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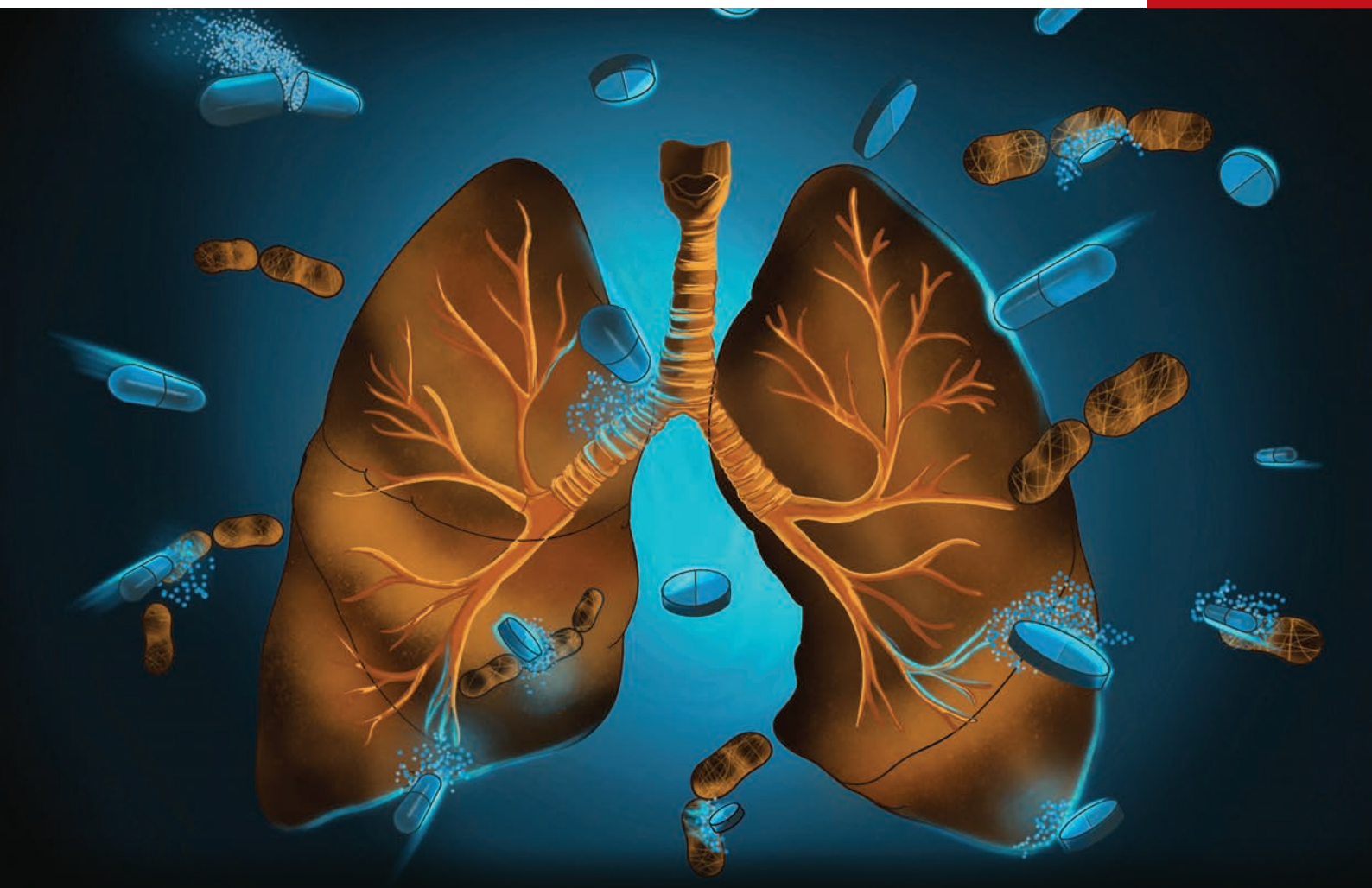

Corticosteroids in critically ill patients with community-acquired pneumonia: A systematic review and Bayesian meta-analysis

Research explores corticosteroid use in critically ill patients with community-acquired pneumonia in Singapore—assessing effects on mortality, ventilation duration and ICU stay, and offering insights for clinical practice in intensive care. (See full article, p.683)

Illustration by Ladyfingers Co.

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Unplanned hospitalisations among subsidised nursing home residents in Singapore: Insights from a data linkage study

Updated consensus guidelines for management of moderate-to-severe atopic dermatitis in Singapore: Integrating biologics, Janus kinase inhibitors and conventional therapies

Gender dysphoria in children and adolescents: A retrospective analysis of cases in Singapore

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EDITORIAL

Evolving therapies for atopic dermatitis: Bridging guidelines and practice

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Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition characterised by dysregulated type 2 immune responses, skin barrier dysfunction and intense pruritus (itching). The disease burden of AD is substantial, affecting at least 171 million individuals worldwide in 2019, representing 2.23% of the global population.[1] Among skin diseases, AD ranks highest in disease burden, as measured by disability-adjusted life-years (DALYs).[2] Its profound impact on patients' quality of life, along with significant economic burdens, underscores its status as a major healthcare challenge.

The pathogenesis of AD is driven by the type 2 cytokine axis, which includes interleukins (IL)-4, -5, -13, -25, -31 and -33, along with thymus- and activation-regulated chemokine (TARC)/CC chemokine ligand 17 (CCL17) and thymic stromal lymphopoietin (TSLP).[3] Additionally, AD is highly heterogeneous, presenting diverse phenotypes differed by factors such as age, disease chronicity, ethnicity, filaggrin mutations and immunoglobulin E (IgE) status.[4] Advances in understanding the molecular mechanisms of AD have paved the way for promising therapeutic strategies. In recent years, biologics and small-molecule therapies have revolutionised the management of moderate-to-severe AD. Numerous guidelines have been updated to incorporate these novel treatments, reflecting their growing role in the evolving treatment paradigm.[5-7]

In this issue of the *Annals,* Yew et al.[8] present a study that updates the 2016 Singapore treatment guidelines for AD,[9] with a focus on biologics and oral Janus kinase inhibitors (JAKi) now approved and available for AD treatment in Singapore. Utilising a modified Delphi consensus approach, the updated guidelines[8] offer recommendations on disease assessment, treatment goals and the incorporation of new therapies including dupilumab, an immunoglobulin G4 monoclonal antibody against IL-4 receptor α (IL-4Rα) targeting IL-4/13 signalling pathway, and JAKi such as abrocitinib, baricitinib and upadacitinib, into treatment paradigms.

While the guidelines primarily focus on pharmacologic treatments for AD, they also stress the fundamental principle of managing the condition—primarily by enhancing the skin barrier. The use of emollients as a basic treatment is highlighted as an essential step, consistently reinforced in global guidelines.[5-7] Clinical studies have demonstrated that regular moisturisation, typically applied twice daily, significantly improves the skin barrier in both adults and children with AD. Long-term studies on flare-ups have shown that daily moisturisation reduces flare frequency and prolongs the time between flare-ups.[10] Furthermore, the importance of educational programmes and counselling for patients and their families is emphasised. A collaborative approach involving patients, caregivers and healthcare providers is crucial, with discussions regarding treatment objectives, expectations, options and plans being essential for effective management.

Yew et al. also emphasise the equal importance of incorporating clinical signs assessed by physicians, symptoms reported by patients, health-related quality of life and long-term control of AD into disease assessment. Tools that evaluate both symptom severity and the impact on quality of life are crucial for customising treatment plans to meet individual patient needs.[11] Their guidelines also emphasise the importance of a correct diagnosis prior to initiating systemic therapy. Life-threatening conditions, such as cutaneous T-cell lymphoma, which is a significant mimicker, should be ruled out. Therefore, dermatologists are crucial in ensuring an accurate diagnosis to prevent the use of inappropriate treatments.

According to the guidelines, dupilumab and JAKi are recommended as first-line treatments for certain patient populations with moderate-to-severe AD. Given that IL-4 and IL-13 are key drivers of type 2 inflammation in AD, which is a type 2 inflammatory disease, dupilumab targets IL-4Rα, inhibiting both IL-4 and IL-13 signalling. This dual action reduces type 2 inflammation and helps interrupt the itch-scratch cycle.[12] In addition to

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clinical improvements, dupilumab has been shown to normalise intraepidermal nerve fibre density, restore skin barrier integrity, decrease *Staphylococcus aureus* abundance, and promote a healthier skin microbiome.[13,14] Approved for AD treatment in Singapore since 2019, this present guideline recommends dupilumab for children and adults aged ≥6 months, particularly those with concurrent type 2 allergic diseases, severe comorbidities or older adults (≥65 years). However, clinicians should ensure that age-appropriate vaccinations are given at least 4 weeks prior to initiating dupilumab, as live attenuated vaccines are contraindicated during treatment. Regarding adverse events, conjunctivitis is a potential side effect associated with dupilumab.

The JAK-signal transducer and activator of transcription signalling pathway plays a central role in the pathogenesis of AD, as it regulates the transcription of various genes following cytokine engagement (e.g. IL-4, IL-13 and IL-22) with their respective receptors. JAKi, which are small molecules that competitively block the phosphorylation of JAK proteins, include abrocitinib, baricitinib and upadacitinib—all of which were approved for AD treatment in Singapore in 2022. Clinical studies have shown that these inhibitors improve AD symptoms and induce skin lesions clearance compared to placebo. They offer an appealing option for patients seeking rapid relief, particularly from pruritus—one of the most common and burdensome symptoms of AD—as the clinical trials demonstrated their efficacy in quickly alleviating pruritus. Common reported side effects of JAKi are nausea, nasopharyngitis, acne and herpes infections.[15] The latest guidelines[8] recommend JAKi for adolescents aged 12–18 years old. Before starting therapy, screening and treatment for latent tuberculosis is essential. These inhibitors are contraindicated when used with immunosuppressive drugs and should be used with caution in patients aged ≥65 years, those at increased risk of major cardiovascular issues (such as stroke or myocardial infarction), smokers or former long-term smokers, individuals with cancer risk and those with factors predisposing them to venous thromboembolism. Regular screening for infections and laboratory monitoring is required to ensure patient safety during treatment.

In conclusion, this updated consensus highlights the importance of accurate diagnosis, patient education, skin barrier enhancement, and the judicious application of both conventional and innovative systemic therapies in managing AD. By embracing these principles, healthcare providers can significantly improve therapeutic outcomes, alleviate the disease burden and enhance the quality of life for patients with AD. As treatment options continue to advance, they bring renewed hope for a future where individuals with AD experience better-controlled symptoms, fewer complications and improved long-term health. Comprehensive and regularly updated guidelines like this one, which adopt a holistic approach addressing both the medical and psychosocial aspects of care, are vital for optimising treatment strategies and transforming the overall patient experience.

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. During the preparation of this work, the author used ChatGPT (OpenAI, version 2) to assist with language refinement. After utilising this tool/service, the author thoroughly reviewed and edited the content as necessary and take full responsibility for the accuracy and integrity of the publication.

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Keywords: *biologics, corticosteroids, dermatology, eczema, Janus kinase inhibitors*

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EDITORIAL

Can a Bayesian approach clarify if corticosteroids are beneficial for severe community-acquired pneumonia?

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Despite advances in the antimicrobial treatment of sepsis and organ support in the intensive care unit (ICU), community-acquired pneumonia (CAP) remains a leading cause of mortality and disability-adjusted life years lost globally.[1] Severe CAP, where CAP becomes complicated by acute hypoxaemic respiratory failure or shock, is also the most common cause of sepsis, where complex and heterogeneous biological mechanisms underlie a dysregulated inflammatory host response that ultimately leads to major organ dysfunction and death. Along with the emerging threats of respiratory pandemics, antimicrobial resistance, ageing populations and the rise of chronic diseases, much research has been conducted to improve the treatment outcomes of CAP via host immunomodulation. These efforts have focused almost exclusively on anti-inflammatory effects of corticosteroids, which have a proven track record of improving outcomes in other forms of sepsis, such as bacterial meningitis, *Pneumocystis jirovecii* pneumonia and severe COVID-19.

Unfortunately to date, corticosteroids have been evaluated in numerous randomised controlled trials (RCTs) as a potential treatment for CAP without having reached a conclusive recommendation due to conflicting results. Early RCTs suffered from small sample sizes and heterogenous outcome measures. This resulted in clinical practice guidelines issuing weak recommendations on the use of corticosteroids due to poor overall quality of evidence and discrepant results in higher quality studies.[2,3] Currently, guidelines cautiously recommend corticosteroid therapy for patients with severe CAP when there is septic shock that is refractory to fluid resuscitation and vasopressor support, which is consistent with previously released sepsis guidelines for septic shock.[4]

Most recently, 2 large, high-quality and double-blind placebo-controlled RCTs were published on corticosteroid therapy in severe CAP. The Extended Steroid in Use in Community Acquired Pneumonia (ESCAPe) trial[5] randomised patients between 2012 and 2016 across 42 hospitals in the US who had severe CAP as defined by the 2007 American Thoracic Society/Infectious Diseases Society of America criteria[6] for severe pneumonia, to receive intravenous methylprednisolone 40 mg per day for 7 days before tapering over a period of 20 days within 72–96 hours after admission versus (vs) placebo. Due to low recruitment, the study enrolment was stopped early at 584 patients out of an intended 1420 target sample size and the primary outcome of 60-day mortality was found to be similar in the intervention and control groups (16% vs 18%, *P*=0.61). The Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD) trial[7] was conducted in 31 French centres from 2015 to 2020 in 800 patients admitted to the ICU for severe CAP to receive either intravenous hydrocortisone of 200 mg per day by continuous infusion for 4 or 7 days that tapered over a period of 8 or 14 days within 24 hours, or placebo. Patients with influenza, septic shock at baseline, chronic corticosteroid usage or those with do-not-resuscitate orders were excluded. In contrast to the ESCAPe investigators, the CAPE COD investigators found a mortality benefit favouring the hydrocortisone group over the placebo group (6.2% vs 11.9%, *P*=0.006).

Despite the larger sample sizes, the differing results of these 2 trials have resulted in more questions than answers. Could the discrepant results be due to differences in the choice of corticosteroid drug and dosing schedule? Or was the earlier timing of initiation of corticosteroid therapy, as evidenced by the CAPE COD trial, the crux to optimising outcomes? Differences in the study cohort characteristics in terms of gender distribution (96% of patients in the ESCAPe study were men vs 69% in CAPE COD); prevalence of diabetes mellitus (more prevalent in the ESCAPe trial at 48.3% vs 22.8%); microbiological aetiology of CAP (the CAPE COD cohort had a high proportion of patients with an identified bacterial pathogen, specifically *Streptococcus pneumoniae* due to exclusion of patients with influenza); and

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biomarkers (70% of CAPE COD participants had raised C-reactive protein), also beg the question of whether there are other patient-specific criteria such as gender, comorbidity and pathogenic aetiology that may modify the efficacy and harm of corticosteroids therapy in CAP. Research on corticosteroids for severe CAP seems destined to suffer from the established track record of the many negative trials in critical care and sepsis.

Many RCTs in critical care and almost all research studies of sepsis are beset by the major problem of having enrolment criteria that result from consensus definitions of archetypical syndromes in critically ill patients (e.g. CAP with acute hypoxaemic respiratory failure), which ignore the clinical heterogeneity of the ICU population. These definitions, while having high sensitivity and are therefore good for screening, perform poorly as diagnostic tests due to low specificity because pneumonia and sepsis involve biologically heterogeneous processes with differing pathogenic agents and inflammatory phenotypes. Additionally, corticosteroids have been shown to be beneficial in both acute respiratory distress syndrome (ARDS) for its anti-inflammatory effect and in septic shock for relative adrenal insufficiency.[4] As a significant proportion of patients with severe CAP are expected to suffer from the complication of either ARDS or septic shock, it will likely remain an enduring challenge for investigators to fully discriminate between the effects of mortality reduction from disease-modifying effects of corticosteroids on ARDS, septic shock and CAP. Clearly, a more precision-based approach to CAP is needed where patients are phenotyped by rapid molecular pathogen diagnostics and inflammatory biomarkers to help guide the selection of various treatments such as corticosteroids.

In this issue of the *Annals*, Chua et al.[8] proposed a different statistical approach to tackling the clinical question with Bayesian inference compared to the more traditional frequentist approach that the traditional RCT is based on and which dominates the medical literature. The frequentist approach is purely data-driven and aims to assign probabilities to a given dataset (i.e. what is the probability of obtaining another dataset at least as extreme as the one collected, thereby giving the *P* value). In contrast, the Bayesian approach that involves the incorporation of prior information into the analysis as more data become available (known as the prior, which can be assigned based on expert beliefs, historical data, or a combination of the two), attempts to assign the probabilities that a particular hypothesis is true given a particular dataset.[9] This is the main advantage of the Bayesian approach over the frequentist approach, where the probability that an intervention is beneficial can be updated as data accrues (the updated probability is called the posterior probability). While clinicians are more familiar with the frequentist approach, the pre-trial assumptions on plausible effect size and outcome rates in RCTs are frequently incorrect, and study designs often lack flexibility to address complex clinical questions reflective of real-world practice or to make mid-trial corrections when pre-trial assumptions are wrong.

Chua et al.'s Bayesian meta-analysis included 6 RCTs for evaluation of mortality benefit and duration of mechanical ventilation, which included both the ESCAPe[5] and CAPE COD[7] studies. The authors found no significant difference in hospital (risk ratio [RR] 0.70, 95% confidence interval [CI] 0.39–1.14) and all-cause mortality (RR 0.68, 95% CI 0.34–1.22), but found a high posterior probability of 94.3% and 93.1% approaching significance that corticosteroids were more likely than not to reduce both hospital and all-cause mortality, respectively. Despite not meeting the posterior probability threshold for significance, the authors should be commended for helping to inform Bayesian researchers of priors regarding the effect of corticosteroids on severe CAP. Limitations of their Bayesian meta-analysis include having a limited set of 6 RCTs where the statistical analysis risks being heavily weighted by the 2 largest studies (ESCAPe and CAPE COD), as well as significant heterogeneity owing to the differences in diagnostic inclusion criteria for severe CAP, exclusion criteria of patients with septic shock and primary outcome across the RCTs analysed.

It is with the limitations of the traditional frequentist statistical approach in mind that the results of the Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) study with recruitment currently in progress[10] are eagerly awaited. REMAP-CAP adopts a Bayesian inference model with a responsive-adaptive randomisation design. Rather than testing individual interventions in a single homogeneous disease state and terminating when that task is complete, responsive-adaptive trials like REMAP-CAP aim to study a broader set of disease states where testing for multiple therapies is carried out simultaneously and sequentially without the need for a separate control group for every 2-way comparison. In this regard, REMAP-CAP is able to study the effect of 240 multiple interventions categorised across 4 treatment domains of antibiotic therapy; antiviral therapy; host immunomodulation with extended macrolide therapy; and various corticosteroid regimens in multiple patient subgroups with a randomisation design, which involves preferential assignment of subjects to interventions

that appear to be most favourable until superiority, equivalence or inferiority thresholds are met—thereby avoiding indeterminate results. With such flexibility and the promise of a single perpetual platform trial, it is hoped that we will eventually be able to answer the pernicious issue of corticosteroids in CAP with a precision-based approach.

Disclosure

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: *antimicrobial treatment, Bayesian, CAP, community-acquired pneumonia, corticosteroids, sepsis*

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ORIGINAL ARTICLE

Gender dysphoria in children and adolescents: A retrospective analysis of cases in Singapore

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ABSTRACT

Introduction: The understanding of gender dysphoria (GD) in children and adolescents is limited in Singapore. This study aims to review the presentation of GD in an outpatient psychiatric clinic, to gain insights into its prevalence and associated factors.

Method: We conducted a retrospective review of medical records for patients diagnosed with GD according to criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth and Fifth editions, at the clinic between 1 January 2017 and 31 December 2021. We collected and analysed demographic, medical and other GD-specific clinical variables.

Results: The study included 107 participants (mean age 16.6 years), comprising 47 natal males and 60 natal females. The prevalence of GD was found to be 1:5434 (0.019%). Incidence rates increased from 2.17 to 5.85 per 100,000 population between 2017 and 2021. The mean age of diagnosis was 15.6 years, with an average delay of 5 years between experiencing gender identity-related concerns and seeking formal assistance. Approximately 45% of participants reported social and physical transitions, and 20.6% reported self-harm or suicidal thoughts.

Conclusion: The study highlights the presentation of GD in an under-researched Asian setting. Supporting individuals with GD in Asia requires sensitivity to cultural and societal factors with a holistic approach to individual well-being.

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Keywords: children and adolescents, gender dysphoria, gender identity

CLINICAL IMPACT

What is New

- The study examines the presentation of gender dysphoria (GD) in children and adolescents at an outpatient psychiatric clinic in Singapore across 5 years.
- There was an increase in new GD diagnoses being made at younger ages which may suggest greater self-awareness and willingness to seek help among younger individuals.

Clinical Implications

- Our findings emphasise the significant distress experienced by children and adolescents with GD, underscoring the need for tailored interventions and support.
- The study provides valuable insights to guide the development of practice guidelines and clinical strategies aimed at enhancing the well-being of this population.

INTRODUCTION

The understanding of gender dysphoria (GD) has evolved significantly, from early conflations of sexual orientation and gender identity to its recognition as a distinct condition characterised by gender incongruence. GD is now classified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[1] GD is currently defined as the discomfort with one's sex-relevant physical characteristics or with one's assigned gender at birth.[1] Western studies estimate the prevalence of GD to range from 0.002% to 0.7%,[1,2] while Asian studies report a range from 0.0015% to 0.92%.[2,3,4] These rates can vary based on study methodologies, sample populations and the sociocultural context of the region.[1,2] In more conservative Asian cultures, the diagnosis may still carry stigma, potentially causing delays in identification and increased risks.

Studies on gender dysphoria in the Asian context are limited. In Singapore, early research estimated a prevalence of up to 35.2 per 100,000 (0.035%),[5] though this likely reflects sampling bias, as it only included individuals who sought services at the country's only provider for gender-affirming surgery. Transgender males were found to be slightly

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younger, with lower educational levels and employment[6] compared to female counterparts.[7] Crossdressing, parent–child relationship issues and early childhood onset were also reported.[8] Follow-up studies of individuals who underwent sex reassignment surgery reported positive post-operative adjustments among transgender males,[9] where only 65% of transgender females were satisfied post-surgery, and 59% reported they would opt for the surgery again if given the choice. With advancements in medicine, policy changes and shifts in service availability, these earlier findings may not accurately represent the current situation. However, no official estimate of present-day prevalence exists, underscoring the need for more research in the Singapore population.

Psychiatric services addressing gender-related issues began with the establishment of the psychiatric ward at Singapore General Hospital (SGH) in 1979. The National University Hospital (NUH) operated a gender identity clinic from the early 2000s until 2008. In 2017, the Institute of Mental Health (IMH) launched a gender care programme that concluded in 2022. Currently, individuals in Singapore must be at least 18 years old or have parental consent if under 21 years old to receive hormonal treatment. In addition to public healthcare services, support can be sought from social services or private agencies. Ongoing efforts to develop clinical practice guidelines for GD highlight the importance of updated insights into the condition within Singapore. GD in Singapore remains poorly investigated. Hence, this study aims to profile young individuals presenting with GD at the Child Guidance Clinic, IMH; estimate the prevalence and incidence of GD based on clinical attendance; and examine the trajectories and outcomes of these individuals over time to better understand factors influencing the onset and presentation of GD.

METHOD

Study design and participants

We retrospectively reviewed the medical records of 107 patients with an existing GD diagnosis at the outpatient psychiatric clinic over a 5-year period between 1 January 2017 and 31 December 2021. Diagnoses were made by a psychiatrist using DSM-4/5 criteria. Ethics approval for the study was granted by the IMH Institutional Research Review Committee (775-2021) and the National Healthcare Group Domain Specific Review Board (2021/01015).

Data collection focused on the documentation of patients' psychiatric background and GD-specific clinical variables, aiming to establish the age when gender issues first surfaced and the details of their transition. Participants were categorised into 3 groups: (1) those diagnosed with GD before another psychiatric disorder, (2) those diagnosed with a psychiatric disorder before GD and (3) those diagnosed with GD only. Social transitioning included changes such as name, gender pronouns and clothing, while physical transitioning involved puberty blockers, hormone replacement therapy (HRT) and chest or genital surgery. Participants were grouped into 3 categories: (1) no concrete steps taken, (2) socially transitioned only and (3) both socially and physically transitioned. HRT information was based on self-reports during clinical consultations, as IMH does not offer HRT, and existing medical records did not capture prescription from other healthcare providers.

Mental health ratings

Participants were assessed using the Children's Global Assessment Scale (CGAS) and Clinical Global Impression-Severity (CGI-S) by their attending clinicians during clinic visits. CGAS is a clinician-rated scale measuring overall functioning, ranging from 1 to 100.[10] CGI-S rates the severity of illness, on a scale of 1 (normal) to 7 (most severely ill). Participants' earliest and most recent CGAS and CGI-S scores were collected as proxy measures of their well-being, given the lack of validated and reliable assessments for GD and the variability in their presentations, which often included other conditions or concerns over time.

