



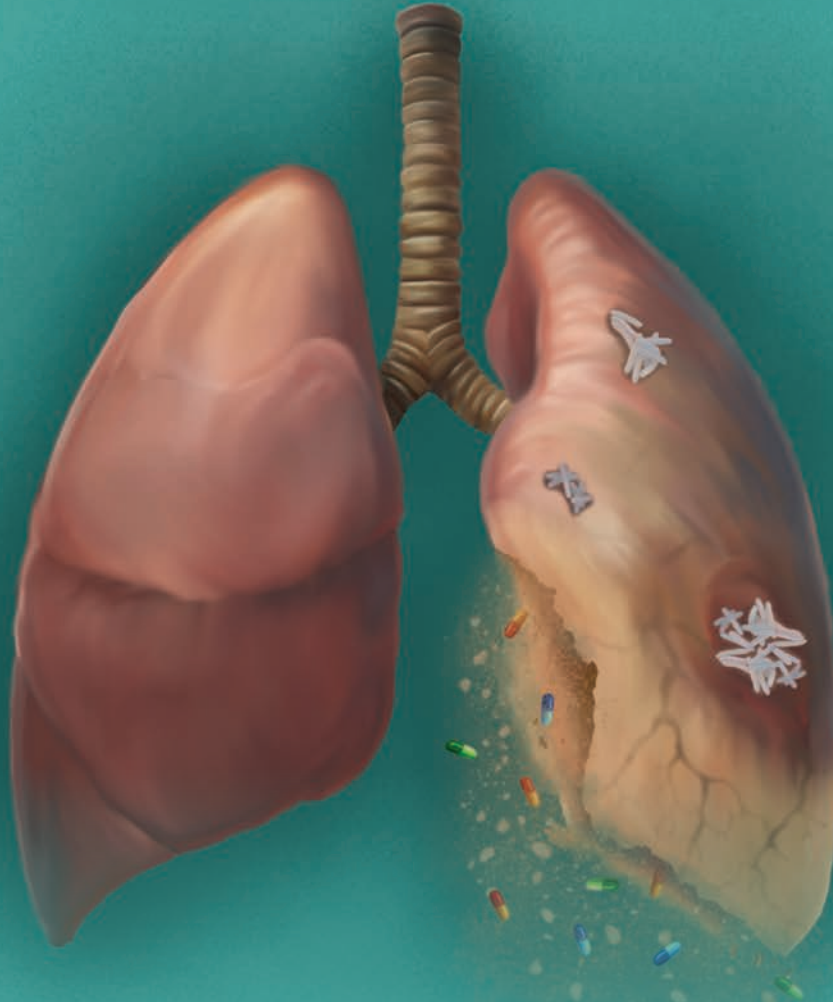
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Treatment outcomes in *Mycobacterium abscessus* pulmonary disease: A systematic review

Complexities of treating *M. abscessus* pulmonary disease include drug resistance, frequent drug-related adverse effects, variable treatment outcome definitions and poor treatment outcomes among patients with underlying chronic lung diseases. (See full article, p. 699)

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The importance of multi-level resilience in healthcare systems in small countries like Singapore

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Leveraging real-world data to develop long-term follow-up programmes for childhood cancer survivors

Panpan Xiao¹ MSc, Grace Pui Yung Tong² MBBS, Jiaoyang Cai³ MD, Yin Ting Cheung^{1,4} PhD

In this issue of the *Annals*, Lam Shang Leen et al. comprehensively audited the late effects experienced by 485 childhood cancer survivors who visited the long-term follow-up (LTFU) clinic of KK Women's and Children's Hospital (KKH), Singapore between 2017 and 2023.¹ The authors found that approximately 80% of survivors had experienced at least 1 late effect. LTFU care, which emphasises the prevention, early detection and treatment of late effects, is an integral part of survivorship care for childhood cancer survivors.² However, most studies describing paediatric LTFU models and practices have been conducted in North America, Europe and Oceania. Consequently, there is a paucity of related studies conducted in Asia.^{3,4} This study represents one of the first reports to systematically evaluate the prevalence of late effects among childhood cancer survivors in Southeast Asia. One notable strength of this study is the use of a well-characterised cohort and the application of the Common Terminology Criteria for Adverse Events to identify and grade late effects, thus facilitating standardised data collection and cross-cohort comparability with similar international cohorts. The resulting data provide a regional benchmark for quantifying the burden of cancer- and treatment-related late effects in Southeast Asia, where the systematic surveillance of chronic health conditions among childhood cancer survivors remains limited.

Moreover, this study exemplifies how international survivorship guidelines can be locally adapted based on real-world evidence. Drawing on the findings from this cohort, the authors implemented a structured cancer- and duration-specific LTFU framework for KKH. They found that the onset of the first late effect occurred substantially later in leukaemia survivors (10–14 years post-diagnosis) than in survivors of central nervous system and solid tumours, who typically developed late effects within 5 years. By delineating the timings of onset and types of late effects across survivors, the authors could identify

the timing, frequency and duration of surveillance for each specific cancer diagnosis group, which in turn informed resource allocation and screening prioritisation. Similar adaptations driven by population data have been implemented in other countries. For example, valuable survivorship data from major multicentre, multidisciplinary childhood cancer cohorts in North America and Europe over the past 5 decades have led to important changes in clinical practice, particularly the development of LTFU surveillance guidelines and targeted interventions.⁵ In the UK, findings from the British Childhood Cancer Survivor Study delineate the excess risks of second malignancies and cardiovascular disease, thus influencing survivorship pathways within the National Health Service and contributing to national guidelines (SIGN 132).⁶ These experiences demonstrate that actual guideline implementation must be adapted to local survivor cohort profiles and healthcare system resources to improve the feasibility and sustainability of LTFU care.

Despite its strengths, a key limitation of this study is its retrospective single-centre design. Singapore is a small island nation with a multiethnic and multireligious population. The development of a national childhood cancer cohort with standardised surveillance guidelines, using its well-established cancer registry as a foundation, represents a more rigorous approach to LTFU programmes in this city-state. Additionally, psychological and psychosocial late effects were under-represented in this study. Although several international guidelines specify that all survivors are at risk of psychological and psychosocial problems, thus warranting routine screening during LTFU care,² these recommendations have not been consistently implemented in clinical practice, and this gap in practice is particularly evident in Asia.⁷ A recent multinational survey study⁴ found that only a third of surveyed institutions in Asia provide systematic screening for psychosocial problems. As the authors pointed out,

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the lack of standardised screening tools may be an important contributor to this gap. To date, countries and regions such as the US,⁸ India⁹ and Latin America¹⁰ have established standards of psychosocial care for paediatric cancer patients and validated assessment tools, such as the Psychosocial Assessment Tool¹¹ and ONPSIPED,¹⁰ aiming to identify at-risk survivors and provide personalised psychosocial interventions. Given Singapore's unique multireligious and multilingual context, similar efforts in this country could be directed towards validating psychosocial screening tools and developing culturally sensitive psychosocial interventions. Given the strength of its existing advocacy infrastructures, such as the VIVA Foundation for Children with Cancer, Singapore is in a key position to address the current gap in psychosocial care and provide capacity-building initiatives to strengthen survivorship efforts in Southeast Asia.

Currently, LTFU care implementation remains challenging in low- and middle-income countries (LMICs) across Asia.⁷ Regional collaboration may be a promising strategy for advancing equitable and sustainable survivorship care across Asia. In Europe, the PanCareSurFup project has built one of the largest childhood cancer cohorts, including over 83,000 survivors from 12 European countries.¹² Beyond generating robust evidence on late effects, this project has emphasised cross-national training and knowledge dissemination, thereby strengthening the capacities of clinicians and researchers throughout the region. In parallel with Lam Shang Leen et al.'s study,¹ the National Children's Medical Center-Shanghai LTFU Study Group has initiated a similar disease-specific LTFU care framework for late effect surveillance in 25 institutions in Hong Kong and mainland China, and is supported by the Hematology and Oncology Long-Term Follow-Up System for standardised treatment summaries and late effects documentation.¹³ Other national childhood cancer survivor cohorts and studies in Asia (e.g. Hong Kong, Japan, South Korea) have been published. Drawing on international experience, future efforts could leverage these existing national cohorts to create a multinational survivor cohort in Asia. Such an initiative could lay the groundwork for developing evidence-based and region-specific survivorship care guidelines for Asian childhood cancer survivors. The next step should also involve facilitating countries in the region, especially LMICs, to develop their own survivor cohorts, as well as the exploration of pooled national data registries. Such a valuable collaborative platform would enable studies on genetic, socioenvironmental and lifestyle risk factors for late effects among childhood cancer survivors and guide the implementation of targeted interventions in the region.

Ethics statement

Not applicable, as no study participants are involved.

Declaration

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

Keywords: cancer, long-term follow-up, paediatrics, survivorship

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***Mycobacterium abscessus* treatment: From empiricism to mechanism**

Stefan H Oehlers^{1,2} PhD, Dorothy Hui Lin Ng^{3,4} MBBS

Singapore has reached an inflection point in mycobacterial disease epidemiology, where nontuberculous mycobacterial (NTM) lung infections now nearly surpass tuberculosis (TB) in both incidence and prevalence.¹ Of the >180 known NTM subspecies, members of the *Mycobacterium abscessus* complex (MABC), comprising 3 phylogenetic subspecies—*abscessus*, *bolletii* and *massiliense*—are disproportionately represented in Singapore, accounting for an estimated 30% of incident NTM lung infections.^{1,2} The trend in “replacement” of TB with pulmonary NTM infection is reflected in other industrialised settings, where better control of TB and better NTM awareness and diagnostics have driven a relative decline in TB and a rise in NTM disease. At the same time, the predominance of MABC over *Mycobacterium avium* complex (MAC) in Singapore appears to reflect environmental and climatic determinants; unlike many temperate settings where MAC is dominant, our tropical climate favours MABC as the major pathogen.³ Together, these indicators suggest we will continue to encounter more MABC infections for the foreseeable future.

The clinical and public health implications for this transition are substantial.⁴ When appropriately treated, drug-susceptible TB is usually curable within a defined treatment course and is not typically characterised by long-term relapse. In contrast, NTM lung infections are often chronic, progressive and prone to relapse despite prolonged and toxic multidrug regimens. The result is cumulative morbidity, reduced quality of life and escalating healthcare utilisation. For MABC in particular, outcomes are frequently poor; refractory, relapsing infection can culminate in respiratory failure and death.⁵

One major driver of this gap is pharmacologic: we have spent decades optimising TB regimens for both drug-susceptible and even multi-drug-resistant TB. No equivalent therapeutic certainty exists for MABC. MABC is intrinsically resistant to most antibiotics⁴; current regimens are largely empiric,

assembled around drug susceptibility testing (DST) results.^{6,7} However, DST for MABC is technically challenging and slow. At present, macrolides are the only oral agents for which in vitro susceptibility consistently correlates with clinical response in MABC pulmonary disease. For most other agents, correlations between the minimum inhibitory concentration and outcomes remain weak or unvalidated.⁸

Two major genetic mechanisms govern macrolide resistance in MABC.⁴ Inducible macrolide resistance is mediated by *erm*(41) (a common resistance mechanism in *M. abscessus* subspecies *abscessus* and *bolletii*). This resistance may not be immediately apparent and can develop over the course of treatment. This is incompletely captured by conventional DST unless prolonged incubation is performed, and molecular testing of *erm*(41) is not yet routine locally. In contrast, *M. massiliense* lacks functional *erm*(41), so macrolides remain predictably active. However, high-level macrolide resistance via *rrl* mutations (in the 23S ribosomal RNA gene) can still be acquired during long-term macrolide therapy. Infections with macrolide-resistant MABC subspecies are especially difficult to control and are associated with persistently culture-positive disease, functional decline and excess mortality.

The systematic review by Lim et al. in this issue of the *Annals* highlights the lack of evidence-based combinations that improve clinically meaningful outcomes, the uncertainty around optimal treatment duration, and a lack of harmonised outcome measures.⁹ This therapeutic uncertainty raises a central question: can we realistically design robust, prospective clinical trials to identify antibiotic regimens that work in different MABC subspecies or genotypes, or is MABC lung disease fundamentally an “unwinnable” disease due to underlying host factors or the pathogen’s environmental ubiquity and high mutability? Singapore is engaged in new efforts to answer this. We are participating in the observational arm of the FORMaT trial, an international prospective study evaluating

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treatment strategies in MABC,¹⁰ and in the Singapore MALADY study (manuscript under preparation), a prospective observational study which tracks host responses and MABC genotypes across treatment and watchful waiting.

The authors further highlight the importance of assessing patient-centric outcomes beyond microbiological sputum conversion or radiological changes.⁹ Quality-of-life questionnaires that capture symptom burden and functional status have been endorsed by the US Food and Drug Administration as the primary endpoint for NTM-pulmonary disease drug trials. In addition, lung function testing can provide objective, complementary measures of clinical response. Preclinical animal models of MABC and TB pathology have demonstrated the central role of immunopathology in mycobacterial disease, highlighting opportunities to develop non-antibiotic, host-directed therapies. Developing strategies to reduce host tissue damage during infection and support post-infection functional recovery will be increasingly important as the burden of NTM lung disease continues to rise.

Singapore stands at the forefront of a shifting mycobacterial disease landscape, one that demands re-examination of diagnostic, therapeutic and research paradigms of disease caused by NTM. Moving forward, the field must pivot from empiricism to mechanism: integrating pathogen genomics, host immune profiling and prospective clinical data. Parallel development biomarker-guided strategies may enable more precise definitions of treatment success and development of personalised therapy. Singapore's confluence of high MABC prevalence, established microbiological infrastructure and translational research capacity positions it uniquely to keep pace with this transition.

Ethics statement

Not applicable as there are no study participants.

Declaration

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

Keywords: *antibiotic, rapidly growing mycobacteria, susceptibility*

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The reported late effects experienced by childhood cancer survivors treated in Singapore: A clinical audit

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ABSTRACT

Introduction: Knowledge of late effects after oncological treatment in Southeast Asia remains limited. This study is among the first comprehensive audits of late effects experienced by paediatric cancer survivors from the long-term follow-up (LTFU) clinic at KK Women's and Children's Hospital in Singapore, between September 2017 and December 2023.

Methods: A total of 485 survivors were examined, all of whom had at least 2 years of treatment and 5 years of remission. Data on cancer diagnoses, treatments and late effects were analysed, with severity classified by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Results: The analysis showed 394 survivors (81%) experienced at least 1 late effect. Body mass index ≥ 23 kg/m² or ≥ 90 th percentile, low bone mineral density (e.g. Z-score ≤ -2.0 standard deviation score) and hearing difficulties were observed in 149 (30.7%), 87 (17.9%) and 73 (15.1%) survivors, respectively. Leukaemia survivors' detection of their first late effect was 10–14 years post-diagnosis, while central nervous system (CNS) and solid tumour survivors detected their first late effect within ≤ 5 years. Majority of late effects were of mild CTCAE severity. The odd ratio of developing late effects in the first 5 years post-diagnosis was 4.88 (95% confidence interval 2.98–7.71, $P < 0.001$) in survivors treated with both chemotherapy and radiotherapy (with and without surgery) compared to chemotherapy (with and without surgery).

Conclusion: Despite risk-adapted protocols, timely screening is recommended to improve early detection of metabolic health, bone health and hearing impairment. Radiotherapy-treated survivors and survivors of CNS tumours and solid tumours would benefit from earlier and frequent screening. Adopting an exposure-based approach to proactively screen for late effects, coupled with survivor education, can help mitigate the biopsychosocial impacts.

Keywords: epidemiology, oncology, paediatrics, quality of life, survivorship

CLINICAL IMPACT

What is New

- This study is among the first clinical audits in Singapore characterising late effects on paediatric cancer survivors.
- Despite risk-adapted protocols, late effects such as obesity, low bone mineral density and hearing difficulties continue to affect survivors.

Clinical Implications

- Radiotherapy-treated survivors and survivors of central nervous system tumours and solid tumours would benefit from earlier screening.
- This audit supports assessing risk factors for late effects to optimise timely screening protocols and enable early detection.
- Audit findings can guide regional survivorship programmes in allocating resources for focused areas.

INTRODUCTION

Advances in diagnostics and therapies have significantly improved paediatric cancer survival in high-income countries, with up to 90% of children living beyond 5 years post-diagnosis.^{1–3} In view of their exposure to anti-cancer agents, survivors are at risk of long-term complications known as late effects, which are defined as health problems related to cancer treatment that persist or develop 5 or more years after therapy.⁴ Severity is influenced by cancer type, age at diagnosis, and treatment-related factors, including therapy type and dosage.⁴

Population-based and multi-institutional studies show that childhood cancer survivors have greater risk

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of late effects than age- and sex-matched controls, with over 60% developing at least 1 chronic condition, and more than 20% experiencing severe or life-threatening complications in adulthood.^{4,6} These chronic issues also elevate early mortality risk,⁷ highlighting the need to identify late effects in specific groups and the importance of timely screening in survivorship care models. Late effects include metabolic and nutritional disorders, endocrinopathies, cardiovascular disorders, musculoskeletal and connective tissue disorders, hearing impairment, psychosocial challenges and increased mortality.^{3–6,8} Severity can be classified by the Common Terminology Criteria for Adverse Events (CTCAE).⁹

While survivorship programmes are well established in Western countries, supported by extensive studies like the Childhood Cancer Survivor Study,^{2,3} St Jude Lifetime Cohort Study,⁴ Dutch DCCSS Later Study¹⁰ and European PanCare FollowUp,¹¹ Asia is only beginning to adopt similar practices. The region lacks robust survivorship data, and care remains fragmented and inconsistent.¹² To address this gap, a comprehensive long-term follow-up (LTFU) programme was established at KK Women's and Children's Hospital (KKH), Singapore in September 2017. This retrospective audit examines the types, severity and onset of late effects in childhood cancer survivors at KKH with goals of refining screening and preventive care, and providing insight to assist regional survivorship programmes.

METHODS

Study design and LTFU care model

A retrospective audit of the LTFU programme at KKH was conducted for patients enrolled between September 2017 and December 2023, with data analysed up to March 2024. Survivors were counselled on late effects by their primary oncologist and when appropriate, transferred to the LTFU programme.

The LTFU programme served survivors who had at least 2 years of treatment and 5 years of remission. The programme comprised the After Cancer Therapy (ACT) and the long-term integrated follow-up and engagement (LIFE) clinic. The ACT clinic monitors survivors until age 18 years with additional emphasis on monitoring anthropomorphic parameters. The LIFE clinic emphasised adult surveillance, including fertility concerns. As 1 of 2 public paediatric oncology centres in Singapore, KKH manages approximately 40–50 new survivors annually, and 60% of national cases. Survivors received at least yearly follow-up and were educated on late effects and symptoms. The estimated clinic retention rate was $\geq 90\%$, with $\leq 10\%$ lost to follow-up.

The multidisciplinary team comprised paediatric oncologists, general paediatricians, nurses, clinical

coordinators, the Children's Cancer Foundation and KKH medical social workers. Subspecialty referrals were made within KKH for survivors <18 years, and to adult hospitals for those ≥ 18 years, according to preference when abnormal screening results were detected. Surveillance was guided by the Passport for Care platform,¹³ the Children's Oncology Group (COG) LTFU Guidelines Version 6.0¹⁴ and local/international guidelines.^{15,16}

Population

Childhood cancer was defined as 0–14 years and adolescent cancer as 15–19 years.¹⁷ Inclusion criteria were (1) survivors who had at least 2 years of treatment and 5 years of remission and (2) living patients. Exclusion criteria were (1) not meeting inclusion criteria and (2) survivors defaulting all LTFU follow-ups. Of the 495 registry entries, 485 survivors were included. Exclusions were due to duplicate entries ($n=3$), survivors that defaulted all LTFU follow-ups ($n=5$) and unverified late effect associated cause of death ($n=2$).

Study outcomes

Data were obtained from the KKH Late Effects Registry, electronic health records (EHRs) and the patient's Passport for Care record.¹³ Collected variables included demographics, cancer type, treatment, late effect onset, type and severity. Cancer types were classified using the International Classification of Childhood Cancer, Third Edition.¹⁸ Clinical notes were reviewed by 4 reviewers to verify late effects, categorised and graded using CTCAE version 5.0.¹⁹ Onset of late effects was determined from screening results, documentation or self-report, and grouped into 6 periods (<5 , 5–9, 10–14, 15–19, 20–24, ≥ 25 years post-diagnosis). Patients without late effects were recorded. Multiple late effects (≥ 2) were documented as separate outcomes. Effects with unclear onset or severity were considered undetermined and excluded. Severity was graded per CTCAE version 5.0¹⁹ as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening/disabling (grade 4) or fatal (grade 5).

Selected late effects were highlighted. As body mass index (BMI) is greatly influenced by body mass composition, age and sex for children/adolescence, overweight/obesity was defined as BMI ≥ 90 th and ≥ 97 th percentile, respectively, for survivors at ages <20 years; and BMI ≥ 23 and ≥ 27.5 kg/m² for those at ages ≥ 20 years.¹⁵ Bone mineral density (BMD) was assessed at ≥ 17 years or earlier where there is fracture history. Low BMD was defined as Z-score ≤ -2.0 standard deviation score (SDS) or T-score ≤ -2.5 SDS, with or without fragility fracture.¹⁶ Hearing was screened every 5 years; first hearing loss combined self-reported symptoms and/or audiometry, with ENT referral for threshold loss >15 dB (1000–8000 Hz).¹⁴

Psychiatric/psychological concerns and subfertility were assessed by self-report, with specialist referral for confirmation. Secondary malignant neoplasms (SMN) were confirmed by biopsy and histology.

This audit was approved by the SingHealth Centralised Institutional Review Board (2018-2022) and SingHealth Data Request (2024-08-00290). Informed consent was obtained from patients or parents depending on age and competence. No identifiers were used. All procedures complied with the Personal Data Protection Act and institutional practices. Data were performed solely on institutional devices with strict security measures. Clinical data are not publicly accessible to protect confidentiality; anonymised data may be available on reasonable request with approval. Generative artificial intelligence (AI) and AI-assisted technologies were not used. The study adhered to STROBE guidelines.²⁰

Statistical analysis

Statistical analyses were performed using Stata version 18 (StataCorp, College Station, TX). Descriptive statistics summarised demographics, malignancy type, treatment and late effect onset. Continuous variables were reported as mean $\pm$ standard deviation, categorical as frequencies and percentages.

Late effects were described as proportions (%) of the cohort unless otherwise specified and classified by CTCAE version 5.0 severity. To minimise misrepresentation from small subgroups, the first appearance of late effects was reported as absolute counts.

Odds ratios (ORs) with 95% confidence intervals (CIs) were reported for treatment and late effect occurrence. Treatment modalities were chemotherapy (with and without surgery) versus chemotherapy with radiotherapy (with and without surgery). Subgroup analyses compared the distribution of specific late effects across cancer types and treatment modalities. All tests were 2-sided, with $P < 0.05$ considered as statistically significant.

RESULTS

Patient characteristics

The total cohort ($n=485$) included 278 (57%) leukaemia, 44 (9%) lymphoma, 61 (13%) central nervous system (CNS) tumour and 102 (21%) solid tumour survivors, respectively. The mean age at diagnosis was 5 ± 4 , 6 ± 5 , 9 ± 4 and 9 ± 5 years for leukaemia, solid tumours, lymphoma and CNS tumours, respectively. The mean age at first LTFU attendance was 21 ± 6 years (range 7–41). The mean time of onset of late effects post-diagnosis was 3 ± 4 , 12 ± 6 , 10 ± 7 and 8 ± 6 years in CNS tumours, leukaemia, lymphoma and solid tumours, respectively. Most survivors were diagnosed between ages <1–14 years ($n=465$, 96%).

The cohort comprised 281 (58%) males and 204 (42%) females, with ethnic distribution of 352 (72%) Chinese, 78 (16%) Malay, 38 (8%) Indian and 17 (4%) others. Overall, 394 (81%) experienced at least 1 late effect, and among these, 270 (56%) had multiple late effects. There were 91 (19%) survivors with no reported late effects. At least 1 late effect was reported in 58 (95%) of CNS tumour survivors, 221 (80%) of leukaemia survivors, 37 (84%) of lymphoma survivors, and 78 (76%) of solid tumour survivors. Within the total cohort, 363 (75%) received chemotherapy without radiotherapy (with and without surgery) and 108 (22%) received chemotherapy with radiotherapy (with and without surgery). In leukaemia and lymphoma survivors, 30 (11%) and 3 (7%) underwent haematopoietic cell transplantation (HCT), respectively. At first entry into the LTFU programme, 122 (25%) entered the ACT clinic and 363 (75%) the LIFE clinic (Table 1).

Observed late effects distribution, cancer type and severity

Among the 394 survivors, 1084 observed/self-reported late effects were documented. The CTCAE version 5.0 categories with high proportion were metabolism and nutritional disorders ($n=212$, 19.6%, including overweight/obesity, anorexia and pH/electrolyte/glucose abnormalities), followed by musculoskeletal and connective tissue disorders ($n=147$, 13.6%), nervous system disorders ($n=110$, 10.1%), endocrine disorders ($n=87$, 8.0%), and ear and labyrinth disorders ($n=82$, 7.6%).

In leukaemia survivors, the most documented late effects were metabolism and nutritional disorders ($n=127$, 23.4%), musculoskeletal and connective tissue disorders ($n=91$, 16.8%), and cardiac disorders ($n=46$, 8.5%). Lymphoma survivors showed similar trends with metabolism and nutritional disorders ($n=19$, 23.2%), musculoskeletal and connective tissue ($n=13$, 15.9%), and cardiac disorders ($n=9$, 11.0%). CNS tumour survivors predominantly experienced nervous system ($n=51$, 19.9%), endocrine ($n=38$, 14.8%), ear and labyrinth ($n=35$, 13.7%), and metabolic and nutritional disorders ($n=33$, 12.9%). Among solid tumour survivors, metabolic and nutritional disorders ($n=33$, 16.2%), ear and labyrinth ($n=29$, 14.2%), and musculoskeletal and connective tissue disorders ($n=26$, 12.7%) were most frequent (Table 2A). Overall severity was mostly mild–moderate (CTCAE grade 1: $n=482$, 44.5%; grade 2: $n=449$, 41.4%; grade 3: $n=137$, 12.6%; grade 4: $n=13$, 1.2%) (Table 2B).

Observed late effects distribution, treatment and severity

There were 406 late effects reported in survivors treated with chemotherapy combined with radiation

Table 1. Baseline characteristics of childhood cancer survivors at KKH LTFU clinic (September 2017–December 2023).

	Leukaemia	Lymphoma	CNS tumours	Solid tumours	Total
Age, years (SD, range)					
Mean age at diagnosis	5 (4, <1–15)	9 (4, 1–17)	9 (5, <1–15)	6 (5, <1–17)	6 (5, <1–17)
Mean age at first LTFU	21 (6, 7–41)	22 (5, 11–34)	21 (5, 11–35)	19 (5, 6–32)	21 (6, 7–41)
Mean age in December 2023	24 (7, 8–44)	26 (6, 13–40)	25 (5, 13–36)	23 (6, 7–37)	24 (6, 7–44)
Mean time of onset of first late effect from diagnosis	12 (6, <1–34)	10 (7, <1–30)	3 (4, <1–19)	8 (6, <1–28)	10 (7, <1–34)
Mean age at first late effect onset	17 (6, 1–41)	19 (7, 3–35)	12 (4, 2–41)	14 (6, 3–28)	16 (6, 1–41)
Age group upon diagnosis, no. (%)					
No. of children upon diagnosis (<1–14 years old)	274 (98.6)	38 (86.4)	54 (88.5)	99 (97.1)	465 (95.9)
No. of adolescent upon diagnosis (15–19 years old)	4 (1.4)	6 (13.6)	7 (11.5)	3 (2.9)	20 (4.1)
Sex, no. (%)					
Male	163 (58.6)	31 (70.5)	39 (64.0)	48 (47.0)	281 (58.0)
Female	115 (41.4)	13 (29.5)	22 (36.0)	54 (53.0)	204 (42.0)
Ethnicity, no. (%)					
Chinese	201 (72.3)	34 (77.3)	43 (70.5)	74 (72.5)	352 (72.5)
Malay	42 (15.1)	5 (11.4)	15 (24.6)	16 (15.7)	78 (16.1)
Indian	25 (9.0)	3 (6.8)	0 (0.0)	10 (9.8)	38 (7.8)
Others	10 (3.6)	2 (4.5)	3 (4.9)	2 (2.0)	17 (3.6)
Late effects, no. (%)					
No late effect	57 (20.5)	7 (15.9)	3 (4.9)	24 (23.5)	91 (18.7)
Single late effect	87 (31.3)	14 (31.8)	3 (4.9)	20 (19.6)	124 (25.6)
Multiple late effects	134 (48.2)	23 (52.3)	55 (90.2)	58 (56.9)	270 (55.7)
Treatment, no. (%)					
Surgery	0 (0.0)	0 (0.0)	4 (6.6)	6 (5.9)	10 (2.1)
Chemotherapy	245 (88.1)	38 (86.4)	0 (0.0)	11 (10.8)	294 (60.6)
Chemotherapy and radiotherapy	33 (11.9)	6 (13.6)	10 (16.4)	3 (2.9)	52 (10.7)
Surgery and chemotherapy	0 (0.0)	0 (0.0)	6 (9.8)	63 (61.8)	69 (14.2)
Surgery, chemotherapy and radiotherapy	0 (0.0)	0 (0.0)	38 (62.3)	18 (17.6)	56 (11.6)
Surgery and radiotherapy	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	2 (0.4)
Radiotherapy	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.2)
No treatment	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.2)
No haematopoietic cell transplant	248 (89.2)	41 (93.2)	60 (98.4)	98 (96.1)	447 (92.2)
Haematopoietic cell transplant	30 (10.8)	3 (6.8)	1 (1.6)	4 (3.9)	38 (7.8)
LTFU proportion, no. (%)					
No. of survivors in ACT LTFU at first visit	67 (24.1)	7 (15.9)	13 (21.3)	35 (34.3)	122 (25.0)
No. of survivors in LIFE LTFU at first visit	211 (75.9)	37 (84.1)	48 (78.7)	67 (65.7)	363 (75.0)

ACT: after cancer therapy; LIFE: long-term integrated follow-up and engagement; LTFU: long-term follow-up; SD: standard deviation

(with and without surgery). The most observed categories were metabolism and nutritional disorders (n=67, 16.5%), nervous system (n=53, 13.1%), endocrine (n=52, 12.8%), and ear and labyrinth (n=43, 10.6%), with mild–moderate severity (CTCAE grade 1: n=171, 42.1%; grade 2: n=166, 40.9%) (Table 3A). Among the 661 late effects in chemotherapy-only survivors (with and without surgery), the majority were metabolism and nutritional disorders (n=141, 21.3%),

musculoskeletal and connective tissue (n=107, 16.2%), cardiac (n=60, 9.1%) and nervous system (n=53, 8%), with mild–moderate severity (CTCAE grade 1: n=303, 45.8%; grade 2: n=276, 41.8%) (Table 3B). Survivors treated with HCT (n=38) had 149 reported late effects. The most common were endocrine (n=21, 14.1%), musculoskeletal and connective tissue disorders (n=21, 14.1%), followed by metabolic and nutrition (n=19, 12.8%) and reproductive system/breast

Table 2. (A) Distribution of observed/documentated late effects. (B) Severity of overall late effects.

