferred doctors to provide nutrition care, a lower proportion of patients felt that doctors had spent sufficient time with them or that their recommendations were easy to follow as compared to dietitians or nurses.

Compared to younger patients, older patients were more likely to prefer doctors to provide nutrition care, possibly due to lower health literacy, evident in a Singapore study by Asharani et al. in 2021.⁷ This may lead to lower awareness of the role of dietitian or nurses in providing nutrition care.

Conversely, patients with higher income of more than SGD6000 were more likely to prefer dietitians, possibly following higher health literacy and awareness of the role of dietitians. We are uncertain about the clinical significance of the association between Malay ethnicity and low preference for dietitian. Further research can explore this association.

To reduce the gap in nutrition care, consultation time of doctors can be increased to dedicate more time to nutrition care and training. Improving awareness of the professional profile and the value-added services of dietitians and nurses in Singapore while increasing patients' accessibility to their services, such as by allowing patients to book consultations with dietitians and nurses directly without requiring a referral from a doctor is crucial. The far-reaching value-added services of dietitians from the clinical setting, such as in providing personalised dietary assessments to dispensing impactful everyday management of food preparation and planning (e.g. through nutrition workshops and cooking demonstrations), can be further publicised. We should also leverage the strength of multidisciplinary teams, and healthcare organisations can consider adopting the Exploration, Preparation, Implementation, Sustainment framework to improve nutritional care delivery service.⁸ Given time constraints faced by doctors, more can be done to publicise the existing tele-nutrition consultation provided by dietitians and tap into mobile phone applications to provide nutrition care.

Singapore's primary care and insurance models could work towards providing increased inclusivity for direct dietitian referrals, extended appointment slots and tele-nutrition. Under a value-based care model, for patients with metabolic risk factors, we could consider a primary care or insurance model that includes a bundled consultation payment model. This could include both a medical doctor and dietitian co-consultation with extended appointment slots, which can be done face-to-face or via teleconsultation.

With the increasing burden of metabolic diseases, nutrition care provided by various HCPs should be optimised to achieve better health outcomes. Further

Table 1. Variables associated with patients' preference for (A) doctors and (B) dieticians, and baseline characteristics of patients (n=438).

Characteristics	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
(A) Preference for doctors				
Older age (23–83 years)	1.04 (1.02–1.06)	<0.001	1.03 (1.01–1.06)	<0.001
Sex				
Male (n=207)		Reference		
Female (n=231)	0.72 (0.48–1.15)	0.08	0.71 (0.49–1.05)	0.09
Ethnicity				
Chinese (n=248)		Reference		
Malay (n=136)	0.95 (0.63–1.44)	0.81	1.01 (0.66–1.55)	0.95
Indian (n=47)	0.75 (0.40–1.39)	0.36	0.76 (0.47–1.44)	0.43
Others (n=7)	0.15 (0.02–1.29)	0.09	0.17 (0.02–1.49)	0.11
Chronic conditions				
Hyperlipidaemia (n=311)		Reference		
Hypertension (n=299)	0.82 (0.64–1.32)	0.41	0.81 (0.62–1.24)	0.33
Diabetes mellitus (n=252)	1.21 (0.86–1.46)	0.62	1.16 (0.84–1.33)	0.61
All 3 chronic conditions (n=163)	0.93 (0.81–1.25)	0.47	0.92 (0.37–1.24)	0.43
Educational level				
Secondary level education and below (n=197)		Reference		
Post-secondary level education and above (n=241)	1.32 (0.81–1.62)	0.84	1.24 (0.79–1.57)	0.78
Household income per month				
Below SGD2000 (n=48)		Reference		
From SGD2000–5999 (n=136)	1.41 (0.71–1.63)	0.47	1.52 (0.73–1.91)	0.45
More than SGD6000 (n=182)	1.13 (0.5–1.54)	0.83	1.25 (0.62–1.71)	0.89
(B) Preference for dieticians				
Older age (23–83 years)	0.95 (0.93–0.97)	<0.001	0.95 (0.93–0.98)	<0.001
Sex				
Male (n=207)		Reference		
Female (n=231)	1.23 (0.82–1.82)	0.32	1.38 (0.90–2.11)	0.14
Ethnicity				
Chinese (n=248)		Reference		
Malay (n=136)	0.67 (0.42–1.06)	0.08	0.60 (0.37–0.98)	0.04
Indian (n=47)	1.01 (0.53–1.94)	0.97	0.95 (0.47–1.89)	0.88
Others (n=7)	4.47 (0.85–23.49)	0.08	2.87 (0.50–16.37)	0.24
Chronic conditions				
Hyperlipidaemia (n=311)		Reference		
Hypertension (n=299)	1.02 (0.61–1.71)	0.94	1.17 (0.68–2.03)	0.57