Data analysis

Data were extracted from existing medical records (CPSS2), with clinic administrators processing and de-identifying the information before it was provided to the study team for analysis. Data on the number of Singapore residents aged 6 to 19 years were gathered from Singapore Department of Statistics to estimate the incidence and prevalence rates of GD from 2017 to 2021. We used the SPSS Statistics software version 26 (IBM Corp, Armonk, NY, US) to analyse demographic details, psychiatric history and GD-specific clinical variables to gain a clear understanding of the presentation of GD in an outpatient psychiatric setting using primarily correlation and regression analyses.

RESULTS

Demographics

The study included 107 participants, aged 6 to 19 years (mean age 16.58 years, standard deviation [SD] 1.77), all diagnosed with GD. Of these, 47 were natal males and 60 were natal females. The

majority of participants (95.3%) were Singapore citizens or Permanent Residents. Additionally, 71% were aged 14 to 17 years (mean age 15.0 years, SD 2.2) and of Chinese ethnicity (75.7%). Demographic characteristics are detailed in Table 2.

Prevalence and incidence of GD

We examined the incidence of newly diagnosed cases of GD from 2017 to 2021 (inclusive) (Table 1). The number of GD cases in the clinic increased over the 5-year study period, from 13 cases in 2017 to 33 in 2021 (Fig. 1). Based on the population of Singapore residents aged 6 to 19,[11,12] the incidence rate of GD increased from 2.17 per 10,000 population in 2017 to 5.85 per 10,000 population in 2021. The prevalence (2017–2021) of GD in the study was 1:5434 (0.019%).

Additionally, a simple linear regression further revealed a significant relationship between year (2017–2021) and number of new GD diagnoses at the clinic, ($F[1, 3]=26.76$, $P=0.014$, $R^2=0.90$, $\beta=0.95$).

Delay in formal help-seeking

During initial consultations, participants provided the age at which they first experienced gender-related issues. Among them, 71 (67%) first experienced gender-related issues before they turned 13 years old. The median age for the onset of these issues was 11 years, while the median age for seeking help from a healthcare provider was 16 years, indicating a 5-year delay in formal help-seeking (Fig. 2). The average age at which participants sought help for their GD concerns was 15.6 years (SD 1.8). A Spearman's rank-order correlation further revealed a positive correlation between age and time of GD diagnosis ($r_s[105]=0.58$, $P<0.01$).

This suggests that participants were diagnosed with GD at a younger age as time passes, decreasing the gap in formal help-seeking. A logistic regression found no difference between assigned sex at birth and delay in formal help-seeking ($F[1, 105]=0.15$, $P=0.70$, $R^2=0.001$).

Comorbid conditions and well-being

In addition to GD, 72 (67.29%) of the participants had psychiatric comorbidities. The most common comorbid diagnoses were mood disorders (n=53), followed by attention deficit hyperactivity disorder (ADHD) (n=21), anxiety disorders (n=12) and autism spectrum disorder (ASD) (n=12). One third of participants (n=32) were diagnosed with GD and at least 1 other psychiatric condition after their GD diagnosis, while 40 participants had a pre-existing psychiatric diagnosis prior to their GD diagnosis (Table 2).

A multiple linear regression model was used to assess how duration of follow-up at the clinic, age, gender and ethnicity contributed to changes in CGI-S and CGAS scores before and after treatment. The model for CGI-S score changes was significant ($F[4, 94]=3.45$, $P=0.01$, $R^2=0.13$), suggesting that participants' overall functioning improved after receiving clinic services. Further analysis showed that duration of follow-up at the clinic was a

Fig. 1. Prevalence and incidence rates of gender dysphoria (GD).

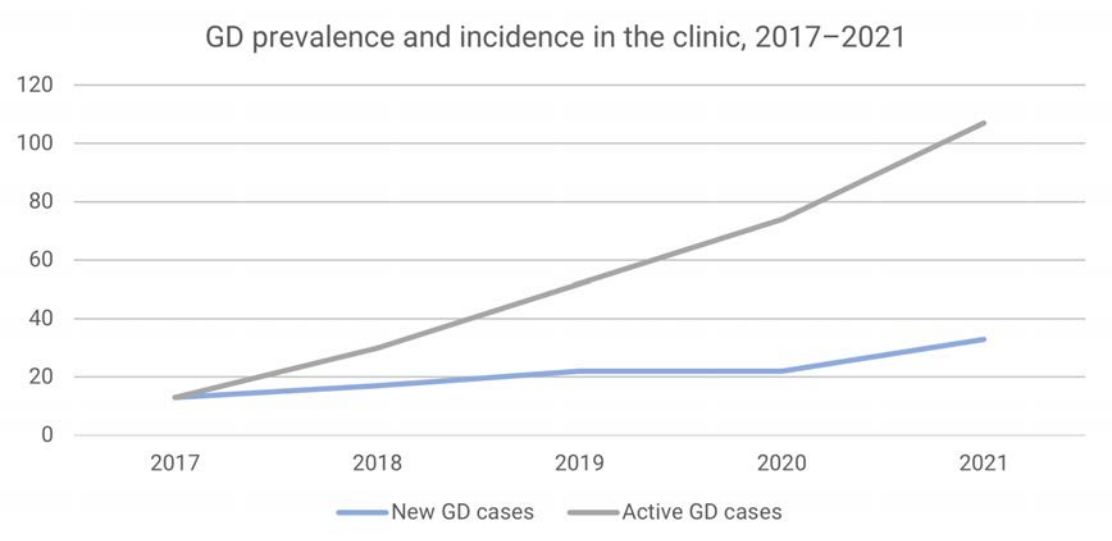


Table 1. Unique cases per year.

Year	Population number (6–19 years old)[a]	New diagnoses of gender dysphoria (n)	Incidence rate (new cases per 100,000 population)
2017	600,510	13	2.165
2018	591,778	17	2.873
2019	589,248	22	3.734
2020	579,900	22[b]	3.794
2021	563,970	33	5.851

[a] Singapore residents statistics from Singapore Department of Statistics
[b] Decrease in figure likely due to reduction in clinic appointment slots following restriction measures and public healthcare services advisories for COVID-19

significant predictor (t=3.70, $P<0.01$), while age (t=-0.88, $P=0.38$), gender (t=0.07, $P=0.95$) and ethnicity (t=-0.63, $P=0.53$) were not. This suggests that the longer they were on follow-up at the clinic, the larger the improvement in their CGI-S score. However, the model for changes in CGAS scores was not significant (F[4, 93]=1.78, $P=0.14$, $R^2=0.03$).

Changes in CGAS and CGI-S scores were analysed for each comorbid diagnosis. A multiple linear regression model was used to evaluate the impact of each comorbid condition on pre- and post-treatment changes in CGI-S and CGAS scores. A significant model was found for CGI-S score changes (F[5, 93]=3.26, $P=0.009$, $R^2=0.10$), with ASD being the only significant predictor (t=2.92, $P=0.004$), while mood disorders (t=1.42, $P=0.16$), ADHD (t=0.41, $P=0.68$) and anxiety (t=-0.88, $P=0.38$) were not. A significant model was also found for CGAS score changes (F[5, 92]=4.29, $P=0.001$), $R^2=0.19$). ASD (t=-2.2, $P=0.030$) was a significant predictor while mood disorders (t=-0.98, $P=0.33$), ADHD (t=0.19, $P=0.85$) and anxiety (t=1.42, $P=0.16$) were not. ASD was a significant predictor of pre- and post- treatment changes in both CGI-S and CGAS scores.

Among the 107 participants, 22 (20.6%) had previously been hospitalised for self-harm or suicidality concerns (e.g. suicidal ideation, verbalisation or attempts). None of the participants had more than 1 admission during the data extraction period. A total of 22 (20.5%) participants had attempted suicide before receiving their GD diagnosis, with 10 continuing to do so after the diagnosis. Additionally, 11 participants (10.3%) had not attempted suicide prior to their diagnosis but reported at least 1 attempt afterwards (Table 3).

Gender transition

In terms of transition, 42 (39.3%) of the participants had transitioned socially only, while 49 (45.8%) had transitioned both socially and physically. The remaining 16 (15%) either did not state their transition plans explicitly or had not attempted any form of transition. No participants had transitioned physically without also transitioning socially. Among those who had transitioned both socially and physically, most received HRT and/or puberty blockers through public healthcare institutions (n=22) or private clinics (n=20). A few did not report the source of their HRT (n=2), while others obtained it through online sources or friends (n=5). Additionally, 8 participants reported having undergone surgery (chest augmentation only, n=4; genital reassignment only, n=3; both, n=1). Moreover, 6 (75%) of participants who underwent surgery reported positive post-operative adjust-ments, while 1 (12.5%) reported feelings of regret. There was no update on the last participant post-surgery. No significant gender differences were found among the 3 transition groups, $r(105)=-0.16$, $P=0.10$.

A multiple linear regression analysis was conducted to examine the influence of demographic factors on HRT receipt. Participants' natal gender, nationality and ethnicity accounted for about 21% of the variance, but the model was not statistically significant ($F[3, 103]=1.60$, $P=0.19$, $R^2=0.21$). No other variables significantly predicted HRT receipt. However, receiving HRT was significantly correlated with improvements in CGAS, $r(96)=0.46$, $P<.0.1$ and CGI-S scores, $r(97)=-0.30$, $P<0.01$. Regression analyses showed that HRT receipt significantly predicted changes in CGAS (F[1, 96]=25.46, $P<0.01$, $R^2=0.21$) and CGI-S scores F[1, 97]=9.22, $P<0.01$, $R^2=0.09$), indicating that participants who received HRT experienced improvements in well-being based on these scores.

DISCUSSION

The incidence rate of GD in our study increased from 2.17 per 100,000 population in 2017 to 5.85 per 100,000 population in 2021. The prevalence

Table 2. Characteristics of participants (n=107).

Characteristics	No. (%)	Mean (SD)
Sex		
Female	60 (56.1)	
Male	47 (43.9)	
Nationality	107	
Singaporean	91 (85.0)	
Permanent Resident	11 (10.3)	
Non-citizens or resident	5 (4.7)	
Ethnicity[a]		
Chinese	81 (75.7)	
Malay	4 (3.7)	
Indian	5 (4.7)	
Others	17 (15.9)	
Age at first visit		15.04 (2.22)
Current age		19.25 (2.42)
Age when diagnosed with GD		16.58 (1.78)
Number of siblings		1.16 (0.96)
0	29 (27.1)	
1	41 (38.3)	
2	25 (23.4)	
≥3	10 (9.3)	
No information	2 (1.9)	
First diagnosis received		
ADHD	11 (10.3)	
Mood disorders	22 (20.56)	
Anxiety disorders	5 (4.7)	
ASD	3 (2.8)	
Eating disorders	1 (0.9)	
GD/gender identity disorder	64 (61.86)	
OCD	1 (0.9)	
Comorbid psychiatric diagnosis		
Mood disorders	53 (50.96)	
Anxiety disorders	12 (11.54)	
ADHD	21 (20.19)	
ASD	12 (11.54)	

Table 2. Characteristics of participants (n=107). (Cont'd)

Characteristics	No. (%)	Mean (SD)
Others	6 (5.77)	
Eating disorders	3 (2.88)	
PTSD	1 (0.96)	
Hallucination	1 (0.96)	
Unspecified	1 (0.96)	
Number of comorbidities		0.97 (0.87)
0	35 (32.7)	
1	45 (42.06)	
2	21 (19.63)	
≥3	6 (5.61)	
Admission		
No	85 (79.4)	
Yes	22 (20.6)	
Father's occupation		
Professional/managerial/executive/technical	47 (43.9)	
Others/self-employed	55 (51.4)	
Not working	2 (1.9)	
Mother's occupation		
Professional/managerial/executive/technical	56 (52.3)	
Others/self-employed	31 (29.0)	
Not working	20 (18.7)	
Age at which gender issue was raised to healthcare provider		15.64 (1.81)
Retrospective age when gender issues surfaced		10.43 (3.61)
Age when diagnosed with GD		16.58 (1.78)
Timeline of GD diagnosis		
GD diagnosis first	32 (29.9)	
GD diagnosis after	40 (37.4)	
GD diagnosis only	35 (32.7)	
Transition group		
No concrete steps taken	16 (15.0)	
Social only	42 (39.3)	
Social and physical	49 (45.8)	
Number of psychotherapy sessions attended in a year	67 (62.6)	8.90 (7.26)

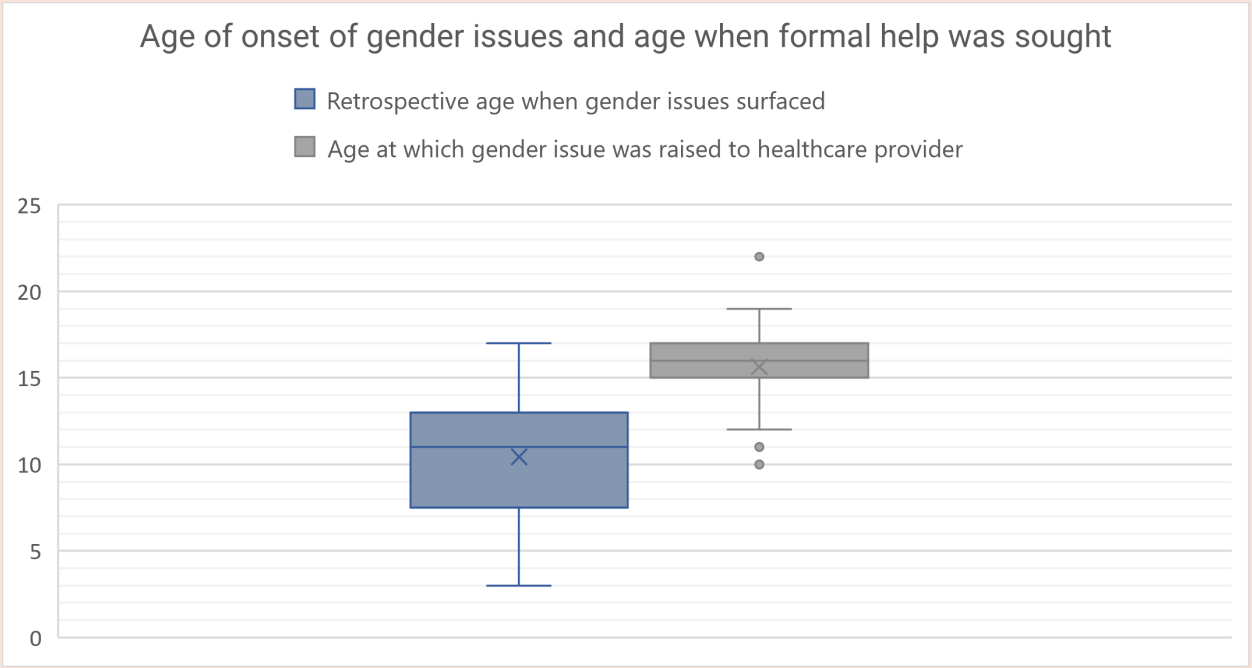
[a] Ethnic composition referenced the Singapore Census 2020[12] whereby Chinese, Malays and Indians constituted 74.3%, 13.5% and 9.0% of the resident population, respectively; 3.2% comprised all other ethnicities.
ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; CGAS: Children's Global Assessment Scale; CGI: Clinical Global Impression; GD: gender dysphoria; OCD: obsessive compulsive disorder; PTSD: post-traumatic stress disorder; SD: standard deviation

Table 3. Frequencies of suicide attempts (n=107)

Suicide attempts	No.	% of total	% cumulative
Pre-GD diagnosis			
Nil	74	69.2%	69.2%
1 attempt	6	10.3%	79.5%
2 attempts	4		
≥3 attempts	1		
Post-GD diagnosis			
Nil	12	11.2%	90.7%
1 attempt	6	9.3%	100%
2 attempts	3		
≥3 attempts	1		

GD: gender dysphoria

Fig. 2. Delay in formal help-seeking (years).



of GD in the study was 1:5434 (0.019%). These statistics are in line with previous prevalence data from other Asian studies.[2,3,4] There was an increase in new diagnoses over the 5-year study period, with diagnoses being made at younger ages. An earlier age of diagnosis may suggest greater self-awareness and willingness to seek help among younger individuals, rather than an earlier onset of GD. It could also reflect an increasingly supportive social environment for gender minorities, leading to younger individuals seeking formal help earlier. Open discussions and psycho-education about GD could foster a more positive and collaborative approach to treatment, reduce unsafe practices and decrease stigmatisation.

While there was a high rate of comorbid conditions, no significant difference in the severity of impairment or distress between natal males and females was observed, which may be due to participants' age (under 19 years). Past studies

reported a high level of psychiatric comorbidities,[13] including increased rates of suicide attempts in 9.3% of the population,[14] a 3-fold increased risk of anxiety disorders,[15] and higher rates of personality disorders compared to cisgender individuals.[16] Although the rate of suicide-related behaviours in our study was not higher than in other studies,[17] it remains a concerning issue. Additionally, our study reported similar rates of co-occurring neurodevelopmental disorders in GD. Past studies reported 6% to 26% of ASD and 4.3% to 20.4% of ADHD.[18] Greater gender non-conformity, dissatisfaction and societal pressure for gender conformity are associated with increased psychological distress.[19] Commonly reported issues include self-deprecation, irritability, mood swings and parental conflicts.[20] The severity of these challenges is likely to increase as individuals age and continue to navigate their gender identity.

The aetiology of GD is complex and multifaceted. Twin studies suggest that genetic factors may account for up to 38% of the variance,[21] while other factors such as the mother–child relationship, higher level of depression[22] and staying in urban and populated areas have been implicated.[23] A disparate sex ratio[24]—more natal males than females—also suggests a contribution of physical sexual differentiation in development that may involve biological, social and cultural determinants. The variability in persistence of GD further complicates the picture; about 80% of children reported GD desistance when they reached puberty.[25] A higher age of identification of GD has been associated with greater likelihood of persistence.[26]

The American Academy of Child and Adolescent Psychiatry advocates for evidence-based, individualised clinical care.[27] The Guidelines for Psychological Practice with Transgender and Gender Nonconforming People[28] and the Standards of Care for the Health of Transsexual, Transgender and Gender Nonconforming People[29] recommend affirmative treatment, which emphasises acceptance for diverse gender expressions and identities.[30] Currently, there is no evidence-based intervention for changing gender identity.[31] While affirmative treatment is supported, there is a recognised risk of iatrogenic harm, prompting the suggestion of exploratory psychotherapy (neither affirmative nor conversion) as a first-line treatment to provide psychological support.[32] Medical interventions may include hormone therapy and gender reassignment surgery,[33] though evidence assessing the risks of hormone therapy remains limited.[34,35] Extensive consultation, rigorous monitoring and follow-up with medical professionals are recommended.[36] There is also a lack of controlled studies and validated outcome measures for those who undergo gender reassignment surgery.[37] The decision to transition is often influenced by factors such as sexual orientation, the intensity of dysphoria and societal expectations.[38,39,40]

The availability of HRT from unlicensed sources poses significant health risks, particularly given the lack of evidence supporting its use in children and adolescents. The absence of significant findings related to risk and predictive factors in our study highlights the complexities of the subject, though this may also be due to the small sample size and limited study duration.

Our study has several notable limitations. Without matched controls, we are unable to determine whether the rate and severity of comorbid conditions in individuals with GD are higher than expected in the general population, nor can we draw conclusions about the timing of various diagnoses. The incidence rate and prevalence should be interpreted cautiously, as the study is based on data from a single hospital in Singapore and only includes individuals who have sought help. As a result, our figures likely underestimate the true prevalence of GD in the community. We also acknowledge the potential sampling bias in our population, which limits the generalisability of our findings. Additionally, the lack of standardised protocols for managing individuals with GD means there are no consistent indicators for systemic evaluation or comparison. Despite these limitations, our study provides valuable information and offers some insight into the complex presentation of GD in today's youths.

Further research into aetiological factors, such as comparisons with transgender individuals without GD, and longitudinal studies covering physical, mental and social aspects of functioning, including rates of desistance, the role of psychotherapy, vocational and social adjustment, physical health concerns and mental health well-being, would provide insights into the factors contributing to the development of GD. Many studies on GD rely on self-reports and retrospective data, limiting the accuracy, reliability and generalisability of findings. This, in turn, hinders the development of evidence-based treatment and management strategies, affecting the well-being of individuals with GD. There is also an urgent need for clear guidelines on the assessment and management of GD, especially in the youth population. While international guidelines offer useful references, it is essential to account for the unique social and cultural factors in the Asian context. The timely identification of GD, along with support for both individuals and their families and long-term monitoring, should be prioritised. Professionals working with gender-diverse youth

must recognise that variations in gender expression and identity are a normal part of human development. They should work collaboratively with individuals with GD and their families to develop personalised treatment plans, grounded in evidence-based care, that address the specific mental health needs and overall well-being of the individual.

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.

Ethics statement

The manuscript was approved by the IMH Institutional Research Review Committee (775-2021) and the National Healthcare Group's Domain Specific Review Board (2021-01015).

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ORIGINAL ARTICLE

Unplanned hospitalisations among subsidised nursing home residents in Singapore: Insights from a data linkage study

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ABSTRACT

Introduction: Hospitalisations can pose hazards and may not be an appropriate care setting for frail nursing home (NH) residents. Few studies have quantified the extent of NH resident hospitalisations in Singapore, hence we aimed to address this knowledge gap by studying characteristics of unplanned hospitalisations over a 1-year period.

Method: This was a retrospective cohort study of 9922 subsidised residents across 59 NHs in Singapore, with analysis using administrative healthcare data. Key measures included inpatient admission and emergency department visit rates, final discharge diagnoses and estimated costs. We examined correlates of inpatient admissions with a multivariable zero-inflated negative binomial regression model incorporating demographics, institutional characteristics and Charlson Comorbidity Index.

Results: There were 6620 inpatient admissions in 2015, equivalent to 2.23 admissions per 1000 resident days, and the majority were repeat admissions (4504 admissions or 68.0%). Male sex (incidence rate ratio [IRR] 1.23), approaching end-of-life (IRR 2.14), hospitalisations in the past year (IRR 2.73) and recent NH admission within the last 6 months (IRR 1.31–1.99) were significantly associated with inpatient admission rate. Top 5 discharge diagnoses were lower respiratory tract infections (27.3%), urinary tract infection (9.3%), sepsis (3.1%), cellulitis (1.9%) and gastroenteritis (1.1%). We estimated the total system cost of admissions of subsidised residents to be SGD40.2 million (USD29.1 million) in 2015.

Conclusion: We anticipate that unplanned hospitalisation rate will increase over time, especially with an increasing number of residents who will be cared for in NHs. Our findings provide a baseline to inform stakeholders and develop strategies to address this growing problem.

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Keywords: geriatric medicine, healthcare utilisation, hospitalisation, nursing homes, retrospective study

CLINICAL IMPACT

What is New

- This study is among the first to provide system-level data for the hospitalisations of subsidised nursing home residents across Singapore.
- Findings underscore the extent of hospitalisations, and could inform policymaking or guide resource allocation and quality improvement efforts.

Clinical Implications

- As the most common causes of hospitalisations are related to infections, strategies for improvement include proactive risk assessment, preventive care, early detection and management.
- Anticipatory care, including strengthening palliative care and promoting advance care planning, should also be encouraged.

INTRODUCTION

Hospitalisations pose hazards and safety risks to nursing home (NH) residents who may be frail, cognitively impaired, suffering from multimorbidities and physically dependent,[1] with propensity to develop adverse outcomes such as functional, psychological or cognitive decline, iatrogenic complications, and be subjected to over-investigation.[2] There is an imperative for health systems to reduce hospitalisations in this group, not only for cost containment but also to reduce the risk of harm.[3]

Between 6.8% and 45.7% of residents in NHs were hospitalised for various time periods of follow-up, based on a systematic review of 21 studies across

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the US, Canada, China and 4 European countries.[4] In Singapore, few studies have quantified the extent of NH resident hospitalisations at the health system level. One study in 2003 examining referrals from community step-down facilities (including NHs) to a single hospital emergency department (ED) noted that a high proportion of visits (82%) resulted in hospital admission, with the most common complaints being shortness of breath, fever and falls. However, the study did not assess whether the ED visits were appropriate.[5] A more recent study within 1 NH reported an inpatient admission rate of 1.53 per 1000 resident days, citing pneumonia, urinary tract infection (UTI) and sepsis as the most common reasons for admissions.[6]

Hence, our key objectives were to bridge this knowledge gap and establish baseline data by describing the characteristics and correlates of hospitalisations of NH residents in Singapore, which would inform stakeholders in developing strategies to reduce unplanned hospitalisations among this vulnerable group.

