



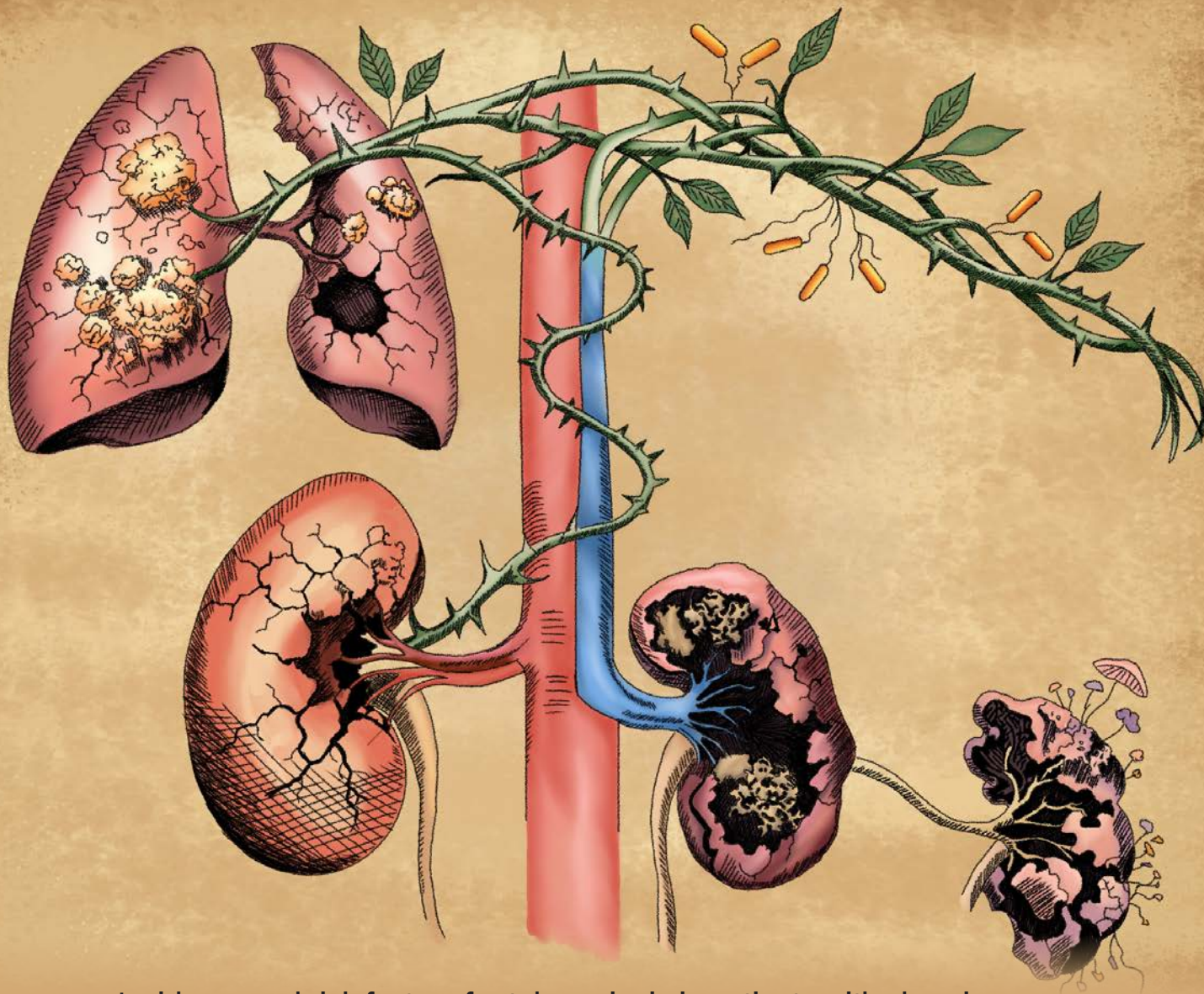
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Incidence and risk factors for tuberculosis in patients with chronic kidney disease in Singapore

Male sex, smoking history and dialysis treatment were found to be associated with the development of tuberculosis following a CKD5 diagnosis. (See full article, p. 64)

Illustration by Maria De-Castro

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Selection of pyroptosis-related genes and potential pharmacological targets in sepsis-induced myopathy

Laryngeal preservation versus upfront laryngectomy in advanced laryngeal cancer

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Screening for tuberculosis in chronic kidney disease patients

Alvin Kuo Jing Teo^{1,2,3} PhD, Qiang Lou^{4,5} PhD, Boon Wee Teo⁵ MB BCh

Tuberculosis (TB) is the leading infectious cause of morbidity and mortality globally.¹ Singapore is considered a lower-moderate incidence country (estimated TB incidence at 10–49 per 100,000 population); yet TB remains a persistent public health challenge driven by an ageing population and the burden of TB infection.^{2,3} This challenge is compounded by intersecting risk factors and syndemics, including chronic conditions such as diabetes and chronic kidney disease (CKD), which are increasingly prevalent in ageing populations. Globally, CKD affects approximately 14% of adults, and its prevalence is rising, including in Singapore where rates are among the highest in the region.⁴ People with CKD have a significantly elevated risk of TB due to impaired immunity and increased opportunity for infectious exposures during frequent medical visits.⁵

Metussin et al. estimated that TB incidence among CKD patients (279–630 per 100,000 population) was significantly higher than that of the general population (32.6–41.1 per 100,000 population) in Singapore.⁶ The study identified older age, male sex, dialysis treatment, history of smoking and coexisting diabetes as key risk factors for TB among CKD patients. These findings raise questions on who, what and when to screen, and how to align practice with international and local guidance.

The World Health Organization (WHO) recommends that in settings where the TB prevalence in the general population is 100 per 100,000 population or higher, systematic screening for TB disease may be considered for individuals with risk factors, who are seeking or already receiving healthcare.⁷ In Singapore, universal screening for TB among dialysis patients is recommended in the updated TB management guidelines.⁸ Yet, translating recommendations into routine practice can be uneven. Across the Western Pacific Region, several high TB burden countries have policies for systematic screening of dialysis patients, but implementation varies—often limited by funding, workforce and infrastructure.⁹ In Singapore, screening

incident dialysis patients for TB is not regularly performed. Anecdotally, only one institution performs universal screening introduced during the COVID-19 pandemic as a quality improvement measure to reduce “noise” by placing incident dialysis patients with respiratory symptoms out to ambulatory satellite dialysis centres. Given the elevated TB risk among CKD and dialysis patients, more proactive screening for TB disease is warranted. WHO guidance supports the use of symptom screening, chest X-ray or molecular diagnostics in high-risk groups.⁷ At a minimum, CKD patients should be screened for TB disease before initiating dialysis in line with national guidelines.⁸ A more comprehensive approach would ideally include screening for both TB disease and TB infection,⁵ but further evaluation is needed to determine the optimal screening frequency, implementation strategies and cost-effectiveness. Integrating standardised symptom checks and chest X-rays (including routine review of radiographs taken for other clinical reasons) into dialysis workflows could be considered to improve early detection and reduce the risk of transmission in dialysis facilities.

While Metussin et al. did not measure the prevalence of TB infection among CKD patients, a systematic review has shown a high TB infection rate in CKD, particularly in haemodialysis cohorts.¹⁰ A healthy individual with TB infection has a 5–10% chance of progressing to TB, and the risk increases among immunosuppressed populations. This strengthens the case for targeted TB infection testing and TPT before dialysis or transplant.¹¹ Some argue that universal screening for TB in dialysis patients is not cost-effective due to the competing risk of death in dialysis patients.¹² The upfront cost of testing and treatment for TB infection to prevent a TB case is added to the dialysis programme. Moreover, the benefits of treating TB infection accrue with increasing survival time. It is uncertain what cost-effectiveness data are available for a Singapore incident dialysis cohort. However, universal screening may be needed for

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infection control in ambulatory satellite dialysis centres where the same patients regularly meet.

Assuming a base case of 3000 patients per year and a TB incidence of 406 per 100,000 person-years (with TB infection prevalence of 15%), the expected person-years over 5 years is 11,465. Interferon-gamma release assay (IGRA) test (QFT-G [QIAGEN, Hilden, Germany]) was costed at S\$72 (US\$57) per test, TB infection treatment at S\$72 (US\$57) per case for a 6-month isoniazid, or INH treatment, and drug-sensitive TB treatment at S\$15,000 (US\$11,852) per person.¹³ Societal costs including contact tracing were valued at S\$800 (US\$632) per TB case.¹⁴ Five-year survival among dialysis patients was estimated at 56.9%.¹²

Over 5 years, the expected baseline burden without screening is 46.5 TB cases. Considering a baseline of 46.5 TB cases over 5 years without screening and IGRA tests positive in 437 cases (true 360, false 77), screening will avert 2.57 cases in 5 years. Under universal screening, 437 individuals would test IGRA-positive (360 true positives and 77 false positives), compared with 145.67 positives under targeted screening. Based on fixed effectiveness estimates, screening would avert approximately 2.57 TB cases over 5 years.

The 5-year programme's cost for universal screening is S\$192,936.96 (US\$152,455.47), comprising S\$172,800 (US\$136,534) for testing (assuming 80% screening adherence) and S\$20,136.96 (US\$15,911.44) for latent TB infection treatment (assuming 64% treatment uptake). Costs avoided from averted TB cases total S\$40,532.01 (US\$32,024.95), incorporating both healthcare and societal savings. This results in a net programme cost of S\$132,267.99 (US\$104,512.58) and an incremental cost-effectiveness ratio (ICER) of S\$51,466.14 (US\$40,743.94) per TB case averted. The ICER could be reduced to approximately S\$6,641.24 (US\$5,248.04) if a targeted strategy is employed, screening only 1000 patients at the highest risk per year (e.g. males, ex- or current smokers, people with diabetes and Malay ethnicity). The ICER can be reduced below the S\$50,000 (US\$39,512) threshold for universal screening and less than S\$118.35 (US\$93.53) for higher-risk targeted screening if the IGRA test costs less than S\$45 (US\$36).

Importantly, if Singapore's broader TB control strategy is to eliminate TB, a longer time horizon is required, during which higher upfront costs may be acceptable to achieve long-term reductions in transmission. This highlights the need for more detailed modelling of programme costs and the projected long-term impact on TB prevalence in Singapore.

TB control in Singapore is making steady progress, but disproportionate risk among specific populations,

such as those with CKD, means that a one-size-fits-all approach will fall short. Metussin et al.'s findings⁶ reinforce the need to systematically screen CKD populations and expand preventive treatment to those most at risk, aligning practice with WHO recommendations and updated Singapore guidelines. However, universal screening at current prices of screening using IGRA and the ambulatory treatment cost of drug-sensitive TB is likely not cost-effective. A targeted approach for higher-risk patients with longer life expectancy is more likely to offer better value. Nevertheless, further analyses that account for potential cost changes and the long-term impact of systematically screening CKD and dialysis patients for TB in Singapore are needed.

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 kidney disease, dialysis, epidemiology incidence, Singapore, tuberculosis

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Rethinking risk: Mental health and resilience of migrant workers and migrant domestic workers in Singapore

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Over the past 5 years, there has been growing attention to the health and well-being of international migrant workers (MWs) in Singapore, particularly low- to semi-skilled MWs and migrant domestic workers (MDWs). To promote well-being, the government has introduced several initiatives, including mandatory rest days and improved living facilities.^{1,2} Non-profit groups, such as HealthServe, have also established peer support networks and a counselling hotline.^{3,4}

Despite these efforts, ongoing monitoring and programme development have been constrained by limited evidence. Globally, research on MWs is challenging due to difficulties accessing this population along with language, cultural and literacy barriers. In Singapore, very few studies have documented the prevalence, risk factors and protective factors related to mental health among MWs and MDWs.

To address this gap, Koh et al. present the largest mental health study of MWs in Singapore to date in this issue of *Annals*.⁵ The authors conducted a cross-sectional survey of 1465 MWs and 1462 MDWs, capturing symptoms of depression and anxiety through the widely-used Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), alongside sociodemographic factors, stress, sleep, social support and resilience.

As the primary finding, the authors reported that MWs and MDWs had lower prevalence of mental health symptoms compared to the host population in Singapore. In their sample, 0.8% of MWs and 4% of MDWs met criteria for moderate-to-severe depression symptoms, while 1% of MWs and 4% of MDWs had moderate-to-severe anxiety symptoms. In contrast, a recent study of the Singapore population reported that 9% had moderate-to-severe depression symptoms, while 7% had moderate-to-severe anxiety symptoms.⁶

The finding that MWs have fewer mental health symptoms is counterintuitive. It challenges a commonly held belief that MWs face greater risk due to economic

and social disadvantages. Rather than heightened vulnerability, these results suggest psychological resilience within the population.

Although counterintuitive, the findings align with the well-documented “healthy migrant effect”. This is a global phenomenon describing how international MWs tend to have better health outcomes than the host population across disease categories.⁷ While the mechanisms for this effect remain speculative, this could be because migrant populations are younger or that self-selection results in healthier individuals opting to migrate.⁸ Researchers have also proposed protective mechanisms such as having strong communal ties or a reliance on religion and spirituality.⁹

The authors note that while Koh et al. reported lower rates of mental health symptoms than the Singapore population, earlier studies found more modest differences.^{10,11} For example, in a survey conducted among 1011 MWs by this editorial’s authors,¹¹ rates of severe or extremely severe depression, anxiety and stress were comparable to the general Singapore population. However, these studies were conducted during the height of the COVID-19 pandemic. Koh et al. reasonably speculate that the post-pandemic easing of restrictions and well-being initiatives may have alleviated mental distress.

As a further departure from the literature, prior studies outside Singapore suggest that the “healthy migrant effect” diminishes over time, with migrants’ health converging toward or falling below host populations after 5 to 15 years.¹² In contrast, Koh et al. found that longer employment duration was associated with a lower likelihood of depressive symptoms. This discrepancy may reflect several factors such as Singapore’s compact geography, which may foster a sense of community that protects against psychological distress. It may also reflect the stability that comes with having a steady income over time.

More generally, the factors contributing to an individual’s mental health are complex and multifac-

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torial. For example, Koh et al. observed differing rates of depression and anxiety between MDWs and MWs, and across nationalities, age and education levels. This may suggest both distinct stressors (e.g. job demands, pay structure) and coping strategies across subgroups. Accordingly, more studies are needed to draw stronger conclusions about the mechanisms of the “healthy migrant effect” in Singapore and whether mechanisms differ across migrant subpopulations.

At this juncture, concerned readers may reasonably wonder whether Koh et al.’s study has accurately captured mental health symptoms among MWs and MDWs. It is conceivable that symptoms were under-reported due to underlying stigma or fear of repercussions. Cross-culturally, Asian respondents also tend to express psychological distress through somatic symptoms (e.g. stomachaches), which are not well-captured by Western-developed questionnaires such as the PHQ-9 or GAD-7.¹³ These considerations underscore the need for caution when interpreting the study and a need to triangulate with other data sources—for example, by tracking general practitioner visits for somatic complaints.

How might Koh et al.’s results inform policy and practice? First, regardless of the prevalence rate, there needs to be continued investment in migrant mental health. Both the process of migration and financial insecurities remain significant stressors that can place an MW at risk for poorer mental health. In psychiatry, the “diathesis-stress model” describes how situational stressors combine with pre-existing vulnerabilities to accrue risk.¹⁴ Applied to MWs, it is plausible that while many adapt successfully to migration-related stressors, those with pre-existing vulnerabilities may face an elevated risk of developing mental health conditions.

Second, both prior research and the study by Koh et al. observed differences in rates of depression and anxiety among subpopulations. This suggests that risk may differ across subpopulations, and that policies should be tailored to the specific needs of each subpopulation. For example, while current policies mainly target MWs, it is MDWs who face higher rates of depression and anxiety.⁵ These higher rates may be linked to the live-in and highly variable nature of MDWs’ work, increasing the risk of isolation and overwork. Tighter policies regulating job scopes could be implemented to reduce burden—for example, by limiting the number of family members an MDW cares for.

Third, Koh et al. identified several factors associated with poorer mental health including long working hours, high stress, poor sleep and limited social support. Potential measures to target these risk factors may include: nationwide education on psychological resilience and sleep hygiene for MWs and community-building interventions. Further, unlike countries such as

Hong Kong and Taiwan with universal health systems independent of employers,^{15,16} healthcare access for MWs and MDWs remains largely employer-dependent in Singapore. To promote help-seeking, it may be timely to review mental healthcare access across employers.

Finally, Koh et al.’s study highlights several areas that warrant further research. Future studies can employ longitudinal designs to understand mechanisms underlying the “healthy migrant effect”, and to monitor trajectories of mental health over time—particularly rates of depression and anxiety. Qualitative and quantitative studies are also needed to evaluate the impact of well-being policies and interventions (e.g. mandatory rest days, working hour limits) across MW and MDW subpopulations.

In conclusion, Koh et al.’s cross-sectional study represents a significant advancement in understanding depression and anxiety among MWs and MDWs in Singapore. The findings provide crucial evidence in a post-pandemic context, and point to opportunities for policy refinement and further research.

Ethics statement

Not applicable as no study participants were recruited.

Declaration

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

Keywords: depression, mental health, psychiatry, psychology, public health

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Incidence and risk factors for tuberculosis in patients with chronic kidney disease in Singapore

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ABSTRACT

Introduction: The authors aim to determine tuberculosis (TB) incidence and ascertain risk factors for TB in patients with stage 5 chronic kidney disease (CKD5) in the Singapore population.

Methods: A retrospective cohort study of all stage CKD5 patients registered in Singapore's renal registry who developed active pulmonary and extra-pulmonary TB between 2012 and 2021, after their CKD5 diagnosis.

Results: TB incidence among CKD5 patients was significantly higher compared to the general Singapore population, ranging from 279 to 630 per 100,000 CKD5 population over the period from 2012 to 2021, versus 32.6 to 41.1 per 100,000 general population during the same period. In univariable comparisons, statistically significant risk factors for development of TB disease in CKD5 patients were: male sex (odds ratio [OR] 1.66, 95% confidence interval [CI] 1.3–2.12, $P < 0.001$), Malay ethnicity (OR 1.33, 95% CI 1.02–1.72, $P = 0.03$) and reported history of "ever smoking" (OR 2.93, 95% CI 2.15–4.03, $P < 0.001$). CKD5 patients who were on any type of dialysis were also observed to have a significantly higher risk of developing TB disease, haemodialysis (OR 2.31, 95% CI 1.69–3.23, $P < 0.001$), peritoneal dialysis (OR 2.53, 95% CI 1.46–4.23, $P = 0.001$) or a combination of haemodialysis and peritoneal dialysis (OR 2.55, 95% CI 1.63–3.95, $P < 0.001$), compared to those who had not been initiated on dialysis. These factors remained significant in the multivariable models except ethnicity.

Conclusion: CKD5 patients have an increased risk of developing TB, particularly when certain risk factors are present, such as male sex or receiving dialysis. Clinicians should maintain a high degree of suspicion for TB in CKD5 patients with compatible clinical symptoms.

Keywords: chronic kidney disease, dialysis, incidence, Singapore, tuberculosis

CLINICAL IMPACT

What is New

- This study provides context-specific evidence for the increased risk of developing tuberculosis among stage 5 chronic kidney disease patients.
- Findings underscore the potential disease burden in this population.

Clinical Implications

- This study can increase awareness among clinicians to maintain a high degree of suspicion of tuberculosis for stage 5 chronic kidney disease patients with compatible clinical symptoms.

INTRODUCTION

Tuberculosis (TB) remains a major global infectious disease threat, particularly to vulnerable people or

those in resource-limited settings.¹ Estimated TB incidence has continued upward post-COVID-19 pandemic, with a rise of 3.9% between 2020 and 2022 (from 128 to 133 cases per 100,000 population), and reflects a reversal in the progress made over the past 20 years.² In Singapore, the incidence rate was 28.9 cases per 100,000 population in 2023 compared to 30.4 cases per 100,000 in 2022³ and continued a downward trend in 2024 with a reported incidence rate of 27.6 cases per 100,000 residents.⁴

While TB incidence among residents in Singapore has dropped, a substantial number of TB cases occur in population subgroups who are elderly, immunocompromised, patients with chronic kidney disease or on dialysis.^{1,2,5–8} Determining the burden of TB in groups at risk is therefore critical in prioritising population groups and interventions to reduce TB transmission.² Identifying key population groups at risk for TB represents a crucial step to direct efforts and resources for TB screening and the allocation of preventive therapy thereafter. This process aligns with one of the agreed global targets announced at the

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second United Nations High-Level Meeting on the fight against tuberculosis, held in November 2023, which was to record a 90% increase in TB preventive treatment by 2027.^{5,9-13} Evidence has consistently shown that within the renal patient population, dialysis patients and renal transplant recipients are at higher risk of developing TB.^{8,14-17} Chronic renal impairment, with or without progression to dialysis, has been associated with multiple comorbidities including increased risk of infection. The pathogenesis behind this increased risk is based on immune alteration, which is associated with the uraemic state in chronic kidney disease (CKD) leading to impaired T and B cells function.^{8,18,19} In addition to adaptive immune system alterations, defects in the innate immune system have also been suggested.²⁰

The incidence of stage 5 CKD (CKD5) has increased in Singapore with reported rates of 513.2 per million population in 2018, signalling a 34% rise from 383.9 per million population in 2010.²¹ The latest Singapore Renal Registry Annual Report in 2022 indicated that the crude incidence rate was 540.5 per million population in 2021, although the age-standardised incidence rate remained stable and ranged between 266.7 and 299.2 per million population during the period from 2012 to 2021.²²

In March 2024, Singapore also published updated management guidelines for drug susceptible TB disease and pulmonary disease, which includes screening for TB in dialysis patients.⁶ The objectives of this study were therefore to (1) determine the incidence of TB disease in CKD5 patients in Singapore and (2) examine specific risk factors associated with developing TB after a diagnosis of CKD5.

METHODS

Study design, setting and population

We conducted a retrospective cohort study of all patients diagnosed with CKD5 who were registered in Singapore's renal registry and who developed active TB disease between 2012 and 2021, after their CKD5 diagnosis.

The study population included all patients diagnosed with CKD5 with an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m², patients on renal replacement therapy, (i.e. haemodialysis), peritoneal dialysis and persons with a renal transplant. The outcome of interest was a diagnosis of active TB following CKD5 diagnosis, obtained after matching patient records in the National TB Registry (2012–2021) with CKD5 cases recorded in the National Renal Registry from 2012–2021 (followed up to 2023).

Data sources

Records from the 2 national registries were matched to conduct this study, both of which collect

comprehensive national-level patient data in Singapore. The Renal Registry receives CKD5 case notifications from public hospitals, dialysis centres, private nephrology clinics, kidney transplant centres and the National Organ Transplant Unit Singapore.²² Patient demographics, aetiology of renal disease and kidney function (creatinine, eGFR) at the onset of CKD were collected at the time of CKD5 diagnosis.