A	Leukaemia, no.				Lymphoma, no.				CNS tumours, no.				Solid tumours, no.				Total	
		%		%		%		%		%		%		%		%	Total	%
Metabolism and nutritional disorders	127	23.4	19	23.2	33	12.9	33	16.2	212	19.6			26	12.7	147	13.6		
Musculoskeletal and connective tissue disorders	91	16.8	13	15.9	17	6.6	17	12.7	147	13.6			8	3.9	110	10.1		
Nervous system disorders	43	7.9	8	9.8	51	19.9	38	14.8	87	8.0			7	3.4	87	8.0		
Endocrine disorders	38	7.0	4	4.9	38	14.8	35	13.7	82	7.6			29	14.2	82	7.6		
Ear and labyrinth disorders	17	3.1	1	1.2	35	13.7	3	1.2	72	6.6			14	6.9	67	6.2		
Cardiac disorders	46	8.5	9	11.0	3	1.2	10	3.9	47	4.3			15	7.4	47	4.3		
Reproductive system and breast disorders	37	6.8	5	6.1	26	10.2	8	3.1	42	3.9			20	9.8	42	3.9		
Eye disorders	12	2.2	2	2.4	26	10.2	7	2.7	40	3.7			5	2.5	37	3.4		
Neoplasms (benign, malignant and unspecified)	11	2.0	3	3.7	6	2.3	6	2.3	33	3.0			9	4.4	33	3.0		
Skin and subcutaneous tissue disorders	25	4.6	3	3.7	2	0.8	2	0.8	9	0.8			6	2.9	37	3.4		
Psychiatric disorders/psychosocial concerns	22	4.1	3	3.7	3	1.2	3	1.2	24	2.2			15	7.4	24	2.2		
Respiratory, thoracic and mediastinal disorders	16	3.0	2	2.4	3	1.2	3	1.2	20	1.8			7	3.4	20	1.8		
Renal and urinary disorders	5	0.9	1	1.2	3	1.2	3	1.2	13	1.2			1	0.5	13	1.2		
Gastrointestinal disorders	7	1.3	3	3.7	3	1.2	3	1.2	10	0.9			2	1.0	10	0.9		
Vascular disorders	6	1.1	2	2.4	4	1.6	2	0.8	9	0.8			0	0.0	9	0.8		
Hepatobiliary disorders	6	1.1	2	2.4	3	1.2	3	1.2	7	0.6			0	0.0	7	0.6		
Investigations	8	1.5	0	0.0	1	0.4	1	0.4	0	0.0			0	0.0	0	0.0		
Infections and infestations	7	1.3	1	1.2	1	0.4	1	0.4	0	0.0			0	0.0	0	0.0		
Blood and lymphatic disorders	8	1.5	1	1.2	0	0.0	0	0.0	0	0.0			0	0.0	0	0.0		
Immune system disorders	7	1.3	0	0.0	0	0.0	0	0.0	0	0.0			0	0.0	0	0.0		
Pregnancy, puerperium and perinatal conditions	3	0.6	0	0.0	0	0.0	0	0.0	0	0.0			0	0.0	3	0.3		
Total	542	50.0	82	7.6	256	23.6	204	18.8	1084	100.0								

B	CTCAE										Total	
	1	%	2	%	3	%	4	%	5	%	Undetermined	%
Metabolism and nutritional disorders	32	15.1	129	60.8	46	21.7	5	2.4	0	0.0	0	0.0
Musculoskeletal and connective tissue disorders	97	66.0	43	29.3	7	4.8	0	0.0	0	0.0	0	0.0
Nervous system disorders	54	49.1	44	40.0	10	9.1	1	0.9	0	0.0	1	0.9
Endocrine disorders	12	13.8	71	81.6	3	3.4	0	0.0	0	0.0	1	1.1
Ear and labyrinth disorders	32	39.0	15	18.3	34	41.5	1	1.2	0	0.0	0	0.0
Cardiac disorders	60	83.3	11	15.3	1	1.4	0	0.0	0	0.0	0	0.0
Reproductive system and breast disorders	18	26.9	43	64.2	6	9.0	0	0.0	0	0.0	0	0.0
Eye disorders	38	80.9	5	10.6	3	6.4	1	2.1	0	0.0	0	0.0
Neoplasms (benign, malignant and unspecified)	24	57.1	6	14.3	12	28.6	0	0.0	0	0.0	0	0.0
Skin and subcutaneous tissue disorders	27	67.5	13	32.5	0	0.0	0	0.0	0	0.0	0	0.0
Psychiatric disorders/psychosocial concerns	15	40.5	19	51.4	1	2.7	1	2.7	0	0.0	1	2.7
Respiratory, thoracic and mediastinal disorders	25	75.8	7	21.2	0	0.0	1	3.0	0	0.0	0	0.0
Renal and urinary disorders	11	45.8	11	45.8	2	8.3	0	0.0	0	0.0	0	0.0
Gastrointestinal disorders	6	30.0	7	35.0	5	25.0	2	10.0	0	0.0	0	0.0
Vascular disorders	3	23.1	8	61.5	2	15.4	0	0.0	0	0.0	0	0.0
Hepatobiliary disorders	12	92.3	0	0.0	1	7.7	0	0.0	0	0.0	0	0.0
Investigations	6	60.0	3	30.0	1	10.0	0	0.0	0	0.0	0	0.0
Infections and infestations	4	44.4	4	44.4	1	11.1	0	0.0	0	0.0	0	0.0
Blood and lymphatic disorders	4	44.4	4	44.4	1	11.1	0	0.0	0	0.0	0	0.0
Immune system disorders	2	28.6	5	71.4	0	0.0	0	0.0	0	0.0	0	0.0
Pregnancy, puerperium and perinatal conditions	0	0.0	1	33.3	1	33.3	1	33.3	0	0.0	0	0.0
Total	482	44.5	449	41.4	137	12.6	13	1.2	0	0.0	3	0.3
												1084
												100.0

CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events
Type of malignancy is indicated in the table.

CTCAE version 5.0 severity includes mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening/disabling (grade 4) and fatal (grade 5). Undetermined is indicated when the severity and onset of the late effect cannot be determined with certainty. Cumulatively, a total of 1084 late effects were observed in 394 survivors.

Table 3. Table 3. (A) Distribution and severity of late effects in relation to chemotherapy and radiation (with and without surgery), (B) chemotherapy (with and without surgery), (C) severity of late effects in relation to haematopoietic cell transplant.

A

Chemotherapy + radiation (with and without surgery)	CTACE										Undetermined	%	Total	%
	1	%	2	%	3	%	4	%	5	%				
Metabolism and nutritional disorders	18	26.9	35	52.2	11	16.4	3	4.5	0	0.0	0	0.0	67	16.5
Nervous system disorders	30	56.6	16	30.2	6	11.3	0	0.0	0	0.0	1	1.9	53	13.1
Endocrine disorders	6	11.5	43	82.7	2	3.8	0	0.0	0	0.0	1	1.9	52	12.8
Ear and labyrinth disorders	11	25.6	8	18.6	24	55.8	0	0.0	0	0.0	0	0.0	43	10.6
Musculoskeletal and connective tissue disorders	21	53.8	15	38.5	3	7.7	0	0.0	0	0.0	0	0.0	39	9.6
Eye disorders	19	67.9	5	17.9	3	10.7	1	3.6	0	0.0	0	0.0	28	6.9
Reproductive system and breast disorders	6	23.1	19	73.1	1	3.8	0	0.0	0	0.0	0	0.0	26	6.4
Neoplasms (benign, malignant and unspecified)	9	50.0	3	16.7	6	33.3	0	0.0	0	0.0	0	0.0	18	4.4
Skin and subcutaneous tissue disorders	12	92.3	1	7.7	0	0.0	0	0.0	0	0.0	0	0.0	13	3.2
Cardiac disorders	10	76.9	3	23.1	0	0.0	0	0.0	0	0.0	0	0.0	13	3.2
Respiratory, thoracic and mediastinal disorders	7	63.6	3	27.3	0	0.0	1	9.1	0	0.0	0	0.0	11	2.7
Psychiatric disorders/psychosocial concerns	7	63.6	3	27.3	1	9.1	0	0.0	0	0.0	0	0.0	11	2.7
Renal and urinary disorders	4	66.7	2	33.3	0	0.0	0	0.0	0	0.0	0	0.0	6	1.5
Infections and infestations	1	20.0	3	60.0	1	20.0	0	0.0	0	0.0	0	0.0	5	1.2
Hepatobiliary disorders	4	80.0	0	0.0	1	20.0	0	0.0	0	0.0	0	0.0	5	1.2
Gastrointestinal disorders	1	25.0	3	75.0	0	0.0	0	0.0	0	0.0	0	0.0	4	1.0
Vascular disorders	1	33.3	2	66.7	0	0.0	0	0.0	0	0.0	0	0.0	3	0.7
Immune system disorders	1	33.3	2	66.7	0	0.0	0	0.0	0	0.0	0	0.0	3	0.7
Investigations	2	66.7	0	0.0	1	33.3	0	0.0	0	0.0	0	0.0	3	0.7
Pregnancy, pureperium and perinatal conditions	0	0.0	0	0.0	1	50.0	1	50.0	0	0.0	0	0.0	2	0.5
Blood and lymphatic disorders	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Total	171	42.1	166	40.9	61	15.0	6	1.5	0	0.0	2	0.5	406	100.0

B

Chemotherapy (with and without surgery)	CTACE										Undetermined	%	Total	%
	1	%	2	%	3	%	4	%	5	%				
Metabolism and nutritional disorders	14	9.9	91	64.5	34	24.1	2	1.4	0	0.0	0	0.0	141	21.3
Musculoskeletal and connective tissue disorders	76	71.0	27	25.2	4	3.7	0	0.0	0	0.0	0	0.0	107	16.2
Cardiac disorders	50	83.3	9	15.0	1	1.7	0	0.0	0	0.0	0	0.0	60	9.1
Nervous system disorders	21	39.6	26	49.1	5	9.4	1	1.9	0	0.0	0	0.0	53	8.0
Reproductive system and breast disorders	12	29.3	24	58.5	5	12.2	0	0.0	0	0.0	0	0.0	41	6.2
Ear and labyrinth disorders	21	55.3	7	18.4	9	23.7	1	2.6	0	0.0	0	0.0	38	5.7
Endocrine disorders	6	17.6	27	79.4	1	2.9	0	0.0	0	0.0	0	0.0	34	5.1
Skin and subcutaneous tissue disorders	15	55.6	12	44.4	0	0.0	0	0.0	0	0.0	0	0.0	27	4.1
Psychiatric disorders/psychosocial concerns	8	30.8	16	61.5	0	0.0	1	3.8	0	0.0	1	3.8	26	3.9
Respiratory, thoracic and mediastinal disorders	18	81.8	4	18.2	0	0.0	0	0.0	0	0.0	0	0.0	22	3.3
Neoplasms (benign, malignant and unspecified)	14	63.6	3	13.6	5	22.7	0	0.0	0	0.0	0	0.0	22	3.3
Renal and urinary disorders	7	38.9	9	50.0	2	11.1	0	0.0	0	0.0	0	0.0	18	2.7
Eye disorders	17	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	17	2.6
Gastrointestinal disorders	5	33.3	3	20.0	5	33.3	2	13.3	0	0.0	0	0.0	15	2.3
Vascular disorders	1	11.1	6	66.7	2	22.2	0	0.0	0	0.0	0	0.0	9	1.4
Blood and lymphatic disorders	3	37.5	4	50.0	1	12.5	0	0.0	0	0.0	0	0.0	8	1.2
Hepatobiliary disorders	7	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	7	1.1
Investigations	4	57.1	3	42.9	0	0.0	0	0.0	0	0.0	0	0.0	7	1.1
Infections and infestations	3	75.0	1	25.0	0	0.0	0	0.0	0	0.0	0	0.0	4	0.6
Immune system disorders	1	25.0	3	75.0	0	0.0	0	0.0	0	0.0	0	0.0	4	0.6
Pregnancy, pureperium and perinatal conditions	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Total	303	45.8	276	41.8	74	11.2	7	1.1	0	0.0	1	0.2	661	100.0

Table 3. (A) Distribution and severity of late effects in relation to chemotherapy and radiation (with and without surgery), (B) chemotherapy (with and without surgery), (C) severity of late effects in relation to haematopoietic cell transplant. (Cont'd)

C	Haematopoietic cell transplant	CTCAE										Total	%
		1	%	2	%	3	%	4	%	5	%	Undetermined	%
	Endocrine disorders	2	9.5	18	85.7	1	4.8	0	0.0	0	0.0	0	0.0
	Musculoskeletal and connective tissue disorders	16	76.2	5	23.8	0	0.0	0	0.0	0	0.0	0	0.0
	Metabolism and nutritional disorders	4	21.1	11	57.9	4	21.1	0	0.0	0	0.0	0	0.0
	Reproductive system and breast disorders	2	13.3	10	66.7	3	20.0	0	0.0	0	0.0	0	0.0
	Respiratory, thoracic and mediastinal disorders	9	81.8	2	18.2	0	0.0	0	0.0	0	0.0	0	0.0
	Cardiac disorders	7	87.5	1	12.5	0	0.0	0	0.0	0	0.0	0	0.0
	Skin and subcutaneous tissue disorders	6	85.7	1	14.3	0	0.0	0	0.0	0	0.0	0	0.0
	Ear and labyrinth disorders	2	28.6	2	28.6	3	42.9	0	0.0	0	0.0	0	0.0
	Vascular disorders	0	0.0	4	80.0	1	20.0	0	0.0	0	0.0	0	0.0
	Infections and infestations	2	40.0	3	60.0	0	0.0	0	0.0	0	0.0	0	0.0
	Immune system disorders	2	40.0	3	60.0	0	0.0	0	0.0	0	0.0	0	0.0
	Hepatobiliary disorders	4	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Neoplasms (benign, malignant and unspecified)	1	25.0	0	0.0	3	75.0	0	0.0	0	0.0	0	0.0
	Psychiatric disorders/psychosocial concerns	2	50.0	1	25.0	0	0.0	1	25.0	0	0.0	0	0.0
	Nervous system disorders	0	0.0	2	50.0	2	50.0	0	0.0	0	0.0	0	0.0
	Eye disorders	2	66.7	1	33.3	0	0.0	0	0.0	0	0.0	0	0.0
	Renal and urinary disorders	0	0.0	1	50.0	1	50.0	0	0.0	0	0.0	0	0.0
	Gastrointestinal disorders	1	50.0	1	50.0	0	0.0	0	0.0	0	0.0	0	0.0
	Blood and lymphatic disorders	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0
	Investigations	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0
	Pregnancy, pureperium and perinatal conditions	0	-	0	-	0	-	0	-	0	-	0	-
	Total	62	41.6	67	45.0	19	12.8	1	0.7	0	0	0	0

CTCAE: Common Terminology Criteria for Adverse Events

CTCAE version 5.0 severity includes mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening/disabling (grade 4) and fatal (grade 5).

Undetermined is indicated when the severity and onset of the late effect cannot be determined with certainty.

disorders (n=15, 10.1%), with mild–moderate severity (CTCAE grade 1: n=62, 41.6%; grade 2: n=67, 45.0%) (Table 3C).

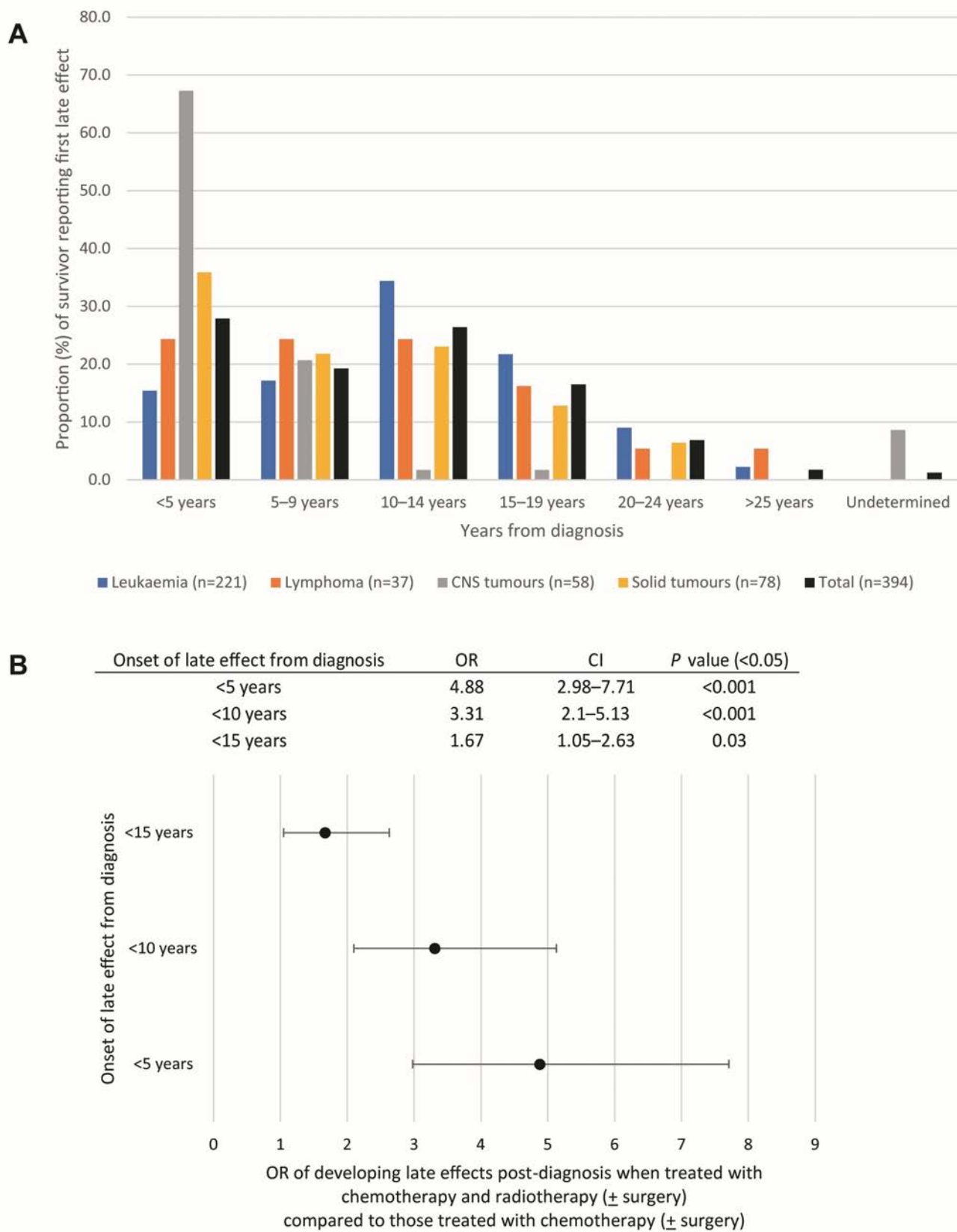
Onset of late effects in relationship to cancer type and treatment

CNS and solid tumour survivors most often developed their first late effect within 5 years post-diagnosis (n=39, 67.2% and n=28, 35.9%, respectively). Leukaemia survivors peaked at 10–14 years (n=76, 34.4%), while lymphoma survivors showed steady onset across the first 14 years (n=9, 24.3%) (Fig. 1A). In survivors treated with chemotherapy and radiotherapy (with and without surgery), the odd ratio of developing late effects in the first 5 years post-diagnosis was 4.88 (95% CI 2.98–7.71, $P<0.001$) compared to chemotherapy (with and without surgery). Survivors treated with surgery, radiotherapy or no treatment alone were excluded from this analysis due to small numbers (Fig. 1B).

Onset of particular late effects in relation to cancer type

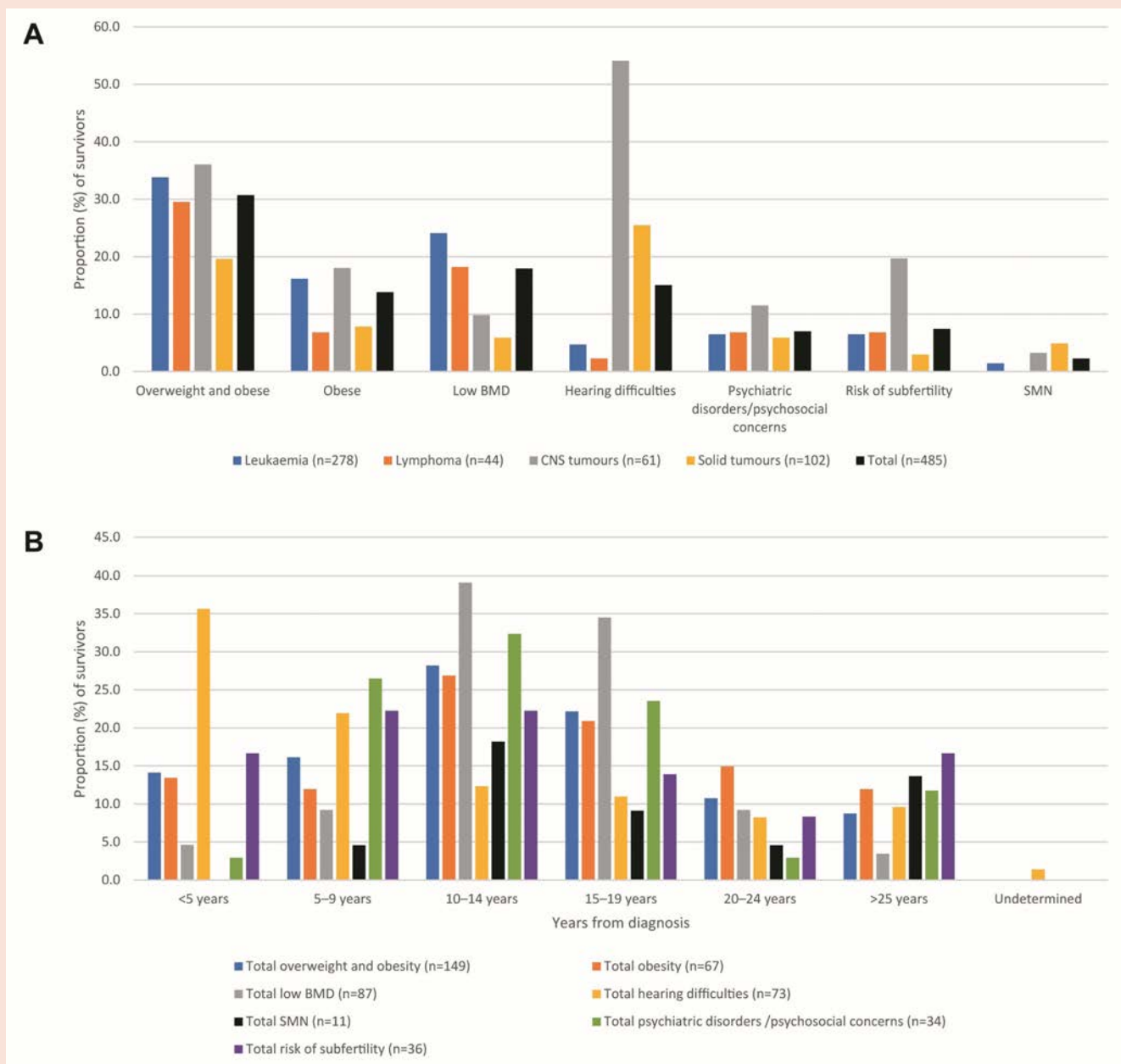
Overweight and obesity (n=149, 30.7%), obesity alone (n=67, 13.8%), low BMD (n=87, 17.9%) and hearing difficulties (n=73, 15.1%) affect a notable proportion of total survivors. Other late effects of interest among all survivors were psychiatric/psychosocial concerns (n=34, 7.0%), risk of subfertility (n=36, 7.4%), SMN (n=11, 2.3%), neurocognitive impairment (n=14, 3.0%) and intellectual disability (n=5, 1.0%). By subgroup, obesity had a high proportion in leukaemia (n=45, 16.2%) and CNS tumour survivors (n=11, 18.0%). Low BMD was commonly seen in leukaemia survivors (n=67, 24.1%). Hearing difficulties were observed in 54.1% of CNS tumour survivors (n=33) and 25.5% of solid tumour survivors (n=26). Psychiatric/psychosocial concerns (n=7, 11.5%) and subfertility risk (n=12, 19.7%) were also notable in CNS tumour survivors (Fig. 2A).

Fig. 1. (A) No. of survivors reporting first late effects at various time points from diagnosis. (B) Forest plot of odd ratio of onset of late effects from diagnosis in relation to treatment.



CI: confidence interval; CNS: central nervous system; OR: odds ratio
 P value of <0.05 is considered statistically significant.
 ±: with and without

Fig. 2. Proportion of survivors reporting first observed/documentated specific late effects (A) in relation to type of malignancies and (B) over years from diagnosis.



BMD: bone mineral density; SMN: secondary malignant neoplasms

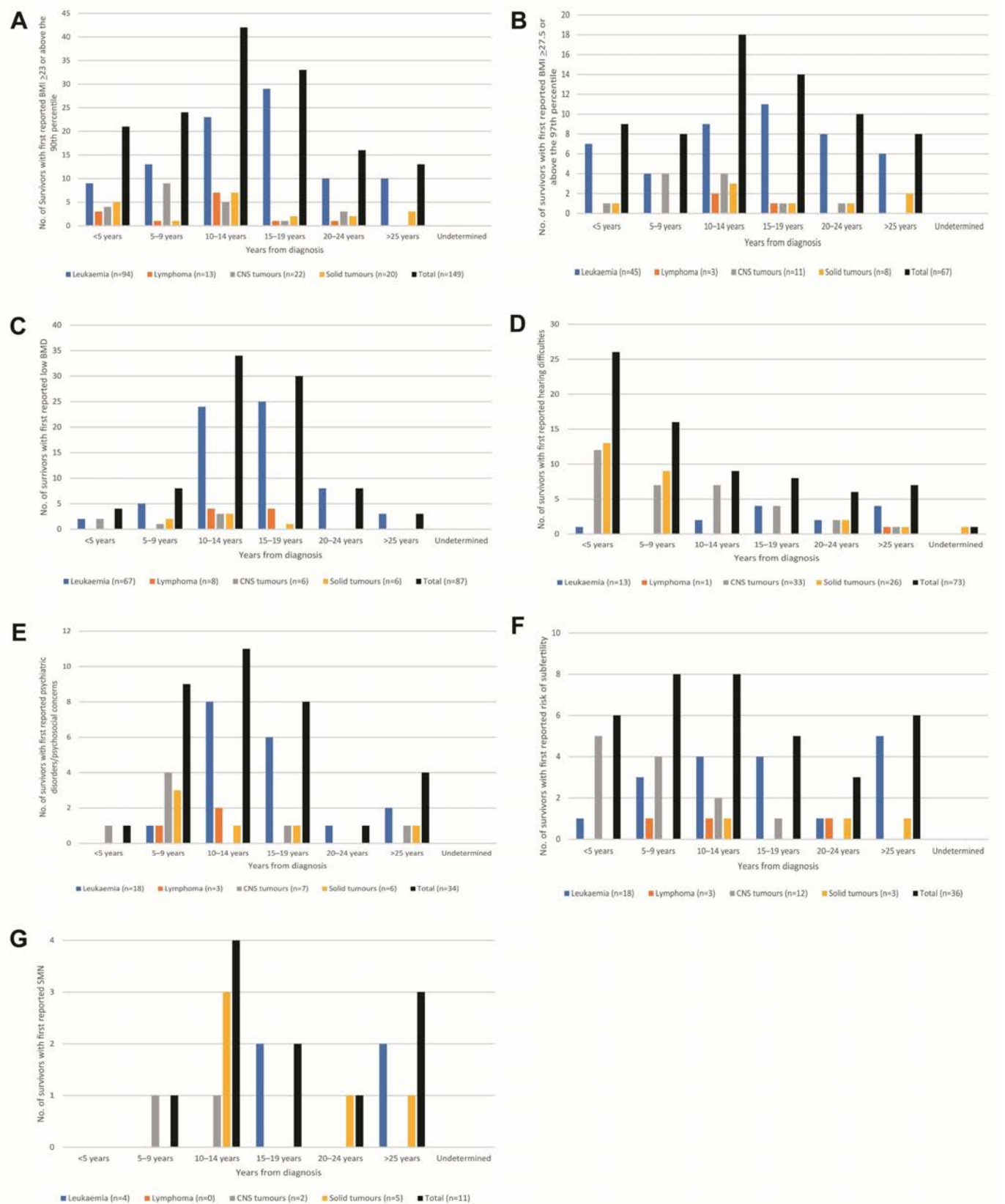
Temporal analysis showed that overweight/obesity and low BMD in leukaemia and the overall cohort occurred 10–19 years post-diagnosis, while hearing difficulties in CNS and solid tumour survivors typically occurred within the first 5 years. Psychological/psychosocial concerns, SMN and subfertility risk continued to emerge even >25 years post-diagnosis (Figs. 2B, 3A–G).

