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Patient-centred outcomes and cost-effectiveness of a hospital-at-home service model for older adults

Hospital-at-home service is a cost-effective alternative to inpatient hospitalisation with positive benefits, such as shorter length of stay and better caregiver experiences. (See full article, p. 189)

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Also in this issue

Immune response to SARS-CoV-2 vaccination among chronic myeloid leukaemia patients on tyrosine kinase inhibitors

Cognition and arthritis in adults over 50: Evidence from CHARLS, HRS, and ELSA

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EDITORIAL

Different risks, different responses: COVID-19 vaccination in immunocompromised patients

Ooiean Teng, Raymond Chee Seong Seet 176

ORIGINAL ARTICLES

Immune response to SARS-CoV-2 vaccination among chronic myeloid leukaemia patients on tyrosine kinase inhibitors

Chin Sum Cheong, Leh Ching Diana Ng, Siew Hwei Yap, Reena Rajasuriar, Normala Arshad, Nurul Syuhada Zulhaimi, Boon Hong Kong, I-Ching Sam, Ping Chong Bee, Jesinda P Kerishnan, Gin Gin Gan 179

Patient-centred outcomes and cost-effectiveness of a hospital-at-home service model for older adults

Toon Li Boh, Yun Hu, Annie Tan, Jia Hui Chai, Yanan Zhu, Luming Shi, Yeuk Fan Ng, Yan Hoon Ang 189

Cognition and arthritis in adults over 50: Evidence from CHARLS, HRS, and ELSA

Litao Huo, Fei Wang, Yifan Niu, Jie Cui, Ying Jiang, Jialin Shi, Yongyu Hao, Jiaxu Wang, Shibo Huang, Lin Tan, Bo Gao 199

COMMENTARY

Serving as a medical expert witness: Avoiding common errors and potential pitfalls

Sin Yew Wong 209

LETTERS TO THE EDITOR

Additive value of non-invasive haemodynamic and fluid profiling in emergency department congestive cardiac failure patients

Li Yang Loo, Zhenghong Liu, Ivan Si Yong Chua, Swee Han Lim 214

Talk to the bot: A scoping review on using AI-powered transcription tools in qualitative research

Ying Jun Lim, Ngiap Chuan Tan 217

Faculty-led mindfulness-based social-emotional learning workshops for radiology residents: Building self-awareness, resilience and community

Wenwen Ni, Chaoyan Dong, Cynthia Assimta Peter, Vidya Subrahmanya Upadhyaya 221

A comparison of Epstein-Barr virus digital PCR and quantitative PCR for identifying nasopharyngeal cancer

Valerie JW Tong, Wei Keat Teo, Hon Man Chan, Chun Kiat Lee, Chuan Keng Goh, Zhi Kang Chin, Luvita Suryani, Chor Hiang Siow, Han Lee Goh, Melvin Lee Kiang Chua, Jianjun Liu, Raymond King Yin Tsang, Johnson Ng, Kwok Seng Loh, Benedict Yan, Joshua K Tay 224

"Gender-focused mental health services in Singapore: A brief history and future direction": Correspondence

Daniel Shuen Sheng Fung, Swapna Verma, Say How Ong, Yee Ming Mok 228

Different risks, different responses: COVID-19 vaccination in immunocompromised patients

Ooiean Teng¹ PhD, Raymond Chee Seong Seet² MBBS

Immunocompromised individuals, including those with haematological malignancies, autoimmune diseases, or solid organ dysfunction, as well as those receiving long-term immunosuppressive therapy, bear a disproportionate burden from COVID-19, with markedly higher risks of severe disease and death than the general population.^{1,2} Yet the magnitude and durability of vaccine-induced protection in these groups remain highly variable, shaped not merely by the underlying diagnosis but by the specific immunosuppressive agents in use. Importantly, protection against SARS-CoV-2 is mediated by both humoral and cellular immunity, and these 2 arms can be affected differentially by specific immunosuppressive regimens. A complete appraisal of vaccine-induced protection therefore requires more than measurement of neutralising antibody titres alone. Understanding this heterogeneity is now essential for translating vaccine research into individualised clinical practice.

The study in this issue examines this question in a focused and clinically relevant population: patients with chronic myeloid leukaemia (CML) receiving tyrosine kinase inhibitors (TKIs).¹ In this longitudinal cohort, CML patients on TKIs developed robust initial antibody responses after primary vaccination that were broadly similar to those of healthy controls, and T-cell responses remained comparable throughout follow-up. However, the proportion with positive neutralising activity against Omicron BA.1 declined significantly at 6 months after booster vaccination (50.0% versus [vs] 88.9% in controls, $P=0.003$), before recovering by 12 months. These findings were not materially influenced by TKI class (imatinib vs nilotinib) or duration of treatment. The spontaneous recovery in Omicron-neutralising activity between 6 and 12 months, in the absence of further intervention, is of particular biological interest and is consistent with progressive affinity maturation of memory B cells, through which continued germinal-centre selection yields antibodies of higher avidity and broader variant coverage over time. Equally important, T-cell responses in this cohort were preserved throughout follow-up, and because SARS-CoV-2-specific T-cell

epitopes were distributed across the entire viral proteome rather than being concentrated within the spike receptor-binding domain, cellular immunity was comparatively resistant to escape by variants of concern. Taken together, these observations suggest that the transient 6-month reduction in Omicron-neutralising positivity is unlikely to translate into a clinically meaningful window of vulnerability in a cohort in which T-cell immunity remains intact.

The study's longitudinal design, use of World Health Organization-standardised assays, and assessment of both humoral and T-cell immunity are notable strengths. Its limitations include the small single-centre sample, substantial attrition among controls that necessitated recruitment of a replacement cohort, delayed anti-nucleocapsid testing in the CML group, restriction to BNT162b2 vaccination, and, most importantly, the lack of clinical outcome data.

The importance of these findings becomes clearer when viewed alongside earlier studies of vaccine responses in immunocompromised patients. In a prospective Singapore cohort of 519 individuals, including patients with autoimmune diseases, chronic comorbidities, and healthy controls, not all immunocompromised groups were equally vulnerable.² Patients with neuromyelitis optica and those receiving mycophenolate or rituximab were most likely to have subprotective vaccine responses, with mycophenolate use emerging as the strongest independent predictor of poor response (odds ratio 13.7). By contrast, patients with chronic comorbidities such as hypertension, diabetes, and hyperlipidaemia had antibody levels comparable to healthy controls, suggesting that their higher COVID-19 mortality is unlikely to be due to vaccine failure alone. These findings argue against broad, diagnosis-based booster policies and favour instead targeted serological monitoring and additional vaccine doses for the narrower subset of patients whose humoral responses are genuinely impaired, especially those on B-cell-depleting or -suppressing agents. The same cohort also highlighted the value of hybrid immunity.² Vaccinated individuals with breakthrough infection had neutralising antibody

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¹ Department of Medicine, National University of Singapore, Singapore

² Division of Neurology, Department of Medicine, National University Hospital, Singapore

Correspondence: Dr Ooiean Teng, Department of Medicine, National University of Singapore, MD6, Centre for Translational Medicine, 14 Medical Drive, Level 9 South, Singapore 117599. Email: ooiean@nus.edu.sg

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levels that were 28.7% higher (95% confidence interval 24.7–32.7) than vaccinated individuals without prior infection at 6 months after boosting, across all disease groups. Infection during the Delta wave also conferred cross-protective Omicron neutralisation comparable to Omicron infection itself, whereas natural infection alone in unvaccinated individuals produced markedly weaker responses. Together, these findings reinforce that vaccination remains essential even after prior infection, and that hybrid immunity provides the broadest and most durable cross-variant protection.

Two additional longitudinal studies provide important context. In the 2-year COVAXID follow-up study, Chen and colleagues studied 355 immunocompromised patients across 6 diagnostic groups and showed that initial poor responders, including solid organ transplant recipients and patients with CLL receiving ibrutinib, gradually developed neutralising antibodies after repeated boosters, ultimately reaching levels comparable to healthy controls.³ Notably, no participant was hospitalised with severe COVID-19 between 12 and 24 months, suggesting that even modest serological responses may still confer meaningful protection when T-cell immunity is preserved. This clinical protection, despite ongoing humoral variability, is consistent with a growing body of evidence positioning cellular immunity as an independent, and in some settings the dominant, correlate of protection against SARS-CoV-2. Early functional T-cell responses are associated with rapid viral clearance and milder disease following infection,⁷ and the onset of vaccine-induced protection after mRNA vaccination coincides with the detection of spike-specific T cells before neutralising antibodies are induced.⁸ T cells have also been shown to expand and support abortive clearance of SARS-CoV-2 in exposed seronegative individuals,⁹ and have emerged as the most important predictor of protection against symptomatic breakthrough infection in vaccinated cohorts prior to hybrid immunity.¹⁰ Because T-cell epitopes span the entire SARS-CoV-2 proteome rather than being confined to the spike receptor-binding domain, this arm of immunity is less susceptible to variant escape than neutralising antibodies and provides a biologically coherent explanation for continued protection despite waning Omicron neutralisation.

Ciabattini and colleagues reported similar findings across five immunocompromised groups, showing that the first booster was the most important intervention, restoring both antibody and spike-specific memory B-cell responses in most patients.⁴ They further found that Omicron-adapted vaccines generated variant-specific B-cell responses more effectively than natural infection alone, supporting the use of updated boosters rather than reliance on breakthrough infection.

A smaller subgroup of persistent low responders, mainly solid organ transplant recipients, remained unresponsive despite repeated boosting, underscoring the need for alternative preventive strategies such as pre-exposure monoclonal antibodies in selected patients.

These studies highlight several clear priorities. First, booster strategies should be calibrated to the specific immune deficit created by the underlying disease or treatment, rather than applied uniformly based on diagnosis. For patients whose humoral responses are profoundly impaired, particularly those on B-cell-depleting or -suppressing agents such as rituximab, mycophenolate, or ibrutinib, and recipients of solid organ transplants—repeated updated, variant-adapted boosters and, where appropriate, pre-exposure monoclonal antibodies remain important. For patients such as those with CML on TKIs, in whom T-cell immunity is preserved and humoral responses are only transiently attenuated, the incremental benefit of aggressive variant-specific boosting beyond the standard schedule is less clear, and routine boosting strategies aligned with those used in the general population are likely to be sufficient. Second, future research needs to link immunological findings to clinical outcomes, such as breakthrough infection, hospitalisation, and disease severity, to determine the real-world importance of these serological differences. Incorporating T-cell readouts alongside humoral markers will be particularly valuable, given the current reliance of most clinical monitoring on antibody titres that may underestimate protection in cohorts with preserved cellular immunity. Third, vaccination strategies should be tailored according to treatment class and immune profile, rather than diagnosis alone. Risk-prediction models already validated in other immunocompromised populations show that data-driven tools can be integrated into practice and offer a useful framework for individualising vaccine timing and monitoring.^{5,6} Overall, the evidence points to a consistent message: immunocompromised patients are biologically diverse, and vaccine strategies must reflect that diversity.

The CML data reported here are largely reassuring. The transient reduction in Omicron-neutralising antibody positivity at 6 months after boosting, which resolved spontaneously by 12 months alongside fully preserved T-cell responses, is unlikely to represent a period of meaningful clinical vulnerability. For patients receiving B-cell-depleting or B-cell-suppressing therapies such as rituximab, mycophenolate, or ibrutinib, standard schedules may be inadequate. For many others, including patients with CML on TKIs, hybrid immunity, and preserved T-cell responses together provide meaningful protection. The task ahead

is not simply to generate more data, but to translate existing evidence into more individualised and equitable clinical 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. No funding was received for this work.

Keywords: *chronic myeloid leukaemia, hybrid immunity, immunocompromised patients, SARS-CoV-2 vaccination, tyrosine kinase inhibitors*

REFERENCES

1. Cheong CS, Ng LCD, Yap SH, et al. Immune response to SARS-CoV-2 vaccination among chronic myeloid leukemia patients on tyrosine kinase inhibitors. *Ann Acad Med Singap* 2026;55:179-88.
2. Quek AML, Wang S, Teng O, et al. Hybrid immunity augments cross-variant protection against COVID-19 among immunocompromised individuals. *J Infect* 2024;89:106238.
3. Chen P, Bergman P, Blennow O, et al. Real-world assessment of immunogenicity in immunocompromised individuals following SARS-CoV-2 mRNA vaccination: a two-year follow-up of the prospective clinical trial COVAXID. *EBioMedicine* 2024; 109:105385.
4. Ciabattini A, Pettini E, Fiorino F, et al. Longitudinal immunogenicity cohort study of SARS-CoV-2 mRNA vaccines across individuals with different immunocompromising conditions: heterogeneity in the immune response and crucial role of Omicron-adapted booster doses. *EBioMedicine* 2025;113:105577.
5. Jackson K, Anderson V, Zhao Z, et al. Applying a risk prediction model for bloodstream infection in a febrile, nonseverely neutropenic cohort of pediatric stem cell transplant patients. *Cancer* 2023;129:1591-601.
6. Lind ML, Mooney SJ, Carone M, et al. Development and Validation of a Machine Learning Model to Estimate Bacterial Sepsis Among Immunocompromised Recipients of Stem Cell Transplant. *JAMA Netw Open* 2021;4:e214514.
7. Tan AT, Linster M, Tan CW, et al. Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients. *Cell Rep* 2021;34:108728.
8. Kalimuddin S, Tham CYL, Qui M, et al. Early T cell and binding antibody responses are associated with COVID-19 RNA vaccine efficacy onset. *Med* 2021;2:682-8.e4.
9. Swadling L, Diniz MO, Schmidt NM, et al. Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. *Nature* 2022;601:110-7.
10. Zhong Y, Kang AYH, Tay CJX, et al. Correlates of protection against symptomatic SARS-CoV-2 in vaccinated children. *Nat Med* 2024;30:1373-83.

Immune response to SARS-CoV-2 vaccination among chronic myeloid leukaemia patients on tyrosine kinase inhibitors

Chin Sum Cheong¹ MMed, Leh Ching Diana Ng² MMed, Siew Hwei Yap¹ PhD, Reena Rajasuriar¹ PhD, Normala Arshad³ Dip (Oncology), Nurul Syuhada Zulhaimi¹ MSc, Boon Hong Kong⁴ PhD, I-Ching Sam⁵ FRCPath, Ping Chong Bee¹ MMed, Jesinda P Kerishnan¹ PhD, Gin Gin Gan¹ FRCP

ABSTRACT

Introduction: Chronic myeloid leukaemia (CML) patients on tyrosine kinase inhibitors (TKIs) show adequate antibody responses to SARS-CoV-2 vaccination, but T-cell responses remain unclear. This study investigates the overall immune responses in these patients after vaccination.

Methods: In this longitudinal study, CML patients on TKIs who received at least 3 doses of the SARS-CoV-2 vaccine were assessed for neutralisation activity against the wild-type (WT) and Omicron variants at multiple time-points: baseline (D0), week 4 (D28), month 6 (M6), and after the booster dose at months 3 (B3), 6 (B6), and 12 (B12). T-cell responses were evaluated at B6 and B12, with comparisons made to healthy controls (HC).

Results: Twenty-seven CML patients and 113 HC were included. Neutralising activity against WT was similar across groups at all time points. Fewer CML patients exhibited positive neutralisation against Omicron at B6 (50.0% versus 88.9%, $P=0.003$), with higher antibody levels in CML patients at D28 and M6, but lower levels at B6 ($P<0.05$). T-cell responses were similar between groups at B6 and B12.

Conclusion: Neutralising activity against WT and Omicron was similar, with a decline at B6, while T-cell responses were comparable across groups. These findings highlight the importance of continued vaccination in CML patients.

Keywords: chronic myeloid leukemia, COVID-19 vaccine, neutralising antibodies, Omicron variant, vaccine durability

CLINICAL IMPACT

What is New

- Neutralising activity (defined as inhibition $>30\%$) after the 2-dose primary vaccination series against wild-type were similar between chronic myeloid leukemia (CML) patients and healthy subjects; however, the neutralising activity against Omicron BA.1 are lower among CML patients 6 months post booster dose.
- To the authors' knowledge, this is the first study that specifically determined the antibody and T-cell responses after SARS-CoV-2 vaccines in TKI-treated CML patients, in particular to the Omicron variant.

Clinical Implications

- The different immunological responses to variants like Omicron, particularly after the booster dose, suggest that CML patients may need individualised vaccination plans and rigorous post-vaccine monitoring.
- These results point to the potential benefits of next-generation vaccines against immune-evasive variations of COVID-19 infections and encourage the ongoing prioritisation of booster doses. These results are crucial for directing improved vaccination policy and optimising benefit in this group of patients.

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2, led to widespread illness and profound social and economic disruption. The impact of COVID-19 infection is particularly significant in patients with underlying cancer. A meta-analysis that involved more than 46,000 patients showed a 66% higher risk of death and

a 56% increased likelihood of requiring admission to the intensive care unit, compared with those without cancer.¹ Patients with lung and haematological malignancies were at particularly greater risk. This increased risk may reflect the immunocompromised state associated with the underlying disease and associated treatments such as ongoing chemotherapy, which can affect vaccine responses.^{2,3}

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¹ Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

² Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Sarawak, Malaysia

³ Department of Nursing, Universiti Malaya Medical Center, Kuala Lumpur, Malaysia

⁴ Department of Molecular Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

⁵ Department of Medical Microbiology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia

Correspondence: Professor Dr Gan Shiao Sze/Gan Gin Gin, Department of Medicine, Faculty of Medicine, Universiti Malaya, 50603 Kuala Lumpur, Malaysia. Email: gangg@ummc.edu.my

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Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm, which is characterised by the presence of the Philadelphia chromosome. With the introduction of tyrosine kinase inhibitors (TKIs), overall survival in patients has greatly improved. The use of TKIs is associated with altered B-cell immunity, and responses to COVID-19 vaccination in TKI-treated CML patients may be affected because of off-target inhibitory effects on B-cell signalling kinases.⁴ Several studies have shown that CML patients on TKI exhibit a robust humoral immune response to COVID-19 vaccination and develop significant levels of SARS-CoV-2 spike-specific IgG antibodies comparable to healthy individuals.^{5,6} Furthermore, the persistence in these antibodies over time was also similar to that of the general population.⁶ While humoral responses are promising, T-cell immunity is crucial for long-term protection. TKIs have been reported to affect various T-cell immune functions, including reducing effector CD8⁺ T-cell responses and interfering with T-lymphocyte signalling.^{7,8} Diminished T-cell responses may, in general, affect the effectiveness and durability of vaccine protection.⁹ The long-term impact of these molecularly targeted drugs on immune function is still not clearly defined.¹⁰

In Malaysia, epidemiological data on CML are limited, and the prevalence was reported to be approximately 69 per million.¹¹ As of 2024, the total population of Malaysia is estimated at 34.1 million; therefore, the number of CML patients is likely to exceed 2000.¹² Research on vaccine responses in patients with haematological cancers in Malaysia is scarce, and the only published study that included haematological cancer patients only determined the seroconversion rate following various SARS-CoV-2 vaccines.¹³ There has been thus far no study that specifically evaluated antibody and T-cell responses after SARS-CoV-2 vaccination in TKI-treated CML patients in Malaysia, particularly against the Omicron variant.

During the COVID-19 pandemic in Malaysia, the virus evolved through multiple waves with different dominant variants. The first wave (early 2020) mainly involved imported Wuhan strains.¹⁴ From April 2021 to January 2022, the fourth wave was dominated by the Delta variant, with high case numbers, hospitalisations, and deaths—particularly among unvaccinated individuals, when only 6.3% of the population was fully vaccinated at its peak.¹⁵ The fifth wave emerged in late 2021, led by the Omicron variant, which rapidly displaced Delta and caused a higher monthly case peak within a shorter time frame. Despite this, there were fewer severe cases and deaths, likely owing to a high vaccination rate (78.9%) and Omicron's lower virulence.¹⁴

This study was conceived during the pandemic where we aimed to ascertain immune responses following SARS-CoV-2 vaccination in CML patients on

TKI, and to assess the durability of these immune responses achieved, including against the Omicron variant. Now endemic, COVID-19 continues to pose a threat to public health, especially to immunocompromised individuals. The results of this study will offer crucial insights into the overall effectiveness of vaccines for CML patients on TKI therapy.

METHODS

Study design and study participants

This was a longitudinal study of TKI-treated CML patients receiving 2 doses of SARS-CoV-2 vaccine, followed by 1 booster dose, at a teaching hospital in Malaysia. The inclusion criteria were adult CML patients aged 18 years and above who had been treated with TKI for at least 6 months before the vaccination date, had no other underlying malignancies or autoimmune disease, and were not receiving other immunosuppressive therapy. Patients who had received a SARS-CoV-2 vaccine within 2 weeks before screening, had a self-reported history of COVID-19 infection, ongoing pregnancy or breastfeeding, a history of bleeding disorders or severe adverse reactions associated with prior vaccination, an acute febrile episode within 72 hours before recruitment, or were unwilling to commit to protocol-mandated blood sampling were excluded. Sampling was performed between June 2021 and May 2023, coinciding with the Delta (August to October 2021) and Omicron waves (January to April 2022) in Malaysia. A total of 60 controls were recruited at study entry. Age-matched healthy individuals without CML or other immunosuppressive disease who were attending vaccine appointments at the same centre were approached as controls. A new group of 53 age-matched controls was recruited when the booster dose was administered because 55 of the 60 initial controls were lost to follow-up. The sex and ethnicity of the new cohort were matched to those of the first cohort. These controls were co-opted opportunistically from another ongoing study at our institution, involving patients from the Geriatric Clinic and Primary Care Clinic. All participants provided written informed consent, and the study protocol was approved by the Universiti Malaya Medical Center Medical Research Ethics Committee (UMMC MREC) with registration number of 2021524-10164.

Collection of demographic data and samples

Patients' baseline demographic data were collected. All participants had blood drawn at 6 time points: prior to the first dose (baseline, D0), 1 month (D28) and 6 months (M6) after the second dose when the booster was administered, then 3 months (B3), 6 months (B6), and 12 months (B12) after the booster. All blood samples processed in this study were handled in the

same laboratory using standard protocols. Blood samples from study participants were transferred to the laboratory, and plasma was isolated within 4 hours of collection. Samples were then stored at -80°C until further analysis, which was performed in batches.

Antibody binding, neutralisation assay, and QuantiFERON SARS-CoV-2 assay

Antibody titres against the receptor-binding domain (RBD) of the spike protein and nucleocapsid (N) were measured using the quantitative Elecsys Anti-SARS-CoV-2 S and N-protein assays (Roche Diagnostics, GmbH, Germany), respectively, on the Cobas e601 analyser (Roche Diagnostics) according to the manufacturer's instructions. The Roche Elecsys system uses an automated system with appropriate calibration and internal control steps, which ensures reproducibility and accuracy across different runs and reagent lots; 1 unit(U)/mL of anti-S antibodies reported by this assay corresponds to 1 binding antibody U/mL according to the First World Health Organization (WHO) International Standard for anti-SARS-CoV-2 immunoglobulin (human) (NIBSC 20/136).¹⁸

The positivity threshold for the anti-S assay was defined as ≥ 0.8 U/mL, while the anti-N assay used a cut-off index (COI) of ≥ 1.0 . Samples that exceeded the upper detection limit of >250 international units (IU)/mL for the anti-S assay were assigned a value of 250 IU/mL for analysis.

The anti-N assay was performed only in the healthy control group 1 at D0, D28, and M6, but it was expanded to both CML patients and healthy controls group 2 at B3, B6, and B12 after additional funding was obtained. The new batch of controls was co-opted opportunistically from another ongoing study at the authors' institution from B3 onwards because of the high attrition in the initial control cohort.

Neutralisation activity against SARS-CoV-2 wild-type and the Omicron BA.1 (B.1.1.529) variant was assessed using the SARS-CoV-2 surrogate viral neutralisation assay kit (cPass Neutralisation Kit, GenScript Biotech, US). Relative inhibition was determined based on the mean absorbance of the negative control, with a threshold of 30% indicating positive neutralisation activity. Equivalent IU/mL conversions were obtained using data extrapolated from cPass calibration against the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin (human) through a publicly available online tool, via https://github.com/Lelouchzhu/cPass-to-IU_Conversion, as previously described.²⁰ The assay against wild-type was done for only 2 time points (D28 and M6), whereas the assay against Omicron BA.1 was carried out at all time points except baseline: at D28, M6, B3, B6, and B12. Internal controls to monitor batch variation reported ranges of 10–20%, which is appropriate for result reproducibility.¹⁹

T-cell responses against SARS-CoV-2 spike sub-unit antigens were measured using the QuantiFERON SARS-CoV-2 assay kit (Qiagen, Germany) according to manufacturer's instructions. This assay includes 3 antigen tubes—SARS-CoV-2 Ag1, Ag2, and Ag3, which use combinations of SARS-CoV-2-specific antigens to stimulate lymphocytes in heparinised whole blood, targeting cell-mediated immunity. The Ag1 tube contains CD4+ epitopes derived from the S1 subunit (RBD) of the spike protein; Ag2 contains CD4+ and CD8+ epitopes from the S1 and S2 subunits of the spike protein; and Ag3 comprises CD4+ and CD8+ epitopes from S1 and S2, along with immunodominant CD8+ epitopes derived from the entire genome.²¹ The concentration of Interferon-gamma (IFN)- γ in plasma from the stimulated samples was measured using ELISA. An IFN- γ response was classified as reactive if it exceeded 0.15 IU/mL. This assay was conducted at the B6 and B12 sampling time points.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 23.0 (IBM Corp, Armonk, NY, US) and GraphPad Prism 8 (GraphPad Software, US). Comparisons of anti-S antibody levels and inhibition activity against SARS-CoV-2 wild-type and its variants between CML patients and controls were performed using the Mann-Whitney U test. The percentages of CML patients and controls with positive neutralising activity were compared using the Chi-square and Fisher's exact tests. *P* value of <0.05 was considered statistically significant.