METHOD

We present a retrospective cohort study, analysing hospitalisations of NH residents from 1 January 2015 to 31 December 2015 using administrative healthcare data. We focused our analysis on unplanned hospitalisations (i.e. excluding planned admissions, for instance, for elective procedures). Ethics approval was granted by the National Healthcare Group Domain Specific Review Board (2017/00115).

Data sources

Access to administrative healthcare data was granted by the Ministry of Health (MOH). We obtained billing and subvention data from 4 datasets: Intermediate and Long-Term Care Information System (ILTC-IS2G) for long-term care utilisation, Casemix and Subvention (C&S) dataset for inpatient admissions, Emergency Department (ED) dataset for ED visits as well as death data from the Registry of Births and Deaths through the Immigration and Checkpoints Authority. **Only residents in NHs** who received operating subvention or subsidies from MOH were included **in** the analysis. Data for private or unsubsidised NH residents were not available.

Data extraction was performed by an MOH-approved vendor, and anonymisation was carried out by the same vendor by replacing the resident's National Registration Identity Card number or Foreign Identification Number with a project unique identifying number (PUIN). The different datasets were linked using deterministic rules via the PUIN.

Study cohort

The study cohort consisted of all prevalent, publicly-subsidised NH residents in Singapore, identified through service codes from the ILTC-IS2G dataset. We assessed that the data from ILTC-IS2G were fairly representative of the entire NH resident cohort, as more than 90% of residents are publicly subsidised and their billing and subvention records were comprehensively captured. Based on referral and placement criteria, NH residents were (1) aged 16 years and above; (2) semi-ambulant, wheelchair- or bed-bound; (3) required long-term skilled nursing care and/or assistance in activities of daily living; and (4) had no available or competent caregiver or have exhausted alternative care arrangements.

All NHs were licensed by MOH and classified according to their operator status. Of the 59 NHs, 33 were licensed as NHs operated by voluntary welfare organisations, i.e. charity or faith-based organisations, 22 NHs by private or for-profit organisations under the MOH NH Portable Subsidy Scheme and 4 under the Build-Own-Lease Scheme where the government bore infrastructural costs and conducted an open tender for operators to run these homes. Twelve NHs were operated by private organisations, and residents with short-term respite stays of fewer than 30 days were excluded from the analysis.

NH residents who had at least 1 hospital admission to 1 of 7 public hospitals and a tertiary medical centre in Singapore were identified through inpatient episodes in the C&S dataset and entered into the study. Data on admissions to private hospitals were unavailable.

Measures

Demographics and baseline characteristics

Demographic data included age group, sex, ethnicity and per-capita household income which was used to determine government subsidy bands (a proxy indicator for socioeconomic status). Comorbidities were identified from the C&S dataset using diagnoses coded with the International Classification of Diseases, 10th edition with clinical modification (ICD-10CM). We then applied an earlier developed algorithm to derive the Charlson Comorbidity Index (CCI) using the ICD-10CM codes,[7] with a 3-year look-back period of both primary and secondary diagnoses.

Length of residence, remaining lifespan and end-of-life (EoL)

The follow-up period was from 1 January 2015 to 31 December 2015, or to the latest hospital admission within the year 2015 for hospitalised residents, whichever was earlier. We computed the NH length

of residence from the date of admission into the NH to the date of discharge or death for decedents, or to 31 December 2015 for non-decedents. Remaining lifespan was calculated using the time interval to the date of death for decedents. We then created an EoL indicator using the definition of remaining lifespan of 1 year or less, based on guidelines developed by the National Strategy for Palliative Care Implementation Taskforce.[8]

Unplanned hospitalisation measures

These included the rate of ED visits and inpatient admissions per 1000 resident days (in which the resident days are calculated as the number of residents multiplied by the length of residence during the follow-up period). For ED visits and its outcome, we reported the triage status according to the Patient Acuity Category Scale (PACS) as defined by MOH.[9] For inpatient admissions, we included length of stay (LOS), discharge outcome, intensive care unit (ICU) utilisation and readmissions within 3, 15 and 30 days from the index admission. All inpatient admissions included in the analysis had at least a 24-hour LOS and 24-hour separation between consecutive admissions. ICD-10CM codes were used to identify final principal discharge diagnoses.

Healthcare costs

The healthcare system cost was the patient bill, including government subsidies, while the out-of-pocket (OOP) cost was computed as the patient bill after deducting the government subsidies. All costs were recorded in SGD.

Statistical analysis

Summary statistics were reported using frequencies for categorical variables and mean with standard deviation (SD) or median with interquartile range for continuous variables. Comparisons were made using independent sample t-tests for means and Pearson's chi-square test for proportions between groups with the normality assumption met.

We examined factors associated with inpatient admissions using a zero-inflated negative binomial regression model, and used the likelihood ratio test for over-dispersion to assess model fit. Patient-level characteristics included in the model were age group, sex, ethnicity, per-capita household income, length of residence in NH, the EoL indicator, CCI indicators and prior hospitalisation in the past 1 year; while facility-level predictors were NH operator type, bed capacity and an indicator for multi-site providers. We reported the incidence rate ratio (IRR), measuring the relative difference in incidence rates of the exposed group to the comparator group, with 95% confidence interval (CI). Unless otherwise stated, statistical significance was taken as $P<0.05$.

All statistical analyses were conducted using Stata software version 14.1 (StataCorp LLC, College Station, TX, US).

RESULTS

Cohort characteristics

Data from 9922 unique residents across 59 NHs were analysed (Table 1). Compared with those without hospitalisations, residents who had at least 1 inpatient admission were more likely to be male, approaching the EoL or deceased within the study period (all $P<0.001$). They were older, had shorter length of residence in the NH and higher comorbidity burden, with significantly higher proportions of comorbidities in all CCI indicators except AIDS/HIV.

Hospital utilisation

ED visits

A total of 7821 ED visits were recorded in 2015, equivalent to 2.63 visits per 1000 resident days (Table 2). The vast majority of ED visits (94.5%) were triaged as P1 (requiring resuscitation) or P2 (critical care) cases on PACS, and more than 81% of ED visits resulted in inpatient admission.

Inpatient admissions

Multiple inpatient admissions were common: averaging 1.8 admissions per resident per year, and ranging from 1 admission (58.1%) to >10 admissions per resident (0.3%), with the highest being 16 admissions by a single resident. "Frequent admitters" (i.e. residents who had 3 or more admissions within 12 consecutive months as defined by MOH) formed 18.8% of the cohort, but contributed to 42.5% of total admissions. The average LOS per episode was 7.8 days (median 6 days). Moreover, 5.6% of the cohort had prolonged LOS exceeding 21 days.

Readmissions

We further analysed non-risk-adjusted readmission rates. A total of 1252 readmissions (18.9% of total admissions) occurred within 30 days from the index admission. Of these, 760 (11.5% of total or 60.7% of 30-day readmissions) were within 15 days of discharge. A total of 227 readmissions (3.4% of total) occurred within only 72 hours post-discharge.

ICU utilisation

A small proportion (0.9%, n=60) of admissions included an ICU stay, and there were 24 direct admissions to ICU from ED.

Table 1. Baseline characteristics of nursing home residents in 2015.

Demographic characteristic	Total n=9922		With admission in 2015 n=3645		Without admission in 2015 n=6277		*P* value[a]
	N	%	N	%	N	%	
Age group (years)							
60 and below	1092	11.0	347	9.5	744	11.9	<0.001
61–70	1867	18.8	618	17.0	1249	19.9	
71–80	2535	25.6	930	25.5	1605	25.6	
81–90	3011	30.4	1224	33.6	1787	28.5	
Above 90	1402	14.1	526	14.4	877	14.0	
Sex							
Male	4963	50.0	2018	55.4	2947	47.0	<0.001
Ethnicity							
Chinese	8413	84.8	3051	83.7	5357	85.3	0.010
Malay	813	8.2	311	8.5	483	7.7	
Indian	519	5.2	203	5.6	313	5.0	
Others	165	1.7	80	2.2	112	1.8	
PCHI (subsidy band)[b]							
SGD700 and below (75%)	8734	88.0	3160	86.7	5574	88.8	<0.001
SGD700–1000 (60%)	608	6.1	227	6.2	381	6.1	
SGD1101–1600 SGD (50%)	393	4.0	185	5.1	208	3.3	
SGD1601–1800 SGD (40%)	70	0.7	31	0.9	39	0.6	
SGD1801–2600 SGD (20%)	109	1.1	38	1.0	71	1.1	
Length of residence in NH (years), mean (SD)	3.88 (4.03)	NA	3.70 (3.80)	NA	3.98 (4.15)	NA	<0.001
CCI, mean (SD)	3.0 (2.8)	NA	3.7 (3.0)	NA	2.5 (2.6)	NA	<0.001
Residents approaching EoL	754	6.3	475	13.0	279	4.4	<0.001
Died in 2015	1424	14.4	1041	28.6	383	6.1	<0.001
CCI indicators	**Total n=8534**		**With hospitalisations n=3645**		**Without hospitalisations n=4709[c]**		***P* value**
	n	%	n	%	n	%	
Myocardial infarction	930	11.1	580	15.9	350	7.4	<0.001
Congestive heart failure	760	9.1	433	11.9	327	6.9	<0.001
Peripheral vascular disease	414	5.0	264	7.2	150	3.2	<0.001
Cerebrovascular disease	2329	27.9	1108	30.4	1221	25.9	<0.001
Dementia	2597	31.1	1259	34.5	1338	28.4	<0.001
Chronic pulmonary disease	569	6.8	351	9.6	218	4.6	<0.001
Rheumatic disease	58	0.7	34	0.9	24	0.5	0.021
Peptic ulcer disease	214	2.6	118	3.2	96	2.0	0.001

Table 1. Baseline characteristics of nursing home residents in 2015. (Cont'd)

Demographic characteristic	Total n=9922		With admission in 2015 n=3645		Without admission in 2015 n=6277		*P* value[a]
	n	%	n	%	n	%	
Mild liver disease	340	4.1	181	5.0	159	3.4	<0.001
Moderate or severe liver disease	50	0.6	31	0.9	19	0.4	0.009
DM without complications	1733	20.7	988	27.1	745	15.8	<0.001
DM with complications	2708	32.4	1364	37.4	1344	28.5	<0.001
Hemiplegia or paraplegia	1120	13.4	529	14.5	591	12.6	0.001
Renal disease	1708	20.5	1011	27.7	697	14.8	<0.001
Any malignancy	506	6.1	306	8.4	200	4.3	<0.001
Metastatic solid tumour	187	2.2	124	3.4	63	1.3	<0.001
AIDS/HIV	15	0.2	7	0.2	8	0.2	0.812

AIDS/HIV: acquired immunodeficiency syndrome/human immunodeficiency syndrome; CCI: Charlson Comorbidity Index; DM: diabetes mellitus; EoL: end-of-life (with remaining lifespan of 1 year or less); NA: not applicable; NH: nursing home; PCHI: per-capita household income; SD: standard deviation

[a] *P* values reflect the differences between those with inpatient admissions in 2015 and those without inpatient admissions. The chi-squared test was used to compare differences in frequencies, while the independent-sample t-test was used to compare means.

[b] Only publicly subsidised individuals (subsidy band >0%) are included in the analysis.

[c] As the CCI was computed based on available International Classification of Diseases, 10th edition with clinical modification codes from the C&S dataset, residents without any hospitalisations in the 3-year look-back period to 2012 would not have any records for computation, hence there is a possibility that these figures are underestimated. Missing values were replaced by zeros.

Table 2. Hospital utilisation characteristics.

Characteristics	n	%
ED visits		
Total no. of ED visits (including ED observations)	7821	NA
Total NH resident bed days	2,975,148	NA
No. of residents with ED visits, % of total	4145	39.5
Mean no. of visits per resident (of those with visits)	1.89	NA
ED visit rate per 1000 resident days	2.63	NA
Priority status[a]		
P1 (resuscitation)	2661	34.0
P2 (critical care)	4731	60.5
P3 (ambulatory)	426	5.5
P4 (non-emergency)	NA[b]	NA
Outcome of ED visit		
Admitted or transferred to another institution[c]	6352[d]	81.2
Discharged with outpatient follow-up	1365	17.5
Death/death on arrival	69	0.9
Unclassified	35	0.5

Table 2. Hospital utilisation characteristics. (Cont'd)

Characteristics	n	%
Inpatient admissions		
Total no. of inpatient admissions	6620	NA
No. of residents admitted, % of total	3645	36.7
No. of admissions per resident (of those with admissions)		
Mean	1.82	
Median (IQR)	2 (1–4)	
Admission rate (all-cause) per 1000 resident days	2.23	
No. of residents		
with 1 admission	2116	58.1
with 2 admissions	844	23.2
with 3 admissions	343	9.4
with 4 admissions	165	4.5
with 5–10 admissions	167	4.6
with >10 admissions	10	0.3
No. of admissions by "frequent admitters"	2816	42.5
Hospital LOS		
Mean LOS per inpatient admission (days, SD)	7.8 (8.4)	
Median LOS (days, IQR)	6 (3, 9)	
Mean LOS per resident in 2015	14.1	
LOS categories per inpatient admission		
1–3 days	1899	28.7
4–7 days	2430	36.7
8–14 days	1524	23.0
>14 days	767	11.6
≥21 days ("long stayers")	367	5.6
Discharge outcome		
Step-down (i.e. back to NH) Follow-up at SOC[e]	4138 1122	62.5 17.0
Death	700	10.6
Discharged	600	9.0
Others	60	0.9
ICU utilisation (n=60)		
ICU average length of stay (days, SD)	3.7 (4)	NA
By ICU discharge outcome		
Others/step-down care	26	43.3
Death	19	31.7

Table 2. Hospital utilisation characteristics. (Cont'd)

Characteristics	n	%
Follow-up at SOC	10	16.7
Others/unclassified	5	8.3
Readmissions		
No. of 30-day readmissions, % of total admissions	1252	18.9
No. of 15-day readmissions, % of total admissions	760	11.5
Readmissions within 72 hours of discharge	227	3.4

ED: emergency department; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; NA: not applicable; NH: nursing home; SD: standard deviation; SOC: specialist outpatient clinics

[a] Priority classification is made at the point of triage at the ED, using the Patient Acuity Category (PAC) status defined by MOH.
[b] Due to restrictions on data confidentiality, aggregate counts/values with frequencies less than 5 are not released by MOH.
[c] This refers to other public/restructured hospitals, community hospitals or short-stay units.
[d] The figures here differ from the earlier number of hospital admissions in Table 2 as they include direct inpatient admissions or admissions from SOCs.
[e] SOCs refer to specialist care in hospitals or tertiary medical centres delivered in an outpatient setting.

Discharge outcomes

While the majority of hospitalised residents were discharged to step-down care (i.e. back to NH, 62.5%) or with outpatient follow-up (17.0%), 10.6% of admissions (n=700) had death as the discharge outcome. Of the ICU admissions, 31.7% (n=19) had death as the discharge outcome.

Principal causes of inpatient admission

Infections were among the top final principal discharge diagnoses in 2015 (Table 3), with lower respiratory tract infections (including pneumonia 20.5%, aspiration pneumonitis 4.0% and other lower respiratory infections 2.8%), UTI (9.3%), sepsis (3.1%), cellulitis (1.9%) and gastroenteritis/colitis (1.1%) ranking among the top 10. Cumulatively, the top 10 final principal discharge diagnoses accounted for almost half of all admissions.

By diagnostic categories grouped by ICD-10CM codes, we observed that respiratory conditions (J00-J99), which included infections as well as exacerbations of chronic respiratory illnesses, and genitourinary tract disorders (N00-N99) were the top 2 categories (33.0% and 11.2%, respectively); followed by "ill-defined injuries" (S00-T98, 9.1%) which include complications arising from prosthetic devices such as urinary catheters; and other infectious diseases (A00-B99, 7.5%) and digestive tract diseases (K00-K93, 7.4%).

Falls or traumatic injuries leading to head injury (1.1%), peritrochanteric fracture (0.6%) and neck of femur fractures (0.6%) accounted for <3% of all admissions. Other chronic conditions also accounted for a relatively small proportion of primary discharge diagnoses, mainly from acute and chronic complications of diabetes mellitus and cardiovascular disease.

Cost of hospitalisations

The total system cost of hospitalisations of NH residents was SGD40,247,000 in 2015 (USD29,164,000) or approximately 11% of public expenditure on NHs in financial year 2015 (SGD360 million, or USD261 million).[10] Total OOP was approximately SGD12,630,000 (USD9,152,000; 31.4% of system cost of hospitalisations).

The mean cost of inpatient admissions ("system cost") of NH residents was SGD6100 per episode in 2015 (SD: SGD6700), of which slightly under a third of the system cost was borne by the resident and family/next-of-kin through OOP costs (mean OOP: SGD1900, SD: SGD2000). This translated to an average system cost of SGD780 (or SGD245 in OOP) per inpatient bed-day (Table 4).

Multivariable modelling

Men had a significantly higher incidence rate (IRR 1.23, 95% CI 1.10–1.37) of inpatient admission, and hospitalisation rate of residents who were approaching EoL was more than twice than those who had not approached EoL (IRR 2.14, 95% CI 1.86–2.46) (Table 5). Furthermore, the hospitalisation rate of residents who had prior hospitalisations in the past year was nearly 3 times that of residents without any hospitalisations (IRR 2.73, 95% CI 2.38–3.12). Age group, ethnicity and per-capita household income differences, which were statistically significant in the univariate analysis, became non-significant.

Compared with those who had been admitted to NH for more than 5 years, residents admitted within 3 months to NH had higher hospitalisation rate (IRR 1.99, 95% CI 1.62–2.45) followed by those within 4–6 months (IRR 1.31, 95% CI 1.11–1.55).

Table 3. Final principal discharge diagnoses[a] by International Classification of Diseases, 10th edition with clinical modification codes.

ICD-10 code	Top 30 final principal discharge diagnoses	n	%	Cumulative %[b]
J18.9	Pneumonia, unspecified	1356	20.5	20.5
N39.0	Urinary tract infection, site not specified	616	9.3	29.8
J69.0	Pneumonitis due to food and vomit	264	4.0	33.8
A41.9	Sepsis, unspecified	204	3.1	36.9
J22	Unspecified acute lower respiratory infection	183	2.8	39.6
T83.5	Infection due to prosthetic device, implant in urinary system	158	2.4	42.0
L03.1	Cellulitis of other parts of limb	128	1.9	43.9
S09.9	Unspecified injury of head	73	1.1	45.0
A09.9	Gastroenteritis and colitis of unspecified origin	72	1.1	46.1
K92.2	Gastrointestinal haemorrhage, unspecified	64	1.0	47.1
I50.0	Congestive heart failure	64	1.0	48.1
J06.9	Acute upper respiratory infection, unspecified	63	1.0	49.0
E11.7	Type 2 diabetes mellitus: multiple complications	58	0.9	49.9
K59.0	Constipation	57	0.9	50.8
E14.6	Unspecified diabetes mellitus: other specified complications	53	0.8	51.6
E11.6	Type 2 diabetes mellitus: other specified complications	52	0.8	52.4
J44.0	COPD with acute lower respiratory infection	51	0.8	53.1
I63.9	Cerebral infarction, unspecified	41	0.6	53.7
R50.9	Fever, unspecified	41	0.6	54.4
G40.9	Epilepsy, unspecified	41	0.6	55.0
S72.1	Pertrochanteric fracture	41	0.6	55.6
E14.7	Unspecified diabetes mellitus: with multiple complications	39	0.6	56.2
E14.2	Unspecified diabetes mellitus: with renal complications	38	0.6	56.8
A41.5	Sepsis due to other Gram-negative organisms	36	0.5	57.3
J45.9	Asthma, unspecified	34	0.5	57.8
E11.2	Type 2 diabetes mellitus: with renal complications	32	0.5	58.3
E11.0	Type 2 diabetes mellitus: with coma	32	0.5	58.8
S72.0	Fracture of neck of femur	31	0.5	59.2
R29.6	Tendency to fall, not elsewhere classified	30	0.5	59.7
I21.4	Acute subendocardial myocardial infarction	29	0.4	60.1
ICD-10 chapter	**Title of ICD-10 chapter**	**N**	**%**	**Cumulative %**
J00-J99	Diseases of the respiratory system	2186	33.0	33.0
N00-N99	Diseases of the genitourinary system	742	11.2	44.2
S00-T98	Injury and poisoning	600	9.1	53.3
A00-B99	Infectious and parasitic diseases	495	7.5	60.8

Table 3. Final principal discharge diagnoses[a] by International Classification of Diseases, 10th edition with clinical modification codes. (Cont'd)

ICD-10 code	Top 30 final principal discharge diagnoses	n	%	Cumulative %[b]
K00-K93	Diseases of the digestive system	488	7.4	68.1
E00-E90	Endocrine, nutritional and metabolic diseases	466	7.0	75.2
I00-I99	Diseases of the circulatory system	414	6.3	81.4
R00-R99	Symptoms and signs not elsewhere classified	325	4.9	86.3
L00-L99	Diseases of the skin and subcutaneous tissue	295	4.5	90.8
G00-G99	Diseases of the nervous system	148	2.2	93.0
C00-D48	Neoplasms	130	2.0	95.0
M00-M99	Diseases of the musculoskeletal system and connective tissue	123	1.9	96.9
F00-F99	Mental and behavioural disorders	81	1.2	98.1
D50-D89	Diseases of blood and blood-forming organs	44	0.7	98.8
H00-H59	Diseases of the eye and adnexa	34	0.5	99.3
Z00-Z99	Factors influencing health status	32	0.5	99.8
H60-H95	Diseases of the ear and mastoid process	14	0.2	100

COPD: chronic obstructive pulmonary disease
[a] Obtained from the Casemix & Subvention (C&S) dataset for inpatient admission episodes.
[b] Percentages may not add up due to rounding.

Table 4. Average system cost and out-of-pocket for inpatient admissions.

Characteristic	Result, SGD
System cost per admission	
Mean (SD)	6079.65 (±6675.24)
Median (IQR)	4210.23 (2547.84–7233.96)
90th percentile	12,146.63
OOP per admission	
Mean (SD)	1907.82 (±1956.66)
Median (IQR)	1397.81 (852.33–2277.88)
90th percentile	3677.19

IQR: interquartile range; OOP: out-of-pocket; SD: standard deviation, SGD: Singapore dollar
Note: All costs are recorded in 2015 Singapore dollars.

NH operator type, "chain" operator status (organisations operating multiple sites or branches) and bed capacity were not significantly associated with the hospitalisation rate.

DISCUSSION

Our findings highlighted the impact of unplanned hospitalisations among NH residents in Singapore. NH residents (about 36.7% of the cohort) were hospitalised at a rate of 2.23 inpatient admissions per 1000 resident days in 2015, approximating to a crude rate of 667.2 admissions per 1000 residents, which was almost twice the rate of 292.9 (females) – 347.6 (males) per 1000 for the general older population aged 65 & above.[11] The volume of hospitalisations is expected to increase with the growing number of NH places (in tandem with a rapidly ageing population), which has reached 18,157 beds at the end of 2022,[12] and is planned to almost double to 31,000 beds by 2030.[13]

Table 5. Factors associated with hospital admissions,[a] using multivariable zero-inflated negative binomial regression model.

Characteristic	Crude IRR	95% CI for IRR	*P* value
Age group (years)			
60 and below	(ref)	NA	NA
61–70	0.95	0.82–1.11	0.551
71–80	0.93	0.80–1.09	0.353
81–90	0.94	0.79–1.12	0.487
Above 90	0.91	0.76–1.09	0.305
Sex			
Male	1.23	1.10–1.37	<0.001
Ethnicity			
Chinese	(ref)	NA	NA
Malay	0.96	0.86–1.09	0.538
Indian	0.92	0.77–1.09	0.315
PCHI (subsidy band)			
SGD700 and below	(ref)	NA	NA
SGD701–1100	1.18	0.80–1.73	0.401
SGD1101–1600	1.33	0.98–1.79	0.064
SGD1601–1800	1.15	0.85–1.57	0.358
SGD1801–2600	1.15	0.88–1.50	0.319
Length of residence in NH			
>5 years	(ref)	NA	NA
0–3 months	1.99	1.62–2.45	<0.001
4–6 months	1.31	1.11–1.55	0.001
7–9 months	1.05	0.88–1.25	0.597
10–12 months	0.93	0.79–1.10	0.411
1–2 years	0.84	0.74–0.96	0.010
2–5 years	0.90	0.79–1.01	0.075
NH licensing type			
VWO	(ref)	NA	NA
PNH	1.11	0.88–1.38	0.385
BOL	1.07	0.82–1.38	0.618
Organisations operating NHs in multiple sites ("chain" operator)	1.20	0.97–1.49	0.087
NH capacity			
<100 beds	(ref)	NA	NA
100–149 beds	0.75	0.53–1.05	0.093
150–249 beds	0.87	0.68–1.10	0.248
≥250 beds	0.89	0.70–1.15	0.381

Table 5. Factors associated with hospital admissions[a]: multivariable zero-inflated negative binomial regression model. (Cont'd)

Characteristic	Crude IRR	95% CI for IRR	*P* value
Residents approaching EoL	2.14	1.86–2.46	<0.001
CCI indicators			
Myocardial infarction	1.43	1.26–1.62	<0.001
Congestive heart failure	1.15	1.01–1.31	0.041
Peripheral vascular disease	1.47	1.22–1.76	<0.001
Cerebrovascular disease	1.26	1.13–1.40	<0.001
Hemiplegia-paraplegia	1.06	0.92–1.23	0.404
Diabetes mellitus (without complications)	1.49	1.32–1.68	<0.000
Diabetes mellitus (with chronic complications)	0.99	0.88–1.11	0.862
Dementia	1.43	1.31–1.56	<0.001
COPD	1.54	1.41–1.79	<0.001
Renal disease	1.43	1.29–1.59	<0.001
Mild liver disease	1.30	1.07–1.57	0.007
Moderate-severe liver disease	1.14	0.80–1.63	0.469
Any malignancy	1.44	1.24–1.68	<0.001
Metastatic solid tumour	1.14	0.89–1.44	0.300
Prior history of hospital admission in past 1 year	2.73	2.38–3.12	<0.001

P values in bold denote statistically significant result *P*<0.05.
BOL: build-own-lease; CCI: Charlson Comorbidity Index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EoL: end-of-life; IRR: incidence rate ratio; NA: not available; NH: nursing home; PCHI: per-capita household income; PNH: for-profit organisations under the MOH NH Portable Subsidy Scheme; VWO: voluntary welfare organisation

This would be further compounded by the changing demographics of NH residents who are expected to be older, with greater frailty and multi-morbidity burden, and closer to the EoL.