Undetermined is indicated when the severity and onset of the late effect cannot be determined with certainty.

DISCUSSION

This study is among the first comprehensive reviews in Southeast Asia to curate late effects associated with specific paediatric cancer treatments using substantial dataset. Through this retrospective audit, the late effects in childhood cancer survivors in Singapore were evaluated. Most survivors experienced at least 1 CTCAE grades 1–2 late effect, with patterns varying by cancer type and treatment, underscoring the need to refine guidelines for earlier detection and management.

Fig. 3. No. of survivors reporting first observed/documentated (A) BMI ≥ 23 or ≥ 90 th percentile, (B) BMI ≥ 27.5 or ≥ 97 th percentile, (C) BMD, (D) hearing difficulties, (E) psychiatric disorders/psychosocial concerns, (F) risk of subfertility and (G) secondary malignant neoplasm (SMN) over years from diagnosis.



BMD: bone mineral density; BMI: body mass index; CNS: central nervous system; SMN: secondary malignant neoplasms
Undetermined is indicated when the severity and onset of the late effect cannot be determined with certainty.

LTFU care in Asia remains inconsistent due to differences in care models, knowledge gaps, limited awareness, cultural barriers and resource constraints.^{12,21,22} In this study's cohort, CNS and solid tumour survivors often developed hearing loss within 5 years of diagnosis, while leukaemia survivors commonly presented with overweight/obesity at 10–14 years. As international cohorts report chronic conditions into later adulthood, the findings highlight the need for lifelong surveillance.^{3,4,8,10,11,23} Identifying time points for specific late effects can tailor screening schedules, improve efficiency and prioritise resource.

Consistent with Western and Asian studies,^{3,4,8,23,24} similar late effect burdens were found, including obesity, hearing difficulties and low BMD. The type and frequency of late effects varied by cancer type, mirroring Western cohorts.²⁵ The similarities may reflect the adaptation of Western protocols, refined locally through risk stratification, precision therapy, treatment de-escalation and adherence to global screening recommendations.^{14,26} The data reinforce that LTFU should be diagnosis-, onset- and treatment-specific.²⁵ Similarity to Western cohorts supports the global standardisation of LTFU models with local adaptation.

Overweight/obesity was prominent among leukaemia and CNS tumour survivors. While multifactorial, corticosteroid exposure likely contributes by altering fat deposition, impairing glucose uptake and inducing insulin resistance.²⁷ Additionally, Asians are predisposed to truncal obesity through genetic–environmental interactions.²⁸ Corticosteroids further compromise bone health by reducing osteoblast and stimulating osteoclast.²⁹ These mechanisms may underline the high proportion of these late effects in this study's cohort.

Survivors treated with chemotherapy and radiotherapy developed late effects earlier, especially with CNS, endocrine and auditory disorders. This reflects the localised impact of cranial radiation and CNS-directed therapies.^{30–35} The consequences of hearing loss on speech, learning and psychosocial development are well-established,³² underscoring the importance of early detection. The late effect burden in HCT survivors was consistent with published literature, notably endocrine and musculoskeletal disorders.³⁶ However, with growing HCT survivors, the spectrum may shift in observing other late effects like infections.³⁶ Recognising these patterns allows providers to counsel survivors on risk, adjust follow-up intensity and optimise care.

In response, this study implemented a structured, cancer- and duration-specific LTFU framework with screening tailored to diagnosis, treatment history and individual risk, guided by international guidelines,

which include asymptomatic survivors. Leukaemia and lymphoma survivors require long-term monitoring for metabolic, cardiac and musculoskeletal late effects, extending beyond 25 years. In contrast, CNS and solid tumour survivors need closer follow-up during the first decade, when neurocognitive, endocrine and auditory toxicities emerge. To address this, KKH established a CNS-specific LTFU clinic for intensive surveillance. Solid tumour survivors similarly require comprehensive early follow-up, focusing on metabolism, musculoskeletal health and hearing. Risk-based guidelines provide a framework for individualising surveillance, especially for high-risk groups who received combined chemotherapy and radiotherapy, where late effects often appear within 5 years but persist decades later.^{12,14}

The authors have provided late effect education for survivors, families and healthcare professionals to raise awareness before entering LTFU. The authors also aim to promote regional advocacy focusing on standardised guidelines, resource allocation, multidisciplinary models of care and structured transition protocols to adult services to maintain continuity. Personalised, risk-based approaches can optimise outcomes and improve survivor's quality of life.^{12,14}

This study has several limitations. As it involves only a single institution, the late effects observed may reflect local practices. The peak in low BMD likely reflects the practice of initiating BMD assessments after age 17 to minimise radiation exposure, possibly missing earlier cases. Collaboration with other centres in Singapore and the region will be essential to harmonise LTFU models. Future refinements should align screening with population-specific risks and COG guidelines. The recent establishment of the LTFU clinic also meant some survivors had long gaps before their first review, where the oldest survivor presented at 44 years post-diagnosis, leading to missing data and underestimation of late effect representation. As a retrospective study, reliance on EHRs may cause incomplete data capture, especially for outcomes like metabolic syndrome, where detail was often insufficient for CTCAE grading. Despite potential selection bias, the audit has impacted improvements in the LTFU framework.

Psychological late effects were underrepresented, as a concurrent study³⁷ utilised hardcopy questionnaires that were not captured in EHRs. Similarly, neurocognitive impairment,^{34,35} intellectual disability³³ and infertility/subfertility³⁸ were underrepresented, as these outcomes were not systematically screened. Contributing factors include limited assessment tools, time constraints and reliance on patient reporting. Longer follow-up may be required for these conditions to manifest. In this audit, the incidence and

prevalence of these late effects cannot be determined. Future studies incorporating number-at-risk analyses would provide greater clarity.

Lifestyle factors, such as diet, physical activity, alcohol use, smoking, education and socioeconomic status were not routinely screened, but incorporating them would improve the holistic design of survivorship care. Another limitation is that the audit preceded the use of CAR-T and immunotherapies like blinatumomab. These are now part of the institutional practice and carry unique risks, including hypogammaglobulinemia, cytopenia, immune-related complications, infections, neurotoxicity and cardiac effects.^{39,40} Therefore, ongoing surveillance will need to capture their evolving late effect profiles.

CONCLUSION

Despite limitations, this comprehensive audit of a large Southeast Asian cohort provides important insights into late effect burden to improve the survivorship platform of KKH. High proportion of overweight/obesity, low BMD and hearing difficulties emphasise the need for proactive, structured follow-up and targeted interventions. The earlier onset of late effects in CNS and solid tumour survivors, and those treated with radiotherapy, underscores the urgency of initiating LTFU early in these high-risk groups. Early detection may mitigate long-term complications and reduce healthcare burden. The findings also offer regional insights into prioritising late effect for surveillance resource allocation. The similarity of the results with Western cohorts highlights the universality of these issues, while underscoring the applicability of international guidelines in local healthcare settings and the need for culturally adapted survivorship models in Asia. Therefore, prospective studies with standardised, comprehensive data collection are necessary to ensure accurate late effect identification. Such efforts will strengthen evidence, guide refinement of care protocols and enhance the impact of survivorship research in Asia. Furthermore, tailored, evidence-based LTFU strategies are essential to improve outcomes and quality of life for childhood cancer survivors globally.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2018-2022) and SingHealth Data Request (2024-08-00290).

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. Portions of this work were presented at the SIOP Annual Congress 2024 in Honolulu, Hawaii, US.

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Treatment outcomes in *Mycobacterium abscessus* pulmonary disease: A systematic review

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ABSTRACT

Introduction: *Mycobacterium abscessus* complex (MABC) is an emerging global threat due to its intrinsic and acquired resistance to many antibiotics, making treatment particularly challenging. This systematic review aimed to evaluate current treatment regimens and clinical outcomes in patients with MABC pulmonary disease.

Methods: A comprehensive electronic search of PubMed, Embase and Cochrane databases was conducted for studies published between 1 January 2010 and 31 December 2024. A total of 28 studies met the inclusion criteria, comprising 24 retrospective chart reviews and 4 multicentre prospective studies.

Results: Sputum culture conversion (SCC) was reported in 25 studies, with rates ranging from 29% to 77%. Radiographic improvement was observed in 33% to 54% of patients, while clinical improvement varied widely, ranging from 14% to 91%. Notably, infections caused by *M. massiliense* were consistently associated with superior clinical, radiologic, and microbiologic outcomes compared to *M. abscessus*. Although surgical intervention was reported in selected cases, it was associated with higher SCC rates and remains a definitive treatment option in refractory disease. The overall risk of bias across studies was moderate to high, largely due to the predominance of retrospective study designs and heterogeneity in treatment protocols and outcome measures.

Conclusion: These findings underscore the suboptimal outcomes associated with current treatment strategies for MABC pulmonary disease. There is an urgent need for large-scale, multicentre prospective studies utilising standardised treatment outcome definitions and unified therapeutic regimens to improve patient care and clinical outcomes.

Keywords: antimicrobials, bronchiectasis, lung disease, *Mycobacterium abscessus*, non-tuberculous mycobacteria, respiratory medicine, treatment regimen

CLINICAL IMPACT

What is New

- This systematic review underscores the complexity of treating *M. abscessus* pulmonary disease, including drug resistance, frequent drug related adverse effects, variable treatment outcome definitions and poor treatment outcomes among patients with underlying chronic lung diseases.
- The findings highlight the potential disease burden in an ageing population with rising prevalence of chronic lung diseases.

Clinical Implications

- The review highlights the urgent need for the development of novel therapies, multicentre prospective studies using standardised treatment outcomes and unified therapeutic regimens to optimise patient care and clinical outcomes.

INTRODUCTION

Mycobacterium abscessus complex (MABC) is a group of rapidly growing, non-tuberculous mycobacteria (NTM) increasingly recognised as clinically significant pathogens worldwide.^{1,2} The complex comprises 3 subspecies: *Mycobacterium abscessus* subspecies *massiliense* (*M. massiliense*), *Mycobacterium abscessus* subspecies *bolletii* (*M. bolletii*), with *Mycobacterium abscessus* subspecies *abscessus* (*M. abscessus*) being the most frequently isolated.^{3,4} NTM are ubiquitous in the environment—particularly in soil and water—with municipal water systems serving as notable reservoirs.⁵ Pulmonary disease caused by MABC predominately affects immunocompromised individuals, such as

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patients receiving immunosuppressive therapy, and individuals with underlying structural lung diseases, notably bronchiectasis and cystic fibrosis.^{6,7} Despite the increasing incidence of MABC infections, diagnostic delays and misdiagnosis remain common due to overlapping clinical features with other chronic cough, weight loss, dyspnoea, fever and fatigue, which often mimic diseases like tuberculosis or non-MABC NTM infections. Importantly, MABC pulmonary disease is associated with recurrent pulmonary exacerbations, leading to airway remodelling and progressive lung damage.

Diagnosis of MABC pulmonary disease requires the integration of clinical, radiographic and microbiologic criteria as recommended by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA).⁶ Clinically, patients typically present with chronic respiratory symptoms. Radiographic imaging may reveal nodular or cavitary opacities, bronchiectasis, or tree-in-bud patterns. Microbiological confirmation is essential, necessitating either 2 positive cultures from separate expectorated sputum samples or 1 positive culture from bronchoalveolar lavage, bronchial wash or lung tissue biopsy showing histopathologic evidence of mycobacterial infection. Notably, other differential diagnoses—particularly pulmonary tuberculosis—must be rigorously excluded before establishing a definitive diagnosis.⁶ Management of MABC pulmonary disease remains challenging. The ATS/IDSA guidelines underscores the absence of a standardised, highly effective treatment regimen.⁶ Currently, therapy typically involves prolonged multidrug regimens, often centred around a macrolide in combination with intravenous agents such as amikacin, imipenem or tigecycline. However, these regimens are frequently associated with limited efficacy, poor tolerability and significant toxicity.

Treating MABC is difficult due to intrinsic and acquired antibiotic resistance.⁸ Key mechanisms include efflux pumps, drug-modifying enzymes, target gene mutations in *erm* (41) and *rrl*, and low membrane permeability.⁸ In refractory cases, surgical resection may be considered despite its risk.⁹ To standardise outcome reporting, the NTM-Network European Trials (NTM-NET) group proposed definitions such as sputum culture conversion (SCC), microbiological cure, clinical cure, treatment failure, relapse, reinfection and treatment discontinuation.¹⁰ In practice, outcomes are assessed through clinical symptoms, imaging and SCC—defined as sustained negative sputum cultures over time.⁶

Despite the increasing recognition of MABC as a major pulmonary pathogen, there is a lack of consolidated evidence assessing the comparative effectiveness of various antibiotic regimens in real-

world clinical settings. Furthermore, heterogeneity in study design, outcome measures and follow-up durations complicates the interpretation of existing data. Therefore, we conducted a systematic review of the literature to evaluate the treatment regimens used for MABC pulmonary disease and assess their impact on clinical, microbiologic and radiologic outcomes in accordance with internationally accepted criteria.

METHODS

This systematic literature review was conducted to identify and synthesise evidence on treatment regimens and clinical outcomes in patients with *M. abscessus* pulmonary disease. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and a PRISMA flow diagram is included in Fig. 1.

Search strategy

A comprehensive electronic search was conducted in 3 databases: PubMed, Embase and Cochrane Library, for studies published between 1 January 2010 and 31 December 2024. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text keywords related to *M. abscessus*, treatment regimens and pulmonary disease, using Boolean operators. The full search strategy is provided in Supplementary Table S1. All references were managed using EndNote X9 (Clarivate Analytics, Philadelphia, PA, US), and Covidence (Veritas Health Innovation, Melbourne, Australia) was used for duplicate removal, title/abstract screening and full-text review.

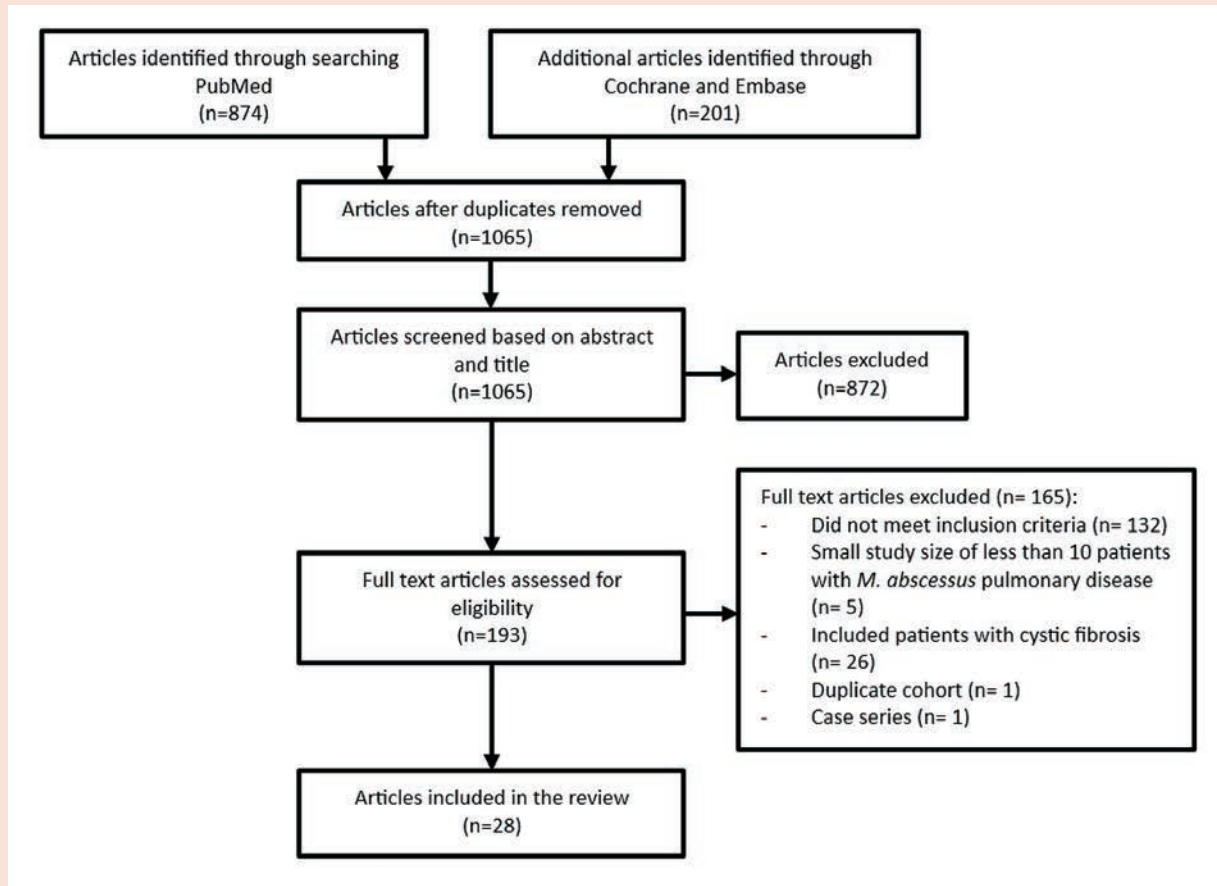
Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) published in English between 2010 to 2024; (2) reported on antimicrobial treatment regimens for *M. abscessus* pulmonary disease; and (3) reported treatment outcomes based on clinical, microbiologic or radiologic parameters. Studies were excluded if they were (1) conference abstract, editorials, letters to the editor, guidelines or narrative reviews; (2) case reports or small case series (fewer than 10 patients); (3) focused exclusively on cystic fibrosis populations; (4) not specifying treatment regimens and/or treatment outcomes; or (5) published in a non-English language.

Study selection

Title and abstract screening were conducted independently by 2 reviewers in a double-blind manner using Covidence. Full texts of potentially relevant studies were retrieved and assessed against inclusion criteria. Disagreements were resolved

Fig. 1. Flowchart of study selection.



through discussion and consensus. Reference lists of included studies were also manually searched; however, no additional eligible studies were identified.

Data extraction

Data extraction was conducted using a standardised data extraction template. One reviewer extracted data, which were independently verified by a second reviewer. Extracted variables included: (1) study design and setting, (2) sample size and population demographics, (3) treatment regimens (drug combinations, duration), (4) clinical outcomes (e.g. symptom improvement), (5) microbiological outcomes (e.g. sputum culture conversion), (6) radiologic outcomes (e.g. computed tomography or x-ray findings), (7) adverse events and complications and (8) follow-up duration.

Risk of bias assessment

The ROBINS-I tool (Risk of Bias in Non-randomised Studies – of Interventions) was used to assess the quality of included studies. The tool evaluates bias across 7 domains, including confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result.

RESULTS

A total of 1076 articles were identified in the initial search. Following screening and eligibility assessment, 28 studies were included in this review (Fig. 1).^{9,11-37} Table 1 summarises sample sizes, demography and underlying lung diseases of study population. Table 2 presents treatment regimens, adverse events and outcomes.

Study characteristics

Of the 28 included studies, 2 were prospective cohort studies^{14,15} and 26 were retrospective.^{9,11-13,16-37} Outcomes assessed included survival,²³ amikacin toxicity and pharmacokinetics,¹⁹ long-term disease progression²³ and treatment success.³⁴ Four studies were multicentre.^{25,27,28,37} Geographically, studies were conducted in 6 countries: South Korea,^{9,11-23,36,37} Japan,²⁴⁻²⁸ China,²⁹⁻³¹ Taiwan,^{32,33} Brazil³⁴ and the US.³⁵

Study participants

Across 28 studies, 4183 patients were diagnosed with MABC pulmonary disease based on the 2007 ATS/IDSA guidelines,⁶ of whom 2769 received treatment. The pooled prevalence of *M. abscessus* among treated patients was 72.4% (95% confidence interval

Table 1. Demography and underlying lung diseases of study population.

Author, year	Population (n)	No. of patients with underlying/previous lung disease	Mean age (SD) or median (range) in years	Female (%)
Huang 2010 (Taiwan)	Patients diagnosed with <i>M. abscessus</i> infection (n=22).	3 COPD, 7 previous PTB, 16 structural lung disease	NR	NR
Koh 2011 (South Korea)	Newly diagnosed with MABC lung disease with isolates that were typeable (n=145); <i>M. abscessus</i> (n=64) and <i>M. massiliense</i> (n=81).	11 COPD, 11 lung cancer, 77 previous PTB	57.6 (13.0) (<i>M. abscessus</i> patients) 56.0 (12.9) (<i>M. massiliense</i> patients)	74.5%
Lyu 2011 (South Korea)	Diagnosed with <i>M. abscessus</i> pulmonary disease and who were treated based on ATS guidelines without loss to follow-up or transfer to another hospital (n=41).	1 ILD, 25 previous PTB	53.2 (11.7)	75.6%
Harada 2012 (Japan)	diagnosed with <i>M. abscessus</i> lung disease excluding those with <i>M. boletii</i> (n=99), <i>M. abscessus</i> (n=72) and <i>M. massiliense</i> (n=27).	5 COPD, 6 interstitial pneumonia, 19 previous PTB, 19 MAC lung disease	68, no SD reported Range: 27–94	62.5%
Lyu 2014 (South Korea)	Patients who were diagnosed with MABC lung disease and received treatment without loss to follow up (n=48); <i>M. abscessus</i> (n=26) and <i>M. massiliense</i> (n=22).	21 previous PTB	57.7 (11.6)	72.9%
Tung 2014 (Taiwan)	All patients who had more than 1 positive culture of respiratory specimens for MABC (n=106).	29 bronchiectasis, 28 previous PTB, 2 previous MAC pulmonary diseases, 37 previous mycobacterium pulmonary diseases, 65 pre-existing pulmonary diseases	64.6 (14.05)	58.5%
Griffith 2015 (USA)	Patients who had isolation of <i>M. abscessus</i> during MAC lung disease therapy (n=21).	21 MAC pulmonary diseases	75.5 (8.5)	90%
Kang 2015 (South Korea)	Patients who had adjunctive pulmonary resection for NTM lung disease (n=70); MAC (n=45, 64%), <i>M. intracellular</i> / <i>M. avium</i> (n=24, 21%), MABC (n=23, 33%) and <i>M. abscessus</i> / <i>M. massiliense</i> (n=2, 3%).	6 recurrent NTM lung disease, 45 previous PTB	50, no SD reported	60%
Koh 2016 (South Korea)	Patients diagnosed with <i>M. abscessus</i> pulmonary disease who received antibiotic therapy for ≥12 months (n=67).	45 previous PTB, 7 previous <i>M. abscessus</i> pulmonary diseases, 2 previous MAC pulmonary diseases, 3 previous pulmonary diseases from other NTM	Median: 57 Range: 48–64	78%
Koh 2016 (South Korea)	<i>M. massiliense</i> lung disease who initiated antibiotic treatment of at least 12 months excluding patients with more than 1 month of macrolide containing antibiotic therapy or who underwent surgical resection within 3 months of drug therapy (n=71).	6 previous NTM, 39 previous PTB, 5 chronic pulmonary aspergillosis	60, no SD reported (4-week IV group) 57, no SD reported (2-week IV group)	4-week IV group- 89% 2-week IV group- 84%
Namkoong 2016 (Japan)	Patients with <i>M. abscessus</i> pulmonary disease who received the combination therapy and intravenous AMK therapy for more than 3 months (n=13).	5 MAC pulmonary disease, 2 pulmonary aspergillosis, 1 COPD, 1 sarcoidosis	63.6 (8.5)	84.6%
Park 2017 (South Korea)	Patients diagnosed with MAPD lung disease, without coinfection of other NTM bacteria, with a follow-up period of at least 6 months (n=110); <i>M. abscessus</i> (n= 56) and <i>M. massiliense</i> (n=54).	48 previous PTB, 18 COPD, 7 asthma	Median: 64 (<i>M. abscessus</i> patients) Median: 63 (<i>M. massiliense</i> patients)	64.5%

Table 1. Demography and underlying lung diseases of study population. (Cont'd)

Author, year	Population (n)	No. of patients with underlying/previous lung disease	Mean age (SD) or median (range) in years	Female (%)
Choi 2018 (South Korea)	Patients diagnosed with acquired macrolide-resistant <i>M. abscessus</i> pulmonary disease (n=13).	6 prior NTM pulmonary disease, 8 previous PTB, 1 COPD, 12 bronchiectasis, 1 chronic pulmonary aspergillosis	Median: 54 Range: 55–78	62%
Lee 2017 (South Korea)	Patients with <i>M. abscessus</i> lung disease who initiated antibiotic treatment (n=48).	36 previous PTB, 37 bronchiectasis, 3 COPD	Median: 57 Range: 52–66	70.8%
Yang 2017 (South Korea)	Patients with <i>M. abscessus</i> pulmonary disease who received clofazimine (n=42).	11 PTB, 36 bronchiectasis, 3 COPD, 5 chronic pulmonary aspergillosis	Median: 60 Range: 53–69	79%
Guo 2018 (China)	Patients aged >16 years being treated for <i>M. abscessus</i> pulmonary disease, received oral CLA-based combination treatment, have follow-up for >6 months, not being treated for active tuberculosis, no previous history of NTM disease, no co-infection with another NTM, negative HIV status (n=100).	45 previous PTB, 3 COPD	Median: 58 Range: 44–66 (CLA-resistant group) Median: 56 Range: 32–64 (CLA-sensitive group)	57%
Jhun 2018 (South Korea)	Patients who were started on AMK inhalation therapy for refractory MABC pulmonary disease, none had previously received AMK inhalation therapy (n=48); <i>M. abscessus</i> (n=35) and <i>M. massiliense</i> (n=12) and <i>M. bolletii</i> (n=1).	57 previous PTB, 17 chronic pulmonary aspergillosis, 9 COPD	Median: 60 Range: 53–69	69%
Kobayashi 2018 (Japan)	Patients with <i>M. abscessus</i> pulmonary disease according to ATS diagnostic criteria who had at least 1 year of follow-up (n=30).	5 previous PTB, 13 other NTM lung diseases, 1 bronchial asthma, 4 COPD, 2 lung cancer, 1 interstitial pneumonia, 1 aspergillosis	75, no SD reported	63.3%
Monteiro 2018 (Brazil)	Patients diagnosed with NTM pulmonary infection without concurrent isolation of <i>M. tuberculosis</i> (n=17).	6 isolated bronchiectasis, 5 associated bronchiectasis, 2 COPD and/or asthma and/or GERD	62.4 (13.7)	76.5%
Morimoto 2018 (Japan)	Patients with MABC (n=121); <i>M. abscessus</i> (n=68) and <i>M. massiliense</i> (n=53).	38 previous NTM disease, 27 previous PTB, 7 bronchial asthma, 3 COPD, 10 pneumonia, 7 aspergillosis	Median: 66 Range: 55–72	71.9%
Shin 2018 (South Korea)	NTM lung disease caused by mixed infection with MAC and MABC excluding those with prior antibiotics therapy for >1 month (n=71); MAC + <i>M. abscessus</i> (n=24) and MAC + <i>M. massiliense</i> (n=47).	23 previous PTB, 10 previous NTM, 2 COPD	Median: 60 Range: 49–68	79%
Yoshida 2018 (Japan)	Patients with non-CF bronchiectasis with isolates of <i>M. abscessus</i> who were not co-infected with other NTM species (n=24); <i>M. abscessus</i> (n=17) and <i>M. massiliense</i> (n=7).	NR	Median: 68 Range: 41–79 (unfavourable outcome patients) Median: 74 Range: 69–78 (favourable outcome patients)	58.3%
Chen 2019 (China)	Patients >16 years without co-infection with active tuberculosis or another NTM, HIV and with a follow-up period lasting >12 months (n=244): <i>M. abscessus</i> (n=185) and <i>M. massiliense</i> (n=59).	127 prior TB/NTM, 208 bronchiectasis, 16 COPD, 15 asthma	Median: 56.0 Range: 49–65.8	73%

Table 1. Demography and underlying lung diseases of study population. (Cont'd)

Author, year	Population (n)	No. of patients with underlying/previous lung disease	Mean age (SD) or median (range) in years	Female (%)
Jhun 2020 (South Korea)	Patients newly diagnosed with MAC or MABC pulmonary disease that was radiologically classifiable, with further subspecies identification. Patients with <i>M. bolletii</i> isolates or lacking death certificates, if applicable, were excluded (n=1445); includes pulmonary disease caused by MABC and MAC.	566 previous PTB, 147 COPD/ bronchial asthma, 31 chronic pulmonary aspergillosis, 45 pulmonary malignancy	Median ^a : 60 Range: 51–68 (*patients MAC+ MABC)	75.6%
Li 2019 (China)	Patients with <i>M. abscessus</i> lung disease who received antibiotics regimen (n=50).	NR	Median: 48 Range: 39.8–55.3 (conventional regimen) Median: 39.5 Range: 36–43.8 (intensified regimen)	88%
Moon 2019 (South Korea)	MAC or MABC pulmonary disease patients without fibrocavitary, cavitary nodular bronchiectasis or unclassifiable form, MABC pulmonary disease without further species identification and <i>M. bolletii</i> (n=1021) (includes NTM pulmonary disease caused by <i>M. avium</i> , <i>M. intracellulare</i> , <i>M. abscessus</i> or <i>M. massiliense</i>).	314 previous PTB, 178 COPD	59, no SD reported	68%
Park 2021 (South Korea)	Patients diagnosed with <i>M. abscessus</i> pulmonary disease treated with treated intravenous AMI and beta-lactams for ≥4 weeks (n=82).	73 bronchiectasis, 5 COPD,	58.7 (11.4)	65.9%

AMI: amikacin; ATS: American Thoracic Society; CLA: clarithromycin; cf: cystic fibrosis; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; ILD: interstitial lung disease; IV: intravenous; *M. abscessus*: *Mycobacterium abscessus* subspecies *abscessus*; *M. massiliense*: *Mycobacterium abscessus* subspecies *massiliense*; *M. bolletii*: *Mycobacterium abscessus* subspecies *bolletii*; MABC: *Mycobacterium abscessus* complex; MAC: *Mycobacterium avium* complex; MABC: *Mycobacterium abscessus* complex; NTM: non-tuberculosis *Mycobacterium*; NR: not reported; PTB: pulmonary tuberculosis; SD: standard deviation; TB: tuberculosis

[CI] 56.7–85.7) (Fig. 2). Subspecies identification was inconsistent; 7 studies did not specify the subspecies.^{12,21,23,29,32–34} Eighteen studies reported on 1047 patients with *M. abscessus*,^{9,11,13,14,16,18–20,22,24–28,30,31,35,37,38} and 11 studies documented 568 patients with *M. massiliense*.^{9,11,13,15,16,22,25–27,30,36} A history of pulmonary tuberculosis (PTB) was reported in 1452 patients (35.4%) across 22 studies, while NTM disease was noted in 124 patients (3%) from 11 studies. One study grouped prior PTB and NTM infections for analysis.³⁰ HIV status was reported in 13 studies, with only 1 study identifying 2 HIV-positive cases,³³ indicating low co-infection prevalence in this cohort.