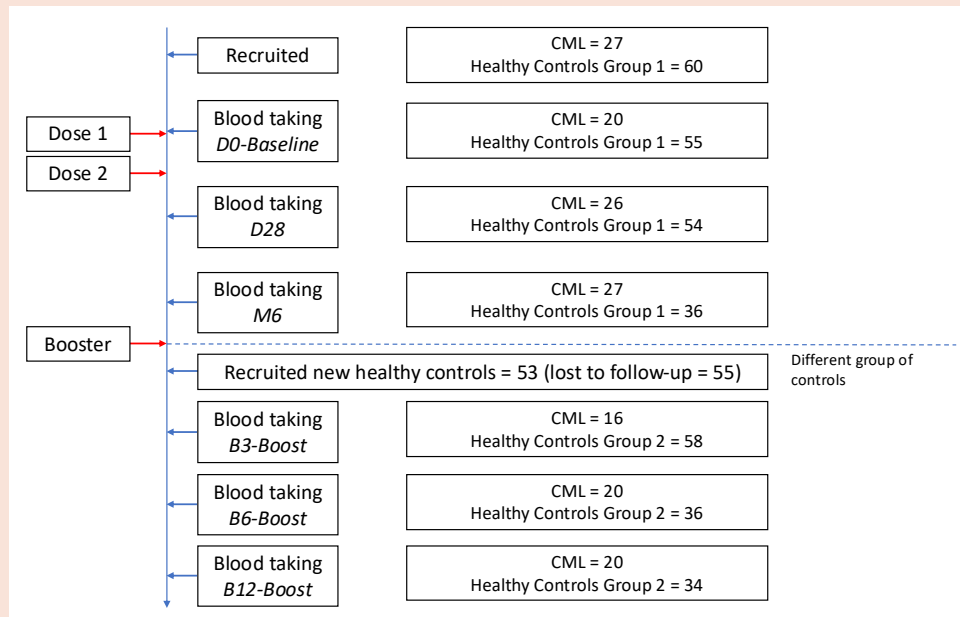
RESULTS

A total of 87 participants (27 CML patients and 60 controls) consented at the study entry. Over the course of the study, 19 controls were lost to follow-up at M6. New controls ($n=53$) were recruited at B3 because 55 controls who had participated at study entry were lost to follow-up (Fig. 1).

The median ages of CML patient and controls were 49 (interquartile range [IQR] 39–59) and 40 (IQR 33–51) years, respectively. The majority of CML patients were male (59.3%) and of Chinese ethnicity (55.6%). In comparison, controls comprised 64.6% males, with the majority being of Malay ethnicity (38.1%). The majority of CML patients (88.9%) and all controls received the BNT162b2 mRNA vaccine. The demographics of the participants are shown in Table 1.

Humoral responses following vaccination were estimated using measurements of total anti-S titres. All participants seroconverted (defined as anti-S1 levels >0.8 IU/mL) and median total anti-S1 titres after the 2-dose primary vaccination series and a booster were comparable in CML patients and controls (Fig. 2). Anti-N was not performed in CML patients

Fig. 1. Enrolment of participants.



B3: 3 months after the booster; B6: 6 months after the booster; B12: 12 months after the booster; CML: chronic myeloid leukaemia; D0: prior to the first dose (baseline); D28: 1 month after the first dose; M6: 6 months after the second dose when the booster was administered

Table 1. Demographics of CML cases and controls at study entry.

	CML (n=27)	Controls (n=113)	P value
Age, median (IQR), years	49.4 (39.3–59.1)	40.0 (32.9–50.6)	0.036 ^a
Sex, no. (%)			0.656
Male	16 (59.3)	73 (64.6)	
Female	11 (40.7)	39 (34.5)	
Missing		1 (0.9)	
Ethnicity, no. (%)			0.095
Malay	9 (33.3)	43 (38.1)	
Chinese	15 (55.6)	39 (34.5)	
Indian	2 (7.4)	25 (22.1)	
Missing	1 (3.7)	6 (5.3)	
Vaccine dose 1, no. (%)			0.010 ^a
BNT162b2	24 (88.9)	113 (100.0)	
CoronaVac	2 (7.4)	-	
Vaxzevria	1 (3.7)	-	
Vaccine dose 2, no. (%)			0.010 ^a
BNT162b2	24 (88.9)	113 (100.0)	
CoronaVac	2 (7.4)	-	
Vaxzevria	1 (3.7)	-	
Vaccine dose 3, no. (%)			0.256
BNT162b2	20 (95.2)	58 (100.0)	
CoronaVac	1 (4.8)	-	
Vaxzevria	-	-	
TKI duration (months)	138 (105–169)	-	
TKI type, no. (%)			
Imatinib	21 (77.8)	-	
Nilotinib	5 (18.5)	-	
Dasatinib	1 (3.7)	-	

CML: chronic myeloid leukaemia IQR: interquartile range; TKI: tyrosine kinase inhibitor

^a indicates P values <0.05

at D0, D28, and M6. After excluding patients who received CoronaVac, 15 (26.7%), 19 (47.4%), and 19 patients (56.5%) were reactive to anti-N at B3, B6, and B12, respectively. After the booster dose, 58 (39.7%), 36 (63.9%), and 34 (67.6%) controls were reactive to anti-N at M3, M6, and M12, respectively (Fig. 2).

All participants had detectable neutralising activity (defined as inhibition >30%) and neutralising antibody levels after the two-dose primary vaccination series against the wild-type (Fig. 3a and 3b).

Neutralising activities against Omicron BA.1 were not significantly different between CML patients and healthy controls at all time points except for at B6 ($P=0.003$). Only 19.2% and 14.8% of CML patients had >30% neutralising activities, compared with 14.8% and 9.3% of healthy subjects at D28 and M6 ($P=0.748$ and $P=0.702$). The proportion of subjects with >30% neutralising activities rose to 68.4%, 50.0%, and 80.0% among CML patients, and 78.0%, 88.9%, and 85.7% among healthy subjects at B3, B6, and B12, respectively ($P=0.539$, $P=0.003$, and $P=0.709$) (Table 2). Neutralising antibody levels against Omicron BA.1 were significantly higher in CML patients at D28 ($P=0.004$) and M6 ($P<0.001$), but were significantly lower at B6 ($P<0.001$); however, this did not translate to clinical relevance because the WHO-defined threshold for positive neutralisation was >30% (Fig. 3c).

We further investigated whether the type of TKI used in CML patients was associated with immunogenicity following vaccination. In analyses stratified

by the type and duration of TKI treatment in CML patients, no significant difference in the neutralising activity positivity rate was observed between imatinib- and nilotinib-treated CML patients or between patients who had been treated for less than 10 years and those treated for 10 years or more (Table 2).

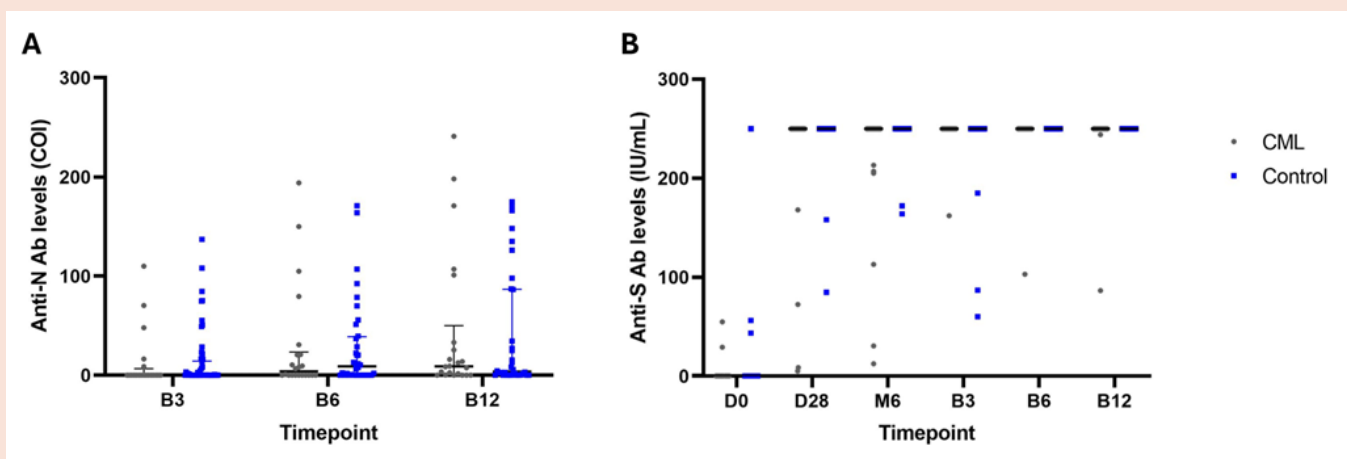
There was no significant difference in T-cell responses, assessed by IFN- γ levels against spike antigens, between CML patients and controls at B6 and B12 (Fig. 4a, 4b and 4c). Similarly, T-cell responses were similar between CML patients on imatinib and nilotinib at B6 and B12 (Fig. 4d, 4e and 4f).

DISCUSSION

In this study, SARS-CoV-2 vaccination was evaluated in patients with CML receiving TKIs. Despite the robust immunogenicity demonstrated by the SARS-CoV-2 vaccines in the general population, this may not be the case in immunocompromised groups, particularly those with haematologic malignancies receiving long-term immunomodulating agents.

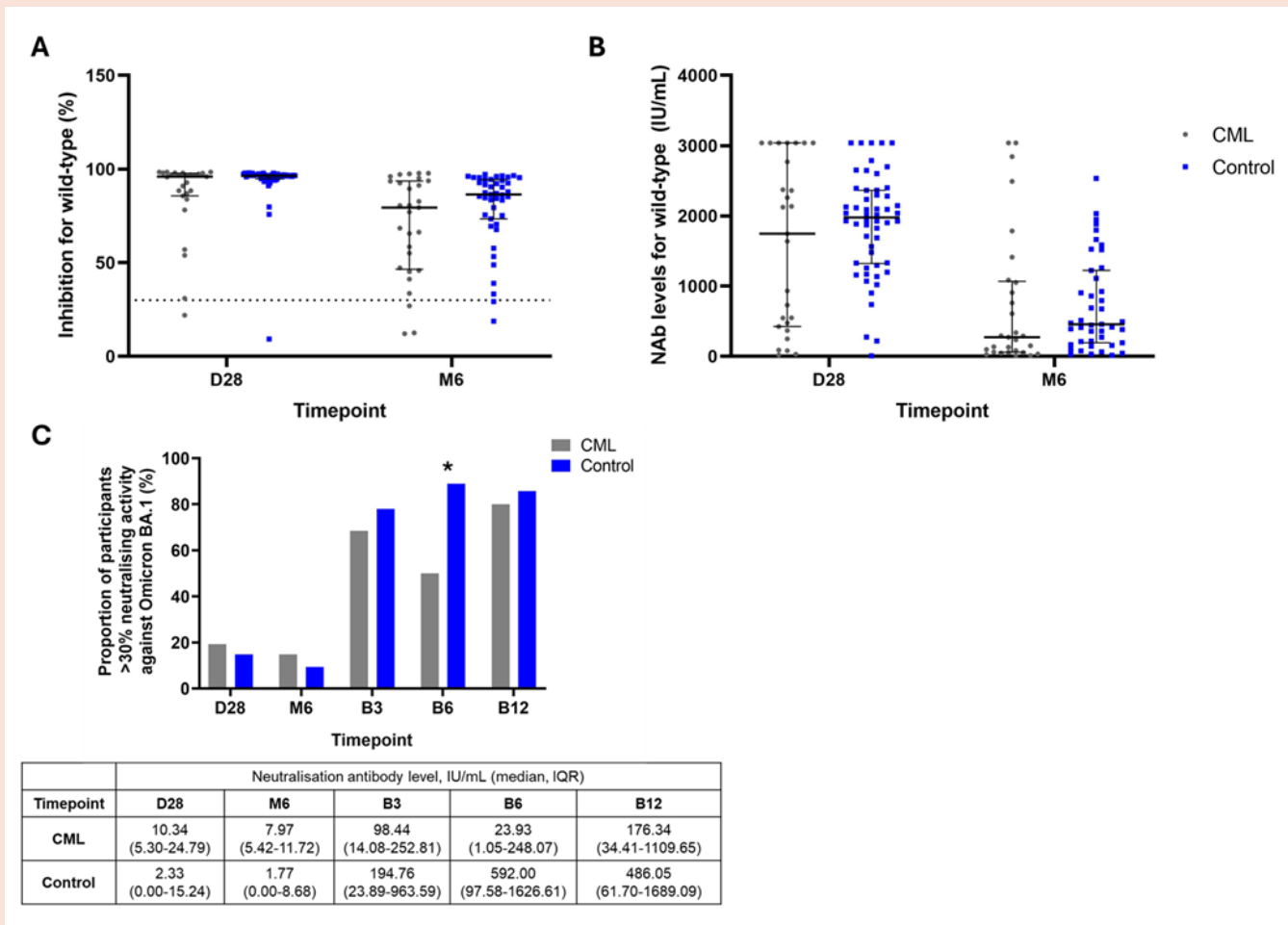
All participants, including CML patients on TKI, showed seroconversion after the 2-dose primary vaccination series against the wild-type, suggesting robust vaccine-induced humoral immunity. These results are in line with other studies showing that TKI-treated CML patients have relatively intact immune responses when compared with patients with other haematological malignancies.^{22,23} The observation that anti-S1 levels were comparable between CML patients and controls further supports the hypothesis that TKIs, despite

Fig. 2. Total anti-SARS-CoV-2 nucleocapsid (A) and spike (B) antibody levels following vaccination in CML patients compared to controls.



B3: 3 months after the booster; B6: 6 months after the booster; B12: 12 months after the booster; COI: cut-off index; CML: chronic myeloid leukaemia; D0: prior to the first dose (baseline); D28: 1 month after the first dose; M6: 6 months after the second dose when the booster was administered. The horizontal dotted line indicates the minimum threshold cut-off for positivity; ≥ 1.0 COI for total anti-N and ≥ 0.8 IU/mL for total anti-S1. Comparisons between CML patients and controls were performed using Mann-Whitney U test. Error bars correspond to median and interquartile range.

Fig. 3. Neutralising activity assessed by ACE2 binding blockade assay (expressed as percentage inhibition) (A) and neutralising antibody levels against variants of concern (wild-type) (B) and Omicron (C) measured following vaccination in CML patients compared to controls.



B3: 3 months after the booster; B6: 6 months after the booster; B12: 12 months after the booster; COI: cut-off index CML: chronic myeloid leukaemia; D0: prior to the first dose (baseline); D28: 1 month after the first dose; M6: 6 months after the second dose when the booster was administered. The horizontal dotted line indicates the minimum threshold cut-off for positivity, which is $\geq 30\%$ for neutralisation activity. Comparisons between CML patients and controls were performed using the Mann-Whitney U test. Error bars correspond to median and interquartile range.

their immune effects, do not significantly impair the initial antibody production.

In this study, anti-N was measured in CML patients only from B3 onwards, while these assays were performed in controls in both the first and second cohorts due to funding constraints. Although anti-N assays were only performed later in CML patients, this would not affect the interpretation of prior or breakthrough infections as SARS-CoV-2 antibodies have been shown to persist for over 18 months.^{24,25}

While all participants initially developed neutralising antibody responses against the wild-type virus, neutralising activity was markedly reduced in both groups against the Omicron BA.1 variant following the initial vaccine regimen. However, following the booster dose, the proportion of healthy control participants

exhibiting positive neutralising activity was significantly higher at B6 than in the CML cohort, suggesting a possible shortfall in CML patients' long-term or variant-specific immunogenicity. However, the proportion of healthy subjects with a positive neutralising activity was not significantly different from that in the CML cohort at B12. This could indicate transient waning of the neutralising activity in the CML cohort and is important because the Omicron variant is known to evade the immune system owing to reduced neutralisation by antibodies induced by prior infection or immunisation.²⁶

These results are consistent with previous studies showing SARS-CoV-2 variants of concern may significantly decrease vaccine-induced neutralisation.^{27,28} The observed decrease during follow-up may be

Table 2. Neutralising activity among CML patients and controls, and among CML patients based on tyrosine kinase inhibitors and duration of treatment.

Inhibition for Omicron BA.1										
	CML	Controls	P value	Imatinib	Nilotinib	P value	TKI <10 years	TKI ≥10 years	P value	
D28**										
	21 (80.8)	46 (85.2)	0.748	17 (85.0)	3 (60.0)	0.252	7 (77.8)	14 (82.4)	1.000	
	5 (19.2)	8 (14.8)		3 (15.0)	2 (40.0)		2 (22.2)	3 (17.6)		
Unadjusted (Exp[B], 95% CI)***	1.369 (0.400 – 4.688)		0.617	3.778 (0.431 – 33.077)		0.230	0.750 (0.101 – 5.576)		0.779	
Adjusted (Exp[B], 95% CI)***	1.403 (0.357 – 5.514)		0.627	3.233 (0.344 – 30.372)		0.305	0.975 (0.118 – 8.068)		0.981	
M6**										
	23 (85.2)	39 (90.7)	0.702	18 (85.7)	4 (80.0)	1.000	8 (88.9)	15 (83.3)	1.000	
	4 (14.8)	4 (9.3)		3 (14.3)	1 (20.0)		1 (11.1)	3 (16.7)		
Unadjusted (Exp[B], 95% CI)***	1.696 (0.387 – 7.438)		0.484	1.500 (0.122 – 18.441)		0.751	1.600 (0.142 – 18.000)		0.704	
Adjusted (Exp[B], 95% CI)***	0.968 (0.154 – 6.083)		0.973	1.690 (0.130 – 22.017)		0.689	1.457 (0.122 – 17.358)		0.766	
B3**										
	6 (31.6)	13 (22.0)	0.539	5 (35.7)	1 (25.0)	1.000	1 (16.7)	5 (38.5)	0.605	
	13 (68.4)	46 (78.0)		9 (64.3)	3 (75.0)		5 (83.3)	8 (61.5)		
Unadjusted (Exp[B], 95% CI)***	0.612 (0.195 – 1.927)		0.402	1.667 (0.135 – 20.578)		0.690	0.320 (0.28 – 3.600)		0.356	
Adjusted (Exp[B], 95% CI)***	0.606 (0.188 – 1.958)		0.402	1.603 (0.128 – 20.100)		0.715	0.335 (0.029 – 3.829)		0.379	
B6**										
	10 (50.0)	4 (11.1)	0.003*	6 (42.9)	4 (80.0)	0.303	4 (57.1)	6 (46.2)	1.000	
	10 (50.0)	32 (88.9)		8 (57.1)	1 (20.0)		3 (42.9)	7 (53.8)		
Unadjusted (Exp[B], 95% CI)***	0.125 (0.032 – 0.487)		0.003*	0.188 (0.016 – 2.137)		0.178	1.556 (0.244 – 9.913)		0.640	
Adjusted (Exp[B], 95% CI)***	0.136 (0.034 – 0.538)		0.005*	0.164 (0.013 – 2.088)		0.164	1.630 (0.235 – 11.320)		0.621	
B12**										
	4 (20.0)	5 (14.3)	0.709	2 (14.3)	2 (40.0)	0.272	1 (14.3)	3 (23.1)	1.000	
	16 (80.0)	30 (85.7)		12 (85.7)	3 (60.0)		6 (85.7)	10 (76.9)		
Unadjusted (Exp[B], 95% CI)***	0.667 (0.157 – 2.836)		0.583	0.250 (0.024 – 2.577)		0.244	0.556 (0.047 – 6.629)		0.642	
Adjusted (Exp[B], 95% CI)***	0.703 (0.163 – 3.034)		0.637	0.245 (0.022 – 2.766)		0.255	0.475 (0.035 – 6.516)		0.475	

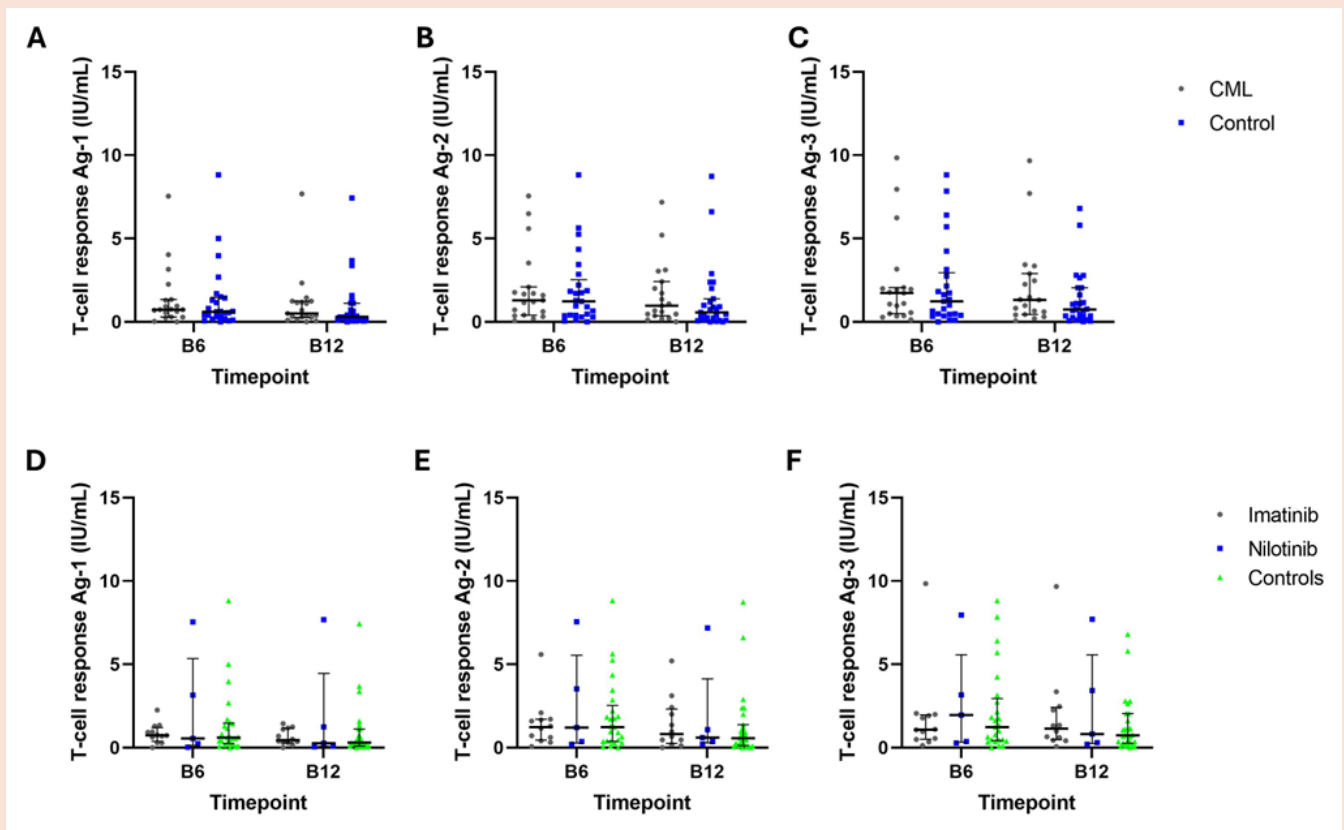
CI: confidence interval; CML: chronic myeloid leukaemia IQR: interquartile range; TKI: tyrosine kinase inhibitor

* indicates P values <0.05.

** Group comparisons were performed using the Chi-square test.

*** Binary logistic regression analyses were conducted with and without adjustment for age. Control group, imatinib treatment, and TKI duration <10 years were used as reference categories.

Fig. 4. T-cell responses in CML patients and controls (A, B, and C) and in CML patients on imatinib and nilotinib (D, E, and F).



B3: 3 months after the booster; B6: 6 months after the booster; B12: 12 months after the booster; CML: chronic myeloid leukaemia; D0: prior to the first dose (baseline); D28: 1 month after the first dose; M6: 6 months after the second dose when the booster was administered

Comparisons between CML patients and controls were performed using the Mann-Whitney U test. Error bars correspond to median and interquartile range.

due to immunological exhaustion, impaired memory B-cell function, or heterogeneous T follicular helper-cell responses as a result of long-term TKI treatment, even though the initial neutralisation benefit in CML patients is somewhat unexpected. Interestingly, neither the treatment duration nor the specific TKI used (imatinib vs nilotinib) significantly affected the neutralising capacity, suggesting that treatment-related immune suppression in this context is not dose- or agent-dependent. This finding is consistent with the observation of Katagiri et al., who reported limited differences in vaccine responses across different TKIs.²⁹

The preserved nature of T-cell-mediated immunity in TKI-treated CML patients may enhance their ability to mount a robust cellular response. Measurements of IFN- γ at 6 and 12 months following the booster showed no significant differences between CML patients and controls, reflecting preserved T-cell reactivity. This finding is reassuring, as T-cell responses are vital for sustained protection and cross-protection

against viral variants. Previous work has emphasised the strength of T-cell responses in immunocompromised individuals, including cancer patients, even when humoral responses are weakened.³⁰ Cellular immunity, particularly through CD8⁺ T-cell responses, may offer protection by targeting recognised epitopes and acting as a secondary line of defence against variants such as Omicron.³¹

While this study aimed to assess the response of the SARS-CoV-2 vaccine in CML patients on TKI, detailed reporting of adverse events was not included in the current findings. Nevertheless, the literature confirms that mRNA vaccines are well tolerated in this population, with a side-effect profile comparable with that of healthy controls.³² Future studies with full safety data would be helpful in guiding vaccine policy in patients undergoing long-term TKI therapy.

Nevertheless, this study has some limitations. The numbers of patients and controls included here were small, and the study was conducted at a single centre, which may limit generalisability to the broader

community. There were no clinical outcome measures, breakthrough infection or hospitalisation, and this also limits our ability to correlate the immune responses measured with clinical protection in the real world. As most of the participants received BNT162b2, the findings from this study may not be applicable for cohorts who received other types of SARS-CoV-2 vaccinations such as rates of breakthrough infection or hospitalisation, and this limited the authors' ability to correlate the immune responses measured with real-world clinical protection. As most participants received BNT162b2, the findings of this study may not be applicable to cohorts who received other types of SARS-CoV-2 vaccines. Further continuance of this research is needed to address newer variants, newer bivalent vaccines, and other treatment regimens.