Table 1. Variables associated with patients' preference for (A) doctors and (B) dietitians, and baseline characteristics of patients (n=438). (Cont'd)

Characteristics	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Diabetes mellitus (n=252)	0.88 (0.54–1.44)	0.62	1.16 (0.68–1.96)	0.59
All 3 chronic conditions (n=163)	0.70 (0.18–2.77)	0.61	1.16 (0.24–5.59)	0.85
Educational level				
Secondary level education and below (n=197)		Reference		
Post-secondary level education and above (n=241)	2.20 (1.46–3.33)	<0.001	1.70 (0.96–3.01)	0.07
Household income per month				
Below SGD2000 (n=48)		Reference		
From SGD2000–5999 (n=149)	3.14 (1.32–7.49)	<0.01	2.66 (1.07–6.58)	0.28
More than SGD6000 (n=241)	3.43 (1.48–7.97)	<0.01	1.69 (1.27–4.44)	0.03

CI: confidence interval; OR: odds ratio; SGD: Singapore dollar

P values in bold are statistically significant.

research is needed to explore the format, duration, content and type of HCP nutritional counselling that should be tailored to patients' age, goals of care, level of health literacy, disease complexity, stages of changes and lifestyle priorities.

Supplementary materials

Table S1. Summary of sociodemographic data of patients.

Fig. S1. Factors affecting patients' preferences as well as perceptions towards nutrition care provided by healthcare professionals.

Appendix S1. Sample of the research questionnaire.

Ethics statement

Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (DSRB Reference: 2022/00855).

Declaration

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

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Keywords: chronic conditions, diet, nutrition, perceptions, preferences

REFERENCES

1. Epidemiology & Disease Control Division, Ministry of Health, Singapore; Institute for Health Metrics and Evaluation. The Burden of Disease in Singapore, 1990–2017: An overview of the Global Burden of Disease Study 2017 results. Seattle, WA: IHME, 2019:22.
2. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1223–49.
3. Ball L, Desbrow B, Leveritt M. An exploration of individuals' preferences for nutrition care from Australian primary care health professionals. *Aust J Prim Health* 2014;20:113–20.
4. Cash T, Desbrow B, Leveritt M. Utilization and preference of nutrition information sources in Australia. *Health Expect* 2015;18:2288–95.
5. Lepre B, Mansfield KJ, Beck EJ. Attitudes, work roles and barriers to nutrition care – interviews with Australian and UK-based medical doctors. *J Hum Nutr Diet* 2023;36:920–31.
6. Epidemiology & Disease Control Division and Policy, Research & Surveillance Group, Ministry of Health and Health Promotion Board, Singapore. National Population Health Survey 2022 (Household Interview and Health Examination). <https://www.moh.gov.sg/others/resources-and-statistics/nphs-2022>. Accessed 3 June 2025.
7. Asharani PV, Lau JH, Roystonn K, et al. Health Literacy and Diabetes Knowledge: A Nationwide Survey in a Multi-Ethnic Population. *Int J Environ Res Public Health* 2021;18:9316.
8. McGuier EA, Kolko DJ, Stadnick NA, et al. Advancing research on teams and team effectiveness in implementation science: An application of the Exploration, Preparation, Implementation, Sustainment (EPIS) framework. *Implement Res Pract* 2023;4:26334895231190855.