Reported mortality

Mortality was reported in 13 of 27 studies (48.1%),^{9,15,17,18,22,24–26,32–36} with 328 deaths among 1334 treated patients, yielding an overall mortality rate of 24.6%. Three studies did not provide mortality data.^{15,24,35} A large population-based study found no significant difference in mortality between treated and untreated NTM pulmonary disease patients.²² Survival varied by subspecies: patients with *M. massiliense*

(n=174) had better outcomes than those with *M. abscessus* (n=129). Compared to *Mycobacterium avium* (*M. avium*), *M. abscessus* had a higher adjusted hazard ratio (aHR 2.19), while *M. massiliense* showed no increased risk (aHR 0.99), indicating poorer prognosis with *M. abscessus* infection.

Treatment regimens

Combined treatment regimes

Fourteen studies used a combination of a macrolide, amikacin and either cefoxitin or imipenem, with SCC rates ranging from 8% to 93%.^{11–20,22,29,31,37} Seven of these studies also included fluoroquinolones, reporting SCC rates between 40% and 100%.^{11,14,15,22,29,31,37}

Inhaled amikacin

Five studies evaluated inhaled non-liposomal amikacin as adjunct therapy.^{17,18,21,22,36} Jhun et al. reported an SCC rate of 13%, with clinical and radiological improvement in 44% and 33% of patients, respectively.³⁶ Adverse events, mainly ototoxicity, affected 38% (29 patients), leading to discontinuation in 27% (21

Table 2. Treatment regimens, adverse events and outcomes.

References	Treatment regimen and dosages (n=number of patients on treatment)	Duration of treatment % treatment completion	Adverse events (n, %)	Relapse (n, %)	Treatment outcomes (n, %)
Huang 2010 (Taiwan)	CLA + other antimicrobials for 4–8 months (n=10) Tigecycline for 2 weeks + CLA for 8 months (n=1) A variety of combination of antibiotics including AMK, cefoxitin, fluoroquinolones, CLA (n=11) No dosage reported	Duration: 12 months Treatment completion: 100%	NR	NR	Microbiological outcomes: Persistent SCC: <i>M. abscessus</i> (n=7, 31.8%) Clinical outcomes: Clinical cure: <i>M. abscessus</i> (n=5, 22.7%); improved: <i>M. abscessus</i> (n=3, 13.6%); Failure: <i>M. abscessus</i> (n=6, 27.2%); Indeterminate: <i>M. abscessus</i> (n=8, 36.3%). Radiological outcomes: NR Death: 3 deaths due to non-NTM related causes
Koh 2011 (South Korea)	CLA-containing 3-drug oral regimen: CLA (1000 mg/d), CIP (1000 mg/d), DOX (200 mg/d), along with an initial 4-week course of AMK (15 mg/kg/d in 2 divided doses) and cefoxitin (200 mg/kg/d; maximum, 12 g/d in 3 divided doses) (n=67)	Mean (SD) duration: 23.1 (12.9) months (<i>M. abscessus</i>) 21.6 (7.7) (<i>M. massiliense</i>) Treatment completion: NR	NR	<i>M. abscessus</i> infection (n=4, 40%) <i>M. massiliense</i> infection (n=3, 9%)	Microbiological outcomes: Persistent SCC: <i>M. abscessus</i> (n=6, 25%) and <i>M. massiliense</i> (n=29, 88%) Clinical outcomes: Improved: <i>M. abscessus</i> (75%) and <i>M. massiliense</i> (97%) Radiological outcomes: Improved: <i>M. abscessus</i> (42%) and <i>M. massiliense</i> (82%) Death: NR
Lyu 2011 (South Korea)	Macrolide (CLA (1000 mg/day)/ AZI (250 mg/ day) and AMK (15 mg/kg/day, maximum 1 g/day) (n=17) Macrolide and 2 IV agents (AMK and cefoxitin [10 g/day in 3 divided doses] or imipenem [500 mg, 3 times a day]) (n=24) Other antibiotics: DOX (n=2); CIP (n= 18; MOX (n=3) Surgery (n= 13): 7 from 2 IV drugs group and 3 from 1 IV drug group	Median (range) duration (overall): 511 (164–1249) days Median (range) duration (IV AMK): 230 (60–601) days Median (range) duration (IV cefoxitin or imipenem): 83 (25–288) days Treatment completion: 100%	43.9% (n=18) patients experienced adverse events: 17.1% (n=7) DILI 12.2% (n=5) GI symptoms 9.8% (n=4) Tinnitus/hearing difficulties 7.3%(n=3) Skin eruptions 7.3%(n=3) Fever 4.9%(n=2) Leukopenia 2.4%(n=1) Arthralgia 2.4%(n=1) Nephrotoxicity	N=4, 10%	Microbiological outcomes: Persistent SCC: <i>M. abscessus</i> (n=33, 80.5%) Clinical outcomes: Improved: <i>M. abscessus</i> (n=33, 80.5%) Radiological outcomes: NR Death: NR

Table 2. Treatment regimens, adverse events and outcomes. (Cont'd)

References	Treatment regimen and dosages (n=number of patients on treatment)	Duration of treatment % treatment completion	Adverse events (n, %)	Relapse (n, %)	Treatment outcomes (n, %)
Harada 2012 (Japan)	Macrolide, rifampicin and ethambutol (n=8)	Mean (range) duration: 33 (3–178) months for <i>M. abscessus</i>	NR	<i>M. abscessus</i> infection (n=13, 65%)	Microbiological outcomes: Persistent SCC: <i>M. abscessus</i> (n=13, 65%) and <i>M. massiliense</i> (n=7, 70%).
	Macrolide, carbapenem and aminoglycoside (n=6)	Mean (range) duration: 33 (1–122) months for <i>M. massiliense</i>		<i>M. massiliense</i> infection (n=3, 30%)	Clinical outcomes: NR
	Macrolide only (n=8)	Treatment completion: 100%			Radiological outcomes: Improved: <i>M. abscessus</i> (n=17, 29%) and <i>M. massiliense</i> (n=12, 44%).
	Macrolide and fluoroquinolone (n=6).				Death: NR
	Isoniazid, rifampicin and ethambutol (n=2)				
Lyu 2014 (South Korea)	Other regimens (n=12)				
	No dosage reported				
	Macrolide, AMK and cefoxitin (n=19)	Mean (SD) duration: 14.3 (9.4) months for <i>M. abscessus</i>	12.5% (n=6) patients mainly with GI problems attributed to clarithromycin	n=23, 47.9%	Microbiological outcomes: Persistent SCC: <i>M. abscessus</i> (n=11, 42.3%) and <i>M. massiliense</i> (n=21, 95.5%).
	Macrolide, AMK and imipenem (n=12)	Mean (SD) duration: 16.3 (11.6) months for <i>M. massiliense</i>			Clinical outcomes: Improved: <i>M. abscessus</i> (n=13, 50%) and <i>M. massiliense</i> (n=16, 72.7%).
	Macrolide and AMK (n=11)	Treatment completion: 100%			Radiological outcomes: Improved: <i>M. abscessus</i> (n=9, 34.6%) and <i>M. massiliense</i> (n=16, 72.7%). Deteriorated: <i>M. abscessus</i> (n=8, 30.8%) and <i>M. massiliense</i> (0%).
Tung 2015 (Taiwan)	Macrolide and cefoxitin (n=4)				Death: NR
	Macrolide and imipenem (n=2)				
	Macrolide dosage: CLA (1000 mg/day) (n=42) and AZI (250 mg/day) (n=6)				
	Surgery (n=9) (8 with <i>M. abscessus</i> and 1 with <i>M. massiliense</i>)				
Tung 2015 (Taiwan)	CLA only (n=17)	Mean (SD) duration: 13.2 (13.19) months	NR	n=3, 17.6%	Microbiological outcomes: Persistent SCC after 1 year: <i>M. abscessus</i> (n=17, 65.4%)
	CLA and AZI (n=2)	Treatment completion: 24.5%			Clinical outcomes: Clinical success: <i>M. abscessus</i> (n=15, 57.7%); Improved: <i>M. abscessus</i> (n=3, 11.5%); Failure: <i>M. abscessus</i> (n=3, 11.5%)
	CLA and MOX (n=9)				Radiological outcomes: NR
	CLA and CIP (n=5)				Death: 15 deaths due to other causes
	IV AMK only (n=1)				
	IV AMK and meropenem (n=1)				
	IV AMK and imipenem/cilastatin (n=1)				
	Isoniazid, ethambutol, rifampicin and pyrazinamide (n=7)				
	No dosage reported				

Table 2. Treatment regimens, adverse events and outcomes. (Cont'd)

References	Treatment regimen and dosages (n=number of patients on treatment)	Duration of treatment (% treatment completion)	Adverse events (n, %)	Relapse (n, %)	Treatment outcomes (n, %)
Kang 2015 (South Korea)	Preoperative: All patients received macrolide (CLA or AZI) ± fluoroquinolone (CIP or MOX) with IV AMK and cefoxitin (or imipenem) for 4 weeks (6 patients had streptomycin injection) Perioperative: 19 patients received IV AMI, cefoxitin or imipenem Postoperative: Macrolide and/or oral fluoroquinolone for ≥12 months (n=23 combined medical and surgical treatment) No dosage reported	Median (range) duration of preoperative antibiotics: 8.3 (3.8–14.7) months Median (range) duration of perioperative antibiotics: 28 (25–33) days for MABC-PD Treatment completion: NR	8.3% (n=3) Skin rash or perioral tingling sensation due to streptomycin 21% (n=15) patients with postoperative complications	n=0	Microbiological outcomes: SCC: <i>M. abscessus</i> (n=16, 69.6%) Clinical outcomes: NR Radiological outcomes: NR Death: <i>M. abscessus</i> : (n=1) due to complex pneumonia
Koh 2016 (South Korea)	Inpatient regimen: 4 weeks of macrolides (CLA or AZI), fluoroquinolones (CIP or MOX), DOX, IV AMK and IV cefoxitin. Followed by outpatient regimen: macrolide ± fluoroquinolone ± DOX for ≥12 months after SCC (n=67) DOX and fluoroquinolone were excluded from the treatment protocol beginning in February 2008 and March 2011, respectively Surgery (n=9) No dosage reported	Duration: >12 months Treatment completion: NR	NR	n=6, 17.6%	Microbiological outcomes: Persistent SCC: <i>M. abscessus</i> (n=28, 41.8%) Clinical outcomes: NR Radiological outcomes: NR Death: NR
Koh 2016 (South Korea)	CLA (1000 mg/day), fluoroquinolone and 4 weeks IV AMK and cefoxitin. Followed by, CLA and fluoroquinolone for 24 months (n=28) CLA or AZI (250 mg/day) and 2 weeks of IV AMK and cefoxitin. (7 patients had a fluoroquinolone added to their regimen), followed by macrolides for 12 months or until their sputum cultures were negative (n=43) Surgery (n=5)	Mean duration (4-week of IV group): 23.9 months Mean duration (2-week IV group): 15.2 months Treatment completion: 100%	Adverse events such as neutropenia and DILI associated with cefoxitin occurred more frequently in the 4-week IV group (n=17, 61%) than in the 2-week IV group (n=3, 7%)	4-week IV group (n=2, 7%) 2-week IV group (n=3, 7%)	Microbiological outcomes: SCC (<i>M. massiliense</i>): 4-week IV group (n=28, 100%) and 2-week IV group (n=39, 91%) Clinical outcomes: Improved (<i>M. massiliense</i>): 4-week IV group (n=25, 89%) and 2-week IV group (n=43, 100%) Radiological outcomes: Improved (<i>M. massiliense</i>): 4-week IV group (n=22, 79%) and 2-week IV group (n=39, 91%) Death: 0

Table 2. Treatment regimens, adverse events and outcomes. (Cont'd)

References	Treatment regimen and dosages (n=number of patients on treatment)	Duration of treatment % treatment completion	Adverse events (n, %)	Relapse (n, %)	Treatment outcomes (n, %)
Namikoong 2016 (Japan)	A variety of combinations of IV AMK, CLA, sitafloxacin, faropenem, imipenem/ cilastatin and meropenem (n=13) Prior antibiotic treatment with CLA ± rifampicin ± ethambutol (n=10) No dosage reported	Median (range) duration: 4 (3–9) months Treatment completion: NR	NR	n=4, 30.8%	Microbiological outcomes: SCC: <i>M. abscessus</i> (n=10, 77%); Persistent SCC after 1 year: <i>M. abscessus</i> (n=8, 62%) Clinical outcomes: Improved (<i>M. abscessus</i>): Cough (n=3, 23.1%); Sputum (n=4, 30.8%); Dyspnoea (n=2, 23%); Haemoptysis (n=3, 23.1%); Fever (n=1, 7.7%); Fatigue (n=1, 7.7%) Radiological outcomes: Improved: <i>M. abscessus</i> (n=7, 53.8%) Death: NR
Park 2017 (South Korea)	Macrolide and 32 IV agents such as AMK, cefoxitin, or imipenem for ≥3 weeks (n=29), followed by macrolide and IV AMK Surgery (n=5) No dosage reported	Median (range) duration: 61 (28–116) weeks (<i>M. abscessus</i>) Median (range) duration: 87 (64–120) weeks (<i>M. massiliense</i>) Treatment completion: NR	NR	<i>M. abscessus</i> infection (n=6, 24%)	Microbiological outcomes: Persistent SCC: <i>M. abscessus</i> (n=5, 26.3%) and <i>M. massiliense</i> (n=14, 82.4%) Clinical outcomes: NR Radiological outcomes: NR Death: NR
Choi 2017 (South Korea)	All patients received a 4-week of IV AMK (15–20 mg/kg/day) and either cefoxitin (200 mg/kg/day; maximum, 12 g/day, in three divided doses) or imipenem (750 mg, 3 times per day), along with macrolide antibiotics (CLA 1000 mg/day or AZI 250 mg/day) (n=14)	Median (range) duration: 18.6 (14.7–24.1) months Treatment completion: 79%	NR	NR	Microbiological outcomes: SCC: <i>M. abscessus</i> (n=13, 93%) Clinical outcomes: NR Radiological outcomes: NR Death: 2 deaths due to other causes
Choi 2018 (South Korea)	After detection of macrolide-resistance: Macrolide (CLA 1000 mg/day or AZI at 250 mg/day) (n=11) IV AMK, 15 mg/kg/day in 2 divided doses or 15 mg/kg/day with adjustment of a once-daily dose to target peak serum drug level of 55 to 65 g/mL (n=6) IV cefoxitin (200 mg/kg/day; maximum of 12 g/day in three divided doses) or imipenem (750 mg three times per day) (n=6)	Median (range) duration: 24 (16–43) months Treatment completion: 84.6%	NR	NR	Microbiological outcomes: SCC after surgery: <i>M. abscessus</i> (n=1, 8%) Clinical outcomes: Favourable outcome: <i>M. abscessus</i> (n=0) Radiological outcomes: NR Death: 2

Table 2. Treatment regimens, adverse events and outcomes. (Cont'd)

References	Treatment regimen and dosages (n=number of patients on treatment)	Duration of treatment (% treatment completion)	Adverse events (n, %)	Relapse (n, %)	Treatment outcomes (n, %)
	Fluoroquinolone (CIP at 1000 mg/day or MOX at 400 mg/day) (n=1) CFZ, 100 mg/day (n=10) AMK inhalation, 250–500 mg/day (n=7) (n=13) Surgery (n=2)				
Yang 2017 (South Korea)	Initial treatment: CFZ (100 mg/day), macrolide (CLA 1000 mg/day or AZI 250 mg/day) and 4- week IV AMK (15 mg/kg/ day), IV cefoxitin (200 mg/kg/day, maximum 12 g/day) or imipenem (n=15) Salvage treatment: Macrolide, fluoroquinolones and IV combination antibiotics for 6 months (n=27) (13 patients re-hospitalised and had CFZ with 4 weeks of combination IV antibiotic treatment; CFZ was added to 14 patients on macrolide)	Median (range) duration: 48 (25.2–48) weeks Treatment completion: 57%	52% (n=12) GI symptoms 39% (n=9) Skin colour change 4% (n=1) Dizziness	NR	Microbiological outcomes: SCC: <i>M. abscessus</i> (n=10, 24%) Clinical outcomes: Improved: <i>M. abscessus</i> (n=34, 81%) Radiological outcomes: Improved: <i>M. abscessus</i> (n=13, 31%) Death: NR
Guo 2018 (China)	4-week of IV AMK (15 mg/kg/d in 2 equally divided doses) and IV cefoxitin (200 mg/ kg/d with a maximum of 12 g/d in 3 equally divided doses) (n=100) Treatment completion: 100%	Median (range): 18 (9–30) months (CLA-resistant) Median (range): 15 (9–22) months (CLA-sensitive)	NR	n=12, 12%	Microbiological outcomes: Persistent SCC: <i>M. abscessus</i> (n=40, 40%) Clinical outcomes: NR Radiological outcomes: Improved: <i>M. abscessus</i> (n=47, 47%) Death: NR
Jhun 2018 (South Korea)	AMK 250 mg inhalation once daily be up- titrated to 500 mg once daily 2 to 4 weeks later (protocol was changed from 500 mg once daily to 500 mg 3 times weekly from September 2016) (n=48) Patients also received macrolide (100%) and CFZ (90%)	Median (IQR) duration: 12 (6.8–12) months Treatment completion: 96%	38% (n=29) patients had adverse effects: 19% (n=15) Ototoxicity 9% (n=7) Fatigue 5% (n=4) Tinnitus 3% (n=2) Cough 1% (n=1) Hoarseness	NR	Microbiological outcomes: 3 consecutive negative cultures: <i>M. abscessus</i> (n=6, 13%) Clinical outcomes: Improved: <i>M. abscessus</i> (n=21, 44%); Unchanged: <i>M. abscessus</i> (n=11, 23%); Deteriorated: <i>M. abscessus</i> (n=16, 33%) Radiological outcomes: Improved: <i>M. abscessus</i> (n=16, 33%); Unchanged: <i>M. abscessus</i> (n=11, 23%); Deteriorated: <i>M. abscessus</i> (n=21, 44%) Death: 10 deaths

Table 2. Treatment regimens, adverse events and outcomes. (Cont'd)

References	Treatment regimen and dosages (n=number of patients on treatment)	Duration of treatment % treatment completion)	Adverse events (n, %)	Relapse (n, %)	Treatment outcomes (n, %)
Kobayashi 2018 (Japan)	Macrolide, rifampicin and ethambutol (n=9) Macrolide, rifampicin, ethambutol and IV amikacin ± imipenem (n=14) No dosage reported	Duration: >12 months Treatment completion: 100%	NR	n=3, 13%	Microbiological outcomes: SCC: <i>M. abscessus</i> (n=8, 34.8%) Clinical outcomes: NR Radiological outcomes: NR Death: NR
Monteiro 2018 (Brazil)	1st regimen: CLA (500mg q12hr), ethambutol (1200 mg q24hr) and rifampicin (600 mg q24hr) 2nd regimen: add IM AMK (500 mg, 3 times/ week) or IM streptomycin (1 g, 3 times/ week) to the 1st regimen. 3rd regimen: add IV imipenem (500 mg, q6hr) to the 2nd regimen (n=17)	Duration: NR Treatment completion: 82.4% (1st regimen)	NR	NR	Clinical outcomes: After 1st regimen: <i>M. abscessus</i> (n=3, 17.6%); After 2nd/3rd regimen: <i>M. abscessus</i> (n=10, 91.0%) Clinical outcomes: Improved: <i>M. abscessus</i> (n=3, 17.6%); Failure: <i>M. abscessus</i> (n=11, 64.8%) Radiological outcomes: NR Death: 1 death
Shin 2018 (South Korea)	Initial antibiotics (2–4 weeks) – IV AMK, cefoxitin (or imipenem), and macrolide, ethambutol, rifampicin and/or fluoroquinolone ± CFZ MAC+M. <i>abscessus</i> (n=24) MAC+M. <i>massiliense</i> (n=47) No dosage reported	Median duration: 25.7 months (MAC+M. <i>abscessus</i>) Median duration: 18.5 months (MAC+M. <i>massiliense</i>) Treatment completion: 100%	NR	(MAC+M. <i>abscessus</i>): (n=0) (MAC+M. <i>massiliense</i>): (n=12, 57.1%)	Microbiological outcomes: SCC at 12 months: MAC+M. <i>abscessus</i> (n=3, 25) and MAC+M. <i>massiliense</i> (n=19, 61%) Clinical outcomes: (MAC+M. <i>abscessus</i>) — Improved: (n=11, 92%); Deteriorated (n=1, 8%); (MAC+M. <i>massiliense</i>) — Improved: (n=28, 90%); Deteriorated (n=1, 3%) Radiological outcomes: (MAC+M. <i>abscessus</i>) — Improved: (n=11, 92%); Deteriorated (n=1, 8%); (MAC+M. <i>massiliense</i>) — Improved: (n=28, 90%); Deteriorated (n=3, 10%) Death: NR
Yoshida 2018 (Japan)	A variety of antibiotics combinations: macrolides (CLA 800 mg/day or AZI 250 mg/ day), fluoroquinolone (sitafloxacin 100 mg/ day), and ≥2 IV antibiotics, such as AMK 400 mg/day and imipenem 1500 mg/day (n=21)	Median (range) duration (unfavourable group) (oral): 958 (219–1266) days Median duration (favourable group) (oral): 119 days Median (range) duration (unfavourable group) (oral + IV abx): 1623 (481–2975) days Median (range) duration (favourable group) (oral + IV abx): 32 (28–37) days Treatment completion: 100%	NR	19.1%	Microbiological outcomes: SCC (<i>M. abscessus</i>) – 5.9% (1/17); SCC (<i>M. massiliense</i>) – 28.6% (2/7) Clinical outcomes: NR Radiological outcomes: NR Death: 2 deaths

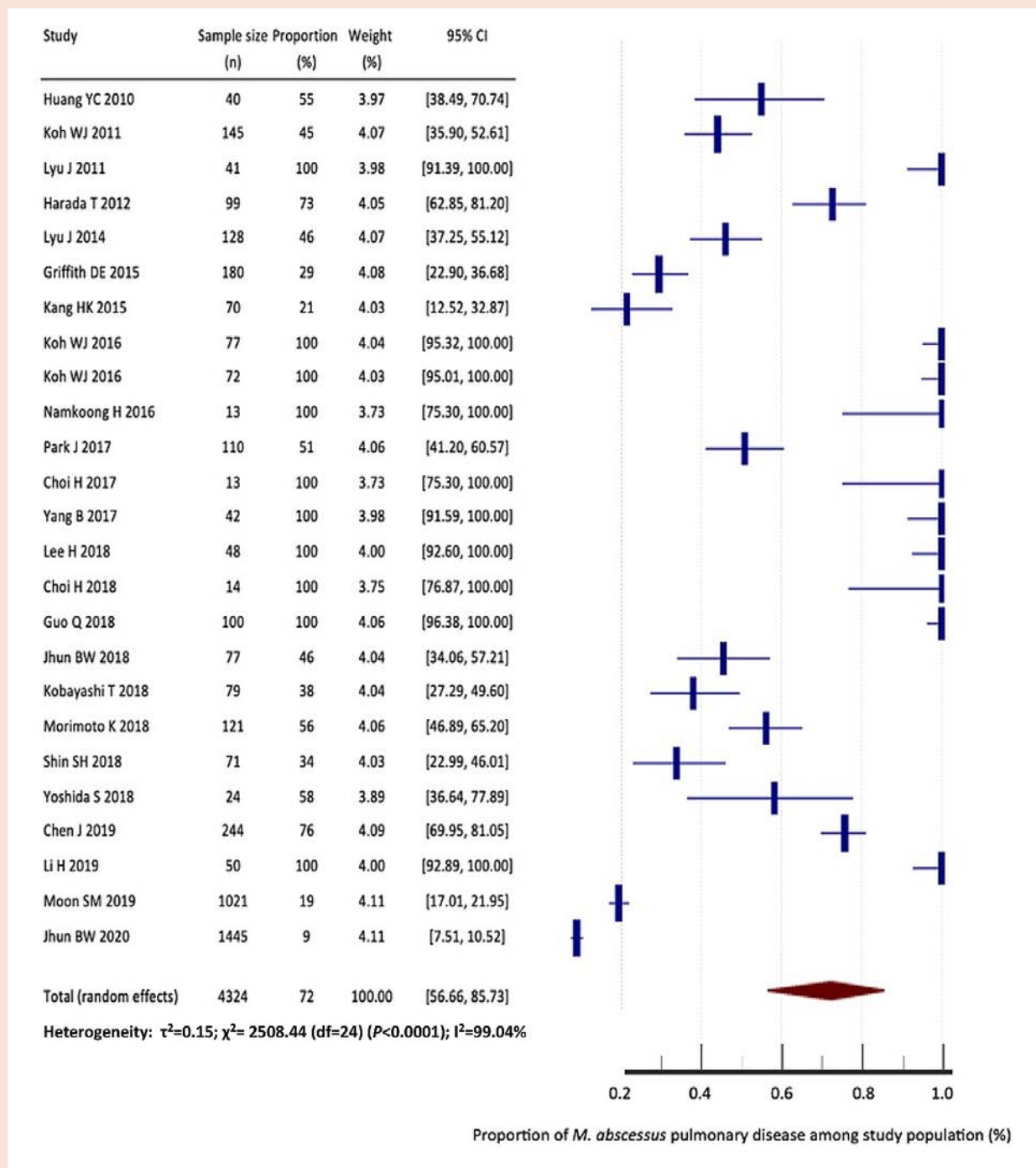
Table 2. Treatment regimens, adverse events and outcomes. (Cont'd)