CONCLUSION

In conclusion, the present study shows that CML patients receiving TKI therapy can also produce humoral and cell-mediated immune responses to the SARS-CoV-2 vaccine that are, for the most part, similar to those of healthy controls. However, the differential immunological responses to variants such as Omicron, particularly after the booster dose, suggest that this group may need individualised vaccination plans and rigorous post-vaccine monitoring. These results point to the potential benefits of next-generation vaccines against immune-evasive variants and support the ongoing prioritisation of booster doses. These findings are important for informing improved vaccination policy and optimising benefit in this group of patients.

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Ethics statement

All participants provided written informed consent, and the study protocol was approved by the Universiti Malaya Medical Center Medical Research Ethics Committee review board (MREC number 202158-10126).

Declaration

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REFERENCES

- Giannakoulis VG, Papoutsis E, Siempos, II. Effect of Cancer on Clinical Outcomes of Patients With COVID-19: A Meta-Analysis of Patient Data. *JCO Glob Oncol* 2020;6:799-808.
- Lee LYW, Tilby M, Starkey T, et al. Association of SARS-CoV-2 Spike Protein Antibody Vaccine Response With Infection Severity in Patients With Cancer: A National COVID Cancer Cross-sectional Evaluation. *JAMA Oncol* 2023;9:188-96.
- Hua T, Fan R, Fan Y, et al. Immune response of COVID-19 vaccines in solid cancer patients: A meta-analysis. *Hum Vaccin Immunother* 2024;20:2357424.
- de Lavallade H, Khoder A, Hart M, et al. Tyrosine kinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. *Blood* 2013; 122:227-38.
- Miljkovic D, Reynolds CJ, Sandoval DM, et al. COVID-19 vaccine boosted immunity against Omicron in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. *Leukemia* 2023;37:244-7.
- Rodriguez-Mora S, Corona M, Solera Sainero M, et al. Regular Humoral and Cellular Immune Responses in Individuals with Chronic Myeloid Leukemia Who Received a Full Vaccination Schedule against COVID-19. *Cancers (Basel)* 2023;15.
- Chen J, Schmitt A, Chen B, et al. Nilotinib hampers the proliferation and function of CD8+ T lymphocytes through inhibition of T cell receptor signalling. *J Cell Mol Med* 2008; 12:2107-18.
- Giansanti P, Preisinger C, Huber KV, et al. Evaluating the promiscuous nature of tyrosine kinase inhibitors assessed in A431 epidermoid carcinoma cells by both chemical- and phosphoproteomics. *ACS Chem Biol* 2014;9:1490-8.
- Dhawan M, Rabaan AA, Fawarah MMA, et al. Updated Insights into the T Cell-Mediated Immune Response against SARS-CoV-2: A Step towards Efficient and Reliable Vaccines. *Vaccines (Basel)* 2023;11:101.
- Shyam Sunder S, Sharma UC, Pokharel S. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. *Signal Transduct Target Ther* 2023;8:262.
- Kuan JW, Melaine Michael S. The epidemiology of chronic myeloid leukaemia in southern Sarawak, Borneo Island. *Med J Malaysia* 2018;73:78-85.
- Current population estimate. <https://www.dosm.gov.my/portal-main/release-content/current-population-estimates-2024>. Accessed 6 August 2025.
- Song CV, Ahmad Bustamam RS, Gin Gin G, et al. Antibody Response Following COVID-19 Vaccination in Malaysian Cancer Patients and Healthy Individuals. *Cureus* 2024;16:e73528.
- Yu CY, Wong SY, Liew NWC, et al. Whole genome sequencing analysis of SARS-CoV-2 from Malaysia: From alpha to Omicron. *Front Med (Lausanne)* 2022;9:1001022.
- Suah JL, Tok PSK, Ong SM, et al. PICK-ing Malaysia's Epidemic Apart: Effectiveness of a Diverse COVID-19 Vaccine Portfolio. *Vaccines (Basel)* 2021;9.
- Laner-Plamberger S, Siller A, Lauth W, et al. Stable SARS-CoV-2 antibody levels and functionality in serum and COVID-19 convalescent plasma after long-term storage. *Vox Sang* 2025; 120:784-92.
- Meyers E, Coen A, Padalko E, et al. Short- and long-term stability of SARS-CoV-2 antibodies on dried blood spots under different storage conditions. *Microbiol Spectr* 2024;12:e0111324.

18. Elecsys Anti-SARS-CoV-2 S product insert. <https://assets.roche.com/f/173850/x/3a97af77d1/anti-sars-cov-2-s-09289267190-en-can.pdf>. Accessed 7 January 2026.
19. Lexmond W, der Mee J, Ruiter F, et al. Development and validation of a standardized ELISA for the detection of soluble Fc-epsilon-RI in human serum. *J Immunol Methods* 2011;373:192-9.
20. Zhu F, Althaus T, Tan CW, et al. WHO international standard for SARS-CoV-2 antibodies to determine markers of protection. *Lancet Microbe* 2022;3:e81-2.
21. QuantiFERON® SARS-CoV-2 ELISA Kit Instructions for Use. <https://www.qiagen.com/fi/resources/download.aspx?id=3d27842e-c811-442c-bcad-a9d42945e59c&lang=en>. Accessed 22 July 2025.
22. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood* 2021;137:3165-73.
23. Greenberger LM, Saltzman LA, Senefeld JW, et al. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. *Cancer Cell* 2021;39:1031-33.
24. L'Huillier AG, Meyer B, Andrey DO, et al. Antibody persistence in the first 6 months following SARS-CoV-2 infection among hospital workers: a prospective longitudinal study. *Clin Microbiol Infect* 2021;27:784 e1-8.
25. Besevic J, Lacey B, Callen H, et al. Persistence of SARS-CoV-2 antibodies over 18 months following infection: UK Biobank COVID-19 Serology Study. *J Epidemiol Community Health* 2023;78:105-8.
26. Cao Y, Wang J, Jian F, et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature* 2022;602:657-63.
27. Barriere J, Carles M, Audigier-Valette C, et al. Third dose of anti-SARS-CoV-2 vaccine for patients with cancer: Should humoral responses be monitored? A position article. *Eur J Cancer* 2022;162:182-93.
28. Liu L, Iketani S, Guo Y, et al. Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. *Nature* 2022;602:676-81.
29. Katagiri S, Akahane D, Otsuki S, et al. Tyrosine Kinase Inhibitors Do Not Promote a Decrease in SARS-CoV-2 Anti-Spike IgG after BNT162b2 Vaccination in Chronic Myeloid Leukemia: A Prospective Observational Study. *Vaccines (Basel)* 2022;10.
30. Goel RR, Painter MM, Apostolidis SA, et al. mRNA vaccines induce durable immune memory to SARS-CoV-2 and variants of concern. *Science* 2021;374:abm0829.
31. Redd AD, Nardin A, Kared H, et al. Minimal cross-over between mutations associated with Omicron variant of SARS-CoV-2 and CD8+ T cell epitopes identified in COVID-19 convalescent individuals. *bioRxiv* 2021.
32. Xu W, Ren W, Wu T, et al. Real-World Safety of COVID-19 mRNA Vaccines: A Systematic Review and Meta-Analysis. *Vaccines (Basel)* 2023;11:1118.

Patient-centred outcomes and cost-effectiveness of a hospital-at-home service model for older adults

Toon Li Boh¹ MBBS, Yun Hu² MBBS, Annie Tan² BSocSc (Hons), Jia Hui Chai^{3,4} MPH, Yanan Zhu^{3,4} PhD, Luming Shi^{3,4,5} MBBS, Yeuk Fan Ng^{6,7} MBBS, Yan Hoon Ang¹ MBBS

ABSTRACT

Introduction: Medical Home (MH) is a hospital-at-home (HaH) service model developed to deliver multidisciplinary acute medical care for patients in their homes. This study evaluated the patient-centred outcomes and cost-effectiveness of the MH service compared with usual care (UC).

Methods: This quasi-experimental study involved 250 patients recruited from July 2021 to May 2023. Data on costs, healthcare resource utilisation, and patient-centred outcomes were collected at index admission, discharge, and 90 days post-discharge. Regression analyses were employed to estimate the incremental differences in patient-centred outcomes and net monetary benefit (NMB) between MH and UC groups, while adjusting for confounders. A probabilistic sensitivity analysis (PSA) was conducted to evaluate the uncertainty surrounding the data inputs for cost-effectiveness analysis. Subgroups excluding U-turn patients (i.e. patients admitted to the hospital before discharge from MH) and deaths were analysed for patient-centred and cost-effectiveness outcomes.

Results: There was no statistically significant difference between the 2 groups in clinical, functional, and experience outcomes, except for length of stay and caregiver's overall experience in which the MH group had significantly better results compared with UC group. Compared to the UC group, the MH group showed a positive incremental NMB of SGD6895 (approximately USD5361; 95% confidence interval SGD1945–11,845) indicating the cost-effectiveness of the MH service. Results from the PSA showed that the MH group was cost-effective across a range of willingness-to-pay thresholds. Subgroup analyses were consistent with the base case for patient-centred and cost-effectiveness outcomes.

Conclusions: We conclude that an HaH care model like MH is a value-based and cost-effective alternative to admission to hospital for selected frail elderly patients, making it the preferred strategy.

Keywords: cost-effectiveness, geriatric medicine, hospital-at-home, older adults, patient-centred outcomes

CLINICAL IMPACT

What is New

- To the authors' knowledge, this study is the first to evaluate the hospital-at-home (HaH) care model for frail older adults in Singapore.
- Findings reveal that HaH is a cost-effective alternative to inpatient hospitalisation with positive benefits, such as shorter length of stay and better caregiver experiences.

Clinical Implications

- This study's findings will guide future healthcare planning and delivery and support the shift from hospital-centric to community-based care. This is especially relevant for Singapore, being one of the fastest-ageing nations globally.

INTRODUCTION

Singapore faces a significant demographic transition, with the proportion of residents aged 65 years and above projected to reach 25% by 2030.¹ This shift, coupled with an increased prevalence of multimorbidity, poses substantial challenges to healthcare sustainability through increased hospital utilisation and frequent readmissions.²

In response, innovative care models like hospital-at-home (HaH) programmes have emerged as alternatives to traditional acute hospital care, delivering hospital-level care in patients' homes. HaH not only offers potential cost savings through reduced bed occupancy but also mitigates hospitalisation-associated risks.³ This is relevant in Singapore, where 11.7% of adult patients in acute hospitals acquire

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¹ Geriatric Medicine, Khoo Teck Puat Hospital, Singapore

² Office of Data Management and Analytics, Khoo Teck Puat Hospital, Singapore

³ Health Economics and Outcome Research, Singapore Clinical Research Institute, Consortium for Clinical Research and Innovation Singapore, Singapore

⁴ Cochrane, Singapore

⁵ Duke-NUS Medical School, Singapore

⁶ Corporate Development, Khoo Teck Puat Hospital, Singapore

⁷ Saw Swee Hock School of Public Health, National University of Singapore, Singapore

Correspondence: Dr Yan Hoon Ang, Geriatric Medicine, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828.

Email: ang.yan.hoon@nhghealth.com.sg

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healthcare-associated infections.⁴ Hospitalisation also contributes to functional decline in older patients.⁵

Previous research has demonstrated potential benefits of HaH programmes, including improved patient satisfaction⁶⁻⁸ and positive outcomes for caregivers.⁸⁻¹⁰ Studies from Western healthcare systems have shown promising clinical outcomes, including reduced hospital readmission rates, albeit with longer length of stay and higher costs.¹¹⁻¹⁵ However, the effectiveness and cost-effectiveness of such schemes in Asian healthcare contexts, particularly for older or frail patients, remain understudied. Moreover, the transferability of these findings to Asian populations, where family dynamics, living arrangements, and healthcare-seeking behaviours differ significantly from Western contexts, requires careful evaluation.

Khoo Teck Puat Hospital, a tertiary acute care hospital in Singapore, manages the national hospital-to-home programme through its Ageing-in-Place community care team (AIP-CCT). This post-discharge transitional home care service targets complex patients and older adults at risk of readmission. However, this model has limitations, particularly when patients develop new acute medical conditions that necessitate a return to the emergency department (ED).

To address these gaps, the hospital introduced the Medical Home (MH) service, a novel acute medical care model to deliver care by a multidisciplinary team in patients' homes. This service facilitates admission avoidance by accepting patients referred from the ED, specialist outpatient clinic (SOC), or AIP-CCT and early supported discharge for suitable inpatients who can safely continue treatment at home.

We hypothesised that the MH service would achieve comparable clinical and functional outcomes compared with usual care (UC), while providing better patient and caregiver experiences⁸ as well as generating cost savings for both patients and the healthcare system through reduced bed days, particularly among older adults. This aligns with Singapore's healthcare transformation efforts to promote value-based and patient-centred care, and to shift focus from hospital-centric to community-based care models.

This study evaluated the patient-centred outcomes and cost-effectiveness of the MH service compared with conventional inpatient ward care in Singapore's acute hospital setting.

The findings of this study have the potential to significantly influence healthcare policy and practice in Singapore and similar healthcare systems. By providing evidence on MH's effectiveness and cost-effectiveness, and synthesising insights from global HaH research and contextualising them to Singapore's healthcare landscape, this study aims to inform resource allocation and care delivery model decisions for the ageing

population, ultimately contributing to the development of more efficient and patient-centred care strategies.

METHODS

Design

This quasi-experimental prospective study was conducted at Khoo Teck Puat Hospital, Singapore. The MH intervention group included patients who met the inclusion criteria (Supplementary Annex S1) and were referred from several different sources: ED, SOC, or AIP-CCT patients, who would otherwise have required admission, as well as inpatients admitted for less than 48 hours in wards, deemed suitable for early supported discharge to continue care at home. The UC group consisted of patients who met the inclusion criteria but either declined MH service, resided outside the catchment area, or could not be enrolled due to capacity constraints, and were therefore subsequently admitted to the hospital itself. The primary caregiver was defined as the main nominated healthcare spokesperson who was overall in charge of the patient's care decisions and coordination, excluding live-in domestic helpers.

Sample size and recruitment

The study aimed to recruit 250 patient-caregiver dyads, comprising 125 pairs in each of the MH intervention and UC groups. Recruitment occurred from July 2021 to May 2023. MH nurses screened clinical notes to identify potential participants, followed by MH doctors' confirmation of eligibility based on predetermined criteria (detailed in Supplementary Annex S1). A total of 250 patients were recruited, comprising 125 patients in the MH group and 125 in the UC group. Additionally, 150 caregivers were recruited, with 100 for the MH group and 50 for the UC group. The recruitment disparity between patients and caregivers was attributed to 3 main factors: some patients did not have caregivers, some caregivers declined participation, and recruitment opportunities were limited by COVID-19 visiting restrictions, particularly for the control group. Informed consent was obtained from all participants in both MH and UC groups for study participation and data analysis. Patient flow is detailed in Supplementary Annex S2.

Data collection

The study collected comprehensive data encompassing patients' baseline characteristics and patient-centred outcomes, including clinical, functional, and patient and caregiver's experience outcomes. Additionally, health services utilisation, healthcare cost, and health-related quality of life were collected for cost-effectiveness outcomes. Detailed definitions and measurements are listed in Table 1.

Table 1. Definitions and measurements of outcomes.

Indicators	Definitions and measurements	Timepoints
Baseline characteristics		
CFS	Validated 9-point scale ranging from 1 (very fit) to 9 (terminally ill)	At admission
Patient Acuity Category Scale	Used to measure the severity of patients' health condition and level of care required in 4 categories, P1, P2, P3, and P4; only available for patients who presented through the ED	At admission
CCI	Used to measure comorbidity burden; validated tool that predicts mortality by weighting various comorbid conditions	At admission
Clinical outcomes		
90-day readmission	Readmission to hospital within 90 days post-index discharge	From discharge to 90 days post-index discharge
90-day mortality	Death within 90 days post-index discharge	From discharge to 90 days post-index discharge
Institutionalisation	Nursing home placement within 90 days post-index discharge	From discharge to 90 days post-index discharge
Duration of care	Length of stay during index admission (days)	From admission to discharge
Adverse events	Occurrence of any of the following during index admission: • Thrombophlebitis • Medication error • New pressure sores • Falls • Catheter-related urinary tract infection • Acute delirium	From admission to discharge
Functional outcomes		
MBI	Used to measure a person's independence in performing activities of daily living with a total score ranging from 0 to 100, higher scores indicate better function	At admission, discharge and 90 days post-index discharge
EQ-5D-5L	Used to measure health-related quality of life by asking about 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of severity. Utility scores were calculated based on the Singapore value set.	At admission, discharge and 90 days post-index discharge ^a
Experience outcomes		
Patient's overall experience	Overall satisfaction rating by a single-item 4-point scale: 1=Excellent, 2=Good, 3=Poor, 4=Very Poor	At discharge
Caregiver's overall experience	Overall satisfaction rating by a single-item 4-point scale: 1=Excellent, 2=Good, 3=Poor, 4=Very Poor	At discharge
Caregiver burden	ZBI-12, a 12-item validated scale from 0 to 48; higher scores indicate greater burden	At admission, discharge and 90 days post-index discharge
Cost-effectiveness outcomes		
Health service utilisation	Data obtained from hospital databases consist of: • ED visits • Hospital readmissions • Specialist outpatient clinic visits	From index admission to 90 days post-index discharge
Healthcare costs	Healthcare costs obtained from hospital databases consisting of: • Index admission costs (professional visits, consultations, transport, treatment fees, medications, investigations for MH; ward charges and treatment fees for usual care) • Post-discharge costs (outpatient, inpatient, ED visits)	From index admission to 90 days post-index discharge
QALY	Calculated using EQ-5D-5L utility scores; time-weighted average (area under curve)	From index admission to discharge and 90 days post-index discharge ^a

CCI: Charlson Comorbidity Index; CFS: Clinical Frailty Scale; ED: emergency department; EQ-5D-5L: EuroQol-5 dimension-5 levels; MBI: modified Barthel index; MH: Medical Home; QALY: quality-adjusted life year; ZBI-12: Zarit-12 Burden Interview

^a For missing data due to lost to follow-up, it was assumed that utility scores remained as previously recorded. In cases of death, utility scores were assumed to be 0.

Statistical analyses

Baseline characteristics of participants in the 2 groups were obtained via descriptive statistics. Based on their distribution, continuous variables were expressed either as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were reported as absolute numbers and percentages. Tests for significance were performed using either independent t-test or Mann-Whitney U test as appropriate, depending on the distribution of the continuous variables. Categorical data were tested using Pearson chi-square tests.

Patient-centred outcomes: Clinical, functional, and experience outcomes

The efficacy of MH service measured in clinical, functional, and experience outcomes as outlined in Table 1 was further assessed by multiple logistic regressions and multiple linear regressions for dichotomous and continuous outcomes, respectively, with adjustment for potential confounders such as age, sex, education level, Charlson Comorbidity Index score, Clinical Frailty Scale (CFS) score at admission, and Patient Acuity Category Scale.

For outcomes with repeated measurements—such as modified Barthel index (MBI) score, EuroQol 5-dimension (EQ-5D) utility score and caregiver burden score—when there was no statistically significant difference between the 2 groups for the baseline results, balance was assumed for baseline. Therefore, MBI, EQ-5D, and caregiver burden scores at follow-up visits were directly used as outcomes in regression models instead of change scores. Subgroup analyses were explored by excluding U-turn (i.e. patients who had to be admitted to the hospital before being discharged from MH) patients and deaths.

Cost-effectiveness

A health system perspective was adopted for the cost-effectiveness analysis, covering costs from index admission to 90 days post-discharge. All costs were adjusted to 2024 values using Singapore's consumer price index¹⁶ and reported in Singapore dollars (SGD), with no discounting applied due to the follow-up period being within 1 year. The exchange rate for reference to United States dollars (USD) is at the prevailing rate at the time of publication.¹⁷

Cost-effectiveness was evaluated using incremental net monetary benefit (NMB), calculated by multiplying the quality-adjusted life year (QALY) by the willingness-to-pay (WTP) threshold and then subtracting the total cost between the 2 groups. A positive incremental NMB indicates cost-effectiveness when compared to the alternative. The WTP threshold was set at Singapore's 2024 gross domestic product per

capita,¹⁸ in line with the World Health Organization's recommendation.¹⁹

A multiple linear regression analysis estimated the incremental NMB of the MH group versus the UC group, adjusting for the same set of confounding factors as the analyses for patient-centred outcomes. Incremental costs and QALYs were estimated separately using regression models with the same adjustments.

To assess the uncertainty in costs and outcomes, 10,000 bootstrapping iterations were conducted in a probabilistic sensitivity analysis (PSA). Results were summarised by calculating the probability of the MH group being cost-effective across various WTP thresholds, plotted in a cost-effectiveness acceptability curve (CEAC). The same subgroup analyses by excluding U-turn patients and deaths were performed to assess the cost-effectiveness.

RESULTS

Table 2 shows the baseline characteristics of patients and associated outcomes from the study. Patients in the MH group were generally older (UC 78.1, SD 10.2; MH 81.0, SD 10.1; $P=0.022$), the majority had no formal education (UC 25%; MH 47%; $P=0.002$), and exhibited higher CFS at admission compared with those in the usual care group (UC 5.0, SD 1.4; MH 5.3, SD 1.2; $P=0.043$).

Patient-centred outcomes: Clinical, functional, and experience outcomes

Patient-centred outcomes are presented in Table 3. Clinical outcomes, including readmission, mortality, and adverse event rates within 90 days post-index discharge, did not reveal significant differences between the 2 groups. In contrast, the MH group had a statistically significant shorter length of stay, averaging 5.7 days (SD 2.8), compared with 6.8 days (SD 4.1) in the UC group. Multiple regression analysis, adjusted for confounders, showed a reduction of 1.81 days (standard error [SE] 0.51; $P<0.001$) in the MH group compared with the UC group.

Functional outcomes measured by MBI and EQ-5D scores revealed no significant differences between the 2 groups at admission, discharge, and 90 days post-index discharge.

The experience outcome that assessed caregiver burden showed a significant difference at 90 days post-index discharge, with an average score of 10.78 (SD 6.94) in the UC group versus 7.67 (SD 6.60) in the MH group. However, this statistically significant result did not persist after adjustment for confounders. Additionally, caregiver's overall experience score was statistically different between the 2 groups (UC 1.96, SD 0.50; MH 1.62, SD 0.53; $P<0.001$), with a lower score (indicating better experience) in the MH group after adjustment (-0.35 , SE 0.11; $P=0.002$).

Table 2. Baseline characteristics.

Characteristics	Usual care, n=125	Medical Home, n=125	P value
Age, mean (SD), years	78.1 (10.2)	81.0 (10.1)	0.022
Sex, no. (%)			
Male	49 (39)	49 (39)	>0.999
Female	76 (61)	76 (61)	
Ethnicity, no. (%)			
Chinese	73 (58)	76 (61)	0.735
Malay	27 (22)	30 (24)	
Indian	20 (16)	14 (11)	
Eurasian and others	5 (4)	5 (4)	
Education level, no. (%)	n=125	n=108	0.002
No formal education	31 (25)	51 (47)	
Primary school and below	44 (35)	31 (29)	
Secondary school/pre-university/polytechnic	49 (39)	25 (23)	
University	1 (0.8)	1 (0.9)	
CCI score, mean (SD)	n=125	n=117	
	7.3 (3.3)	7.4 (3.0)	0.805
CFS, mean (SD)	5.0 (1.4)	5.3 (1.2)	0.043
Patient Acuity Category Scale, no. (%)	n=117	n=87	0.181
P2	117 (100)	85 (98)	
P3	0 (0)	2 (2)	

CCI: Charlson Comorbidity Index; CFS: Clinical Frailty Scale; SD: standard deviation; UC: usual care
P values in bold indicate statistical significance.

There was no significant difference in the patients' overall experience scores.

Similar results were observed in the subgroup analyses (Supplementary Annexes S3 and S4). The MH group had a statistically significantly lower length of stay and better caregiver's overall experience score, after adjustment, compared with the UC group.

Cost-effectiveness

The base-case results of the cost-effectiveness analysis, spanning from index admission to 90 days post-index discharge, indicate that the MH group is more cost-effective than the UC group (Table 4). The UC group incurred costs of SGD11,111 (SE 3860), while the MH group incurred SGD6356 (SE 3660), yielding a cost saving of SGD4755 (95% confidence interval [CI] -SGD8053 to -SGD1456) for the MH group after adjusting for confounders. Furthermore,

the MH group achieved an incremental QALY gain of 0.02 (95% CI -0.01 to 0.04), demonstrating its dominance due to lower costs and higher QALY gains. The incremental NMB of SGD6895 (95% CI SGD1945 to SGD11,845) at the WTP of SGD121,161 further supports the cost-effectiveness of the MH group. The PSA, comprising 10,000 iterations of bootstrapping, demonstrated a 100% likelihood of MH group being cost-effective across all evaluated WTP thresholds, as illustrated in the CEAC in Fig. 1. The results from the sensitivity analysis are consistent with the base-case results, indicating the robustness of the base-case. The healthcare resource utilisation during index admission and 90 days post-index discharge are detailed in Supplementary Annexes S5 and S6, respectively.

Subgroup analyses, excluding U-turn cases and deaths, corroborate the base-case findings, showing positive incremental NMB of SGD7361 (95%

Table 3. Patient-centred outcomes: clinical, functional, and experience outcomes.