A review of fertility preservation in women in Singapore from 2010 to 2019

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Dear Editor,

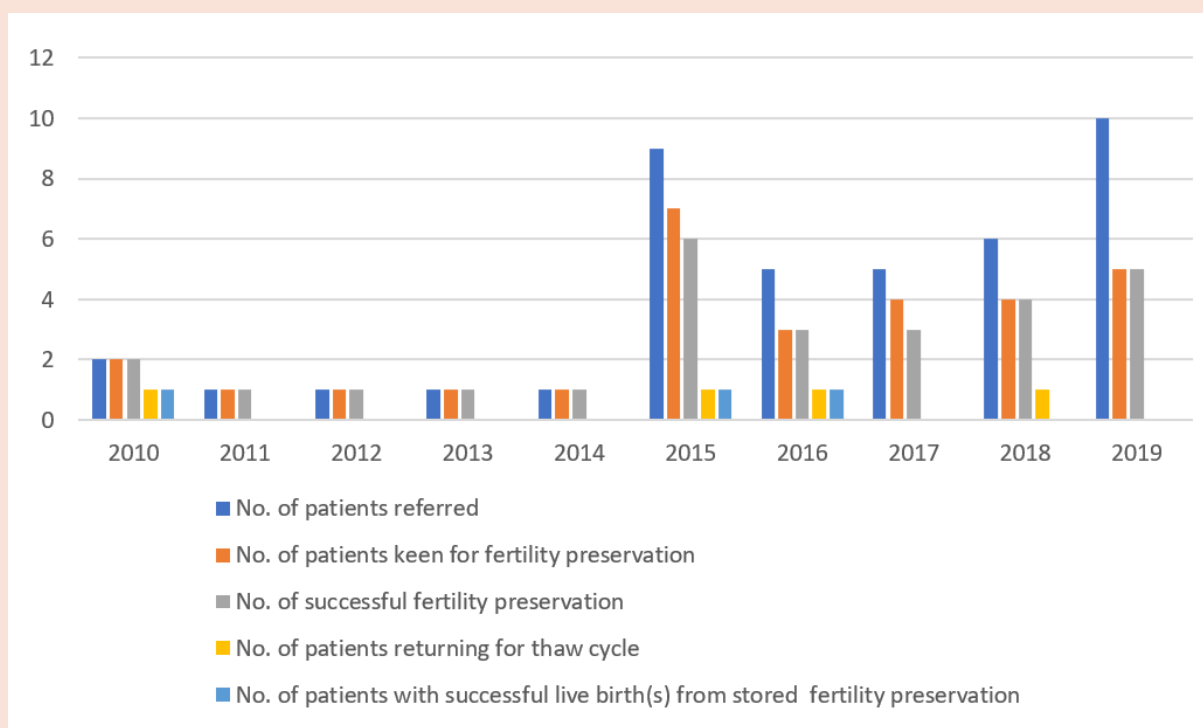
Cancer cases in Singapore have increased nearly sevenfold from 12,072 in 1968–1972 to 84,002 in 2017–2021.¹ Despite this, survival rates have improved due to early detection and advancements in treatment, resulting in a shift in focus to long-term survivorship and quality of life. Women who survive cancer are increasingly interested in fertility preservation, especially before gonadotoxic treatments. The American Society of Clinical Oncology advises oncologists to discuss fertility risks with reproductive-age patients and refer them to specialists when necessary.² However, referral rates remain low globally, highlighting an unmet need. A Hong Kong survey found high interest among women in learning about and considering fertility preservation, even if it delays cancer treatment.³

Options include embryo and oocyte cryopreservation, which are well-established methods, while ovarian tissue cryopreservation and in-vitro maturation are less commonly used. Currently, Singapore lacks data on fertility preservation referral practices, types of procedures performed and outcomes, which this review aims to present.

This retrospective study reviewed all female patients at KK Women's and Children's Hospital from 2010 to 2019 who sought fertility preservation. It aimed to assess uptake rates, identify barriers, analyse the types of procedures performed, and evaluate fertility outcomes. The study received approval from SingHealth Centralised Institutional Review Board (Reference number: 2019/2854).

Fig. 1 illustrates the annual referral rates and a breakdown of women who successfully underwent

Fig. 1. Referral rates from 2010 to 2019.