Residents with higher hospitalisation rates were men, those with comorbidities and approaching the EoL, those with history of prior hospital admission(s) in the preceding year, and those recently admitted to the NH (0–6 months) as compared with residents with longest stay of more than 5 years. The impact of sex differences,[4] multi-morbidity[14] and EoL[15] on hospital utilisation are well documented in previous studies. Approaching the EoL as a correlate for unplanned hospitalisations also emphasises the importance of advance care planning (ACP) and palliative care provision in NHs, which aim to protect such residents from unnecessary and often futile hospitalisations which do little to improve quality of life or even prolong survival.

Unsurprisingly, most cases necessitating hospitalisation among NH residents were related to infections (lower respiratory tract infections, UTI, cellulitis and gastroenteritis), which are also leading causes of morbidity and mortality in the same population.[16] These contrast with the overall top 10 conditions of hospitalisation across all age groups in Singapore, where accidents, poisoning and violence (8.2%), cancer (6.0%), pneumonia (3.0%), ischaemic heart disease (3.1%) and intestinal infectious diseases (2.6%) ranked among the top conditions.[17] Risk factors for such infections in the NH population include frailty, high functional dependency, polypharmacy, low vaccination rates, long-term nasogastric tube feeding and urinary catheterisation.[18] These are common clinical issues in the NH care setting and could serve as potential targets for intervention. National infection prevention and control guidelines issued by the MOH could serve as guidance for NHs to put in place basic precautions and prevention measures including surveillance, environmental controls and vaccinations in the long-term care setting.[19] Many older residents may also have underlying dysphagia of varying degrees, which predisposes them to repeated aspiration and hence pneumonia,

emphasising a focus on early detection and management.

Another factor which could contribute to hospitalisations is the management of care transitions,[20] where recent admissions into an NH pose significant risks of re-hospitalisation during this phase. Newly admitted residents may have relatively less stable health conditions immediately following discharge from the hospitals, and together with lack of familiarity with the residents' care needs initially, this could leave the NH to manage such complex care needs exceeding their capabilities. Recent hospitalisations also increase susceptibility of infections which may lead to rehospitalisation.

Our findings on the readmissions also call upon the current model of care in NHs to be reviewed. There is a need to adopt a more proactive mode to assess and anticipate crises early and manage them pre-emptively before hospitalisation. It is also imperative that, to manage "unnecessary" or "preventable" transfers to hospitals, NH staff be upskilled and equipped to manage certain acute and subacute conditions effectively on site, or consider reskilling or job redesigning to manage the increasingly complex NH population and improve continuity of care.

Systematic reviews, which studied "potentially avoidable hospitalisations (PAH)", have found components of initiatives that could potentially reduce the burden of hospitalisation, including enhancing primary and geriatric care in the NH, palliative care,[21,22] the use of nurse practitioners or physician assistants to enhance the medical care[23] and programmes or interventions for early identification and evaluation of acute changes in a resident's condition.[24]

Anticipatory care in the form of ACP and goals of care setting should also be encouraged in the NHs, especially in partnership with hospitals and hospices where it could be initiated. For residents who may be at EoL, palliative care should be made available in the NHs. To this end, programmes involving collaborations between hospital care teams and NHs, such as Project Care that integrates geriatric care, ACP and upskilling of NHs to manage common EoL symptoms should be scaled up significantly.[25] The recently published National Strategy for Palliative Care by the MOH also calls for general palliative care models to be developed in NHs, combined with systematic screening and timely identification of residents who would benefit from specialist care.[26]

Strengths and limitations

To the best of our knowledge, this is the first study describing the extent of unplanned hospitalisations of a large cohort of NH residents across Singapore. It establishes a comprehensive baseline that could inform and guide various stakeholders on strategies to reduce unplanned hospitalisations and therefore reduce harm and healthcare costs.

Our focus on subsidised residents could introduce selection bias. However, as mentioned earlier, we minimised bias by including data from all subsidised residents from public administrative databases with a high coverage (>90% of entire cohort). Due to the retrospective cohort design of this study, we were unable to assess causality of the factors identified, and the impact of ongoing interventions that could impact hospitalisation rates. Notably, the data sources we used and the multivariable model we developed did not allow for more detailed analysis of clinical factors associated with hospitalisations, such as functional impairment, implementation of ACP, mood and cognition, and health stability. Notably, there were a large amount of missing baseline clinical information (15.8%, n=1568) from the cohort that did not have hospital admissions due to the lack of records. In prospective studies, reduced physical function, polypharmacy and malnutrition in NH residents were associated with increased risk of hospitalisations.[18] Future studies could characterise these factors using comprehensive assessment tools, such as the interRAI LTCF.[27] Other facility- or systems-level factors may also have an impact, such as the overall quality of care in NHs, the impact of staffing ratios or skills mix of NH staff,[28] and the role of incentives and public health policies to influence hospitalisations in other comparable healthcare systems which were not assessed in this study. Additional studies are needed to better understand these factors in Singapore. Finally, we also acknowledge the limited generalisability of our findings to NH populations beyond Singapore given our study cohort.

CONCLUSION

With the rising numbers of NH residents, reduction of hospitalisations should be a key metric for the long-term care sector to target for quality improvement. Our findings suggest the need for a multipronged approach involving various stakeholders that include the following strategies: identify those at higher risk of hospitalisations, enhance capabilities of NHs for early detection and management of

acute conditions on-site, strengthen palliative care and ACP, and improve care transitions to the NH. It also calls for a need to transform care models in the NH towards that of a preventative focus.

Ethics statement

The study was approved by the National Healthcare Group Domain Specific Review Board (2017/00115).

Declaration

The author(s) 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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REVIEW ARTICLE

Updated consensus guidelines for management of moderate-to-severe atopic dermatitis in Singapore: Integrating biologics, Janus kinase inhibitors and conventional therapies

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ABSTRACT

Introduction: Since 2016, several therapies have been approved for treating atopic dermatitis (AD) in Singapore, including biologics, oral Janus kinase (JAK) inhibitors and topical crisaborole. This study supplements the 2016 Singapore treatment guidelines for AD, focusing on newer therapies for moderate-to-severe disease, while revisiting older treatment regimens to accommodate changes in knowledge and practice.

Method: A modified Delphi panel was held, led by 2 co-chairs. The voting expert panel consisted of 12 dermatologists experienced in managing AD in Singapore. Delphi survey rounds were conducted between 24 July and 27 October 2023. Panellists indicated their agreement with drafted statements using a 5-point Likert scale. Consensus was defined as ≥80% agreement. An expert meeting was held to facilitate the consensus process between rounds 1 and 2 of voting.

Results: All expert panellists participated in both survey rounds, with a 100% response rate. Thirty-nine statements, classified into general principles, conventional treatments, biologics and JAK inhibitors, were proposed. Of these, 27 statements reached consensus at the end of round 1. After the expert meeting, 17 statements were included in round 2, of which 16 statements reached consensus. One statement did not reach consensus. Key updates are the inclusion of dupilumab and JAK inhibitors as potential first-line treatments for moderate-to-severe AD, in certain populations.

Conclusion: This modified Delphi study generated consensus among Singapore dermatology experts, to update treatment guidelines in moderate-to-severe atopic dermatitis. The consensus statements developed are intended to supplement the 2016 Singapore treatment guidelines for AD. Further revisions may be required when new evidence and/or treatments become available.

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Keywords: biologics, calcineurin inhibitors, corticosteroids, eczema, Janus kinase inhibitors, phosphodiesterase-4 inhibitors

CLINICAL IMPACT

What is New

- This updated treatment guideline for moderate-to-severe atopic dermatitis (AD) is based on consensus statements generated via a modified Delphi panel of dermatologists in Singapore.

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- The statements address newer approved treatments such as biologics and oral Janus kinase (JAK) inhibitors, while revisiting older therapies to accommodate changes in knowledge and practice.

Clinical Implications

- The consensus statements are intended to supplement the 2016 Singapore treatment guideline for AD.
- Dupilumab and JAK inhibitors have been included as potential first-line treatments for moderate-to-severe AD in certain populations.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterised by dry skin, localised red scaly patches, intense itching and skin pain.[1-4] Although its onset most commonly occurs before the age of 5, AD can develop during later childhood, adolescence or adulthood.[1-3] Recurrence can also follow extended periods of remission.[1-3] A 2018 community-based cross-sectional survey confirmed a high AD prevalence of 13.1% in Singapore (20.6% in children aged ≤18 years; 11.1% in adults).[5] Heat, dust and physical exercise were the most common aggravating factors.[5]

In the 2021 Global Burden of Disease study, AD was ranked first among skin diseases in terms of burden measured by disability-adjusted life years.[6] Among children and adults in Singapore, a significantly higher proportion of AD patients (89%) reported suboptimal quality of life (QoL), measured using the EQ-5D visual analogue scale, compared to those without AD (77.4%).[5]

Several treatment options can alleviate the symptoms of AD and improve QoL.[7] In the 2016 guidelines developed by the Dermatological Society of Singapore (DSS), treatment strategies are tailored to the severity of AD.[8] In general, patients are advised to moisturise their skin with emollients and are prescribed topical anti-inflammatory therapies such as corticosteroids or topical calcineurin inhibitors (TCIs).[8] For severe disease, more potent topical corticosteroids, phototherapy and systemic therapy can be considered.[8] Individualised therapy,[4] in combination with patient education, is key to achieving good outcomes.[8]

Since 2016, several new therapies have been approved for the treatment of AD in Singapore, including biologics (e.g. dupilumab) in 2019,[9-11] as well as oral Janus kinase (JAK) inhibitors (e.g. abrocitinib,[12,13] baricitinib,[14,15] upadacitinib[16,17]) and crisaborole ointment in 2022.[18,19]

The objective of this study was to supplement the 2016 Singapore treatment guidelines for AD, focusing on the newer therapies for moderate-to-severe AD, while revisiting older treatment regimens to reflect any changes in current practice. A modified Delphi panel method—a technique widely used in health services research to generate consensus[20]—was employed as it offers a systematic, robust and reproducible methodology for developing consensus statements via iterative rounds of anonymised voting.[21,22]

METHOD

This guideline update was initiated by the DSS, led by 2 co-chairs (YWY and HYL), who provided subject matter expertise in developing consensus statements for voting by an expert panel. Costello Medical, a third-party healthcare consultancy, generated evidence to inform statements by completing a targeted literature review and coordinated anonymised voting on consensus statements by the expert panel, ensuring that all experts were blinded from each other's inputs.

Recruited panellists were practising dermatologists in Singapore with expertise and interest in managing AD in adults and/or children, as demonstrated by authorship of AD publications (including the previous 2016 AD guidelines), participation in advisory boards or as invited speakers on relevant topics, experience as primary or site investigators for AD trials/research studies, and extensive senior consultant experience at specialist clinics, including eczema clinics at hospitals in Singapore. Additionally, recruitment aimed to ensure representation from both the public restructured healthcare institutions and the private sector. To avoid bias, the co-chairs did not participate in voting on consensus statements during the Delphi rounds. All participating experts are authors of this guideline.

Targeted literature review

Key recommendations from the 2016 Singapore AD treatment guidelines were summarised.[8] The reference list for the Global Guidelines in Dermatology Mapping Project (GUIDEMAP) systematic literature review (SLR) publication was hand-searched to identify international AD guidelines published between 1 April 2016 and 1 April 2021.[23] Additional supplementary Google searches were performed to identify guidelines published after 1 April 2021 up to 10 April 2023. Google was used because some treatment guidelines published in grey literature (e.g. medical society websites) may not be indexed in medical literature databases like MEDLINE.

Identified guidelines were assessed for relevance based on the population of interest being patients

with moderate-to-severe AD, discussion of new therapies such as JAK inhibitors, biologics and topical crisaborole, and inclusion of treatment recommendations outside of the 2016 Singapore guidelines. Consensus statements were drafted based on the outputs of the targeted literature review and finalised with feedback from the co-chairs.

Modified Delphi process

The Delphi technique refers to a structured method for consensus generation, characterised by its iterative process, allowing the incorporation of controlled feedback, with participant anonymity, to avoid social pressure to conform to a dominant view.[24, 25]

Delphi survey rounds were conducted between 24 July 2023 and 27 October 2023, using an online survey platform that maintained anonymity. During each survey round, panellists indicated their agreement with each statement on a 5-point Likert scale (strongly disagree; disagree; neutral; agree; strongly agree).[26] In addition, free text boxes allowed for qualitative feedback and comments, which were used to inform revisions or the formulation of additional statements. An a priori consensus threshold of ≥80% agreement (selection of "strongly agree"/"agree") or disagreement (selection of "strongly disagree"/"disagree") among the expert panel was defined.

An expert meeting was convened following the circulation of results from round 1. The meeting allowed for the exchange of clinical opinions, insights and knowledge to support the reformulation of statements that did not reach consensus. During the expert meeting, panellists were advised to prioritise the best available treatment approaches, without being influenced by cost considerations, given that subsidy status in Singapore may change over time.

Revisions of non-consensus statements and the formulation of additional statements were conducted under the guidance of the co-chairs, based on the discussions during the expert meeting. Panellists then voted on the updated statements in round 2 of the Delphi survey. All voting took place via online surveys under standard Delphi conditions of participant anonymity.[24] Statements that did not reach consensus in round 2 were excluded from the final guideline supplement.

RESULTS

Targeted literature review

A total of 54 AD guidelines were identified from the literature search. Prioritisation strategies were implemented to identify the most relevant guidelines for the Singapore context. Guidelines not in the English language (n=8) and with Appraisal of Guidelines for Research & Evaluation (AGREE) II average scores <5, as reported in the GUIDEMAP SLR, were deprioritised (n=21).[27] Additionally, only the most recent guideline from each country was included (n=4 excluded). For guidelines identified via supplementary Google searches, documents from lower-income countries (based on the World Bank categorisation of economies)[28] were deprioritised (n=3).

In total, 18 guidelines were included and reviewed (Supplementary Fig. S1). Data extraction focused on divergences from the 2016 Singapore guidelines, identifying 4 broad categories of treatment: new systemic, new topical, older systemic and older topical therapies. Where reported, the patient indication for each treatment, the recommendation (recommended, not recommended, unclear), and the level of evidence supporting the statements were extracted, in order to identify gaps that formed the basis for the development of consensus statements for voting in round 1 of the Delphi survey.

Delphi survey

The voting expert panel consisted of 12 experts, 58% (n=7) of whom practised primarily in public healthcare settings, with the remaining 42% (n=5) practising in private healthcare. The majority (58%, n=7) had an even mix of adult and paediatric patients, with 4 panellists who treated adults more often and 1 panellist who mostly treated children. The expert panel included members with subspecialty interests in paediatric dermatology (n=4), immunodermatology (n=4), inpatient dermatology (n=3) and photodermatology (n=1). All panellists participated in both survey rounds with no missing responses.

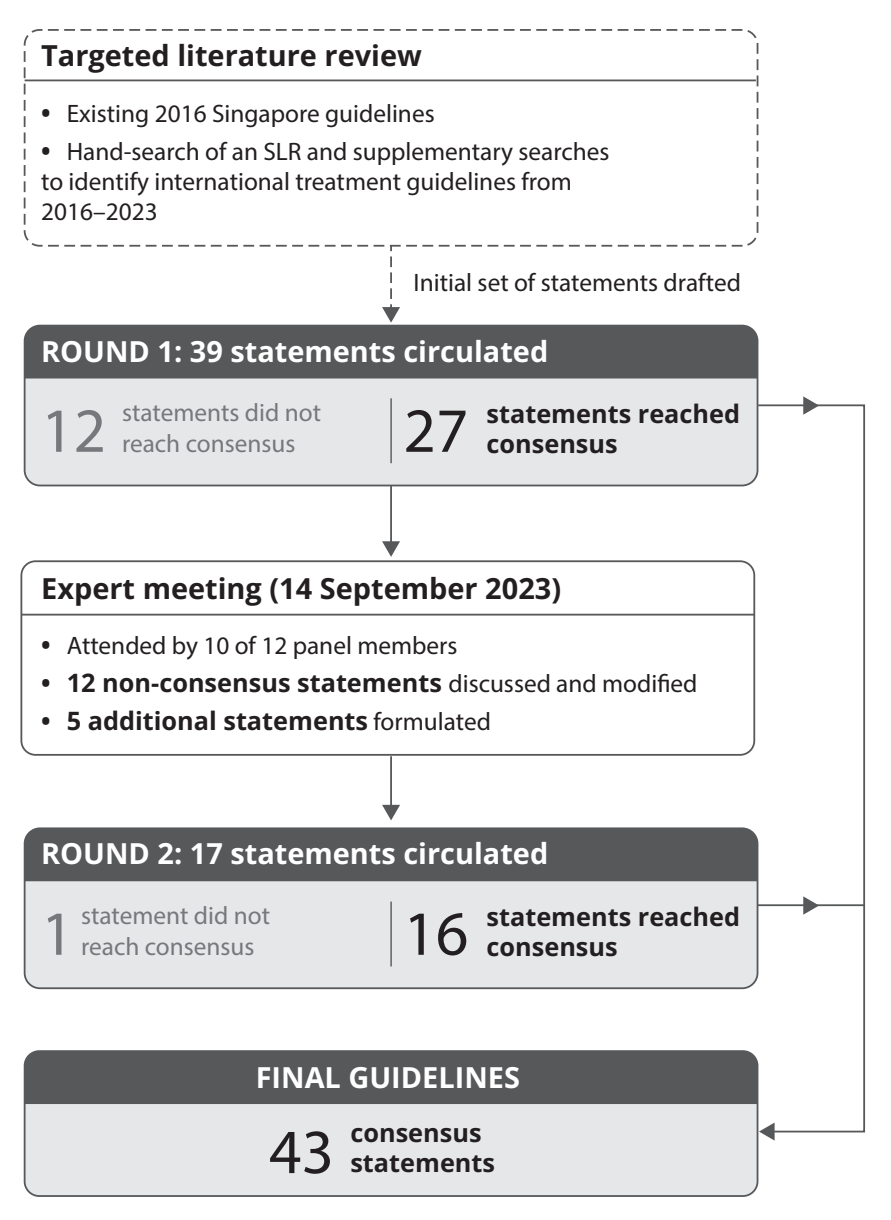
The virtual expert meeting was attended by 10 of 12 experts. While 2 individuals were unable to attend due to scheduling conflicts, all panellists were invited to comment over email and minutes were circulated post-meeting to collect any further feedback.

Fig. 1 summarises the results of the modified Delphi panel. There were 39 statements initially proposed, classified into general principles, conventional treatments, biologics and JAK inhibitors. Of these, 27 statements reached consensus at the end of round 1. After the expert meeting, 17 statements were included in the round 2 survey, of which 16 statements reached consensus. A full illustration of the evolution of the consensus statements in the Delphi rounds, alongside voting results, is available in Supplementary Table S1.

General principles

Table 1 summarises the consensus statements under general principles for the management of AD.

Fig. 1. Summary of results of the modified Delphi panel.



SLR: systematic literature review

Disease assessment

It is recommended to assess disease severity based on objective clinical signs, symptom severity and QoL impact. Outcome measures, such as the SCORing Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI),[29,30] may be useful for monitoring disease and guiding therapy.

Treatment goals

The establishment of disease control, minimisation of symptoms and reduction of QoL impact are key goals of AD treatment. Initial targets to measure treatment response are SCORAD-50, EASI-50, a ≥4-point reduction of Dermatology Life Quality Index (DLQI),[31] a ≥3-point reduction of Itch Numeric Rating Scale (NRS) or a ≥4-point reduction of Patient Oriented Eczema Measure (POEM) within 3 months of treatment initiation.[32,33] While not part of the consensus statement, the Investigator's Global Assessment (IGA) scale score is another possible tool to assess treatment success,[34] as noted by some panellists.

Treatment approach

A collaborative approach between patients, caregivers and healthcare providers is essential.

Table 1. Consensus statements on general principles of moderate-to-severe atopic dermatitis treatment.

No.	Statement	Voting results (% of panellists)
1	An assessment of AD disease severity should be performed. This assessment should encompass objective clinical signs, as well as the severity of symptoms and the impact of AD on the patient's quality of life.	83% Strongly agree 17% Agree
2	In addition to a dermatological examination, outcome measures such as SCORAD, EASI, DLQI, NRS and POEM complement the assessment, and are useful for monitoring disease activity and impact, as well as to guide overall therapy.	42% Strongly agree 58% Agree
3	The goal of AD treatment is to establish disease control, minimise symptoms and reduce impact on patients' quality of life.	92% Strongly agree 8% Disagree
4	Useful initial targets to measure treatment response among moderate-to-severe AD patients include achieving a 50% reduction of SCORAD points (SCORAD-50), achieving a 50% reduction of EASI points (EASI-50), a reduction of DLQI by at least 4 points, a reduction of NRS by at least 3 points or a reduction of POEM by at least 4 points within 3 months of treatment initiation.	83% Agree 17% Neutral
5	A collaborative approach involving shared decision-making among patients, caregivers and healthcare providers is essential. Discussions should involve treatment goals, expectations, treatment plans, treatment options, potential adverse effects, and the preferences of the patients and caregivers.	92% Strongly agree 8% Agree
6	The decision to initiate systemic therapies (conventional and novel [including biologics and small molecules]) for moderate-to-severe AD should be made by dermatologists, due to the potential for misdiagnoses (e.g. cutaneous T-cell lymphoma) and adverse reactions.	75% Strongly agree 17% Agree 8% Neutral

AD: atopic dermatitis; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; NRS: Itch Numeric Rating Scale; POEM: Patient Oriented Eczema Measure; SCORAD: SCORing Atopic Dermatitis

Discussions should encompass treatment goals, expectations, options and plans, taking into account potential adverse effects and patient/caregiver preferences in decision-making. This may also include consideration of the patient's medical comorbidities.

When indicated, systemic therapies should be initiated by dermatologists as specialty knowledge is required for assessment, to prevent misdiagnosis, as well as to monitor for adverse effects.

Conventional treatments

Table 2 summarises the consensus statements concerning conventional treatments in moderate-to-severe AD.

Treatment paradigm for moderate-to-severe AD

For moderate-to-severe AD, emollients remain the mainstay of general disease management. Additionally, topical corticosteroids (TCS) are first-line therapy for both acute exacerbations as well as maintenance of AD control for non-sensitive areas. For sensitive areas (e.g. eyelids, neck and genital areas), TCIs or topical phosphodiesterase-4 inhibitors (e.g. crisaborole) should be considered, as TCS use is likely to be associated with adverse events. Phototherapy could be considered as an alternative for the control of chronic moderate-to-severe AD, before using any systemic anti-inflammatory agents.

In cases of persistent moderate-to-severe AD, a holistic assessment is needed for the initiation of systemic therapy. The assessment should take into account the severity of disease, QoL, adherence, alternative diagnoses and response to previous treatments, such as intensive topicals and phototherapy.

Among conventional systemic anti-inflammatory agents, ciclosporin has the best evidence in the treatment of moderate-to-severe AD.[35] Systemic corticosteroids should be considered only as rescue therapy for acute flares, and not for long-term use in chronic AD. Similarly, long-term high-potency TCS use for moderate-to-severe AD is not recommended. Wet-wrap therapy should be used with caution in combination with high-potency TCS, to minimise potential adverse events.