Patient-centred outcomes	Usual care, n=125	Medical Home, n=125	P value	Multiple regressions with adjustment ^a	
Clinical outcomes				OR (95% CI)	P value
Readmission up to 90 days post-discharge, no. (%)	45 (36.0)	44 (35.2)	>0.999	0.85 (0.42–1.69)	0.642
Mortality within 90 days post-discharge, no. (%)	7 (5.6)	10 (8.0)	0.617	0.29 (0.04–1.41)	0.160
Nursing home placement at 90 day post-discharge, no. (%)	0 (0)	0 (0)	>0.999	-	-
Length of stay during index admission, mean (SD)	6.8 (4.1)	5.7 (2.8)	0.011	Coefficient (SE) -1.81 (0.51)	<0.001
Length of stay during index admission, median (IQR)	6.0 (4.0–8.8)	5.0 (4.0–6.0)	0.053		
Adverse event, no. (%)	5 (4.0)	2 (1.6)	0.443	OR (95% CI) 0.23 (0.01–1.67)	0.203
Thrombophlebitis	1 (0.8)	0 (0)			
Medication error	0 (0)	0 (0)			
New pressure sores	0 (0)	0 (0)			
Falls	0 (0)	1 (0.8)			
Catheter-related urinary tract infection	0 (0)	1 (0.8)			
Acute delirium	4 (3.2)	0 (0)			
Functional outcomes					
Modified Barthel Index score				Coefficient (SE)	
Upon admission, mean (SD)	69.51 (27.81)	68.02 (33.61)	0.703	-	-
Upon discharge, mean (SD)	72.97 (27.04)	69.44 (33.01)	0.379	0.46 (2.88)	0.873
90-day post-discharge, mean (SD)	76.72 (26.81)	74.75 (29.39)	0.627	0.77 (3.09)	0.803
EQ-5D-5L utility score					
Upon admission, mean (SD)	0.34 (0.44)	0.38 (0.45)	0.461	-	-
Upon discharge, mean (SD)	0.52 (0.44)	0.46 (0.47)	0.357	0.06 (0.05)	0.229
90-day post-discharge, mean (SD)	0.48 (0.45)	0.51 (0.47)	0.628	0.10 (0.06)	0.067
Experience outcomes					
Caregiver burden score					
Upon admission, mean (SD)	12.90 (8.79)	12.32 (7.84)	0.685	-	-
Upon discharge, mean (SD)	12.19 (7.95)	10.77 (7.50)	0.301	0.24 (1.70)	0.890
90-day post-discharge, mean (SD)	10.78 (6.94)	7.67 (6.60)	0.020	-2.12(1.55)	0.177
Patient's overall experience, mean (SD)	1.77 (0.47)	1.66 (0.48)	0.153	-0.10 (0.09)	0.279
Caregiver's overall experience, mean (SD)	1.96 (0.50)	1.62 (0.53)	<0.001	-0.35 (0.11)	0.002

CCI: Charlson Comorbidity Index; CFS: Clinical Frailty Scale; CI: confidence interval; EQ-5D-5L: EuroQol-5 dimension-5 level; OR: odds ratio; IQR: interquartile range; SD: standard deviation; SE: standard error

^a Multiple logistic regressions for dichotomous outcome and multiple linear regression for continuous outcome, with adjustment for age, sex, education level, CCI score, CFS, and Patient Acuity Category Scale.

P values in bold indicate statistical significance.

CI SGD2423 to SGD12,299) and SGD5049 (95% CI SGD728 to SGD9370), respectively, shown in Supplementary Annexes S7 and S8.

DISCUSSION

Main findings

This study demonstrates that MH is a cost-effective alternative to conventional inpatient care, with an incremental NMB of SGD6895 (95% CI SGD1945 to SGD11,845) generated from cost savings of SGD4755 and QALY gain of 0.02 per patient at the WTP threshold of SGD121,161. These benefits were achieved while maintaining comparable clinical and functional outcomes, with no significant differences in 90-day readmission rates, mortality, institutionalisation, and adverse event rates. Notably, the MH group had shorter length of stay (5.7 versus [vs] 6.8 days; $P=0.011$ and adjusted $P<0.001$) with

better caregiver experiences (1.62 vs 1.96; $P<0.001$ and adjusted $P=0.002$), suggesting value-based care and more efficient resource utilisation.

Comparison with existing literature

This study's findings align with but extend beyond previous research in several ways. While an earlier study by Leff et al. demonstrated the feasibility of HaH programmes, it reported longer lengths of stay and higher costs.⁷ In contrast, this study observed both reduced length of stay and cost savings. The cost-effectiveness observed (incremental QALY gain: 0.02) is comparable to findings from Harris et al., who reported similar QALY gains in their randomised controlled trial, though in a younger population.⁹

Strengths and limitations of study

This study demonstrates several strengths. First, it focused on the impact of HaH on an older frail patient

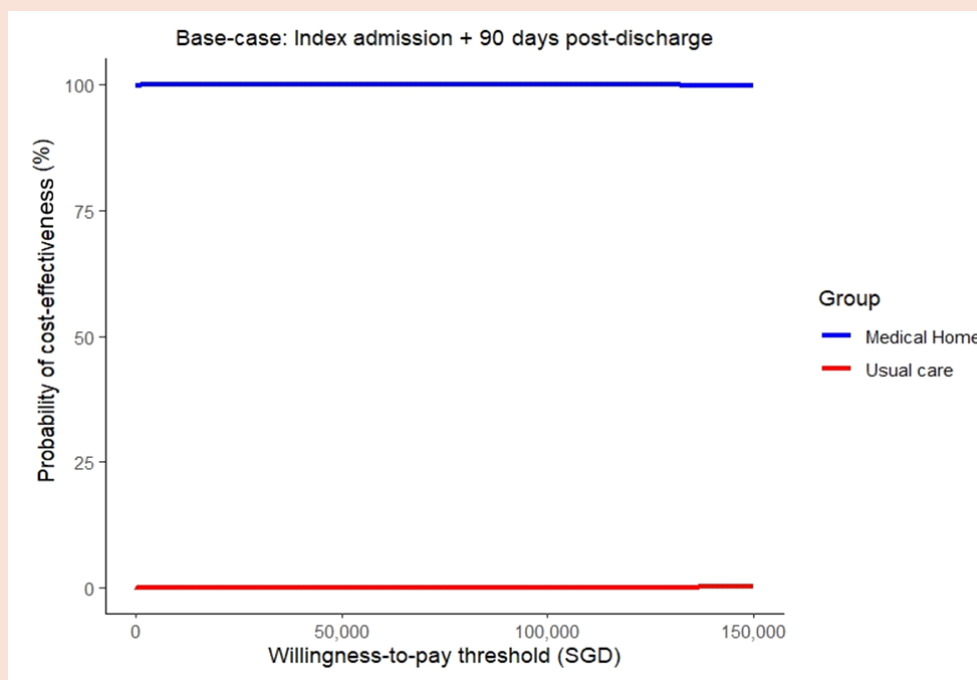
Table 4. Cost-effectiveness analysis results from index admission to 90 days post-index discharge.

Strategies	Cost (SE) ^a	Incremental Cost (95% CI) ^a	QALY (SE) ^a	Incremental QALY (95% CI) ^a	Incremental NMB (95% CI) ^a
Usual care	SGD11,111 (3860)	-	0.13 (0.03)	-	-
Medical Home	SGD6356 (3660)	-SGD4755 (-SGD8053 to -SGD1456)	0.15 (0.03)	0.02 (-0.01 to 0.04)	SGD6895 (SGD1945 to SGD11,845)

CI: confidence interval; NMB: net monetary benefit; QALY: quality-adjusted life year; SE: standard error

^aAdjusted for age, sex, education level, Charlson Comorbidity Index, Clinical Frailty Scale, and Patient Acuity Category Scale.

Fig. 1. Cost-effectiveness acceptability curve from a probabilistic sensitivity analysis of cost-effectiveness analysis.



population, which is currently under-studied. These patients are often admitted to the wards as they are considered unsafe for home treatment due to perceived higher risk of deterioration and complexity of care. However, this conventional approach increases the risk of iatrogenic complications such as acute delirium, falls, functional decline, and nosocomial infections leading to prolonged hospitalisation, consistent with the observation of longer length of stay and higher inpatient care episode costs in the UC group. This study's findings suggest that when appropriately selected, older frail patients with suitable medical conditions can be safely and effectively cared for under HaH, and reap the benefits of person-centred value-based care with shorter length of stay and improved caregiver satisfaction at lower costs.

A second key strength of this study lies in the extended 90 days post-discharge follow-up period, providing insight into longer-term outcomes, which were potentially missed in shorter evaluations. The study captured the full spectrum of healthcare utilisation patterns, showing comparable readmission rates between MH and UC (36% vs 35%; $P>0.999$). Additionally, this study demonstrated sustained functional outcomes through MBI scores and notably, revealed lasting benefits for caregivers, with significantly reduced caregiver burden scores at 90 days (MH vs UC: 7.67 vs 10.78; $P=0.02$). The loss of significance in the multiple regression analysis is likely the result of the small sample size.

Another strength of this study is its relevance in Asian healthcare contexts where family caregivers play a crucial role in long-term care arrangements, an area currently not well studied in the Asian HaH context. Contrary to perceived concerns, HaH care resulted in better caregiver experiences and lower caregiver stress levels at 90 days post-discharge. The positive outcomes could be attributed to the programme's focus on caregiver empowerment and education during MH care, resulting in improved caregiver confidence when caring for patients at home even in the longer term. HaH care also enables the care team to better understand and address caregiving concerns early, facilitating timely implementation of necessary community care support services.

This study had several limitations. The non-randomised design of the study may introduce selection bias, although it was adjusted for key confounders. Additionally, more robust tools such as the National Early Warning Score updated (NEWS2) could have been used to ensure better comparability of clinical acuity between the 2 groups of patients. The generalisability of the findings is limited by the small sample size and single-centre setting within Singapore's healthcare context.

Furthermore, the single-item 4-point scale used to assess overall patient and caregiver experiences was not a validated or internationally recognised tool. The authors analysed such discrete data as continuous data. While this approach is common and allows for the use of parametric statistical methods, it may not fully capture the ordinal nature of the data. Consequently, this simplification could affect the precision and interpretation of the results. The presence of live-in domestic helpers may reduce the physical caregiving burden on primary caregivers and could potentially influence their reported experiences. However, this does not invalidate the findings because the study aimed to evaluate empowerment, confidence, stress levels, and overall experiences among primary caregivers, which can remain significant even when some physical tasks are delegated. Future research should consider adopting validated satisfaction measures and explore the impact of household help on caregiver-reported outcomes to enhance comparability and robustness of findings.

In the cost-effectiveness analysis, the authors evaluated costs from the health system perspective only, due to the absence of data on the caregivers' and patients' productivity losses. Without these data, the authors were unable to incorporate broader societal costs. The exclusion of these indirect and informal care components may lead to an underestimation of the total economic burden associated with home care services. As such, future evaluations incorporating these indirect costs would offer a more comprehensive understanding of the true economic burden to society.

CONCLUSION

An HaH care model like MH is a value-based and cost-effective alternative to inpatient admission for selected frail older patients, who present with acute medical conditions. The model has comparable clinical and functional outcomes, achieved with shorter length of stay at reduced cost. Improved caregiver experiences as well as lower caregiver stress levels at 90 days post-discharge make HaH care the preferred strategy over conventional inpatient ward care for frail older adults in Singapore.

The results of this study, in an ageing population, lend great support to the move towards shifting care from hospitals to the community. The findings have crucial long-lasting implications for future healthcare system planning and care model delivery, especially to guide strategies to help the frail patient population avoid admission or prolonged hospitalisation.

Future research directions

There are several key areas for future investigation. Priority should be given to developing predictive

models to identify optimal patient selection criteria for HaH-type of services. Further research is also needed to evaluate cost-effectiveness across different healthcare settings and funding models, particularly in diverse Asian contexts. Additionally, studies examining the integration of remote monitoring technologies and qualitative research, further exploring patient and caregiver experiences, could inform service improvements and optimise the model's implementation in different cultural settings.

Ethics statement

Ethics approval was granted by the National Healthcare Group Domain Specific Review Board (2020/00326).

Declaration

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Supplementary materials

Annex S1. Medical home patient selection criteria: inclusion and exclusion criteria.

Annex S2. Patient flow.

Annex S3. Subgroup analysis by excluding U-turn patients: patient-centred outcomes.

Annex S4. Subgroup analysis by excluding deaths: patient-centred outcomes.

Annex S5. Healthcare resource utilisation and associated costs during index admission.

Annex S6. Healthcare resource utilisation and associated costs during 90 days post-index discharge.

Annex S7. Subgroup analysis by excluding U-turn patients: cost-effectiveness outcomes.

Annex S8. Subgroup analysis by excluding deaths: cost-effectiveness outcomes.

REFERENCES

1. National Population and Talent Division, Singapore Department of Statistics, Ministry of Home Affairs, et al. Population in Brief 2023. <https://www.population.gov.sg/files/media-centre/publications/population-in-brief-2023.pdf>. Accessed 1 April 2026.
2. Rodrigues LP, de Oliveira Rezende AT, Delpino FM, et al. Association between multimorbidity and hospitalization in older adults: systematic review and meta-analysis. *Age Ageing* 2022;51:afac155.
3. Megido I, Sela Y, Grinberg K. Cost effectiveness of home care versus hospital care: a retrospective analysis. *Cost Eff Resour Alloc* 2023;21:13.
4. Cai Y, Venkatachalam I, Tee NW, et al. Prevalence of Healthcare-Associated Infections and Antimicrobial Use Among Adult Inpatients in Singapore Acute-Care Hospitals: Results From the First National Point Prevalence Survey. *Clin Infect Dis* 2017; 64:S61-7.
5. Creditor MC. Hazards of hospitalization of the elderly. *Ann Intern Med* 1993;118:219-23.
6. Oh KM, Warnes AM, Bath P. Effectiveness of a rapid response service for frail older people. *Nurs Older People* 2009;21:25-32.
7. Leff B, Burton L, Mader SL, et al. Hospital at home: feasibility and outcomes of a program to provide hospital-level care at home for acutely ill older patients. *Ann Intern Med* 2005;143: 798-808.
8. Wang X, Stewart C, Lee G. Patients' and caregivers' perceptions of the quality of hospital-at-home service: A scoping review. *J Clin Nurs* 2024;33:817-38.
9. Harris R, Ashton T, Broad J, et al. The effectiveness, acceptability and costs of a hospital-at-home service compared with acute hospital care: a randomized controlled trial. *J Health Serv Res Policy* 2005;10:158-66.
10. Rossinot H, Marquestaut O, de Stampa M. The experience of patients and family caregivers during hospital-at-home in France. *BMC Health Serv Res* 2019;19:470.
11. Caplan GA, Sulaiman NS, Mangin DA, et al. A meta-analysis of "hospital in the home". *Med J Aust* 2012;197:512-9.
12. Arsenaault-Lapierre G, Henein M, Gaid D, et al. Hospital-at-Home Interventions vs In-Hospital Stay for Patients With Chronic Disease Who Present to the Emergency Department: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2021;4:e2111568.
13. Liu AL, Taylor DM. Adverse events and complications among patients admitted to hospital in the home directly from the emergency department. *Emerg Med (Fremantle)* 2002;14:400-5.
14. Mas MÀ, Santaegüenia SJ, Tarazona-Santabalbina FJ, et al. Effectiveness of a Hospital-at-Home Integrated Care Program as Alternative Resource for Medical Crises Care in Older Adults With Complex Chronic Conditions. *J Am Med Dir Assoc* 2018; 19:860-3.
15. Montalto M, Lui B, Mullins A, et al. Medically-managed Hospital in the Home: 7 year study of mortality and unplanned interruption. *Aust Health Rev* 2010;34:269-75.

16. Singapore Department of Statistics. Consumer Price Index (CPI) Highlights. <https://www.singstat.gov.sg/find-data/explore-data-themes/economy-prices/consumer-price-index/latest-news-data>. Accessed 23 July 2025.
17. Monetary Authority of Singapore. Exchange Rates. SGD/USD. <https://www.mas.gov.sg/statistics/exchange-rates>. Accessed 2 April 2026.
18. Singapore Department of Statistics. Gross Domestic Product: Per Capita CNI and Per Capita GDP At Current Prices, Annual. <https://tablebuilder.singstat.gov.sg/table/TS/M01512>. Accessed 23 July 2025.
19. Tan-Torres Edejer T, Baltussen R, Adam T, et al (Eds). Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. Geneva: World Health Organization; 2003.

Cognition and arthritis in adults over 50: Evidence from CHARLS, HRS, and ELSA

Litao Huo*¹ MD, Fei Wang*¹ MD, Yifan Niu¹ MD, Jie Cui² MD, Ying Jiang¹ MD, Jialin Shi¹ MD, Yongyu Hao¹ MD, Jiaxu Wang¹ MD, Shibo Huang¹ MD, Lin Tan¹ MD, Bo Gao¹ MD

ABSTRACT

Introduction: Arthritis and cognitive decline are significant health challenges in ageing populations, yet their association across diverse socioeconomic and cultural contexts remains insufficiently understood. This study examines the relationship between cognitive function and arthritis prevalence among adults aged 50 years and older, utilising data from 3 longitudinal ageing cohorts: the China Health and Retirement Longitudinal Study (CHARLS), the Health and Retirement Study (HRS), and the English Longitudinal Study of Ageing (ELSA).

Methods: The analysis included 18,562 participants from CHARLS, 23,238 from HRS, and 9848 from ELSA, all aged ≥ 50 years with physician-diagnosed arthritis and cognitive assessments. Cognitive function was evaluated across memory, orientation, and executive function domains, standardised as z-scores within each cohort. Generalised Estimating Equations (GEE) and Generalised Linear Mixed Models assessed the longitudinal association between cognition and arthritis, adjusting for socio-demographic factors, lifestyle variables, and comorbidities. Sensitivity analyses validated the findings' robustness.

Results: In fully adjusted GEE models, executive function was significantly associated with arthritis. Each 1-standard deviation (SD) lower executive score was associated with higher arthritis odds: CHARLS odds ratio (OR) 1.000 (95% confidence interval [CI] 1.000–1.001, $P=0.016$), HRS OR 1.13 (95% CI 1.01–1.28, $P=0.037$), and ELSA OR 1.07 (95% CI 1.02–1.12, $P=0.009$). Neither episodic memory nor orientation showed significant associations (all $P>0.10$), and total cognition in HRS was significant. Mixed-model estimates were concordant, and alternative correlation structures yielded consistent executive–arthritis links.

Conclusion: Across 3 major ageing cohorts, impaired executive function is independently associated with higher odds of arthritis in adults aged ≥ 50 years. Targeting executive deficits may enhance early identification and integrated management of arthritis and cognitive health in ageing populations.

Keywords: ageing, arthritis, cognitive function, cross-national analysis, epidemiology, geriatric medicine, longitudinal cohorts, statistics

CLINICAL IMPACT

What is New

- This study demonstrates a consistent association between impaired executive function and higher odds of arthritis across 3 large ageing cohorts from China, US, and the UK.
- Among cognitive domains, executive function—but not memory or orientation—was independently linked to arthritis risk in adults aged ≥ 50 years.

Clinical Implications

- Executive function assessment may serve as a practical tool for early identification of individuals at increased risk of arthritis in ageing populations.
- Integrating cognitive evaluation into routine clinical care could support more comprehensive management strategies addressing both cognitive and musculoskeletal health.

INTRODUCTION

The world is transitioning towards older age groups, with the share of people aged 60 years and above expected to increase 2-fold by 2050.¹ This demographic transition poses significant public health challenges, notably the rising incidence of cognitive impairment and dementia, which severely impact the well-being of older adults and place considerable strain on healthcare systems.² Identifying modifiable risk factors associated with cognitive decline is critical for devising strategies to mitigate its onset and progression. Among these factors, arthritis—a chronic condition affecting approximately 23% of adults in the US, with prevalence escalating with age—has garnered increasing attention.³ Beyond its well-documented effects on physical mobility and quality of life, arthritis may also influence

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¹ Department of Spine Surgery, The Ninth Medical Center of People's Liberation Army General Hospital, Beijing, China

² Department of Radiology, The Ninth Medical Center of People's Liberation Army General Hospital, Beijing, China

*Joint first authors

Correspondence: Dr Bo Gao, Department of Spine Surgery, The Ninth Medical Center of People's Liberation Army General Hospital, Beijing, 100101, China. Email: doctorko@163.com; Dr Lin Tan, Department of Spine Surgery, The Ninth Medical Center of People's Liberation Army General Hospital, Beijing, 100101, China. Email: 18401720886@163.com

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cognitive function through multiple pathways, warranting further investigation.

Arthritis, encompassing conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA), is characterised by chronic pain and inflammation, both of which have been implicated in cognitive decline. Research indicates that persistent pain can impair cognitive performance by disrupting sleep, elevating depressive symptoms, and necessitating medications with cognitive side effects.⁴ Systemic inflammation, a common feature of arthritis, is also recognised as a contributor to neurodegenerative processes, including those underlying dementia.⁵ Moreover, arthritis often restricts physical activity and social participation—lifestyle factors known to bolster cognitive resilience.⁶ Preliminary studies have reported associations between arthritis and increased risks of cognitive impairment, yet the evidence remains fragmented, often limited to specific populations or lacking longitudinal depth.^{7,8}

Despite these insights, significant gaps persist in understanding the relationship between arthritis and cognitive function, particularly across diverse socioeconomic and cultural contexts. Much of the existing research originates from high-income countries, leaving the association underexplored in low- and middle-income settings where healthcare access and lifestyle factors may differ markedly. Cross-national investigations are thus essential to determine whether this relationship holds universally or varies due to regional influences. To address these deficiencies, this study harnesses data from 3 prominent longitudinal ageing cohorts: the China Health and Retirement Longitudinal Study (CHARLS), the Health and Retirement Study (HRS) in the US, and the English Longitudinal Study of Ageing (ELSA) in the UK. These datasets offer detailed, representative information on health, socioeconomic status, and cognitive outcomes among middle-aged and older adults, facilitating robust, comparative analyses.

This study primarily aims to examine the overall association between arthritis and cognitive function in adults aged 50 years and older, utilising data from CHARLS, HRS, and ELSA. Secondary objectives include exploring potential mediators, such as pain, inflammation, and physical inactivity, and assessing whether the association differs across countries or demographic subgroups. By integrating these rich, multinational datasets, this research seeks to provide a comprehensive understanding of how arthritis relates to cognitive health, offering insights that could guide targeted interventions to preserve cognitive function in ageing populations globally.

METHODS

Study population and data sources

A longitudinal cohort analysis was conducted using harmonised data from 3 nationally representative ageing surveys: CHARLS, HRS, and ELSA. CHARLS is a biennial survey of Chinese adults aged ≥ 45 years and their spouses, with baseline data collected in 2011–2012 using multistage probability sampling and face-to-face interviews.⁹ Initiated in 1992, HRS is a biennial panel survey of US adults born before 1947 and their spouses, aimed at investigating health, economic, and family transitions associated with retirement.¹⁰ ELSA commenced in 2002 with follow-up waves every 2 years, enrolling English residents aged ≥ 50 years in a multidisciplinary protocol aligned with HRS.¹¹

For each cohort, the baseline is defined as the first wave in which both arthritis status and cognitive measures were concurrently available (CHARLS wave 1 [2011], HRS wave 9 [2008], and ELSA wave 5 [2010]). Participants were eligible if they were aged ≥ 50 years, had physician-diagnosed arthritis information, completed at least 2 waves of cognitive assessments, and had non-missing data on key sociodemographic covariates (gender, education, marital status). After sequential exclusions for age < 50 years, missing arthritis or cognitive measures, missing covariates, and fewer than 2 waves of follow-up, the analytic samples comprised 18,562 (CHARLS), 23,238 (HRS), and 9848 (ELSA) participants (Fig. 1).

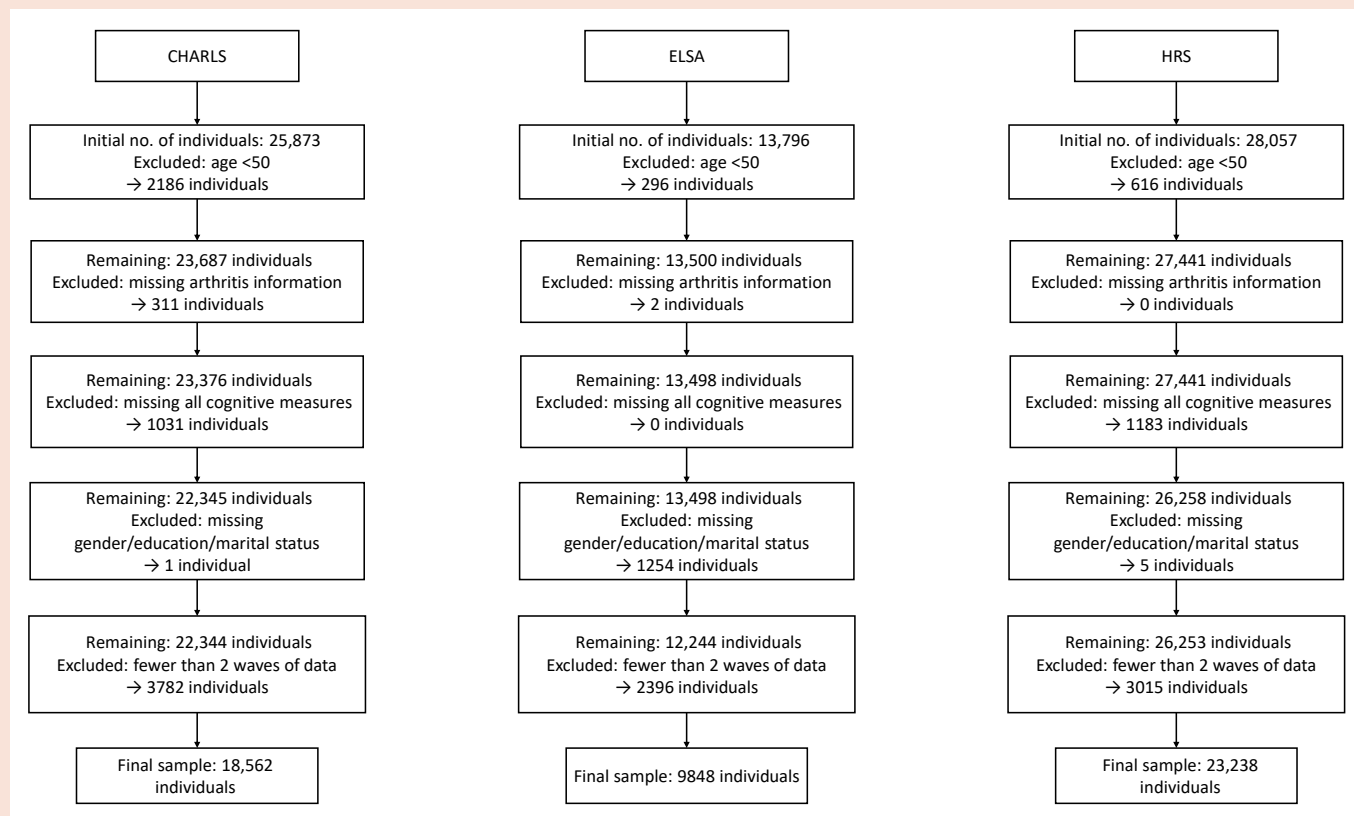
Assessment of arthritis

Arthritis status was ascertained via self-report of a physician diagnosis in all 3 cohorts, a method validated against medical records with high specificity for OA and RA in older adults.¹² In CHARLS and HRS, participants answered “Has a doctor ever told you that you have arthritis?”; ELSA used a parallel question in its health interview module. Affirmative responses were treated as prevalent arthritis at each wave. To account for incident cases, arthritis status was updated at each follow-up and included as a time-varying exposure.