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fertility preservation, as well as those who returned for a thaw cycle and achieved live births. There has been a general upward trend in the number of patients referred for fertility preservation over the years.

A total of 41 women were referred for fertility preservation from 2010 to 2019, and 29 (70.7%) opted for fertility preservation. Among them, 27 successfully banked oocytes, embryos or ovarian tissue. Embryo cryopreservation was the most common (44.4%), followed by oocyte cryopreservation (33.3%). A small subset (11%) underwent ovarian tissue cryopreservation, primarily for urgent cancer treatment or in prepubertal girls. The procedures yielded promising outcomes: 4 women achieved successful live births—3 via cryopreserved gametes and 1 from spontaneous conception post-cryopreservation.

The following case studies illustrate the potential for success in Singapore:

- A 22-year-old woman with ovarian cancer underwent ovarian tissue extraction and ex vivo oocyte maturation, resulting in a live birth—the first reported case from ex-vivo oocytes globally.⁴
- A 32-year-old woman with breast cancer successfully had a baby after embryo transfer from cryopreserved tissues.
- A woman with thyroid cancer stored oocytes before radioactive iodine therapy, leading to 2 live births following embryo transfer.
- A woman with gastric cancer conceived spontaneously post-therapy, delivering a healthy baby.

While these successes are encouraging, in our study, 12 out of 41 patients (29.2%) declined fertility preservation. The following are the reasons as barrier to utilisation: financial constraints were cited by 4/12 women (33.3%), while other women were deemed unsuitable for fertility preservation/informed of low success rates (3/12; 25%) or chose not to delay treatment (2/12; 16.6%).

The cost of fertility preservation procedures in Singapore ranges from SGD10,000 to SGD17,000 per cycle. Government schemes offer partial subsidies—particularly for married women under 40 years, and allow MediSave withdrawals of up to SGD6000 per cycle with a lifetime cap of SGD15,000. However, this coverage is insufficient, especially for single women or those who do not meet eligibility criteria. The high out-of-pocket costs, in addition to indirect expenses, deter many women from pursuing preservation. Unlike Singapore, countries like Japan and South Korea offer partial insurance coverage for some fertility preservation options.⁵ In August 2024, Singapore's Ministry of Health outlined plans to extend co-funding and insurance

support for young cancer patients,⁶ reflecting governmental commitment to promoting fertility and parenthood, though this initiative is still under development.

Additionally, the lack of systematic referral pathway is another reason for low fertility preservation uptake. Until recent years, there was minimal data on fertility preservation referral practices, procedure types and outcomes in Singapore. The absence of such data hampers the development of targeted policies or resource allocation strategies aimed at bridging these gaps. Unlike countries like Israel, which have successfully implemented dedicated onco-fertility referral algorithms, Singapore lacks a formalised national protocol. This results in inconsistent referral practices, missed opportunities and lower awareness among both oncologists and patients. A study of Italy's PREgnancy and FERtility project demonstrated that structured referral pathways could significantly increase counselling and treatment uptake.⁷ Having a specific referral algorithm for women with breast cancer led to 34.6% (55/159) of participants receiving comprehensive reproductive counselling at fertility clinics, with 52.7% (29/55) of counselled women opting for fertility preservation, similar to Singapore's interest rate of 70.7%.

To our knowledge, our study is the first on fertility preservation uptake and usage rate in Singapore. However, its retrospective design bears inherent limitations, including potential data loss and recall bias.

Nevertheless, in conclusion, this study has shown that Singapore is facing pressing challenges in providing equitable and timely access to fertility preservation. Addressing these gaps would require strengthening multidisciplinary referral pathways, increasing public and clinician awareness, and expanding government support to alleviate the cost of fertility preservation procedures. These measures may improve the uptake of fertility preservation. Establishing a nationwide, prospective, multicentre registry could also improve follow-up, resource allocation and ultimately, reproductive outcomes for women affected by cancer.

Ethics statement

The study received approval from the SingHealth Centralised Institutional Review Board (2019/2854).