Longitudinal data on lifestyle factors—such as history of smoking (categorised as no smoking or ever smoking), comorbidities including diabetes mellitus, cardiovascular disease, acute myocardial infarction, malignancy and disease outcomes or death—were updated yearly. The treatment modality variable was categorised into “haemodialysis (HD), peritoneal dialysis (PD), renal transplant and no dialysis.” Patients coded as “no dialysis” included CKD5 patients with stable eGFR <15 mL/min/1.73m² not yet initiated on dialysis, as well as those opting for non-dialytic conservative management of renal failure.

Singapore's National TB Registry records all patients diagnosed with TB disease. Under the Infectious Diseases Act of 1976, TB notification is mandatory. Data fields were predetermined and selected variables were included from each data set, using a codebook for each dataset.

Statistical analysis

The analysis was conducted in 2 parts. After matching the datasets using a unique identifier, the authors derived TB incidence with 95% confidence interval (CI) in the study population, where incidence was defined as the total number of new TB cases each year divided by the total number of CKD5 patients at risk in that same year.

For the second part of the analysis, a multivariable logistic regression model was initially performed to examine factors associated with TB development during the entire study period. This approach provided odds ratios for ever-developing TB, treating it as a binary outcome. A complete case analysis was used; odds ratios and adjusted odds ratios were derived; *P* values <0.05 were considered statistically significant.

However, given the generally high risk of death in this cohort and the time-to-event nature of TB development, the authors conducted a primary analysis using a competing risks model. This survival analysis approach accounts for death as a competing risk that prevents TB occurrence and treats patients without TB disease who remain alive as censored at last follow-up. The competing risks framework is more appropriate for this study population as it properly handles the substantial mortality risk in CKD5 patients and provides unbiased estimates of TB risk over time.

Cumulative incidence analysis was performed to show the association of risk factors including age at which CKD5 is diagnosed, smoking, history of malignancy and types of dialysis, with the probability of TB disease. Gray's test was used for equality of cumulative incidence functions across groups of each factor.²¹ Furthermore, a proportional subdistribution hazard model was fitted to assess the effect of the risk factors on the subdistribution of TB development in a competing risks setting, providing subdistribution hazard ratios that represent effects on cumulative TB incidence.^{20,22} Results are reported according to the STROBE guidelines for observational studies.²³ All analyses were conducted using Stata v16 (StataCorp, College Station, TX, US) and R software (R Core Team, Vienna, Austria).

RESULTS

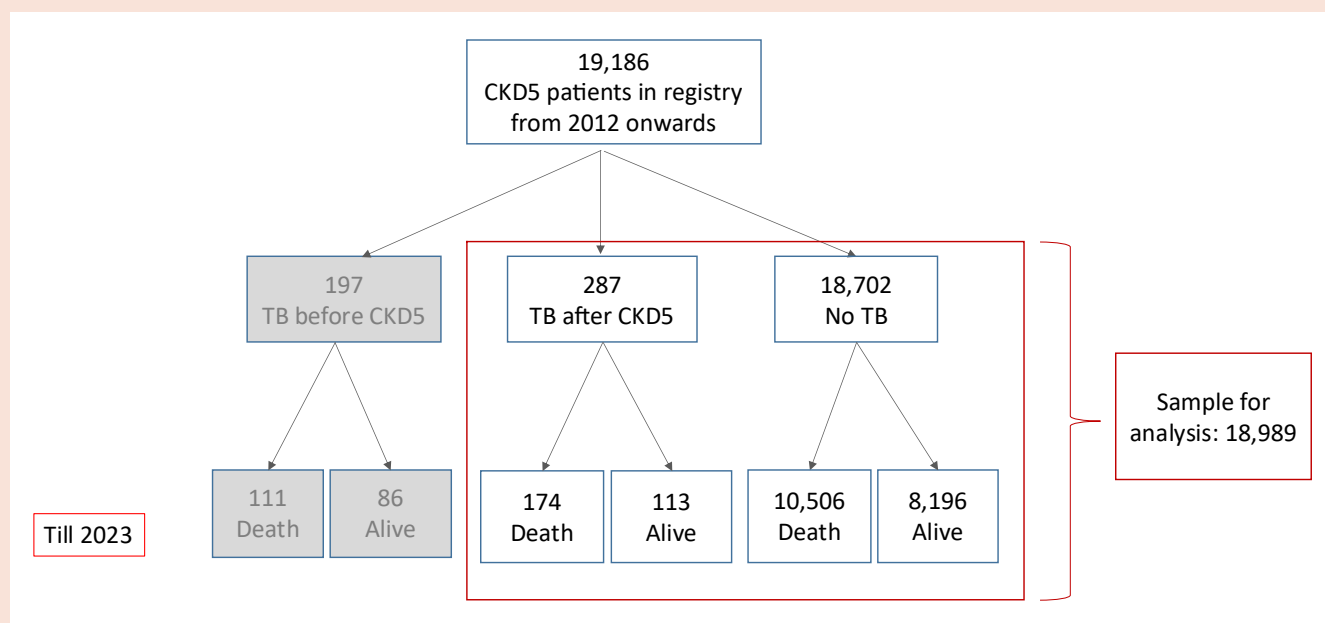
A total of 19,186 patients diagnosed with CKD5 and registered between 2012 and 2021 were included in the study (Fig. 1). After excluding 197 patients diagnosed with TB prior to CKD5 diagnosis, 18,989 eligible CKD5 patients were included in the analysis. A total of 287 eligible CKD5 patients were diagnosed with TB after their CKD5 diagnosis and 18,702 did not develop TB during the study period. Of those CKD5 patients who developed TB, 174 died during the study period, while 113 were still alive. Among the 18,702 CKD5 controls who did not develop TB, 8,196 were still alive by the end of the study period.

The annual TB incidence in this cohort of CKD5 patients ranged from 279 to 630 per 100,000 population over the period from 2012 to 2021, significantly higher than annual TB incidence in the general Singapore population which ranged between 32.6 and 41.1 per 100,000 population during the same period (2012–2021). These trends are depicted in Fig. 2. However, given that the vast majority of CKD5 patients were above 50 years of age, which differs from the age structure of the general population, the authors performed an age-adjusted comparison using age-specific TB incidence rates from Singapore's general population. When applying the general population's age-specific TB rates to the CKD5 cohort's age distribution, the authors would expect approximately 95 TB cases per year. In contrast, the authors observed an average of 489 TB cases per year in the CKD5 cohort, representing a 5.2-fold higher risk after accounting for age differences.

Univariate analysis of risk factors for TB disease post-CKD5 diagnosis

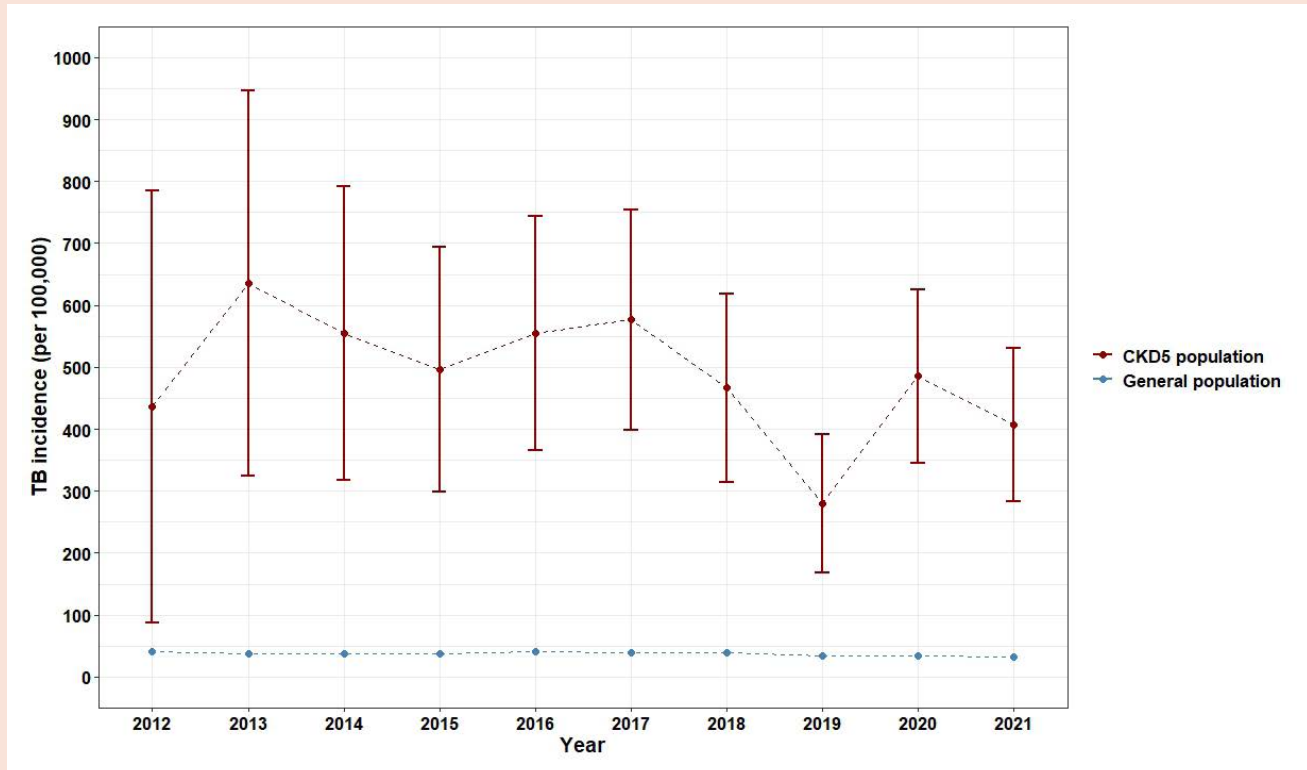
Description of the study cohort and the univariate analysis of potential risk factors for TB disease in CKD5 patients are shown in Table 1. The mean age of the cohort was 66 years old. CKD5 patients who developed TB were significantly more likely to be male (odds ratio [OR] 1.66, 95% CI 1.3–2.12, $P < 0.001$), Malay (OR 1.33, 95% CI 1.02–1.72, $P = 0.03$) or report a history of "ever smoking" (OR 2.93, 95%

Fig. 1. Study sample from the TB (2012–2021) and CKD registries (diagnosed in 2012–2021) with follow-up until 2023.



CKD5: stage 5 chronic kidney disease; TB: tuberculosis

Fig. 2. Annual TB incidence in chronic kidney disease patients and in the general population in Singapore.



CKD5: stage 5 chronic kidney disease; TB: tuberculosis

Error bar for CKD5 population indicates the 95% confidence interval of the estimated TB incidence.

CI 2.15–4.03, $P < 0.001$). In contrast, the 80 years and older age group suggested lower odds of being diagnosed with TB disease (OR 0.38, 95% CI 0.23–0.63, $P < 0.001$) when compared with the age group below 50 years.

For the CKD5 patients included in the study, nearly one-third (30.8%) did not receive dialysis; 54.2% were on haemodialysis only; 5.4% were on peritoneal dialysis only; and 9.6% had been treated with both haemodialysis and peritoneal dialysis. Renal transplantation was performed in 2.9% of this cohort. CKD5 patients who were on any type of dialysis had significantly increased odds of TB infection; haemodialysis with OR 2.31, 95% CI 1.69–3.23, $P < 0.001$, peritoneal dialysis with OR 2.53, 95% CI 1.46–4.23, $P = 0.001$; or a combination of haemodialysis and peritoneal dialysis with OR 2.55, 95% CI 1.63–3.95, $P < 0.001$, compared to those who had not been initiated on dialysis.

Multivariable analysis of risk factors for TB disease post-CKD5 diagnosis

Results from multivariable logistic regression showed that male sex, age ≥ 80 years, having ever smoked, dialysis and presence of malignancy were independently associated with the development of TB disease

in people with CKD5, as shown in Table 2. Creatinine and eGFR were excluded from the model, given that 20% of values were missing for these variables.

The statistical modelling demonstrates that being 80 years and above was associated with lower odds of developing TB disease (adjusted odds ratio [aOR] 0.41, 95% CI 0.19–0.85, $P = 0.020$). Haemodialysis and peritoneal dialysis remained associated with increased odds of TB disease (aOR 2.04, 95% CI 1.24–3.52, $P = 0.007$ and aOR 2.38, 95% CI 1.10–4.97, $P = 0.023$, respectively). Similarly, reporting a history of ever smoking was positively correlated with higher odds of TB disease post-CKD5 diagnosis (aOR 2.19, 95% CI 1.53–3.15, $P < 0.001$).

The plots of cumulative incidence for TB show those 4 risk factors that significantly impact the probability of TB disease over a period of 10 years post-CKD5 diagnosis. Having never smoked, history of malignancy, being 80 years and above and CKD5 “not on dialysis” correlated with lower risk of TB disease (Fig. 3). Competing risk comparisons for key variables are shown in Supplementary Table S1.

Results from a proportional subdistribution hazards regression model are shown in Table 3. Male sex was significantly associated with an increased risk

Table 1. Key characteristics of CKD5 patients with and without TB: univariate results and crude odds ratio.

Variables	Total (N=18989)	TB (N=287)	Non-TB (N=18702)	Crude OR	95% CI	P value
Sex, n (%)						
Female	8957 (47.2)	101 (35.2)	8856 (47.4)	Reference	Reference	Reference
Male	10032 (52.8)	186 (64.8)	9846 (52.6)	1.66	(1.3–2.12)	<0.001
Age, mean (SD)	66.3 (14.4)	63.1 (11.9)	66.3 (14.4)	0.99	(0.98–0.99)	<0.001
Age group, n (%)						
<50 years old	2313 (12.2)	41 (14.3)	2272 (12.1)	Reference	Reference	Reference
50–59 years old	3362 (17.7)	68 (23.7)	3294 (17.6)	1.14	(0.78–1.7)	0.5
60–69 years old	5077 (26.7)	86 (30)	4991 (26.7)	0.95	(0.66–1.4)	0.809
70–79 years old	4588 (24.2)	67 (23.3)	4521 (24.2)	0.82	(0.56–1.22)	0.325
≥80 years old	3649 (19.2)	25 (8.7)	3624 (19.4)	0.38	(0.23–0.63)	<0.001
Ethnicity, n (%)						
Chinese	12,756 (67.2)	183 (63.8)	12,573 (67.2)	Reference	Reference	Reference
Indian	1407 (7.4)	14 (4.9)	1393 (7.4)	0.69	(0.38–1.15)	0.184
Malay	4469 (23.5)	85 (29.6)	4384 (23.4)	1.33	(1.02–1.72)	0.03
Others	357 (1.9)	5 (1.7)	352 (1.9)	0.98	(0.35–2.15)	0.957
Smoking, n (%)						
Never	12,103 (63.7)	66 (23)	12,037 (64.4)	Reference	Reference	Reference
Ever	6196 (32.6)	98 (34.1)	6098 (32.6)	2.93	(2.15–4.03)	<0.001
NA	690 (3.6)	123 (42.9)	567 (3)	NA	NA	NA
eGFR (mL/min) at ESRD, mean (SD)	12 (4.7)	11.6 (3.1)	12 (4.7)	0.96	(0.92–1.01)	0.109
Creatinine (mg/dL) at 1st dialysis, mean (SD)	8.3 (3.5)	9.1 (3.5)	8.3 (3.5)	1.06	(1.03–1.1)	<0.001
Modality type, n (%)						
No dialysis	5854 (30.8)	46 (16)	5808 (31.1)	Reference	Reference	Reference
PD only	1019 (5.4)	20 (7)	999 (5.3)	2.53	(1.46–4.23)	0.001
HD only	10298 (54.2)	185 (64.5)	10113 (54.1)	2.31	(1.69–3.23)	<0.001
PD + HD	1818 (9.6)	36 (12.5)	1782 (9.5)	2.55	(1.63–3.95)	<0.001
Transplant, n (%)						
No	18,432 (97.1)	284 (99)	18148 (97)	Reference	Reference	Reference
Yes	557 (2.9)	3 (1)	554 (3)	0.35	(0.09–0.91)	0.068
Diabetes mellitus, n (%)						
Non- diabetic	5096 (26.8)	79 (27.5)	5017 (26.8)	Reference	Reference	Reference
Diabetic	13,892 (73.2)	208 (72.5)	13,684 (73.2)	0.97	(0.75–1.26)	0.791
NA	1 (0)	NA	1 (0)	NA	NA	NA
Malignancy, n (%)						
No	16,667 (87.8)	266 (92.7)	16,401 (87.7)	Reference	Reference	Reference
Yes	2321 (12.2)	21 (7.3)	2300 (12.3)	0.56	(0.35–0.86)	0.012
NA	1 (0)	NA (NA)	1 (0)	NA	NA	NA

CI: confidence interval; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HD: haemodialysis; NA: not available; PD: peritoneal dialysis; OR: odds ratio; SD: standard deviation; TB: tuberculosis
P values in bold denote statistical significance.

of TB disease in patients with CKD5 (adjusted hazard ratio [aHR] 1.72, 95% CI 1.30–2.28). Dialysis, regardless of modality, was associated with an increased risk of developing TB disease (aHR 2.05, 95% CI 1.18–3.58 for haemodialysis only; aHR 1.7, 95% CI 1.16–2.5 for peritoneal dialysis only; and aHR 1.76, 95% CI 1.08–2.88 for those receiving both modalities). In contrast, a history of malignancy was significantly associated with a lower risk of TB disease (aHR 0.61,

95% CI 0.39–0.96). In this model, age, diabetes and smoking status were not significant.

DISCUSSION

TB incidence in CKD5 patients versus general population

The findings suggest a significantly higher incidence of TB disease in patients with CKD5, compared to

Table 2. Adjusted odds ratio and 95% confidence interval for TB disease in CKD5 patients from a multivariable logistic model.

Variable	aOR	95% CI	P value
Age group			
<50 years old	reference	reference	reference
50–59	1.12	(0.71–1.78)	0.636
60–69	0.73	(0.46–1.18)	0.197
70–79	0.63	(0.37–1.07)	0.089
80 and above	0.41	(0.19–0.85)	0.020
Sex			
Female	reference	reference	reference
Male	1.51	(1.01–2.29)	0.049
Ethnicity			
Chinese	reference	reference	reference
Indian	0.62	(0.29–1.17)	0.178
Malay	1	(0.69–1.42)	0.985
Others	0.84	(0.21–2.25)	0.767
Dialysis modality			
No dialysis	reference	reference	reference
PD only	2.38	(1.1–4.97)	0.023
HD only	2.04	(1.24–3.52)	0.007
PD + HD	1.65	(0.82–3.29)	0.152
Never smoked	reference	reference	reference
Ever smoked	2.19	(1.53–3.15)	<0.001
Diabetes	0.66	(0.47–0.92)	0.013
History of malignancy	0.57	(0.29–1.02)	0.080

aOR: adjusted odds ratio; CI: confidence interval; HD: haemodialysis; PD: peritoneal dialysis

the incidence of TB disease in the general Singapore resident population (406 per 100,000 population vs 32.6 per 100,000 in 2021) over the same period. A similar study, conducted in 2011 by Dobbler et al., found TB incidence to be 66.8 per 100,000 population per year in CKD patients receiving dialysis in Australia, compared to the general population incidence of 5.7 per 100,000 population.¹⁵ This study—conducted in a medium TB incidence setting with overall incidence adjusted for TB incidence by country of birth—echoes findings observed in several other international studies.^{17,8} In a recent study published in the US population, TB incidence in the kidney failure population ranged from 26.1 to 45.4 per 100,000 population, in contrast with general population TB incidence of 2.1 to 3.5 per 100,000 population.²⁴ The findings are also consistent with evidence on the vulnerability of CKD patients to TB, attributable to alterations in the immune system resulting from elevated uraemia and impairment of humoral and cell-mediated immune function.^{8,18,20}

Of the patients included in the study, the odds of TB disease for patients on dialysis were at least two-fold higher than those who never received dialysis. The authors postulate the reason for this is the competing risk of death in patients with CKD5 who did not receive dialysis, as this group

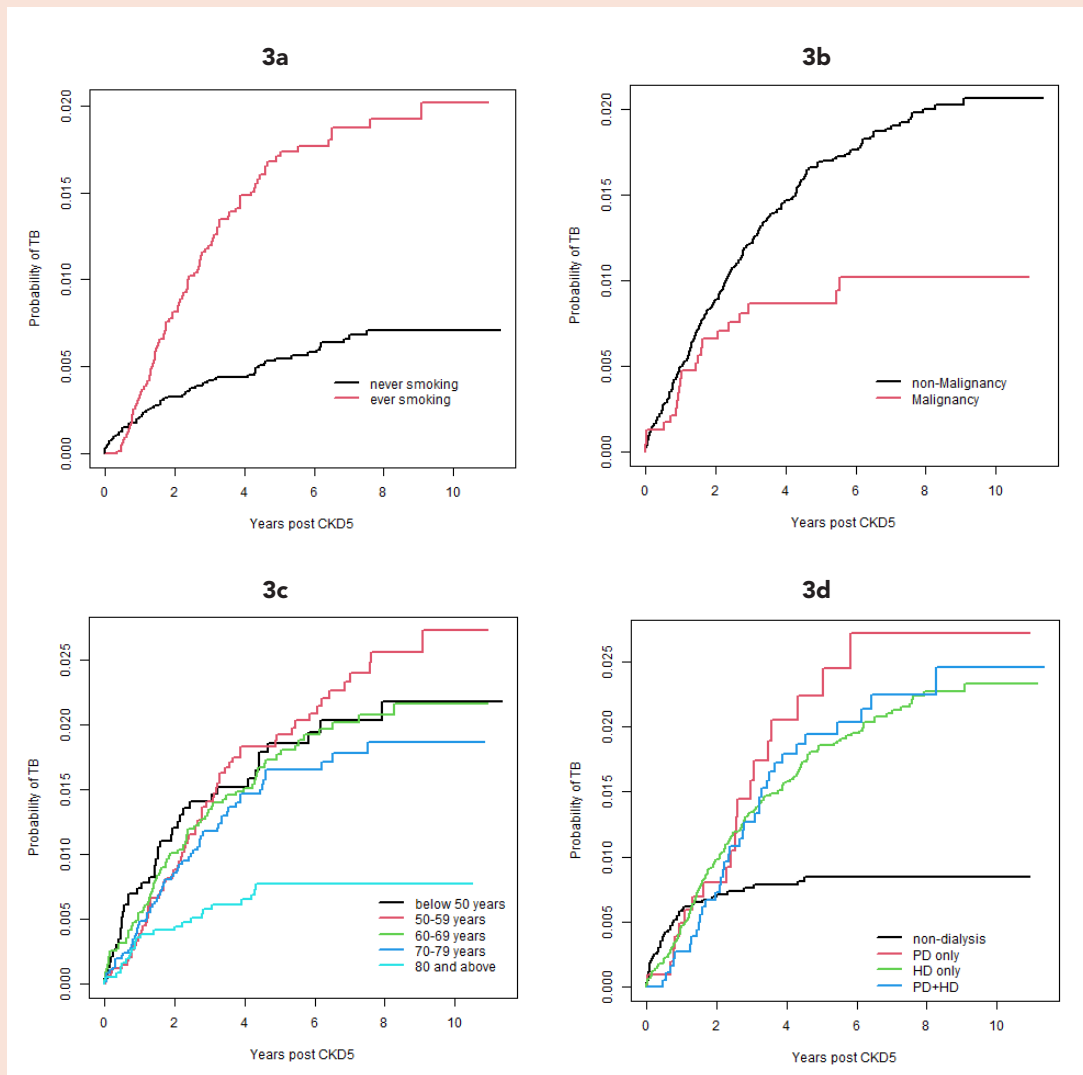
of patients likely died before they had time to develop or reactivate TB disease, compared to those who received dialysis. Second, dialysis patients—especially those on haemodialysis—are at a greater risk of TB as they are often younger and therefore had a longer time to develop or reactivate TB.