Cognitive function measures

Cognitive performance was evaluated across 3 domains—episodic memory, orientation, and executive function—as well as a composite total score. Episodic memory comprised immediate and delayed recall of a 10-word list, scored 0–10 in CHARLS (mean of the 2 trials) and 0–20 in HRS and ELSA (sum).¹³ Orientation was assessed via questions on date, day of week, and

Fig. 1. Participants selection flowchart.



season (scored 0–5) in CHARLS and HRS; ELSA did not include an orientation subscale, so orientation data were from CHARLS and HRS only. Executive function was measured by verbal fluency (animals named in 1 minute; truncated at 45 seconds in HRS and ELSA) and a pentagon-drawing test (0–1) in CHARLS.¹³ Total cognition scores were created by summing available domain scores within each cohort. To facilitate cross-cohort comparison, all domain and total scores were standardised (z-scores) within each dataset, with higher values indicating better cognition. The substantial heterogeneity in cognitive measurement across the cohorts is acknowledged, such as the absence of an orientation subscale in ELSA and variations in specific executive function items. Analytically, standardising domain scores mitigates some of these variabilities, though conceptual differences in the underlying constructs remain.

Covariates

The authors adjusted for baseline sociodemographic factors, lifestyle behaviours, and comorbidities known to confound the arthritis–cognition relationship. Covariates included age (continuous), gender (male/female), residence (urban/rural in CHARLS; region in HRS/ERCLA; England only in ELSA), marital status (married versus [vs] other), and education (primary,

secondary, tertiary).^{9,11} Lifestyle factors comprised self-reported smoking (yes/no) and drinking (yes/no) status, and body mass index (BMI, kg/m²) derived from objectively measured height and weight. Chronic health conditions—hypertension, diabetes, heart disease, stroke, cancer, and psychiatric disorders—were self-reported physician diagnoses. Depressive symptoms were assessed using the 10-item Center for Epidemiologic Studies-Depression (CES-D) in CHARLS (cut-off ≥10) and HRS/ELSA (8-item CES-D cut-off ≥3; 12-item EURO-D cut-off ≥4). All covariates were measured at baseline.

Statistical analysis

The primary analysis employed Generalised Estimating Equations (GEE) to examine the longitudinal association between cognitive function and arthritis, accounting for repeated measures within individuals.⁴ An exchangeable correlation structure was specified, and 5 models were fitted per cohort: one for each cognitive domain (memory, orientation, executive function, total cognition) and one for the multi-domain model. The GEE model was defined as:

$$\text{logit}(P(\text{arthritis}_{it})) = \beta_0 + \beta_1 \text{cognition}_{it} + \beta_2 \text{covariates}_{it}$$

Results are expressed as odds ratios (ORs) accompanied by their 95% confidence intervals (CIs).

To assess robustness, Generalised Linear Mixed Models (GLMM) with random intercepts for participant ID were conducted as a secondary analysis⁵:

$$\text{logit}(P(\text{arthritis}_{it})) = \beta_0 + \beta_1 \text{cognition}_{it} + \beta_2 \text{covariates}_{it} + u_i$$

Sensitivity analyses tested the stability of findings. (1) Cognition as tertiles: cognitive scores were categorised into tertiles (low/mid/high) and analysed using multinomial GEE to evaluate dose–response relationships; (2) alternate correlation structures: GEE models were refitted using independence and first-order autoregressive (AR-1) working correlation matrices to verify that findings were not contingent on the exchangeable assumption.¹⁴ All sensitivity models included the same covariate set as the main analysis. Results across CHARLS, HRS, and ELSA were synthesised descriptively, rather than pooled, due to differences in covariate distributions and measurement protocols.

Analyses were conducted in R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria), utilising geepack for GEE and lme4 (R Foundation for Statistical Computing, Vienna, Austria) for GLMM. Statistical significance was set at a two-tailed $P < 0.05$.

RESULTS

This study included 51,648 participants aged 50 years and older from 3 longitudinal cohorts: 18,562 from CHARLS (China), 23,238 from HRS (US), and 9848 from ELSA (UK). The median baseline age was 58 years (interquartile range [IQR] 52–64) in CHARLS, 60 years (IQR 54–71) in HRS, and 63 years (IQR 57–72) in ELSA. Females comprised 48.8% of CHARLS, 42.1% of HRS, and 45.8% of ELSA participants. Across all cohorts, participants with arthritis were significantly older, more likely to be female, and had lower education levels compared to those without arthritis (all $P < 0.001$). Cognitive function scores were consistently lower in the arthritis groups, with total cognition z-scores of 0.02 (IQR -0.74–0.64) vs 0.27 (IQR -0.49–0.88) in CHARLS, 0.07 (IQR -0.63–0.54) vs 0.19 (IQR -0.41–0.66) in HRS, and 0.90 (IQR 0.44–1.25) vs 1.02 (IQR 0.67–1.37) in ELSA (all $P < 0.001$). Participants with arthritis also exhibited higher BMI, greater prevalence of hypertension, diabetes, heart disease, stroke, cancer, psychiatric disorders, and depressive symptoms, alongside lower rates of drinking and smoking (all $P < 0.05$). These findings underscore significant demographic, cognitive, and health-related differences associated with arthritis in older adults across the cohorts (Fig. 1) (Supplementary Tables S3–S5).

The overall association between domain-specific cognitive performance and odds of physician-diagnosed arthritis was first examined using GEE with an exchangeable correlation structure. In the fully

adjusted GEE models, impaired executive function emerged as the cognitive domain significantly associated with elevated arthritis risk across all 3 cohorts. Specifically, each 1-standard deviation (SD) decrement in executive score corresponded to a 1.000-fold increase in odds of arthritis in CHARLS (OR 1.000, 95% CI 1.000–1.001, $P = 0.016$), a 1.13-fold increase in HRS (OR 1.13, 95% CI 1.01–1.28, $P = 0.037$), and a 1.07-fold increase in ELSA (OR 1.07, 95% CI 1.02–1.12, $P = 0.009$). In contrast, neither memory nor orientation scores demonstrated significant associations with arthritis (all $P > 0.10$), and the total cognition score models lacked consistent significant associations across cohorts (Supplementary Table S1, Fig. 2).

To assess the robustness of these findings when accounting for intra-individual variability, the authors fitted GLMM with random intercepts for participant ID. The GLMM results paralleled those of the GEE analyses, further underscoring the specific role of executive impairment in arthritis risk. In HRS, a 1-SD lower executive score was associated with a 1.13-fold higher odds of arthritis (OR 1.13, 95% CI 1.02–1.26, $P = 0.021$), whereas CHARLS and ELSA yielded ORs of 1.17 (95% CI 1.05–1.32, $P = 0.007$) and 1.07 (95% CI 1.03–1.11, $P = 0.0003$), respectively. Neither memory nor orientation domains reached statistical significance under the GLMM framework (all $P > 0.05$), and the total cognition GLMM estimates remained consistent in HRS but imprecise in CHARLS and ELSA ($P > 0.05$). These parallel analytic approaches confirm that the observed executive–arthritis association is not an artifact of model selection or unmeasured individual-level heterogeneity (Supplementary Table S2, Fig. 3).

In sensitivity analyses, the authors first varied the GEE working correlation structure to independence and AR-1 specifications. Across CHARLS, HRS, and ELSA, the inverse relationship between executive function and arthritis remained robust: each 1-SD decrement in executive score continued to predict significantly higher odds of arthritis under both independence and AR-1 structures (all $P < 0.01$). By contrast, when overall cognition was recoded into tertiles (low, middle, high), no significant associations emerged in any cohort (all $P > 0.10$), confirming that the tertile categorisation attenuated the effect. These findings underscore that the executive-domain result is not an artifact of the chosen correlation matrix and that dichotomising or trichotomising global cognition obscures the specific executive–arthritis linkage observed in the main analyses (Supplementary Table S6).

DISCUSSION

In this large, multinational cohort analysis of 51,648 adults aged ≥ 50 years from CHARLS, HRS, and ELSA,

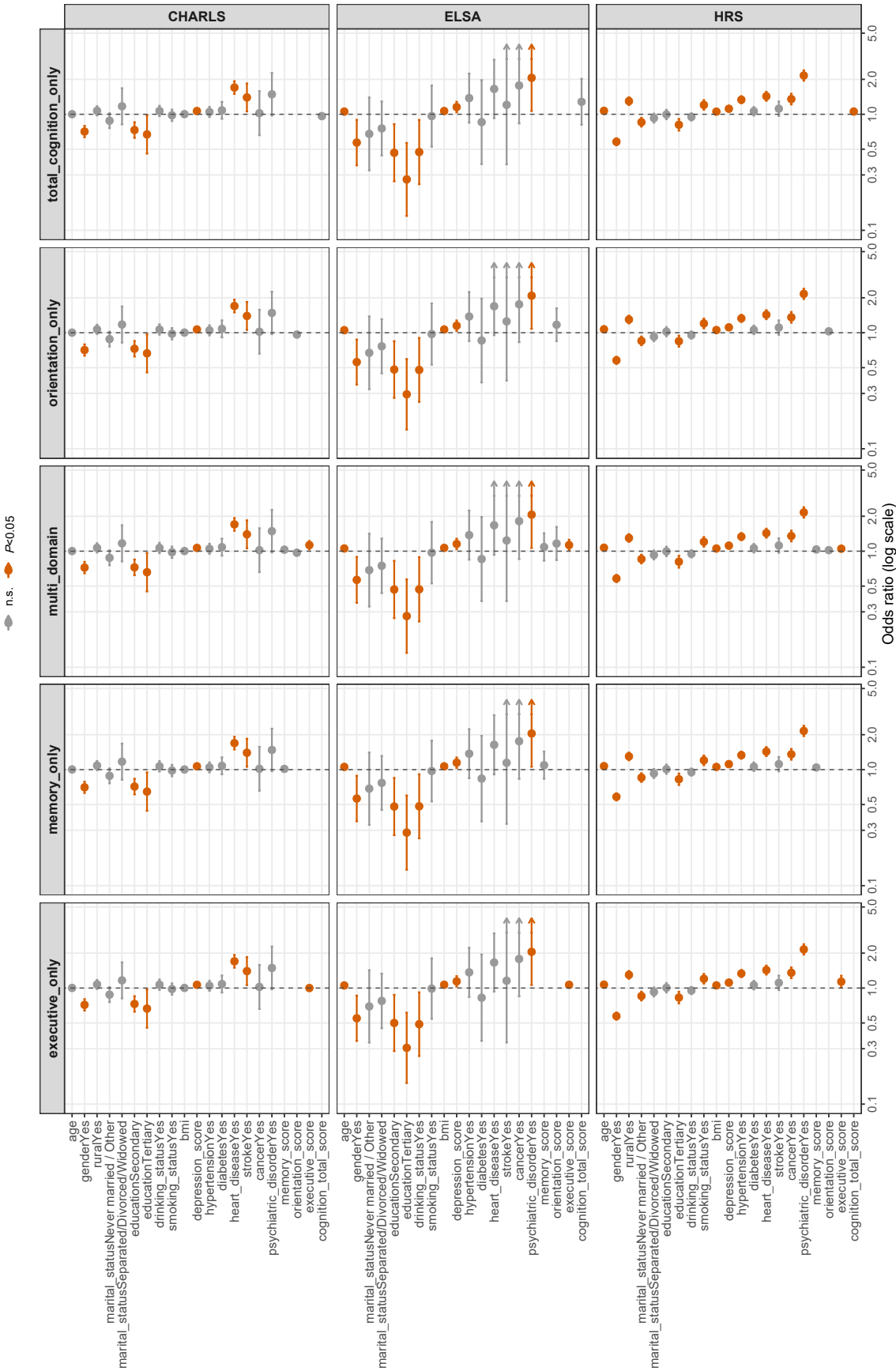


Fig. 2. Associations between cognitive function and arthritis in CHARLS, HRS, and ELSA using GEE.

BMI: body mass index; CHARLS: China Health and Retirement Longitudinal Study; ELSA: English Longitudinal Study of Ageing; GEE: Generalised Estimating Equations; HRS: Health and Retirement Study; OR: odds ratio

Results are derived from 5 GEE models per dataset (15 models total), adjusted for covariates including age, gender, rural residence, marital status, education, drinking status, smoking status, BMI, depression score, hypertension, diabetes, heart disease, stroke, cancer, and psychiatric disorders, with an exchangeable correlation structure. The x-axis displays ORs on a logarithmic scale, while the y-axis lists cognitive domains and datasets. Significant correlations ($P < 0.05$) are marked with orange dots and non-significant correlations are marked with grey dots.

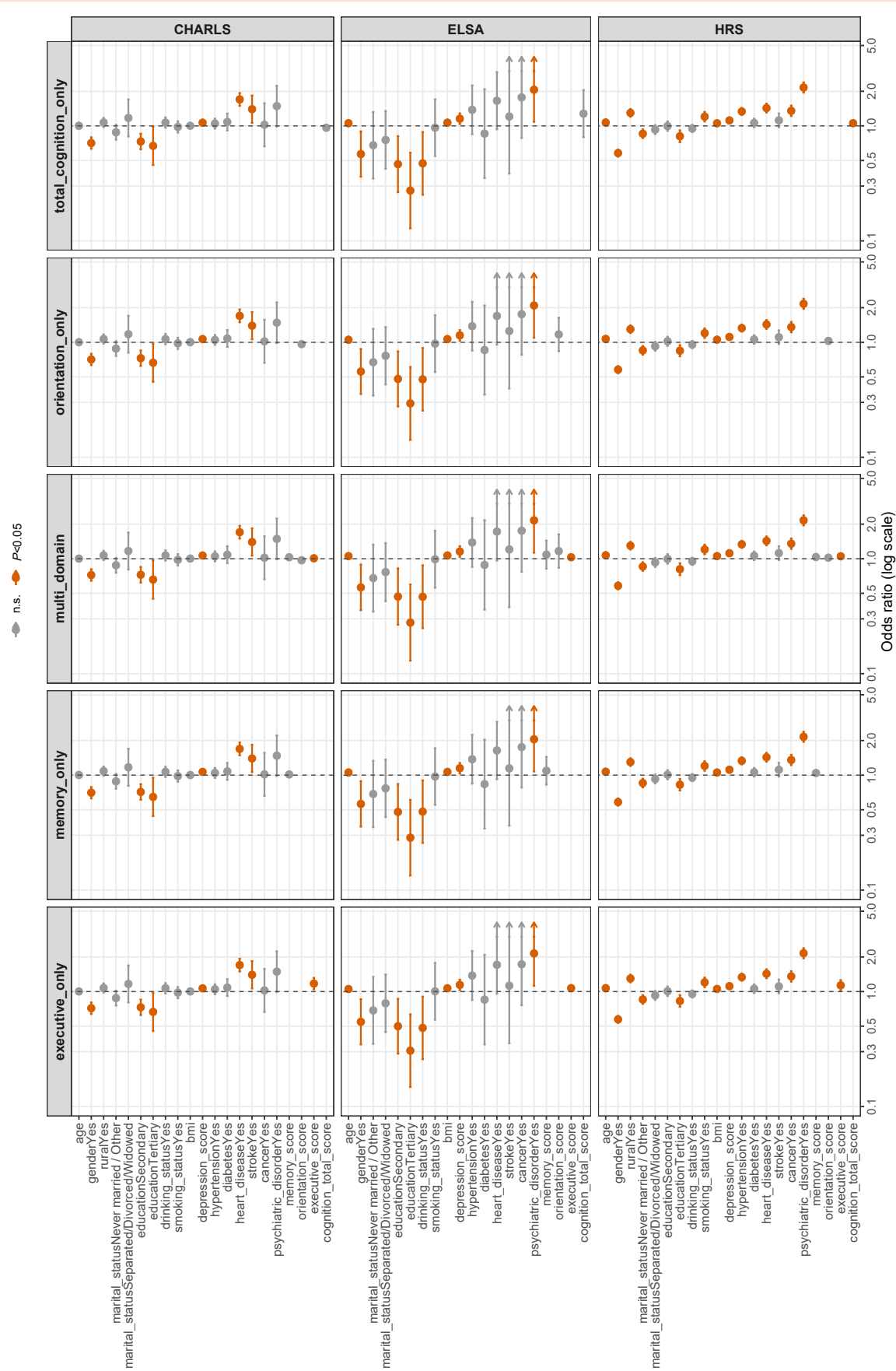


Fig. 3. Associations between cognitive function and arthritis in CHARLS, HRS, and ELSA using GLMM.

BMI: body mass index; CHARLS: China Health and Retirement Longitudinal Study; ELSA: English Longitudinal Study of Ageing; GLMM: Generalised Linear Mixed Models; HRS: Health and Retirement Study; OR: odds ratio

Models are adjusted for the same covariates as in the GEE analysis: age, gender, rural residence, marital status, education, drinking status, smoking status, BMI, depression score, hypertension, diabetes, heart disease, stroke, cancer, and psychiatric disorders. The x-axis shows ORs on a logarithmic scale, and the y-axis categorises results by cognitive domain and dataset. Significant correlations ($P<0.05$) are marked with orange dots and non-significant correlations are marked with grey dots.

a consistent, independent association between lower executive function and higher odds of physician-diagnosed arthritis was observed across 3 culturally distinct populations. Each 1-SD decrement in executive function predicted a 7–17% increase in arthritis risk, findings that were robust across GEE and GLMM frameworks and persisted under alternative correlation structures. Notably, neither episodic memory nor orientation exhibited significant associations after full adjustment, and global cognition showed only a significant positive trend in HRS. These results highlight the specificity of executive dysfunction as a correlate of arthritis, suggesting that processes subserved by prefrontal networks may be particularly vulnerable to the systemic and behavioral sequelae of joint disease.

Comparison with previous studies

The results align with emerging evidence that systemic joint disease may herald or exacerbate cognitive decline. A recent Korean longitudinal study found that individuals with cognitive impairment had a 47.6% incidence of arthritis over 12 years vs 30.1% for those with normal cognition, underscoring bidirectional risk.¹⁵ A recent meta-analysis demonstrated that OA confers a 1.25- to 1.80-fold elevated risk of dementia, alongside neuroimaging evidence of focal cerebral atrophy.^{16,17} In RA, patients exhibited higher rates of cognitive impairment—up to 71% in some cohorts—linked to chronic inflammation and white matter changes.^{18,19} This study complements these findings by focusing on arthritis as a predictor rather than cognitive decline, and by controlling for a comprehensive set of confounders, including depressive symptoms and cardiovascular comorbidities.

Potential mechanisms

Multiple pathways may underpin the cognitive–arthritis nexus. First, chronic inflammation is a shared hallmark; elevated C-reactive protein (CRP) and interleukin-6 in RA patients have been associated with poorer executive and memory performance.²⁰ Low-grade systemic inflammation was also linked to long-term cognitive decline in a community-based cohort of 2000 adults over 18 years.^{21–23} Second, persistent pain inherent to OA and RA can disrupt sleep and increase depressive symptoms, both detrimental to cognition; rodent models of OA demonstrate measurable deficits in object recognition tasks following joint pain induction.²⁴ Third, arthritis often curtails physical activity and social engagement—behaviours shown to bolster cognitive reserve—suggesting that reduced stimulation may accelerate cognitive ageing.²⁵ Finally, arthritis treatments may modulate neuroinflammation; disease-modifying antirheumatic drugs and tumor necrosis factor (TNF) inhibitors have shown promise in reducing neuroinflammatory markers and improving cognitive metrics in pilot studies.^{20,26}

Strengths and limitations

The key strengths of this study include the use of 3 nationally representative cohorts with harmonised cognitive and arthritis measures, long follow-up, and rigorous sensitivity analyses confirming the stability of the findings. By employing both GEE and GLMM, the authors accounted for within-person correlation and unobserved heterogeneity. However, certain limitations merit consideration. The observational design precludes causal inference, and residual confounding—particularly by unmeasured factors such as pain severity, specific medication use (e.g. analgesics), and objective physical activity levels—cannot be excluded. Dementia incidence was not uniformly defined across cohorts, potentially introducing misclassification, although the primary focus on executive–arthritis associations reduces dependence on dementia ascertainment. Reverse causality is another concern. Early executive declines might impair arthritis self-management, reducing treatment adherence and leading to worse joint outcomes. Nonetheless, sensitivity analyses excluding early arthritis cases produced similar estimates, mitigating this possibility. Last, cognitive domain measures varied slightly by cohort (e.g. absence of orientation subscale in ELSA), although consistent executive associations across datasets suggest robustness. Furthermore, the reliance on self-reported physician diagnosis of arthritis may introduce non-differential misclassification. However, such bias would likely push the observed associations toward the null, suggesting that the true relationship between executive function and arthritis might be even stronger than reported here.

Clinical and public health implications

The findings have several practical implications. First, clinicians managing older adults with arthritis should be alert to potential concomitant cognitive deficits and consider routine cognitive screening, as early identification may facilitate interventions to preserve function. While the individual-level effect sizes observed in this study are modest (e.g. ORs ranging from 1.07 to 1.17), the high prevalence of both arthritis and cognitive decline in ageing populations means that this association translates into a substantial clinical and public health burden. Second, integrated strategies targeting inflammation and pain management—such as optimised use of disease-modifying anti-rheumatic drugs or non-steroidal anti-inflammatory drugs (NSAID)—could yield cognitive benefits, as suggested by a 12% reduction in dementia risk among long-term NSAID users in a Rotterdam study.²⁷ Third, interventions promoting physical activity and social participation in arthritis populations may confer dual benefits for joint health and cognitive

resilience. Finally, public health efforts should emphasise arthritis prevention and early treatment as part of broader dementia risk-reduction frameworks.

Future directions

Prospective trials are needed to test whether arthritis therapies can slow cognitive decline. Mechanistic studies should elucidate the relative contributions of systemic vs neuroinflammation, perhaps leveraging imaging biomarkers and cerebrospinal fluid analyses. Additionally, research exploring genetic predispositions linking arthritis and Alzheimer's-type pathology—such as the role of human leukocyte antigen DR (HLA-DR) alleles—could reveal novel therapeutic targets. Finally, expanding cross-cultural studies to low- and middle-income settings will clarify the generalisability of the cognitive–arthritis link and inform resource-appropriate interventions.

CONCLUSION

Across 3 major ageing cohorts, impaired executive function emerged as a specific and consistent correlate of arthritis in middle-aged and older adults. This executive–arthritis link likely reflects intertwined pathways of pain, systemic inflammation, and physical inactivity, with significant implications for identifying at-risk individuals and designing targeted interventions. Addressing executive deficits in arthritis care may offer a valuable strategy to preserve both joint and cognitive health in ageing populations.

Supplementary materials

Table S1. Summary of GEE model results for the association between cognitive function and arthritis in CHARLS, HRS, and ELSA.

Table S2. Summary of GLMM model results for the association between cognitive function and arthritis in CHARLS, HRS, and ELSA.

Table S3. Baseline characteristics of the study population in CHARLS (n=18,562).

Table S4. Baseline characteristics of the study population in HRS (n=23,238).

Table S5. Baseline characteristics of the study population in ELSA (n=9848).

Table S6. Sensitivity analysis of the association between cognitive function and arthritis using GEE models with different specifications in CHARLS, HRS, and ELSA.

Ethics statement

CHARLS, HRS, and ELSA each obtained approval from their institutional review boards, and informed consent was secured from all participants at the time of data collection. This analysis employed anonymised, publicly

accessible datasets, obviating the requirement for further ethical clearance.

Declaration

The authors have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. There is no conflict of interest and funding to declare. Generative artificial intelligence (AI) tools were used in the preparation of this manuscript for tasks such as improving grammar, refining language, and suggesting phrasing. The authors retain full responsibility for the scientific analysis, interpretation of results, and conclusions. No AI was involved in data analysis or the generation of scientific content.

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REFERENCES

1. United Nations. World population ageing, 2019: highlights. <https://digitallibrary.un.org/record/3846855>. Accessed 10 May 2025.
2. Alzheimer's Disease International. World Alzheimer Report 2019: Attitudes to dementia, 20 September 2019. <https://www.alzint.org/resource/world-alzheimer-report-2019/>. Accessed 10 May 2025.
3. US Centers for Disease Control and Prevention. Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation — United States, 2013–2015. <https://www.cdc.gov/mmwr/volumes/66/wr/mm6609e1.htm>. Accessed 10 May 2025.
4. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol* 2011;93:385–404.
5. Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol* 2015;14:388–405.
6. Sofi F, Valecchi D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med* 2011;269:107–17.
7. Katz MJ, Lipton RB, Hall CB, et al. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia and Alzheimer's dementia in blacks and whites: a report from the Einstein Aging Study. *Alzheimer Dis Assoc Disord* 2012;26:335–43.
8. Wallin K, Solomon A, Kåreholt I, et al. Midlife rheumatoid arthritis increases the risk of cognitive impairment two decades later: a population-based study. *J Alzheimers Dis* 2012;31:669–76.
9. Zhao Y, Hu Y, Smith JP, et al. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). *Int J Epidemiol* 2014;43:61–8.
10. Sonnega A, Faul JD, Ofstedal MB, et al. Cohort Profile: the Health and Retirement Study (HRS). *Int J Epidemiol* 2014;43:576–85.
11. Steptoe A, Breeze E, Banks J, et al. Cohort profile: the English longitudinal study of ageing. *Int J Epidemiol* 2013;42:1640–8.