References	Treatment regimen and dosages (n=number of patients on treatment)	Duration of treatment (% treatment completion)	Adverse events (n, %)	Relapse (n, %)	Treatment outcomes (n, %)
Chen 2019 (China)	A variety of antibiotics combinations: CLA, AZI, AMK, tigecycline, linezolid, imipenem, meropenem, ceftioxin, CLP, MOX, DOX, minocycline, and levofloxacin (n=244) No dosage reported	Duration: NR Treatment completion: NR	78.7% (n=192) patients had adverse events Severe effects that resulted in treatment modification included: 48.4% (n=29) GI distress (mainly caused by tigecycline) 23.3% (n=14) ototoxicity (caused by AMK) 10% (n=6); myelosuppression (mainly caused by linezolid)	NR	Microbiological outcomes: SCC: <i>M. abscessus</i> (n=62, 33.5%) and <i>M. massiliense</i> (n=48, 81.4%), Clinical outcomes: NR Radiological outcomes: NR Death: NR
Jhun 2020 (South Korea)	Initial treatment (2 to 4 weeks): IV AMK, imipenem (or ceftioxin), oral macrolide and oral fluoroquinolone (or DOX) Followed by oral regimens. Some patients with refractory NTM PD received oral CFZ or inhaled AMK <i>M. abscessus</i> (n=129) <i>M. massiliense</i> (n=174) No dosage reported	Duration: NR. Treatment completion: NR	NR	NR	Microbiological outcomes: NR Clinical outcomes: NR Radiological outcomes: NR Death: <i>M. massiliense</i> mortality 5-year (7.3%), 10-year (18.1%), 15-year (23.5%); <i>M. abscessus</i> mortality 5-year (11.4%), 10-year (29.8%), 15-year (50.6%)

Table 2. Treatment regimens, adverse events and outcomes. (Cont'd)

References	Treatment regimen and dosages (n=number of patients on treatment)	Duration of treatment (% treatment completion)	Adverse events (n, %)	Relapse (n, %)	Treatment outcomes (n, %)
Li 2019 (China)	Convention regime (1 July 2010–31 July 2017): Macrolides (CLA [1000 mg/d] or AZI [250 mg/d], MOX 400 mg/d. Initial 12-week of IV cefoxitin (2 g, BD) and IV AMK (400 mg/d for weight ≤50 kg, 600 mg/d for weight >50 kg)	Duration: NR Treatment completion: NR	14% (n=7) Leukopenia 12% (n=6) Hepatotoxicity 20 % (n=10) Nausea and vomiting 2% (n=1) Anaemia 4% (n=2) Arthralgia	8%	Microbiological outcomes: SCC at 1 month: <i>M. abscessus</i> : conventional Rx (n16, 47%) and Intensified Rx (n=12, 75%); SCC at 18 months: <i>M. abscessus</i> : Conventional Rx (n=9, 26.5%) and Intensified Rx (n=10, 62.5%) Clinical outcomes: Improved: at one month (n=28, 56%) and after 18 months (n=19, 38%) Radiological outcomes: NR Death: NR
	Intensified regime (1 August 2017–1 February 2018). AZI (250 mg/d), MOX (400 mg/d), linezolid (600 mg/d for the first 3 months, followed by 300 mg/d for the following months); initial 4-week IV cefoxitin (12 g/d) and 12-week IV AMK (400 mg/d for weight ≤50 kg, 600 mg/d for weight >50 kg) Both the conventional and intensified regimens continued 12 months after the first sputum conversion (n=50).				
Park 2021 (South Korea)	Initial antibiotics-IV AMK (median 8.9 weeks) and IV beta-lactam (median 5.3 weeks), and macrolide (100%), CFZ (28%), MOX (31.7%) and linezolid (4.9%) (n=82). No dosage reported	Median (IQR) duration: 15.4 (9.5–24.5) months Treatment completed: 100%	4.9 % (n=4) Skin abnormalities 7.3% (n=6) Fever 2.4% (n=2) GI abnormalities 25.6% (n=21) Haematologic abnormalities 9.8% (n=8) DILI 3.7% (n=3) nephrotoxicity 4.9% (n=4) ototoxicity 1.2% (n=1) peripheral neuropathy	NR	Microbiological outcomes: SCC: Abscesses (n=43, 52.4%); microbiological cure: <i>M. abscessus</i> (n=34, 41.5%) Clinical outcomes: NR Radiological outcomes: Improved: <i>M. abscessus</i> (n=35, 42.7%); Unchanged: <i>M. abscessus</i> (n=37.8 37.8%); Deteriorated: <i>M. abscessus</i> (n=16, 19.5%) Death: NR

abx: antibiotics; AML: amikacin; AZI: azithromycin; BD: twice a day; CLA: clarithromycin; CFZ: cefazolin; CIP: ciprofloxacin; COPD: chronic obstructive pulmonary disease; DILI: drug induced liver injury; DOX: doxycycline; GI: gastrointestinal; HIV: human immunodeficiency virus; IM: intramuscular; ILD: interstitial lung disease; IQR: interquartile range; IV: intravenous; *M. abscessus*: *Mycobacterium abscessus* subspecies *abscessus*; *M. bolletii*: *Mycobacterium abscessus* subspecies *bolletii*; *M. massiliense*: *Mycobacterium abscessus* subspecies *massiliense*; MABC: *Mycobacterium abscessus* complex; MAC: *Mycobacterium avium* complex; MABC: *Mycobacterium abscessus* complex; MOX: moxifloxacin; NR: not reported; NTM: non-tuberculosis *Mycobacterium*; PTB: pulmonary tuberculosis; TB: pulmonary tuberculosis; SCC: sputum culture conversion

Fig. 2. Prevalence of *M. abscessus* pulmonary disease among study population.

CI: confidence interval

patients). Reducing dosing frequency to 3 times per week decreased adverse effects.

Tigecycline and clofazimine

Tigecycline was used in 2 studies,^{30,32} both showing favourable outcomes, particularly for *M. abscessus*.³⁰ Clofazimine was included in 7 studies.^{17–22,37} Yang

et al. reported an SCC rate of 24%, including 15% in refractory *M. abscessus*. Gastrointestinal side effects occurred in 43% of patients, prompting dose adjustments or discontinuation, though no severe events were reported.¹⁹

Ten studies reported macrolide-contained regimens for all patients.^{11,13,14,17,20,21,24,27,32,37} For subgroup analysis

on the association between treatment duration and SCC rates for these regimens: median (range) SCC rates were 28.4 (25–31.8) for 1-year treatment, 42.1 (25–52.4) for 2-year treatment and 44.5 (24–65) for treatment exceeding 2 years. There was no statistically significant difference among the treatment durations, which may be attributed to small sample size (1-year versus [vs] 2-year treatment, $P=0.3$; 1-year vs exceeding 2-year treatment, $P=1$). Six studies used macrolide-intravenous (IV) amikacin contained regimens for all patients.^{11,13,14,17,21,37} There was no statistically significant difference in SCC rates between studies reported of all versus some patients that received the macrolide-IV amikacin regimens (median [range]: 42.1 [46.6–93] vs 33.3 [38.9–65] respectively, $P=0.6$).^{20,24,27,32} This may be attributed to small sample size.

Surgical treatment

Adjunctive pulmonary resection was reported in 9 studies.^{9,12-17,20,37} The criteria for surgery included inadequate response to medical therapy or recurrent NTM pulmonary disease with persistent sputum culture positive, cavitory lesions and or severe focal bronchiectasis with complications such as massive haemoptysis.^{9,12,13,15} In 5 studies, SCC rates post-surgery ranged from 42% to 100%.^{9,12,14,15,18} Choi et al. reported SCC in a patient with macrolide-resistant *M. abscessus* following surgery.¹⁸ Outcomes varied: Lyu et al. found no significant difference between surgical and medical therapy,¹² whereas Kang et al. reported an SCC rate of 81% with a 21% complication rate.⁹ Koh et al. noted higher SCC at 36 months in the surgery-plus-antibiotics group compared to antibiotics alone (54% vs 42%).¹⁴ Reported complications included pneumonia, bronchopleural fistula and wound dehiscence.¹³ In comparing SCC rate, patients who received both antibiotic therapy and surgical treatment had a higher SCC rate than those who received antibiotic therapy alone (median [range]: 76.9% [65–100%] vs 34.2% [5.9–93%], $P=0.007$).

Treatment-related adverse effects

Ten studies (35.7%) reported treatment-related side effects, which were experienced by 356 patients (12.8% of 2769).^{9,12,13,15,19,20,30,31,36,37} Among these, 147 patients required dose reduction or discontinuation of treatment due to adverse effects.

Amikacin-related adverse effects

Amikacin was administered via inhalation and intravenous (IV) routes.

Inhaled amikacin

Five studies evaluated inhaled non-liposomal amikacin.^{17,18,21,22,36} Jhun et al. reported detailed safety outcomes,³⁶ where all patients receiving 500 mg

once daily experienced adverse effects, leading to a reduced frequency (3 times weekly), which minimised further events. Overall, 29 patients (38%) experienced side effects, and 21 (27%) discontinued treatment. Common adverse events included ototoxicity (19.5%), fatigue (9.1%), tinnitus (5.2%) and cough (2.6%).

Intravenous amikacin

IV amikacin was included in 20 studies.^{11-22,24,26,28-31,33,37} No adverse effects were reported in 6 studies.^{13,15,19,20,28,31} Reported dosages ranged from 8 to 20.2 mg/kg/day.^{13,15} Two studies documented adverse events in 23 patients (8.1%), including ototoxicity, tinnitus and nephrotoxicity.^{12,30} Dosages varied: 6 studies used 15 mg/kg/day,^{11,12,17,18,20,29} while 2 used 400 mg/day.^{26,31} Therapeutic drug monitoring was noted in some studies: Namkoong et al. adjusted dosing based on trough levels,²⁸ Lee et al. used peak serum levels (Cmax) for dose optimisation.¹⁹

Cefoxitin-related adverse effects

Cefoxitin was used in 17 studies as part of combination therapy.^{9,11-22,29-31,37} Four studies reported adverse effects, primarily hepatotoxicity (11.2–14.3%) and leukopenia (9.9%).^{12,15,31,37} Symptoms typically resolved after switching to imipenem, highlighting the need for close monitoring and timely regimen adjustment.

Tigecycline-related adverse effects

Tigecycline was used in 2 studies,^{30,32} and was associated with gastrointestinal toxicity. Chen et al. reported nausea, vomiting, diarrhoea and abdominal pain as the most common effects.³⁰ Among 244 patients, 14 (5.7%) required dose reduction or discontinuation due to severity.

Clofazimine-related adverse effects

Clofazimine was included in 7 studies,^{17-22,37} with adverse effects reported in 2.^{19,20} In 1 cohort,²⁰ 55% experienced side effects, including gastrointestinal symptoms (26%) and skin discoloration (12%). These led to dose reduction in 12% and discontinuation in 43% of cases. While not life-threatening, these reactions impacted adherence and tolerability.

Treatment outcomes

Treatment outcomes were evaluated across 3 primary domains: clinical response, microbiological response (measured via SCC) and radiological improvement. Due to heterogeneity in outcome definitions and assessment methods, direct comparisons between studies were limited.

Clinical outcomes

Twelve studies assessed clinical outcomes based on symptoms such as cough, sputum production, dyspnoea and physician-assessed respiratory

status.^{11-13,20,21,26,28,32-34,36} However, interpretation was limited by the lack of standardised definitions for clinical improvement. Four studies used both symptom and radiological findings to evaluate response,^{21,26,32,33} with improvement rates ranging from 13.6% to 91% and a pooled estimate of 37.1 % (95% CI 29.3–45.2%) (Fig. 3).

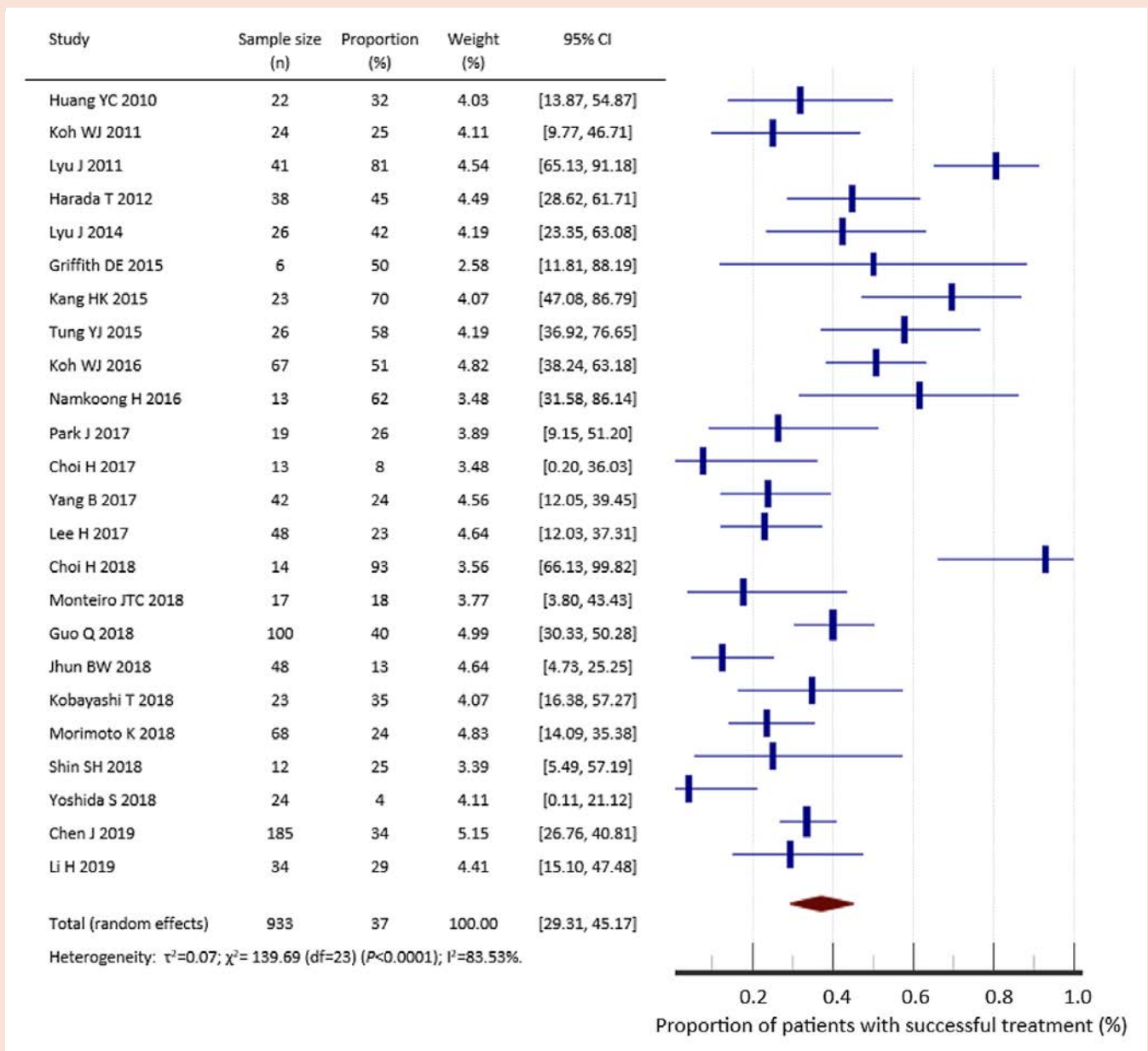
Six studies assessing symptoms alone reported improvement rates between 17.6% and 100%, reflecting heterogeneity in regimens, disease severity and study populations.^{13,15,20,28,34,36} Koh et al. found

higher response rates in *M. massiliense* (97%) than in *M. abscessus* (75%), emphasising the influence of subspecies.¹¹ Notably, 1 study reported spontaneous symptom improvement in 42.5% of untreated patients, suggesting possible host-related or self-limiting disease mechanisms.³³

Microbiological outcomes

SCC was reported in 25 studies,^{9,11-18,20,21,23-33,36,37} with 12-month SCC rates ranging from 29% to 77%. *M. massiliense* consistently showed higher SCC rates

Fig. 3. Successful treatment for *M. abscessus* pulmonary disease.



CI: confidence interval

(72.4–100%) compared to *M. abscessus* (31–81.3%). Park et al. reported SCC in 82.4% of *M. massiliense* cases versus 26.3% in *M. abscessus*.¹⁵ In an untreated cohort, Moon et al. observed spontaneous SCC in 34% (157/459),²³ although 26 later developed NTM disease from different species, highlighting the dynamic nature of NTM colonisation. A large study by Park et al. reported SCC and microbiological cure rates of 52.4% and 41.5%,³⁷ respectively, based on NTM-NET definitions.¹⁰ These findings emphasise the importance of standardised outcome measures in evaluating treatment efficacy.

Radiological outcomes

Nine studies assessed radiological response using high-resolution computed tomography (HRCT).^{11,13,15,20,27-29,36,37} Among 6 studies focusing on MABC,^{13,20,28,29,36,37} radiographic improvement ranged from 33–53.8%, with 23–37.8% showing no change and 19.5–33% demonstrating deterioration. Subspecies differences were evident. Koh et al. reported 91% radiologic improvement in *M. massiliense* cases after 2 weeks of IV antibiotics.¹⁵ Similarly, Koh et al. and Harada et al. found higher response rates in *M. massiliense* (82% and 48%) compared to *M. abscessus* (42% and 29%).^{11,29} In contrast, Tung et al. observed deterioration in 77% of patients, with only 13.9% showing improvement and 44.4% remaining stable.³²

Other factors associated with treatment outcomes

Three studies analysed demographic, clinical, and genetic factors potentially influencing treatment outcomes.^{22,23,29}

Genotypic associations

Guo et al. found that bacterial genotype significantly influenced outcomes, including SCC rates, radiological improvement and overall treatment success.²⁹ In their multivariate analysis, patients infected with clarithromycin-resistant genotypes were significantly less likely to experience favourable treatment outcomes compared to those with clarithromycin-sensitive genotypes (adjusted odds ratio: 0.185, 95% CI 0.059–0.579, $P=0.004$).

Host-related factors

Findings on the influence of age, sex, body mass index (BMI) and comorbidities on treatment outcomes were mixed. Guo et al. reported no significant association between these variables and treatment success.²⁹ Conversely, Jhun et al. identified several factors linked to increased mortality in NTM pulmonary disease, including age ≥ 65 years, male sex, low BMI (<18.5 kg/m²) and comorbidities such as chronic pulmonary aspergillosis, malignancy, chronic cardiac or hepatic disease.²² Moon et al. observed spontaneous SCC in 34% of untreated patients;²³ however,

some later developed NTM disease due to different species, highlighting the dynamic interaction between host immunity and pathogen behaviour.

DISCUSSION

Treatment of *M. abscessus* pulmonary disease remains highly challenging due to factors such as bacterial genotype, subspecies, antimicrobial resistance and patient-specific clinical variables. These elements contribute to heterogeneity in treatment outcomes and complicate cross-study comparisons. Clinical success depends on appropriate antibiotic selection, accurate subspecies/genotype identification, and host factors including comorbidities, immune status and underlying lung disease. Antibiotic regimens vary significantly across regions and institutions, influenced by drug availability and local protocols. The organism's intrinsic and acquired resistance limits consistent treatment responses. Interpretation of outcomes is further complicated by the absence of standardised definitions for clinical, microbiological and radiological responses, and differences in follow-up duration.

In this review, SCC rates for combination regimens—including a macrolide, amikacin and cefoxitin or imipenem—ranged from 8% to 93%. Some studies reported improved outcomes with the addition of fluoroquinolones. However, sustained SCC was more consistently linked to subspecies differences, with *M. massiliense* infections showing better microbiological response than *M. abscessus*. Tigecycline, clofazimine and inhaled amikacin were effective options for refractory cases.^{19,30,36}

Studies have underscored the importance of macrolide susceptibility as a key predictor of outcome. For instance, Choi et al. reported the poorest outcomes in patients with macrolide-resistant strains,¹⁷ while Park et al. emphasised that clarithromycin susceptibility significantly influenced treatment success.¹⁶ These findings reinforce the need for routine genotypic testing, including *erm*(41) and *rrl* mutations, to guide personalised antimicrobial therapy and improve prognostication.

Earlier studies and clinical guidelines have supported the use of inhaled amikacin in patients with refractory *M. abscessus* pulmonary disease,³⁸⁻⁴² although its application has been inconsistent across clinical settings. Jhun et al. reported low SCC rates but moderate clinical and radiological improvement with amikacin inhalation therapy.³⁸ However, frequent adverse events, particularly ototoxicity, necessitated a protocol adjustment from daily to thrice-weekly dosing, which reduced the incidence of toxicity. These findings suggest a potential role for inhaled amikacin as a supportive adjunct but emphasise the need for standardised protocols that balance efficacy and tolerability.

Emerging antimicrobials such as clofazimine and tigecycline have shown potent *in vitro* activity against *M. abscessus*,⁴ and their incorporation into multidrug regimens has yielded promising early clinical results.^{17,30} However, in most cases, their use was at the discretion of the treating physician and, therefore, direct causal conclusions regarding their individual efficacy could not be established. Future randomised controlled trials are warranted to determine the clinical utility of clofazimine and tigecycline as potential first-line agents, especially in patients infected with macrolide-resistant strains of *M. abscessus*. Surgical resection remains an important adjunctive therapy, particularly in cases of localised or drug-resistant disease. Several studies reported SCC rates exceeding 40% in patients undergoing surgical intervention. For instance, Kang et al. reported high SCC rates with a low incidence of postoperative complications, suggesting that surgical management should be considered in appropriately selected patients, especially those with multidrug-resistant or treatment-refractory disease.⁹

Treatment outcomes also vary significantly between MABC subspecies. Patients with *M. massiliense* infection consistently demonstrated better clinical, microbiological and radiological responses compared to those with *M. abscessus*.^{11,16,27} This is largely attributed to the dysfunctional *erm*(41) gene in *M. massiliense*, which results in macrolide susceptibility,²⁶ thereby improving the efficacy of macrolide-based regimens. Whole-genome sequencing (WGS) and genotypic analysis may therefore play a critical role in tailoring therapy, enabling more accurate predictions of antimicrobial response. Notably, Park et al. reported that clarithromycin susceptibility alone accounted for approximately 40% of the variation in treatment outcomes, highlighting the interplay of bacterial genetics and host-specific factors in determining treatment success.¹⁶

The interpretation of treatment outcomes remains challenging due to a lack of standardised definitions among the studies. Many studies relied on subjective criteria, such as symptom relief and radiological improvement, which are prone to bias and inter-observer variability. The NTM-NET group proposed outcome definitions such as SCC, microbiological cure, clinical cure, treatment failure, relapse, reinfection and treatment discontinuation, which are important for standardisation of treatment outcome reporting in future studies.¹⁰ While SCC is often used as a more objective outcome, recent studies have emphasised that patient-reported outcomes, quality of life and long-term survival may be more meaningful endpoints for evaluating therapy in MABC lung disease.⁴³ Furthermore, this review also revealed important methodological limitations in the existing literature. Of the 28 included studies, only 8 enrolled more than 100 participants;^{11,16,22,23,25,29,30,33} the remaining 20

studies were largely single-centre and retrospective, with limited sample sizes, thereby constraining the generalisability of findings. Additionally, most studies did not evaluate the pharmacokinetic or pharmacodynamic relationships of antibiotics, nor did they assess non-pharmacologic interventions, such as airway clearance techniques or nutritional status, which may also influence outcomes.

In addition to currently available treatment options, repurposing anti-tubercular drugs presents a promising strategy for developing new chemotherapeutic alternatives against *M. abscessus* complex (MABC) infections.⁴⁴ Several potential molecular targets have been identified, including RNA polymerase, aspartate decarboxylase PanD, enzymes involved in peptidoglycan synthesis, mycolic acid transport and the F-ATP synthase, a critical component of oxidative phosphorylation. Notably, rationally designed rifabutin analogs have demonstrated 50- to 100-fold increased potency against *M. abscessus* by targeting RNA polymerase.⁴⁵ Additionally, a first-in-class inhibitor of PanD has recently been identified, showing promising activity. A combination therapy involving the oral β -lactam tebipenem, which targets L,D-transpeptidases (LdtMab1 and LdtMab2) and D,D-transpeptidases (PonA1, PonA2 and PbpA), with the β -lactamase inhibitor avibactam, has shown low micromolar, bactericidal activity against *M. abscessus*, and may be co-administered with existing anti-MABC agents to enhance efficacy.⁴⁶

Further breakthroughs have emerged with validation of novel targets such as MmpL3, a transporter of mycolic acids across the plasma membrane,^{47,48} and InhA, the enoyl-ACP reductase involved in fatty acid synthesis.⁴⁹ While most current drugs target biomass-generating pathways, increasing attention has turned toward bioenergetic pathways, particularly the F-ATP synthase, which remains essential in both replicating and non-replicating bacterial states—the latter being highly drug-tolerant. Recent work has identified several F-ATP synthase inhibitors with promising *in vitro* and *in vivo* activity. These include repurposed compounds such as squaramide SQ31f,⁵⁰ the diarylquinoline bedaquiline,⁵¹ and newer analogues TBAJ-876 and TBAJ-5307.^{52,53} Novel inhibitors such as GaMF1 and Ep1MabF1 have also been developed, offering additional scaffolds for the discovery of curative regimens.^{54,55}

The persistently poor treatment outcomes in *M. abscessus* pulmonary disease emphasise the urgent need for stronger antimicrobials, improved drug delivery systems and resistance-reversing strategies. The intrinsic resistance mechanisms of *M. abscessus*, particularly its mycolic acid-rich, impermeable cell wall, continue to pose major barriers to drug efficacy.⁵⁶ Nonetheless, advances in whole-cell phenotypic screening and synergistic drug combination assays

have begun to yield new candidate molecules with potent anti-MABC activity.⁵⁶⁻⁵⁸ Improved delivery systems also hold potential. Novel pulmonary drug delivery technologies, including nanoparticle-based inhalation therapies and dry-powder formulations, may allow for higher local drug concentrations while minimising systemic toxicity.⁵⁹ Currently, treatment success relies on eradicating of *M. abscessus*, which often fails and does not reflect patients' functional status. Coping with daily activities may be more important to patients than the eradication of *M. abscessus*. Thus, functional status should be given importance equally as radiological and microbiological outcomes for indicating treatment response in NTM disease. It indicates the extent of clinical symptoms experienced in the daily activities of patients. This functional approach explains real life suffering rather than just pathological and radiological symptoms.⁶⁰

Finally, the development of relevant experimental models is critical to support the preclinical evaluation of new therapies. These models must accurately replicate host-pathogen interactions and reflect the complex immunopathology of *M. abscessus* infections.

CONCLUSION

This review highlights the complexity of treating *M. abscessus* pulmonary disease, largely due to intrinsic drug resistance, variable treatment responses, and frequent adverse effects. Outcomes are influenced not only by antibiotic regimens but also by bacterial subspecies, genotype and host-related factors. Surgical resection remains a valuable adjunct, particularly in localised or refractory cases, and is associated with higher sputum culture conversion (SCC) rates. Macrolide-IV amikacin contained regimens may potentially increase SCC rate and hence, is a preferred treatment option, particularly when *M. abscessus* is susceptible to these drugs. Optimising treatment will require integration of genotypic profiling, novel therapeutic agents and advanced drug delivery systems, supported by robust clinical and microbiological endpoints to enable more personalised and effective management strategies.

Supplementary material

Table S1. Search strategy with Boolean operators.

Ethics statement

Ethical approval was not required for this study as it used publicly available, anonymised data.

Declaration

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

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Advancing cardiology pharmacy practice: A position paper on physician-led, pharmacist-enabled model for sustainable cardiovascular care

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ABSTRACT

Introduction: Cardiovascular disease remains a leading cause of morbidity and mortality in Singapore, with rising demand for longitudinal cardiovascular care driven by ageing and metabolic risk factors. Cardiology pharmacists support medication optimisation, transitions of care and patient education across hospital, ambulatory and community settings. However, limited specialist accreditation pathways, uneven service distribution and emerging digital requirements constrain scalable delivery to match national needs.

Methods: This position paper was developed by the Pharmaceutical Society of Singapore Cardiology Pharmacy Working Group. A multidisciplinary consensus approach was adopted, guided by RIGHT and AGREE II principles to ensure transparency, applicability and editorial independence. Evidence synthesis drew from published literature, national epidemiology and institutional experience, contextualised within governance under the Healthcare Services Act and Collaborative Prescribing Agreement.

Results: Cardiology pharmacists are essential to medication safety, adherence support and protocol-

guided dose optimisation under physician oversight. Key gaps include delayed post-discharge follow-up, fragmented hospital-primary care alignment, telehealth implementation challenges and a limited pipeline of accredited specialists, restricting capacity to achieve guideline-directed therapy targets and sustained continuity of care.

Conclusion: Five priorities were endorsed: strengthening specialist workforce capability; enhancing early post-discharge reviews; integrating pharmacists across care settings; leveraging digital-enabled care; and expanding medication-focused roles in prevention, atrial fibrillation, palliative heart failure and precision medicine. Cardiology pharmacists are critical contributors to a safe, coordinated and future-ready cardiovascular care ecosystem. A physician-led, pharmacist-enabled model supports national goals under Healthier SG.

Keywords: cardiology pharmacist, digital health, Healthier SG, multidisciplinary cardiovascular care, telehealth, transitions of care, workforce development

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CLINICAL IMPACT

What is New

- First multidisciplinary consensus reflecting on pharmacists' role with the current governance under the Healthcare Services Act and Collaborative Practice Agreement.
- Clearly defines cardiology pharmacists' remit within physician-led practice.
- Identifies workforce, service distribution and digital readiness gaps.
- Proposes a scalable roadmap aligned with Healthier SG and value-based models.