Declaration

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

Keywords: cancer, fertility preservation, obstetrics and gynaecology, oncofertility, reproductive medicine

REFERENCES

1. Health Promotion Board, Ministry of Health, Singapore. Singapore Cancer Registry 50th Anniversary Monograph (1968–2017). <https://www.nrdo.gov.sg/publications/cancer>. Accessed 17 June 2025.
2. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients. *J Clin Oncol* 2006;24:2917-31.
3. Fisch B, Abir R. Female fertility preservation: past, present and future. *Reproduction* 2018;156:F11-27.
4. Prasath EB, Chan ML, Wong WH, et al. First pregnancy and live birth resulting from cryopreserved embryos obtained from in vitro matured oocytes after oophorectomy in an ovarian cancer patient. *Hum Reprod* 2014;29:276-8.
5. Harzif AK, Santawai VPA, Maidarti M, et al. Investigation of Society for Fertility Preservation in Asia. *Front Endocrinol* 2019;10:151.
6. Ministry of Health, Singapore. Speech by MOS Rahayu on the Adjournment Motion on Fertility Preservation for Young Cancer Patients. 6 August 2024. <https://www.moh.gov.sg/newsroom/speech-by-mos-rahayu-on-the-adjournment-motion-on-fertility-preservation-for-young-cancer-patients>. Accessed 17 June 2025.
7. Lambertini M, Anserini P, Fontana V, et al. The PREgnancy and FERtility (PREFER) study: an Italian multicenter prospective cohort study on fertility preservation and pregnancy issues in young breast cancer patients. *BMC Cancer* 2017;17:346.

Postpartum urinary incontinence: Longitudinal risk factors and trajectories in Singapore

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Dear Editor,

Postpartum urinary incontinence is common and continues to negatively impact quality of life. Few studies have provided longitudinal data on postpartum urinary incontinence and its risk factors are not well understood. Majority of existing evidence concentrates on Caucasian populations,¹ not representing our Southeast Asian counterparts. This study aims to describe the time course and severity of postpartum urinary incontinence and identify its risk factors in women in Singapore.

This study recruited women who delivered from December 2017 to February 2018 at Singapore General Hospital (SGH). Exclusion criteria were women who were under the age of 21, unable to read and understand English and who declined to provide informed consent. Of the remaining 222, 187 women who attended at least 1 follow-up assessment were included in the study. Ethics approval was obtained from SingHealth Centralised Institutional Review Board 2017/2848).

Data collected included continence status in pregnancy, maternal age, pre-pregnancy body mass index (BMI), parity, birth weight and mode of delivery (normal vaginal delivery, forceps delivery, vacuum delivery or Caesarean delivery). Given the limited numbers in the vacuum delivery category (n=12), normal vaginal delivery and vacuum delivery were combined on the basis of their similar maternal and neonatal injury rates as compared with forceps delivery² to optimise statistical power.

At 3, 8 and 12 months post-delivery, patients self-reported volume and frequency of urinary leakage with the universally validated severity index International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form.³ Incontinence severity was analysed as an ordinal variable with an ordinal 10-level scale. Continuous variables were summarised with mean and standard deviations, and categorical variables as percentages and frequencies. Risk

factors of incontinence severity over time were identified using proportional odds mixed-effects regression modelling.

Mean age in our cohort was 32 years (standard deviation [SD]=5), mean pre-pregnancy BMI was 24.2 (SD=6), mean parity was 1.8 and mean birth weight was 3.2 kg (SD=0.7). Around half of the women (52%) had urinary incontinence in pregnancy. In addition, 39% of the women delivered via caesarean delivery, 48% via normal vaginal delivery and 13% with instrumentation. At the final follow-up timepoint (month 12), about 15%, 6% and 3% of women had mild, moderate and severe incontinence severity, respectively. Among women who provided responses at 3 and 12 months postnatally, more than half who were categorised as severe at 3 months improved to none or mild at the end of follow-up, whereas approximately 30% of women categorised as having no incontinence at the 3-month timepoint were in the mild or moderate categories at the end of follow-up. The presence of pre-delivery incontinence was most strongly associated with greater incontinence severity during post-delivery follow-up. Other baseline characteristics that were independently associated with greater incontinence severity included baby weight and delivery mode. Women with a pre-pregnancy BMI of 27 kg/m² had 2.1 (95% confidence interval [CI] 0.9–4.7) times the odds of greater post-delivery incontinence severity compared with women with a pre-pregnancy BMI of 21 kg/m², but this association did not achieve statistical significance.