Steroid tapering and phobia

TCS are an effective treatment for moderate-to-severe AD, but tapering should be initiated upon achieving adequate control. Tapering strategies may include using less potent TCS, reducing the application frequency of potent TCS or using TCS in combination with TCIs or phosphodiesterase-4 inhibitors.

There is a need to address steroid phobia in order to improve adherence to TCS in the management of AD. This should include screening for steroid phobia at treatment initiation and follow-ups,

Table 2. Consensus statements on conventional treatments for moderate-to-severe atopic dermatitis.

No.	Statement	Voting results (% of panellists)
7	For moderate-to-severe AD, emollients remain the mainstay of general disease management.	67% Strongly agree 17% Agree 16% Disagree
8	Topical corticosteroids are used as first-line therapy to treat acute exacerbations and maintain AD control in non-sensitive areas (e.g. hands and feet).	75% Strongly agree 17% Agree 8% Neutral
9	The use of topical calcineurin inhibitors should be considered, particularly for sensitive areas (e.g. neck, eyelids and genital areas) where topical corticosteroid use is likely to be associated with adverse events.	58% Strongly agree 42% Agree
10	The use of topical phosphodiesterase-4 inhibitors (e.g. crisaborole) should be considered, particularly for sensitive areas (e.g. neck, eyelids and genital areas) where topical corticosteroid use is likely to be associated with adverse effects.	50% Strongly agree 50% Agree
11	For the control of chronic moderate-to-severe AD, phototherapy could be considered as an alternative before using any systemic anti-inflammatory agents.	17% Strongly agree 75% Agree 8% Neutral
12	In cases of persistent moderate-to-severe AD, a holistic assessment is needed to decide when to initiate systemic therapy. This assessment should consider disease severity, quality of life, patient factors (e.g. adherence, avoidance of irritants and optimisation of treatment), alternative diagnoses and whether intensive topical treatment and phototherapy have been trialled.	83% Strongly agree 17% Agree
13	Among conventional systemic anti-inflammatory agents, ciclosporin has the best evidence in the treatment of moderate-to-severe AD.	8% Strongly agree 92% Agree
14	Systemic corticosteroids should be considered only as rescue therapy for acute flares, and not for long-term use in chronic AD.	83% Strongly agree 17% Agree
15	Long-term high-potency topical corticosteroid use for moderate-to-severe AD is not recommended.	17% Strongly agree 67% Agree 16% Disagree
16	Wet-wrap therapy in combination with high-potency topical corticosteroids should be used with caution to minimise potential adverse events.	42% Strongly agree 58% Agree
17	Topical corticosteroids are an effective treatment for moderate-to-severe AD. Tapering of corticosteroids should be initiated on adequate control of disease.	50% Strongly agree 42% Agree 8% Neutral
18	Tapering strategies can include using less potent corticosteroids, reducing application frequency of potent corticosteroids or using topical corticosteroids in combination with topical calcineurin inhibitors or phosphodiesterase-4 inhibitors.	33% Strongly agree 59% Agree 8% Neutral
19	There is a need to address steroid phobia to improve adherence to topical corticosteroids in the management of AD. At treatment initiation and follow-ups, healthcare providers should screen for steroid phobia (e.g. using the Topical Corticosteroid Phobia [TOPICOP] scale) and individualise patient education if patients express concerns about steroid use.	33% Strongly agree 59% Agree 8% Disagree

AD: atopic dermatitis

although not all panellists agreed on the Topical Corticosteroid Phobia (TOPICOP)[36] scale as the most appropriate instrument for assessment. If patients express concerns about steroid use, they should be provided with individualised education to address their concerns.

Biologics

Twelve statements on biologics reached consensus, as summarised in Table 3.

Dupilumab is currently approved for use in Singapore for the treatment of adult and paediatric patients aged ≥6 months, with moderate-to-severe AD requiring chronic treatment, and whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[11] Dermatologists in Singapore agreed that dupilumab could be considered for first-line systemic treatment in patients with moderate-to-severe AD.

Dupilumab is recommended as a first-line systemic treatment for patients with concomitant type 2 allergic disease (e.g. moderate-to-severe asthma, severe chronic rhinosinusitis with nasal polyps).

Table 3. Consensus statements on biologics.

No.	Statement	Voting results (% of panellists)
20	Dupilumab could be considered for first-line systemic treatment in patients with moderate-to-severe AD.	42% Strongly agree 50% Agree 8% Disagree
21	Dupilumab is recommended as the first-line systemic treatment for patients with both moderate-to-severe AD and concomitant type 2 allergic disease.	25% Strongly agree 59% Agree 8% Neutral 8% Disagree
22	Dupilumab may be preferred in moderate-to-severe AD patients with severe comorbidities, such as end-stage organ disease/dysfunction, or cardiovascular and venous thromboembolism risk factors.	42% Strongly agree 41% Agree 17% Neutral
23	Based on the available evidence, dupilumab is considered safe and effective in elderly patients compared with conventional systemic agents.	33% Strongly agree 67% Agree
24	Dupilumab should be used with caution in patients who are pregnant or lactating due to the lack of safety/toxicity data in this subpopulation.	33% Strongly agree 67% Agree
25	Dupilumab-induced conjunctivitis can occur during treatment in AD patients. However, topical treatment with anti-inflammatory eyedrops can be considered for the management of conjunctivitis in selected cases, without the need to discontinue dupilumab treatment.	58% Strongly agree 42% Agree
26	In severe or persistent cases of dupilumab-induced conjunctivitis, referral to an ophthalmologist is recommended.	83% Strongly agree 17% Agree
27	For AD patients with a history of recurrent or moderate-to-severe eye inflammation, or ocular surface disorders such as conjunctivitis or keratitis, consider consulting an ophthalmologist before starting treatment with dupilumab.	50% Strongly agree 42% Agree 8% Neutral
28	There is no routine pre-treatment laboratory screening recommended prior to starting dupilumab.	17% Strongly agree 75% Agree 8% Disagree
29	Live attenuated vaccines should be avoided while on dupilumab treatment. Therefore, screening for age-appropriate vaccinations should be conducted at least 4 weeks prior to starting biologic treatment for AD patients.	25% Strongly agree 67% Agree 8% Neutral
30	There is no requirement for specific laboratory tests to monitor AD patients using dupilumab.	25% Strongly agree 67% Agree 8% Neutral
31	Rituximab, omalizumab and ustekinumab treatment are not recommended for use in AD patients due to lack of evidence for their efficacy.	50% Strongly agree 50% Agree

AD: atopic dermatitis; TOPICOP: topical corticosteroid phobia

Dupilumab may also be preferred in moderate-to-severe AD patients with severe comorbidities, such as end-stage organ disease/dysfunction, or cardiovascular and venous thromboembolism risk factors. Based on the available evidence, dupilumab is considered safe and effective in elderly patients (e.g. ≥65 years) compared with conventional systemic agents.[37,38] However, dupilumab should be used with caution in patients who are pregnant or lactating, due to the lack of safety and toxicity data in this subpopulation.

In terms of adverse events, dupilumab-induced conjunctivitis can occur during treatment in AD patients. However, topical treatment with anti-inflammatory eyedrops can be considered for the management of conjunctivitis in selected cases, without needing to discontinue dupilumab treatment. In severe or persistent cases of dupilumab-induced conjunctivitis, referral to an ophthalmologist is recommended. For AD patients with a history of recurrent or moderate-to-severe eye inflammation or ocular surface disorders, such as conjunctivitis or keratitis, clinicians should consider consulting an ophthalmologist before starting treatment with dupilumab.

There is no routine pre-treatment laboratory screening recommended prior to starting dupilumab, and no specific laboratory tests are required to monitor AD patients using dupilumab. However, as live attenuated vaccines should be avoided

while on dupilumab treatment, screening for age-appropriate vaccinations should be conducted at least 4 weeks prior to starting biologic treatment.

Rituximab, omalizumab and ustekinumab treatment are not recommended for use in AD patients, due to limited evidence for their efficacy.

JAK inhibitors

Consensus statements on JAK inhibitors are summarised in Table 4.

Baricitinib, abrocitinib and upadacitinib can be considered for first-line systemic treatment in certain adults with moderate-to-severe AD. In particular, systemic JAK inhibitor treatments can be considered when fast-acting treatments are required. Treatment with a JAK inhibitor can also be an option in moderate-to-severe AD patients with a history of severe ocular surface disease (e.g. corneal and conjunctival diseases). Abrocitinib and upadacitinib may be considered for adolescents (12–18 years old) with moderate-to-severe AD.

Table 4. Consensus statements on Janus kinase inhibitors.

No.	Statement	Voting results (% of panellists)
32	JAKi (baricitinib, abrocitinib, upadacitinib) can be considered for first-line systemic treatment in certain adults with moderate-to-severe AD.	58% Strongly agree 34% Agree 8% Disagree
33	JAKi treatments can be considered when fast-acting treatments are required.	58% Strongly agree 42% Agree
34	JAKi treatment could be used as an option in moderate-to-severe AD patients with a history of severe ocular surface disease.	42% Strongly agree 58% Agree
35	JAKi (abrocitinib and upadacitinib) may be considered for adolescents with moderate-to-severe AD (12–18 years old).	58% Strongly agree 25% Agree 17% Neutral
36	In moderate-to-severe AD patients with latent tuberculosis, JAKi treatments should only be used after the latent tuberculosis has been adequately treated or in consultation with relevant tuberculosis specialists.	50% Strongly agree 50% Agree
37	The use of JAKi in combination with other potent immunosuppressants, such as ciclosporin, is not recommended in AD treatment as it might cause an overly suppressed immune system and increased risk of infection and lymphoma.	34% Strongly agree 50% Agree 8% Neutral 8% Disagree
38	JAKi treatment should not be used during pregnancy, in patients planning for pregnancy or breastfeeding patients.	58% Strongly agree 34% Agree 8% Neutral
39	JAKi treatment should be used with caution in the following patient groups: patients aged ≥65 years, patients at increased risk of major cardiovascular problems (stroke or myocardial infarction), smokers or patients who had smoked for a long time in the past, patients at increased risk of cancer and patients with risk factors for venous thromboembolism.	50% Strongly agree 50% Agree
40	Prior to JAKi treatment initiation, routine screening for hepatitis B, hepatitis C and tuberculosis should be conducted. Screening for HIV should be conducted in at-risk individuals.	50% Strongly agree 50% Agree
41	In addition to routine infective screening, pre-treatment laboratory screening of baseline full blood count (including a differential white cell count), liver enzymes (especially transaminases), renal function and lipid levels is recommended before JAKi treatment initiation.	25% Strongly agree 75% Agree
42	Live attenuated vaccines should be avoided while on JAKi treatment. However, inactivated herpes zoster vaccination could be considered for all patients.	33% Strongly agree 59% Agree 8% Disagree
43	After JAKi treatment initiation, regular laboratory screening should be carried out as part of routine patient management.	25% Strongly agree 75% Agree

AD: atopic dermatitis; HIV: human immunodeficiency virus; JAKi: Janus kinase inhibitors

In moderate-to-severe AD patients with latent tuberculosis, JAK inhibitors should only be used after the latent tuberculosis has been adequately treated, or in consultation with relevant tuberculosis specialists. The use of JAK inhibitors in combination with other potent immunosuppressants, such as ciclosporin, is not recommended as it might cause an overly suppressed immune system and increased risk of infection and malignancies, such as lymphoma. Additionally, JAK inhibitors should not be used during pregnancy, in patients planning for pregnancy or lactating patients.

In the following patient groups, JAK inhibitor treatment should be used with caution: patients aged ≥65 years; patients at increased risk of major cardiovascular problems (stroke or myocardial infarction); smokers or patients who have smoked for a long time in the past; patients at increased risk of cancer; and patients with risk factors for venous thromboembolism.[39]

Laboratory screening

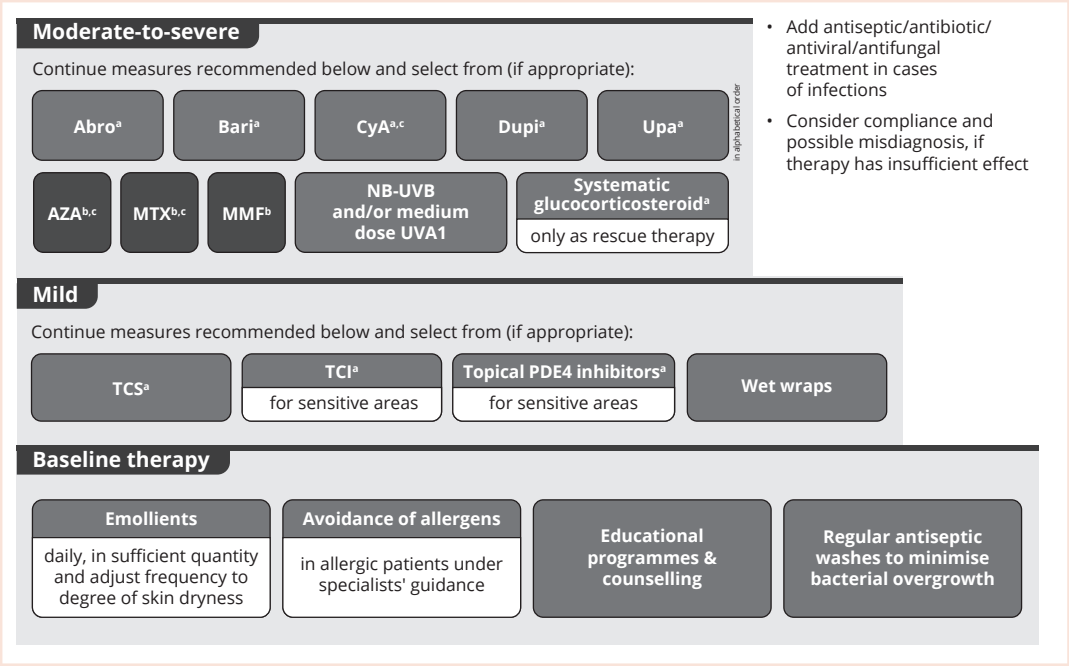
Prior to treatment initiation with JAK inhibitors, routine screening for hepatitis B, hepatitis C and tuberculosis should be conducted. HIV screening should also be conducted for at-risk individuals. Pre-treatment laboratory screening of baseline full blood count (including a differential white cell count), liver enzymes (especially transaminases), renal function and lipid levels, is also recommended. Live attenuated vaccines should be avoided while on JAK inhibitors, but inactivated herpes zoster vaccination could be considered for all patients in view of possible herpes zoster reactivation. After JAK inhibitor treatment initiation, regular laboratory screening should be carried out as part of routine patient management.

DISCUSSION

Consensus statements generally aligned with recommendations in other international AD consensus statements and guidelines, including those from Europe (EuroGuiDerm), Portugal, Japan and Saudi Arabia.[40-44] Fig. 2 illustrates a proposed treatment algorithm, developed based on the consensus statements generated. A key outcome of the consensus process was that, in the appropriate context, biologics and JAK inhibitors could be considered as first-line treatments for moderate-to-severe AD in Singapore, in addition to conventional treatments.

Nevertheless, efficacy, safety and cost should always be considered during the initiation of systemic treatments. At the time of this Delphi

Fig. 2. Proposed treatment algorithm based on the consensus statements.



Adapted from EuroGuiDerm guideline.[41]
Abro: abrocitinib; AZA: azathioprine; Bari: baricitinib; CyA: ciclosporin A; Dupi: dupilumab; MMF: mycophenolate mofetil; MTX: methotrexate; NB-UVB: narrow-band ultraviolet B; PDE4: phosphodiesterase-4; TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; Upa: upadacitinib; UVA1: ultraviolet A1.
[a] Licensed indication.
[b] Off-label treatment.
[c] Refer to restrictions as listed within this guideline and EuroGuiDerm.[41]

survey, many newer AD treatments were not eligible for subsidy in Singapore via the Medication Assistance Fund (MAF) or the Ministry of Health Standard Drug List. Hence, treatment with such agents may result in significant out-of-pocket costs.

A common theme expressed in open-ended comments and during the expert meeting was the importance of considering the affordability of a treatment for a specific patient, when making treatment decisions in clinical practice.[45]

However, as of 1 March 2024, after the conclusion of the Delphi voting, abrocitinib has since been listed for subsidy under the MAF for the treatment of moderate or severe atopic dermatitis (Physician Global Assessment score of 3 or 4 and EASI ≥16) in patients who have had an inadequate response, intolerance or contraindication to at least 1 systemic therapy such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil.[46] This decision was based on an assessment of patient population size and unmet need, clinical effectiveness, cost-effectiveness, incremental cost and budget impact.[46] Initiatives like the MAF are crucial for mitigating financial barriers to effective treatments and promoting societal health equity.

Additionally, it was highlighted that the decision to initiate systemic treatments should be made by dermatologists. Specialist knowledge is necessary to appreciate the differential diagnoses (such as mycosis fungoides, psoriasis, tinea),[47] reduce misdiagnosis as well as monitor adverse events. A skin biopsy may be considered prior to therapy initiation in cases where the AD diagnosis is unclear, especially for elderly patients.[48-50]

As outlined in Supplementary Fig. S1, a number of statements did not reach consensus in round 1. After discussion and modification, almost all statements were able to reach consensus in round 2, except for 1 statement regarding the discontinuation of phototherapy. Panellists did not agree on the acceptability of co-administration of phototherapy with systemic anti-inflammatory agents. In the comments, it was highlighted that the contraindication may be true of some agents, such as ciclosporin and/or azathioprine, but that phototherapy may be used together with methotrexate and dupilumab. Experts also noted evidence that the risk of photocarcinogenesis may be lower in the Asian population,[51] and highlighted that temporary overlaps between treatments may occur in clinical practice while bridging treatments.

The consensus statements reflect the current treatment availability in Singapore at the time of the study. Other treatment options, such as topical JAK inhibitors (delgocitinib ointment and ruxolitinib cream) and other biologics (tralokinumab, lebrikizumab and nemolizumab), may become available in the future and could play a role in AD management.[52,53] In clinical practice, some treatments may also be used off-label, such as mycophenolate mofetil, an oral systemic immunosuppressant that is considered by some clinicians in Singapore as third- or fourth-line treatment, when licensed options are exhausted.

The strengths of this supplementary guideline update include the use of Delphi methodology, which is a structured and robust technique for collecting opinions from experts and generating group consensus.[24] The process allows for controlled feedback between rounds, such that panellists are informed of the current status of collective opinion and may be reminded of considerations that they may have previously missed.[24] The Delphi process was modified in this study to include an expert meeting to support statement reformulation following round 1 voting. While this meant that members of the expert panel were aware of each other while exchanging clinical opinion, voting records were kept confidential and no voting took place during this meeting. This ensured that dominant perspectives did not shape the consensus generation.

Limitations

While a full systematic review to assess the level of evidence supporting each statement was not conducted, many existing guidelines are already available globally for AD. Thus, the statements were developed based on a review of relevant international treatment guidelines, with expert input from the co-chairs.

The sample size for the Delphi panel was limited to 12 participants; however, recruitment aimed to identify key opinion leaders in the field of dermatology in Singapore, who would have the expertise and experience to advise on best practice,[54] while ensuring representation across public and private practice. Future updates (supplementary or full) to the 2016 guidelines should consider including patients and policymakers, to gather input on the feasibility of implementing recommendations in clinical practice.

Lastly, although the current consensus discussed the risks associated with the use of biologics and JAK inhibitors, including the importance of pre-treatment screening and ongoing monitoring, it did not provide detailed guidance on specific monitoring timelines or adverse event management. This omission stems from the restricted scope of a 2-round Delphi panel and the intention to remain non-prescriptive, allowing flexibility for clinicians to tailor approaches based on local circumstances. While relevant screening and monitoring guidance has already been published,

for example by Samuel et al. (2023),[55] these considerations should be included in future updates to the 2016 guidelines.

CONCLUSION

This modified Delphi study was undertaken to develop updated guidance, based on consensus among dermatologists in Singapore, regarding newer treatments in moderate-to-severe AD. The consensus statements developed are intended to supplement the original guidelines,[8] particularly in treatment approaches for moderate-to-severe AD, and to ensure that the guidelines account for changing treatment paradigms. Further revisions to this guideline may be required when new evidence and/or new treatments in AD become available.

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HYL is a Trial Investigator for Abbvie, Amgen, Aslan, Eli-Lilly, Galderma, Novartis, Sanofi, participated in advisory boards for Amgen, DKSH, Pfizer and Sanofi, and has been a speaker for Abbvie, Pfizer and Sanofi. YWY is a trial Investigator for Abbvie, Amgen, Aslan, Eli-Lilly, Galderma and Sanofi, and participated in advisory boards for Abbvie, Pfizer and Sanofi, and has been a speaker for Abbvie, Pfizer and Sanofi. DA has received honoraria and sponsorships from Sanofi, Pfizer, Abbvie, Eli Lilly, Galderma, DKSH and LEO Pharma. CYN has served as expert panellist in a baricitinib advisory board meeting for DKSH. RC has received honoraria from, and participates in advisory boards for AbbVie, Bioderma, DKSH, Galderma, Hyphens Pharma, LEO Pharma, Pfizer, Ego Pharmaceuticals and Sanofi. HYK has received honorarium for speaker fees from DKSH, LEO Pharma and Ego Pharmaceu-ticals. TSY participated in advisory board(s) for Pfizer and has been a speaker for Pfizer. YKT has no disclosures to report. KJLC is a trial Investigator for Abbvie, Amgen, Aslan, Eli-lily, Galderma and Novartis, participated in advisory boards for Medtronic and L'Oréal, has been a speaker for Pfizer and Sanofi, and received sponsorship from Abbvie, Hyphens and Sanofi. SXL has no disclosures to report. UA participated in advisory boards for DKSH and L'Oréal, and has been a speaker for Hyphens, DKSH and Sanofi. MT has received speaking honoraria, participated in advisory boards and/or conducted clinical trials for the following companies: AbbVie, Bioderma Naos, DKSH, Eli-Lilly, Galderma, GSK, Hyphens, Kao, Janssen, LEO Pharma, L'Oréal, Menarini, Pfizer and Sanofi-Regenerno. NSC has received fees for participation in advisory boards from AbbVie, Johnson & Johnson, Sanofi, Pfizer, DKSH, L'Oréal and Novartis, investigator fees for clinical trials from AbbVie, Novartis, Amgen, Sanofi and Boehringher Ingelheim and speaker honoraria from Galderma, Johnson & Johnson, LEO Pharma, Pfizer, Sanofi and Lion Corporation. MJAK has received research grants and funding from Galderma, Hyphens, Amryt, Lilly, Abbvie, Aslan and L'Oreal, has been a speaker for LEO Pharma, Galderma, GSK, Hyphens, Menarini, Ego, Bioderma, Good Pharma, Sanofi, Pfizer, Zuellig, Novartis, Lion Corporation and L'Oréal/LaRoche Posay, and has participated in advisory boards for Pfizer, Abbvie, Novartis, Sanofi, Astra-Zeneca, Lion Corporation, LaRoche Posay/L'Oréal, DKSH, and Lilly. SFG and AL are employees of Costello Medical, Singapore, which was funded by the Dermatological Society of Singapore to support with conducting this study.

Ethics statement

This study did not involve collection of patients' confidential data that could violate patients' right to privacy.

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REVIEW ARTICLE

Corticosteroids in critically ill patients with community-acquired pneumonia: A systematic review and Bayesian meta-analysis

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ABSTRACT

Introduction: This systematic review and meta-analysis aimed to evaluate the effectiveness and safety of adjunct systemic corticosteroid therapy in patients admitted to the intensive care unit (ICU) with bacterial community-acquired pneumonia (CAP).

Method: We searched MEDLINE, Embase and the Cochrane Library to identify randomised controlled trials (RCTs) published from the databases' inception to February 2024. All RCTs evaluating the effect of systemic corticosteroids on mortality, compared to standard of care among adult bacterial CAP patients admitted to ICU were included. Bayesian meta-analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Independent authors reviewed each study for eligibility, extracted data and assessed risk of bias in duplicate, with discrepancies referred to senior reviewers.

Results: A total of 6 RCTs comprising 1585 patients were included for analysis. In ICU patients with severe CAP who were treated with corticosteroids, there was no significant reduction in hospital mortality (risk ratio [RR] 0.70, 95% confidence interval [CI] 0.39–1.14, certainty of evidence: ⊕⊕⊖⊖ low) or all-cause mortality (RR 0.68, 95% CI 0.34–1.22, ⊕⊕⊖⊖ low) compared with placebo. The use of corticosteroids showed a significant reduction in mechanical ventilation post-intervention (RR 0.58, 95% CI 0.37–0.86, ⊕⊕⊕⊕ high) compared with placebo. In a subgroup analysis of patients treated with hydrocortisone, hospital mortality was significantly reduced (RR 0.45, 95% CI 0.20–0.88, ⊕⊕⊖⊖ low) compared with placebo. There was no significant increase in gastrointestinal bleeding, secondary infections or hyperglycaemia in patients treated with corticosteroids.