Clinical Implications

- Enhances continuity and optimisation of pharmacotherapy across care transitions.
- Supports coordinated medication governance between hospital and primary care.
- Applies digital tools to expand pharmacist-enabled care safely and sustainably.
- Reinforces cardiology specialist pharmacists' capacity without compromising statutory boundaries.

INTRODUCTION

Cardiovascular disease (CVD) remains one of Singapore's leading causes of morbidity and mortality, accounting for a growing proportion of hospital admissions and chronic disease burden^{1,2} This trend reflects an ageing population and an increasing prevalence of metabolic risk factors such as diabetes, hypertension and dyslipidaemia.³ As the nation advances towards Healthier SG, a national strategy that prioritises preventive, community-based and longitudinal care, the management of cardiovascular conditions must evolve in tandem.⁴

Within this landscape, cardiology pharmacists play a pivotal role in optimising pharmacotherapy, supporting adherence and ensuring medication safety across the continuum of care. Their contributions are particularly evident in heart failure (HF) titration clinics, post-acute myocardial infarction (AMI) follow-up,^{5,6} anticoagulation management and lipid optimisation services. These services exemplify collaborative, physician-led but pharmacist-enabled practice—augmenting specialist capacity without substituting medical authority. However, despite their integral presence in multidisciplinary teams, most pharmacists practising cardiology today have developed their expertise through institutional training and on-the-job experience rather than through structured, accredited

pathways. This results in variability in practice depth and limited scalability of advanced services, especially as cardiovascular care becomes more complex.

The runway to specialisation for pharmacists under the Singapore Pharmacy Council and national residency frameworks remains long and resource-intensive, with only a handful of formally accredited cardiology specialist pharmacists across Singapore's public healthcare system.^{7,8} Many capable practitioners operate at advanced levels of clinical service but lack a clearly recognised pathway for progression, creating challenges in sustainability recognition and workforce development.

This position paper arises from that need. It seeks to articulate the role, scope and governance of cardiology pharmacists in Singapore's evolving healthcare system—not as independent providers, but as clinically embedded partners who extend cardiologists' reach and strengthen medication-related outcomes. The paper proposes a physician-led, pharmacist-enabled model of care, aligned with existing regulatory frameworks such as the Collaborative Prescribing Agreement (CPA), Healthcare Services Act (HCSA) and national competency standards for advanced practice pharmacists.

The intention is not to redefine medical authority, but to ensure that medication optimisation, adherence support and pharmacovigilance receive the depth of attention they deserve throughout the cardiac patient's journey (Table 1). Through this partnership model, pharmacists contribute to safer, more efficient and more patient-centred cardiovascular care—a necessity as Singapore faces an escalating burden of CVD² and increasing demands on its specialist workforce.⁸

Table 1. What this position paper is not proposing.

This position paper does not advocate for autonomous or independent clinical practice by pharmacists in cardiology. Rather, it supports a physician-led, pharmacist-enabled model that reinforces collaboration, safety and accountability within Singapore's regulatory frameworks.

Specifically, this statement does not propose that pharmacists:

- (1) Independently diagnose, manage or determine treatment plans for acute coronary syndromes, heart failure or arrhythmias, or other cardiovascular problems.
- (2) Order or interpret diagnostic tests beyond privileges defined in the Collaborative Prescribing Agreement or institutional policies, or operate outside the governance of the Healthcare Services Act.
- (3) Conduct standalone or parallel clinics that replace cardiologist-led consultations or compete with specialist services.

Pharmacists practise within defined collaborative agreements approved by supervising cardiologists, focusing on medication optimisation, adherence support and pharmacovigilance. This ensures that care remains integrated, team-based and patient-centred, augmenting, not replacing, physician-led cardiovascular care.

METHODS

Consensus development

Governance and frameworks

This position paper was developed under the Pharmaceutical Society of Singapore to describe the scope, practice standards and strategic directions of cardiology pharmacy in Singapore. The development process was guided by principles from the Reporting Items for Practice Guidelines in Healthcare (RIGHT) Statement and Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument to ensure transparency, inclusivity and editorial independence, though not all domains were applied in full.⁹ The process was contextualised within Singapore's HCSA and CPA frameworks, which govern multidisciplinary prescribing and advanced practice models.¹⁰

Working group composition

A national expert panel of 22 members was convened in January 2024 under the auspices of the Pharmaceutical Society of Singapore. Members were invited as independent subject matter experts, representing cardiology pharmacists, cardiologists from recognised specialty chapters and senior nursing and academic leaders across major restructured hospitals and professional bodies in Singapore.

The working group was divided into 3 disease-focused teams: acute coronary syndrome (ACS), HF and arrhythmias (atrial fibrillation [AF] and related conditions)—each comprised cardiology-trained pharmacists with a physician and nursing collaborator. Each subgroup examined current practice, emerging trends and service gaps within its assigned domain, drawing upon published Singapore data to propose forward-looking recommendations. A central coordination team, comprising the chair, methods lead and secretariat, ensured alignment across the 3 groups and consistency in the framing of recommendations.

Scope and approach

Each subgroup reviewed its assigned disease area following a common framework encompassing:

- (1) Disease burden and prevalence within Singapore and comparable regions;^{11,12}
- (2) Current models of care and pharmacist roles across hospital, ambulatory and community settings;
- (3) Challenges and service gaps identified from literature and institutional experience; and
- (4) Future-state aspirations for workforce, technology and service integration.

Information sources included peer-reviewed articles, Singapore's Ministry of Health (MOH) and Health

Promotion Board publications and government statistics and institutional data. Searches were conducted between February and April 2024, using databases such as PubMed and MOH repositories with keywords including: cardiology pharmacist, HF, myocardial infarction, AF, Singapore, collaborative prescribing and telehealth.

Evidence was appraised for relevance and applicability in Singapore rather than through formal Grading of Recommendations Assessment, Development and Evaluation system scoring, as this work represents a consensus position statement rather than a clinical practice guideline. Nonetheless, development and reporting were informed by established quality frameworks: RIGHT principles supported clarity of purpose, rationale and evidence presentation, while AGREE II domains guided stakeholder involvement, structured deliberation and assurance of editorial independence.¹³ Feasibility within CPA governance structures and health-service implementation considerations in Singapore were prioritised to ensure the recommendations are deliverable within current regulatory and care models.

Development

Draft statements were generated independently by each subgroup and synthesised by the methods lead. A 3-stage consensus process was then conducted:

- (1) Initial drafting: Subgroups prepared narrative summaries and draft recommendations supported by evidence tables and key references.
- (2) Panel review: Statements were circulated to all 22 members for iterative feedback. Divergent points were discussed during virtual meetings and via email exchanges to harmonise scope and terminology.
- (3) Final reconciliation: The full panel met in July 2024 to review and endorse the consolidated draft. Consensus was achieved through structured discussion and majority agreement, ensuring all statements reflected collective and multidisciplinary endorsement.

Although a formal Delphi process was not undertaken, the methodology incorporated its core elements of iterative feedback, anonymity of opinion during drafting and transparent documentation of changes.^{14,15}

Conflict of interest and editorial independence

The workgroup comprised independent experts in cardiology practice who were invited to contribute their professional perspectives. Members had no prior affiliations beyond their clinical scope and received no honoraria or financial incentives. The work received no external or industry funding, and editorial

independence was maintained by the writing group and the Pharmaceutical Society of Singapore secretariat, consistent with RIGHT item 19.

Consensus context and applicability

Implementation considerations were guided by prevailing regulatory and institutional frameworks at the time of drafting. Each recommendation was developed with reference to publicly available guidance from MOH and relevant professional standards to ensure consistency with existing governance under CPA and HCSA. While no formal implementation audit was conducted, feasibility and alignment with clinical practice were discussed by the working group to ensure practical applicability. The statements presented herein reflect consensus agreement at the time of publication. Future updates may be considered should substantive regulatory or policy changes arise.

Cardiology pharmacy practice in Singapore

Cardiology pharmacy practice in Singapore has evolved within a structured national framework that recognises pharmacists as integral partners in multidisciplinary cardiovascular care. Within the physician-led, pharmacist-enabled model, pharmacists extend specialist capacity by ensuring that pharmacotherapy decisions are evidence-based, safe and contextualised to the patient's comorbidities, care goals and care setting. Their role complements that of physicians, nurses and allied health professionals, reinforcing medication governance, continuity of care and therapeutic precision within institutional and national frameworks.¹⁶

Evolution of cardiology pharmacy practice in Singapore

To meet the growing demand for advanced cardiovascular expertise, MOH later established the National Pharmacy Residency Programme, including Residency Year 2 Programme (R2) in Cardiology Pharmacy, launched in 2016. The programme employs a portfolio-based exit assessment and provides structured, longitudinal training across acute, ambulatory and community settings. It also cultivates competencies in clinical leadership, research and education—reflecting the evolution of pharmacy from a product-oriented to a patient- and outcomes-oriented discipline.

Cardiology pharmacy practice now operates through 2 progressive tiers. One tier comprises cardiology-trained pharmacists. They are practitioners with advanced, disease-specific knowledge who practice within CPA frameworks under physician oversight. They co-manage conditions such as acute and chronic coronary syndromes and HF, focusing on drug optimisation, adherence and safe transitions of care.

The other tier comprises cardiology specialist pharmacists who operate at a higher tier of clinical and system leadership. They manage complex or overlapping cardiovascular conditions such as pulmonary hypertension, cardio-oncology or advanced HF requiring device or transplant support. Beyond clinical practice, they lead service design, formulary governance, clinical research, education and often represent pharmacy in interprofessional working groups that shape national guidelines, policy frameworks and quality metrics.

Together, these tiers form a continuum of practice that supports Singapore's move towards Healthier SG, a national strategy centred on preventive, team-based and longitudinal care. As cardiovascular care grows more complex, specialist pharmacists are increasingly required to manage multimorbidity, device-based therapies and precision medicine considerations under physician direction. Conditions such as HF with preserved ejection fraction, AF with renal impairment and polypharmacy in older adults demand advanced pharmacotherapy judgement, rapid dose adjustments and close monitoring that extend beyond generalist skills. Cardiology specialist pharmacists therefore function as force multipliers to cardiologists—supporting safe expansion of services into ambulatory and primary care settings while maintaining governance and clinical accountability. By embedding pharmacists within multidisciplinary pathways, the model ensures that therapy decisions made in tertiary hospitals are sustained through follow-up in ambulatory and community settings, reducing fragmentation and enhancing care consistency.¹⁷

Clinical roles across the care continuum

Cardiology pharmacists are strategically embedded across the hospital, ambulatory and community continuum, providing expertise that ensures medication safety, treatment optimisation and continuity between care settings.¹⁸

Hospital and critical care services

In tertiary and teaching hospitals, cardiology pharmacists provide co-managed care for patients admitted with ACS, HF, AF or complex cardiovascular comorbidities.¹⁹ They participate in multidisciplinary rounds, perform medication reconciliation, evaluate drug-disease and drug-drug interactions and adjust dosing for renal or hepatic impairment. Within CPA frameworks, they implement protocol-guided titration of evidence-based therapies such as renin-angiotensin-aldosterone system inhibitors, beta-blockers, sodium-glucose cotransporter-2 inhibitors and diuretics once indications and targets are established by cardiologists. Pharmacist involvement in ACS and HF co-

management has been associated with reduced medication errors, improved optimisation of guideline-directed medical therapy and lower rates of adverse event-related readmissions.^{5,20}

In high-dependency and coronary care units, pharmacists contribute to the management of critically ill patients requiring vasoactive infusions, mechanical circulatory support or complex anticoagulation. They provide dosing and monitoring recommendations for agents used in extracorporeal membrane oxygenation or continuous renal replacement therapy, where pharmacokinetic profiles are altered. These contributions are vital in maintaining therapeutic precision and reducing iatrogenic risk.

Pharmacists also play a stewardship role in anticoagulation management programmes, reviewing the appropriateness of warfarin and direct oral anticoagulants, assessing bleeding risk and coordinating follow-up with cardiologists or respective medical subspecialties.²¹ Their structured documentation within CPA systems enhances accountability, auditability and cross-disciplinary communication.

Ambulatory and specialist clinics

In outpatient settings, cardiology pharmacists provide early post-discharge reviews (typically within 2–4 weeks) to identify medication-related problems such as hypotension, renal impairment or non-adherence (see Appendix S1 for examples of ambulatory pharmacist-led cardiology clinics in Singapore). Early pharmacist-supported reviews within 2–4 weeks post-discharge have demonstrated faster achievement of target therapy doses and improved adherence compared with standard care. They conduct structured medication reviews, reinforce education on side-effect recognition and coordinate investigations under physician direction.^{22,23}

They are also integral to disease-specific clinics, such as HF optimisation, lipid management and anticoagulation safety. Within these programmes, pharmacists titrate therapies toward guideline-directed medical therapy (GDMT) targets, track patient-reported outcomes and document progress through shared care plans. These services have been shown to enhance adherence, improve biomarker control and reduce unplanned readmissions.²⁴ As for niche specialised areas such as cardio-oncology, pharmacist medication optimisation clinic had shown to similarly strengthen therapy safety and continuity for patients receiving cardiotoxic cancer treatments.²⁵

Community and telehealth integration

Aligned with Healthier SG, pharmacists increasingly participate in transitional and community-based care, ensuring that medication plans initiated in hospitals are appropriately continued in the primary care

setting. They liaise with general practitioners and community pharmacists to ensure that dose adjustments reduce polypharmacy, and contraindications and monitoring intervals are clearly communicated.²⁶ Telehealth platforms and home-based monitoring technologies now allow cardiology pharmacists to review remote vital signs, wearable device data and medication adherence in real time, offering timely interventions and improving patient convenience. These innovations strengthen accessibility and continuity for patients with chronic cardiovascular disease, especially those with mobility or financial constraints.

Advanced pharmacotherapy and collaborative prescribing

Advanced cardiology pharmacy practice centres on therapeutic optimisation and collaborative prescribing. Pharmacists interpret clinical and laboratory data to guide medication adjustments that achieve therapeutic goals while maintaining safety within CPA-defined boundaries.

The Collaborative Prescribing Programme has formalised this model nationally, enabling credentialled pharmacists to prescribe and monitor medications for chronic diseases, including cardiovascular conditions within the CPA. Cardiology specialist pharmacists often act as pharmacy service leads—designing protocols, ensuring adherence to evidence-based standards, mentoring newly credentialled colleagues and serving as institutional champions for medication governance.

This tiered and accountable system ensures scalability while maintaining safety and regulatory integrity. It exemplifies how pharmacist involvement can extend specialist reach without encroaching upon physician oversight, aligning professional accountability with national healthcare transformation goals.²⁷

Education, leadership and research

Cardiology pharmacists are not only clinicians but also educators, researchers and leaders driving quality and innovation in cardiovascular care.

They:

- Educate and mentor pharmacy residents, junior doctors and nurses on cardiovascular pharmacotherapy, ensuring standardisation and competence in complex drug regimens.
- Teach in national and postgraduate programmes, integrating evidence-based practice, patient safety and interprofessional learning.
- Lead quality-improvement and formulary initiatives, optimising medication use, cost-efficiency and adherence to national guidelines.

- Conduct and support research in clinical pharmacy, service design and health outcomes—such as medication adherence, readmission rates and patient satisfaction.

At the specialist level, pharmacists engage in health services and implementation research, contributing to the evidence base for designing models of care. Many serve on policy or professional committees, influencing the development of prescribing frameworks, credentialing standards and training curricula. This scholarly and leadership dimension reinforces the sustainability of the cardiology pharmacy workforce and promotes continuous professional growth.²⁸

Integration, governance and future directions

Cardiology pharmacy practice today represents a mature, integrated model aligned with Singapore's national priorities for chronic disease management. It links acute stabilisation, ambulatory titration and community prevention through a unified framework of clinical governance and collaborative accountability.

The next phase of development will focus on:

- Expanding telehealth and digital prescribing infrastructure to support hybrid models of care.
- Building workforce resilience through continuous education, mentorship and interprofessional collaboration.

As cardiovascular disease continues to be a leading cause of morbidity and mortality in Singapore, cardiology pharmacists are poised to play an increasingly important role in sustaining safe, effective and patient-centred care.

Identifiable care gaps

To clarify the evolving role of cardiology pharmacists in Singapore, this section presents 2 categories of gaps identified by the working group: (A) gaps in cardiovascular care that pharmacists are well-positioned to address and (B) limitations in pharmacy workforce, training and infrastructure that must be overcome to support that role (see Appendix S2A–3B for projections of Singapore's cardiovascular disease burden and future service demand).

(A) Gaps in cardiovascular care that pharmacists can address

1. Insufficient access to early post-discharge follow-up care

Reliable access to early post-discharge review is essential to safeguarding the high-risk transition period from hospital to home. When timely follow-up is not available, therapy optimisation and close monitoring may be delayed, reducing opportunities to detect

and address issues such as intolerance, hypotension, renal impairment or non-adherence. This gap occurs precisely when patients are most clinically vulnerable and at greatest risk of preventable deterioration and readmission. Enhancing early ambulatory access is therefore a critical, system-level lever to sustain guideline-directed therapy momentum, reinforce self-management and ultimately improve long-term cardiovascular outcomes.^{29,30}

2. Need for stronger hospital-community alignment

The lack of coordinated care between hospitals and primary care facilities, such as polyclinics, leads to duplicated efforts, patient confusion and inefficient resource use. This is particularly problematic in medication adjustments and managing cardiovascular risk factors, where disjointed communication can result in conflicting treatment plans and delayed care. Improved coordination and communication between healthcare providers are essential to streamline patient care, reduce redundancies and optimise disease management across settings.

3. Challenges in telehealth implementation

Limited administrative and technical support hinders the effective implementation of telehealth services. This lack of infrastructure often leads to inefficient teleconsultations, disrupting continuity of care and patient management. The absence of seamless integration between telehealth platforms and existing healthcare systems further complicates the process, leading to delays in medication management, challenges in patient monitoring and difficulties in conducting comprehensive assessments. Inadequate training in telehealth technology exacerbates these issues, reducing the effectiveness of remote care and intervention strategies.³¹

4. Emerging opportunities for specialist pharmacist involvement

Cardiology pharmacist ambulatory care services currently focus mainly on post-ACS and HF management. However, pharmacists are increasingly needed in emerging domains such as:

- **AF:** Management of AF in primary care faces significant challenges, including undiagnosed AF, inadequate anticoagulation and lack of expertise in interpreting electrocardiograms. Enhanced pharmacist involvement could improve screening, anticoagulant use and patient education, reducing the risk of complications like stroke.
- **HF and palliative care:** Palliative care for end-stage HF remains underdeveloped. Pharmacists can play a crucial role in symptom management

and deprescribing. Integrating palliative care with HF management can significantly enhance patient outcomes.³²

- **Multimorbid patients:** These patients present with complex pharmacotherapy needs spanning coronary syndromes, HF, AF, renal impairment and frailty. Cardiology-trained pharmacists can manage these regimens within multidisciplinary teams.
- **Pharmacogenomics:** As personalised medicine becomes more prevalent, pharmacists are well-positioned to provide guidance on genetic testing, dose optimisation and patient counselling.

(B) Gaps in pharmacy workforce, training and practice capacity

1. Workforce and training capacity requires review and scaling up

A shortage of cardiology-trained pharmacists across care settings hampers optimal medication management, especially in complex cases. Limited R2 Cardiology Residency positions are offered in Singapore each year and as of 2024. Nationally, uptake of the R2 Cardiology Residency positions has been limited. As of 2024, across Singapore, there are about 60 pharmacists who provide cardiology-related services but only a subset are cardiology specialist pharmacists. This constrained training pipeline limits the ability to scale services.

2. Uneven distribution of services and manpower

Although cardiology pharmacy services exist in 14 hospitals and polyclinics, projections suggest that 20–30 service points will be needed nationally to match population health needs. The current manpower does not adequately cover community and primary care sectors, where cardiovascular burden is growing.

3. Limited role recognition and accreditation pathways

Many cardiology-trained pharmacists provide advanced clinical services without formal recognition or specialist accreditation. This lack of structured career pathways, credentialing support and institutional incentives impedes professional growth; service development leading to service innovation is constrained; and long-term career sustainability for cardiology pharmacists remains uncertain.

Bridging to recommendations

Addressing these systemic and workforce gaps will require coordinated action across professional, institutional and policy levels. Expanding specialist training and recognition, strengthening care

coordination and embedding pharmacists in digital and community health ecosystems are essential steps to take. The following section outlines the recommendations and strategic priorities proposed by the expert panel to advance cardiology pharmacy practice in Singapore.

RESULTS

Recommendations and strategic priorities

Addressing the identified gaps in workforce capacity, service structure and governance requires coordinated national action. The following recommendations were developed through expert consensus and endorsed across multiple institutions. They outline strategic priorities for advancing cardiology pharmacy practice within a physician-led, pharmacist-enabled framework that is anchored in patient safety, digital transformation and interprofessional collaboration.

1. Strengthening workforce capacity and specialist training

A sustainable cardiology pharmacy workforce is essential for delivering quality cardiovascular care and ensuring service continuity. Although the number of cardiology-trained pharmacists has increased, the pool of formally accredited specialists remains small. Expanding and retaining talent are required to support advanced practice development.

Strategic priorities:

- Build a cardiology pharmacist community of practice with strong mentorship.
- Raise awareness among junior pharmacists and administrators of resourcing needs.
- Develop accredited training programmes (e.g. workshops, courses, clinical attachments) to standardise cardiovascular education.
- Expand advanced cardiology training via early-career pathways and continuing professional development.
- Fast-track specialist accreditation for in-service pharmacists.
- Secure sustainable manpower by linking reimbursement and protected headcounts to clear key performance indicators.
- Inclusion of cardiology pharmacists in value-based care models that are being piloted under the national Healthier SG framework.
- Exploring integration into bundled payment systems for cardiovascular episodes of care (e.g. post-AMI bundles), where pharmacist interventions reduce readmissions.

2. Enhancing early post-discharge reviews and transitions of care

The post-discharge period remains a vulnerable transition point associated with high rates of medication discrepancies, non-adherence and avoidable readmissions. Embedding pharmacists into co-managed reviews with cardiologists and nurses can ensure timely titration and safer continuity of care.

Strategic priorities:

- Launch co-managed, early post-discharge clinics with cardiologists and advanced practice nurses.
- Implement protocol-guided titration and monitoring of cardiovascular therapies to pre-defined targets under CPA oversight, with explicit escalation criteria for abnormal findings.
- Integrate pharmacists into hospital-to-home programmes and community nursing teams, ensuring consistent medication reconciliation and patient education across care settings.
- Monitor impact through outcome indicators such as adherence rates, GDMT target achievement and 30-day readmission reduction.

3. Integrating pharmacist support across the care continuum

Cardiology pharmacists are trained to provide comprehensive care across critical, inpatient, outpatient and community settings. Their integration into multidisciplinary teams improves medication optimisation, reduces inappropriate polypharmacy and enhances clinical outcomes, while easing the burden on cardiologist clinics. New care models, such as the Acute Myocardial Infarction: Allied Health-Oriented, Patient-Centred Technology-Enabled (AMI-HOPE) programme,³³ launched in October 2022, exemplify this shift. This initiative leverages pharmacists, telemonitoring and teleconsultations to improve post-AMI outcomes and reduce costs. Patients share vital signs with pharmacists for timely intervention soon after discharge, with stable cases transitioning to polyclinic follow-up.

Strategic priorities:

- Embed pharmacists in multidisciplinary teams managing disease-specific programmes (e.g. HF, lipid management and anticoagulation) under direct cardiology supervision.
- Identify and engage primary care physician champions to advocate for pharmacist cardiology services.
- Establish pharmacist HF clinics in primary care, modelled after the AMI-HOPE framework.

- Publish and disseminate guidelines and escalation protocols for primary care pharmacists managing cardiovascular diseases.
- Integrate pharmacists' clinical input in co-developing shared-care protocols with primary care providers to define referral pathways, communication standards and follow-up intervals.

4. Leveraging digital health, telemonitoring and artificial intelligence (AI)

Digital transformation provides a scalable platform for optimising pharmacotherapy and patient engagement. Telehealth, wearables and data-driven tools can extend pharmacist-enabled services while maintaining oversight through defined clinical governance.

Strategic priorities:

- Incorporate wearable-derived data (e.g. blood pressure, heart rate, body weight) into shared dashboards for proactive dose titration and escalation to supervising physicians.
- Pilot AI-assisted triage and adherence tools that provide reminders, safety alerts and predictive insights under established data-governance frameworks.
- Strengthen administrative and technical support for seamless virtual care.

5. Expanding roles in prevention, AF, palliative HF and precision medicine

As Singapore's population ages, cardiology pharmacists must evolve beyond acute management to address prevention, chronic care and personalised medicine. The National Population Health Survey 2020³⁴ highlights a significant burden from newly diagnosed hypertension, hyperlipidaemia and diabetes, necessitating a systemic approach to preventive cardiology. Pharmacists are well-positioned to strengthen this aspect of care, leveraging their expertise in pharmacogenomics, deprescribing and patient counselling to deliver holistic and person-centred support.

Strategic priorities:

- Expand pharmacist integration into preventive cardiology by embedding pharmacists within programmes to support risk-factor optimisation, lifestyle interventions and medication adherence.
- Enhance AF detection and management by implementing opportunistic community screening and integrating pharmacist into anticoagulation and rate/rhythm control support within primary care under cardiologist oversight.

- Incorporate pharmacist roles in HF care across the disease trajectory, including optimisation of guideline-directed therapy and palliative support, such as medication rationalisation and deprescribing with specialist involvement.
- Enable pharmacogenomics-informed cardiovascular therapy through structured pathways for genotype-guided optimisation medicines (e.g. clopidogrel, statins), supported by validated laboratory and governance frameworks.
- Align service development with the specialist training pipeline so that emerging care priorities inform R2 curriculum design, ensuring that competencies in multimorbidity management, cardiology therapeutics and advanced communication continue to evolve with system needs.

These expanded roles will ensure cardiology pharmacists remain essential contributors to Singapore's shift towards preventive, personalised and sustainable cardiovascular care. While Singapore's cardiovascular care is already anchored in established essential service domains, Table 2 maps these existing areas and critically outlines the emerging service roles in which pharmacists can add value under physician-led governance, with suggested indicators to stage adoption, assure safety and demonstrate impact.

Collectively, these recommendations provide a pragmatic framework to strengthen governance, training and service innovation within Singapore's cardiovascular care ecosystem. They emphasise that the cardiology pharmacist's role is not autonomous but integrative—embedded within multidisciplinary, physician-led teams that prioritise safety, continuity and evidence-based optimisation of therapy. As the profession evolves toward digitally enabled and outcomes-driven practice, these strategies offer a foundation for sustainable implementation and measurable impact at both institutional and national levels.

CONCLUSION

These recommendations outline a pragmatic and forward-looking roadmap for advancing cardiology pharmacy services in Singapore. By strengthening workforce capability, embedding pharmacists within multidisciplinary physician-led models and embracing digital innovation, the profession can play a transformative role in achieving the goals of Healthier SG—a healthcare system that is safe, coordinated and future-ready.

Supplementary materials

Appendix S1. Emerging cardiology pharmacist services in Singapore.

Appendix S2A–B. Projection of the cardiovascular disease burden in Singapore.

Ethics statement

Not applicable as no study participants were involved.

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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Table 2. Essential and emerging cardiology pharmacy services.