In this longitudinal study of 187 women, we found that almost a quarter of women reported having urinary incontinence 1 year post-delivery. Risk factors associated with greater incontinence severity over time were incontinence in pregnancy, birth weight, mode of delivery and pre-pregnancy BMI. In our study, the prevalence of postpartum urinary incontinence was 34% at 3 months and 24% at 1 year post-delivery, consistent with results from previous studies.^{4,5} Our finding that the odds for urinary incontinence reduced

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Table 1. Patient characteristics, incontinence severity and factors associated with incontinence severity.

Participants (n=187)				
Continuous variables	25th percentile	50th percentile	75th percentile	Mean ± SD
Maternal age, years	29.0	32.0	35.5	32.1 ± 4.8
Weight, kg	51.0	58.0	68.0	61.0 ± 15.0
BMI, kg/m2	20.3	22.6	26.9	24.2 ± 5.7
Parity, no. of previous deliveries	1.0	2.0	2.0	1.8 ± 0.9
Birth weight, kg	2.8	3.1	3.5	3.1 ± 0.7
Categorical variables	No. (%)			
Pre-delivery incontinence	98 (52)			
Delivery mode				
Caesarean	72 (39)			
Normal	90 (48)			
Vacuum	12 (6)			
Forceps	13 (7)			
Incontinence post-delivery	3 months (n=122)	8 months (n=75)	12 months (n=155)	
Mean incontinence severity ± SD	1.0 ± 2.0	0.7 ± 1.5	0.9 ± 1.9	
Incontinence severity category	No. (%)			
None	81 (66)	54 (72)	118 (76)	
Mild	33 (27)	17 (23)	24 (15)	
Moderate	1 (1)	2 (3)	9 (6)	
Severe	7 (6)	2 (3)	4 (3)	
Comparison	OR (95% CI)		P value	
Time since delivery 3 months versus (vs) 12 months	1.9 (1.1–3.1)		0.01	
Maternal age, years 39 vs 29	0.8 (0.4–1.6)		0.60	
Pre-delivery incontinence Present vs absent	6.3 (2.5–16.2)		<0.001	
BMI, kg/m2 27 vs 20	2.1 (0.9–4.7)		0.12	
Participants (n=187)				
Parity 1 vs 3 previous deliveries	1.8 (0.6–5.1)		0.58	
Birth weight, kg 3.5 vs 2.8	2.2 (1.3–3.6)		<0.01	
Delivery mode Forceps vs caesarean section	2.4 (0.4–14.3)		0.35	
Normal/vacuum vs caesarean section	3.1 (1.2–7.9)		0.02	

BMI: body mass index; CI: confidence interval; OR: odds ratio; SD: standard deviation

Results shown are from proportional odds mixed-effects regression models. Adjusted ORs (95% CI) estimate the odds of greater post-delivery incontinence severity at the 75th vs the 25th percentile values for time since delivery, maternal BMI and baby weight. For example, other variables being equal, mothers with the baby weighing 3.5 kg (75th percentile) had, on average, 2.2 times (95% CI 1.3–3.6 times) the odds of having greater incontinence severity relative to mothers with the baby weighing 2.8 kg (25th percentile). For count and categorical variables, comparisons are made at distinct variable levels. For example, other variables being equal, mothers with pre-delivery incontinence had, on average, 6.3 times (95% CI 2.5–16.2 times) the odds of having greater incontinence severity relative to mothers without pre-delivery incontinence.

over time may be attributed to the reduction of pressure onto the pelvic floor post-delivery and the months after with gradual reduction in bodyweight with recovery. Despite this reduction, almost a quarter of women had persistent urinary incontinence 1 year postnatally, with previous studies having the same consensus.^{6,7}

Importantly, we found that incontinence severity is not static and may fluctuate over time. Around a quarter who were continent at 3 months reported incontinence symptoms of varying severity at 1 year. Our findings highlight the need for early education and identification of at-risk women, especially when women with postpartum incontinence have been shown to be resistant against independently seeking help as they (1) have poor understanding of the condition and (2) misbelieve that their symptoms will resolve with time.⁸

The presence of incontinence in pregnancy was the strongest risk factor for incontinence over time, concurring with previous studies.^{6,9} This emphasises the importance of integrating urinary incontinence screening into routine antenatal and postnatal consults. The presented positive association between birth weight and incontinence severity may be explained by the increased stretch of structures within the pelvis in pregnancy.