Risk factors for TB in CKD patients

The study found several risk factors associated with developing TB disease following a CKD5 diagnosis: they included being male, of Malay ethnicity and having a history “ever smoking”. Other studies have also found significant associations between smoking and TB, including a study of latent TB infection (LTBI) in CKD patients in Indonesia by Bandiara et al. which found interferon-gamma release assay (IGRA) positivity to be more frequent in smokers.¹⁴ Cigarette smoke contains harmful components which lead to peribronchial inflammation and fibrosis, disruption of mucociliary clearance and subsequently increase susceptibility to pulmonary infections including TB progression. However, they did not observe significant association between age and sex otherwise.¹⁴

In this analysis, it is observed that the age group 80 years old and above correlated with a lower rate of TB disease compared to the age group below 50 years old. The authors also found that 74% of CKD5 patients

Fig. 3. Estimated cumulative incidence curves of TB disease with death as competing event (death was not plotted) for significant risk factors: smoking (3a), history of malignancy (3b), age groups (3c) and CKD5 treatment modality (3d).



CKD5: stage 5 chronic kidney disease; TB: tuberculosis

who were not on dialysis were aged >70 years old. This is likely a reflection of an individualised clinical decision-making process made between the managing renal physician with the patient after weighing risks and benefits of dialysis initiation including the impact on quality of life and expected survival outcomes.²⁵ The authors hypothesised that the seemingly lower risk for TB disease in CKD5 patients aged 80 years and above may be due to the shorter time and lower chance they have of developing TB prior to death from other causes, rather than a protective effect of older age. Another potential explanation for this could be that elderly patients may have increased social isolation and frailty.²⁶ This hypothesis may be borne out in another study where most TB-dialysis patients were also in the age range of 55–74 years.¹⁴ These findings would

suggest that patients of advanced age may benefit the least from TB screening, as compared to younger patients, given the high competing risk of death.

Additionally, the observation of higher odds of TB in dialysed patients is consistent with findings from studies modelling transmission in enclosed and less ventilated, institutional settings like dialysis centres—showing that TB transmission may be facilitated especially when patients attend 3 times a week.^{7,27} Dialysis centres are often environments with closed, limited air exchanges per hour and minimal UV light exposure thereby providing an ideal environment for airborne particles containing *M. tuberculosis* to remain viable and infectious.^{7,27} Measuring TB transmission is challenging as it depends on multiple factors, such as the infectiousness of the index patient,

Table 3. Relative risk of each risk factor for TB disease in CKD5 patients from a proportional sub-distribution hazards regression model.

Variable	Sub-distribution hazard ratio Adjusted (relative risk)	95% CI	P value
Age group	Reference	Reference	Reference
<50 years old	1.13	(0.76–1.68)	0.540
50–59 years old	1.05	(0.72–1.55)	0.790
60–69 years old	0.63	(0.69–1.61)	0.810
70–79 years old	1.72	(0.36–1.1)	0.100
80 years old and above			
Sex	Reference	Reference	Reference
Female	1.72	(1.3–2.28)	<0.001
Male			
Ethnicity	Reference	Reference	Reference
Chinese	0.65	(0.37–1.11)	0.120
Indian	1.28	(0.98–1.66)	0.072
Malay	0.92	(0.38–2.24)	0.860
Others			
Dialysis modality	Reference	Reference	Reference
No dialysis	2.05	(1.18–3.58)	0.011
PD only	1.7	(1.16–2.5)	0.007
HD only	1.76	(1.08–2.88)	0.024
PD + HD			
Diabetes	0.92	(0.7–1.21)	0.55
History of malignancy	0.61	(0.39–0.96)	0.031

CKD5: stage 5 chronic kidney disease; HD: haemodialysis; PD: peritoneal dialysis; TB: tuberculosis

the immunity of exposed individuals, the frequency and proximity of exposure and lastly the environment in which the exposure occurred.⁷

CKD5 patients with a history of malignancy were less likely to develop TB disease although the authors believe this may result from other confounding factors either directly or indirectly related to the malignancy itself. Often, patients who are diagnosed with malignancy undergo screening for TB infection prior to most chemotherapy regimens. They might therefore have been diagnosed with TB infection and received preventive therapy, which subsequently reduces the risk of TB reactivation. Alternatively, they may not have had enough time to develop TB disease given their individualised limited prognosis and lifespan from the malignancy point of view.

Case detection and screening for TB

Given the findings of a higher incidence of TB in patients with CKD5, particularly those on dialysis, the authors would suggest increased vigilance in this patient population to test for TB, with the understanding that the clinical presentation of TB in dialysis patients is often atypical.⁸ The presence of unexplained systemic symptoms should prompt a detailed clinical history and physical examination, and a high suspicion of TB disease including extrapulmonary disease.⁸

Further, given the high incidence of TB, patients with CKD5 who are planned for initiation of dialysis

or already on dialysis could benefit from latent TB screening. This typically involves screening with IGRA. A positive IGRA test would likely lead to efforts to exclude active TB, which would typically include a chest X-ray, acid-fast bacilli smear and mycobacterial cultures. These tests would help to differentiate between LTBI and asymptomatic TB disease.^{15,28} Those diagnosed with LTBI would typically be treated with a 4-month course of rifampicin. The treatment of LTBI and/or TB disease would not only provide individual benefits, but also be beneficial from a public health perspective. This is in line with the updated Singapore Tuberculosis Management Guidelines 2024.^{6,28} However, the cost effectiveness of this approach is unclear and requires further analysis.²⁹

Study strengths and limitations

The main strength of this study includes access to 2 well-established, systematic national registries with comprehensive data on key outcomes and variables of interest. The authors' primary analysis therefore used a complete case analysis and used independent variables with the least missing values for statistical modelling (max 10–20%). The large number of patients included in the analysis allows generalisability of the findings to the Singapore's local context.

However, the authors identified that a major limitation was the lack of complete data for certain variables; for instance, eGFR values were unavailable

for 35% of the TB cohort. While missing data may have influenced results by excluding observations from the model fitting, to address this concern a sensitivity analysis was conducted using multiple imputation to handle the missing values. Multiple imputation was performed, accounting for the probability of missingness and both the multivariable logistic regression and Fine-Gray competing risks models were re-run including the imputed values. The results from the sensitivity analysis were consistent with the main findings. Another limitation of this study was the reliance on established registry datasets, which may not collect all variables desired for the authors' analysis, including the proportion of pulmonary TB versus extra-pulmonary TB in CKD5 patients or the proportion of CKD5 patients who received or did not receive a tuberculin skin test or IGRA testing upon dialysis initiation or as part of their CKD work-up. While this may not have influenced the results, these variables could provide additional insights into TB prevalence in the CKD5 patients locally and should be considered in future analysis.

CONCLUSION

The findings strengthen the evidence on the increased risk among CKD5 patients of developing TB disease, compared to the general population, especially in a moderate TB incidence country with a growing CKD5 population such as Singapore. This, together with the risk factors associated with developing TB disease in this population group—being male, of Malay ethnicity, having a history of smoking or receiving dialysis—should be considered to target case detection and screening for TB in CKD5 patients. Further studies are also needed to assess the interval benefit of latent TB screening, to assess the feasibility and cost-effectiveness of reducing TB incidence in the CKD5 population in Singapore and to quantify the magnitude of benefit from treating LTBI in a population with high-competing risk of death.

Supplementary materials

Table S1. STROBE Statement—Checklist of items that should be included in reports of cohort studies.
Table S2. Competing risk comparisons for key variables.

Ethics statement

Patient data were aggregated and de-identified for this research, and the use was approved by the Ministry of Health as custodians of the TB Registry, and the National Registry of Diseases Office Policy, Research and Surveillance Division for the Renal Registry data (10/09/2025).

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. This research received no specific grant from any funding agency.

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Depressive and anxiety symptoms among migrant workers and migrant domestic workers in Singapore

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ABSTRACT

Introduction: Enhancing the understanding of mental health of migrant workers (MWs) and migrant domestic workers (MDWs) is both economically and morally important. This study aimed to examine the prevalence and correlates of depressive and anxiety symptoms among MWs and MDWs in Singapore.

Methods: This cross-sectional study recruited 1465 MWs from August 2022 to July 2023, and 1462 MDWs from March 2023 to November 2023 through convenience sampling. Depressive symptoms were assessed using Patient Health Questionnaire-9, whereas anxiety symptoms were evaluated using the Generalized Anxiety Disorder-7. Both scales were dichotomised at a cut-off score of 10. Covariates included in the analysis were sociodemographic characteristics, stress level, insomnia, social support and resilience. Correlates were examined using multivariable logistic regression models.

Results: Among MWs, 0.83% had moderate-to-severe depressive symptoms and 1.25% had mild-to-severe anxiety symptoms. Among MDWs, 4.05% had moderate-to-severe depressive symptoms and 4.23% had moderate-to-severe anxiety symptoms. MWs were more likely to develop anxiety symptoms if they had low resilience (adjusted prevalence ratio [APR] 2.41), and less likely to develop anxiety symptoms if they had high resilience (APR 0.71). MDWs were more likely to develop depressive symptoms if they worked >14 hours per day (APR 1.42), and less likely to develop depressive symptoms if they had high resilience (APR 0.55).

Conclusion: Enhancing resilience among both groups is vital for protection against depressive and anxiety symptoms. The findings also highlight the detrimental effects of overworking on the mental health of MWs and MDWs.

Keywords: depression, mental health, psychiatry, psychology, public health

CLINICAL IMPACT

What is New

- This study examined the prevalence of depressive and anxiety symptoms among MWs and MDWs within a large sample.
- The authors also identified significant correlates of depressive and anxiety symptoms, such as having resilience and long working hours.

Clinical Implications

- Enhancing resilience among both groups is essential to protect against depressive and anxiety symptoms.
- Furthermore, the findings underscore the detrimental effects of overworking on the mental health of MWs and MDWs.

INTRODUCTION

Approximately 68.4% of international migrants in the labour force are located in higher-income countries.¹ These migrants may be low-to-semi-skilled migrant workers (MWs) and migrant domestic workers (MDWs), who faced limited job opportunities and poverty in their home countries. Although their contributions fuel the economic growth of their host countries, numerous studies have documented the challenges that they face, which include poor living conditions, increased risk of workplace injuries and stigmatisation by locals.²⁻⁴

These challenges make them vulnerable to mental health problems, such as depression and anxiety.^{3,5} A systematic review and meta-analysis of 7 studies on MWs reported the overall prevalence of depression

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at 38.99% and anxiety at 27.31%.⁵ Poor mental health outcomes were also associated with various factors, including sociodemographic, psychological, biological, occupational and environmental characteristics.⁵ As an often overlooked segment of society, coupled with the intangible nature of mental health, MWs' and MDWs' mental health may often be neglected. As such, tackling the issue of migrant mental health is pertinent because (1) it is a basic human right,⁶ and (2) understanding and safeguarding their well-being reinforce the economic and political reputation of the host country.

Singapore is one of the many countries that relies on a migrant workforce to alleviate its shortage of low and semi-skilled labour. Its labour force comprises 1,138,200 semi-skilled MWs.⁷ Male MWs primarily work in construction, marine shipyards and process sectors, while female MDWs predominantly engage in caregiving and domestic work. With rising societal awareness and interest in humanitarian issues, extensive research on MWs' and MDWs' mental health has been conducted in Singapore before and during the COVID-19 pandemic.

For instance, a Singapore-based study among male construction MWs found that 29% had moderate-to-extreme severe depression and 37% had moderate-to-extreme severe anxiety.⁸ Farwin et al. further showed that among low-wage MWs, the reasons for mental health burden include poor living conditions, fear of deportation, lack of avenues to seek help and difficulty in accessing healthcare services.² Among MDWs, a study found that 52.5% of them were stressed and 20% felt isolated.⁹

The massive COVID-19 outbreak among dormitory-residing MWs in 2020 highlighted the overcrowded and poor living conditions, as well as the lack of mental health literacy and mental healthcare support. This led to various schemes such as the Dormitories Transition Scheme and New Dormitory Standards being implemented to improve MWs' living conditions.^{10,11} For instance, to enhance livability and maximise space, each room is limited to 12 persons and the spacing between beds is minimally 1 metre.^{10,11} In November 2020, Singapore's Ministry of Manpower (MOM) together with government psychologists, the Institute of Mental Health, and non-governmental organisations such as the Migrant Workers' Centre and HealthServe, set up the Project Dawn taskforce and launched a multi-year framework to raise mental health literacy, build a support ecosystem for MWs and improve access to care services.¹² Since April 2022, MOM has also established a primary care system dedicated to providing accessible and affordable primary care to MWs, including mental healthcare.¹³

For MDWs, employers are required to provide 1 mandatory rest day each month that cannot be compensated from 1 January 2023 onwards.¹⁴ The Care Sisters group was also formed to train MDWs to provide mental well-being support to fellow MDWs who may be facing issues.¹⁴ It is against this backdrop that this study was conducted to examine the prevalence and correlates of depression and anxiety among MWs and MDWs.

METHODS

This mixed-method study design comprised 2 phases: qualitative and quantitative. This analysis only examined the quantitative aspect of the study, which had a cross-sectional study design, and investigated the prevalence and correlates of psychological distress among MWs and MDWs.

The study sample included the 3 largest nationalities among MWs, namely Indian, Chinese and Bangladeshi, as well as major nationalities among MDWs, namely Filipino, Indonesians and Burmese. For MWs, they were required to be employed in the construction, marine shipyard or process sectors at the time of participation. For MDWs, they had to be working in Singapore at the time of participant recruitment. Additionally, participants had to be of legal working age (MW ≥ 18 years and MDW ≥ 23 years). The questionnaire was available in English and the participants' native languages (Tamil, Mandarin, Bengali, Tagalog, Bahasa Indonesia and Burmese) to ensure they could respond in the language they best understood. Forward translation of questionnaires was performed by a certified translation firm. The research team also vetted the questionnaires to ensure that the concepts were conveyed appropriately.

The sample size was calculated using descriptive statistics from a validation study conducted in Macau on Filipino MDWs.¹⁵ A minimum size of 487 for each nationality was sufficient to estimate the true mean value within $\pm 7\%$ at a 95% confidence level, with a power of 80% and a probability of the confidence interval width being 0.80.^{16,17}

The MW sample was obtained through convenience sampling at designated dormitories and recreation centers for MWs ($n=1465$) and at various locations where MDWs gathered on weekends ($n=1462$). MOM facilitated access to participants by connecting the research team with recreational centres and construction sites management team. For MOM recreational centres, the research team members briefed the MWs on the survey and guided interested MWs to the research stations. For construction sites, the company's person-in-charge helped to direct interested MWs to the research stations. The study

was conducted by recruiting all the MWs first (from August 2022 to July 2023) before proceeding to recruit all the MDWs (from March 2023 to November 2023). There was no movement restriction due to COVID-19 during the study period.

The interviewers were experienced researchers who were involved in several large epidemiology surveys and could speak the native languages of the participants. Moreover, the study recruited volunteers proficient in Bengali and Burmese, who were also then trained to administer the questionnaire. As participants' literacy levels varied, researchers explained the meaning of certain words to participants in simpler terms if they expressed difficulty in understanding.

Before the interview, all participants were assured that the data were anonymised, and that their participation in the survey would not affect their employment or the services they received (e.g. healthcare, company insurance). To provide further reassurance, verbal informed consent was obtained from them instead of written consent. All participants were given a help-seeking brochure and received SGD25 cash reimbursement. If participants reported distress, the study had follow-up protocols to provide immediate support and access to mental healthcare. This study was approved by the National University of Singapore Institutional Review Board (2021-724).

Outcome: Depressive and anxiety symptoms

The outcomes of this analysis were the assessment of depressive and anxiety symptoms. Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9),¹⁸ which comprises 9 items rated on a 4-point Likert scale. The overall score was obtained by summing scores of all items, with higher scores implying greater severity of depressive symptoms. The analysis categorised the scores into no-to-mild depressive symptoms (score <10) and presence of depressive symptoms (moderate-to-severe) (score ≥10).¹⁹

Anxiety symptoms were evaluated using the Generalized Anxiety Disorder-7 (GAD-7),²⁰ which has 7 items rated on a 4-point Likert scale. The total score was calculated by adding all item scores, with a higher score indicating greater severity of anxiety symptoms. The scores were categorised into no-to-mild anxiety symptoms (score <10) and the presence of anxiety symptoms (moderate-to-severe) (score ≥10) in the analysis.¹⁹

In the dataset, PHQ-9 was shown to have acceptable-to-good internal consistency (Cronbach's alpha for MWs and MDWs: 0.8). Similarly, GAD-7 had good internal consistency (Cronbach's alpha for MWs and MDWs: 0.9). Both scales were well-validated in other migrant settings.¹⁵

Covariates: Sociodemographic, stress, insomnia, social support and resilience

The covariates included in this analysis were sociodemographic characteristics, stress, insomnia, social support and resilience. The following sociodemographic data were collected: age, nationality, educational qualification, marital status, salary, number of work hours per day, number of years in Singapore, attachment to an employment agency and having a day off. The following variables were categorised into tertiles: salary, number of work hours per day and number of years in Singapore.

Stress level was assessed using the stress component of the Depression Anxiety and Stress Scales.²¹ It consists of 7 items rated on a 4-point Likert scale. Responses were reverse coded before adding to calculate the total score, with a higher score indicating a higher stress level. The total scores were grouped into no stress level (score <15) and mild-to-extremely severe stress level (score ≥15).

Insomnia was evaluated using the 7-item Insomnia Severity Index,²² with higher scores indicating a higher severity of insomnia. All responses were dichotomised at a cut-off score of 10.²²

The Multidimensional Scale of Perceived Social Support was administered to assess social support.²³ It is a 12-item questionnaire that examines perceived social support received from family, friends and significant other. Responses were rated on a 7-point Likert scale, with higher scores indicating better perceived social support received. All scores were categorised into low perceived support (score 12–35), medium perceived support (score 36–60) and high perceived support (score 61–84).²³

The Brief Resilience Scale was used to evaluate resilience.²⁴ It has 6 items rated on a 5-point Likert scale, with a higher total score indicating higher resilience. The scores were grouped into low resilience (1–2.99), normal resilience (3–4.3) and high resilience (4.31–5).²⁴ The scale has poor-to-acceptable internal consistency (Cronbach's alpha: MWs 0.7 and MDWs 0.6).

Statistical analysis

PHQ-9 and GAD-7 scores were summarised as median (interquartile range [IQR]). Additionally, the categorisation of these scores and the covariates were summarised as percentages and counts. Correlates of depressive and anxiety symptoms were examined using negative binomial regression and adjusted for the aforementioned covariates. This approach was chosen because the distributions of PHQ-9 and GAD-7 scores among MWs and MDWs were skewed to the right. The results of the negative binomial regression models were presented as adjusted prevalence ratio

(APR) and 95% confidence interval (CI). All statistical analyses were conducted using SPSS Statistics software version 23.0 (IBM Corp, Armonk, NY, US) and Stata/MP version 18.0 (StataCorp, College Station, TX, US) with 2-sided tests at a significance level of 0.05. Missing data were handled via listwise deletion.

RESULTS

The sample sizes for MWs and MDWs are presented in Fig. 1. The participants' characteristics are summarised in Table 1 for MWs and Table 2 for MDWs. The highest proportion of MWs were aged 30–39 years (42.46%, $n=622$), had secondary school educational qualification (47.81%, $n=700$), were married (72.70%, $n=1065$) and had a day off (87.21%, $n=1255$). Moreover, 1.71% ($n=25$) endorsed mild-to-extremely-severe stress symptoms, 4.05% ($n=56$) endorsed insomnia, 8.22% ($n=120$) reported low resilience and 1.37% ($n=20$) reported having low social support. Table S1 presents the salary structure of MWs stratified by nationality.

For MDWs (Table 2), the highest proportion of them were aged 30–39 years (39.47%, $n=577$), had secondary school educational qualification (56.09%, $n=820$), single (39.75%, $n=580$) and had a rest day (97.25%, $n=1412$). Furthermore, 8.00% ($n=117$) endorsed mild-to-extremely-severe stress symptoms, 14.92% ($n=215$) endorsed insomnia, 13.60% ($n=198$) reported low resilience and 8.65% ($n=125$) reported having low social support. Table S2 presents the salary structure of MDWs stratified by nationality.

The median PHQ-9 score was 1 (IQR 0–1) for MWs and 1 (IQR 0–3) for MDWs. The median GAD-7 score was 0 (IQR 0–1) for MWs and 0 (IQR 0–3) for MDWs. Among MWs (Table 1), 5.15% (95% CI 4.12–6.42%) had mild depressive symptoms and 0.83% (95% CI 0.47–1.46%) had moderate-to-severe depressive

symptoms. Moreover, 5.05% (95% CI 4.03–6.31%) had mild anxiety symptoms and 1.25% (95% CI 0.79–1.97%) had moderate-to-severe anxiety symptoms (Table 1).

Among MDWs (Table 2), 13.57% (95% CI 11.83–15.51%) had mild depressive symptoms and 4.05% (95% CI 3.11–5.25%) had moderate-to-severe depressive symptoms. Furthermore, 10.21% (95% CI 8.72–11.93%) had mild anxiety symptoms and 4.23% (95% CI 3.28–5.44%) had moderate-to-severe anxiety symptoms.