Essential cardiology services	Emerging cardiology pharmacist services	Suggested/possible KPIs
Cardiovascular risk reduction , e.g. secondary prevention of cardiovascular disease through the management of diabetes mellitus, hyperlipidaemia, hypertension.	Management of the “3 highs” , i.e. diabetes mellitus, hyperlipidaemia and hypertension along with cardiometabolic syndromes (e.g. obesity) in the primary prevention of cerebro- and cardio-vascular events and renal complications. Initiation of nicotine-replacement therapy and the management of nicotine withdrawal.	- Achieve LDL-C, blood pressure and HbA1c goals within 6 months ($\geq 70\%$) via titration clinic. - Medication adherence $\geq 80\%$ by refill. - Quit attempt initiation $\geq 75\%$ of identified smokers. 30-day verified quit rate $\geq 25\%$. - Provision of nicotine-replacement therapy counselling and therapy 100% where indicated.
Acute coronary syndrome (also known as unstable angina and myocardial infarction) and chronic coronary disease in patients with atherosclerotic disease (also known as ischaemic heart disease).	The multimorbid patient with ischaemic heart disease and other cardiovascular conditions, including but not limited to, heart failure, stroke, cardiac dysrhythmia, antithrombotics, renal impairment, frailty.	- Time to initiation of dual antiplatelet therapy per guidelines $\geq 95\%$. - Drug counselling prior to discharge for 100% percutaneous coronary intervention patients. - MRA and SGLT2i optimisation in post-acute coronary syndrome heart failure patients $\geq 70\%$.
Cardiac dysrhythmias , including but not limited to, rate and rhythm control in atrial fibrillation .	Primary prevention of stroke due to atrial fibrillation through community screening for atrial fibrillation and appropriate referral for diagnosis.	DOAC dose appropriateness (adjusted for age, weight, renal function): 100%.
Heart failure with reduced, mildly reduced, preserved and improved ejection fraction.	Optimisation of pharmacotherapy and patient education in the management of patients with cardiomyopathy and end-stage heart failure on palliative care.	- GDMT at target or maximally tolerated dose $\geq 75\%$. - Heart failure readmission reduction target: $\geq 15\%$ year on year. ≥ 1 structured heart failure education before discharge for 100%.
Antithrombotics , i.e. anticoagulants and antiplatelets in the treatment and/or prevention of thromboembolic diseases, stroke prevention, device-related (Impella [Abiomed, Danvers, MA, US] IABP) major adverse cardiovascular events and the supportive and reversal of haemorrhagic conditions.	Antithrombotic stewardship programmes including dosing validation, peri-procedural anticoagulation coordination and drug-drug interaction surveillance to reduce bleeding and thrombotic risks.	- High-risk bleed audit with reversal protocol adherence $\geq 95\%$. - Comprehensive drug-drug interactions/renal review 100% pre-administration.
Cardiac critical care , including but not limited to hypertensive urgency or emergency, cardiogenic shock, acute decompensated heart failure patients requiring vasopressors and/or inotropes.	Medication stewardship in critical care including vasopressor/inotrope optimisation, anticoagulation for mechanical support and sedation-analgesia standardisation in cardiac ICUs.	- Reconciliation within 24h of ICU admission $\geq 95\%$. - Avoidable drug-related events in CCU: zero target. - Sedation-analgesia optimisation audits $\geq 90\%$ adherence.
Pulmonary hypertension , including the monitoring and titration of disease using specific drugs such as epoprostenol, selexipag and PDE-5 inhibitors.	Long-term follow-up of pulmonary hypertension therapies and management of prostacyclin-associated complications.	- Dose-titration milestones achieved $\geq 85\%$. - Adverse event monitoring compliance $\geq 95\%$.
Cardiothoracic surgery-related conditions, including but not limited to, endocarditis, valvular heart diseases of the aortic and mitral valves, cardiothoracic bypass grafting.	Transitions-of-care support for valve-dependent patients including education on anticoagulation, infection prophylaxis and device-specific therapy.	- Peri-operative antimicrobial optimisation $\geq 90\%$. - Anticoagulation management plan pre-discharge 100%.
Devices used in cardiovascular patients , including but not limited to IABP, extracorporeal membrane oxygenation, left atrial appendage occluders, pacemakers and left-ventricular assisted devices.	Ambulatory device-care pathways, including long-term anticoagulation oversight, pump-failure risk medication adjustments and remote monitoring enablement.	- High-risk drug monitoring parameters documented $\geq 95\%$. - Anticoagulation protocol variance $\leq 5\%$.
Management of complex cardiovascular pharmacotherapy in high-risk or variable-response patients (e.g. statin intolerance, clopidogrel hyporesponse, warfarin dose variability).	Implement pharmacogenomics in the management of cardiovascular conditions of clinical impact.	- PGx-informed prescribing in eligible patients $\geq 80\%$. - Turnaround-time for PGx decisions ≤ 72 hours.

CCU: critical care unit; DOAC: direct oral anticoagulant; GDMT: guideline-directed medical therapy; Hb: haemoglobin; IABP: intra-aortic balloon pump; ICU: intensive care unit; KPI: key performance indicators; LDL-C: low-density lipoprotein cholesterol; MRA: mineralocorticoid receptor antagonist; PDE: phosphodiesterase; PGx: pharmacogenomics; SGLT2i: sodium-glucose cotransporter-2 inhibitors

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Augmented intelligence: An emerging paradigm for AI in healthcare

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ABSTRACT

Artificial intelligence (AI) is rapidly transforming healthcare, providing tools that support diagnosis, streamline workflows and enhance patient outcomes. However, its adoption has been uneven—hindered by ethical, legal and operational concerns. We propose that augmented intelligence (AugI)—AI designed to enhance, rather than replace, human decision-making—is the most practical and ethically sound model for integrating AI into healthcare. Key challenges in AI adoption include responsibility gaps, stakeholder resistance and outdated expectations about how clinicians should work. AugI provides a middle ground: preserving human oversight while leveraging the power of machine learning. As AI becomes an indispensable part of modern medicine, healthcare systems must shift toward a paradigm that embraces AI as a collaborative partner.

Keywords: artificial intelligence, augmented intelligence, clinical decision support, digital transformation, healthcare technology

INTRODUCTION

Artificial intelligence (AI) has become a transformative force across industries, including healthcare. In medicine, AI promises to assist in diagnosis, clinical documentation, triage and medical imaging interpretation, among other tasks.¹⁻³ Despite its potential, AI adoption in healthcare remains limited, largely due to ethical, legal and practical concerns.^{4,5} Various experts have suggested a more human-centred approach, often termed “augmented intelligence”, to address these challenges. This framework places human experts at the centre while leveraging machine learning for support, emphasising enhancement over replacement and aligning better with the realities of clinical accountability and patient care.²⁻⁶ To avoid acronym ambiguity, we will use “AugI” when referring to augmented intelligence and reserve “AI” for artificial intelligence.

The responsibility gap: Why full automation falls short

A defining limitation of current AI systems is their inability to assume responsibility for outcomes. In the use of many AI-enhanced diagnostic or decision-making models, industries still require a human expert to review the results and approve them. This reflects a broader issue across healthcare AI: even highly accurate systems cannot operate independently because of the unresolved question of legal liability.⁴

This is not unique to healthcare. The same concern is evident in the slow adoption of fully autonomous vehicles. Accidents involving self-driving cars raise challenging legal and ethical questions. Who is at fault—the car, software, manufacturer or human passenger? These questions are particularly amplified in healthcare, where a misdiagnosis can result in severe and catastrophic consequences. As Gerke et al. described, the black box nature of many AI systems further complicates accountability and trust.⁴

An AugI model sidesteps this issue by preserving human oversight while integrating AI to improve performance. In this model, clinicians retain responsibility while AI serves as a powerful analytical tool.⁵ Examples of real-world applications include AI triaging of chest x-rays before radiologist review, AI-assisted pathology to improve diagnostic consistency, and oncology algorithms that suggest treatment options with final clinician oversight. These examples demonstrate collaboration in action, enhancing the productivity of clinicians while engaging and involving them.

The human factor: Incentives, ownership and resistance

When one attempts to launch AI-driven projects in a clinical setting, institutional resistance may sometimes be palpable. Stakeholders may cite competing priorities and a lack of resources. Past negative experiences with information technology systems—particularly electronic medical records (EMR)—have

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heightened clinician skepticism, as early EMRs have also contributed to physician burnout due to the increased administrative burden involved. Potential risks posed by AI are also an added burden to implementation, though conversely, its potential to significantly reduce administrative work is an incentive for implementation.

Despite the potential to streamline workflows, the lack of clear and immediate incentives has created a barrier. This challenge reflects a recurring theme in the implementation of AI in healthcare: successful adoption requires more than technological feasibility—it demands alignment with user motivations.^{7,8} The question of “what is in it for me now” for the user, whether in terms of ownership, credit or incentives, can significantly impact support or adoption.

AI systems are not plug-and-play. They require customisation, training, validation and maintenance. In environments where clinicians are already overextended, introducing a novel tool—however promising—will likely fail unless it brings tangible benefits to those investing the time and effort to implement it. As described by Davenport and Kalakota, the success of AI projects hinges on user trust and perceived value at the individual level.³

Moreover, healthcare AI development is a team endeavour. Without a sense of ownership and creative investment, it is difficult to garner support. These social and organisational dynamics must be addressed upfront when introducing AI projects. Specific strategies for creative investment include clinician co-design workshops, innovation grants for pilot AI projects, and incorporating AI leadership into promotion pathways.

The new normal: AI is not a good-to-have but a must-have

In daily clinical life, the use of AI-enabled tools is becoming increasingly common. Generative AI, such as ChatGPT and other large language models, is utilised to aid in drafting clinical notes, patient instructions and academic writing.^{6,9} This review itself was initially drafted through dictation using speech-to-text voice recognition and later refined using AI.

AI has also significantly advanced fields, such as cancer detection by improving accuracy, speed and accessibility through applications in imaging and genomics, leading to better outcomes and reduced mortality rates. While clinical integration remains challenging due to issues such as data quality, regulatory concerns and model transparency, these barriers can be overcome through interdisciplinary collaboration using multimodal approaches, explainable AI and federated learning.¹⁰ An essential aspect

of deployment is the ongoing monitoring of AI performance, including the detection of model drift, bias and accuracy over time, to ensure continued safety and effectiveness. For example, AI-assisted mammography and colonoscopy have been associated with earlier cancer detection and improved survival outcomes in population studies (e.g. the National Cancer Institute’s Surveillance, Epidemiology, and End Result and World Health Organization reports).¹¹

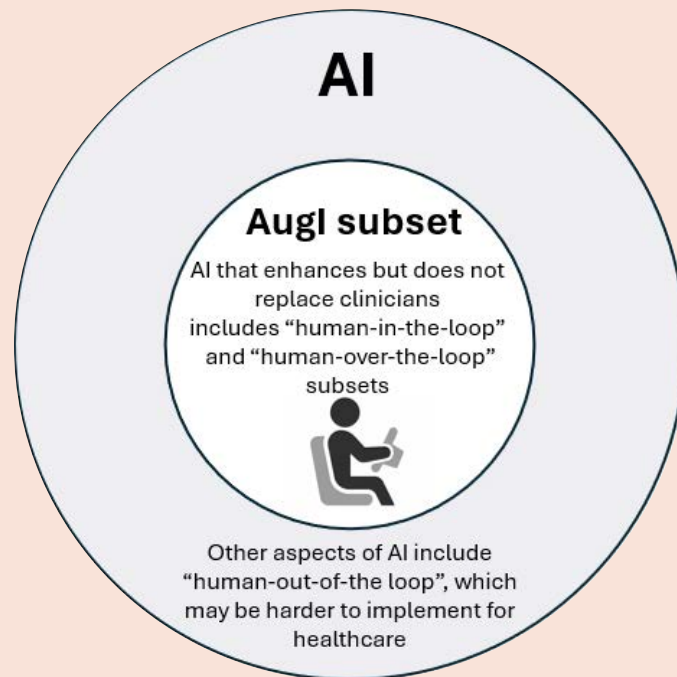
Still, the stigma surrounding AI use persists. In outdated expectations of work, doctors are dissuaded from using AI, and students are discouraged from using AI tools to assist in writing their assignments or theses. While intended to preserve academic integrity, this approach overlooks a crucial shift: AI tools are becoming foundational to modern work. Rajkomar et al. argued that machine learning in medicine should not be viewed as a threat, but as a means to enhance clinician performance through data synthesis and decision support.⁷

We feel that an analogy to calculators is apt. Just as we expect financial professionals to use spreadsheets and engineers to use modelling software, the clinicians of tomorrow will need to be proficient in AI-assisted decision-making. If an accountant fails to use the appropriate accounting tools, they will be called into question. Similarly, a clinician of the future who fails to utilise the appropriate, approved and generally accepted AI tool could be held accountable for negligence.

Augl: A more trustworthy model

The term “artificial intelligence” evokes ideas of synthetic, potentially untrustworthy agents. In contrast, “augmented intelligence” suggests partnership, support and human-centred design. The American Medical Association has endorsed the use of this latter term to reflect AI’s appropriate role in clinical care, as a tool that enhances human judgement without supplanting it.² Human-AI collaboration can be understood as occurring at 3 levels: (1) human-in-the-loop, where clinicians are actively involved in each decision; (2) human-over-the-loop, where clinicians oversee multiple AI processes without direct involvement at every decision point; and (3) human-out-of-the-loop, which is generally unacceptable in healthcare. Augmented human intelligence encompasses primarily (1) and (2), balancing safety with scalability. Fig. 1 demonstrates how Augl is a subset of AI where humans remain in the loop, while acknowledging that there are many aspects of AI where humans are no longer in the loop (Fig. 1). We think that the Augl subset is where the use of AI healthcare is best accepted and understood at present.

Fig. 1. Graph depicting how AugI is a subset of AI that keeps humans in the loop, while AI as a whole includes models where humans are no longer in the loop.



AI: artificial intelligence; AugI: augmented intelligence

Topol et al. have emphasised that the future of high-performance medicine lies in collaboration between human intelligence and algorithmic processing.⁶ In this framework, clinicians are not replaced by machines but are empowered by them, with AugI functioning as a tireless assistant in a data-rich, time-limited environment. A responsible car driver may not need to know how the car is built, but they will need to drive the car safely and responsibly on the road the moment their hands are placed on the steering wheel. This is no different from AugI. The new generation of healthcare practitioners will not need to know anything about coding; however, to deliver AugI-enabled care to patients, it is critical that the consumers, in this case, healthcare practitioners, be trained on the basics of using AI tools in a safe and responsible manner. This framing also better addresses concerns about ethics, transparency and patient trust.^{9,12,13} Yu et al. emphasised the need for AI systems to be interpretable, reliable and accountable to human oversight.¹⁴ Patient involvement at all levels will further ensure patient relevance in the development and implementation of processes.¹⁵ Implementation and social sciences are crucial, as the adoption of AugI tools requires an understanding of clinician behaviour,

workflow dynamics and organisational culture, which are as important as technical performance.

CONCLUSION

Lakhani states “AI won’t replace humans—but humans with AI will replace humans without AI”.¹⁶ In the same way, AI will not replace doctors. However, doctors who utilise AI may replace those who do not. As data volume and clinical complexity increase, AI will become a necessary companion in medicine. The key is to adopt a model that enhances rather than replaces the clinician, that is, AugI. This approach respects the ethical, legal and emotional stakes of healthcare decisions while allowing us to harness the best of what AI has to offer. It also reminds us that the standard expected in healthcare is now higher, with the augmentation that technology now provides.

Clinicians, educators, developers and regulators must collaborate to design systems that are not only powerful but also user-friendly, transparent and equitable. By doing so, we can build a future where AI is not an intruder in medicine, but a trusted partner.

Ethics statement

Not applicable as no study participants are involved.

Declaration

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The importance of multi-level resilience in healthcare systems in small countries like Singapore

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The COVID-19 pandemic highlighted the critical importance of developing resilient health systems that can adapt to crises while maintaining essential healthcare functions. The World Health Organization (WHO) defines resilience as the ability to prepare for, absorb, adapt to and recover from shocks while maintaining core operations.¹ To this, one must add the ability to learn continuously, apply lessons in real time and adjust strategies as a crisis unfolds. In Singapore, effective coordination among government agencies, healthcare organisations, professionals and the community was essential in addressing both the immediate crisis and the underlying challenges of an ageing population and rising chronic disease burden. Thus, resilience should be viewed as a multi-dimensional construct that extends beyond the healthcare system itself.

Singapore's compact geography and integrated governance structure enabled rapid coordination, setting it apart from larger and more fragmented systems. Although it lacked the spare capacity available to bigger nations, this limitation was offset by tightly synchronised decision-making across government ministries and agencies, allowing for swift reallocation of manpower and logistics. During COVID-19, ministries such as manpower, defence and digital development played pivotal roles: the Ministry of Manpower oversaw containment and care within migrant worker dormitories; the Singapore Armed Forces provided essential logistical and engineering support; and the Ministry of Digital Development and Information, renamed from the Ministry of Communications and Information on 8 July 2024, facilitated national communications and digital initiatives. At the national level, governance and financing form the bedrock of health system resilience. The WHO's Health Systems Resilience Toolkit emphasises the integration of preparedness within universal health coverage.¹ Resilience should therefore be understood as a continuous process—of preparing, absorbing, recovering and adapting. Singapore's pandemic response exemplified these principles. Chua et al. identified

6 pillars underpinning the national response: strong leadership and governance, transparent communication, early detection, maintenance of essential healthcare services, crisis financing and a robust legal framework to enable policy implementation.²

Singapore's geographic realities play a pivotal role in shaping its approach to resilience. As a global port and aviation hub with one of the world's highest population densities, Singapore is inherently vulnerable to infectious disease importation, zoonotic spillover and disruptions in global supply chains. These risks are further intensified by climate change, which brings additional threats such as heat stress, dengue proliferation and flooding. Moreover, Singapore's economic vitality is deeply tied to its openness and connectivity. Consequently, national resilience planning must extend beyond healthcare to incorporate robust border health measures, climate adaptation strategies and sustainable urban development. Hospitals and Singapore's healthcare clusters, organised into 3 geographic regions, serve as the operational engines of resilience. They translate national policy into practice through surge capacity management, service continuity and the protection of staff welfare.³ Maintaining public trust requires that both the healthcare system and its professionals act with transparency and competence.⁴ During the pandemic, Singapore's hospitals implemented triage innovations, expanded telemedicine platforms and established step-down facilities, while strengthening partnerships with primary and community care providers.

Digital infrastructure further reinforced these efforts. The widespread adoption of Electronic Health Records (EHRs) and the National Electronic Health Record, coupled with HealthHub (Singapore's integrated digital health platform that enables users to access health records, appointments and transactions with public healthcare institutions) enhanced the capacity to harness data-driven systems.⁵ EHRs and personal digital health records have created interlinked datasets that will underpin the next phase of resilience building. Public hospitals and healthcare clusters were

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also deployed to support migrant worker dormitories, setting up on-site medical posts to manage testing, isolation and treatment in collaboration with the Ministry of Health (MOH) and non-governmental partners.^{6,7} In parallel, transitional care facilities were rapidly established in venues such as Changi Expo to accommodate medically stable patients discharged from acute hospitals, alleviating bed pressures and sustaining continuity of care. These facility and service innovations—borne of necessity—preserved critical hospital capacity during the crisis.

Overall, the pandemic catalysed the rapid adoption of telehealth, digital triage and remote monitoring, demonstrating how technology can enhance system resilience when integrated effectively into clinical workflows. Singapore's TraceTogether and SafeEntry systems, developed collaboratively by the Government Technology Agency (GovTech) and the MOH, illustrated the nation's ability to deploy large-scale digital solutions rapidly within an integrated Smart Nation framework.⁸ These tools were rolled out nationwide within weeks, supported by close coordination across GovTech, MOH and private-sector partners. Hansen and Dahiya characterised TraceTogether as emblematic of Singapore's governance model—balancing innovation, coordination and citizen engagement within a coherent resilience framework. However, as Tan et al. observed, digital contact tracing also raised questions regarding trust, transparency and the boundaries of surveillance, underscoring that technological success depends not only on functionality but also on sustained public legitimacy.⁹ Low et al. highlighted longstanding concerns about infrastructure strain arising from Singapore's ageing population, a challenge expected to intensify in the coming years.¹⁰ Building future resilience must therefore extend beyond crisis preparedness towards proactive adaptation to demographic and epidemiological transitions. The growing burden of ageing, multimorbidity and chronic disease demands deeper integration across health and social care sectors. Strengthening primary care, embedding preventive services and developing home- and community-based care models are key strategies being advanced under Healthier SG—the national initiative by Singapore's MOH to shift from reactive to preventive healthcare that was launched in July 2023.¹¹

Healthcare professionals form the human backbone of system resilience. The WHO recognises that workforce adaptability and well-being are fundamental to the sustainability of health systems.¹² The Organisation for Economic Cooperation and Development has similarly identified workforce shortages and burnout as major vulnerabilities.² During the pandemic, Singapore's healthcare professionals demonstrated

exceptional flexibility—adapting rapidly to new care models and maintaining service delivery under intense pressure. Nevertheless, it remains essential to address these stressors in tangible and sustained ways.¹³ Building workforce resilience for the future requires structural redesign and process optimisation. Automation can alleviate repetitive administrative tasks, allowing clinicians to devote more time to complex and high-value care. Greater integration of allied health professionals and nurse practitioners can distribute workloads more equitably, while continuous professional education should emphasise digital literacy, systems thinking and crisis management skills. Embedding these reforms into organisational culture will help ensure that resilience is institutionalised and sustained beyond the most recent crisis.¹⁴

Singapore's compactness and operational efficiency will remain core strengths; however, future resilience will hinge on addressing cross-cutting challenges such as population ageing, workforce sustainability and climate adaptation through anticipatory governance. A data-driven, digitally connected ecosystem, guided by transparent leadership and supported by a strong community collaboration, will be essential to the next generation of healthcare resilience. The goal is not merely to withstand future shocks but to evolve and emerge stronger from them.¹⁵

The community remains an indispensable partner in building and sustaining resilience. The WHO emphasises that engaged and well-informed communities enhance system resilience by fostering compliance, participation and trust.¹⁶ In Singapore, high levels of public cooperation during the COVID-19 pandemic were grounded in transparent communication and a strong foundation of societal trust. However, the disproportionate burden experienced by migrant workers highlighted that inclusivity is integral to resilience and requires continued strengthening. Gilson has noted that trust functions as a social institution, shaping how populations perceive and respond to public health measures.¹⁷

Resilience operates across multiple, interconnected levels. Blanchet et al.¹⁴ proposed that governance capacity is distributed across system, organisational, professional and community tiers rather than being concentrated within ministries. Singapore's experience exemplifies this layered resilience: national leadership coordinated resources; hospital clusters operationalised policies; healthcare professionals adapted care delivery; and communities provided the social legitimacy that sustained public health efforts. As a small, manpower- and resource-constrained nation, Singapore must continually reinforce, practise and refine this coordinated approach. With the possibility of future pandemics or major health crisis, learning,

adapting and strengthening our collective capacity for resilient response remain imperative.

Ethics statement

Not applicable as no patient data was used.

Declaration

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

Keywords: COVID-19 pandemic, crisis preparedness, health system resilience

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The impact of oppressive behaviours on female general surgical trainees' educational experience in Malaysia

April Camilla Roslani¹ FRCS, Retnagowri Rajandram¹ PhD, Anthonia Ginika Uzoigwe² MSc, Wah Yun Low³ PhD

Dear Editor,

Although projected to attain high-income country status by 2028,¹ Malaysia is still critically short of specialist surgeons with 1.2 per 10,000 population² compared with the OECD average of 7.23 per 10,000. The majority (60%) of Malaysian medical students are women, but they form a minority of the general surgical workforce (10%). The proportion across Southeast Asia varies widely, from 3.5% (Indonesia) to 50% (Thailand).³ Worldwide, surgery is declining in popularity, particularly among women, with lifestyle factors identified as key deterrents.⁴⁻⁶

In addition, oppressive behaviours in the workplace negatively influence career decisions among prospective trainees, disproportionately affecting women.⁴⁻⁶ In Australasia, 49% of respondents to a survey commissioned by the Royal Australasian College of Surgeons (RACS) had experienced oppressive behaviours, and female trainees were more highly affected.⁷

Following a commission by the College of Surgeons, Academy of Medicine of Malaysia (CSAMM), we designed a structured questionnaire based on the RACS report,⁷ comprising 17 items on demographics and career plans, and 66 items on work-life balance, job satisfaction, quality of life support system

(WHOQOL-BREF)⁸ and oppressive behaviours in the workplace.⁷ Where rating was required, a 7-point Likert scale was used. Discrimination was defined as unjust or prejudicial treatment of different categories of people.⁹ Bullying was the use of superior strength or influence to intimidate a subordinate, forcing the person to conform to one's desire.¹⁰ Harassment was the use of aggressive pressure on, or intimidation of others⁷ while sexual harassment was any unwelcome/unwanted physical, verbal or visual sexual advances to another person.^{6,7}

All female general surgical trainees across all Malaysian training programmes were invited to participate with informed consent. Sixty-three out of 74 invited participants (85%) responded, with 62 completing the survey. The mean age was 32.5 ± 1.9 years. Ethnic distribution approximated national proportions (Malays 54%, Chinese 29%, Indians 14.5%). Nearly half (45.2%) were married with children and worked, on average, for 75 ± 19.59 hours a week. Work-family role conflict was experienced by 45.5% of the participants. A significant proportion (40.3%) were not satisfied with their health (Table 1).

Nearly half of the respondents had experienced at least 1 of the oppressive behaviours in the workplace (discrimination 43.5%; bullying 45.2%;

Table 1. Descriptive statistics of all study variables.

Variables	n	Minimum	Maximum	Mean	Standard deviation
Work-family role conflict	62	22.00	60.00	39.25	9.27
Social support	62	13.00	60.00	47.95	8.46
Intention to quit	62	4.00	18.00	7.90	3.74
Quality of life (overall)	62	6.00	18.00	13.00	3.02
Physical health	62	8.00	18.29	14.05	2.12
Psychological health	62	7.33	20.00	13.40	2.27
Social relationships	62	5.33	20.00	13.62	3.29
Environmental health	62	7.00	18.50	13.72	1.99

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sexual harassment 19.4%; harassment 27.4%). In 61.3% of cases, the perpetrator was male. Obstacles to seeking redress were worries about impact on career progression (27.4%), loss of reputation to self (22.6%), fear of being blamed (21%) and the stress of filing a complaint (16.1%). Fear of not being believed (12.9%) or being victimised (11.3%) were also of concern. Interestingly, a small proportion (4.3%) worried about loss of reputation for the perpetrator.

Actions taken included direct confrontation (27.4%), peer discussions (24.2%), legal consultations (14.5%), formal complaints (1.6%) and police reports (1.6%). Only 65.8% reported satisfactory resolution. For 8.1%, the behaviour has continued.

The suggested preventive measures included training of trainers, delivered by the hospitals (59.7%) or by CSAMM (40.3%); resources to support better communication (66.1%); better support mechanisms such as counselling services (66.1%) and greater leadership by surgical departments (69.4%). Nearly half (49.1%) coped through family support. While 67.7% were considering another job, only 35.5% were contemplating quitting the profession altogether. Undeterred, 75.8% were considering further training in a subspecialty.

Surgery is still appealing to medical graduates, but resilience is required to remain and practice in the field. Despite compelling evidence to the contrary,^{5,6} surgical culture has been built on the myth that oppressive behaviours in the workplace are necessary to train surgical excellence.

We have shown that oppressive behaviours in Malaysian surgical workplaces are more prevalent than global pooled figures,¹¹ negatively impacting female general surgical trainees.¹² Perpetrators are often highly respected members of the fraternity, and trainees may not know or feel that they can seek redress. Avenues for redress can result in punitive outcomes, for either party, so trainees may choose against lodging complaints.⁴

This experience is not unique to general surgery. Malaysian orthopaedic trainees report gender discrimination in career opportunities (28%) and daily work (60%) favouring men while women were more likely to experience verbal (32%) and physical (11%) sexual harassment.⁶ Female paediatric surgical trainees were more likely than men to face work-life conflicts.⁵ Even in internal medicine, female trainees were more likely to experience verbal bullying or sexual harassment, with a greater likelihood of negative personal consequences.¹³

Improving surgical working conditions for women would positively impact surgical culture as a whole,^{4,6} supporting sustainability of the surgical workforce. Nevertheless, changing ingrained surgical culture is

difficult. While a top-down approach (i.e. administrative directives) is helpful, only bottom-up implementation can ensure true and meaningful change. While policies supporting flexible working hours, maternity and breastfeeding leave exist, these depend on approval by administrative heads and may conflict with training requirements. However, as there are existing policies, in some respects, this is an easier battle, as trainees can be empowered to defend their rights.¹⁴

Changing oppressive behaviours in the workplace is much more challenging. There are few policies on dealing with complaints; there are none relating to prevention. Within some training programmes, trainers are explicitly briefed on their roles and responsibilities, including appropriate behaviour in the workplace, and trainees are informed of their rights and avenues for complaint. Nevertheless, this does not occur uniformly.¹⁴ While oppressive behaviours usually occur in the direction of the power distance (i.e. the powerful oppress the weak, trainers oppress trainees), this can be affected by gender (e.g. female trainer sexually harassed by male trainee). Therefore, measures must be in place to protect both trainees and trainers from fabricated allegations.¹⁵

Prior to 2022, only the amended Employment Act 2012 provided recourse for sexual harassment in the workplace in Malaysia. The Anti-Sexual Harassment Act 2022 was a step forward in providing legal foundation for action.¹⁴ Nevertheless, while some educational institutions have started to establish policies, implementation has been challenging, often relying on the efforts of individuals. We recommend that training institutions also focus on changing workplace culture, utilising implementation science strategies. Such organisational support is essential for empowering and sustaining young female would-be surgeons in the profession.

Ethics statement

Ethics approval was obtained from University Malaya Research Ethics Committee (UM.TNC2/RC/H&E/UMREC-114). Informed consent forms were signed by all participants as per approved guidelines.

Declaration

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Keywords: *bullying, discrimination, general surgery, harassment, medical education, oppressive behaviour,*

sexual harassment, social science, sociology, surgery, surgical training, women in surgery

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Virtual reality as an adjunctive therapy for geriatric depression: A case report

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Dear Editor,

Like many other developed countries, Singapore is currently facing a rapidly ageing population that is anticipated to reach 1 in 4 persons above the age of 65 years by 2030.¹ Given that the rates of clinical and subclinical depression among the elderly in Singapore range between 4.4–11.9%,² the disease burden of elderly depression is likely to increase in the upcoming decade. However, manpower constraints in the healthcare sector remain an issue,³ resulting in calls to rely on innovative technology to meet these needs.⁴

Virtual reality (VR) is one such technological innovation that has potential to meet our growing mental healthcare needs. Although relatively nascent, recent studies on the use of VR in the treatment of elderly mental health have been encouraging,^{5,6} especially for those residing in long-term care facilities.⁶ This article illustrates the use of VR as an adjunctive treatment for elderly depression.