Although not statistically significant, the positive association between higher pre-pregnancy BMI and greater odds of incontinence severity was consistent with that of previous studies.¹⁰ The association was also consistent with and with our current physiological understanding that increased downward pressure within the pelvis caused by increased bodyweight can overwhelm structures supporting the bladder neck with increased intra-abdominal pressure, resulting in urinary incontinence.

In conclusion, around 1 in 4 women continue to experience urinary incontinence 1 year after delivery and it is possible for symptoms of incontinence to develop only after their postnatal follow-up at 6 weeks. Given that women with incontinence in pregnancy and those who deliver babies with higher birth weight have substantially higher odds of incontinence, they may form clinically important subgroups for close monitoring. An important implication drawn from this study is the significant usefulness of clinical intervention studies such as education and supervised pelvic floor training programmes integrated into national maternal health programmes before delivery. Education in the form of public outreach to raise awareness and inform the public can prove to be beneficial. Such studies, if undertaken in patient cohorts with the aforementioned identified risk factors, can aid in investigating whether early intervention strategies can mitigate the severity and possible persistence of

postpartum urinary incontinence, reducing postpartum symptoms and their sequelae. Guidelines in the prevention and management of postpartum urinary incontinence can then be formulated, addressing the lack in recommendations for antenatal and postnatal urinary incontinence screening in Singapore.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2017/2848).

Declaration

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

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Keywords: *incontinence, obstetrics and gynaecology, postpartum, pregnancy, prevalence, quality of life, urinary, urogynaecology*

REFERENCES

- Cheung RYK, Chan SSC, Shek KL, et al. Pelvic organ prolapse in Caucasian and East Asian women: a comparative study. *Ultrasound Obstet Gynecol* 2019;53:541-5.
- Muraca GM, Boutin A, Razaz N, et al. Maternal and neonatal trauma following operative vaginal delivery. *CMAJ* 2022;194:E1-12.
- Gartland D, MacArthur C, Woolhouse H, et al. Frequency, severity and risk factors for urinary and faecal incontinence at 4 years postpartum: a prospective cohort. *BJOG* 2016;123:1203-11.
- Hansen BB, Svare J, Viktrup L, et al. Urinary incontinence during pregnancy and 1 year after delivery in primiparous women compared with a control group of nulliparous women. *Neurourol Urodyn* 2012;31:475-80.
- Brown S, Gartland D, Perlen S, et al. Consultation about urinary and faecal incontinence in the year after childbirth: a cohort study. *BJOG* 2015;122:954-62.
- Gartland D, Donath S, MacArthur C, et al. The onset, recurrence and associated obstetric risk factors for urinary incontinence in the first 18 months after a first birth: an Australian nulliparous cohort study. *BJOG* 2012;119:1361-9.
- Quiboeuf E, Saurel-Cubizolles MJ, Fritel X, et al. Trends in urinary incontinence in women between 4 and 24 months postpartum in the EDEN cohort. *BJOG* 2016;123:1222-8.
- Wagg AR, Kendall S, Bunn F. Women's experiences, beliefs and knowledge of urinary symptoms in the postpartum period and the perceptions of health professionals: a grounded theory study. *Prim Health Care Res Dev* 2017;18:448-62.
- Diez-Itza I, Arrue M, Ibañez L, et al. Factors involved in stress urinary incontinence 1 year after first delivery. *Int Urogynecol J* 2010;21:439-45.
- Cheung RYK, Shek KL, Chan SSC, et al. Pelvic floor muscle biometry and pelvic organ mobility in east Asian and Caucasian nulliparae. *Ultrasound Obstet Gynecol* 2015;45:599-604.

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