Table 3 presents the regression results for MWs. MWs were more likely to develop depressive symptoms if they were of Chinese nationality (versus [vs] India, APR 1.92, 95% CI 1.02–3.61); Bangladesh nationality (vs India, APR 1.46, 95% CI 1.07–1.99); had pre-tertiary education (vs secondary, APR 1.52, 95% CI 1.17–1.98) or tertiary educational qualification (vs secondary, APR 1.99, 95% CI 1.30–3.04); worked 8–10 hours per day (vs ≤ 8 hours, APR 1.56, 95% CI 1.11–2.19); had mild-to-extremely severe stress symptoms (vs no stress symptoms, APR 3.75, 95% CI 1.74–8.11); reported insomnia (vs no insomnia, APR 3.86, 95% CI 2.32–6.44); and had low resilience (vs normal resilience, APR 2.07, 95% CI 1.38–3.10).

The participants were less likely to develop depressive symptoms if they had a monthly salary greater than SGD1600 (vs $\leq$ SGD675; APR 0.48, 95% CI 0.26–0.87); worked in Singapore either for 1.5–9 years (vs ≤ 1.5 years; APR 0.59, 95% CI 0.43–0.81) or more than 9 years (vs ≤ 1.5 years; APR 0.59, 95% CI 0.40–0.88); and had high resilience (vs normal resilience; APR 0.71, 95% CI 0.53–0.97).

Moreover, they were more likely to develop anxiety symptoms if they had pre-tertiary (vs secondary education; APR 1.42, 95% CI 1.07–1.89) or tertiary educational qualification (vs secondary education;

Fig. 1. Flowchart showing the sample sizes for migrant workers and migrant domestic workers.

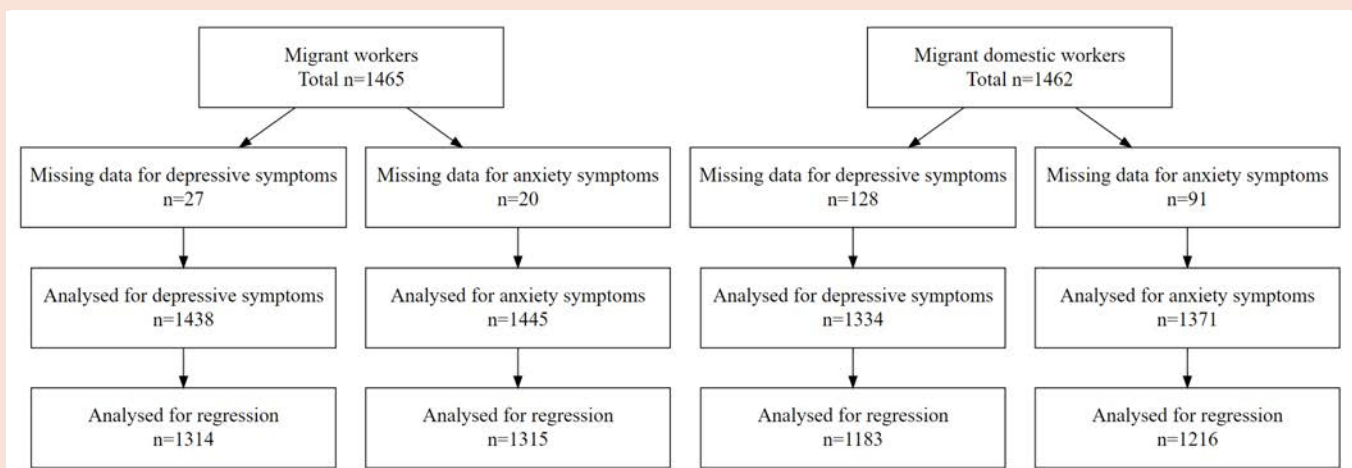


Table 1. Characteristics of migrant workers (n=1465).

Variables	no. (%)
Age group, years	
20–29	390 (26.62)
30–39	622 (42.46)
40–49	352 (24.03)
50–62	101 (6.89)
Nationality	
China	488 (33.31)
India	488 (33.31)
Bangladesh	489 (33.38)
Educational qualification ^a	
Primary and below	105 (7.17)
Secondary	700 (47.81)
Pre-tertiary	504 (34.43)
Tertiary	151 (10.31)
Others	4 (0.27)
Marital status	
Married	1065 (72.70)
Single	375 (25.60)
Separated/widowed/divorced	20 (1.37)
Cohabiting	5 (0.34)
Monthly salary, SGD	
≤675	484 (33.43)
>675–1600	486 (33.56)
>1600	478 (33.01)
No. of hours worked per day	
≤8	779 (53.32)
>8–0	538 (36.82)
>1	144 (9.86)
No. of years in Singapore	
≤1.5	504 (34.64)
>1.5–9	518 (35.60)
>9	433 (29.76)
Do you have a day off?	
No	184 (12.79)
Yes	1255 (87.21)

Table 1. Characteristics of migrant workers (n=1465). (Cont'd)

Variables	no. (%)
Depressive symptoms	
No-to-mild	1426 (99.17)
Moderate-to-severe	12 (0.83)
Anxiety symptoms	
No-to-mild	1427 (98.75)
Moderate-to-severe	18 (1.25)
Stress symptoms	
No	1437 (98.29)
Mild-to-extremely severe	25 (1.71)
Insomnia	
No	1327 (95.95)
Yes	56 (4.05)
Resilience	
Low	120 (8.22)
Normal	1038 (71.10)
High	302 (20.68)
Perceived social support	
Low	20 (1.37)
Medium	495 (33.95)
High	943 (64.68)

SGD: Singapore dollars

^a It is possible that respondents selected the closest matching option from the list.

Missing data: educational qualification (n=1), monthly salary in SGD (n=17), no. of hours worked per day (n=4), no. of years in Singapore (n=10), do you have a day off (n=26), depressive symptoms (n=27), anxiety symptoms (n=20), stress symptoms (n=3), insomnia (n=82), resilience (n=5), perceived social support (n=7).

APR 1.96, 95% CI 1.22–3.15); worked 8–10 hours per day (vs ≤8 hours; APR 1.85, 95% CI 1.27–2.70); had mild-to-extremely severe stress symptoms (vs no stress symptoms; APR 4.11, 95% CI 1.80–9.43); reported insomnia (vs no insomnia; APR 3.72, 95% CI 2.10–6.57); and had low resilience (vs normal resilience; APR 2.41, 95% CI 1.57–3.72).

They were less likely to develop anxiety symptoms if they were older (40–49 vs 20–29 years: APR 0.59, 95% CI 0.36–0.98; 50–62 vs 20–29 years: APR 0.48, 95% CI 0.23–0.99); of Bangladesh nationality (vs India; APR 0.65, 95% CI 0.47–0.90); had a monthly salary greater than SGD1600 (vs ≤SGD675, APR 0.39, 95% CI 0.20–0.74); had a day off (OR 0.52, 95%

Table 2. Characteristics of migrant domestic workers (n=1462).

Variables	no. (%)
Age group, years	
20–29 ^a	247 (16.89)
30–39	577 (39.47)
40–49	521 (35.64)
50–60	117 (8.00)
Nationality	
Philippines	487 (33.31)
Myanmar	488 (33.38)
Indonesia	487 (33.31)
Educational qualification ^b	
Primary and below	85 (5.81)
Secondary	820 (56.09)
Pre-tertiary	418 (28.59)
Tertiary	136 (9.30)
Others	3 (0.21)
Marital status	
Married	547 (37.49)
Single	580 (39.75)
Separated/widowed/divorced	327 (22.41)
Cohabiting	5 (0.34)
Monthly salary, SGD	
≤650	566 (38.82)
>650–750	432 (29.63)
>750	460 (31.55)
No. of hours worked per day	
≤12 hours	691 (47.66)
>12–14 hours	350 (24.14)
>14 hours	409 (28.21)
No. of years in Singapore	
≤4 years	467 (34.62)
>4–10 years	473 (35.06)
>10 years	409 (30.32)
Do you have a day off? ^c	
No	40 (2.75)
Yes	1412 (97.25)

Table 2. Characteristics of migrant domestic workers (n=1462). (Cont'd)

Variables	no. (%)
Depressive symptoms	
No-to-mild	1280 (95.95)
Moderate-to-severe	54 (4.05)
Anxiety symptoms	
No-to-mild	1313 (95.77)
Moderate-to-severe	58 (4.23)
Stress symptoms	
No	1318 (91.85)
Mild-to-extremely severe	117 (8.15)
Insomnia	
No	1226 (85.08)
Yes	215 (14.92)
Resilience	
Low	198 (13.60)
Normal	1084 (74.45)
High	174 (11.95)
Perceived social support	
Low	125 (8.65)
Medium	494 (34.19)
High	826 (57.16)

SGD: Singapore dollars

^a The youngest age is 23 years, which is the legal working age for migrant domestic workers (MDWs).^b It is possible that respondents selected the closest matching option from the list.^c Each MDW was given a Ministry of Manpower (MOM) hotline information pamphlet prior to the survey and it was mentioned to the MDWs that they can refer to MOM for any assistance. Missing data: marital status (n=3), monthly salary in SGD (n=4), no. of hours worked per day (n=12), no. of years in Singapore (n=113), do you have a day off? (n=10), depressive symptoms (n=128), anxiety symptoms (n=91), stress symptoms (n=27), insomnia (n=21), resilience (n=6), perceived social support (n=17).

CI 0.36–0.74); and high resilience (vs normal resilience, APR 0.71, 95% CI 0.51–0.99).

Table 4 shows the regression results for MDWs. MDWs were more likely to develop depressive symptoms if they worked >14 hours (vs ≤12 hours, APR 1.42, 95% CI 1.16–1.74); had mild-to-extremely severe stress symptoms (APR 2.47, 95% CI 1.81–3.39); and had symptoms of insomnia (APR 3.02, 95% CI 2.40–3.81). They were less likely to develop depressive symptoms if they were of Indonesian

Table 3. Regression results for migrant workers.

Variables	Depressive symptoms (n=1314)		Anxiety symptoms (n=1315)	
	APR (95% CI)	P value	APR (95% CI)	P value
Age group, years				
20–29	Ref		Ref	
30–39	1.01 (0.70–1.45)	0.969	0.95 (0.63–1.44)	0.818
40–49	0.79 (0.50–1.25)	0.319	0.59 (0.36–0.98)	0.043
50–60	0.82 (0.43–1.57)	0.543	0.48 (0.23–0.99)	0.048
Nationality				
India	Ref		Ref	
China	1.92 (1.02–3.61)	0.043	1.36 (0.68–2.75)	0.387
Bangladesh	1.46 (1.07–1.99)	0.016	0.65 (0.47–0.90)	0.010
Educational qualification				
Primary and below	1.28 (0.80–2.06)	0.302	1.02 (0.61–1.70)	0.954
Secondary	Ref		Ref	
Pre-tertiary	1.52 (1.17–1.98)	0.002	1.42 (1.07–1.89)	0.016
Tertiary	1.99 (1.30–3.04)	0.001	1.96 (1.22–3.15)	0.005
Others	2.50 (0.35–18.10)	0.363	1.26 (0.12–13.21)	0.845
Marital status				
Married	Ref		Ref	
Single	0.95 (0.66–1.36)	0.764	0.92 (0.61–1.38)	0.685
Separated/widowed/divorced	1.10 (0.45–2.69)	0.843	2.07 (0.79–5.37)	0.137
Cohabiting	2.27 (0.49–10.54)	0.296	2.27 (0.4–12.94)	0.356
Monthly salary, SGD				
≤675	Ref		Ref	
>675–1600	0.75 (0.55–1.01)	0.058	1.01 (0.73–1.40)	0.957
>1600	0.48 (0.26–0.87)	0.016	0.39 (0.20–0.74)	0.004
No. of hours worked per day				
≤8	Ref		Ref	
>8–10	1.56 (1.11–2.19)	0.010	1.85 (1.27–2.70)	0.001
>10	1.39 (0.87–2.22)	0.170	1.07 (0.64–1.80)	0.784
No. of years in Singapore				
≤1.5	Ref		Ref	
>1.5–9	0.59 (0.43–0.81)	0.001	0.86 (0.60–1.23)	0.403
>9	0.59 (0.40–0.88)	0.009	0.74 (0.48–1.14)	0.169
Do you have a day off?				
No	Ref		Ref	
Yes	0.84 (0.60–1.18)	0.321	0.52 (0.36–0.74)	<0.001

Table 3. Regression results for migrant workers. (Cont'd)

Variables	Depressive symptoms (n=1314)		Anxiety symptoms (n=1315)	
	APR (95% CI)	P value	APR (95% CI)	P value
Stress symptoms				
No	Ref		Ref	
Yes	3.75 (1.74–8.11)	0.001	4.11 (1.80–9.43)	0.001
Insomnia				
No	Ref		Ref	
Yes	3.86 (2.32–6.44)	<0.001	3.72 (2.10–6.57)	<0.001
Resilience				
Low	2.07 (1.38–3.10)	<0.001	2.41 (1.57–3.72)	<0.001
Normal	Ref		Ref	
High	0.71 (0.53–0.97)	0.032	0.71 (0.51–0.99)	0.044
Perceived social support				
Low	2.43 (1.00–5.90)	0.051	1.27 (0.46–3.49)	0.649
Medium	Ref		Ref	
High	1.14 (0.89–1.46)	0.289	1.18 (0.90–1.54)	0.243

APR: adjusted prevalence ratio; CI: confidence interval; SGD: Singapore dollars
P values in bold indicate statistical significance.

Table 4. Regression results for migrant domestic workers.

Variables	Depressive symptoms (n=1183)		Anxiety symptoms (n=1216)	
	APR (95% CI)	P value	APR (95% CI)	P value
Age group, years				
20–29	Ref		Ref	
30–39	1.03 (0.79–1.35)	0.817	1.06 (0.77–1.47)	0.729
40–49	0.92 (0.66–1.27)	0.602	0.80 (0.54–1.19)	0.272
50–60	0.96 (0.61–1.50)	0.848	0.95 (0.55–1.65)	0.861
Nationality				
Philippines	Ref		Ref	
Myanmar	0.84 (0.66–1.08)	0.169	0.62 (0.46–0.85)	0.002
Indonesia	0.75 (0.59–0.95)	0.016	0.80 (0.60–1.05)	0.106
Educational qualification				
Primary and below	1.18 (0.82–1.69)	0.367	1.13 (0.74–1.72)	0.581
Secondary	Ref		Ref	
Pre-tertiary	1.17 (0.96–1.42)	0.115	0.97 (0.76–1.22)	0.782
Tertiary	1.28 (0.96–1.71)	0.096	1.11 (0.78–1.57)	0.573
Others	0.33 (0.02–5.10)	0.431	1.06 (0.11–10.66)	0.960

Table 4. Regression results for migrant domestic workers. (Cont'd)

Variables	Depressive symptoms (n=1183)		Anxiety symptoms (n=1216)	
	APR (95% CI)	P value	APR (95% CI)	P value
Marital status				
Married	Ref		Ref	
Single	1.10 (0.89–1.35)	0.370	1.24 (0.97–1.60)	0.089
Separated/widowed/divorced	0.90 (0.72–1.14)	0.390	1.11 (0.84–1.46)	0.459
Cohabiting	1.12 (0.33–3.79)	0.852	1.32 (0.20–8.72)	0.771
Monthly salary, SGD				
≤650	Ref		Ref	
>650–750	1.13 (0.89–1.43)	0.306	0.80 (0.60–1.07)	0.138
>750	0.95 (0.74–1.23)	0.715	0.85 (0.62–1.17)	0.320
No. of hours worked per day				
≤12	Ref		Ref	
>12–14	1.15 (0.93–1.41)	0.204	1.23 (0.96–1.58)	0.100
>14	1.42 (1.16–1.74)	0.001	1.45 (1.14–1.84)	0.003
No. of years in Singapore				
≤4	Ref		Ref	
>4–10	0.85 (0.67–1.08)	0.183	0.86 (0.65–1.14)	0.291
>10	0.79 (0.59–1.05)	0.103	0.81 (0.56–1.15)	0.231
Do you have a day off?				
No	Ref		Ref	
Yes	1.62 (0.89–2.96)	0.115	1.82 (0.87–3.80)	0.110
Stress symptoms				
No	Ref		Ref	
Yes	2.47 (1.81–3.39)	<0.001	2.71 (1.88–3.90)	<0.001
Insomnia				
No	Ref		Ref	
Yes	3.02 (2.40–3.81)	<0.001	3.32 (2.52–4.37)	<0.001
Resilience				
Low	1.11 (0.87–1.42)	0.393	1.26 (0.95–1.68)	0.111
Normal	Ref		Ref	
High	0.55 (0.42–0.73)	<0.001	0.58 (0.42–0.81)	0.001
Perceived social support				
Low	1.23 (0.90–1.68)	0.198	1.47 (1.01–2.16)	0.046
Medium	Ref		Ref	
High	1.17 (0.97–1.41)	0.094	1.11 (0.89–1.39)	0.346

APR: adjusted prevalence ratio; CI: confidence interval; SGD: Singapore dollars

nationality (vs Filipino, APR 0.75, 95% CI 0.59–0.95); and had high resilience (vs normal resilience, APR 0.55, 95% CI 0.42–0.73).

Furthermore, they were more likely to develop anxiety symptoms if they worked >14 hours (vs ≤12 hours, APR 1.45, 95% CI 1.14–1.84); had mild-to-extremely severe stress symptoms (APR 2.71, 95% CI 1.88–3.90); had symptoms of insomnia (APR 3.32, 95% CI 2.52–4.37); and had low social support (vs medium social support, APR 1.47, 95% CI 1.01–2.16). They were less likely to develop anxiety symptoms if they were of Burmese nationality (vs Filipino, APR 0.62, 95% CI 0.46–0.85), and had high resilience (vs normal resilience, APR 0.58, 95% CI 0.42–0.81).

DISCUSSION

This study examined the prevalence and correlates of moderate-to-severe depressive and anxiety symptoms among MWs (depressive 0.83%, anxiety 1.25%) and MDWs (depressive 4.05%, anxiety 4.23%) in Singapore. It was conducted during a distinctive period—in the aftermath of the COVID-19 pandemic and initiation of programmes aimed at enhancing the well-being of MWs and MDWs. This context has implications for the findings.

The prevalence of depressive and anxiety symptoms among MWs and MDWs was lower than the pooled prevalence reported from a systematic review on migrant workers,⁵ as well as prior research on MWs and MDWs in Singapore.²⁵ This discrepancy in prevalence could be attributed to 2 reasons. First, the study was conducted following the COVID-19 pandemic. With the lifting of regulations and restrictions previously imposed to curb the spread of COVID-19, the fears and concerns of MWs and MDWs^{26,27} related to these measures were eased, which may have reduced their depressive and anxiety symptoms. Many MWs who left for home during the pandemic had anecdotally shared the challenges they faced in securing employment in their own countries and their sense of relief in gaining employment again in Singapore during the post-COVID period. Second, various organisations including MOM,^{11,14} voluntary welfare organisations¹⁴ and dormitory operators had introduced various policies and programmes to enhance the well-being of MWs and MDWs during and after the COVID-19 pandemic. The beneficial effects of these programmes might have led to favourable results in this study.

Moreover, MWs and MDWs reported lower prevalence of depressive and anxiety symptoms than the residents in Singapore.²⁸ While limited number of studies have compared the prevalence of depressive and anxiety symptoms between migrant population and residents in Singapore, the difference in prevalence

could be attributed to effective coping strategies among the migrant population.^{29,30} For instance, a qualitative study on MWs during the COVID-19 period reported that the participants coped with the stressors during the crisis by engaging in their religion or faith, staying connected with family, staying informed of news updates and ensuring their needs were met.³⁰

This study also found that among MWs and MDWs, depressive and anxiety symptoms were negatively associated with resilience, which is the ability to cope or bounce back from adversities.²⁴ This finding corroborated the observations of other studies, including a cross-sectional study on Iranian immigrants in Australia before the COVID-19 pandemic³¹ and a survey of MWs in India during the pandemic.³² These findings imply that resilience plays a vital role in safeguarding mental well-being, especially in times of difficulty such as the pandemic. Hence, enhancing resilience among MWs and MDWs through the appropriate interventions is key to help foster good mental health. Existing interventions emphasise fostering resilience among migrants by strengthening their ecosystems, such as highlighting the community's existing strengths and skills,³³ and teaching migrants to cope with adversities by reinforcing their cultural strengths.

Among MWs, a higher educational attainment was positively associated with depressive and anxiety symptoms. This finding differs from other similar studies, which shows either no association or negative association after adjustment of covariates.^{34,35} One possible reason could be that those with higher educational qualifications were underemployed. A study in Australia found that among males, those who were over-skilled were more likely to have poorer mental health.³⁶ In the migrant setting, this situation is a possibility because MWs may accept jobs below their skill level for a higher salary.

This study revealed that overworking was associated with poor mental health outcomes. Among MWs, those without days off were more likely to have anxiety symptoms. Having at least 1 rest day per week is mandated by the national legislation for non-migrant populations in many countries, but the published literature on its impact on mental health is scarce. The findings underscore the critical role of rest days for the mental well-being of MWs. Among MDWs, those with a higher number of working hours per day were more likely to have depressive and anxiety symptoms. This finding aligned with another qualitative study on MDWs in Hong Kong, which reported overworking as a reason that affected MDWs' mental health.³⁷ Currently, in Singapore, employers are mandated to give 1 rest day per month that cannot be compensated away for MDWs to recuperate from their long working

hours.¹⁴ Nonetheless, future studies can investigate the long-term effects of mandating a rest day on the association between overworking and mental well-being.

The findings on the association between nationality and mental health symptoms for MWs showed that those from Bangladesh were more likely to develop depressive symptoms but less likely to develop anxiety symptoms. Moreover, MDWs of Filipino nationality were more likely to have depressive symptoms than those of Indonesian nationality, and more likely to have anxiety symptoms than those of Burmese nationality. However, given the quantitative nature of this study, the authors are unable to further elucidate the reasons for the difference in depressive and anxiety symptoms among the different nationalities. Nonetheless, the significant association between nationality and mental health symptoms implies the need to monitor mental health disparities across nationalities and develop culturally tailored support measures for specific migrant communities.

Compared to previous studies in Singapore,^{8,9,38} this study had a large sample size for the examination of MWs' and MDWs' mental well-being through the evolution of safe management policies of the COVID-19 pandemic. However, this study has some limitations. First, the cross-sectional study design does not permit causal inference. Second, the use of convenience sampling limits the generalisability of the findings to the wider population of interest. Third, the prevalence of depression and anxiety could be under-reported. Participants might provide socially desirable answers due to various reasons, such as the stigma around mental illness and the fear that their responses may jeopardise their employment status. However, the researchers had put in measures to minimise this by not collecting any identifiers and providing assurance of anonymity. Fourth, the authors were unable to examine potential correlates, such as indebtedness as a factor affecting mental health, as these were not collected in the study. Last, the authors did not adjust for type I error because adjusting for multiple comparison remains a debated topic with no clear consensus. Although adjusting for type I error using Bonferroni correction may be easy to implement, it can increase type II error. Nonetheless, to maintain transparency in the findings, the authors acknowledge this limitation. Moreover, all relevant statistical results are included in this article so that readers can apply their own adjustment.