12. Hootman JM, Helmick CG, Barbour KE, et al. Updated Projected Prevalence of Self-Reported Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation Among US Adults, 2015–2040. *Arthritis Rheumatol* 2016;68:1582-7.
13. De Looze C, Feeney J, Seeher KM, et al. Assessing cognitive function in longitudinal studies of ageing worldwide: some practical considerations. *Age Ageing* 2023;52:iv13-25.
14. DeRuiter S. Chapter 16 Correlation Structures I STAT 245 Course Notes. https://stacyderuiter.github.io/s245-notes-bookdown/correlation-structures.html?utm_source=chatgpt.com. Accessed 10 May 2025.
15. Kim JI, Kang B. A comparative retrospective longitudinal study of arthritis risk and cognitive decline in older adults. *Sci Rep* 2024;14:24739.
16. Guo R, Ou YN, Hu HY, et al. The Association Between Osteoarthritis with Risk of Dementia and Cognitive Impairment: A Meta-Analysis and Systematic Review. *J Alzheimers Dis* 2022;89:1159-72.
17. Guo R, Ou YN, Ma LY, et al. Osteoarthritis, osteoarthritis treatment and risk of incident dementia: a prospective cohort study based on UK Biobank. *Age Ageing* 2024;53:afae167.
18. Shin SY, Katz P, Wallhagen M, et al. Cognitive impairment in persons with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:1144-50.
19. Qidwai M, Ahmed K, Tahir MF, et al. Cognitive implications of rheumatoid arthritis: A call for comprehensive care and research focus. *Immun Inflamm Dis* 2023;11:e1065.
20. Mena-Vázquez N, Ortiz-Márquez F, Ramirez-García T, et al. Impact of TNF inhibitors on inflammation-associated cognitive dysfunction in patients with rheumatoid arthritis: a prospective analysis. *Front Med (Lausanne)* 2025;12:1561140.
21. Nicassio PM, Ormseth SR, Kay M, et al. The contribution of pain and depression to self-reported sleep disturbance in patients with rheumatoid arthritis. *Pain* 2012;153:107-12.
22. Tarasovs M, Skuja S, Svirskis S, et al. Interconnected Pathways: Exploring Inflammation, Pain, and Cognitive Decline in Osteoarthritis. *Int J Mol Sci* 2024;25:11918.
23. Fonseca-Rodrigues D, Rodrigues A, Martins T, et al. Correlation between pain severity and levels of anxiety and depression in osteoarthritis patients: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2021;61:53-75.
24. Lv T, Yu H, Ji Z, et al. The association between arthritis and cognitive function impairment in the older adults: Based on the NHANES 2011-2014. *PLOS One* 2024;19:e0310546.
25. Mekhora C, Lamport DJ, Spencer JPE. An overview of the relationship between inflammation and cognitive function in humans, molecular pathways and the impact of nutraceuticals. *Neurochem Int* 2024;181:105900.
26. Fazel SD, Carollo M, Tap L, et al. Impact of Disease-Modifying Antirheumatic Drugs on Cognitive Function in Older Adults with Rheumatoid Arthritis. *Drugs Aging* 2025;42:295-313.
27. Vom Hofe I, Stricker BH, Ikram MK, et al. Long-Term Exposure to Non-Steroidal Anti-Inflammatory Medication in Relation to Dementia Risk. *J Am Geriatr Soc* 2025;73:1484-90.

Serving as a medical expert witness: Avoiding common errors and potential pitfalls

Sin Yew Wong¹ MMed (Int Med)

ABSTRACT

The medical expert witness plays a crucial role in providing objective, informed opinions that can influence the outcome of court trials and disciplinary proceedings. It is critical for physicians and surgeons with specialised knowledge in the Singapore setting to provide relevant opinions to ensure fair and consistent outcomes when medical disputes occur in Singapore. This commentary draws from the author's experience to highlight common errors and potential pitfalls, which doctors may face in their capacity as an expert witness.

Keywords: avoid pitfalls, common errors, court attendance, expert witness, writing expert reports

INTRODUCTION

With rising education levels and affluence in Singapore, there has been an increase in the public's expectation for high standards of medical care, and greater transparency and accountability by both the medical profession as well as healthcare institutions. This has contributed towards a more litigious culture and consequently, the need for medical experts to provide independent opinions (referred to as the expert's report) in legal proceedings. Medical doctors in Singapore do not receive formal training in their undergraduate and postgraduate curriculum to serve as medical expert witnesses. Additionally, while clinical experience helps, it is often insufficient to equip oneself to serve as a medical expert witness in court and disciplinary tribunal (DT) proceedings.¹ Attending courses such as the medical expert witness training conducted by the Academy of Medicine, Singapore (in collaboration with the Singapore Medical Association, Singapore Academy of Law, and Law Society of Singapore), provide a guided learning experience through simulations in writing expert witness reports, oral testimony, and cross examination.

An effective medical expert witness is expected to understand the proper procedures in court or DT hearings, and also be able to communicate well. The contents of this commentary has been distilled

from the author's experience as both an expert witness, as well as chairman/member of DT proceedings. This commentary aims to serve as a primer to acting as a medical expert witness, and aims to help readers avoid common errors and pitfalls when acting as a medical expert witness.

The basic requirements

The necessary qualifications

In section 47 of the Evidence Act 1893,² and order 12 of the Rules of Court 2021,³ an expert is defined as a "person with scientific, technical or other specialised knowledge based on training, study or experience." Their role is to provide an independent and unbiased opinion about a particular factual issue relating to the case based on their specialised knowledge. In legal terms, the bar is not difficult to cross. Expert evidence is typically provided in a standardised, formal written medical expert report called an Affidavit of Evidence in Chief (AEC), as well as subsequent oral testimony in court or DT hearings. These are vital components in arriving at an equitable and fair decision in medical disputes.^{4,5}

A medical expert witness must therefore have the appropriate medical qualifications, relevant specialty training, and sufficient clinical experience. It may be helpful for the expert to include his or her relevant professional appointments and committee roles in professional medical organisations and with the Ministry of Health in their curriculum vitae submitted to counsel, the court, or tribunal.

In medico-legal cases where clinical care is often the subject of dispute, a well-published researcher who does not have significant clinical responsibilities arguably has less (but not no) credibility. Therefore, an expert's years of clinical practice in his or her specialty, with a strong track record of patient care will be invaluable when providing opinions which involve hands-on clinical care. This was illustrated in the Coroner's Inquiry into the death of Frankin Heng Ang Tee, where the State Coroner preferred the evidence of the expert who was an anaesthetist, given

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¹ Infectious Disease Partners, Singapore

Correspondence: Dr Sin Yew Wong, Infectious Disease Partners, 6 Napier Road, #05-13 Gleneagles Medical Centre, Singapore 258499.

Email: symswong@singnet.com.sg

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that the likely cause of death was asphyxia from airway obstruction rather than multiple iatrogenic punctures of the intestine during liposuction.²

In practice, expert witnesses will usually demonstrate their expertise by providing their expert opinion on specific medical issues in dispute. Ultimately, it will be the presiding judge and DT members who will determine if the evidence provided by the expert witness was useful in the proceedings. Alternatively, the expert witness may be criticised by the presiding judge if he or she was poorly prepared, illogical, or unconvincing in his or her testimony.⁶

Strong communication skills

A medical expert witness is often asked to explain complex medical concepts to judges, tribunal members, and lawyers who have little to no medical knowledge or training. Possessing strong and effective communication skills will help an expert to present their opinions clearly and persuasively. A cautionary note is appropriate when preparing an expert opinion, experts will have the benefit of hindsight. A complex case with hindsight bias may appear straightforward and easy to explain. Expert witnesses should therefore beware to avoid over-simplifying their opinions and instead, ensure that it is rendered within the proper context.

Understanding the legal process

Familiarity with the legal process, including the role of expert evidence and cross-examination, is likely to be helpful. For a more in-depth summary of the legal process, one can consider taking courses or attending seminars on what being an expert witness entails.

Staying current in one's field

Continuing education is crucial for an expert to maintain his credibility. Additionally, relying on the latest knowledge and practices helps one to ensure that their medical expert opinion remains accurate and grounded.

The work of the expert

Understanding medical negligence

As stated earlier, medical expert witnesses are only required in cases where the factual disputes involve specialised medical knowledge to resolve. The majority of such cases are those involving medical negligence. Medical negligence occurs when a healthcare professional fails to provide the standard of care expected in their field, resulting in harm to the patient. In many cases, this will involve being asked to evaluate whether the care provided met the accepted standards, and to identify any deviations that may

have led to the patient's poor outcome. These can be divided into 3 broad, but distinct categories:

- (1) **Misdiagnosis:** This involves incorrect or delayed diagnosis of a medical condition. An expert witness may be asked to assess whether the healthcare provider failed to recognise symptoms, order appropriate tests, or interpret test results accurately.
- (2) **Mismanagement:** This refers to the improper handling of a patient's treatment or care. Relevant facts include whether the healthcare provider followed the correct protocols, administered the right medications, and provided appropriate follow-up care.
- (3) **Departure from guidelines:** Related to the above, experts are typically asked to examine whether the healthcare provider had deviated from accepted practice standards or clinical guidelines in their management of the patient's condition. Readers should note however that clinical guidelines are meant to assist clinicians and should not be considered as setting determinative medicolegal standards. A useful expert opinion is one which differentiates between "errors of judgment" and "errors of clinical reasoning".

Dealing with diagnostic errors

Diagnostic errors often stem from faulty data collection or lack of synthesis of data. The expert witness is often asked to assess whether the healthcare provider collected sufficient data, interpreted it correctly, and made appropriate clinical decisions based on the information available.

The following considerations may help frame the common areas commonly examined in negligence cases.

Errors of judgment

Errors of judgment occur when a healthcare provider makes a decision that, in hindsight, may not have been the best choice, but was reasonable given the circumstances and information available at the time. These errors are often subjective and can be influenced by factors such as experience, intuition, and situational context. For example, a doctor might choose a particular treatment plan based on their professional judgment, even if another equally qualified doctor might have chosen a different approach. These errors are usually one-off events and are not repeated errors. Nevertheless, even a single error of judgment can have catastrophic consequences. In the case cited in Coroner's Inquiry 10/2010, the aesthetic physician was found guilty of professional misconduct by the DT. In the subsequent appeal process, the Court of

Three Judges stated that it “...was among the most egregious cases of medical cases we have come across” and struck the doctor from the medical register.⁷

Errors of clinical reasoning

Errors of clinical reasoning, on the other hand, involve flaws in the cognitive processes used to arrive at a diagnosis or treatment plan.⁸ These errors are more objective and can be traced to specific mistakes in data collection, interpretation, or synthesis. Clinical reasoning errors include:

- **Faulty data collection:** Failing to gather all relevant information, such as missing key symptoms or not ordering necessary tests.
- **Lack of data synthesis:** Inability to integrate and interpret the collected data correctly, leading to incorrect conclusions.
- **Misapplication of knowledge:** Applying medical knowledge incorrectly or failing to consider differential diagnoses.

Key differences between the different errors

In summary, the differences between the 2 kinds of errors are as follows:

- (1) **Subjectivity versus (vs) objectivity:** Errors of judgment are usually subjective and based on individual decision-making, while errors of clinical reasoning are objective and based on cognitive processes.
- (2) **Decision vs process:** Errors of judgment pertain to the final decision made by the healthcare provider, whereas errors of clinical reasoning pertain to the process leading up to that decision.
- (3) **Reasonableness vs flaws:** Errors of judgment can be reasonable given the circumstances, even if they were not the best choice in hindsight. However, this does not mean that they are excusable, especially if the error is particularly egregious. On the other hand, errors of clinical reasoning are inherently flawed and indicate a failure in the cognitive process.

Understanding the difference between these types of errors is essential in medical negligence cases. While errors of judgment may not necessarily constitute negligence if they were reasonable at the time, errors of clinical reasoning can be more clearly identified as deviations from accepted standards of care. For a more in-depth review of medical negligence, readers are referred to textbooks which cite cases in Singapore.^{9,10}

It is important to be mindful of hindsight bias and complexity of clinical care when reviewing the case records and how the case had evolved to result in a poor clinical outcome. In the context of medical care in Singapore, it is not common for a single event to result in a bad outcome.

The legal process

Medical negligence and professional misconduct

In medical disputes, the claimant usually makes a statement of claim (SOC) with medical negligence as a common or the main allegation. When the Singapore Medical Council (SMC) prosecutes a doctor in Singapore, the respondent doctor will be referred to the DT and the charge is usually for professional misconduct. The comments on medical negligence also apply to professional misconduct in DT proceedings. The medical expert witness is often asked if there was a breach of care and injury from medical negligence by the accused doctor. The medical expert witness provides the independent and unbiased opinion in the charges of professional misconduct in DT proceedings. It is important to clarify that it will be the DT members or presiding judge who will determine guilt and not the medical expert witness.

Preparing medical expert reports

Medical expert reports (in the form of AEIC) are the cornerstone of medical negligence cases. These reports provide detailed analysis and opinions on the medical aspects involved (Table 1). As a medical expert witness, one should be well-versed in:

- Reviewing charges (for criminal and DT proceedings) or SOC.
- Understanding the Letter of Instruction also known as LOI from appointed lawyers.
- Focusing on areas such as misdiagnosis, mismanagement, and departures from accepted practice standards in clinical management.

Table 1. Affidavit of Evidence in Chief checklist.

Upon receipt of a Letter of Instructions (LOI) and a first read of the relevant case notes, the following are practical considerations:	
☐	(1) Is there a conflict of interest?
☐	(2) Does the doctor have the relevant knowledge and expertise to serve as a medical expert witness in this particular case?
☐	(3) Can the timeline provided be met?
☐	(4) After the first read of the case notes, what type of errors (if any) were evident – misdiagnosis, mismanagement, miscommunication?
☐	(5) Did the respondent doctor's practice follow established guidelines and provide an acceptable level of care?
☐	(6) Provide references that predate the event in question and use them to support the opinion(s) sought.
☐	(7) Care must be taken to review the charges filed/Statement of Claim and the LOI again before answering the specific questions posed.
☐	(8) Communications to clarify the questions posed in the LOI may be necessary.
☐	(9) Beware of hindsight bias and the complexity of clinical care.
☐	(10) The primary function of the expert witness is to serve the court.

The requirements for a good expert witness report have been elaborated previously,² and is worthwhile highlighting and clarifying what it should contain and provide here:

- Details of the expert's qualifications and clinical experience.
- Provides and elaborates on medical literature or published guidelines which the expert has relied on; focusing as far as possible on Singapore data and the literature that was published before the event in question.
- Provides a statement setting out the issues which the experts have been asked to consider (Letter of Instruction) and the basis upon which the evidence was given (case notes, results of investigations, complaint letter, etc.)
- Where there is a range of opinion on the matters dealt with in the report, a summary of the range of opinions and the reasons for which the specific conclusions were reached.
- A summary of the conclusions reached.
- A statement of belief of correctness of the expert opinion.
- A statement that the expert understands that in giving the report, his or her duty is to the court, and that they have complied with the legal requirements of an expert's evidence set out in Order 12 Rule 5 of the Rules of Court.⁴

Testimony and giving evidence in court or DT

A well-written and well-researched AEIC which withstands logical analysis and is reasonable, may obviate the need to attend court. Based on anecdotal experience, more than half of the cases in which the author has acted as expert witness did not go to trial. The case had either been withdrawn (civil proceedings) or parties had opted for early negotiated settlement (alternative dispute resolution via mediation and arbitration) without the need the court proceedings to run its course.

When attending a High Court trial as a medical expert witness, the submitted AEIC would have been scrutinised extensively by the lawyers of the parties concerned before the trial. If there are controversies or disputes about the submitted opinion (which may be diametrically opposite to another expert witness), adequate references will be needed to support the opinion. When there is significant difference in opinions expressed by opposing expert witnesses, the evidence will be tested by oral testimony in court or DT proceedings. This was illustrated in *Goh Guan Sin v Yeo Tseng Tsai and National University Hospital* ("Goh Guan Sin") in which there was dispute among the defendant's factual witnesses' and numerous medical expert witnesses' interpretation of radiological

findings, specifically, on whether the haematoma seen was intra-axonal or extra-axonal and the amount of hematoma that was extra-axonal. The presiding judge reviewed the medical evidence and made the ruling to dismiss the claim by the plaintiff, with one of the reasons being that he preferred the evidence given by the defendant's expert witness over the plaintiff's expert (see in particular, *Goh Guan Sin* from [172] to [224]).¹¹

As dispute cases often take many months and sometimes years for the formal proceedings to begin, it is expected that the counsel will, prior to court or DT proceedings, engage their witnesses (including experts) to review their AEICs, familiarise the witnesses on the format of proceedings and where appropriate, discuss the expected line of questioning by the opposing counsel. However, the author notes that while the counsel may discuss possible questions that may be posed with the expert witness, they are not allowed to coach the expert on what answer he or she should give in court.

An expert should also be prepared to be asked questions outside the scope of the submitted AEIC. The presiding judge may need the expert's active participation in other areas as it is the judge who needs the independent expert witnesses' opinion to inform their ruling on the outcome of the case. In court, rather than refusing to go beyond their remit (i.e. the questions the expert was asked to address in their report), where appropriate, a reasonable and co-operative approach in answering such questions may assist the court, provided the expert remains independent, and cognisant of their role to assist the court.

However, this does not mean an expert has to entertain unreasonable questions from the counsel, and an expert can take comfort in the fact that the counsel who engaged them (and often times the presiding judge) will intervene during cross examination if the opposing counsel acts in an unreasonable or difficult manner.

In the author's experience, judges in Singapore usually accord respect to the medical expert witness, and will usually allow them to express and explain their opinion beyond a yes or no answer demanded by counsel. Some practical considerations during testimony include the following:

- Do not rush to answer the question posed.
- Do not anticipate or preempt the next question.
- Experts are allowed to clarify the question including asking counsel to refer to the specific section in the bundle of documents used in the proceedings.
- In answering, experts are allowed to refer to parts of their AEIC and the agreed "bundle of documents" used. However, they cannot refer to any personal notes or other external material

(i.e. anything that has not been exhibited in the proceedings).

- When answering, the expert should give their answer to the judge or DT chairperson, not to the lawyer who asked the question.
- Lawyers are trained to question witnesses (especially the expert witness) and their many years of court experience will often ensure their court craft is superior. Experts should therefore not be distracted by personal attacks on their qualifications and professional integrity. Opposing lawyers may use and discredit peripheral issues, elicit damaging assumptions or concessions, and magnify inconsistencies and minor mistakes.³
- An expert's participation in medical disputes will be important as Singapore contextual knowledge may at times be valuable in interpreting standards of practice in Singapore.¹

Things to note

Conflicts of interest

Fundamental to providing an unbiased and independent opinion as a medical expert witness is to ensure that there is no conflict of interest (COI). Put simply, COI arises when the legal duty to provide an unbiased and objective opinion, clashes with one's private interests. The COI may be actual, potential, or perceived. In the small and tight-knit Singapore medical community, merely knowing a doctor who is a potential defendant does not preclude one's involvement in a medicolegal case. It will be important to declare acquaintance level relationship. A potential COI may still be raised by opposing parties to discredit the opinion as non-independent, biased, and not credible.

Prepare for challenges

Being a medical expert witness can be challenging. One may face tough cross-examinations and scrutiny from opposing counsel. Prepare for these challenges by thoroughly reviewing case materials, practicing one's testimony, and staying calm under pressure.

Helping a friend or work colleague as an expert

An expert may be asked to assist a friend or work colleague to serve as a witness in a medico-legal case. Where the expert has a prior relationship with the doctor involved, particular care is needed to preserve independence and to distinguish clearly between factual, expert, and character evidence. Once the decision has been made to serve as a medical expert witness, a formatted AEIC should be submitted and preparations made to give testimony in court or DT. The opposing counsel may bring up the relationship as a conflict of interest and opinions rendered (written or verbal) as non-independent.

Assisting a friend or colleague with a written statement to attest to his or her good doctor skills—this will be considered as submission by a character witness. Such statements will usually not be taken as evidence in the court or tribunal proceedings, i.e. it will not be used to determine judgment of guilt. Character witness statements are however, considered during the sentencing stage as a mitigating factor.

Ethical considerations and medical judgment

The evidence from the medical expert witness does contribute to justice and uphold the ethical standards of medical practice in Singapore, especially when one is asked to weigh in on negligent or incorrect treatment. For DT, the charge of professional misconduct may not always relate to provision of medical care and can focus on ethical considerations in instances such as sexual misconduct, dishonesty, wrongful declaration, etc. In a case of overcharging, several SMC prosecution expert witnesses have provided oral testimony of over-charging. The case involved the Disciplinary Committee (the DT as it was previously called) and was referred for appeal with the Court of Three judges.¹² In their judgment, the Court "emphasise[d] that the ethical rule that a doctor must charge a fair and reasonable fee for his or her services" and "what constitutes a fair and reasonable fee for services rendered in any given situation would depend not only on the relevant facts but also on the views of experts in the particular field of practice concerned". Accordingly, the Court upheld the decision of the Disciplinary Committee.¹² In general, the court will be loath to interfere in the findings of the medical expert witness(es) as long as the evidence is logical and withstands scrutiny. In *Dr Khoo James v Gunapathy d/o Muniandy* [2002] SGCA 25 ("Khoo James"); the Court of Three Judges upheld the *Bolam-Bolitho* test and the principle that a judge should not be trying to "substitute his opinion for that of the doctor in the consultation room or operating chamber" and stated that "judges and lawyers should not play at being doctors".¹³

CONCLUSION

Becoming a medical expert witness requires a combination of medical expertise, legal knowledge, and strong communication skills. These considerations may help clinicians approach the role of expert witness more carefully and confidently. Such contributions will ensure an equitable and fair outcome to all affected parties. The duties of a medical expert witness are first and foremost to the court or tribunal, themselves (so that they do not lose credibility), and the party who engaged them, in that order. It is hoped that this commentary will offer a practical starting point for clinicians who may be asked to serve in this role.

Ethics statement

Not applicable, as no study participants were recruited.

Declaration

The author declares he has no affiliations with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

REFERENCES

1. Thirumoorthy, T. Why There Is a National Need for Trained Medical Expert Witnesses. SMA News, February 2017. https://www.sma.org.sg/UploadedImg/1655971290_CMEP.pdf. Accessed 14 January 2026.
2. *Inquest into the death of Franklin Heng Ang Tee* Coroner's Court, State Coroner, CI 10/2010 [186].
3. Supreme Court of Singapore. *Rules of Court 2021*, Order 12, Rule 5. <https://sso.agc.gov.sg/SL-Supp/S914-2021/>. Accessed 14 January 2026.
4. Sheares, J. The Role of the Medical Expert – A Medical Perspective (Part 1). SMA News, January 2015. [https://www.sma.org.sg/news/2015/January/the-role-of-the-medical-expert--a-medical-perspective-\(part-1\)](https://www.sma.org.sg/news/2015/January/the-role-of-the-medical-expert--a-medical-perspective-(part-1)). Accessed 14 January 2026.
5. Sheares, J. Writing the Expert Report and Testifying in Court (Part 2). SMA News, February 2015. <https://www.sma.org.sg/UploadedImg/files/Publications%20-%20SMA%20News/4702/Professionalism.pdf>. Accessed 14 January 2026.
6. *Chua Thong Jiang Andrew v Yue Wai Mun and another* [2015] SGHC119 [216]. https://www.elitigation.sg/gd/s/2015_SGHC_119. Accessed 6 April 2026.
7. *Wong Meng Hang v Singapore Medical Council* [2018] SGHC 253 [4]. https://www.elitigation.sg/gd/s/2018_SGHC_253. Accessed 6 April 2026.
8. Scott Ian. Errors in clinical reasoning : causes and remedial strategies. BMJ 2009;338:b1860.
9. SY Tan. Medical Malpractice: Understanding The Law, Managing The risk. Singapore: World Scientific Publishing; 2006.
10. Kumaralingam Amtirthalingam. Medical Negligence and the duty to advice – beyond autonomy. 2025. <https://law.nus.edu.sg/publications/medical-negligence-and-the-duty-to-advise-beyond-autonomy/>. Accessed 6 April 2026.
11. *Goh Guan Sin v Yeo Tseng Tsai and National University Hospital* [2019] SGHC274 [295]. https://www.elitigation.sg/gd/s/2019_SGHC_274. Accessed 6 April 2026.
12. *Lim Mey Lee Susan v Singapore Medical Council* [2013] SGHC 122 [53]. https://www.elitigation.sg/gd/s/2013_SGHC_122. Accessed 6 April 2026.
13. *James Khoo v Gunapathy d/o Muniandy* [2002] SGCA 25 [3]. https://www.elitigation.sg/gd/s/2002_SGCA_25. Accessed 6 April 2026.

Additive value of non-invasive haemodynamic and fluid profiling in emergency department congestive cardiac failure patients

Li Yang Loo¹ MRCP (UK), Zhenghong Liu² MCEM, Ivan Si Yong Chua² MCEM, Swee Han Lim² FAMS

Dear Editor,

Patient symptoms and physical signs often lag behind haemodynamic changes in conditions, such as heart failure and cardiogenic shock.¹ Haemodynamic parameters, including cardiac index (CI) and stroke volume index (SVI), have shown prognostic value, with goal-directed therapies improving outcomes like hospital length of stay.² However, physicians' ability to accurately estimate these parameters remains limited. Non-invasive haemodynamic monitoring devices are increasingly available in the clinical settings, offering detailed evaluation of complex parameters and facilitating targeted therapy. For example, impedance cardiography can differentiate cardiac from non-cardiac dyspnoea and guide treatment in chronic heart failure.³ Its utility has yet to be established in the emergency department (ED).