Conclusion: Corticosteroids significantly reduced mechanical ventilation requirements, and hydrocortisone significantly reduced hospital mortality. Further work is required to determine whether other corticosteroids reduce mortality among ICU patients with CAP.

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Keywords: Bayesian meta-analysis, community-acquired pneumonia, corticosteroids, critically ill, ICU, mortality

CLINICAL IMPACT

What is New

- Corticosteroids significantly reduced mechanical ventilation and hydrocortisone significantly reduced hospital mortality in patients with community-acquired pneumonia (CAP) who required admission to the intensive care unit (ICU).
- There was no significant increase in gastrointestinal bleeding, secondary infections or hyperglycaemia in patients treated with corticosteroids compared with patients given placebo.

Clinical Implications

- Our findings support the Society of Critical Care Medicine guidelines on the use hydrocortisone.
- This study also highlights the need for future studies to determine whether other corticosteroids reduce mortality among ICU patients with CAP and inform priors for future Bayesian studies.

INTRODUCTION

Community-acquired pneumonia (CAP) is a common cause of hospital mortality. Each year, in the US alone, more than 1.5 million pneumonia patients

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are hospitalised, and 1 in 3 of them die within 1 year.[1] Mortality is the highest among patients requiring organ support in the intensive care unit (ICU). These patients meet the definition of sepsis, where a dysregulated immune response to infection has resulted in life-threatening organ dysfunction. If sustained hypotension occurs, they would meet the definition of septic shock.[2] For the past 20 years, Surviving Sepsis Campaign guidelines have recommended using corticosteroids in patients with septic shock because these have been demonstrated to reduce mortality.[3,4] However, although the rate of mortality of CAP patients admitted to the ICU is similar to those seen in those with septic shock, the use of steroids in the former group remains controversial, highlighted by divergent results reported in the 2 largest studies to date. The Extended Steroid in Use in Community Acquired Pneumonia (ESCAPe, NCT01283009) trial by Meduri et al. found no significant mortality benefit whereas the Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD, NCT02517489) trial by Dequin et al. demonstrated a significant 5.6% reduction in mortality with the use of corticosteroids.[5,6] Despite this, the updated 2024 guidelines by the Society of Critical Care Medicine (SCCM) strongly recommended corticosteroids in patients with severe bacterial CAP.[7]

We performed a comprehensive systematic review and Bayesian meta-analysis to complement the recent SCCM guidelines, and evaluated the effectiveness and safety of adjunct systemic corticosteroid therapy in patients admitted to the ICU with bacterial CAP. Bayesian inference is common in clinical reasoning; clinicians make decisions by weighing pre-existing information with new evidence.[8,9] Bayesian methods can be used in systematic reviews, allowing us to assess how the probability of the intervention's effectiveness has evolved with new data.

METHOD

This systematic review and meta-analysis adhered to the reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses.[10] The study protocol was registered with PROSPERO (CRD42023451607).

Information source and search strategy

A systematic search was conducted in 3 databases: MEDLINE (using the PubMed platform), Embase and the Cochrane Library, using Medical Subject Headings (MeSH) and keywords. Keywords and MeSH terms synonymous with "corticosteroids" and "community-acquired pneumonia" formed the basis of the search strategy. The reference list of relevant published articles was hand searched for relevant trials. The search included articles from inception of the databases to February 2024. Only full-text articles published in the English language were included. The full search strategy and search terms are included in the Supplementary Table S1. References were imported into EndNote X9 (The EndNote Team, Clarivate, Philadelphia, US) for the initial removal of duplicates.

Eligibility criteria

All randomised controlled trials (RCTs) evaluating adjunctive systemic corticosteroids compared with the standard of care regarding mortality among adult bacterial CAP patients in ICU were considered eligible. Data from non-peer-reviewed articles, conference proceedings or abstract presentations were excluded. We excluded trials involving paediatric populations, hospital-acquired pneumonia, viral pneumonia, aspiration pneumonia, patients with septic shock at randomisation and patients on long-term steroids (Fig. 1).

Primary and secondary outcomes

Hospital mortality was selected as the primary outcome. ICU mortality was used when hospital mortality was not reported. Secondary outcomes included all-cause mortality, mechanical ventilation requirement, secondary infections, hyperglycaemia and gastrointestinal bleeding.

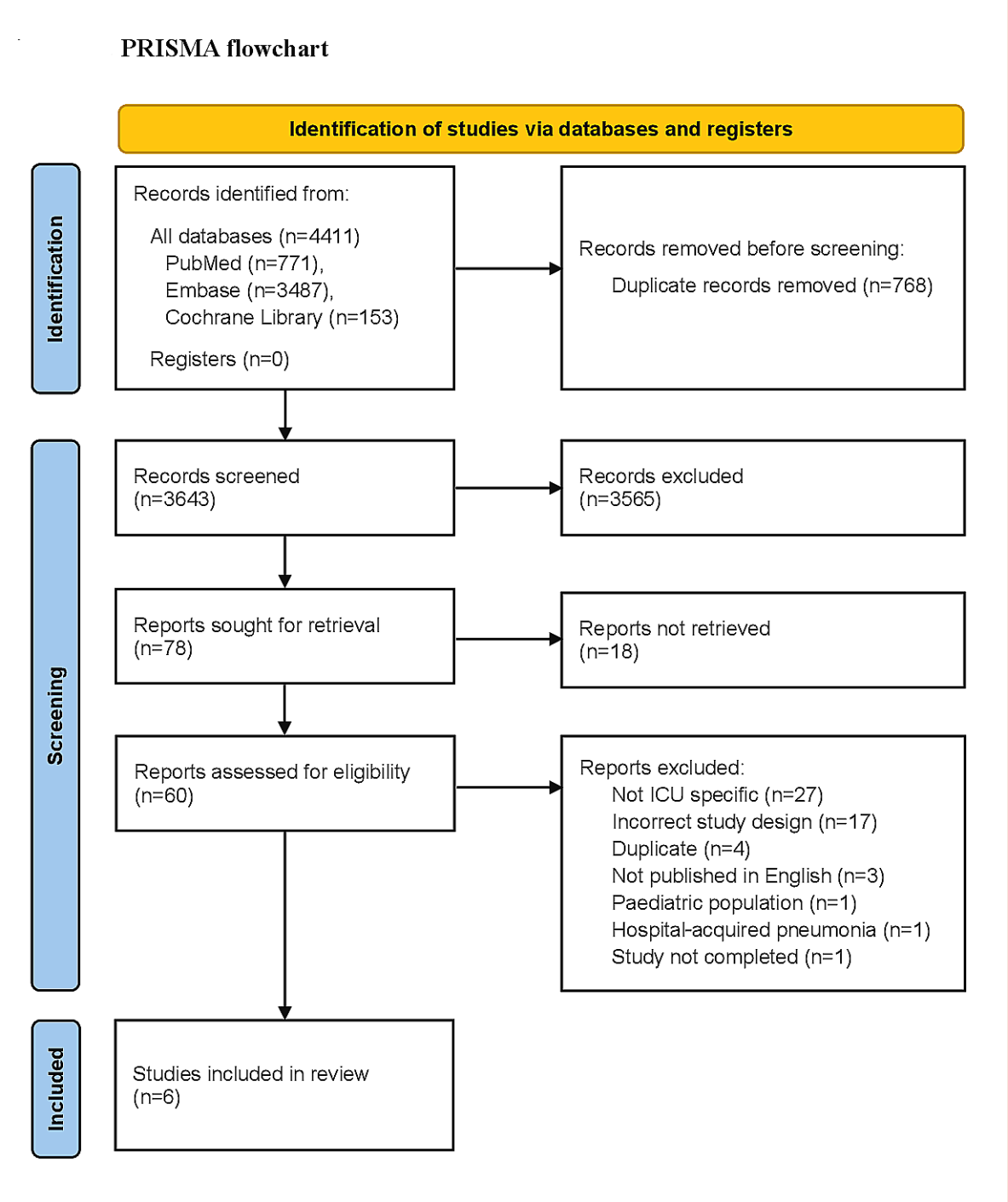
Study selection and data extraction

Four investigators independently screened titles and abstracts to identify potentially eligible studies (authors WYC, NC, SCI and RG) and independently assessed full-text copies for inclusion. Senior reviewers (MC and JS) were consulted to reach a consensus. The same 4 investigators independently extracted information from the RCTs, including authors, publication year, study site, clinical trial number, recruitment period, corticosteroid dosage and duration, age and sex, sample size, and withdrawals. Discrepancies were resolved by senior reviewers (MC and JS).

Risk of bias and certainty of evidence assessment

Risk of bias was assessed using the Cochrane risk-of-bias 2.0 tool.[11] Four investigators (WYC, NC, SCI, and RG) independently reviewed the included studies. They rated the studies as having "low risk," "some concerns" or "high risk" of bias based on the randomisation process, deviations from intended interventions, missing outcome data, measurement of outcome and selection of reported result. Senior reviewers (MC and JS) were consulted to resolve disagreements.

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart.



ICU: intensive care unit

Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[12] We defined the levels of evidence as "high", "moderate", "low" or "very low" based on the risk of bias, indirectness of evidence (population, intervention, control and outcomes), unexplained heterogeneity, inconsistent results and probability of publication bias. A summary of the findings for assessing the certainty of the evidence for each outcome is available in Supplementary Table S3.

Data analysis

Bayesian meta-analysis was conducted using R version 4.3.2 (R Core Team, Vienna, Austria) with vague priors (log of the risk ratio [RR] assumed to have a normal distribution with a mean of 0 and a standard deviation of 2). The random effects

model was used to estimate the pooled RRs and their corresponding 95% confidence intervals (CI). An RR <1 indicated that corticosteroids had a lower risk of outcomes. The proportion of variability due to heterogeneity was assessed using the I^2 statistic, and an I^2 statistic of ≥50% was considered significant. We also reported frequentist meta-analysis data using Review Manager 5.4.1 software (Cochrane Collaboration, London, UK).

RESULTS

The search strategy identified 4411 articles across all 3 databases, of which 768 were duplicate studies and excluded. Among the remaining 3643 articles, 3565 were excluded after title and abstract screening. The final 60 articles underwent full-text screening, and 6 studies were deemed eligible for inclusion and final analysis. The baseline characteristics of the included studies are summarised in Table 1. The 6 studies were double-blind RCTs, with 1585 patients and mortality reported in 1573 patients. Among these 1573 patients, 793 (50.4%) were allocated to receive adjunctive systemic corticosteroids and 780 (49.6%) received placebo. The type of corticosteroids varied: intravenous (IV) hydrocortisone was used in 4 trials,[5,13-15] IV methylprednisolone in 1 trial[6] and IV prednisone in 1 trial,[16] with treatment duration ranging from 1 to 20 days.

Primary outcome: hospital mortality

All 6 included studies reported hospital mortality. Other mortality timepoints used in the studies include 8-day,[15] 28-day[5] and 60-day mortality.[6] Hospital mortality rates within the corticosteroid group ranged from 0%[13] to 52%,[16] with an overall mortality rate of 9.4%. In contrast, the control group reported an overall mortality rate of 13.4%, ranging from 9.8%[6] to 60%.[16] In patients who were given any corticosteroid, there was no significant reduction in hospital mortality (RR 0.70, 95% CI 0.39–1.14, GRADE certainty of evidence: ⊕⊕⊖⊖), with a 94.2% posterior probability that corticosteroids reduced hospital mortality (Fig. 2). The certainty in the evidence was low (Supplementary Table S3). In patients who received prednisone/methylprednisolone, hospital mortality was similar to the placebo group (RR 1.01, 95% CI 0.52–1.94, ⊕⊕⊖⊖) with a 48.1% posterior probability that prednisone/methylprednisolone reduced hospital mortality. In trials where patients were given hydrocortisone, hospital mortality was significantly reduced (RR 0.45, 95% CI 0.20–0.88, ⊕⊕⊖⊖), with a 99.0% posterior probability for reduced hospital mortality (Fig. 3). The frequentist method sensitivity analyses demonstrated similar findings (Supplementary Fig. S1).

Secondary outcomes

All-cause mortality was reported in 3 trials.[5,6,15] In patients given any corticosteroid, there was no significant reduction in all-cause mortality (RR 0.68, 95% CI 0.34–1.22, ⊕⊕⊖⊖), with 93.1% posterior probability that corticosteroids reduced all-cause mortality (Fig. 4A). The need for mechanical ventilation after randomisation was reported in 5 trials. We found that corticosteroid use was associated with a significant reduction in mechanical ventilation post-intervention compared to placebo (RR 0.58, 95% CI 0.37–0.86 ⊕⊕⊕⊕), with 99.2% posterior probability that corticosteroids reduced mechanical ventilation requirement (Fig. 4B). Sensitivity analyses using the frequentist method produced similar findings (Supplementary Fig. S1).

The incidence of gastrointestinal bleeding was reported in 4 studies, and we found no significant increase in gastrointestinal bleeding in patients who were given corticosteroid therapy (RR 1.00, 95% CI 0.47–2.16, ⊕⊕⊖⊖) (Fig. 4C). Five studies reported on secondary infections; there was no significant increase in secondary infections in patients who were given corticosteroid therapy compared to placebo (RR 0.66, 95% CI 0.28–1.12 ⊕⊕⊖⊖) (Fig. 4D). Only 1 study reported hyperglycaemia; no significant increase was found in patients who received corticosteroids compared to placebo (RR 1.33, 95% CI 0.46–3.72, ⊕⊕⊕⊖) (Fig. 4E).

Risk-of-bias assessment

Three trials were adjudicated as having a low risk of bias in all domains, and the risk of bias was adjudicated as low for all trials that reported data on hospital mortality (Supplementary Table S2). We also rated the certainty of evidence in other outcomes due to the risk of bias, as shown in Supplementary Table S2.

DISCUSSION

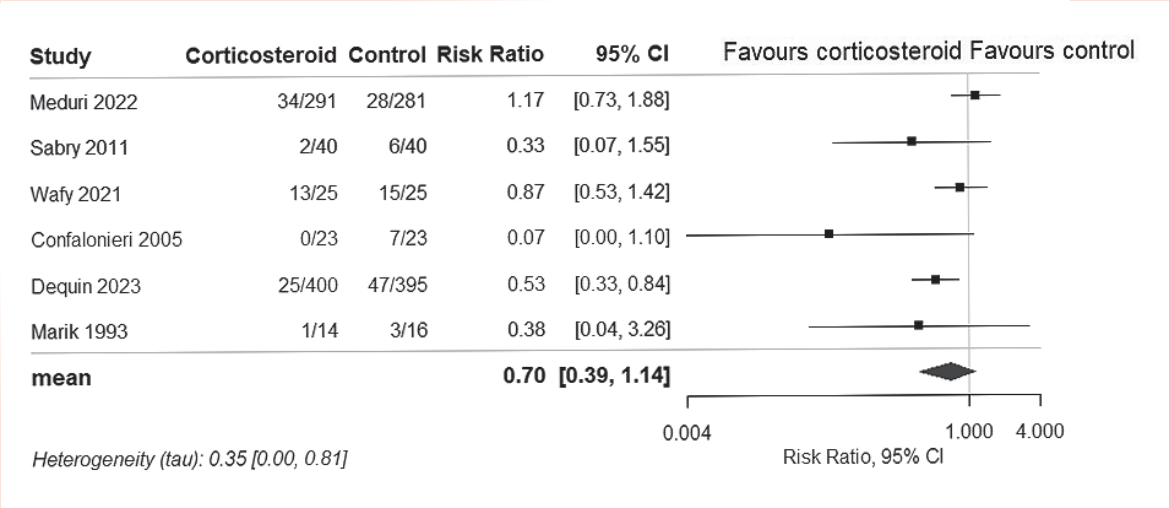
We conducted a comprehensive systematic review and Bayesian meta-analysis to evaluate the effectiveness of corticosteroids in ICU patients with CAP, eventually including 6 RCTs with a total of 1585 patients. We found no significant difference in hospital mortality (RR 0.70, 95% CI 0.39–1.14, ⊕⊕⊖⊖) and all-cause mortality (RR 0.68, 95% CI 0.34–1.22, ⊕⊕⊖⊖), with a posterior probability of 94.3% and 93.1% that corticosteroids were associated with lower hospital mortality and all-cause mortality, respectively. A subgroup analysis found that the type of corticosteroid may be important; hydrocortisone use demonstrated a significant reduction in hospital mortality (RR 0.45, 95% CI 0.20–0.88, ⊕⊕⊖⊖), which was not seen in studies using prednisone/methylprednisolone

Table 1. Baseline characteristics of included studies.

Author, year, country	Study centres	Sample			Type of corticosteroid	Treatment duration	Dosing strategy
		Total	Control group	Steroid group			
Meduri, 2022, US[6]	42	584	287	297	Methylprednisolone	20 days	Methylprednisolone for 20 days. Loading dose 40 mg followed by maintenance infusion on day 0; 40 mg/day on days 1–7. 20 mg/day on days 8–14; 12 mg/day on days 15–17; 4 mg/day on days 18–20.
Sabry, 2011, Egypt[15]	3	80	40	40	Hydrocortisone	7 days	Hydrocortisone for 7 days. Loading dose 200 mg over 30 minutes followed by 300 mg in 500 mL 0.9% saline (rate 12.5 mg/hr) for 7 days.
Wafy, 2021, Egypt[16]	1	50	25	25	Prednisone	7 days	Prednisone for 7 days; 40 mg/day.
Confalonieri, 2005, Italy[13]	6	46	23	23	Hydrocortisone	7 days	Hydrocortisone for 7 days. Loading dose 200 mg followed by 240 mg in 500 mL 0.9% saline (rate 10 mg/hr) for 7 days.
Dequin, 2023, France[5]	31	795	395	400	Hydrocortisone	8/14 days	Hydrocortisone for 8 or 14 days. Dose 200 mg/day for first 4 days. On day 4, medical team used predefined criteria to decide whether to administer hydrocortisone for total 8 or 14 days, depending on whether patient's condition improved.
Marik, 1993, South Africa[14]	1	30	16	14	Hydrocortisone	1 day	Hydrocortisone for 1 day. Single dose of 10 mg/kg 30 minutes prior to commencing antibiotic therapy.

Superscript numbers: refer to REFERENCES

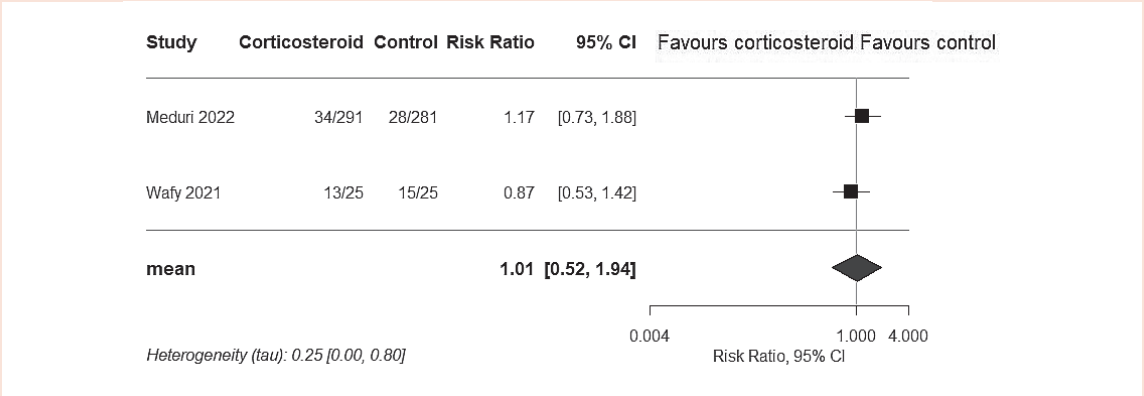
Fig. 2. Forest plot on hospital mortality for the comparison between the outcome of adjuvant systemic corticosteroids and placebo using Bayesian analysis. There was 94.3% posterior probability that corticosteroid was associated with reduced hospital mortality.



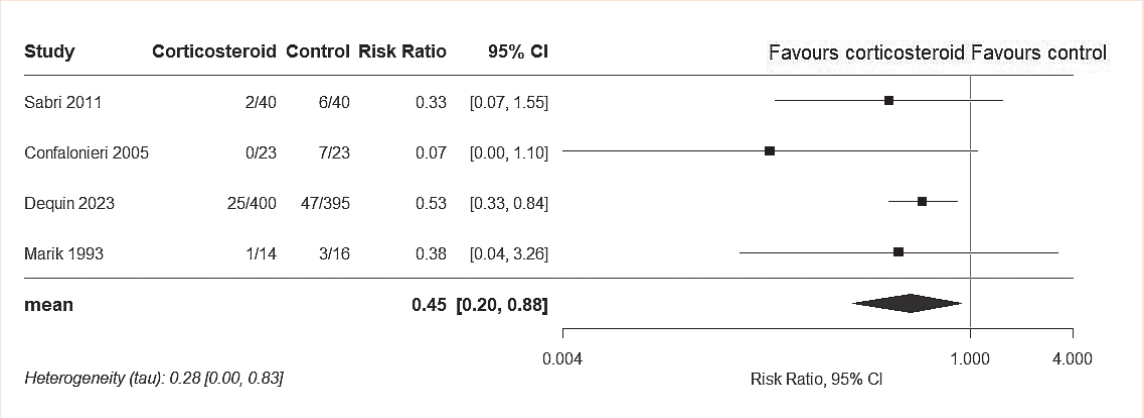
CI: confidence interval

Fig. 3. Forest plot on hospital mortality based on corticosteroid subtype, (A) prednisone/methylprednisolone and (B) hydrocortisone for the comparison between adjuvant systemic corticosteroids and placebo using Bayesian analysis.

(A) Prednisone/methylprednisolone: there was a 48.1% posterior probability that corticosteroid was associated with reduced hospital mortality.



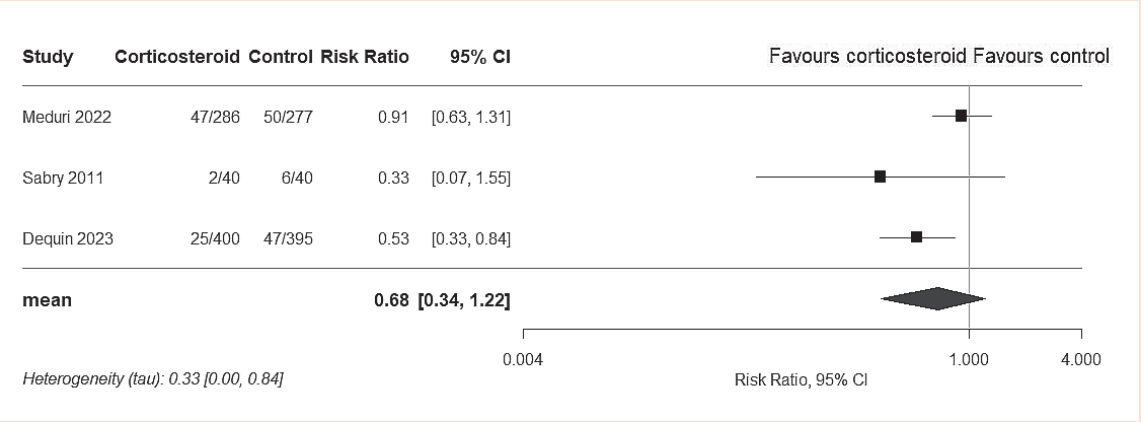
(B) Hydrocortisone: there was a 99.0% posterior probability that corticosteroid was associated with reduced hospital mortality.



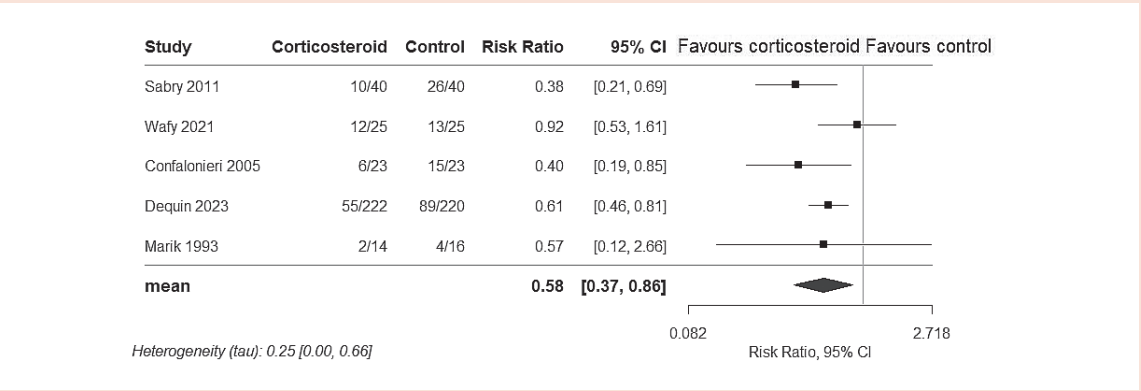
CI: confidence interval

Fig. 4. Forest plot on (A) all-cause mortality, (B) mechanical ventilation post intervention, (C) gastrointestinal bleeding, (D) secondary infections and (E) hyperglycaemia for the comparison between the outcome of adjuvant systemic corticosteroids and placebo using Bayesian analysis.