CONCLUSION

This study examined the prevalence and correlates of depressive and anxiety symptoms among MWs and MDWs. Findings show that having high resilience was negatively associated with depressive and anxiety

symptoms among MWs and MDWs. Not having a rest day was associated with increased anxiety symptoms among MWs, and a higher number of working hours was associated with increased depressive and anxiety symptoms of MDWs. As newly implemented policies and programmes run their course, future studies can be conducted to investigate their long-term impact and effectiveness in providing support to the mental health of MWs and MDWs. Moreover, it is pertinent to continue this drive for change and foster an environment that supports the mental well-being of this population.

Ethics statement

This study obtained approval from the National University of Singapore Institutional Review Board (2021-724) before initiating recruitment process. MOM facilitated access to participants by connecting the research team with recreational centres and construction sites management team.

Declaration

The study received funding from MOM. The funding organisation had no influence in the data collection, analysis and writing of the manuscript. The authors declare they have no affiliations with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Data availability

The data presented in this study are available upon reasonable request to the corresponding author. The data are not publicly available due to institutional policies.

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Supplementary materials

Table S1. Monthly salary stratified by nationality among migrant workers.

Table S2. Monthly salary stratified by nationality among migrant domestic workers.

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Selection of pyroptosis-related genes and potential pharmacological targets in sepsis-induced myopathy

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ABSTRACT

Introduction: Sepsis-induced myopathy (SIM) is a severe complication contributing to long-term morbidity and mortality in sepsis survivors. Emerging evidence highlights the role of pyroptosis in SIM pathogenesis. This study aims to identify pyroptosis-related genes and potential pharmacological targets for SIM and explore their therapeutic implications.

Methods: The GSE13205 dataset from the Gene Expression Omnibus database was analysed to identify differentially expressed pyroptosis-related genes in SIM. Gene Set Variation Analysis, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed to investigate the biological functions and associated pathways. Hub genes were identified through protein–protein interaction network analysis. The Connectivity Map (CMap) database was used to predict candidate therapeutic compounds targeting these genes.

Results: A total of 39 pyroptosis-related genes were identified as differentially expressed in SIM. These genes were primarily associated with apoptosis, regulation of cell death, p53 signalling, circadian rhythm and responses to hypoxia and chemical stress. KEGG pathway analysis revealed enrichment in apoptosis, p53 signalling, microRNA in cancer and endocrine resistance pathways. Ten potential therapeutic compounds were predicted via CMap based on hub gene profiles. However, experimental validation of these compounds in the context of SIM is needed to assess their therapeutic efficacy.

Conclusion: This study identifies key pyroptosis-related genes and potential therapeutic compounds for SIM, providing new insights into its molecular mechanisms and suggesting novel strategies for treatment. Further experimental validation is required to confirm the clinical relevance and therapeutic potential of these findings.

Keywords: drug gene prediction, enrichment analysis, pyroptosis, sepsis, sepsis-induced myopathy

CLINICAL IMPACT

What is New

- Identified 39 differentially expressed pyroptosis-related genes in sepsis-induced myopathy (SIM) using transcriptomic analysis.
- Revealed enrichment in apoptosis, p53 signalling, circadian rhythm and stress-response pathways.
- Predicted 10 candidate therapeutic compounds targeting hub genes through Connectivity Map analysis.

Clinical Implications

- Highlights pyroptosis as a potential mechanistic driver and therapeutic target in SIM.
- Provides candidate small molecules for future preclinical validation.
- Supports development of targeted interventions to reduce long-term muscle dysfunction in sepsis survivors.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.¹ With advancements in medical technology and care, the survival rate of sepsis has significantly improved. However, a substantial portion of survivors progresses to the chronic critical illness phase, developing conditions such as intensive care unit-acquired weakness or sepsis-induced myopathy (SIM).² SIM not only prolongs mechanical ventilation but also leads to long-term impairment of motor function and increases long-term mortality among patients.^{3,4} It is characterised primarily by atrophy and weakness of the respiratory and skeletal muscles.⁵ Currently, the

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mechanisms underlying skeletal muscle atrophy in SIM remain unclear, with key issues being reduced protein synthesis (due to excessive reactive oxygen species production) and accelerated protein degradation (due to enhanced proteasomal protein hydrolysis and autophagic pathways).^{6,7} Effective treatments for SIM are lacking beyond rehabilitation and nutritional support.

Recent evidence suggests that the occurrence of SIM may be associated with the excessive activation of the pyroptosis pathway.^{8,9} Pyroptosis is considered a form of programmed cell death closely associated with inflammation, accompanied by the release of numerous pro-inflammatory cytokines such as interleukin (IL)-1 β and IL-18.⁸ Currently, the signal transduction mechanisms leading to cell pyroptosis include not only caspase-1-dependent classical pathways but also caspase-4/5/11-dependent non-classical pathways,^{10,11} as well as caspase-3-dependent pathways.¹² Their common downstream mechanisms involve membrane perforation mediated by gasdermin-D or gasdermin-E, ultimately leading to cell swelling, rupture and the release of abundant intracellular substances and inflammatory mediators, triggering cascading inflammatory responses. Increasingly, studies suggest a close association between the pyroptosis pathway and conditions such as muscular dystrophy and skeletal muscle atrophy,^{13,14} with the discovery of a range of drugs or molecules capable of alleviating muscle atrophy by inhibiting the pyroptosis pathway.¹⁵ Some studies have hinted at the potentially significant role of pyroptosis-related pathways in SIM.⁸ However, the regulatory mechanisms and target therapeutic effects remain unclear. Therefore, the aim of this study is to identify key pyroptosis-related genes in SIM and predict potential therapeutic drugs, which may contribute to the discovery of novel, personalised treatment strategies for SIM.

In this study, bioinformatics analysis was performed to determine the expression profiles of pyroptosis-related genes in normal skeletal muscle and SIM patient muscle tissues. Differentially expressed genes (DEGs) enriched in cell death pathways were found. Using Cytoscape software, hub genes between clusters of DEGs were screened. Finally, based on the hub genes, candidate drugs or molecules with therapeutic potential for SIM were identified by downloading potential pharmacological targets from the Connectivity Map (CMap) database. In summary, this study offers new strategies for the diagnosis and treatment of SIM.

METHODS

Microarray dataset collection and data processing

Microarray datasets were selected from the Gene Expression Omnibus (GEO) by searching for keywords

“sepsis” and “skeletal muscle” using the following search strategy: (“Sepsis-Induced Myopathy”[MeSH Terms] or “sepsis”[All Fields]) and (“skeletal muscle atrophy”[MeSH Terms] and “Homo sapiens”[porgn] and (“GSE”[Filter] and “Expression profiling by array”[Filter]). The GSE13205 expression profile dataset was obtained from the GEO (<http://www.ncbi.nlm.nih.gov/geo/>), comprising 13 sepsis patient skeletal muscle biopsy samples and 8 control samples.

Screening for pyroptosis-related differentially expressed genes (PRDEGs)

The dataset was collected using the Affymetrix Human Genome U133 Plus 2.0 Array platform (GPL570; Affymetrix, Inc, Santa Clara, CA, US). A total of 755 pyroptosis-related genes were obtained from the “GeneCards” database, and their intersection with differentially expressed genes (DEGs) in GSE13205 was determined. DEGs between the SIM group and the control group were analysed using the “limma” package in R software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria), with adjusted cut-off values set as follows: *P* value <0.05 and fold changes (FC) >1.5. A Venn diagram was employed to visualise the intersection between DEGs and pyroptosis-related genes.

Functional enrichment analysis and protein–protein interaction (PPI) network analysis of PRDEGs

Functional enrichment analysis of PRDEGs, including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, was conducted using the “ClusterProfiler” package in R software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). GO analysis covered 3 main aspects: biological processes (BP), cellular components (CC) and molecular functions (MF), aiding in a comprehensive exploration of the biological significance. KEGG analysis uncovered potential signalling pathway information. Additionally, a PPI network was constructed using the STRING online platform (<https://string-db.org/>) to investigate potential relationships among DEGs related to pyroptosis. Subsequently, the STRING results were imported into Cytoscape software version 3.8.2 (Cytoscape Consortium, San Diego, CA, US), and the CytoHubba plugin was used to identify key subnetworks. Finally, based on the maximum correlation criterion and the Maximal Clique Centrality (MCC) algorithm, the top 3 ranked genes were selected as key genes.

Screening for potential pharmacological targets

The CMap database (<https://clue.io/query>) contains data on gene expression changes induced by 33,609 small molecular compounds. This database enables the comparison of drug-induced gene expression profiles with gene expression, generating connectivity

scores ranging from -100 to 100. A score greater than 0 indicates similarity between the gene expression changes induced by the compound and the uploaded gene expression profile. Conversely, a score less than 0 suggests that the compound induces gene expression changes opposite to the uploaded profile, indicating potential therapeutic potential. Higher connectivity scores reflect greater similarity.

Animal model establishment and tissue collection

A sepsis model was established using the cecal ligation and puncture (CLP) method. Eight-week-old male C57BL/6J mice (22–26 g) were used in the experiments. Mice were anaesthetised by intraperitoneal injection of pentobarbital sodium (40 mg/kg). Mice in the sham group underwent laparotomy without cecal ligation or puncture. In the CLP group, the cecum was ligated and punctured once with a 21-gauge needle, allowing a small amount of fecal content to extrude. The cecum was then repositioned, and the abdominal incision was sutured. All mice received subcutaneous injection of sterile saline (50 mL/kg) for fluid resuscitation. After 48 hours, mice were sacrificed, and the gastrocnemius muscle was harvested for subsequent analysis. All animal experiments were approved by the Animal Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJH-24-06-005) and conducted in accordance with institutional guidelines for animal care and use.

Real-time quantitative polymerase chain reaction (qRT-PCR)

Gastrocnemius muscle tissue was homogenised at 4°C using a PT 10/35 homogeniser (Kinematica AG, Switzerland) in ribonucleic acid (RNA) STAT-60 reagent (Tel-Test, US) to extract total RNA. Complementary deoxyribonucleic acid was synthesised using a reverse transcription kit (Takara Bio Inc, Kusatsu, Shiga, Japan) according to the manufacturer's instructions. qRT-PCR was performed using SYBR Green dye (Takara Bio Inc, Kusatsu, Shiga, Japan) on a real-time PCR system. The thermal cycling conditions were as follows: initial denaturation at 95°C for 30 seconds, followed by 40 cycles of 95°C for 5 seconds and 60°C for 30 seconds. Relative gene expression levels were calculated using the $2^{-\Delta\Delta CT}$ method, with glyceraldehyde-3-phosphate dehydrogenase serving as the internal control.

Statistical analysis

For continuous variables, statistical analysis was performed using Student's t-test or the Kruskal-Wallis H test. For categorical variables, the chi-square test or Fisher's Exact test was applied. All statistical analyses were conducted using R software version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS statistics software version 19.0 (IBM

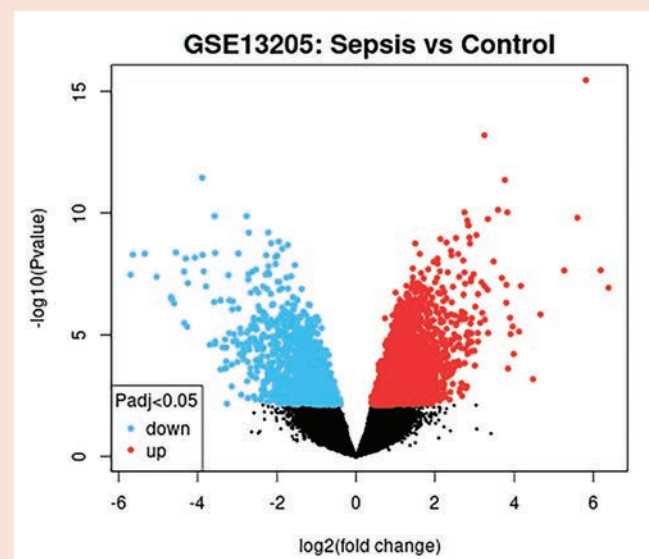
Corp, Armonk, NY, US). In 2-tailed tests, a *P* value less than 0.05 was considered statistically significant.

RESULTS

Differentiation of DEGs

Using GEO2R analysis with the criteria of $P < 0.05$ and $|\log_2 \text{FC}| > 1$, a total of 2232 DEGs were identified in the GSE13205 dataset, comprising 1469 upregulated and 763 downregulated genes. The volcano plot visualised these DEGs, with red and blue dots representing upregulated and downregulated genes, respectively (Fig. 1).

Fig. 1. Analysis of DEGs in sepsis. Volcano plot of gene expression in septic patients from the GSE13205 dataset.



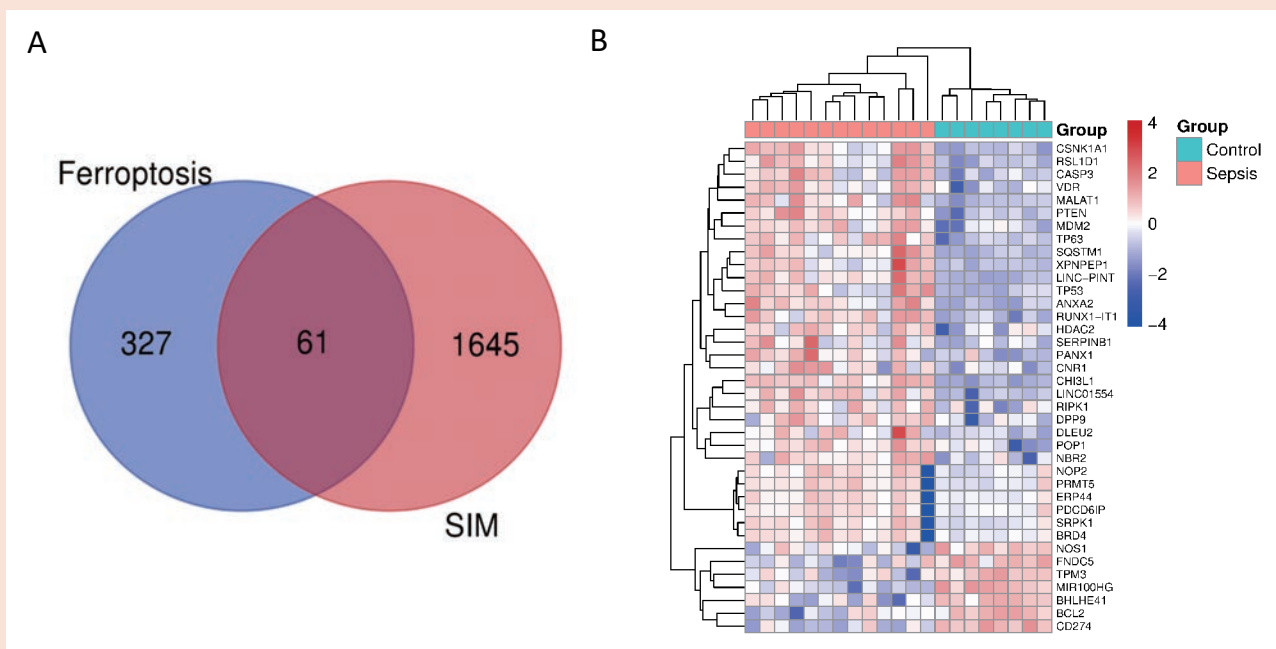
Identification of PRDEGs

Pyroptosis-related genes were obtained from the "GeneCards" database and intersected with DEGs in GSE13205 to identify PRDEGs. As shown in the Venn diagram, after removing duplicate gene symbols, 1667 genes on the left were unique to GSE13205, 39 genes in the middle were pyroptosis-related DEGs, and 716 genes on the right were uniquely related to pyroptosis (Fig. 2A). Visualisation of PRDEGs was further done using a heatmap (Fig. 2B), with 32 genes upregulated and 7 genes downregulated (Supplementary Table S1).

GO and KEGG enrichment analysis of pyroptosis-related DEGs

Metascape database was utilised for GO and KEGG enrichment analysis of PRDEGs and visualisation of the results. In the MF enrichment analysis, PRDEGs were primarily enriched in functions related to enzyme binding, p53 binding, ubiquitin-protein binding, calcium-dependent protein binding, ubiquitin-like

Fig. 2. Pyroptosis-related genes and Venn analysis. (A) Intersection of DEGs related to pyroptosis. (B) Heatmap of pyroptosis-related genes.



SIM: sepsis-induced myopathy

protein binding and protein serine/threonine kinase activity. In the BP enrichment, PRDEGs were primarily associated with the positive regulation of cell apoptosis, cell death, programmed cell death, regulation of the p53 signalling pathway, circadian rhythms and cellular responses to oxygen levels, ischaemia and chemical stimuli. CC enrichment revealed associations with myelin sheath, membrane microdomains, membrane vesicles, promyelocytic leukaemia (PML) bodies, transcription factor com-plexes, nuclear matrix and various vesicles (Fig. 3A). KEGG enrichment analysis highlighted pathways such as the p53 signalling pathway, microRNAs in cancer and associated pathways, apoptosis and endocrine resistance (Fig. 3B).

Construction of PPI network for PRDEGs and identification of hub genes

A PPI network for PRDEGs was constructed using the STRING database with an interaction score threshold of >0.4, resulting in 25 nodes and 140 edges. Among the 39 PRDEGs, 14 genes had no correlations with other genes and did not form molecular networks. These were visualised using Cytoscape software (Cytoscape Consortium, San Diego, CA, US), and the most important module in the PPI network was identified using the MCODE plugin (Figs. 4A, C). Subsequently, hub genes were identified using the CytoHubba plugin in Cytoscape, with the top 10 genes ranked by the MCC algorithm (Supplementary Table S2). Functional enrichment analysis of hub genes using the Metascape database revealed enriched functions and pathways, including *TP53*, *PTEN*, *BCL2*,

CASP3, *MDM2*, *BRD4*, *HDAC2*, *CD274*, *SQSTM1* and *CSNK1A1* (Figs. 4B, D).

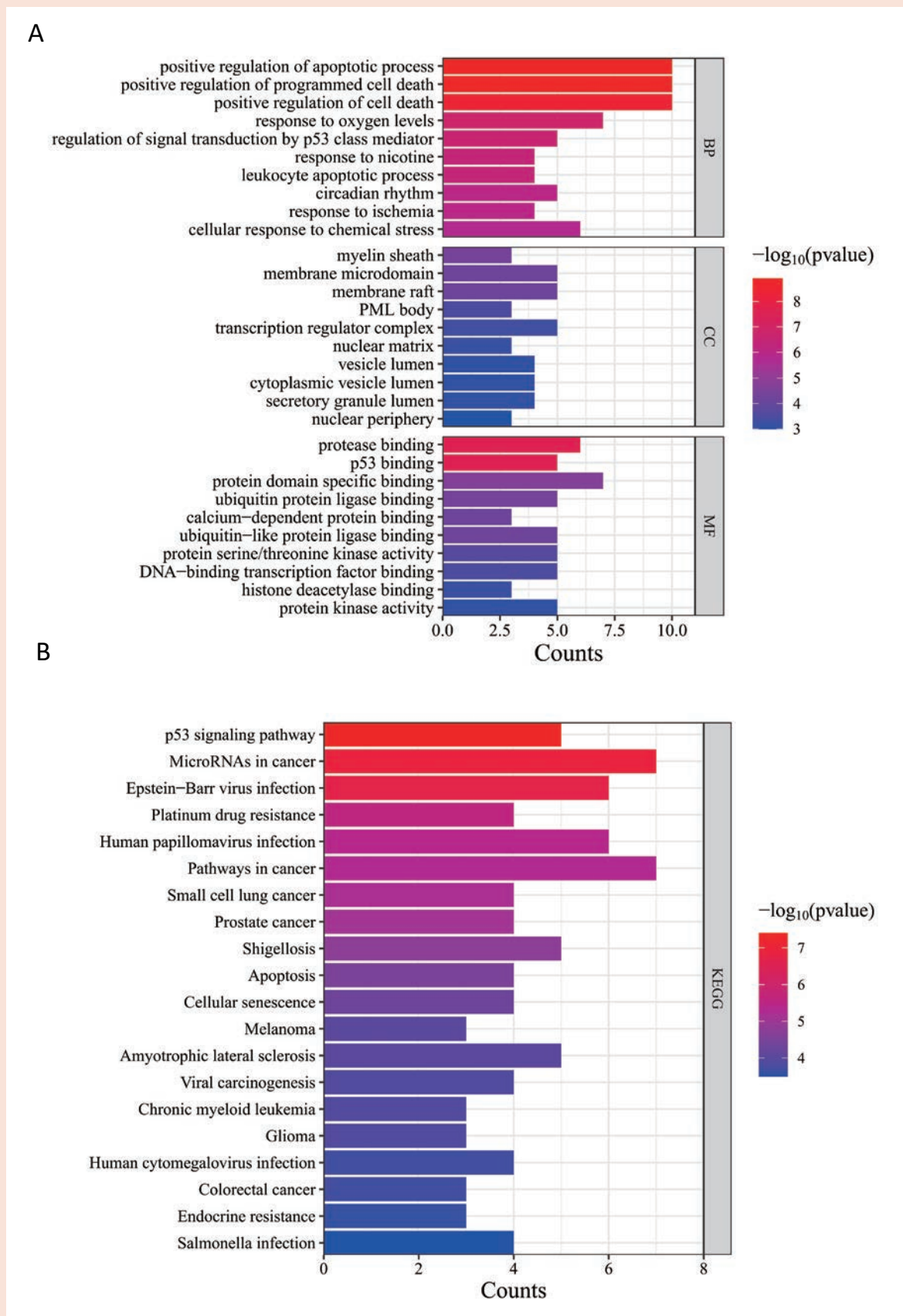
Internal validation of hub gene expression differences

Expression matrices of hub genes were obtained from the GEO database, and their expression differences were visualised using violin plots. Statistical analysis revealed significant upregulation of *TP53*, *PTEN*, *CASP3*, *MDM2*, *BRD4*, *HDAC2*, *SQSTM1* and *CSNK1A1* in the skeletal muscle of sepsis patients compared to the control group, while *BCL2* and *CD274* exhibited significant downregulation (Fig. 5).