The Non-Invasive Cardiac System (NICaS, NI Medical, Israel) uses whole-body impedance cardiography to calculate cardiac output and correlates well with thermodilution methods.⁴ The authors conducted a prospective observational study at the Singapore General Hospital ED from February 2019 to August 2022, evaluating NICaS-derived parameters in patients with congestive cardiac failure (CCF). Adults ≥ 21 years presenting with recurrent or worsening dyspnoea attributable to heart failure were included, while those unable to consent, cooperate or perform NICaS measurements were excluded.

Haemodynamic measurements (systolic blood pressure [SBP], diastolic blood pressure [DBP], mean arterial pressure, heart rate [HR], CI, SVI, total peripheral resistance index [TPRI] and total body water [TBW]) were recorded at baseline and every 10 minutes for 1 hour. NICaS monitoring was performed after participant enrolment in the ED and not extended as patients may transfer out of the ED. Demographics, medical history, chronic medications, laboratory values, interventions, disposition, length of stay, 30-day readmissions and mortality were also collected. Linear regression, Student's t-tests, Mann-Whitney U tests and analysis of variance

analyses were performed to evaluate associations between haemodynamic parameters, comorbidities, chronic medications and clinical outcomes.

A total of 148 patients were recruited (Supplementary Table S1). All except 1 were admitted; 131 were admitted to the general ward while 16 required high-dependency or intensive care. There were 8 occurrences of 30-day mortalities (5.4%). Compared with NICaS reference ranges for normal, patients with CCF showed elevated HR, TPRI and TBW, while CI and SVI were within NICaS reference ranges. TBW was significantly associated with 30-day mortality (odds ratio [OR] 1.375–36.642, $P=0.005$), with an optimal cut-off of 62.5% predicting mortality (sensitivity 85%, specificity 70%, area under receiver operating characteristic curve 0.828). Other non-invasive parameters (CI, SVI, TPRI) and traditional vital signs did not predict mortality (Supplementary Tables S2 and S3).

Non-invasive parameters did not differ significantly when comparing patients requiring intensive care with those who did not, while increased TBW was associated with 30-day mortality. Non-invasive parameters were not predictive of ED reattendance. Multivariable analysis indicated that comorbidities and chronic medications influenced haemodynamic readings: hypertension was linked to higher SBP and TPRI; ischaemic heart disease to lower HR and CI; chronic kidney disease to higher CI and SVI; angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) to lower HR; and calcium channel blockers to lower HR but higher SVI. Other comorbidities and medications showed no significant effect (Supplementary Table S4).

The study demonstrates substantial heterogeneity in haemodynamic profiles generated by the NICaS among CCF patients, with coefficients of variation ranging from 18–43%, consistent with previous data.⁵ TBW was robustly associated with 30-day mortality, reflecting its potential as a prognostic marker. This aligns with prior studies indicating TBW's long-term prognostic relevance.⁶ TBW assessment may help

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¹ Department of Internal Medicine, Singapore General Hospital, Singapore

² Department of Emergency Medicine, Singapore General Hospital, Singapore

Correspondence: Prof Swee Han Lim, Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608.

Email: lim.swee.han@singhealth.com.sg

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quantify severity, guide patient counselling and suggest to the clinician difficulties in managing fluid overload due to pump failure or impaired renal clearance. Unlike traditional physical signs like lung crepitations or peripheral oedema which may be absent in half of patients with high jugular venous pressure,¹ TBW provides an objective measure of fluid status, reflecting the severity of decompensation. In the ED, non-invasive devices like NICaS can rapidly generate multiple haemodynamic parameters without the risks associated with invasive monitoring, offering a practical and safe approach to assessing acutely decompensated patients. This study underscores the potential for non-invasive haemodynamic monitoring to complement conventional ED triage and clinical scoring systems. Objective parameters like TBW and TPRI could be incorporated into future risk stratification models to identify patients at higher risk of adverse outcomes early. Integrating such technology into ED workflows may enhance clinical decision-making, optimise resource allocation and reduce delays in appropriate heart failure management.

Interventions such as diuretics may rapidly alter CI, SVI and TPRI, limiting their prognostic value in the ED,⁷ whereas TBW changes more slowly, retaining its relevance. Other studies have reported associations between SVI, CI and long-term outcomes, but differences in sample size, follow-up duration and patient selection likely explain the discrepancies with this study.⁸ ACE inhibitors or ARBs were associated with a significant reduction in HR, underscoring how chronic medications can directly influence non-invasive haemodynamic measurements and should be considered when interpreting these parameters in patients with CCF.⁹ Lower body weight was associated with higher mortality, suggesting a protective role of non-fluid body mass and highlighting the need to study sarcopenia and weight optimisation in CCF.¹⁰

Limitations of this study include convenience sampling, exclusion of critically ill or obtunded patients, a short monitoring duration, and lack of beat-to-beat analysis. Despite these constraints, the data provide baseline measurements, confirm the feasibility of non-invasive monitoring and suggest TBW as a potential prognostic marker. Several measures were taken to minimise bias: standardised data collection forms ensured consistent recording of variables while all haemodynamic readings were captured automatically by the device, eliminating observer variability. Although convenience sampling may limit external validity, the broad inclusion of patients across multiple years enhances representativeness of the Singapore CCF population. Further studies with larger cohorts, longer monitoring and subgroup analyses are planned to define the utility of non-invasive haemodynamic

parameters in diagnosis, therapy guidance and prognostication in CCF.

In conclusion, non-invasive haemodynamic monitoring using NICaS is feasible in the ED and may provide valuable information for patient-specific prognostication in CCF. TBW appears particularly promising as a prognostic indicator for short-term mortality. Integrating haemodynamic assessment with clinical history, comorbidities and chronic medications is essential, and future research should explore its role in targeted therapeutic strategies.

Ethics statement

Ethics approval was granted by SingHealth Centralised Institutional Review Board (2017-2866).

Declaration

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Supplementary materials

Table S1. Baseline demographics, medical history, chronic medications and outcome measures of patients enrolled.

Table S2. Initial haemodynamic parameters for patients in congestive cardiac failure.

Table S3. Comparison of parameters against outcomes.

Table S4. Linear regression of haemodynamic parameters against comorbidity or use of chronic medication.

Keywords: emergency medicine, heart failure, mortality, non-invasive haemodynamic monitoring, total body fluid profile

REFERENCES

1. Stevenson LW, Perloff JK. The Limited Reliability of Physical Signs for Estimating Hemodynamics in Chronic Heart Failure. *JAMA* 1989;261:884-8.
2. Napoli AM, Corl K, Gardiner F, et al. Prognostic value of noninvasive measures of contractility in emergency department patients with severe sepsis and septic shock undergoing early goal-directed therapy. *J Crit Care* 2011;26:47-53.
3. Marrocco A, Eskin B, Nashed A, et al. Noninvasive bioimpedance monitoring differentiates cardiogenic from pulmonary causes of acute dyspnea in the emergency department. *Acad Emerg Med* 1998;5:476-7.
4. Taniguchi Y, Emoto N, Miyagawa K, et al. Noninvasive and simple assessment of cardiac output and pulmonary vascular resistance with whole-body impedance cardiography is useful for monitoring patients with pulmonary hypertension. *Circ J Off J Jpn Circ Soc* 2013;77:2383-9.

5. Nowak RM, Reed BP, DiSomma S, et al. Presenting phenotypes of acute heart failure patients in the ED: Identification and implications. *Am J Emerg Med* 2017;35:536-42.
6. Sasmita BR, Zhao Y, Gong M, et al. Edema Index Predicts Mortality in Patients with Chronic Heart Failure: A Prospective, Observational Study. *Glob Heart* 2024;19:5.
7. Pickkers P, Dormans TPJ, Russel FGM, et al. Direct Vascular Effects of Furosemide in Humans. *Circulation* 1997;96:1847-52.
8. Matter MA, Shamshiev M, Laumer F, et al. Left ventricular stroke volume index outperforms ejection fraction in predicting 1-year mortality in patients with acute heart failure - data from the SwissHeart Failure Network (SHFN). *Eur Heart J* 2023;44:ehad655.943.
9. Ader R, Chatterjee K, Ports T, et al. Immediate and sustained hemodynamic and clinical improvement in chronic heart failure by an oral angiotensin-converting enzyme inhibitor. *Circulation* 1980;61:931-7.
10. Beltrami M, Fumagalli C, Milli M. Frailty, sarcopenia and cachexia in heart failure patients: Different clinical entities of the same painting. *World J Cardiol* 2021;13:1-10.

Talk to the bot: A scoping review on using AI-powered transcription tools in qualitative research

Ying Jun Lim^{1,2} MD, Ngiam Chuan Tan^{2,3} FAMS

Dear Editor,

Untangling complex social phenomena for health-related problems relies on qualitative research methods like one-to-one in-depth interviews and focus group discussions.¹ However, transcription of these interviews and discussions is costly, labour-intensive² and prone to errors.¹ Furthermore, manual transcription is translational. The transcriber interprets the interview during transcription, inevitably incorporating their own biases during the act of translation,³ affecting subsequent analyses.

Artificial intelligence (AI)-powered transcription tools are set to replace manual transcription. However, there are doubts about the reliability and validity of the transcription, especially in healthcare research. Thus, to understand the usability of AI transcription tools in real-world research settings, researchers need to assess whether these tools can meet their specific needs. This study conducted a scoping review to summarise the studies that have evaluated AI transcription tools for qualitative interviews, and created a guide to help healthcare researchers choose a suitable tool.

A literature search conducted on 2 May 2025 on PubMed, JSTOR and IEEE, generated 6, 83 and 790 hits, respectively. The following search terms were used: ("text analytics" or "text analysis" or "speech analysis" or "speech to text" or "automated speech recognition" or "speech processing" or "visual analytics" or "video analysis") AND ("research interview" or "qualitative interview" or "qualitative research" or "qualitative data") in all fields. Ten additional articles identified via a Google Scholar search were also included. A total of 886 articles were identified after removing duplicates. After excluding articles for reasons such as the study not involving transcription, qualitative research interviews, or being descriptive technical papers, 9 comparative analysis studies were identified.

These 9 articles used 11 different automatic speech recognition tools. Seven studies were published from 2024 to 2025, 1 in 2017 and 1 in 2018. Three studies

transcribed interviews in multiple languages,^{1,4,5} 3 involved interviews conducted in English,^{2,3,6} and the rest were conducted in German,⁷ Indonesian⁸ and Swedish.⁹ Majority involved one-on-one interviews, with 1 study involving both one-on-one and group interviews.²

AI transcription tools were relatively accurate in transcribing interviews, with 8 out of 9 studies supporting its use. The accuracy varied with language, with English interviews unsurprisingly performing best.^{1,5} Audio conditions (e.g. minimal background noise, no crosstalk)^{1,2} and speech (e.g. not heavily accented, slow tempo)³ also improved accuracy. Some researchers found that these errors did not have a significant impact on meaning, and were easily rectified.^{2,6}

Conducting qualitative research in the healthcare setting presents an additional challenge. Medical jargon, colloquial language and non-verbal or tonal cues limit the accuracy of these tools.^{1,2,7,9} More dangerously, biases inherent to the training methods of AI tools reinforce stereotypes. Bircan and Ceylan observed errors (e.g. substitution, insertion errors) that resulted in biases, which reinforced Orientalist and Islamophobic stereotypes.⁴ For instance, "staying in Arab countries is difficult with no visa" was erroneously transcribed to "staying in Arab countries is difficult with all these conflicts."

AI transcription tools can lead to considerable cost and time savings. Eftekhari³ saved GBP3772 from allocated transcribing costs by using Microsoft Teams (Microsoft, Redmond, WA, US), a free tool. KALDI (<http://github.com/kaldi-asr/kaldi>) transcribed at 1.1 times the recording duration¹ Microsoft Teams almost instantaneously³ and Google's Speech-to-Text about 7 times faster than humans.⁷

However, these time savings were, in turn, spent correcting the transcripts manually. Tolle et al. reported correction time ranging from 1.7-fold for Portuguese to 16-fold for Tamil,¹ while Eftekhari required 1.5–3.5 hours correcting interviews averaging 65 minutes.³

AI transcription tools were generally easy to use, with positive feedback. Participants, despite most

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¹ SingHealth Family Medicine Residency Programme, Singapore

² Department of Research, SingHealth Polyclinics, Singapore

³ Duke NUS Medical School, Singapore

Correspondence: Dr Ying Jun Lim, Department of Research, SingHealth Polyclinics, 167 Jalan Bukit Merah, Connection One, Tower 5, #15-10 Singapore 150167. Email address: yingjun.lim@mohh.com.sg

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having no or limited experience with these tools, could independently install the software and use the tools.^{1,8} Tolle et al.'s participants evaluated the tool highly, scoring it 4.42 (standard deviation [SD] 0.90) on perceived usefulness and 4.50 (SD 0.80) on likeliness of future use via 5-point Likert scales.¹

Healthcare research contains especially sensitive data. Researchers can maintain privacy by ensuring that data are kept locally.¹ Cloud- and website-based tools, such as Microsoft Teams and Google's Speech-to-Text, require data upload to external servers, introducing security risks.^{2,5} Researchers should also evaluate vendors' security protocols and compliance with privacy regulations such as the Health Insurance Portability and Accountability Act, and choose vendors that have the necessary approvals and passed relevant security reviews.⁵

Researchers need to prioritise the features of different AI transcription tools to align with the research team's needs. For instance, in dealing with sensitive healthcare data, an AI transcription tool with local data storage offers better security, but requires additional hardware and programming expertise. Paid tools generally offer a more seamless experience and better integration with downstream data analysis software,

but can be costly, cloud-based and therefore susceptible to security breaches. Cloud-based tools should not be considered when working with highly sensitive data, as they require uploading of recordings and may monetise data, compromising participant anonymity.^{10,11} Clinical researchers can consider free or low-cost options, such as aTrain,¹² NoScribe (<https://github.com/kaixxx/noScribe?tab=readme-ov-file>) and MacWhisper (<https://goodsnooze.gumroad.com/l/macwhisper>).

Transcription of interviews that feature technical or colloquial language, strong accents or controversial topics tend to be prone to inaccuracies, leading to higher word error rates (WER). Correcting a transcript with WER >20% can be time-consuming, requiring up to 4-fold the recording time.⁹ Urban and Mehrotra suggested that the research team should consider additional training and customisation of the tool if WER >30%, though not all teams have such resources.¹³

Choosing an AI transcription tool can be a complicated process, especially for the uninitiated. Post-marketing assessments of commercial AI tools are inherently biased, and researchers should aim to assess tools independently. This study proposes a

Table 1. Main considerations in selecting an AI transcription tool for interviews in qualitative research.

Criteria	Considerations	Key queries in selecting an AI transcription tool
Accuracy and reliability	Error rate	What is the language-specific word error rate of the tool? Can it recognise technical or field-specific terminology with ease?
	Speaker differentiation	Can the tool recognise and tag multiple speakers accurately, especially in group settings? Are the strategies in place to improve speaker attribution (e.g. editing speaker attribution during live transcription to improve accuracy)?
	Languages, dialects, accents and speech patterns	How many languages/dialects can it support? Can it recognise multilingual conversations with ease? Can it recognise accented speech or different speech patterns with ease?
	Challenging speech conditions	Can the tool effectively handle interruptions, overlapping speech, unclear speech, background noise?
	Complex speech	Can the tool handle complex and layered dialogue? Is the tool able to identify underlying emotional tones or sentiment in the speech, and code them accordingly (e.g. sentiment analysis)?
	Biases	Is the transcription accuracy affected by systemic biases (e.g. gender, racial bias), which can result in lower transcription accuracy in these groups?
Ease of use	Ready to use	Is the tool ready to use, or is further programming needed?
	Hardware requirements	Is a separate microphone needed? Does the platform run locally or on the cloud? Is internet or intranet required? Does the platform run on mobile phone, tablet, laptop and/or desktop? Does the platform have high hardware requirements (e.g. RAM, memory space)?
	Collaboration	Is there a way for users on the platform to collaborate on the same project? Can varying degrees of rights be assigned to the different collaborators?

Table 1. Main considerations in selecting an AI transcription tool for interviews in qualitative research. (Cont'd)

Criteria	Considerations	Key queries in selecting an AI transcription tool
	Storage	Will the outputs be saved on the platform? How long will the outputs be available on the platform?
	User interface	Is the interface intuitive? Is complex training required? Are tutorials readily available? Is there an easy way to get technical assistance if problems are encountered?
Inputs and outputs	Inputs supported	Can it support live transcription? Is there an input limit for live transcription? Can it support uploading of audio and video files? Is there a limit to the size of audio or video file that can be uploaded? Is there a limit as to how many files can be uploaded?
	Outputs supported	What are the output formats supported (text, audio)? Can the outputs be exported with ease? Can the outputs be integrated seamlessly with other qualitative research software (e.g. NVivo [Lumivero, Denver, CO, US]) or is further processing needed?
Customisability	Transcription adjustments	Can the transcript be edited directly on the platform? If live transcription is possible, can editing be done during live transcription? Is there a way to easily review audio sections of the corresponding transcription (e.g. time stamping, replaying the audio when corresponding transcription is clicked)? If the tool does not allow for editing, can the output be edited easily using another software?
	Custom vocabulary	Can the tool be trained to recognise technical terms or jargon to improve transcription accuracy?
Time efficiency	Turnaround time	How long does it take to perform live transcription? How long does it take to transcribe an uploaded audio or video file? How long does it take to edit and correct the transcript?
	Batch processing	Can the tool handle large volumes of audio or video files simultaneously? How long will it take?
Cost effectiveness	Pricing structure	Is the tool free to use? How much does it cost per word/minute of transcription? Is the pricing on a subscription basis? Is the pricing transparent? Are there any hidden costs? Are there discounts for academic use? Is there a free trial available?
	Additional costs	Are there any additional costs incurred (e.g. purchasing hardware, editing transcript, obtaining relevant approvals)?
Data security	Data privacy	Is the tool local and does not require cloud services? Does the tool harness your data for large language model training, or reserve the right to use it for future purposes? What are the security measures in place to safeguard data? Has the platform obtained necessary approvals and passed relevant security reviews?
	Encryption	Does the service use encryption to protect data during transmission and storage?

framework of major considerations in selecting an AI transcription tool in Table 1.

Researchers should consider post-transcription strategies to “scrub” the AI-generated transcript. Some studies promote using AI transcription tools as a “good enough” first step, with manual cleaning for accuracy.^{1,2} Others suggest using another AI tool, such as ChatGPT, to clean the transcript, though

with caution.⁹ Researchers may opt for manual cleaning for recordings that are challenging for AI tools, such as those involving colloquial or technical language, which is usually the case for interviews conducted in Singapore as they often involve Singlish.

In conclusion, AI transcription tools offer significant time and cost savings in qualitative research, but researchers should address challenges such as

transcription quality, biases, security and trade-offs when selecting a tool. The authors hope that researchers can use Table 1 as a guide to selecting the most appropriate tool, but acknowledge that the considerations are not exhaustive, especially given the evolving nature of AI. Stricter guidelines to identify acceptable AI tools in research from regulatory bodies might aid in addressing these challenges.

Ethics statement

Not applicable as there are no study participants.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. This work was supported by the SingHealth Polyclinics-National Medical Research Council (NMRC) Centre Grant (CG21APR3006 [NMRC/CG3/001/2022-SHP]). During the preparation of this work, the authors used ChatGPT to improve readability of the text. After using this tool, the authors reviewed and edited the content and take full responsibility for the content of the published article.

Keywords: artificial intelligence, interview, qualitative research, tool, transcription

REFERENCES

1. Tolle H, Castro MDM, Wachinger J, et al. From voice to ink (Vink): development and assessment of an automated, free-of-charge transcription tool. *BMC Res Notes* 2024;17:95.
2. Bokhove C, Downey C. Automated generation of 'good enough' transcripts as a first step to transcription of audio-recorded data. *Methodol Innov* 2018;11:2059799118790743.
3. Eftekhari H. Transcribing in the digital age: qualitative research practice utilizing intelligent speech recognition technology. *Eur J Cardiovasc Nurs* 2024;23:553-60.
4. Bircan T, Ceylan D. Machine Discriminating: Automated Speech Recognition Biases in Refugee Interviews. *J Immigr Refug Stud* 2024;1-16.
5. Meanwell E, Walsh A, Berg P, et al. Automated Transcription Service: Enabling Transcription at Scale for Social Science Research. In: *Practice and Experience in Advanced Research Computing 2024: Human Powered Computing*. Providence RI USA: ACM; 2024.
6. Pfeifer VA, Chilton TD, Grilli MD, et al. How ready is speech-to-text for psychological language research? Evaluating the validity of AI-generated English transcripts for analyzing free-spoken responses in younger and older adults. *Behav Res Methods* 2024;56:7621-31.
7. Höhne JK, Lenzner T, Claassen J. Automatic speech-to-text transcription: evidence from a smartphone survey with voice answers. *Int J Soc Res Methodol* 2025;1-8.
8. Adianto R, Satriawan CH, Lestari DP. Transcriber: An Android application that automates the transcription of interviews in Indonesian. In: *2017 International Conference on Advanced Informatics, Concepts, Theory, and Applications (ICAICTA)*. Denpasar: IEEE; 2017.
9. Helin M. Evaluating the Accuracy of Automated Transcription using Open AI's Whisper Model for Swedish IT-Related Interviews: A Comparative Analysis with Manual Transcription, 2024. <https://urn.kb.se/resolve?urn=urn:nbn:se:du-49741>. Accessed 22 January 2025.
10. Da Silva J. Producing 'good enough' automated transcripts securely: Extending Bokhove and Downey (2018) to address security concerns. *Methodol Innov* 2021;14:2059799120987766.
11. Ong JCL, Chang SYH, William W, et al. Ethical and regulatory challenges of large language models in medicine. *Lancet Digit Health* 2024;6:e428-32.
12. Haberl A, Fleiß J, Kowald D, et al. Take the aTrain. Introducing an Interface for the Accessible Transcription of Interviews. *J Behav Exp Finance* 2024;41:100891.
13. Urban E, Mehrotra N. Test accuracy of a custom speech model, 2024. <https://learn.microsoft.com/en-us/azure/ai-services/speech-service/how-to-custom-speech-evaluate-data?pivots=speech-studio>. Accessed 22 January 2025.

Faculty-led mindfulness-based social-emotional learning workshops for radiology residents: Building self-awareness, resilience and community

Wenwen Ni¹ MD, Chaoyan Dong² PhD, Cynthia Assimta Peter¹ MBBS, Vidya Subrahmanya Upadhyaya¹ MD

Dear Editor,

Residency training is a formative yet demanding phase of medical education. Nearly 80% of residents experience burnout, which can harm mental health, academic performance and patient care. In the post-COVID era, physician well-being has received heightened attention. Mindfulness and reflective practices incorporating emotional learning within social contexts have been described in undergraduate and continuing medical education to reduce burnout.¹ However, literature on faculty-led, curriculum-integrated approaches tailored for residency training remains limited. This initiative applied mindfulness-based social-emotional learning (MBSEL), specifically designed for residency training and aligned with Accreditation Council for Graduate Medical Education (ACGME) competencies. The novelty of this work lies in its timing at key developmental transitions and its integration within the residency programme rather than as an optional wellness activity.

MBSEL combines contemplative practices with evidence-based social-emotional learning (SEL) strategies to foster both self-regulation and interpersonal awareness.² Mindfulness, defined as intentional awareness of the present moment with openness and acceptance, promotes emotional balance and self-awareness.³ SEL is grounded in theories of human development and aims to develop emotional intelligence, empathy and responsible decision-making.^{4,5} Together, these complementary components support skills essential for physicians navigating the relational and cognitive complexities of clinical work. This study describes the design, implementation and assessment of faculty-led MBSEL workshops delivered for 5 cohorts of radiology residents since 2022.

Using Kern's 6-step framework,⁶ the authors designed the curriculum integrating core competencies in interpersonal and communication skills, professionalism, practice-based learning and improvement, and systems-based practice. Fig. 1 provides an overview of workshop topics and educational

strategies, illustrating how the MBSEL domains were mapped to these ACGME competencies.

The overarching goal was to enhance residents' SEL competencies in clinical practice through mindfulness-based methods. The learning objectives, adapted from the MBSEL framework, targeted 5 SEL domains: (1) self-awareness: identify personal strengths and values using validated tools and mindfulness practices; (2) self-management: apply self-compassion strategies to regulate emotions and manage stress; (3) social awareness: recognise and consider multiple stakeholder perspectives in clinical contexts; (4) relationship skills: enhance communication and teamwork through reflection, role-play and peer discussion; and (5) responsible decision-making: make value-aligned decisions when navigating clinical dilemmas.

The workshops were interactive. Each 3.5-hour workshop incorporated guided mindfulness practices, individual reflection using Gibbs' reflective cycle, group reflection on real-life scenarios and peer discussions. Storytelling, role-modelling and personal examples by the faculty helped bring abstract concepts such as compassion, self-reflection and growth mindset to life. Participants completed the values in action character strengths survey and Johari window exercises beforehand and shared insights during the sessions.^{7,8}

From the second workshop onwards, topics were expanded to address residents' practical and professional needs. For example, a presentation on financial literacy was included, and senior residents shared personal experiences on navigating clinical rotations, examinations and research. Faculty panels addressed residents' questions on topics such as managing shift work, planning for pregnancy and negotiating leave, which were often overlooked in formal curricula but critical to residents' sense of agency and well-being.