Mr A was a 72-year-old man diagnosed with bipolar disorder and admitted to inpatient care at a restructured hospital in Singapore for a total of 4 months due to a relapse of depression. He also presented with mood-incongruent psychotic features, which were secondary to his non-compliance to medication. Mr A lived alone and was socially isolated. He was estranged from most of his family, apart from occasional visits by his biological brother. He also blamed himself and experienced intense guilt over his divorce. These contributed to his apathy and hopelessness as there was “no point [in trying]”.

Despite being treated with various psychotropics during his stay, he exhibited poor medication tolerance and a sensitivity to side-effects, leading to repeated complaints and medication refusal. He was referred for psychotherapy to address the possible underlying psychological factors, which contributed to his low mood and medication non-compliance, while his ward team continued to adjust his medication.

Psychotherapy commenced but Mr A's engagement and progress was limited due to his significantly depressed mood, low energy, poor motivation and

poor attention. Attempts to further explore Mr A's inner experiences were met with resistance and refusal. After the second session, Mr A informed the ward doctors that sessions were “stressful” and requested to stop.

Although Mr A initially agreed to participate in group occupational therapy, he eventually stopped, expressing that it was “too difficult”. Attempts by different parties to encourage activity engagement in the ward were also met with refusal, and he spent most of his time in bed with limited engagement.

Several attempts were made to increase Mr A's hopefulness by exploring his spirituality and past aspirations. He was ambivalent, but a breakthrough came on 1 occasion when he recounted his desire to scuba dive and explore the ocean. Correspondingly, his affect changed slightly, and he was excited for the first time in 2 months. He verbalised regret that he had not acted on it. Mr A was offered the opportunity to experience scuba diving using a VR headset. Approval was obtained from his psychiatric team, and he was started on 4x 30-minute weekly VR intervention using a commercially available headset and programme that were purchased by the department.

The first session commenced on day 94 of Mr A's inpatient stay. Although he was already on 200 mg sertraline, response was limited and the plan was for him to start on bupropion and cross-titrate. A VR video was selected, simulating the experience of scuba diving. Mr A sat on a stationary swivel chair with handlebars, which allowed him to be immersed in the 360° virtual landscape safely. Mild giddiness was reported by Mr A during the first 5 minutes of VR headset use, but he adjusted to the device and denied any discomfort after. Changes to his mental state were observed during the session. Mr A's affect became more reactive. He was also more verbally expressive during the session, commenting on several aspects of his experience. After the session, Mr A remarked that he was “excited”, that the experience was “interesting”, and that he wanted to continue with the trial.

Subsequent VR sessions involved different video scenes, which were chosen collaboratively with Mr A.

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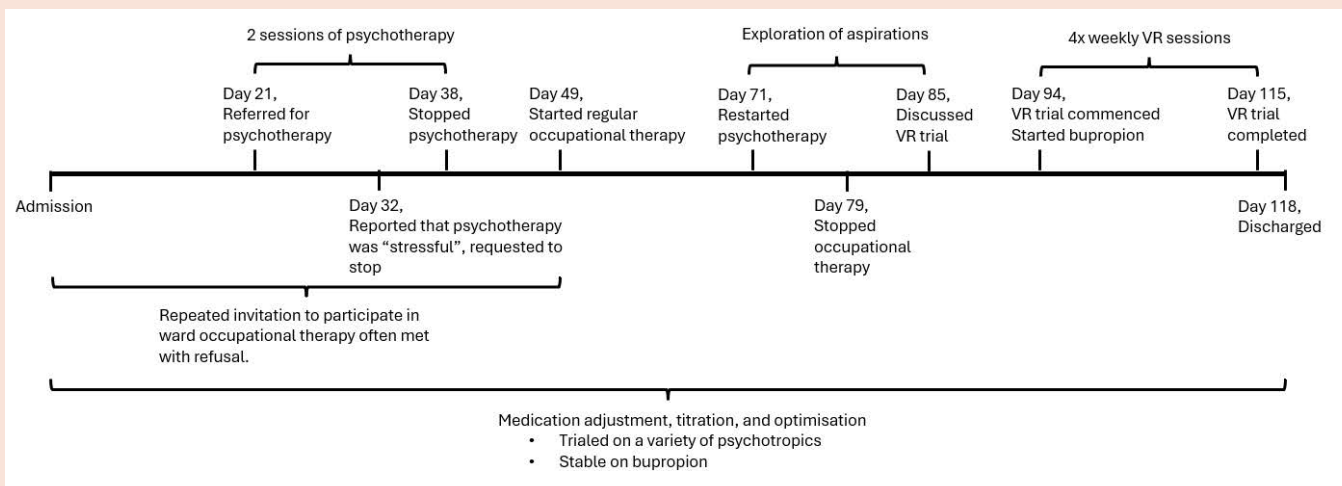
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Fig. 1. Timeline of inpatient treatment.



VR: virtual reality

There were no adverse reactions reported during these sessions as he experienced a virtual tour of the Spanish countryside, a German Christmas market and an animal safari. Beyond mood improvements, Mr A's excitement for sessions was readily observed—he was quick to get off his bed for sessions unprompted. In addition to interacting with these immersive landscapes, VR sessions also included elements of psychotherapy aimed at eliciting Mr A's emotions, thoughts and hopefulness. Mr A eventually started sharing what he would do when discharged from the hospital, and expressed a liveliness to engage in meaningful living that was absent just a month earlier.

Mr A was discharged after 118 days of inpatient stay. He completed the VR trial, and his medication had been optimised (stable on bupropion monotherapy). Although no standardised instruments were used to evaluate his improvement, as he struggled with self-reporting his mood on questionnaires pre-VR intervention, his mental state and presentation were observed to have improved at discharge.

Fortunately, Mr A's experience with VR is not unique. A study conducted in Hong Kong found that the use of VR in the elderly population elicited increased positive affect such as excitement and inspiration, and reduced negative affect such as guilt, distress, irritability and shame.⁷

While the use of VR in Singapore had previously been limited to cognitive screening^{8,9} or to promote active ageing,¹⁰ the current case report demonstrates the potential of VR as an adjunctive treatment for geriatric depression, complementing traditional treatment

modalities such as pharmacotherapy or psychotherapy. While conclusions about the effectiveness of VR in treatment are limited in this case study, rigorous studies using randomised controlled trials can be conducted in future to evaluate the efficacy and utility of VR interventions in elderly depression, especially for patients who are open to technological adoption, whose interests or emotional needs can be met by VR, and who do not present with conditions that contraindicate VR use.

Declaration

The author declares 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.

Ethics statement

Case report of one patient does not meet the definition of research and does not require review by the SingHealth Centralised Institutional Review Board. Patient's identity has been anonymised. Consent was obtained from the patient to present this case report.

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Keywords: depression, geriatric medicine, mental health, psychology, virtual reality

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"Making better clinical decisions: How doctors can recognise and reduce bias and noise in medical practice": Correspondence

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Dear Editor,

We read with great interest the recent commentary by Ng et al.¹ and commend the authors for their timely and thoughtful synthesis of key concepts in clinical reasoning, especially their articulation of cognitive bias and noise as distinct yet intertwined contributors to decision variability. Their proposals for workplace and pedagogical interventions are both practical and mostly grounded in contemporary literature.

That said, we would like to offer several reflections that could add nuance to the conversation.

First, while the authors rightly point out the role of system 1 intuitive reasoning in everyday clinical work, we feel the article underemphasises the fallibility of system 2 analytic reasoning. Deliberate, effortful cognition is also prone to error, especially in the presence of incomplete knowledge, faulty logic or overreliance on data.² System 2 failures, such as base-rate neglect, confirmation bias under the guise of rationalisation or anchoring during premature analytic framing, have been well-documented.³ Clinical reasoning curricula should therefore treat both systems as fallible, and foster skills that support reasoning depending on context and task demands.

Second, while the article alludes to reasoning processes, we note a relative de-emphasis on knowledge structures. Intuitive reasoning is effective, as it is underpinned by richly developed, context-sensitive knowledge structures.⁴ The growing enthusiasm for teaching reasoning strategies should not eclipse the critical role of continuous knowledge acquisition and epistemic calibration. Studies have shown that experts' superior reasoning derives more from their organised knowledge base than from formal logical skill alone.⁵

Third, we share the authors' interest in cognitive bias, but caution against overstating the utility of debiasing strategies. A growing body of literature highlights that most bias recognition or checklist-based strategies have modest or uncertain real-world

efficacy, and some authors speculate that they may foster overconfidence in one's immunity to error.⁶ Instead, we suggest a stronger focus on metacognitive regulation, which has shown more promise in supporting reflective diagnostic reasoning. Guided reflection and "second-look" reasoning strategies may offer more enduring gains than attempts to target individual biases in isolation.⁷

Finally, the emphasis on Bayesian reasoning as a foundational model is conceptually sound, but it requires careful contextualisation. In clinical practice, accurate prevalence estimates or likelihood ratios are often inaccessible, outdated or simply not established for many presentations. While heuristics such as treatment thresholds are helpful, these are approximations, and Bayesian reasoning in clinical settings is often intuitive rather than formalised. Embedding Bayesian reasoning in practice may require not only teaching principles but also supportive tools (e.g. decision aids, clinical calculators or smartphone apps) to scaffold real-time probability updating.⁸ Furthermore, clinical decisions are made within complex environments, influenced by factors such as electronic health records, institutional protocols and interdisciplinary communication. Understanding these contexts is crucial for developing robust clinical reasoning skills and minimising errors.⁹

In summary, Ng et al. have contributed a timely and grounded piece on improving clinical decisions. However, sustained progress in clinical reasoning education will require an integrated focus on knowledge structures, metacognitive practices and pragmatic supports, not only on bias and noise. As the landscape of clinical decision-making evolves with new cognitive and technological tools, it is crucial that we retain a nuanced view of reasoning—not merely as a process to be refined, but as a complex interplay of knowledge, cognition, context and care.

Ethics statement

Not applicable.

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Authors' reply

We thank Mucheli et al. for their kind interest in our paper on improving real-world clinical decision-making through tackling bias and noise in professional judgments.¹

First, we fully agree with the authors' view that system 2 (slow analytical thinking) has significant shortcomings as well, besides lacking practicality in naturalistic clinical practice environments. However, given that the intent of our commentary was to create awareness among clinicians of the dual entity of "bias" and "noise" that can adversely affect real-world clinical judgments, which we contend are predominantly intuitive, we did not explore this area further. Instead, this was discussed in a separate paper on a Bayesian intuitionist model of clinical reasoning, where the authors argued that intuition could, contrary to popular belief, be superior to analytical judgments in ecologically rational environments, such as complex and uncertain situations, where robust pre-

dictions come about with less redundant information or "overfitting".² This suggestion is corroborated by previous studies, which showed that slow analytical thinking is not necessarily more accurate than rapid intuitive responses.^{3,4} Clinicians who performed well tended to have correct intuitions initially (suggesting good foundational knowledge), rather than possessing an ability to revise initially erroneous answers.^{5,6}

Second, we also concur with the view that the role of bias in cognitive errors might be overstated⁷ (itself subject to hindsight bias⁸), and de-biasing interventions have limitations, given that real-world studies evaluating their efficacy have yielded mixed results.² Nonetheless, cognitive biases certainly exist and are more commonly associated with rapid intuitive judgments. Consequently, we argued that there could be a role for practical, heuristics-based de-biasing approaches, such as pivot-and-cluster strategy or contemplation of counter-diagnostic/red-flag features, which we foresee are more likely to be efficacious and easily habituated in routine practice.^{2,9} As the authors rightly pointed out, there is significant value in training metacognitive regulation and engaging in reflective practice to re-calibrate/refine internal illness scripts based on past clinical experiences for improved accuracy in future encounters. Additionally, based on Fleming's suggested metacognitive model of propositional confidence,¹⁰ regularly practising level of confidence/certainty in clinical decision-making with follow-up of outcome improves self-awareness of one's predictive accuracy.² When decisional confidence is closely linked to the accuracy of clinical judgments, it acts as a healthy safeguard against decisional errors where low confidence situations will prompt information-seeking behaviours.²

Third, we thank the authors for elaborating on how the usage of Bayesian-based heuristics, such as testing and treatment thresholds, can be practicalised through the use of diagnostic adjuncts and decisional aids. The utilisation of pedagogical methods, such as simulation practice (with standardised patients and realistic case scenarios) and script concordance tests, can help trainees to contextualise diagnostic and treatment principles to the individual patient in a specific clinical setting.

Moving forward, it may be worth exploring how we could evolve our understanding of clinical thinking as skilled intuition, and consider how such expertise can be developed and adaptable across real-world clinical contexts and practice environments.

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Awareness and uptake of colorectal cancer screening after Healthier-SG launch: A questionnaire survey

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Dear Editor,

Colorectal cancer (CRC) is one of the most common malignancies in high-income countries.¹ Despite Singapore's well-established cancer screening infrastructure, uptake remains below target. Early detection through screening is crucial for improving outcomes, yet many eligible individuals remain unscreened.² In July 2023, the Ministry of Health launched Healthier-SG, a national preventive health initiative encouraging residents aged 40 years and above to take charge of their health. CRC screening using the faecal immunochemical test (FIT) was emphasised for adults aged 50 years and above, with free FIT kits distributed through primary care clinics, community pharmacies and the Singapore Cancer Society.

To assess the impact of this initiative, we conducted a community-based, cross-sectional questionnaire survey in March 2024 among residents aged 50 to 85 years at a public multipurpose complex in Bedok, Singapore. The site was selected due to its high footfall of 280,000 to 300,000 per month and accessibility to residents from diverse socioeconomic backgrounds.³ Using a case-encounter sampling approach, participants were invited to complete an anonymised electronic survey in English. Demographics, awareness of CRC and its screening, history of CRC screening and reasons for participation or non-participation were collected.

A total of 350 participants were recruited. Table 1 below shows most participants were female (60.3%), of Chinese ethnicity (92.0%) and residents of public housing (76.9%). The majority (89.4%) were aware of CRC, and 84.6% were aware of available CRC screening. Overall, 65.1% reported having undergone screening, most commonly through FIT kits (47.4%) or colonoscopy (38.2%). Among those screened, key motivators included routine health checks (41.7%) and recommendations by healthcare professionals (25.0%). Among non-screeners, the primary reason cited was absence of symptoms (47.5%), followed by

a lack of awareness about the test (19.7%).

Further analysis using Poisson regression revealed that participants who were aware of CRC screening were over 8 times more likely to have been screened than those who were unaware (adjusted prevalence ratio: 8.489, 95% confidence interval 3.085–23.363, $P<0.001$).⁴ In contrast, demographic variables, such as sex, education level, income proxy or medical subsidy status, were not significantly associated with screening uptake.

These findings suggest a notable increase in CRC screening compared to national statistics prior to Healthier-SG. According to the National Population Health Survey 2022, only 38.1% of residents aged 50 to 74 years had undergone CRC screening at recommended intervals.⁵ The observed rise to 65.1% in our study likely reflects a combination of enhanced public awareness, stronger engagement by healthcare providers and increased accessibility to free FIT kits. Nevertheless, this level remains below the 70% target commonly cited for effective population-level cancer screening.

Importantly, the gap between awareness and action highlights unresolved misconceptions and behavioural barriers. Many participants who had not undergone screening believed it was unnecessary in the absence of symptoms.⁶ This misunderstanding of the merits of screening undermines the concept of preventive care. CRC screening aims to detect early-stage disease or pre-cancerous lesions before symptoms appear, improving treatment success and reducing mortality. Patient education efforts must therefore address this misconception by reinforcing the value of asymptomatic screening.

Healthcare professionals, particularly family doctors and polyclinic physicians, have a vital role in closing this awareness–action gap. Our findings reinforce evidence from prior local and regional studies showing that primary care physician's recommendation is a powerful motivator for screening.^{7,8} Under the national Healthier-SG programme, primary care professionals,

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Table 1. Participant characteristics.

Variables	Characteristics	No. (%)
Age group ^a	50–59 years old	25 (7.1)
	60–69 years old	128 (36.7)
	70 years and above	196 (56.2)
Sex	Male	139 (39.7)
	Female	211 (60.3)
Ethnic group	Chinese	322 (92.0)
	Malay	13 (3.7)
	Others (Indians and others)	15 (4.3)
Education level	No formal education/primary	81 (23.1)
	Secondary	166 (47.4)
	High school equivalent (A level/diploma (ITE ^b /polytechnic ^c /private school)	57 (16.3)
	University/post-tertiary	44 (12.6)
	Others	2 (0.6)
Marital status	Single	55 (15.7)
	Married	266 (76.0)
	Divorced/separated/widowed	29 (8.3)
Current housing type	Public housing ^d	269 (76.9)
	Private housing ^e	81 (23.1)
Required to pay income tax last year (proxy for income)	No/not applicable	294 (84.0)
	Yes	56 (16.06)
Any medical subsidy received	No	23 (6.6)
	Yes	327 (93.4)
Medi Fund ^f assistance provided	No	325 (92.9)
	Yes	25 (7.1)
Awareness of CRC	No	37 (10.6)
	Yes	313 (89.4)
Awareness of screening for CRC	No	54 (15.4)
	Yes	296 (84.6)
History of CRC (FOBT/FIT or colonoscopy)	No	122 (34.9)
	Yes	228 (65.1)
(If no) Reasons for not going for screening (n=122, more than 1 option can be selected)	Absence of symptoms	58 (47.5)
	I do not know how to collect the FIT tests	2 (1.6)
	I am worried about the discomfort of the procedure	10 (8.2)

Table 1. Participant characteristics. (Cont'd)

Variables	Characteristics	No. (%)
	I am afraid it might be positive for cancer	10 (8.2)
	It feels embarrassing to do the test	1 (0.8)
	Lack of time	5 (4.1)
	I find it inconvenient to collect FIT test at community pharmacies	1 (0.8)
	Not aware of screening available	24 (19.7)
	Others	18 (14.8)
(If yes) Reasons for screening (n=228, more than 1 option can be selected)	Presence of symptoms	38 (16.7)
	Healthcare professionals' recommendation	57 (25.0)
	Through family and friend's recommendation	9 (3.9)
	Family history of CRC	6 (2.6)
	Personal history of other health problems	3 (1.3)
	Routine health check-up	95 (41.7)
	Publicity from media/healthcare institutions	30 (13.2)
	Given free FIT kit	15 (6.6)
	Others	9 (3.9)
(If yes) Location for collection of FIT kits (n=228, more than 1 option can be selected)	Primary care clinics or hospital	108 (47.4)
	Community pharmacy	45 (19.7)
	Collected directly from Singapore Cancer Society	1 (0.4)
	Requested for mailed FIT kit on the Singapore Cancer Society website	15 (6.6)
	Others	16 (7.0)
(If yes) Location of colonoscopy performed (n=228, more than 1 option can be selected)	Hospital	87 (38.2)

CRC: colorectal cancer; FIT: faecal immunochemical test; FOBT: faecal occult blood test; ITE: Institute of Technical Education

^a Total count does not tally due to missing data.

^b Singapore-Cambridge General Certificate of Education Advance Level: An internationally recognised university entrance examination that is conducted annually in Singapore.

^c ITE: A post-secondary educational institution, established by Singapore's Ministry of Education.

^d Public housing: Singapore's public housing system is managed by the Housing Development Board (HDB), and houses around 80% of Singapore's resident population. Public housing includes 1–5 rooms HDB flats.

^e Private housing includes private condominiums or houses, rental rooms or apartments, and maisonette or executive condominiums.

^f MediFund is Singapore's government endowment fund, meant to assist needy patients with their healthcare bills at public healthcare institutions.

including general practitioners, polyclinic physicians and community nurses, are now tasked with building long-term, preventive-focused relationships with patients. They are at the frontline to routinely initiate conversations about CRC screening, clarify doubts and align test options with individual preferences.

To support these efforts, decision aids and digital tools are under development. A locally designed patient decision aid tailored to Singapore's diverse population has shown promise in raising awareness and facilitating informed choices.⁹ However, its current

print-only format limits scalability. Efforts are underway to develop artificial intelligence agents or mobile applications with interactive features and built-in reminders in smart phones to encourage regular annual screening. Such digital health interventions could be particularly useful to complement personal approaches by primary care professionals to nudge at-risk adults to screen for CRC.

Aside from personal interventions, logistical challenges persist. Only 19.7% of those screened obtained FIT kits from community pharmacies, suggesting the

underutilisation of this distribution channel. Innovative delivery methods, such as self-serve kiosks at community hubs or direct-to-home mailing of FIT kits, may help address this gap. Pilot testing of a kiosk has begun, and further research will be needed to assess their effectiveness, feasibility and user experience.

This study has several limitations. The case-encounter sampling method may introduce selection bias, and the participant pool overrepresented Chinese residents (92.0%) relative to the national population aged 50 to 85 years. Additionally, data were self-reported and not independently verified, raising the possibility of recall bias or social desirability bias. Nevertheless, the study provides timely community-level insights into CRC screening behaviour in the early months of the Healthier-SG rollout.

In conclusion, CRC screening awareness and uptake have improved substantially following the launch of Healthier-SG, indicating that national preventive strategies may be making an impact. However, gaps remain, particularly among asymptomatic individuals who remain unconvinced of the need for screening. To increase the CRC screening uptake beyond 70% for the successful implementation of a nationwide preventive health programme, future efforts should prioritise patient education, reinforce the role of trusted healthcare professionals, and expand access for the convenient collection of FIT kits. With coordinated action across primary care, public health and community platforms, Singapore can move closer to its goal of effective CRC prevention for its adult population.

Ethics statement

The study was approved by the SingHealth Centralised Institution Review Board (2021/2603) in accordance with the International Council for Harmonisation Good Clinical Practice guidelines. Informed verbal consent to participate in the study was taken during the recruitment.

Declaration

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Antibiotic use and guideline concordance in primary care acne management: A cross-sectional study

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Dear Editor,

Acne vulgaris, a prevalent dermatological condition, is common in primary care. Despite widespread use in acne treatment, antibiotics pose a significant concern due to their potential contribution to antimicrobial resistance (AMR)—an important public health issue.¹ Acne accounted for the highest volume of antibiotic prescriptions in Singapore primary care.² Antibiotic treatment frequently diverges from recommended guidelines, such as over-reliance on oral and topical antibiotic monotherapy, disregarding heightened AMR risks associated with this practice.³ Alarming, 44.5% of patients with newly diagnosed acne received long-term antibiotics.⁴ General practitioners frequently encounter challenges in management, such as uncertainty in using acne-related medications (ARM) and increased patient pressure to prescribe oral antibiotics.⁵

With current guidelines recommending treatment based on acne severity, it is vital to assess whether antibiotic prescribing and referral patterns in primary care align to these recommendations. Previous studies found that 70% of patients received ARM, but did not investigate whether treatment choices were guideline-concordant and tailored to severity.⁶ Referral patterns may often be influenced by physician habits or patient requests, inaccurately reflecting the need for referrals and increasing burden on specialty resources. This study aims to assess the quality of acne management in primary care, examining factors influencing antibiotic prescribing, adherence to severity-based guidelines and dermatology referral patterns.

A multicentre, cross-sectional study was conducted using medical records of patients aged >12 years, who were diagnosed with acne (International Classification Diseases-10 Diagnosis Code L70.0) at 7 public primary care clinics in Singapore from 2022 to 2023. Trained primary care physicians reviewed

case notes to assess acne severity, classified as mild (predominantly comedonal or limited papules or pustules), moderate (extensive papules or pustules or mild scarring) or severe (multiple nodules or cysts, widespread involvement or extensive scarring) based on the criteria set by the National Institute for Health and Excellence (NICE)⁷ and Dermatological Society of Singapore (DSS).⁸ To reduce assessment bias, acne severity was classified first, using only case note documentation, by reviewers who were blinded to treatment prescribed, referral status and physician experience levels. Treatments were categorised based on the combinations of topical antibiotics (clindamycin gel), oral antibiotics (doxycycline and erythromycin) and topical ARM (benzoyl peroxide, adapalene, tretinoin, and combination sulphur, salicylic acid and resorcinol cream or lotion). Guideline adherence was evaluated using the NICE⁷ and DSS⁸ criteria: (1) mild: ARM +/- topical antibiotic; (2) moderate: ARM + topical or oral antibiotic; (3) severe: ARM + topical antibiotic + dermatology referral or ARM + oral antibiotic.

Any combinations not listed above were considered non-concordant. Anonymised physician experience levels and dermatology referrals were matched to cases.

The study drew from a pool of 2000 patients with acne and used random stratified sampling across 7 clinics, targeting 55 patients per clinic. A minimum sample size of 323 patients was required (5% margin of error, 95% confidence interval [CI]). Data were analysed using SPSS Statistics software version 25.0 (IBM Corp, Armonk, NY, US). Chi-square tests were performed to determine associations between acne severity and treatment, while multivariable logistic regression was used to identify factors influencing appropriate antibiotic use and dermatology referrals.

The study included 385 patients with a median age of 23 years (interquartile range [IQR] 18–29), near-equal sex distribution (52.7% male) and predomi-

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nantly Chinese ethnicity (74.8%) (Table S1). Management was provided by 183 primary care physicians with a median of 9 years of experience (IQR 7–15), 64.2% of whom were accredited family physicians. Insufficient documentation hindered acne severity determination in 27.5% of patients. Complementary ARM was not prescribed with antibiotics in 34.0% (n=131) of cases, and dual antibiotic therapy was given in 4.2% (n=16) of cases. Of the 142 acne cases referred to dermatology (36.9%), 52.8% were requested by patients despite a lack of clinical indication.

Among patients with documented acne severity, antibiotic choice was significantly associated with severity ($P<0.001$). Severe cases were more likely to receive oral antibiotics (odds ratio [OR] 12.0, 95% CI 3.84–37.6), while mild cases were more likely to receive topical antibiotics (OR 2.78, 95% CI 1.71–4.54).

Only 64.7% of patients received guideline-concordant care. On multivariate analysis, inappropriate treatment was more likely with increasing patient age (OR 1.049, 95% CI 1.021–1.079), while acne severity ($P=0.185$) and physician experience ($P=0.673$) had no significant impact (Table 1).

Acne severity was the strongest predictor of dermatology referrals, with moderate (OR 2.33, 95% CI 1.12–4.86) and severe (OR 27.7, 95% CI 7.68–99.7) cases more likely to be referred than mild cases after adjustment for confounders. In contrast, patient requests for dermatology referrals did not significantly affect referral likelihood (OR 1.62, 95% CI 0.75–3.48, $P=0.218$).

Our study highlights key findings regarding acne management in primary care. First, 27.5% of patient records lacked documentation of acne severity, hindering treatment evaluation and guideline adherence. More than one-third of patients did not receive guideline-concordant care, primarily due to the omission of adjunctive ARM with antibiotic therapy.⁶ Previous research showed knowledge gaps and uncertainties with topical treatment and guideline recommendations.⁹ This raises concerns about potentially reduced treatment efficacy and increased risk of AMR.¹⁰ Physicians generally adhered to evidence-based guidelines by reserving oral antibiotics for severe acne cases and opting for topical antibiotics for mild cases. However, increasing age was associated with inappropriate treatment; this may reflect challenges such as managing comorbidities, polypharmacy, diagnostic complexity in older adults—worsening time constraints during consultations. Dermatology referrals were significantly associated with clinical severity, suggesting that primary care physicians generally refer based on clinical judgement. While the high referral rate (36.9%) compared to severe cases (4.7%) suggested over-referral, with 52.8% due to patient requests without clinical indication, physicians effectively declined 72.0% (n=54) these requests, demonstrating sound gatekeeping and highlighting the importance of enhanced shared decision-making in acne management. Further research is needed to better understand referral appropriateness and patient expectations regarding dermatological consultations for acne. Our

Table 1. Multivariate logistic regression of factors affecting appropriateness for antibiotic treatment of acne.

Study variables	β	P value	OR	OR (95% CI)	
				Lower	Upper
Age	0.048	<0.001	1.049	1.021	1.079
Sex (male)	0.410	0.140	1.51	0.87	2.60
Race (reference = Chinese)		0.349			
Malay	0.681	0.132	1.98	0.81	4.79
Indian	-0.363	0.437	0.70	0.28	1.74
Others	-0.157	0.770	0.86	0.30	2.45
Acne severity (reference = mild)		0.185			
Moderate	-0.484	0.113	0.62	0.34	1.12
Severe	0.327	0.530	1.39	0.50	3.85
No. of years of physician experience	0.008	0.673	1.008	0.971	1.047
Accredited primary care physician	-0.023	0.934	0.98	0.56	1.70

CI: confidence interval; OR: odds ratio

study had several limitations, including a notable proportion of cases with insufficient documentation, which may have impacted the precision of the estimates and potentially reduced the study's power. Additionally, inherent biases associated with the study design and sampling methodology may have influenced our findings.

Our study demonstrated suboptimal adherence to acne management guidelines, with significant gaps in documentation and adjunctive therapy. Targeted interventions to improve guideline adherence and documentation may enhance patient outcomes and reduce antimicrobial resistance.

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and reviewed and approved by the Domain Specific Review Board (DSRB) of the National Healthcare Group on 28 June 2023, approval number 2023/00255. The study was conducted with the approval of relevant authorities and in compliance with all applicable institutional policies, regulations and guidelines. A waiver of consent was granted for this study, as it was deemed to be of minimal risk to the participants involved by DSRB.

Declaration

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