CLP-induced sepsis significantly alters the mRNA expression of key genes in mouse skeletal muscle

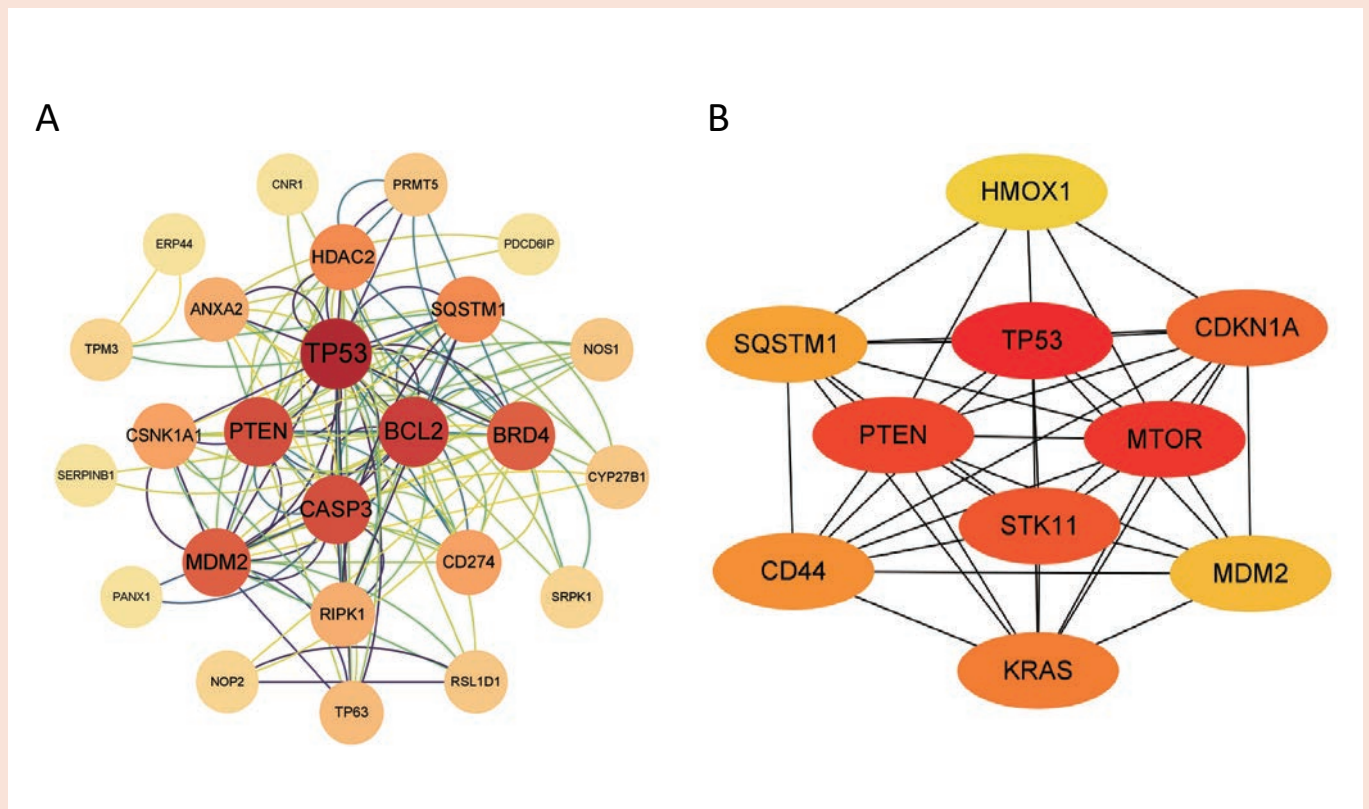
To further confirm the impact of CLP-induced sepsis on gene expression in skeletal muscle, the mRNA levels of 10 key genes in skeletal muscle tissues from sham and CLP mice were examined using qRT-PCR. The results revealed that the mRNA expression levels of *TP53*, *PTEN*, *BCL2*, *CASP3*, *MDM2*, *BRD4*, *HDAC2*, *SQSTM1* and *CSNK1A1* were significantly elevated in the CLP group compared with the sham group (Figs. 6A–F, H–J; $P < 0.001$), suggesting that CLP stimulation markedly activates pathways related to cellular stress, apoptosis and epigenetic regulation. Notably, the expression of the immune checkpoint molecule *CD274* (PD-L1) was significantly decreased in the CLP group (Fig. 6G; $P < 0.001$), which may be associated with the development of an immunosuppressive state. These findings indicate that CLP-induced sepsis profoundly disturbs the expression of multiple critical genes in

Fig. 3. Enrichment analysis of PRDEGs using the metascap database. (A) GO enrichment analysis, including biological processes and cellular components pathways. (B) Kyoto Encyclopedia of Genes and Genomes enrichment analysis.



GO: Gene Ontology; PML: promyelocytic leukaemia; PRDEGs: pyroptosis-related differentially expressed genes

Fig. 4. (A, C) Construction of the protein–protein interaction network using the STRING database. (B, D) Identification of hub genes using the CytoHubba plugin in Cytoscape.



skeletal muscle, involving diverse BP such as cell death, inflammatory regulation and signal transduction.

Screening for potential pharmacological targets

The screening results for potential pharmacological targets were obtained from CMap based on connectivity scores. The top 10 molecular drugs with therapeutic potential for SIM were identified as Quinpirole, Zolpidem, PTB1, CG-930, 9-methyl-5H-6-thia-4,5-diaza-chrysene-6,6-dioxide, VER-155008, Chromanol, Anagrelide, Tipifarnib-P2 and Benproperine (Supplementary Table S3). These drugs hold promise as potential treatments for pyroptosis-induced SIM.

DISCUSSION

Apoptosis is a non-inflammatory cell death process, typically occurring during cellular self-repair and the removal of damaged cells. In contrast, pyroptosis is an inflammatory cell death process triggered by infection or inflammation, accompanied by a significant inflammatory response.⁸ Previous studies have indicated that the activation of the pyroptosis pathway plays a crucial role in the progression of SIM.^{8,16} Preclinical research has identified several related targets that can mitigate muscle wasting.^{16–18} There-

fore, inhibiting the inflammatory signalling pathways associated with pyroptosis holds promise as a therapeutic strategy to improve the prognosis of SIM. However, the role of pyroptosis-related genes in SIM remains incompletely understood, and this study aimed to clarify this role.

To elucidate the expression of pyroptosis-related genes in SIM, the GSE13205 dataset was utilised, and 39 genes associated with pyroptosis were identified. Among these, 32 genes were upregulated and 7 genes were downregulated in SIM compared to normal tissues. This suggests that pyroptosis-related genes may be involved in the pathological processes of SIM. To gain deeper insights into the roles of these pyroptosis-related genes in SIM, the GO enrichment analysis was conducted. The enriched MF included positive regulation of apoptosis process, positive regulation of programmed cell death, positive regulation of cell death, response to oxygen levels, regulation of signal transduction by p53 class mediator, response to nicotine, leukocyte apoptotic process, circadian rhythm, response to ischaemia and cellular response to chemical stress. These findings indicate a predominant involvement of pyroptosis-related genes in positively regulating cell death or apoptosis. It has

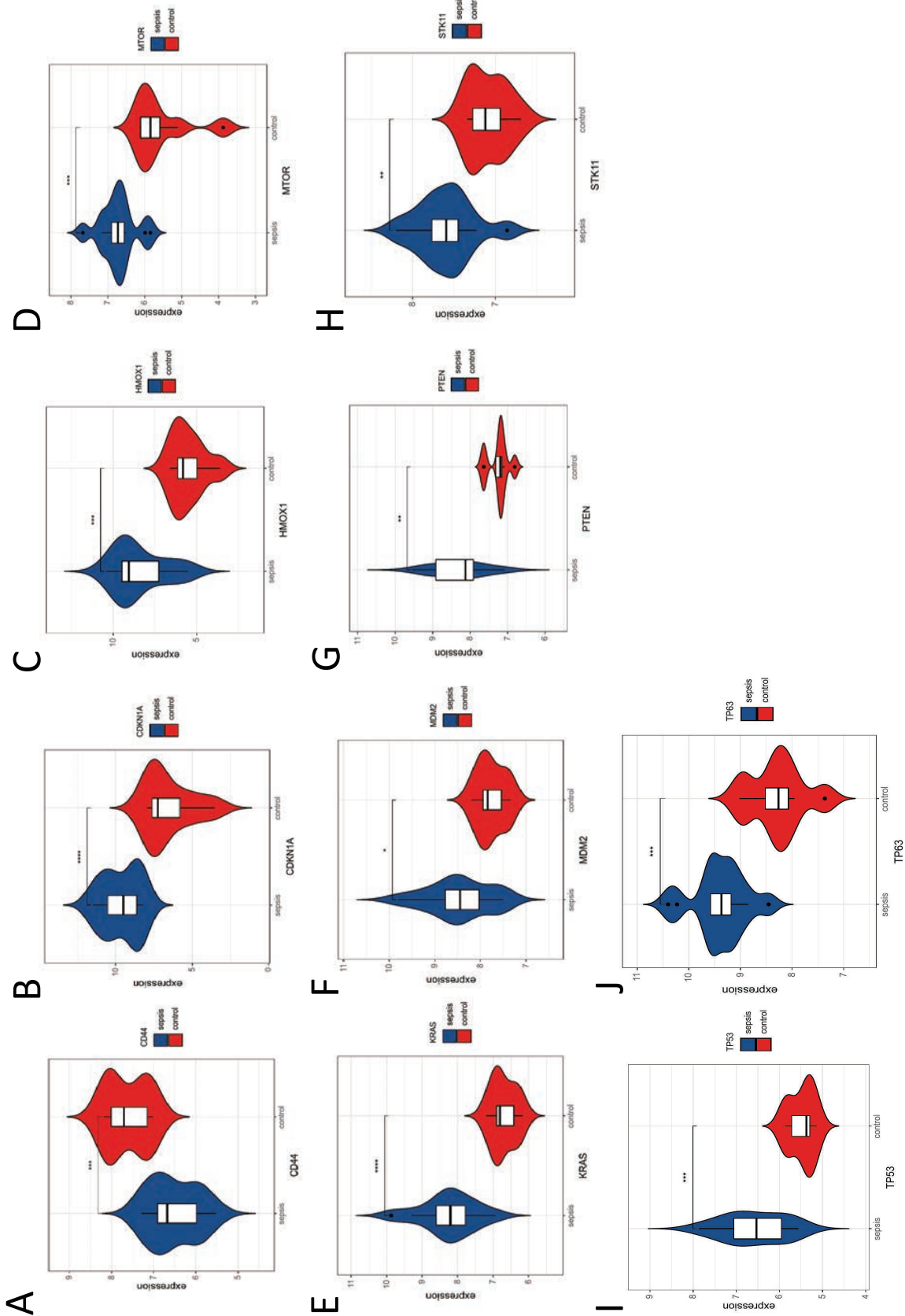
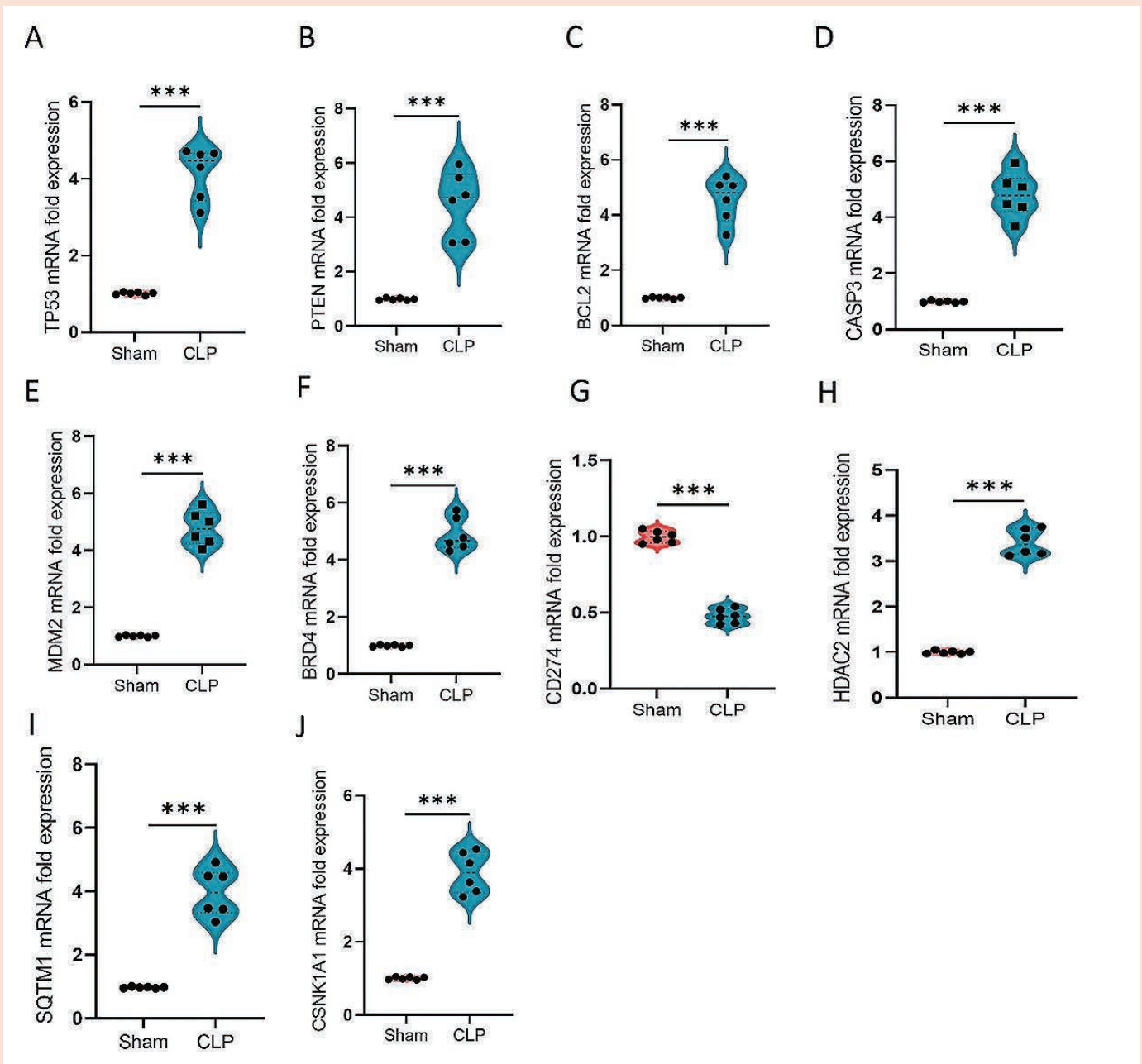


Fig. 5. Expression matrix of hub genes obtained from the GEO database.

GEO: Gene Expression Omnibus
*Comparison with the control group, $P < 0.05$
**Comparison with the control group, $P < 0.01$
***Comparison with the control group, $P < 0.001$

Fig. 6. qRT-PCR was performed to assess the mRNA expression levels of multiple genes associated with programmed cell death, inflammation, and signal regulation in skeletal muscle tissues from sham and CLP groups. The analysed genes included (A) *TP53*, (B) *PTEN*, (C) *BCL2*, (D) *CASP3*, (E) *MDM2*, (F) *BRD4*, (G) *CD274*, (H) *HDAC2*, (I) *SQSTM1* and (J) *CSNK1A1*.



CLP: cecal ligation and puncture; qRT-PCR: real-time quantitative polymerase chain reaction

Note: Except for *CD274*, all other genes were significantly upregulated in the CLP group. Each dot represents an individual mouse (n=6–9). Data are presented as violin plots, with the centre point indicating the median.

***P<0.001, analysed by conducting the non-parametric Mann–Whitney test.

been reported that programmed cell death, including autophagy, apoptosis, pyroptosis and necroptosis, plays a significant role in SIM.^{19,20} Studies have shown that sepsis induces muscle fibre apoptosis, leading to skeletal muscle atrophy.¹⁹ The activation of the NLRP3 inflammasome pyroptosis pathway is also considered a potential mechanism and therapeutic target in SIM,

but the exact contribution of this pathway in SIM remains to be fully validated experimentally.^{16,20,21} Sepsis-induced limb muscle fibre atrophy is associated with enhanced activity of the proteasome and autophagy protein degradation pathways, triggered by the inhibition of protein kinase B (AKT) and mammalian target of rapamycin complex 1 and the activation

of the adenosine monophosphate-activated protein kinase pathway.²² Oxidative stress, such as reactive oxygen species is another critical initiating factor and therapeutic target for skeletal muscle atrophy in sepsis.^{21,23} It is also a key mechanism through which some drugs exert their therapeutic effects on SIM.²⁴ In response to cellular and extracellular stimuli and stress, p53 acts as a transcription factor regulating the expression of downstream genes to help cells/organisms resist these stimuli. Although some studies have identified p53 as a regulator of pyroptosis,²⁵ its role in SIM remains unclear. Interestingly, circadian rhythm is associated with the activation of the NLRP3 inflammasome.²⁶ Research has found that continuous light exacerbates skeletal muscle loss in endotoxemia rats, which is related to changes in the hypothalamic circadian clock and SIRT1.²⁷ The MF highlighted in GO enrichment provides crucial information about the biological roles that these genes may play in SIM, offering insights into the potential role of pyroptosis in SIM.

The impact of PRDEGs in SIM spans multiple biological pathways. KEGG pathway analysis revealed that PRDEGs in SIM are mainly involved in pathways such as the p53 signalling pathway, microRNAs in cancer, Epstein-Barr virus infection, platinum drug resistance, human papillomavirus infection, pathways in cancer, small cell lung cancer, prostate cancer, Shigellosis and apoptosis. Apart from the p53 signalling pathway and apoptosis, these genes are associated with several cancer-related pathways. Cellular pyroptosis is involved in tumour proliferation, invasion and metastasis and is a therapeutic target in numerous cancers.²⁸ Given the similarities in pathological manifestations and characteristics between SIM and cachexia induced by tumours, these enriched pathways could provide novel insights for treatment strategies in SIM. However, experimental validation of these pathways in SIM is required to confirm their role in the disease.^{29,30} These enriched pathways can provide valuable insights and guidance for the treatment of SIM. A PPI network of pyroptosis-related DEGs was also constructed using STRING, and 10 core genes in pyroptosis associated with SIM were identified: *TP53*, *PTEN*, *MDM2*, *SQSTM1*, *CASP3*, *CSNK1A1*, *BRD4*, *BCL2*, *HDAC2*, *CD274*, which were further validated using the CytoHubba plugin in Cytoscape. Further investigation into the functions and interactions of these genes, particularly through in vitro and in vivo experiments, will provide a better understanding of their contribution to SIM and their potential as therapeutic targets. These key genes related to pyroptosis may serve as potential therapeutic targets that require further research.

In addition, the authors screened for potential pharmacological targets by downloading results from the CMap database and ranking and filtering them based on drug connectivity scores. The top 10 molecular drugs identified were Quinpirole, Zolpidem, PTB1, CG-930, 9-methyl-5H-6-thia-4,5-diaza-chrysene-6,6-dioxide, VER-155008, Chromanol, Anagrelide, Tipifarnib-P2 and Benproperine. However, these drugs currently lack preclinical validation in SIM, and their effectiveness in this context needs to be further investigated. Future experimental studies should validate these drugs' potential impact on the pyroptosis-related genes identified in this study.

This study has limitations. First, it lacks relevant clinical information about patient characteristics, such as age, sex and disease duration, which could influence gene expression. Additionally, a larger sample size of SIM patients may be considered to validate the stability of the results of this study. Furthermore, future studies should include in vitro and in vivo experiments to validate the therapeutic potential of the identified compounds.

CONCLUSION

In summary, the pathogenesis of SIM involves multiple BP and signalling pathways. This study has shown significant changes in the expression of pyroptosis-related genes in SIM, suggesting a potential role of pyroptosis in the pathogenesis of this disease. Based on the results, these pyroptosis-related genes may serve as potential pharmacological targets. Interventions targeting these genes could provide a promising approach for regulating the development of SIM. Moreover, this study provides a foundation for further exploration of the role of pyroptosis in sepsis and offers new directions for disease treatment research.

Supplementary materials

Table S1. 39 PRDEGs.

Table S2. Top 10 hub genes identified by CytoHubba.

Table S3. Top 10 small molecular compounds provided by CMap to PRDEGs.

Ethics statement

All animal experiments were conducted in accordance with the ARRIVE guidelines. The experimental protocols were approved by the Animal Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJH-24-06-005). All procedures were carried out in compliance with the UK Animals (Scientific Procedures) Act, 1986 and associated guidelines, the EU Directive 2010/63/EU for animal experiments.

Declaration

This study was supported by grants from Hubei Provincial Natural Science Foundation of China (2023AFB216). The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. The authors also declare there is no conflict of interest.

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Clinical features and outcomes of the adult Singapore IgA vasculitis cohort

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Dear Editor,

Immunoglobulin A (IgA) vasculitis (IgAV), formerly known as Henoch-Schönlein purpura, is an immune-mediated small vessel vasculitis that has a predilection to affect the joints, kidneys, gastrointestinal tract and skin.^{1,2} It is the most frequent systemic vasculitis in children, and while less common in adults, it is often associated with more severe disease. Geographical differences have been reported in the prevalence of adult IgAV including male predominance, gastrointestinal involvement and musculoskeletal complications among Europeans, and lower propensity for genitourinary involvement among Americans.³ The frequency of glomerulonephritis (referred to as IgAV nephritis) in adults is higher than in children and tends to present more severely, with approximately 10–30% of those affected eventually progressing to end-stage renal disease.⁴ There have been several published case series and cohort studies of adult IgAV from the Asia-Pacific region, predominantly from East and Central Asia, but with a paucity of reports from Southeast Asia.^{5,6}

We hereby report our findings from the Singapore IgA Vasculitis Cohort (SIgAVasC), which is a retrospective case records review of consecutive adult patients tagged ≥ 21 years hospitalised in Tan Tock Seng Hospital, a tertiary adult hospital, with the main diagnosis of IgAV during the study period between 2007 and 2020. Included patients fulfilled the 2010 European Alliance of Associations for Rheumatology/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society classification criteria for IgAV.⁷ Demographic characteristics, clinical features, therapies and outcomes of all patients were analysed. Ethics approval was granted by National Healthcare Group Domain Specific Review Board (2018/00721).