Each session was led by 3 wellness champions and supported by 3 rotating faculty members who joined the 45-minute panel discussion. The programme director and a senior resident participated consistently

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¹ Department of Radiology, Sengkang General Hospital, Singapore

² Education Office, Sengkang General Hospital, Singapore

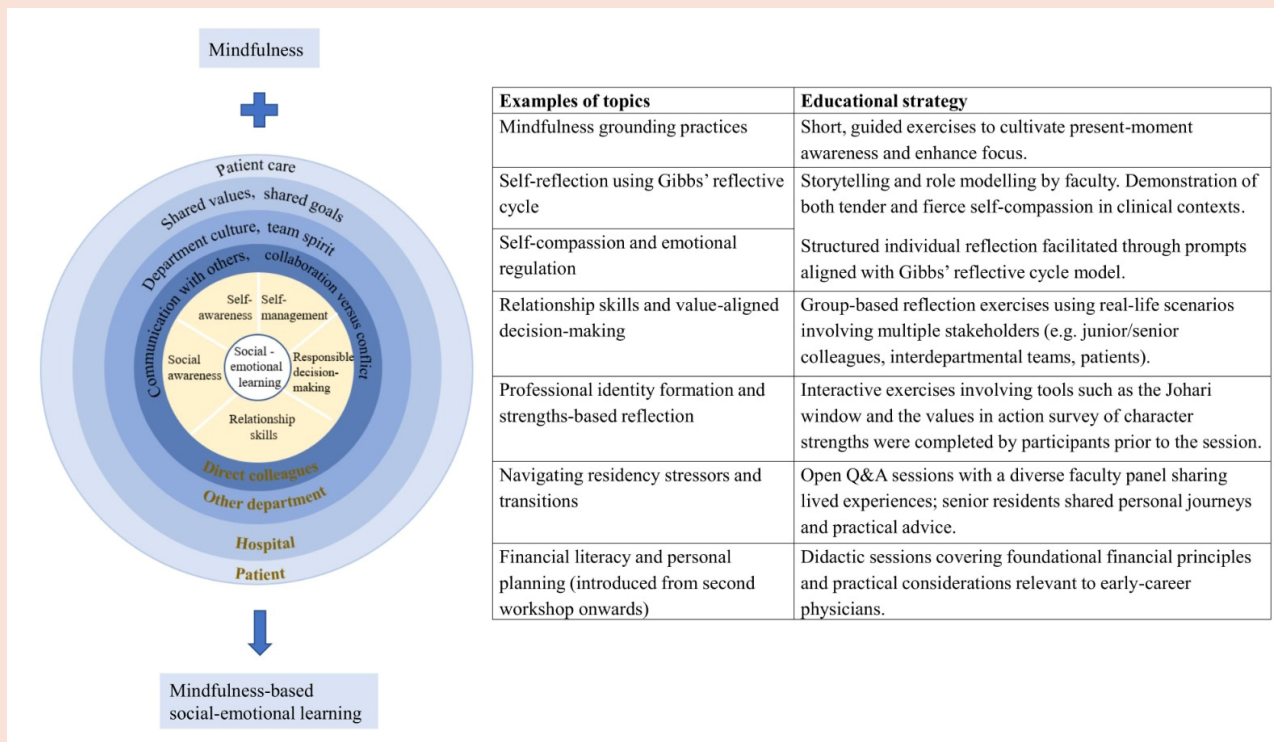
Correspondence: Dr Wenwen Ni, Department of Radiology, Sengkang General Hospital, 110 Sengkang E Wy, Singapore 544886.

Email: wenwen.ni@mohh.com.sg

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Fig. 1. Mindfulness-based social-emotional learning framework adapted from the Collaborative for Academic, Social, and Emotional Learning model for clinical training (left). Overview of workshop topics and corresponding educational strategies (right).



across sessions, bringing total faculty involvement to 5–7 participants per workshop. The core facilitators brought complementary expertise: formal training in mindfulness and positive psychology, senior clinical leadership experience and financial acumen from prior industry work. Rotating faculty representation promoted cross-institutional engagement and diversity of perspectives.

Workshops were tailored for junior (R1) and senior (R4) residents in their protected educational time, to ensure relevance to their training stage. R1 sessions were scheduled 6–9 months into residency, coinciding with the onset of on-call duties, while R4 sessions were held at the beginning of senior residency to address leadership responsibilities. Each session concluded with the distribution of reflective journals to encourage ongoing reflection and self-directed learning.

To assess perceived usefulness and engagement, post-workshop surveys that included both quantitative and open-ended questions were conducted. Quantitative data were analysed descriptively, while qualitative responses underwent thematic analysis using Braun and Clarke's approach.⁹ Across 5 cohorts, 82% of residents (68 of 83) participated, of whom 59 completed the survey. Most (95%) rated the sessions as "useful" or "highly useful" and 81% expressed interest in future workshops.

Qualitative analysis revealed 5 themes: (1) increased self-awareness and reflective capacity, (2) awareness of coping strategies, (3) appreciation of shared experiences, (4) financial literacy and (5) validation and belonging. The strong positive reception of the financial literacy component highlights a previously unmet need within the residency cohort, consistent with literature describing widespread financial insecurity and inadequate preparedness among residents.

The workshops were associated with high levels of resident engagement and perceived relevance across multiple cohorts, which are factors critical for the sustainability of the programme. Adapting the MBSEL framework for postgraduate training extends its applicability to clinical learning. Importantly, the benefits also extend to educators, as teacher and learner SEL are interdependent, and faculty participation may further reinforce a culture of mutual support and psychological safety.

The novelty of this work lies not in mindfulness or self-reflection as standalone interventions, but in their delivery within a community of practice. This approach enabled contextual grounding and authentic connection, likely contributing to the programme's success. Faculty sharing, guided reflection and candid faculty-resident dialogue helped normalise

vulnerability and strengthen trust, likely supporting sustained resident engagement.

These workshops are now embedded within the residency's broader educational framework, complementing mentoring and wellness initiatives such as Safe Space discussion forums.¹⁰ Consistently positive feedback and high participation rate underscore the relevance and potential scalability of MBSEL-based approaches, not only within residency education but also across other healthcare professions and beyond.

This programme evaluation has several limitations. First, outcomes were based on self-reported post-workshop feedback, reflecting perceived value rather than objective impact on participants. Second, the single data point precludes evaluation of longer-term effects on participants. Third, owing to educational and ethical constraints, randomisation and the inclusion of a non-intervention control group were not feasible. Consequently, it was not possible to fully distinguish the workshop's effects from potential confounding factors such as prior experience, peer dynamics and departmental culture. Future studies will include longitudinal evaluation using validated outcome measures.

In conclusion, faculty-led MBSEL workshops provided radiology residents with a structured framework for developing self-awareness, compassion and connection. Such initiatives represent an important step towards nurturing resilient clinicians and fostering healthier learning environments within postgraduate medical education.

Ethics statement

The programme evaluation was designated as a quality improvement initiative and therefore exempted from institutional review (10/02/2026).

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. All authors have no conflicts of interest to declare.

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Keywords: *community, mindfulness, reflection, residency training, social-emotional learning*

REFERENCES

1. Tan MY, Lee SS, Aw MM, et al. Mindfulness and reflective practice pilot programme of Postgraduate Year 1 doctors: perceptions on impact and sustainability. *Singapore Med J* 2023; Online ahead of print.
2. Maloney JE, Lawlor MS, Schonert-Reichl KA, et al. A mindfulness-based social and emotional learning curriculum for school-aged children: the MindUP program. In: Schonert-Reichl KA, Roeser RW, eds. *Handbook of Mindfulness in Education: Integrating Theory and Research into Practice*. New York: Springer; 2016.
3. Kajee N, Montero-Marin J, Saunders KEA, et al. Mindfulness training in healthcare professions: A scoping review of systematic reviews. *Med Educ* 2024;58:671-86.
4. McCormick MP, Cappella E, O'Connor EE, et al. Social-Emotional Learning and Academic Achievement: Using Causal Methods to Explore Classroom-Level Mechanisms. *AERA Open* 2015;1.
5. Collaborative for Academic, Social, and Emotional Learning (CASEL). CASEL's SEL framework: what are the core competence areas and where are they promoted? <https://casel.org/casel-sel-framework-11-2020>. Accessed 4 October 2025.
6. Sweet LR, Palazzi DL. Application of Kern's Six-step approach to curriculum development by global health residents. *Educ Health (Abingdon)* 2015;28:138-41.
7. Niemiec RM. VIA Character Strengths: Research and Practice (The First 10 Years). In: Knoop H, Delle Fave A, eds. *Well-Being and Cultures. Cross-Cultural Advancements in Positive Psychology*. Dordrecht: Springer; 2013.
8. Luft J. The Johari window: a graphic model of awareness in interpersonal relations *Human Relations Training News* 1961;5:6-7.
9. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:77-101.
10. Upadhyaya VS, Lim CHS, Lee ZR, et al. "Safe Space": A wellness initiative for residents. *Med Educ* 2024;58:258-9.

A comparison of Epstein-Barr virus digital PCR and quantitative PCR for identifying nasopharyngeal cancer

Valerie JW Tong^{*1} MBBS, Wei Keat Teo^{*1} BSc, Hon Man Chan² PhD, Chun Kiat Lee² MSc, Chuan Keng Goh^{1,2} BSc, Zhi Kang Chin¹ BSc, Luvita Suryani¹ PhD, Chor Hiang Siow¹ MSc, Han Lee Goh¹ MSc, Melvin Lee Kiang Chua³ PhD, Jianjun Liu⁴ PhD, Raymond King Yin Tsang¹ FRCS, Johnson Ng⁵ PhD, Kwok Seng Loh¹ FRCS, Benedict Yan² FRCPath, Joshua K Tay¹ PhD

Dear Editor,

We are writing to present detailed findings of our recent study comparing digital polymerase chain reaction (dPCR) and quantitative polymerase chain reaction (qPCR) for the quantification of Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) in nasopharyngeal carcinoma (NPC). According to Global Cancer Observatory: Cancer Today 2020 statistics, NPC accounts for an estimated 129,000 new diagnoses and nearly 73,000 deaths annually,¹ underscoring the need for accurate diagnostic and surveillance tools.

EBV is a major risk factor for NPC. While over 90% of the world's population harbour latent EBV infections,² the virus can persist in the nasopharyngeal epithelium and contribute to oncogenic mutations.³ EBV DNA and latent gene products are detectable in NPC and precancerous lesions, supporting its biological relevance.⁴ Persistently detectable plasma EBV DNA after treatment strongly predicts residual or recurrent disease, making serial EBV DNA monitoring an important component of patient follow-up.⁵

Surveillance after primary treatment remains challenging. Radiation-induced fibrosis, local oedema and post-treatment changes can obscure early recurrence on endoscopy or imaging, complicating decision-making.⁶ In this context, a sensitive biomarker like EBV DNA is essential for guiding critical treatment. Our study aimed to evaluate the diagnostic accuracy of dPCR for NPC detection and recurrence, and compare its performance with qPCR.

Although qPCR is the current standard for EBV DNA quantification, its reliance on calibration curves and reduced precision at low copy numbers may limit sensitivity for minimal residual disease (MRD) and early recurrence. dPCR allows absolute quantification

and is expected to improve detection accuracy at low viral loads. We hypothesised that dPCR would outperform qPCR in plasma while recognising that any advantage might be reduced in serum. Accordingly, we compared the performance of dPCR versus qPCR across 2 EBV targets (BamHI-W and EBNA1) in both plasma and serum, and examined their potential clinical applications.

We conducted a case-control study at a single-centre tertiary university hospital, analysing 162 plasma and serum samples under institutional ethics approval. Two EBV gene targets were evaluated: the multi-copy BamHI-W sequence and the single-copy Epstein-Barr Nuclear Antigen 1 (EBNA1) gene.

The study comprised 2 cohorts. First, we prospectively collected 50 plasma samples from 38 NPC patients (stages I–IVA) and 12 healthy controls. Second, we analysed 112 archived serum samples from 28 patients with recurrent NPC and 28 matched healthy first-degree family members, with patient samples corresponding to pre-treatment, post-treatment and recurrence. DNA was extracted using the Reliaprep Blood gDNA Miniprep System (Promega, Madison, WI, US). qPCR was performed on an Applied Biosystem StepOne Plus system (Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, US). dPCR was performed on the Clarity dPCR system (JN Medsys, Singapore), following the manufacturer's protocol. Diagnostic performance was assessed by receiver operating characteristic (ROC) analysis using the Youden J index (additional information for the clinical characteristics of the cohort and methods is in Supplementary Table S1).

The analysis of results from plasma samples showed superior performance of dPCR (Fig. 1). For BamHI-W,

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¹ Department of Otolaryngology–Head & Neck Surgery, National University Hospital Singapore, Singapore

² Molecular Diagnosis Centre, Department of Laboratory Medicine, National University Hospital, Singapore

³ Division of Radiation Oncology, National Cancer Centre Singapore, Singapore

⁴ Human Genetics, Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore

⁵ JN Medsys, Singapore

* Joint first authors

Correspondence: Dr Joshua K Tay, Department of Otolaryngology–Head & Neck Surgery, National University of Singapore, 1E Kent Ridge Road, Level 7, Singapore 119228. Email: jostay@nus.edu.sg; Dr Benedict Yan, Department of Laboratory Medicine, National University Hospital, Singapore, 5 Lower Kent Ridge Road, Level 7, Singapore 1190074. Email: byanjr@nus.edu.sg

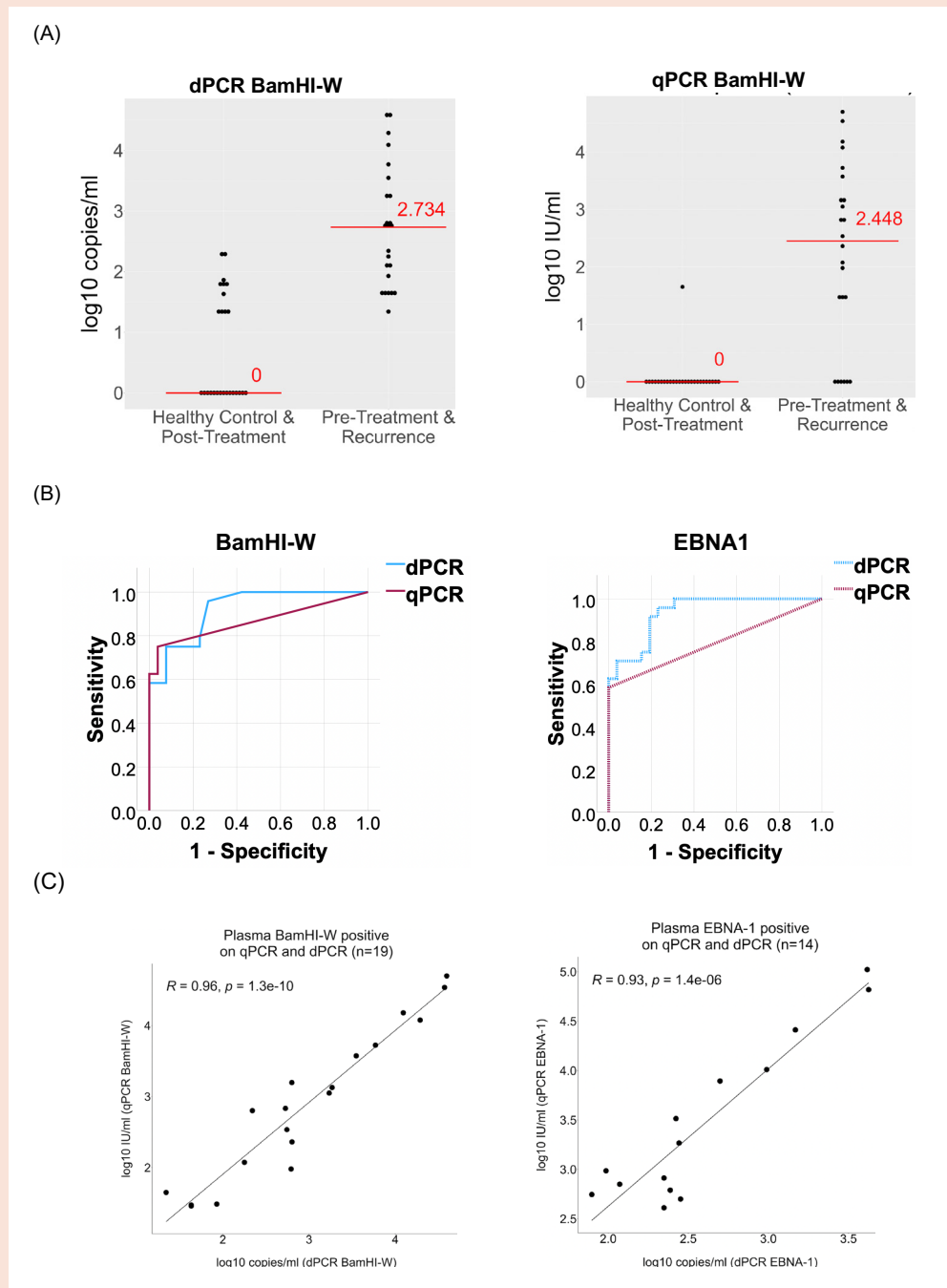
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area under the curve (AUC) was 0.921 for dPCR compared to 0.865 for qPCR. For EBNA1, the difference was more marked (0.936 versus [vs] 0.792). Optimal cut-offs for each test were determined by maximising Youden J (Supplementary Table S2). At a cut-off of 31.5 copies/mL, plasma dPCR for BamHI-W achieved a sensitivity of 95.8% and specificity of 73.1%.

The EBNA1 findings were particularly notable. Despite being a single-copy target, EBNA1 showed strong discriminative performance on dPCR (cut-off 72 copies/mL: sensitivity 95.8%, specificity 76.9%). This challenges the long-held belief that the multi-copy BamHI-W target is inherently superior for detection and suggests that absolute quantification may mitigate the analytical disadvantage of lower gene copy number.⁷

Fig. 1. Comparison of plasma EBV dPCR and qPCR in NPC: (A) BamHI-W levels across patient groups; (B) ROC curves for BamHI-W and EBNA1; and (C) Correlation of dPCR vs qPCR for both targets.



EBNA1: Epstein-Barr Nuclear Antigen 1; EBV: Epstein-Barr virus; dPCR: digital polymerase chain reaction; NPC: nasopharyngeal carcinoma; qPCR: quantitative polymerase chain reaction; ROC: receiver operating characteristic

In contrast, serum analysis showed comparable performance between dPCR and qPCR (BamHI-W AUC 0.821 vs 0.832; EBNA1 AUC 0.683 vs 0.712; Supplementary Fig. S1). Patients with active disease had significantly higher median EBV DNA levels compared to healthy controls (Supplementary Figs. S3, S4). The reduced discriminability in serum is consistent with known differences in circulating DNA integrity and background genomic noise. This likely reflects a combination of biological and methodological factors: serum has lower tumour-derived DNA due to coagulation-associated degradation and greater release of leukocyte genomic DNA during clot formation, resulting in a lower proportion of tumour-specific DNA.⁸ Additional pre-analytical variables inherent to archived serum samples (including storage conditions and freeze–thaw cycles) may further reduce assay performance.⁸ Collectively, these factors may explain why dPCR displays a clear advantage in plasma but not in serum.

The superior performance of dPCR in plasma is attributable to its partitioning of samples into thousands of independent reactions, enabling absolute quantification without calibration curves, improving precision at low copy numbers. This facilitates detection of subtle changes in viral load that may be missed by qPCR.⁷

This work represents one of the first direct comparisons of dPCR and qPCR across 2 EBV targets in both plasma and serum. While plasma remains the preferred specimen for EBV DNA testing due to higher levels of tumour-derived DNA,⁹ serum findings retain clinical relevance in settings where it is routinely collected or when plasma samples are unavailable. Our longitudinal serum cohort also reaffirmed that patients with distant metastasis exhibit significantly higher EBV DNA loads than those with locoregional recurrence ($P < 0.01$), highlighting EBV DNA's value for characterising disease relapse.

Our findings have practical implications for clinical practice. Plasma should be the specimen of choice for EBV DNA quantification in NPC surveillance. dPCR may be particularly valuable in scenarios where sensitivity is critical: post-treatment monitoring, MRD assessment, and cases with equivocal radiological or endoscopic findings. Clinical trials evaluating treatment response with reproducibility and standardisation are crucial. EBNA1, despite being a single-copy gene, demonstrated strong performance on dPCR and warrants further evaluation as a routine clinical target.

In conclusion, our study demonstrates that plasma dPCR offers superior sensitivity and accuracy compared with qPCR for NPC detection and surveillance. Both BamHI-W and EBNA1 are useful targets, with EBNA1 showing unexpected potential in the dPCR setting. Earlier and more reliable identification of recurrence may allow more timely and potentially curative therapies. Further validation in larger prospective

cohorts is needed to explore whether a combined BamHI-W/EBNA1 dPCR assay can provide even greater diagnostic power.

Supplementary materials

Supplementary Fig. S1. Comparison of serum EBV dPCR and qPCR in NPC.

Supplementary Fig. S2. Serum EBV DNA levels (EBNA1) in NPC patients (n=28) at 3 time points (pre-treatment, post-treatment and at recurrence) and healthy controls (n=28). Median values indicated by red lines.

Supplementary Fig. S3. Serum EBV DNA levels for NPC cases with recurrence, based on site of recurrent disease.

Supplementary Table S1. Clinical characteristics.

Supplementary Table S2. Performance of plasma EBV dPCR and qPCR.

Supplementary Table S3. Performance of serum EBV dPCR and qPCR.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and received formal approval from the National Healthcare Group Domain Specific Review Board (2006/00149). Written informed consent was obtained from all participants prior to their inclusion in the study. Use of plasma sample was approved by National Health Group Domain Specific Review Board (2016/00045).

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Declaration

Johnson Ng is founder of JN Medsys, the manufacturer of the dPCR platform used in this study. All data interpretation was independent of Johnson Ng. All other authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: cancer, molecular biology, oncology, otorhinolaryngology, public health

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.

2. Smatti MK, Al-Sadeq DW, Ali NH, et al. Epstein-barr virus epidemiology, serology, and genetic variability of LMP-1 oncogene among healthy population: An update. *Front Oncol* 2018;13;8:211.
3. Farrell PJ. Epstein-Barr Virus and Cancer. *Annu Rev Pathol Mech Dis* 2019;14:29-53.
4. Lee HM, Okuda KS, González FE, et al. Current Perspectives on Nasopharyngeal Carcinoma. In: Rhim, J., Dritschilo, A., Kremer, R. (eds) *Human Cell Transformation. Advances in Experimental Medicine and Biology*, vol 1164. Springer, Cham.
5. Lin J-C, Wang W-Y, Chen KY, et al. Quantification of Plasma Epstein-Barr Virus DNA in Patients with Advanced Nasopharyngeal Carcinoma. *N Engl J Med* 2004;350:2461-70.
6. Ak S, Kiliç C, Özlügedik S. Correlation of PET-CT, MRI and histopathology findings in the follow-up of patients with nasopharyngeal cancer. *Braz J Otorhinolaryngol* 2020;87:643-8.
7. Bio-Rad.com. Digital PCR and Real-Time PCR (qPCR) Choices for Different Applications. <https://www.bio-rad.com/en-sg/applications-technologies/digital-pcr-real-time-pcr-qpcr-choices-for-different-applications?ID=OENHBB15>. Accessed 17 April 2021.
8. Stevens SJC, Pronk I, Middeldorp JM. Toward standardization of Epstein-Barr virus DNA load monitoring: Unfractionated whole blood as preferred clinical specimen. *J Clin Microbiol* 2001;39:1211-6.
9. Liu Y, Fang Z, Liu L, et al. Detection of Epstein-Barr Virus DNA in Serum or Plasma for Nasopharyngeal Cancer: A Meta-Analysis. *Genet Test Mol Biomarkers* 2011;15:495-502.

"Gender-focused mental health services in Singapore: A brief history and future direction": Correspondence

Daniel Shuen Sheng Fung¹ MMed (Psychiatry), Swapna Verma¹ MD, Say How Ong¹ MMed (Psychiatry), Yee Ming Mok¹ MMed (Psychiatry)

Dear Editor,

The authors read with interest the recent Letter to the Editor by Puthran et al.¹ on gender-focused mental health services in Singapore published in the *Annals*.

We wish to provide context regarding the absorption of the Gender Care Clinic into general psychiatric services at the Institute of Mental Health, and to reflect on the broader service transformation considerations in mental healthcare in Singapore.

The decision was not a withdrawal of care, but a recalibration of service delivery within a small resource-constrained healthcare system. In Singapore, where subspecialty manpower remains limited, proliferation of highly siloed clinics risks fragmentation, duplication of effort and inequitable access.² Super-specialisation may inadvertently concentrate expertise while reducing overall system responsiveness, particularly when demand rises across multiple domains of mental health.

A transdiagnostic, integrated model better reflects contemporary psychiatric practice.³ Many individuals presenting with gender-related concerns also experience co-occurring mood, anxiety, trauma-related or neurodevelopmental conditions. Managing these within a general clinic framework allows holistic assessment, continuity of care and alignment with stepped care principles.⁴ Complex cases can still be supported through multidisciplinary consultation, without segregating care pathways in ways that may increase stigma or delay.

Care transformation in small countries requires balancing depth with scalability. Rather than multiplying subspecialty silos, building system-wide competence through training, shared protocols and

collaborative networks may yield more sustainable gains. This approach strengthens the overall psychiatric ecosystem while ensuring that gender-diverse individuals receive competent, respectful and coordinated care within mainstream services.

The future of gender-focused care in Singapore should therefore focus on capability building, integration and national alignment, rather than structural compartmentalisation. Such a strategy promotes equity, resilience and long-term sustainability in the evolving mental health landscape.

Ethics statement

Not applicable, as no study participants were recruited.

Declaration

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REFERENCES

1. Puthran R, Tan HT, Rawtaer I, et al. Gender-focused mental health services in Singapore: A brief history and future directions. *Ann Acad Med Singap* 2026;55:OnlineFirst.
2. World Health Organization. World Mental Health Report: Transforming Mental Health for All. Geneva: WHO; 2022.
3. Dagleish T, Black M, Johnston D, et al. Transdiagnostic approaches to mental health problems: Current status and future directions. *J Consult Clin Psychol* 2020;88:179-95.
4. Lee CYS, Fung DSS. A stepped care approach to mental health in Singapore: challenges and opportunities. *BMC Glob Public Health* 2025;3:73.

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¹ Institute of Mental Health, Singapore

Correspondence: Dr Daniel Fung Shuen Sheng, Institute of Mental Health, 10 Buangkok View, Singapore 539747.

Email: daniel.fung@nhghealth.com.sg

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ANNALS, ACADEMY OF MEDICINE, SINGAPORE

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

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