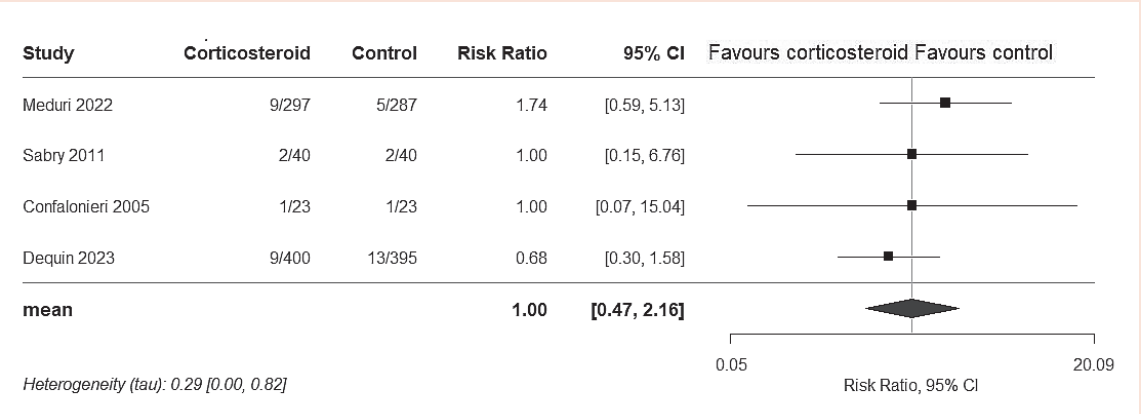
(A) All-cause mortality: there was a 93.1% posterior probability that corticosteroid was associated with reduced mortality.



(B) Mechanical ventilation: there was a 99.2% posterior probability that corticosteroid was associated with reduced risk of mechanical ventilation.



(C) Gastrointestinal bleeding: there was a 50.2% posterior probability that corticosteroid was associated with reduced risk of gastrointestinal bleeding.

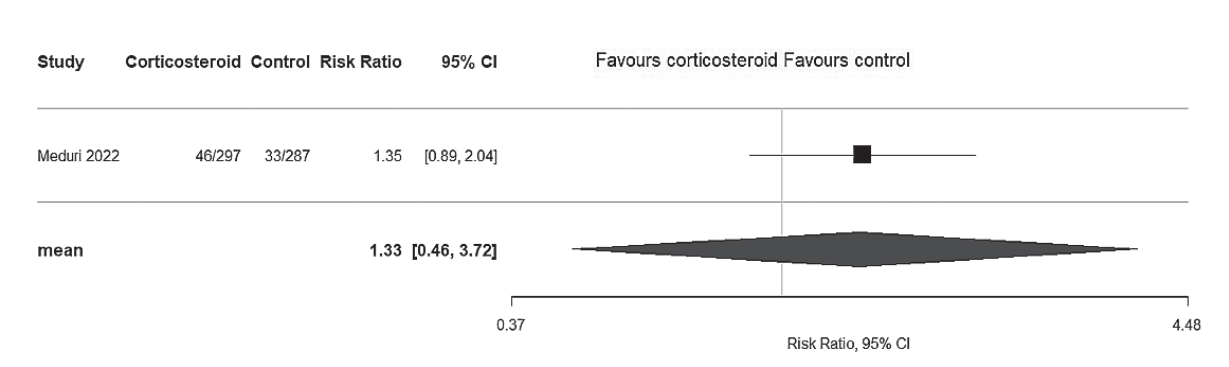


(RR 1.01, 95% CI 0.52–1.94, ⊕⊕⊖⊖). We also found that patients receiving corticosteroids were significantly less likely to require mechanical ventilation, and their use was not associated with any significant increase in the risk of hyperglycaemia, gastrointestinal bleeding or secondary infections.

Literature on the use of corticosteroids for CAP parallels that of septic shock because in the past, corticosteroids had not always been recommended for patients with septic shock in sepsis guidelines.[4] Studies conducted before the 2000s produced conflicting results,[17] and it was not until Annane

(D) Secondary infections: there was a 95.6% posterior probability that corticosteroid was associated with reduced risk of secondary infections.

(E) Hyperglycaemia: there was a 22.8% posterior probability that corticosteroid was associated with reduced risk of hyperglycaemia.



CI: confidence interval

et al.'s multicentre RCT in 2002,[18] supported by subsequent meta-analysis, that the practice of corticosteroid therapy in septic shock was firmly established in guidelines.[19] Although uncertainties reemerged in 2008 when a second multicentre RCT failed to demonstrate a mortality benefit with corticosteroids,[20] a subsequent meta-analysis reinforced the evidence that corticosteroids reduce mortality in patients with refractory septic shock. More recently, corticosteroids have been recommended in patients with acute respiratory distress syndrome (ARDS),[7] and in 2024, SCCM guidelines recommended corticosteroids for adults with severe bacterial CAP.[7] Before these recommendations, patients with CAP typically only received steroids if they had concurrent, refractory septic shock.[4,17] This may reflect that certain illness severity thres-holds need to be reached before patients benefit from corticosteroids. Since CAP mortality in ICU patients is similar to that for septic shock,[21-24] it is logical to investigate the role of corticosteroids in CAP.

Interest in the role of corticosteroids in CAP was further renewed with the publication of the recent large RCT by Dequin et al., which concluded that corticosteroids significantly improved mortality in patients with CAP admitted to ICU, contrary to prior studies and meta-analyses.[5] Therefore, we conducted this Bayesian meta-analysis to determine if this latest trial changes the conclusions of earlier meta-analysis. Our study found no significant decrease in hospital mortality rate with corticosteroid use (RR 0.70, 95% CI 0.39–1.14, ⊕⊕⊖⊖), while the posterior probability of 94.3% suggests—without meeting statistical significance—that corticosteroids are more likely than not to be beneficial, which encourages further investigation.

In contrast, a recent meta-analysis by Wu et al. which investigated the role of corticosteroids in severe CAP, included 7 studies (1689 patients) and concluded that corticosteroids significantly reduced 30-day mortality compared to the placebo.[26] Our study may have drawn different conclusions because we defined severe CAP as requiring ICU admission, whereas Wu et al. defined severe CAP more broadly using the American Thoracic Society/Infectious Diseases Society of America criteria, the Pneumonia Severity Index or ICU admission.[25,26] As a result, they

included a study by Torres et al., a multicentre trial in Spain that recruited 120 hospitalised pneumonia patients for treatment with methylprednisolone or placebo. However, only 70% of the patients were admitted to ICU and the outcomes for ICU patients were not reported separately, thus excluding this study from our analysis. In addition, Wu et al. included an ICU study by El-Ghamrawy et al. for which we were unable to retrieve the full text. We decided not to extract data for this study from other meta-analysis because we could not independently assess the quality of the study. Our application of Bayesian methods is unlikely to explain why Wu et al. drew a different conclusion, because our findings are similar using a frequentist analysis (Supplementary Fig. S1). Notably, both studies by Meduri et al. and Dequin et al. included the 2 largest trials accounting for 1379 patients, i.e. more than 80% of the total patients in both meta-analyses.[5,6]

The choice of corticosteroid may be important. Our subgroup analysis of hydrocortisone use found a statistically significant decrease in hospital mortality; this reduction was not seen with prednisone/methylprednisolone use. Differences in pharmacological properties might explain this; hydrocortisone has higher mineralocorticoid activity than prednisone and methylprednisolone.[27] In large animal sepsis models, mineralocorticoid levels were inversely correlated with the severity of shock and mortality; adding mineralocorticoids reversed this.[28] Our hydrocortisone sub-analysis does support the current 2024 SCCM guidelines and aligns with the conclusions of Wu et al. provided that hydrocortisone is the corticosteroid used. A large international study, the Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP, NCT02735707) is currently studying hydrocortisone in severe CAP, and their findings will help add to existing data on hydrocortisone.

The benefits of corticosteroids may extend beyond mortality. We found that corticosteroids were associated with a significant decrease in the mechanical ventilation requirement, similar to other studies.[25,26] Reducing the need for mechanical ventilation has considerable resource implications but it also protects patients from the potentially harmful effects of mechanical ventilation itself. It is an important finding because the need for mechanical ventilation in CAP predicts increased mortality (odds ratio 18.4, 95% CI 8.65–39.1, $P<0.001$).[29] Since our meta-analysis included only randomised, double-blind trials, our findings are unlikely to be influenced by the clinician's knowledge of which intervention the patient received. It is plausible that patients who had received corticosteroids had higher PaO_2/FiO_2 ratios; this effect of steroids has been reported in ARDS patients,[30] which reduced the perceived need for mechanical ventilation Additionally, by reducing inflammation in CAP, steroids may modify the hypermetabolic state by reducing the work of breathing, lactic acid production and CO_2 production,[30] again reducing the requirement for mechanical ventilation.

A sensible hypothesis for why the reduced requirement for mechanical ventilation did not translate to a mortality benefit could be the offset of any benefit by harmful steroid side effects, such as the increased risk of infection, hyperglycaemia and gastrointestinal tract bleeding. However, our meta-analysis found no association between corticosteroid usage and secondary infections (RR 0.66, 95% CI 0.28–1.12, ⊕⊕⊖⊖). The risk of secondary infection is lower with shorter courses,[31] and in our meta-analysis, corticosteroid therapy was limited (7 days to 20 days, Table 1).[5,6,13,15,16] The ICU context may influence this too, since patients are often individually isolated, limiting opportunities for cross-patient and airborne contamination.[26,32]

Drug-induced hyperglycaemia is a common consequence of corticosteroid use.[33] Interestingly, we found no association between corticosteroid use and hyperglycaemia requiring insulin, perhaps because hyperglycaemia is frequently encountered in critically ill patients, regardless of corticosteroid use.[6] However, patients receiving corticosteroids required higher insulin doses,[5,34] though this could be beneficial since insulin use reduces circulating free fatty acids and improves myocardial glucose uptake, thus enhancing myocardial function and systemic circulation.[35]

We also found that corticosteroid use was not associated with an increased risk of gastrointestinal bleeding. This side effect concerns clinicians, even though robust meta-analyses have suggested that it is not as common as perceived.[36] Corticosteroids did reduce the biosynthesis of gastric mucous, bicarbonate and cytoprotective prostaglandins, but these effects may be counterbalanced by suppressed production of gastric-damaging leukotrienes.[37] Furthermore, proton pump inhibitors or histamine H2 receptor antagonists are commonly started in patients admitted to ICU.

In this study, we applied the Bayesian methods as our primary form of analysis. Unlike the frequentist methods, Bayesian analysis incorporates prior beliefs and knowledge about parameters,[38] allowing integration of existing knowledge, which helps to improve the accuracy and reliability of the predictions[39] and more closely reflects clinical decision-making at the bedside. Furthermore, Bayesian analysis provides a 95% probability of

the true effect of corticosteroids. In our study, the overall posterior probability of 94.3% suggests steroids are more likely than not to improve mortality, without meeting statistical significance. This can inform priors in future Bayesian studies and encourages continued investigation of the effect of corticosteroids in these patients. Future studies should focus on comparing the efficacy of different corticosteroids in these patients and attempt to identify subphenotypes that are more likely to benefit. For example, in COVID-19 pneumonia, corticosteroids were associated with mortality benefit in patients with a hyperinflammatory phenotype, and harm in those with hypoinflammatory phenotypes.[40,41]

Several limitations deserve consideration. First, we could not analyse other important side effects of corticosteroids such as neuropsychiatric and electrolyte disturbances due to insufficient data. Second, we only identified 6 RCTs for final inclusion, not only reflecting the challenges of conducting high-quality RCTs but also exposing our results to the risk of being driven by the 2 largest studies. Third, there is evidence of heterogeneity because the inclusion criteria to determine ICU admission differed slightly across the studies. Four RCTs used the American Thoracic Society criterion,[6,13,15,16] 1 used the British Thoracic Society criterion for severe pneumonia[14] and another used the Pulmonary Severity Index.[5] Adding to heterogeneity of evidence, primary outcomes investigated were not standardised across studies.

CONCLUSION

After conducting our Bayesian analysis, we found that current evidence does not support the conclusion that corticosteroids significantly reduce mortality in bacterial CAP. Nevertheless, the posterior probability of effect is >90%, and a subgroup analysis found that hydrocortisone significantly reduced mortality. Importantly, the use of adjunct corticosteroids reduced the need for mechanical ventilation and was reported as safe, thus encouraging future efforts to study this therapy. Our findings support the 2024 SCCM guidelines on the use hydrocortisone.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Disclosure

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Supplementary materials

Fig. S1. Frequentist analysis of primary and secondary outcomes.
Table S1. Detailed search strategy.
Table S2. Risk-of-bias assessment.
Table S3. Certainty of evidence.

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COMMENTARY

Towards a unified approach: Standardising radiological diagnosis and grading of vertebral compression fractures

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ABSTRACT

Vertebral fragility fractures are a common cause of morbidity in osteoporotic patients. Despite their association with a high risk of future fractures, significant morbidity and increased mortality after fracture, they often do not receive adequate attention from doctors, researchers or patients. Contributing factors include the improper application of current fracture classification systems and the overwhelming volume of imaging studies. The issue is further compounded by the absence of a universal consensus on the identification and grading of vertebral compression fractures. Regular updates to the definitions of osteoporotic vertebral fractures are necessary as more sensitive and specific diagnostic methods emerge. Establishing a practical consensus is crucial for ensuring standardised reporting, equitable clinical trial assessments, accurate reimbursement and appropriate management.

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Keywords: compression fracture, consensus, osteoporosis, radiology, spine

INTRODUCTION

Vertebral compression fractures (VCFs) are frequently missed on frontal and lateral chest radiographs.[1] Even with abdominal computed tomography, where sagittal imaging is readily available, up to 84% of grades 2–3 compression fractures can be unreported.[2] In patients with acute hip fractures, vertebral fractures were found to be unreported in 54% of cases when the spine was evaluated.[3] Clinically, osteoporotic vertebral fractures can be challenging to detect, as symptoms are often mild and attributed to nonspecific musculoligamentous pain. When vertebral fractures are apparent on imaging, there is no clear consensus on how to classify them. The use of various diagnostic and grading systems can make detection and assessment more difficult, although such recognition is increasingly important. Prevalent or incident fractures are often key endpoints in clinical trials for osteoporosis, and variability in fracture detection can significantly impact the outcomes of these trials.

The guidelines from the International Society for Clinical Densitometry (ISCD), International Osteoporosis Foundation (IOF), American College of Radiology, UK and the European guidance lack a clear definition of VCFs. ISCD recommends using the Genant method, while the IOF website lists various references without providing a consensus on VCF detection.[4] The European guidance only addresses vertebral fracture assessment without specifying how to identify VCFs.[5] The American College of Radiology focuses solely on the management of VCFs. UK guidelines reference morphometric, Genant and algorithm-based quality methods for visually evaluating and recognising endplate fractures but do not offer definitive guidelines. Additionally, the Osteoporosis and Metabolism Subcommittee of the European Society of Musculoskeletal Radiology recently published a review providing a comprehensive overview of VCFs.[6] While the article did provide some guidance on how to diagnose these fractures, even going as far as proposing an algorithm on how to do so, it lacked a clear consensus statement, due to the complexity of the problem. It is important to recognise that the Genant method was developed for classifying asymptomatic VCF using radiographs and is not intended for classifying post-traumatic fractures. Traumatic vertebral fractures should instead be classified using alternative systems, such as the AO Spine Thoracolumbar Injury Classification and Severity Score. This system classifies osteoporotic VCFs based on the deformation of 1 or both endplates, with or without posterior wall involvement, and divides these fractures into 5 subgroups.[7] However, the definition of endplate deformation remains unclear, and the 5 subgroups are difficult to apply in practice.

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Reaching a universal consensus on the identification and grading of VCFs is essential for various aspects of healthcare. Without it, patients with similar imaging findings may receive inconsistent diagnoses and varying treatment plans, leading to undertreatment or even no treatment for some individuals. This increases the risk of existing fractures worsening or preventable new fractures occurring. The absence of a consensus also hampers the proper assessment of follow-up imaging and evaluation of treatment response. Furthermore, it complicates the ability of policymakers to establish standardised guidelines for clinical practice when diagnostic agreement is lacking. Reimbursement policies also become more challenging, potentially leading to inequitable costs for patients receiving different therapies despite having similar imaging results. Last, the lack of standardisation can impede research by limiting the ability to compare outcomes from vertebral fracture-based clinical trials, restricting cross-study collaboration and data pooling. Standardising diagnostic methods would improve scientific efforts, enabling more reliable findings and more refined conclusions through easier comparison of different studies.

Genant semiquantitative grading for vertebral fractures

The Genant semiquantitative grading system, introduced in 1993,[8] is the classic method for grading osteoporotic VCF. This method classifies vertebral bodies into 1 of 4 grades based on the degree of height loss, with increasing height loss over time indicating fracture progression. While widely used, the Genant method has certain limitations. First, although Genant emphasised the importance of distinguishing between cortical and endplate fractures, the semiquantitative method does not provide specific guidance on how to address these fractures. When the Genant method is used in isolation, there is no consensus on how to classify fractures that occur without associated height loss. Genant recommended a combined approach, incorporating both the semiquantitative method and more traditional fracture identification patterns, but a unified system would be more clinically valuable.[8] Second, the exclusion of grade 0.5 fractures aims to avoid mislabelling short vertebrae as compression fractures, but some of the fractures, particularly those involving cortical or endplate damage may progress over time. Last, trabecular microfractures, which are identified through marrow oedema on magnetic resonance imaging (MRI) and often occur without height loss after low-energy spinal trauma, are not adequately addressed by the semiquantitative method, despite Genant's recognition of their importance. In addition, the use of area reduction for grading trabecular microfractures had previously been proposed though due to difficulties in calculating percentage of area loss, it was consequently abandoned.

Alternative factors to consider when grading

The grading system proposed by Genant has the potential to overlook certain clinically significant fracture types, leading to under-reporting in clinical trials or insufficient treatment for at-risk patients. This could result in the progression of existing fractures or the occurrence of new fractures, either in the spine or elsewhere. Additionally, factors like patient positioning and angulation of the radiographic beam can affect the estimated vertebral height loss, influencing the fracture grade. Pathologies detected at the edges of radiographs are especially prone to artifact, which may affect the sensitivity of detecting VCF and the accuracy of measuring height loss. Therefore, any standardised system for identifying and grading fractures should be comprehensive enough to ensure proper classification of all fractures.

In a study of over 1500 Chinese women, Wáng et al. demonstrated that participants with mild vertebral fracture (Genant grade 2, subdivided into mild [25–34% height loss] and severe [34–40% height loss]) were at higher risk of developing endplate fractures. Moreover, those with existing endplate fracture had a higher risk of worsening or developing new vertebral fractures compared to those without such fracture.[9] The Genant method does not consider grade 0.5 deformities as true fractures unless accompanied by a cortical or endplate fracture. However, Wáng's study also showed that vertebrae with endplate and cortical fractures at baseline were at risk of further deterioration.[9] These findings suggest that deformities classified as Genant grade 0.5, as well as endplate or cortical fractures without height loss, should be considered true fractures—provided that other causes of endplate disruption, such as Schmorl's nodes, are excluded. Additionally, research from the same group in 2020 indicated that vertebral fracture progression differs between males and females. Males with severe vertebral fractures at baseline had a low likelihood (~5%) of developing new spinal fractures over 4 years, while females with severe vertebral fractures had a much higher likelihood (approximately 30%).[10] This highlights the importance of considering gender when evaluating future spinal fracture risk. Kim et al. emphasised the importance of detecting endplate or cortical fracture, regardless of any associated height loss.[11] However, identifying these fractures on radiographs

can be challenging, as height loss is typically easier to recognise. On MRI, vertebral body bone marrow oedema can be observed even in the absence of endplate or cortical fractures or loss of vertebral height, especially in the acute stage. In the appropriate clinical setting, this bone marrow oedema is indicative of trabecular microfracture. The long-term significance of bone marrow oedema due to microfractures remains unclear, as no studies have determined whether this type of injury progresses over time. Therefore, fracture identification and grading systems should account for the classification of such trabecular microfractures.

Structured reporting

A structured vertebral fracture report should include key elements such as the vertebral body level, the shape of the vertebral body, endplate and/or cortical fractures, and the severity of vertebral height loss. In addition to specifying the degree of height loss, the report should describe the type of deformity (e.g. wedge, biconcave or crush). Clear, standardised terminology is essential for effective structured reporting. If previous imaging is available, the report should also note any interval changes. Additionally, any deformities not caused by fractures, such as osteoarthritic anterior wedging, Scheuermann's disease, congenital or acquired short vertebrae, Schmorl's nodes and metastatic infiltration, should be clearly identified. Future advancements in artificial intelligence technology may assist radiologists in generating comprehensive reports.

CONCLUSION

The identification and classification of vertebral fractures are important for evaluating patient risk, ensuring proper treatment and monitoring changes over time. These processes are also important in assessing outcomes in osteoporotic clinical trials. However, there is currently no comprehensive consensus on how vertebral fractures should be identified and classified. Existing classification systems do not account for recent advancements in imaging technology. Establishing a practical and unified consensus is essential for standardising clinical diagnoses, research trials, therapeutic management and equitable reimbursement in the future.

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Declaration

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LETTER TO THE EDITOR

Natural Language Processing for serious illness communications in palliative surgical oncology

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Dear Editor,

Approximately one-fifth of surgeries performed at major cancer centres worldwide are palliative in nature, and one-third of advanced cancer patients receive surgery during their last year of life.[1,2] Serious illness communication (SIC) is an essential component of palliative care. In the context of palliative surgical oncology, the surgical team will facilitate a shared decision-making with patients who are considered for high-risk palliative surgery or other interventions. This explores the goals of surgery or other proposed interventions and the prognosis; it also clarifies code status, assesses for suitability for hospice care, and explains the associated risks of surgical morbidity and mortality for the advanced cancer patients and their families.[3]

At present, there remains a paucity of high-quality studies that examine the delivery of palliative care to end-of-life surgical patients.[4] A significant challenge in measuring the quality of palliative care processes is the need for manual chart reviews of electronic health records (EHR) which can be time- and labour-intensive.[5] As such, we aim to develop a natural language processing (NLP) algorithm to facilitate the evaluation of SIC in advanced cancer patients undergoing invasive interventions.

We queried a retrospective palliative surgical oncology database in a single tertiary cancer centre—the National Cancer Centre Singapore—and included patients who underwent invasive palliative surgery or other invasive interventions between 2021 and 2022. Unstructured free text in EHR from the index surgical admission was extracted. A multidisciplinary team of surgical oncologists, palliative care physicians, gastroenterologists and interventional radiologists developed a library of key terms to evaluate the 6 components of SIC.[6] The library was constructed based on concept terms and phrases commonly used to document SIC in literature[7]; this was further refined based on additional keywords identified through iterative review of EHR. Blinded manual chart reviews were undertaken by 2 surgical oncologists and 1 palliative care physician who identified components of SIC found in unstructured clinical text in the EHR. This manual chart review constituted the gold standard reference against which the NLP algorithm was compared.

We had previously utilised a regular expression-based NLP pipeline to annotate free text radiological reports.[8] We adapted the same pipeline in Python version 3.11.0 (Python Software Foundation) to examine the frequency and adequacy of SIC components. This study has been approved by the SingHealth Centralised Institutional Review Board, with informed consent obtained from all participants.

There were 98 patients who underwent palliative surgery or other invasive interventions. The final NLP algorithm achieved a sensitivity of 77.8–100%, specificity of 31.6–100%, as well as an agreement of 86.7–100% with the reference standard, together with a Cohen's kappa of 0.43–1.00 in the various components of SIC (Table 1). In the final cohort of patients undergoing palliative surgery or other interventions, the NLP algorithm identified that discussions on goals of care occurred in 16.3%, code status in 2.0%, hospice assessment in 18.4%, disease prognosis in 18.4%, morbidity rates in 93.9%, and mortality rates in 34.7%. Most patients had discussions across several SIC components: 76.6% had 1 or 2 components discussed, and 19.4% had 3 to 5 components discussed. Specialist palliative care referrals were made 38.8% of the time.

Our results highlight the areas of difficulty that clinicians struggle with regard to SIC for advanced

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Table 1. Performance of the Natural Language Processing algorithm in identifying components of serious illness communications in palliative surgical oncology patients (n=96).