The SIgAVasC comprised 136 IgAV patients: median (interquartile range) age 43 (29–57) years, with 23 (16.9%) aged ≥ 65 years at the time of incident admission. Majority were female (74, 54.4%), 91 were Chinese (66.9%), 18 (13.2%) of other ethnicities, 14

(10.3%) Malays and 13 (9.6%) Indians. The median (IQR) time from initial symptom onset to presentation was 14 (7–31) days. Disease manifestations comprised cutaneous (136, 100.0%), renal (57, 41.9%), gastrointestinal (50, 36.8%) and articular (19, 14.0%). Preceding fever (5, 3.7%) and sore throat (13, 9.6%) were uncommon. Microscopic haematuria (41, 30.1%) and proteinuria (14, 10.9%) were the most common renal manifestations. Renal function during the incident admission was as follows: 8 (5.9%) patients had estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73m²; 5 (3.7%) had an eGFR 30–59; and 106 (77.9%) had an eGFR ≥ 60 . There were 25 (18.4%) with underlying hypertension, and 18 (13.2%) with diabetes mellitus. Among 9 (6.7%) patients who underwent renal biopsy, 7 (77.8%) had histological features of crescentic glomerulonephritis and 5 (55.6%) had segmental sclerosis. There were 2 (1.5%) deaths during the incident admission. Among 117 patients with at least 1 year of follow-up data, 5 (4.3%) had an eGFR <30 , 8 (6.8%) had an eGFR in the range 30–59, and 76 (65.0%) had an eGFR of ≥ 60 mL/min/1.73m². One patient developed kidney failure requiring dialysis within a year from incident hospitalisation.

Immunosuppressive therapy comprised prednisolone/methylprednisolone (61, 44.9%), intravenous hydrocortisone (31, 22.9%), oral cyclophosphamide (5, 3.7%) and azathioprine (4, 2.9%). One year after inpatient discharge, 15/117 (12.8%) patients required non-corticosteroid immunosuppressive therapies to maintain disease remission (azathioprine [14, 12.6%], mycophenolate mofetil [2, 1.7%], cyclophosphamide [2, 1.7%] and ciclosporin [1, 0.9%]). The remaining patients achieved drug-free remission. Table 1 summarises the characteristics of the SIgAVasC at incident admission.

Systemic or organ-specific autoimmune disease was diagnosed prior to incident admission in 2 (1.5%) patients who had rheumatoid arthritis and systemic lupus erythematosus with antiphospholipid syndrome. Malignancy was diagnosed in 4/136 (2.9%) prior to or during incident admission, comprising malignant

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Table 1. Characteristics of SIgAVasC cohort at time of incident admission.

Demographics (N=136)	
Female, no. (%)	74 (54.4%)
Age at incident admission, years	
Mean (SD)	44.4 (17.4)
Median (IQR)	43 (29–57)
Age group, no. (%)	
21–44 years	72 (52.9%)
45–54 years	23 (16.9%)
55–64 years	18 (13.2%)
65–74 years	17 (12.5%)
≥75 years	6 (4.4%)
Ethnicity, no. (%)	
Chinese	91 (66.9%)
Malay	14 (10.3%)
Indian	13 (9.6%)
Others	18 (13.2%)
Median no. of days from symptoms onset to admission, no. (IQR)	14 (7–31)
Manifestations	
Cutaneous, no. (%)	136 (100%)
Constitutional, no. (%)	58 (42.6%)
Musculoskeletal, no. (%)	75 (55.1%)
Renal, no. (%)	57 (41.9%)
Respiratory, no. (%)	38 (27.9%)

neoplasm of the stomach, lung, nasopharynx and thyroid. One additional patient developed prostate cancer from the time of incident admission.

The demographic profile of our adult patients with IgAV was similar to that reported in other Asian series, differing in that our series had marginally more females.^{5,6} Extracutaneous involvement occurred in less than 50% of the SIgAVasC, with only 47% requiring systemic corticosteroids (CS) and 5% requiring non-CS induction immunosuppressive therapy (cyclophosphamide or azathioprine) at the incident admission. This observation reflects the presence of both severe (major organ involvement) and non-severe phenotypes (skin-limited with/without joint involvement) in our cohort, which differs from

Table 1. Characteristics of SIgAVasC cohort at time of incident admission. (Cont'd)

Manifestations	
Gastrointestinal, no. (%)	50 (36.8%)
Neurological, no. (%)	12 (8.8%)
Mucous membranes/eye, no. (%)	18 (13.2%)
Cardiovascular, no. (%)	6 (4.4%)
Ear, nose and throat, no. (%)	6 (4.4%)
Others, no. (%)	4 (2.9%)
Treatment	
Any glucocorticoid, no. (%)	
Prednisolone (including methylprednisolone), no. (%)	64 (47.1%)
Dexamethasone, no. (%)	61 (44.9%)
Hydrocortisone, no. (%)	1 (0.7%)
Azathioprine, no. (%)	31 (22.8%)
Cyclophosphamide, no. (%)	4 (2.9%)
Methotrexate, no. (%)	5 (3.7%)
Colchicine, no. (%)	1 (0.7%)
NSAIDs, no. (%)	14 (10.3%)
Haemodialysis, no. (%)	49 (36.0%)
Plasmapheresis, no. (%)	2 (1.5%)
Mortality	
Deaths during incident hospitalisation, no. (%)	2 (1.5%)

IQR: interquartile range; NSAIDs: non-steroidal anti-inflammatory drugs; SD: standard deviation; SIgAVasC: Singapore IgA Vasculitis Cohort

the majority of published adult series, where most patients were described as having a severe phenotype, predominantly attributed to renal involvement. The use of non-CS immunosuppressive therapies 1 year after the incident admission, predominantly azathioprine, reflects the mild-to-moderate severity of patients with extracutaneous involvement in a sub-population of the SIgAVasC.

Renal involvement was the most common extracutaneous involvement, similar to most Asian and non-Asian cohorts.^{5,6} However, the majority in our cohort had mild renal involvement in the form of asymptomatic haematuria and proteinuria, with none requiring long-term renal replacement therapy for up to 5 years following incident admission. Only 6.7% required renal

biopsy, of which the most common histological finding was crescentic glomerulonephritis. The presence of segmental sclerosis reflected underlying chronic kidney disease (9.7%) in the Singapore cohort—contributed by underlying age, hyper-tension and diabetes mellitus. Adult IgAV-related nephritis patients with more crescents have more severe renal manifestations and worse treatment responses, whereas the proportions of crescents were not associated with higher risks for end-stage renal disease (ESRD) or 50% decline in renal function. A more suitable pathological classification standard is needed to predict renal prognosis.⁸ The modest severity of renal involvement in our cohort contrasts with the higher prevalence of 63% in another report.⁸ IgAV associated with malignancy was uncommon in our cohort, similar to the case reports published in the literature on solid organ and haematological cancers.⁹

The treatment of adult IgAV ranges from supportive therapy in mild disease to definitive therapies including CS and non-CS immunosuppressive therapies, biologics (e.g. rituximab), intravenous immunoglobulins and plasma exchange depending on disease severity.^{10,11} In contrast to paediatric IgAV where there has been an attempt at creating consensus guidelines on treatment, there have not been any similar consensus guidelines for adults.

The majority of our adult IgAV cohort did not require long-term immunosuppressive therapy; had generally good renal outcomes at 1 year with only 1 patient requiring renal replacement therapy; and had a low incidence of progressive chronic kidney disease and mortality. The incidence of a concurrent neoplastic trigger was low. The SIgAVasC comprised a heterogeneous cohort of adults with IgAV, with a range of non-severe to severe phenotypes and as reflected by the varying types of immunosuppressive therapies used. End-organ damage, in particular chronic kidney disease was overall uncommon.

Ethics statement

Ethics approval was granted by NHG DSRB (2018/00721).

Declaration

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

Keywords: *glomerulonephritis, immunoglobulin A, immunosuppression therapy, nephrology, rheumatology, vasculitis*

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Laryngeal preservation versus upfront laryngectomy in advanced laryngeal cancer

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Dear Editor,

The management of locally advanced laryngeal cancer presents a complex clinical challenge, requiring a delicate balance between maximising oncological control and preserving the critical functions of the larynx. Historically, total laryngectomy (TL) was the standard of care, but landmark trials in the 1990s and 2000s, including the Department of Veterans Affairs Laryngeal Study and the Radiation Therapy Oncology Group 91-11 trial, established larynx-preservation (LP) strategies with chemoradiation (CRT) or radiotherapy (RT) as viable alternatives.¹⁻³ These studies demonstrated that for many patients, the larynx could be preserved without compromising overall survival (OS), leading to a paradigm shift towards non-surgical approaches. However, subsequent studies have revealed a more nuanced reality, questioning whether anatomical preservation always translates to functional preservation and suggesting that the optimal treatment strategy may depend more on other factors such as tumour stage.^{4,5} Given the high mortality burden of laryngeal cancer in Southeast Asia, this 15-year retrospective study was conducted at Tan Tock Seng Hospital, Singapore to compare the survival and functional outcomes of patients with locally advanced laryngeal squamous cell carcinoma (SCC) treated with either primary surgery or an LP protocol, providing valuable data from an Asian population.⁶

The clinical records of patients diagnosed with stage 3 or 4 laryngeal SCC between 2006 and 2020 were reviewed. To ensure consistency, all patients diagnosed before 2018 were retrospectively re-staged according to the American Joint Committee on Cancer (AJCC) 8th Edition. The study's endpoints were survival outcomes, measured by OS and disease-free survival (DFS) and functional outcomes, measured by swallowing and speech status. Swallowing function was defined by the need for long-term feeding tube support. Voice outcomes were categorised based on

documented speech function. Data were analysed using Stata version 16.0 (StataCorp, College Station, TX, US) with survival analysed using Kaplan–Meier method and Cox proportional hazard models.

A total of 124 patients were included, with 63 undergoing primary TL and 61 receiving primary LP therapy. Within the surgical arm, 42 patients (67%) received adjuvant RT or CRT while 21 patients (33%) had TL alone. In the LP arm, 48 patients (79%) received concurrent CRT and 13 (21%) received RT alone. The patient population was predominantly male (96%) and Chinese (83.9%), with a high prevalence of smoking (91.1%) and alcohol usage (64.5%). The mean age at diagnosis was 66.1 and 64.0 years for the surgery and LP arms, respectively. There were 39 patients (31.5%) with stage 3 and 85 patients (68.5%) with stage 4 disease. Within the surgical arm, 12 patients (19%) had stage 3 and 51 patients (81%) had stage 4 disease. Within the LP arm, 27 patients (44.3%) had stage 3 and 34 patients (55.7%) had stage 4 disease. The 2 treatment arms exhibited significant differences in AJCC stage ($P=0.002$), with the surgery arm containing a higher proportion of patients with stage 4 disease. Base of tongue involvement and major cartilage involvement, key features that often influence the decision for primary TL, were not significantly different statistically between the 2 groups.⁷

This study found a statistically significant survival advantage for patients who underwent primary TL. The 5-year median OS was 35.97 months (lower quartile 16.98, upper quartile was not reached) in the surgery arm compared to 25.28 months (interquartile range [IQR] 11.47–58.49) in the LP arm ($P=0.04$), as shown in Fig. 1A. Similarly, the median DFS of 32.95 months (IQR 16.95–83.87) in the surgery arm was significantly longer ($P=0.02$) than 18.42 months (IQR 6.95–53.84) in the LP arm, as illustrated in Fig. 1B. Multivariate Cox regression analysis identified treatment modality as an independent predictor of outcome. Patients who underwent surgery had a significantly lower hazard

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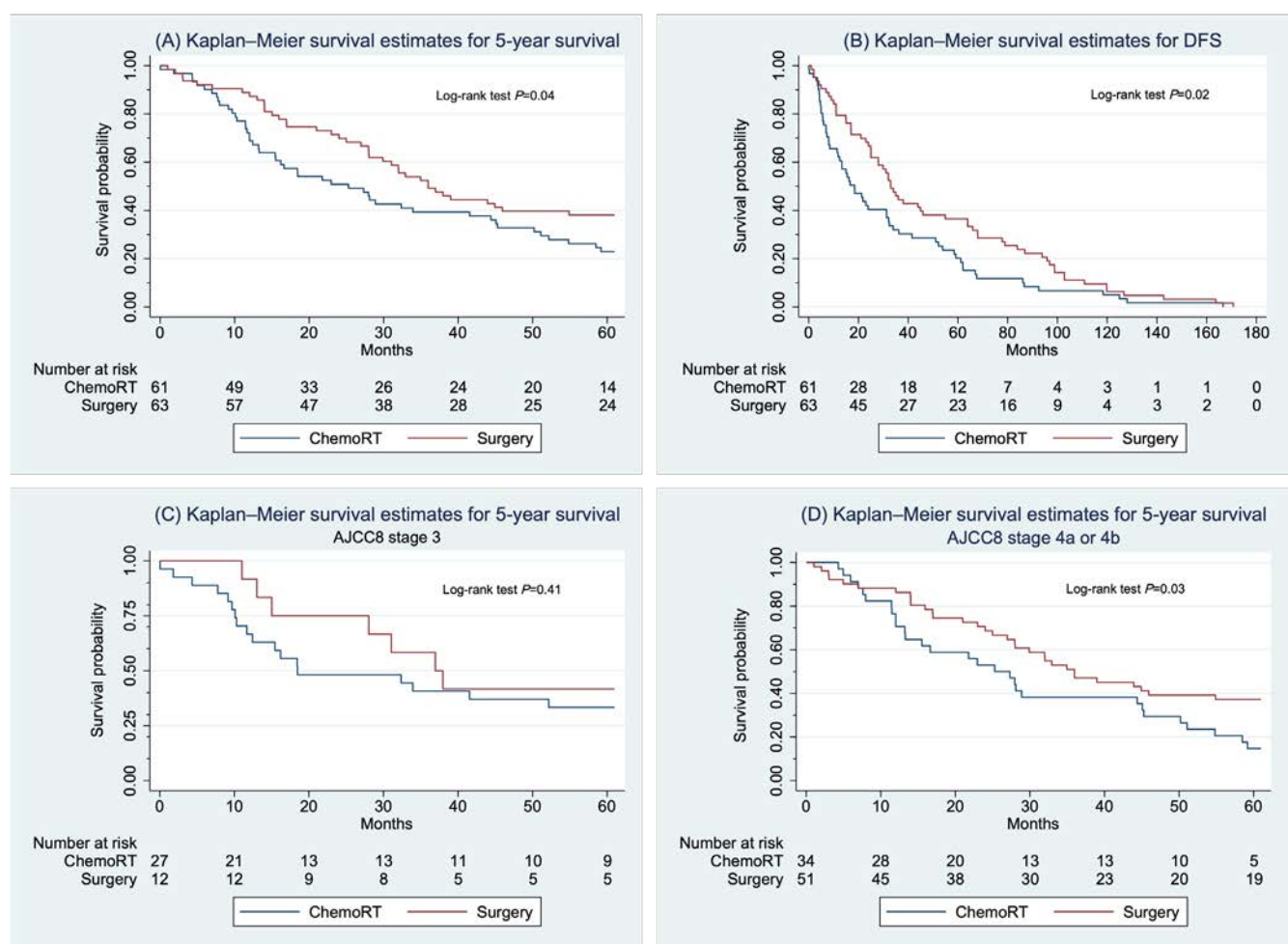
rate (HR) for death (HR 0.52, $P=0.01$) and disease recurrence or death (HR 0.45, $P<0.001$). Subgroup analysis showed that for patients with stage 4 disease, the 5-year OS of the surgery arm was better compared to the CRT arm ($P=0.03$) (Fig. 1D). For patients with stage 3 disease, there was no significant difference in the 5-year OS between the 2 treatment arms ($P=0.41$) (Fig. 1C). These findings are consistent with recent large-scale studies where Tang et al. and Grover et al. showed that the OS was significantly better in the surgery arm compared to the LP arm in T4 disease, while Su et al. showed that there was no difference in OS between the 2 arms in T3 disease.^{4,5,8}

In selecting the primary treatment approach, patient factors such as comorbidities, performance status and patient preference should be considered alongside

disease factors. In this study, the Eastern Cooperative Oncology Group (ECOG) performance status was a statistically significant factor ($P<0.001$) in determining the choice of primary treatment. Among the 14 patients who had an ECOG status of 2 or 3, 10 (71.4%) of them underwent upfront surgery, while the other 4 (28.6%) underwent LP therapy.

Functional outcomes presented a complex trade-off. The surgical arm demonstrated significantly better swallowing function, with 54 patients (85.7%) retaining oral feeding (including modified diets without tube dependence) compared to only 41 (67.2%) in the LP arm ($P=0.017$). The remaining patients were on enteral feeding via a gastrostomy tube or nasogastric tube. Similarly, a meta-analysis done by Pfuetzenreiter et al. found that there was a lower risk of long-term dysphagia

Fig. 1. Kaplan–Meier plot for 5-year survival and DFS outcomes.



(A) Kaplan–Meier survival estimates for 5-year overall survival. (B) Kaplan–Meier survival estimates for DFS. (C) Kaplan–Meier survival estimates for 5-year overall survival in AJCC8 stage 3 patients. (D) Kaplan–Meier survival estimates for 5-year overall survival in AJCC8 stage 4 patients.

AJCC8: American Joint Committee on Cancer 8th Edition; DFS: disease-free survival; RT: radiotherapy

and feeding tube dependence when surgery was performed.⁹ Conversely, the primary functional trade-off of TL is the definitive loss of natural voice. In this cohort, 64% of TL patients were rendered aphonic. To restore voice post-TL, 3 different methods can be used: (1) oesophageal speech, (2) electrolarynx and (3) tracheoesophageal prosthesis (TEP), with TEP exhibiting superior speech intelligibility and voice quality.¹⁰ In this study, only 23 (36%) out of 63 surgical patients achieved functional speech rehabilitation, a low rate potentially influenced by cultural and socioeconomic factors in Singapore. Among them, 12 had a TEP, 9 had an electrolarynx and only 2 managed to master oesophageal speech after a period of rehabilitation.

Despite the evolution of LP treatment over time, there is still a critical role for TL, not only in advanced primary tumours, but also as salvage therapy and for dysfunctional larynx from organ-preserving treatment.^{1,2} In this study, 13.1% of patients in the LP arm required salvage laryngectomy for recurrent or residual disease.

Limitations of this study include a retrospective design, which resulted in inherent selection bias and missing data, such as the lack of speech outcome data for the LP group and the number of patients who required a tracheostomy. Despite the limitations, the findings provide real-world validation of the management of locally advanced laryngeal cancer in Singapore. The superior survival in the surgical arm, which was composed of patients with worse prognosis, highlights the benefits of primary TL for advanced stage 4 tumours. For stage 3 tumours, the decision becomes a nuanced trade-off. LP offers a chance to retain the natural voice but carries risks of severe toxicity and swallowing dysfunction. Conversely, TL may offer better locoregional control and swallowing function but at the expense of a natural voice.

In conclusion, the findings provide strong evidence that primary laryngectomy should be considered the standard of care for patients with stage 4 laryngeal SCC in view of the superior OS and DFS outcomes, while LP should be the preferred approach in stage 3 patients given that it does not compromise the OS. Stage 3 patients with a non-functional larynx should undergo TL. Optimal management requires careful, multidisciplinary patient selection to align the chosen treatment modality with both the oncological imperatives and the functional priorities of each patient.

Ethics statement

This study was approved by the National Healthcare Group Domain Specific Review Board (2020/00068).

Declaration

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

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Implementation of spinal muscular atrophy screening for newborns at a Singapore tertiary hospital

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Dear Editor,

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder due to mutation in the *SMN1* gene leading to progressive muscle weakness, motor decline, feeding and respiratory difficulties, and in severe cases, causing premature mortality.¹ Over 95% of cases arise from homozygous deletion of *SMN1* exon 7, while disease severity is modified by *SMN2* copy number.² The incidence of SMA is about 1:8000 in the Asian population with a carrier frequency of 1:48 individuals.³

Until 2016, SMA was considered untreatable, with management limited to supportive care.⁴ Today, there are 3 approved therapies—nusinersen, risdiplam and onasemnogene abeparvovec.⁵ Importantly, clinical evidence shows that treatment is most effective when started before symptoms appear.⁶ For this reason, many countries have incorporated newborn screening (NBS) programmes for SMA. These include 48 of 50 states in the US, most provinces in Canada, 45% of all newborns across Europe, Taiwan and Australia.⁷ Singapore has yet to introduce such a programme for SMA.

Recognising this gap, we conducted a pilot study at the National University Hospital, Singapore, to evaluate the feasibility, acceptability and operational considerations of SMA NBS implementation, as well as the practicalities of laboratory developed test to identify homozygous *SMN1* exon 7 deletion. Although the study was conducted in a single tertiary hospital, it represents a critical first step towards a potential national implementation of SMA NBS in Singapore, informing future scale-up, financing pathways, and integration with existing national NBS and rare disease registries. Lessons from established regional programmes, such as Taiwan's nationwide SMA NBS since 2017,¹¹ provide valuable context for adapting

screening frameworks to Singapore's healthcare infrastructure.

From January to April 2024, parents of newborns in 2 postnatal wards were invited to participate. Study recruitment and pre-test genetic counselling was completed by the study team comprising a paediatric geneticist, a paediatric neurologist, a genetic counsellor, a genetic counsellor associate, a general paediatrician, 2 nurses and 3 neonatologists. The study team received training about SMA knowledge from the paediatric neurologist and training to conduct pre-test genetic counselling from the paediatric geneticist, and were evaluated by real-time observation before commencing recruitment.

Of the 110 parents surveyed, 100 (91%) agreed to screening after receiving pre-test genetic counselling. Blood samples were collected on dried blood spots via heel prick or venipuncture, concurrent to routine biochemical NBS procedures, and tested using a laboratory-developed quantitative polymerase chain reaction assay that detects homozygous *SMN1* exon 7 deletions.⁸ Positive controls from known SMA patients validated assay performance.

In parallel, parents completed a survey exploring awareness, attitudes, financial considerations and preferred timing of education about SMA (Supplementary Table S1). Only 1 parent (usually the mother, as she was the inpatient at the postnatal ward) was invited to complete the survey after counselling. While both parents often attended counselling sessions, logistical limitations prevented consistent survey collection from both parents. After completion of the pilot study, the healthcare study team of 10 comprising doctors, nurses and genetic counsellors also reflected on their experience via a study team survey (Supplementary Table S1).

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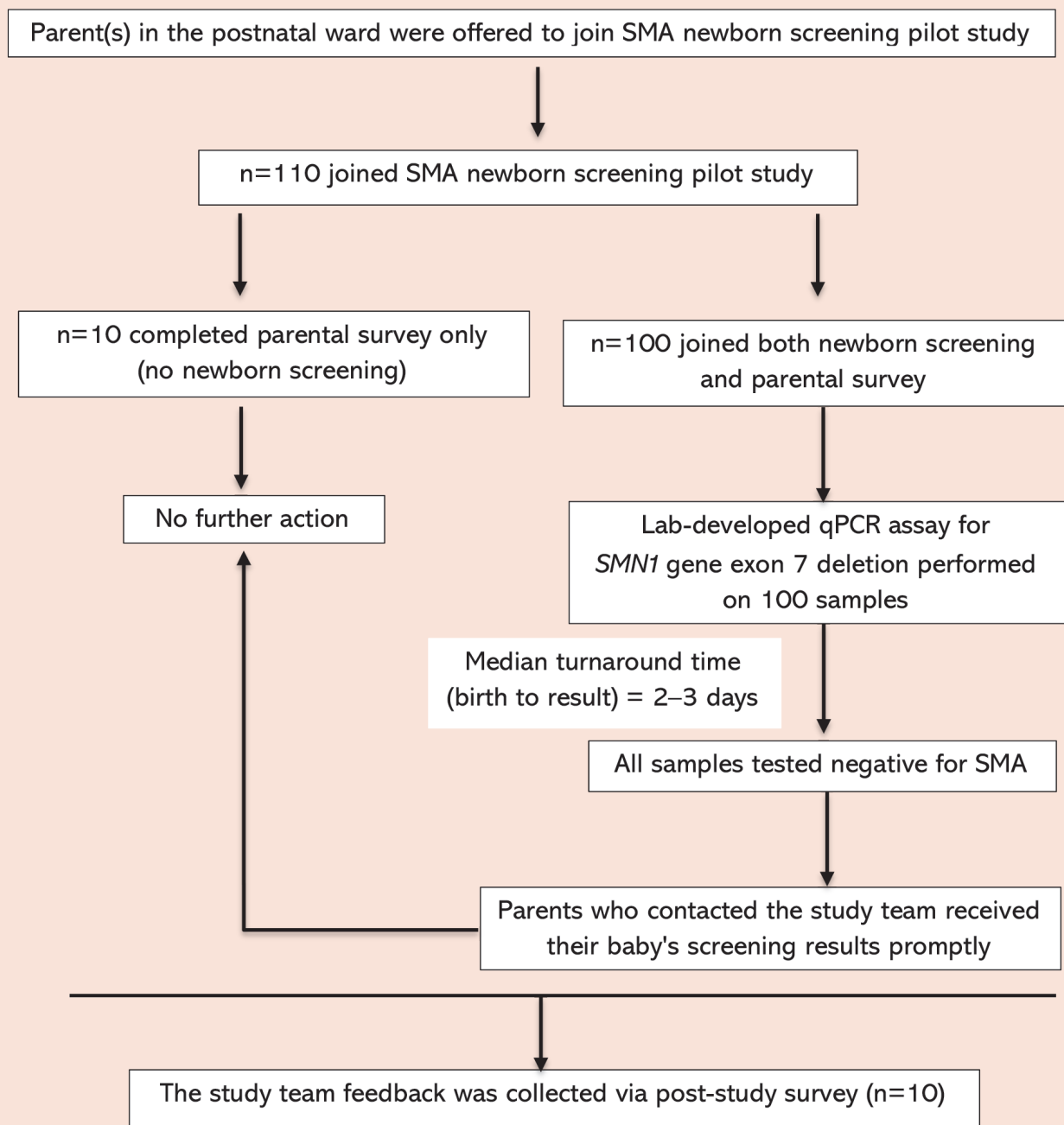
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The study population comprised 110 parents of participants, with mothers representing the majority at 73% (81/110) and fathers accounting for the remaining 27% (29/110). Parental knowledge of SMA was limited: 66% (73/110) had never heard of the condition, and 77% (85/110) were unaware of available treatments. However, once informed, 85% (95/110) believed that SMA NBS could improve outcomes. Financial acceptability was moderate, with 67% (74/110) willing to pay up to SGD70 for screening and

81% (89/110) up to SGD300 for confirmatory testing. Despite potential financial concerns, 69% (76/110) indicated they would choose to have their newborns screened for SMA. Furthermore, even in the face of possible insurance limitations, a considerable 65% (72/110) of respondents maintained their willingness to proceed with SMA screening (Fig. 1).

Notably, most parents (74%, 81/110) preferred to learn about SMA newborn screening during pregnancy, while nearly one-third (29%, 32/110) favoured even

Fig. 1. Schematic representation of the SMA newborn screening pilot study.



qPCR: quantitative polymerase chain reaction; SMA: spinal muscular atrophy

earlier public health messaging before conception. A large majority (78%, 86/110) indicated preference to know their SMA carrier status prior to pregnancy, suggesting that pre-conceptional couple carrier screening may play an important role in future implementation. Moreover, 91% (100/110) of the parents surveyed were agreeable to proceed with the test. Parents who declined the test were mostly concerned about the additional blood collection, psychological stress of a positive screen, insurance implications, and cost for confirmatory testing and treatment.

From a laboratory perspective, all 100 newborn samples tested negative for SMA. The results returned within 5 working days. No false positives or assay failures occurred, confirming the robustness of the test approach.

For the study team survey, pre-test counselling required 15–30 minutes per family. The most significant challenges were time constraints in the immediate postnatal period, low parental familiarity with SMA and questions about additional blood collection. Team members highlighted the value of written materials or short videos to support counselling. They also noted that antenatal education would be more effective than postnatal explanations, when parents are often fatigued or overwhelmed (Supplementary Table S1).

To the authors' knowledge, this is the first SMA NBS pilot study in Singapore. High parental acceptance (91%, 100/110) following counselling is encouraging and consistent with international reports.⁹

Laboratory feasibility was demonstrated, but as with other programmes, the team's assay only detects exon 7 deletions and not rarer point mutations or duplications. For a national programme, follow-up testing with *SMN2* copy number analysis would be essential to guide prognosis and treatment urgency.¹⁰

Infants identified with SMA through newborn screening would require rapid referral to a multidisciplinary care team, comprising paediatric neurology, genetics, respiratory medicine and allied health professionals. Confirmed cases are typically co-managed within a coordinated neuromuscular clinic, facilitating early counselling and initiation of therapy. In Singapore, 3 disease-modifying treatments are currently available: nusinersen, risdiplam and onasemnogene abeparvovec. Of these, risdiplam is the most accessible, with partial government subsidy available, while families may also pursue financial assistance or crowdfunding for other therapies. Prompt, presymptomatic treatment initiation remains a key goal to optimise motor and survival outcomes, underscoring the importance of a well-defined linkage-to-care pathway in any future national programme.

Cost remains a critical issue. While many parents expressed willingness to pay, the long-term sustaina-

bility of a national screening programme would require policy support, integration into existing NBS workflows and careful consideration of funding and subsidy models. Insurance implications also need to be addressed.

Operational barriers included limited time for postnatal counselling, low parental familiarity with SMA and concerns about additional blood collection. These can be mitigated through antenatal education, multimedia counselling aids and integration within existing NBS workflows to streamline implementation.

Nationwide implementation would also require substantial manpower for pre-test counselling, currently taking 15–30 minutes per family. Innovative approaches, such as digital or video-based pre-test education and training of existing healthcare staff, could help improve scalability and resource efficiency.

Finally, public education must begin early. Parents in the study overwhelmingly preferred antenatal or even pre-pregnancy information about SMA screening, allowing time for reflection and decision-making. Integrating such education into routine antenatal care could reduce pressure on postnatal information delivery and improve uptake.

The authors acknowledge that the study is limited by its single-centre nature, which may not fully represent the diverse healthcare landscape across Singapore. The relatively short follow-up period restricts the team's ability to assess long-term outcomes and challenges associated with SMA screening implementation. Additionally, the generalisability of these findings may be limited, as practices and resources in a tertiary hospital setting might differ from those in other healthcare facilities. Despite these limitations, the authors' experience provides valuable insights for the potential nationwide implementation of SMA newborn screening in Singapore, offering a foundation for future multicentre studies and longer-term evaluations.

This pilot study demonstrates that SMA newborn screening is both feasible and acceptable in Singapore. Parents responded positively once informed, and laboratory testing was reliable. However, successful implementation at the national level will depend on addressing key challenges: raising public awareness, providing timely education, ensuring adequate counselling resources and developing sustainable funding strategies. With these considerations in place, a Singapore SMA NBS programme could enable early intervention, improve outcomes and prevent significant morbidity and mortality in infants affected with SMA.

Supplementary material

Table S1. Parental survey.

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We gratefully acknowledge study team members, laboratory team, medical and nursing staff of the postnatal wards in Departments of Neonatology and Obstetrics and Gynaecology, National University Hospital, and parents of the participants for their invaluable support in this study.

Ethics statement

The Spinal Muscular Atrophy exon 7 deletion newborn screening pilot was approved by the National Healthcare Group Domain Specific Review Board (2023/00754).

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. Data are available upon reasonable request from the corresponding author.

Keywords: genetic counselling, implementation, newborn screening, qPCR, spinal muscular atrophy

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Care without walls: Generalist-led integrated home health for life's final chapter

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Dear Editor,

Singapore's aged population is burdened by advanced chronic illnesses with prolonged and unpredictable disease trajectories.¹ More than 70% of Singaporeans want to be cared for at home at the end of life (EOL). Furthermore, 77% want to die at home,² but only 1 in 4 do.³ The home care service (HCS) tends to home-bound patients. However, when patients deteriorate, they are either admitted to an acute hospital or handed over to a home hospice service, resulting in disruption in care continuity.

In this study, authors describe a novel model of care to address this gap. The integrated home health (IHH) programme, which was piloted in St Luke's Hospital, a community hospital in Singapore, embedded generalist palliative care into the existing HCS. The programme was run by family physicians and resident physicians with non-specialist training in palliative care. The aim of the pilot was to study the health outcomes of a programme that sought to empower home care providers to provide EOL care in the community.

The pilot ran from February 2024 to February 2025. Patients under the community hospital's HCS were screened for eligibility, based on the Clinical Frailty Scale, frequency of hospital admissions in the preceding 6 months, and the "surprise question".⁴ To ensure appropriateness of IHH enrolment, clinician judgement served as an adjudicator for the screening tool in identifying suitable patients. IHH clinicians would reference existing HCS documentation to assess for (1) complexities requiring specialist input, (2) patient and family readiness for a shift towards comfort-focused, symptom-directed management and (3) availability of a competent carer, which is crucial for home-based EOL care.

Within 5–8 working days, a physical triage visit would be made, and the patient's needs were evaluated. The IHH journey comprises symptom management, serious illness conversations (SIC), psycho-emotional

support and spiritual care through physical and tele-consultations, with 24/7 tele-support. Post bereavement, caregivers continue to be supported by a dedicated social worker.

IHH is different from the home hospice service. First, in terms of clinical leadership, the former is helmed by generalists with interest and training in palliative care, allowing for democratisation of palliative care in the community, while the latter is led by palliative care specialists with advanced training. Second, in terms of patient profile, IHH cares primarily for non-cancer patients who were already HCS recipients for up to 10 years and would otherwise be transferred to another care provider at EOL if not for a programme like IHH, while home hospice providers care for a mix of cancer and non-cancer patients with a prognosis of less than 1 year. Finally, from the systems standpoint, the former is subsidised under home care subsidies and is meant to plug a missing piece in the public long-term care ecosystem, while the latter is provided free of charge by charities with additional support from the Ministry of Health, Singapore.

Of 45 referrals, 38 patients were enrolled. Most were female (79%, n=30), aged 69–102 years. The top 3 primary life limiting illnesses include: dementia (47%, n=18), stroke (28%, n=11), heart failure (5%, n=2), all of which are non-cancer.

A range of length of service (LOS) was observed with most under 6 weeks: 44% (n=17) under 2 weeks, and 36% (n=14) 3–6 weeks. A minority remained in the programme for longer: 20 to 52 weeks (15%, n=6), with frequent unstable episodes or prolonged gradual deterioration. This does not include the duration of preceding HCS. Many patients in IHH had completed Preferred Plan of Care (PPC) discussions (86%, n=33) and still more had at least 1 SIC with the IHH team (96%, n=36).

Of those who had demised (n=28 as of February 2025), most patients had pneumonia (89%, n=25) as

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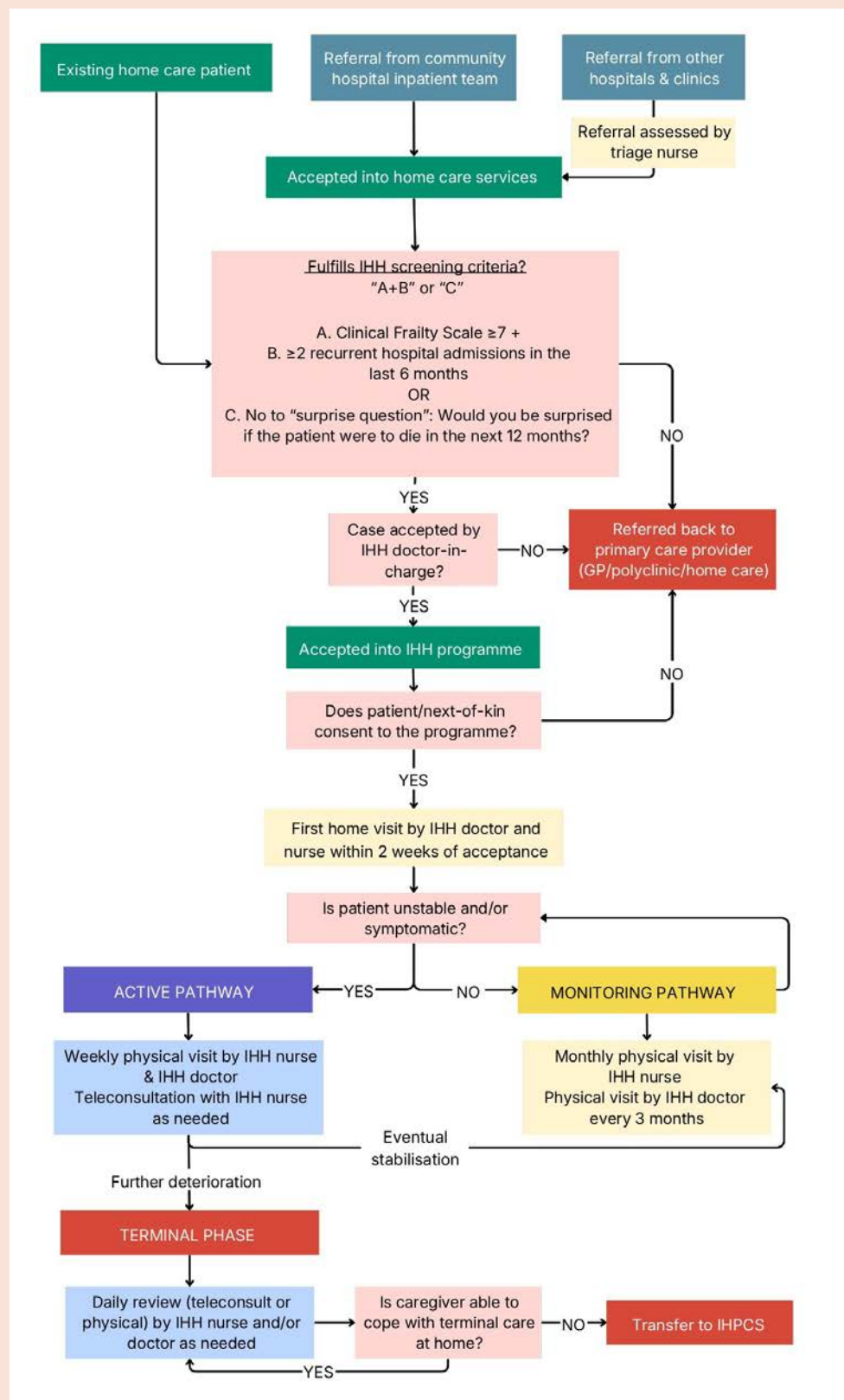
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Fig. 1. IHH programme workflow.



GP: general practitioner; IHH: integrated home hospice; IHPCS: inpatient hospice palliative care service

Note: In deciding between active and monitoring pathways, clinical assessment and the Edmonton Symptom Assessment System-revised (ESAS-r) score, done at each IHH nurse and doctor review, were used. An acute change in or rapid progression of symptoms (represented in the ESAS-r score trend, where a score of ≥ 4 represented at least moderate symptom severity) or haemodynamic instability would necessitate a switch to the active pathway. Terminal phase is defined as having a prognosis of days.

the terminal event. Most passed on in the community (92%, 20 at home, 6 in the inpatient hospice palliative care service [IHPCS]), while 2 patients were transferred to the acute hospital for management of the terminal event.

Preferred place of death (PPoD)-concordance, defined as death occurring at the patient's documented PPoD at enrolment, was 89% of those whose PPoD was known (n=25). Of the 3 patients who did not achieve PPoD-concordance, 2 were transferred to IHPCS while 1 was transferred to the acute hospital.

While advance care planning tends to be low in uptake in generalist settings even among those at EOL (ranging widely from 66% to as low as 5%),⁵⁻⁷ the pilot has achieved high rates of EOL conversations (both SIC and PPC). Compared to national statistics, the pilot has achieved high rates of terminal care in the community (home and IHPCS) and PPoD-concordant care.

About half of the patients were in the “deteriorating” or “terminal” palliative care phase on first visit (47%, n=18), with LOS till death ranging from 1 to 25 days. Interestingly, half of those assessed as “stable” on first visit (52%, n=20) had LOS till death at 28 days and less. The lack of correlation between a patient's initial palliative care phase and survival in the pilot population showcases the challenge of prognostication in non-cancer. Achieving upstream identification of palliative care needs in non-cancer patients is vital in facilitating quality of life (not too late)⁸⁻⁹ without draining resources (not too early).

In summary, IHH, which is the integration of generalist palliative care in existing HCS, is a feasible, value-based and scalable strategy for home-based palliative care, especially in non-cancer. It plugs an existing gap in the traditional HCS model, facilitating continuity of care and proactive rather than reactive care. IHH must be mainstreamed and strengthened with further research to allow data-driven, integrated care for Singapore's aged and multimorbid population.

Ethics statement

The study was approved by St Luke's Hospital Institutional Review Board (SLH IRB) (IRB-01-2026-02-03).

Declaration

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

Keywords: chronic disease management, end-of-life care, frailty, generalist palliative care, home care

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"Fluoride benefits and risks: Lessons from 70 years of water fluoridation in Singapore": Correspondence

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Dear Editor,

Recently Yee et al. published a commentary in the *Annals*,¹ focusing on a meta-analysis of 74 human observational studies by Taylor et al. published in *JAMA Pediatrics*,² which found an inverse association between fluoride exposure and children's intelligence quotient (IQ). Although many of the authors' critiques are directly addressed in Taylor et al. and in their previous commentary,³ the group would like to take this opportunity to respond.

As reported in Taylor et al.² the meta-analysis was performed to the highest standards of transparency and objectivity, following a pre-established, peer-reviewed protocol that outlined all aspects of the analyses including the inclusion and exclusion criteria for study selection to avoid bias.⁴ The comprehensive literature search captured all relevant literature across 8 international databases without language restriction. Two reviewers extracted data and performed risk-of-bias (study quality) evaluations independently, for each relevant study. Data are publicly available and downloadable for anyone to repeat or extend this work (<https://hawcproject.org/assessment/405/>).

Yee et al. are correct that most studies were conducted in countries where fluoride levels in water are above 1.5 mg fluoride/L, and that Taylor et al. included studies with both higher and lower risk of bias. However, they do not also note that the inclusion of all studies, regardless of quality or level of exposure, is consistent with best practices for meta-analyses in environmental epidemiology. The findings by Taylor et al. are not based solely on a single combined set of studies; the study also includes numerous subgroup analyses restricted to studies with exposures below the US Environmental Protection Agency's (EPA's) or the World Health Organization's upper exposure guidelines of 4 mg/L, 2 mg/L and 1.5 mg/L of fluoride in drinking water. Importantly, analyses restricted to the high-quality studies—which represent the strongest and most reliable evidence—consistently supported

the inverse association between fluoride exposure and children's IQ.

Yee et al. noted that there was "evidence of substantial heterogeneity," but did not acknowledge that this is expected for observational studies with a variety of study locations, populations and exposure metrics. In contrast to meta-analyses of randomised controlled trials, where heterogeneity in results can reduce confidence in the findings, heterogeneity in methods across observational studies that provide consistent evidence of an association can strengthen confidence in the findings.³

Yee et al. also claimed that Taylor et al. did not provide justification for the exclusion of studies or explain the "calculated individual effect sizes" for the main analysis. In fact, reasons for exclusion of each study are provided in the Interactive Reference Flow Diagram (eFigure 1b) in the study selection section of the main paper, and are listed for individual studies in eTable 2 of the supplemental materials in Taylor et al.² Additionally, the study selection section of the supplemental material states: "Studies that did not report quantitative effect estimates (mean outcome measures or regression coefficients), measures of variability (95% CIs, SEs, or standard deviations [SDs]), or numbers of participants were excluded. Studies with missing measures of variability but with reported p-values were included, and SDs were calculated following the approach in the Cochrane Handbook for Systematic Reviews."⁵

As explained in the main text and supplemental material for the mean effects meta-analysis, effect estimates were the standardised mean differences (SMDs) for heteroscedastic population variances. SMDs were calculated from the difference in mean IQ scores between an exposed and reference group.²

Yee et al. critiqued Taylor et al.'s reliance on studies reporting spot urinary fluoride values as estimates of total exposure to fluoride. They claim, without supporting evidence or citation, that spot urine

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samples are not "a reliably valid measure of long-term fluoride exposure in individuals." First, it is important to recognise that urinary fluoride data was only one of the measures considered; the inverse associations between fluoride exposure and children's IQ were consistently observed across multiple exposure metrics including fluoride levels in drinking water and estimated fluoride intake. Second, while Taylor et al. acknowledge there are limitations in using spot urinary data, when corrected for dilution, they have been shown to be moderately correlated across individual pregnant women sampled in each trimester of gestation. Spot urinary data have also successfully distinguished between populations consuming fluoridated versus non-fluoridated drinking water;⁶ correction for dilution was an element of the exposure risk-of-bias assessment in Taylor et al. Additionally, regulatory agencies like the US EPA, routinely rely on urinary exposure estimates for risk assessment purposes.

Yee et al. suggest that confounding factors were not "well controlled", to which Taylor et al. disagree. Although confounding factors or covariates were not uniformly accounted for across all studies, the potential for confounding was a critical element of the risk-of-bias evaluation. Studies were only rated as having low risk of bias for confounding if they adequately accounted for key covariates including age, sex, socioeconomic status and co-exposure to other neurotoxicants. Consideration of clustering by city was also included in the risk-of-bias assessment if relevant to the study. A subset of the literature collected through October 2023 was specifically examined for evidence of a pattern of confounding bias that could explain the consistent inverse association between higher exposure to fluoride and lower IQ in children. No such pattern could be discerned, indicating that confounding cannot account for the direction of association.⁷

Finally, regarding the validity of IQ tests, Taylor et al. note that regulatory agencies have relied on IQ tests to evaluate neurotoxicity of substances, such as lead and mercury. The risk-of-bias assessment by Taylor et al. had also considered whether IQ tests were culturally appropriate, blinded to exposure and normed against country-specific populations. The authors appreciate the opportunity to respond and provide these clarifications.

Ethics statement

Not applicable as no study participants were recruited for this Letter to the Editor.

Declaration

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