Components of serious illness communications	Sensitivity (%)	Specificity (%)	Agreement (%)	Cohen's kappa	Frequency no. (%)
Goals of care	88.9	100.0	98.0	0.93	16 (16.3)
Code status clarification	100.0	100.0	100.0	1.00	2 (2.0)
Assessment for hospice	77.8	95.0	91.8	0.73	18 (18.4)
Discussion of disease prognosis	100.0	100.0	100.0	1.00	18 (18.4)
Discussion of morbidity rates	100.0	31.6	86.7	0.43	92 (93.9)
Discussion of mortality rates	91.9	100.0	96.9	0.93	34 (34.7)

cancer patients undergoing invasive treatments. It was noted that surgical teams are adept at explaining surgical or procedural risks, while discussions on goals of care and other important aspects of SIC are often neglected. In Singapore's ageing population with a growing number of patients diagnosed and living with advanced cancer, ensuring access to palliative care, including SIC is essential to facilitate goal-concordant end-of-life care. Our findings highlight the need to improve surgeon-patient communication in the context of life-limiting cancers.

There has been increasing utilisation of computational methods such as NLP in palliative care research in recent years.[7,9] However, literature beyond the US remain sparse, with no studies evaluating SIC in the context of a non-American population. In this study, we were able to develop an NLP algorithm that can accurately identify the various components of SIC from EHR in Singapore's context. Given the differences in linguistic parlance across different cultures and populations, establishing the use of NLP in an Asian context is essential to expand its use locally and in the region.[10] The study also represents an important first step towards the use of locally-trained NLP algorithms to measure palliative care processes in Singapore.

Several limitations of the current study should be noted. First, the NLP algorithm was built on a pre-defined key term library which is non-exhaustive. As an extension to the above point, its performance may also be affected by differences in documentation practices and linguistic parlance across departments, institutions and regions. Validation and further optimisation should therefore be undertaken when the algorithm is adopted in different settings. Furthermore, the adequacy of SIC measured is dependent on reliable clinical documentation practices among healthcare providers. Our evaluation was also limited to index hospitalisation consult notes, and may exclude SIC performed at other care settings. Finally, we acknowledge the relatively low specificity of the algorithm in identifying discussion of morbidity risk at 31.6%, possibly leading to a higher rate of false positives and contributing to the high rates in this domain at 93.9%. This is because the algorithm was unable to differentiate between patient communications regarding complications that have already occurred post-intervention versus those that occur as part of pre-intervention risk counselling.

Overall, while specialist palliative care will continue to play an important role in end-of-life care, it is crucial that the foundational principles of palliative care and SIC are integrated into routine surgical care provided by the surgical team. The current study has demonstrated that advanced computational techniques such as NLP have utility in evaluating and improving on the delivery of care in this aspect. In future works, it is foreseeable that the integration of NLP into EHR pipelines can pave the way for regular review of quality outcome indicators for continued identification of deficiencies in palliative care delivery, which can be translated into development of systems-level quality improvement processes for the betterment of patient outcomes.

Declaration

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Ethics

This study has been approved by the SingHealth Centralised Institutional Review Board (CIRB Reference 2021/2455), with informed consent obtained from all participants.

Keywords: *goals of care, natural language processing, palliative care, palliative interventions, serious illness communications*

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LETTER TO THE EDITOR

Traction alopecia in women: An under-recognised cause of hair loss

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Dear Editor,

Alopecia ranks among the most common clinical complaints encountered by dermatologists.[1] In particular, affected women often experience great psycho-emotional stress leading to a reduction in quality of life.[2]

We conducted a prospective epidemiological study conducted over 77 weeks from 1 August 2022 to 23 January 2024 at an outpatient dermatology clinic at Singapore General Hospital. Our primary aim was to evaluate the aetiology of hair loss in adult women in Singapore. Patients above the age of 21 years consented to participation after a formal diagnosis of alopecia. Patient characteristics were analysed to reflect the various aetiologies causing hair loss in women.

All study procedures were implemented with written informed consent obtained from participants, in accordance with protocols approved by the Nanyang Technological University and Singapore General Hospital Institutional Review Boards (IRB approval number: 2021/2552).

A total of 38 female patients were recruited into this study. The mean age of patients was 46.6 years, with an age range of 25 to 78 years. History and clinical examination, including use of trichoscopy, was used to ascertain the aetiology of alopecia. Two patients underwent scalp biopsy for scarring alopecia.

The ethnic mix of female patients with hair loss (Chinese: 61%, Malay: 16%, Indian: 21%, Others: 3%) was largely in line with the ethnic population of Singapore (Chinese: 76%, Malay: 15%, Indian: 7%, Others: 2%). Indian patients were the exception, comprising 21% in our study despite making up only 7% of the Singapore population (Fig. 1).

Nineteen (50%) out of 38 patients had multiple aetiologies attributed to their hair loss. Patients with more than 1 aetiology were included in both categories. Overall, the most common cause of alopecia was female pattern hair loss (27/38; 71%), followed by traction alopecia (13/38; 34%) and alopecia areata (8/38; 21%), as illustrated in Fig. 2.

Seven different aetiologies for hair loss were identified in the study group. Out of these, 2 were scarring (frontal fibrosing alopecia and folliculitis decalvans) while 5 were non-scarring (female pattern hair loss, alopecia areata, traction alopecia, telogen effluvium and trichotillomania). Half (19/38) of the patients had more than 1 aetiology for alopecia; 9 (47%) of them had alopecia caused by both female pattern hair loss and traction alopecia. Non-scarring alopecia accounted for the bulk of hair loss complaints, which affected 34/38 (90%) patients.

Of note, 12 of the 13 patients (92%) with traction alopecia had 2 aetiologies to their hair loss. Of these 13 patients, 6 (46%) were Indians, 5 (38%) were Chinese and 2 (15%) were Malays, with an average age of 40 years. Interestingly, traction alopecia was a cause of alopecia in 80% of the Indian patients in the study group. The mechanism of traction alopecia was either hair tying or clipping.

In terms of co-existing conditions, seborrhoiec dermatitis (21%) and eczema (16%) were commonly seen in the study group. This is higher than expected, compared to the prevalence of 7% for seborrhoiec dermatitis and 11% for eczema in the Singapore adult population.[3,4]

From the results of this study, Indian patients comprised 21% of female patients with hair loss despite only comprising 7.4% of the Singapore population. This increased proportion of Indian patients may be reflective of cultural hair tying and braiding practices that may predispose individuals to alopecia. Previous literature has shown that there exist significant morphological differences in the hair of various ethnicities such as Asians, Caucasians and Africans.[5] These differences may contribute to the development of alopecia. However, further studies can be conducted to establish a definitive relationship between ethnicity and the incidence of alopecia due to the many confounding factors that exist. This may include differences in hair texture, health-seeking behaviour, hair care practices, climate and nutrition. For example, 80% of Indian patients in this study were affected by traction alopecia.

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Fig. 1. Ethnic distribution of patients in relation to Singapore's population.

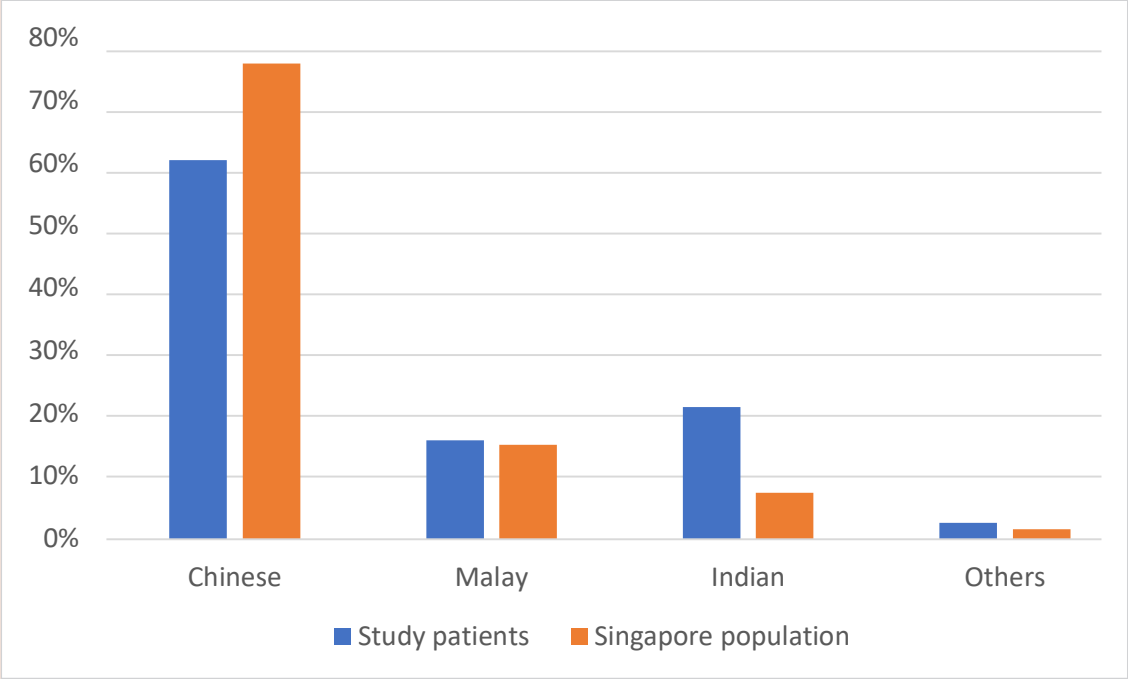
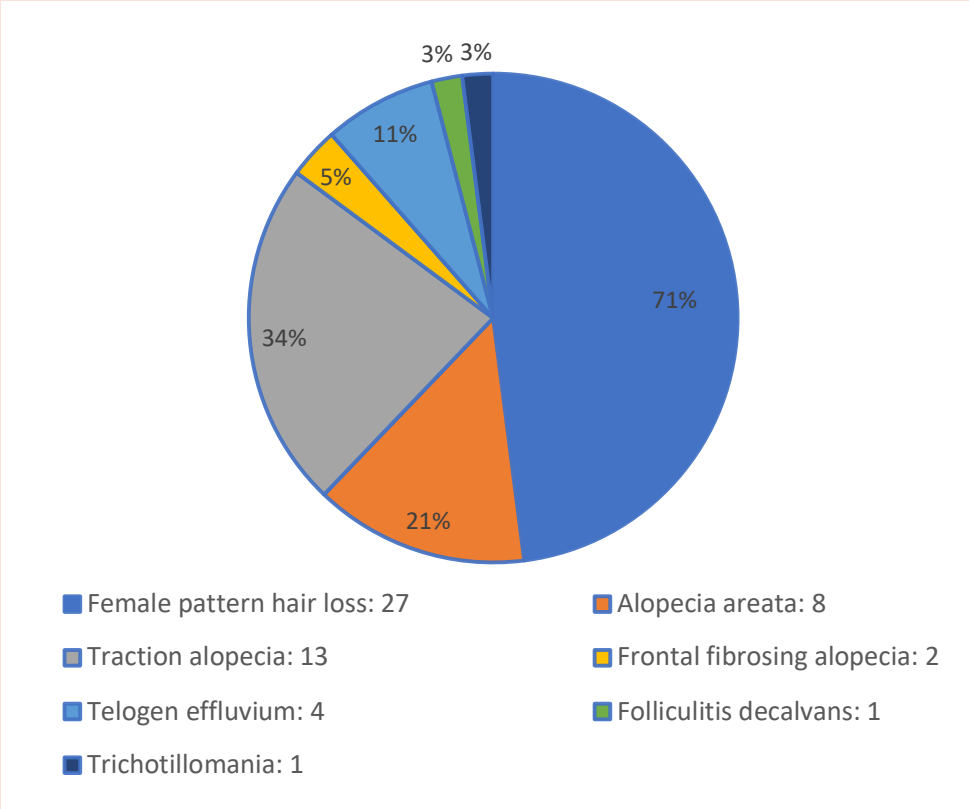


Fig. 2. Aetiology of hair loss.



Possible reasons for this could be hair type and hair practices. Wearing braids, ponytails with elastic band, cornrows, dreadlocks and turbans have been associated with traction alopecia.[6]

Pruritic skin conditions such as eczema and seborrhoeic dermatitis affected 16% and 21% of the study group, respectively. These inflammatory conditions predispose to alopecia through diffuse telogen hair loss.[7] Scratching also damages hair follicles, causing hair shedding. Good control of underlying, primary skin conditions causing itch appears to be important in treating patients with alopecia.

Our study found traction alopecia to be the second most common cause of alopecia in our cohort. It is potentially reversible if detected and treated early. Despite this, traction alopecia is often a neglected entity, mentioned at the end of the list of causes of alopecia in literature.[8] This may be due to the lack of awareness that mechanical factors in common hairstyles across all races and hair types can cause alopecia, not only in those of African descent with tight, spiral curly hair.

All patients in this study who were diagnosed with traction alopecia had either another aetiology for hair loss or were seeking treatment for another condition affecting their scalp. Patients often try various coping mechanisms, such as concealing their hair loss, before seeking professional consultation, often when the disease is more severe.[8] In this study, the secondary factors found to be present may have attributed to the increased severity, prompting medical consultation.

Previously an underdiagnosed aetiology, this study found that one-third of patients suffer from traction alopecia. Raising awareness of this condition and education on methods of hair care to prevent traction alopecia is important. Many occupations, such as those in the food and beverage or service sectors, require hair to be tied back to maintain hygiene and a kempt appearance. Patients can be advised to keep their hair loose or wear low risk hairstyles such as loose low ponytails or buns, ensure their braids are not too tight, use hair extensions only for a short period of time, and to change their hairstyle periodically.[9]

Additionally, we have identified possible risk factors for alopecia such as hair practices common to Indian ethnicity, and co-existing conditions such as seborrhoiec dermatitis and eczema. Identifying patient groups at higher risk of alopecia in this study will help with the early detection and institution of preventive and treatment strategies for alopecia. This study was limited by small sample size. This precluded in-depth comparisons of aetiologies with adequate statistical power. Further studies can be done to substantiate its findings.

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: *alopecia, dermatology, epidemiology, female pattern hair loss, family medicine, women*

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LETTER TO THE EDITOR

Interdisciplinary approach of conservative kidney management with a community nurse-led programme

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Dear Editor,

Conservative kidney management (CKM) should be considered when the burdens of dialysis treatment outweigh the benefits and compromise quality of life. The availability, accessibility and quality of care vary across the world depending on healthcare structure and resources. We explored the feasibility of integrating a nurse-led CKM community programme into nephrology care which is still evolving.

This was a single-centre, prospective cohort study from 1 April 2021 to 1 April 2024 for patients under Sengkang General Hospital who had chronic kidney disease (CKD) stage G5 and opted for CKM. Follow-up and home visit were done at patients' home. They were referred to the renal conservative care team, comprising nephrologists, renal coordinators, medical social workers in the clinic, and specialised nurses and social workers in the community. The primary goal was to provide routine kidney supportive care in a holistic manner, and to integrate community resources to support the well-being of patients and their families. We also aimed to increase awareness of CKM as a viable treatment option. These patients were reviewed regularly in the community with interval outpatient renal clinic visits. Patients who were nursing home residents, enrolled into home hospice programmes, had dialysis withdrawn or had declined home visits were excluded due to needing different healthcare support and funding structure. At each visit. validated instruments were used to measure patients' symptoms, physical status and biopsycho-social needs: Edmonton Symptom Assessment System Revised: Renal (ESAS-r: Renal),[1] Resources Utilisation Group – Activities of Daily Living scale (RUG-ADLs)[2] and Palliative Performance Scale version 2 (PPSv2).[3] The cohort of patients was followed up until demise or 31 May 2024. Individuals who had demised, transferred to hospice care or initiated on dialysis were considered to have exited the programme. Monthly home visit was conducted or earlier review depending on the patient's condition. Communication platforms used were WhatsApp and email that allowed dynamic monitoring and escalation of care within the same day.

A total of 121 patients were enrolled into the CKM community programme during the specified period. Demographics and baseline information were obtained upon entering the programme. Mean age was 79.2±7.7 years, baseline estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration equation was 10.3±3.4 mL/min/1.73 m^2, and Charlson comorbidity index was 8.4±1.9. Among them, 46 (38%) were male and 96 (79.3%) were Chinese. Their comorbidities were diabetes mellitus (76.9%), ischaemic heart disease (34.7%), stroke or transient ischaemic attack (27.3%), dementia (22.3%), malignancy (15.7%) and peripheral vascular disease (13.2%). More than 80% of the patients had no symptoms using ESAS-r: Renal assessment at baseline (Fig. 1a). Majority were independent based on RUG-ADL (Fig. 1b), and PPSv2 scores were between 60 and 70.

Duration in the CKM community programme was calculated from the first to the last home visit, median duration was 5.9 months (interquartile range [IQR]: 2.0, 12.3). During the follow-up, 51 patients (42.1%) demised, 19 (37.3%) of which required inpatient hospice. Forty patients (33%) who required palliative care were referred to home hospice. Eleven patients (9.1%) changed their decision and were started on dialysis. Median survival from first home visit to demise or 31 May 2024 was 10.1 months (IQR: 4.6, 19.2) versus 9.1 months (IQR: 4.3, 15.5) if excluding those who started dialysis (Supplementary Fig. S1).

Dialysis availability results in its perception as the default management option for CKD stage G5.[4] Dialysis patients have access to their healthcare

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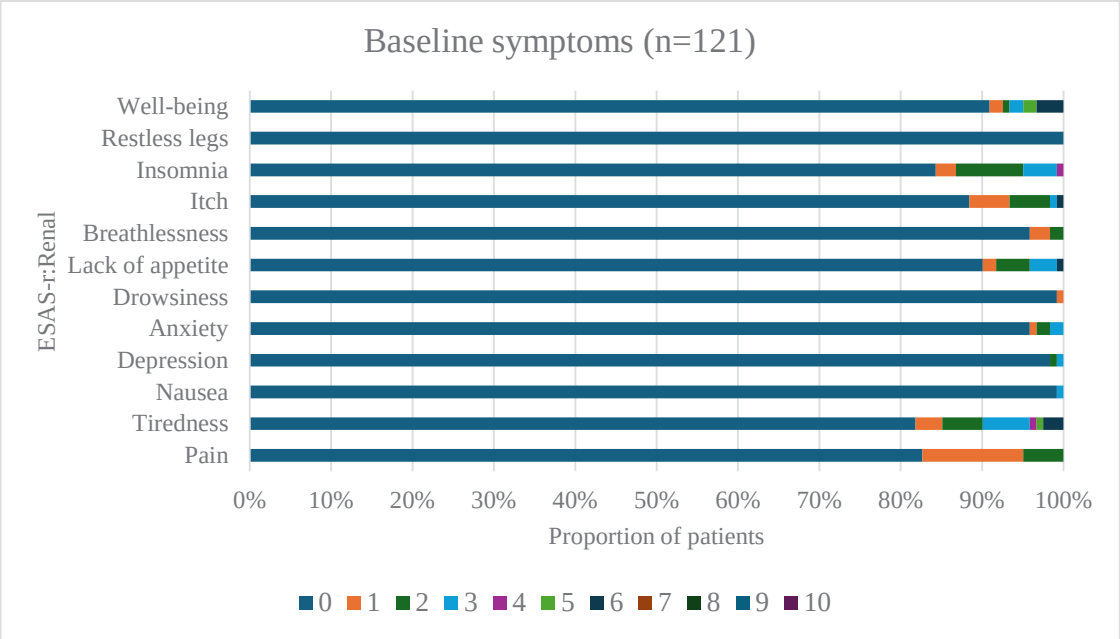
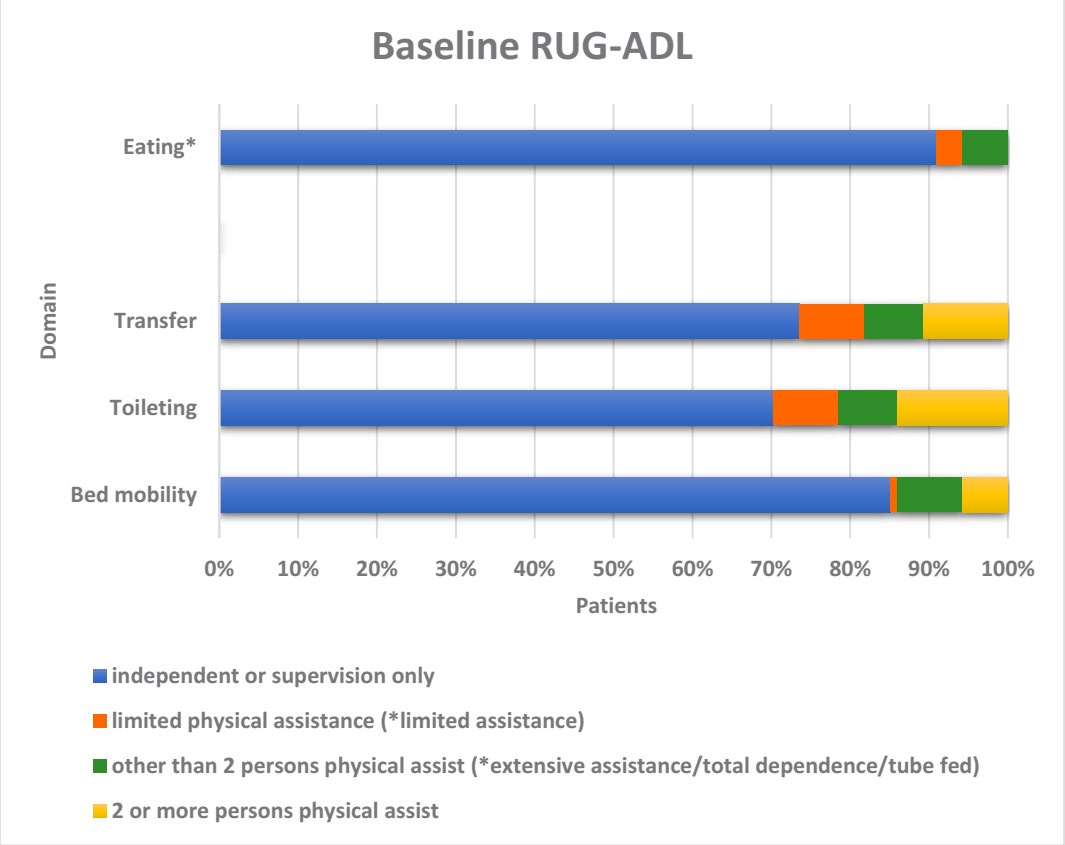
Fig. 1. Baseline characteristics.

(A) ESAS-r:Renal symptoms



ESAS-r: Edmonton Symptom Assessment System Revised

(B) RUG-ADL.



RUG-ADL: Resources Utilisation Group – Activities of Daily Living

providers for their health-related enquiries and support. On the contrary, CKM patients may have limited access to healthcare support, apart from ambulatory visits or home hospice if referred. These CKM patients may feel vulnerable, uncertain and may perceive medical abandonment without support in the community.[5,7,8]

Providing comprehensive care for CKM patients in the ambulatory setting is challenging with time constraints against competing clinical needs. A CKM programme that extends into the community breaks this barrier and allows continuous discussion between the patients, family members and healthcare team. This leads to a continuous discussion from clinic to home setting, which reinforces patient-centric care, apart from regular monitoring of clinical progression. The continuity of care helped deconflict dissonant decisions between patients and caregivers, which are unlikely to happen in a routine clinic review. Home visits enhanced the confidence of families in caring for CKM patients in the community and in being more prepared should the situation change. Direct communication between the community team and nephrologists also allowed prompt and direct care delivery. Primary care physicians may be less comfortable with adjusting larger doses of diuretics or erythropoiesis-stimulating agents in patients with CKD stage G5.

Our CKM patients had relatively low symptom burden in the early phase of CKD stage G5, and decompensation could occur suddenly and rapidly. Without reversible factors, demise would be expected in weeks.[6] Such a tipping point would have been difficult to anticipate if the patients were seen at several months' interval in a clinic setting, much less considering their diminished physical function and mobility to attend these visits. The CKM community nurse identified deteriorating individuals and timely transit to palliative care while in the community setting. Home visits also provided a window into our patients' lives and their coping strategies with chronic disease. Understanding health perceptions and priorities, which have been shaped over years, was crucial in healthcare decision-making and anticipatory guidance on the eventual care needs of patients as symptoms and function worsened.

Our CKM community programme identified challenges in supporting CKM patients before palliative care needs emerged and filled the gaps in the above-described niche areas. We were limited by being a single-centre experience, not comparing those patients under standard of medical care or on dialysis, and practices might differ depending on the resources available. We also did not receive follow-up information of patients who were transferred to home hospice, such as their ESAS-r: Renal, RUG-ADL and PPSv2.

CKM patients are heterogeneous, complex and require dedicated care. The prototype CKM community programme is pragmatic and could fill the gap in existing services. An interdisciplinary CKM programme provides patient-centric, holistic and anticipatory care, supporting patients and families through their CKD stage G5 journey. Identifying suitable patients, practising judicious resource allocation and following a team-based approach are important components of a high-quality programme.

Supplementary material

Fig. S1. Survival analysis for patients under conservative kidney management programme.

Ethics statement

The study was approved by the SingHealth Centralised Institutional Review Board (2021/2451). This project had institutional review board exemption and waiver of consent as it was part of the service development.

Declaration

The authors declare there are no financial interest in the subject matter or materials discussed in this manuscript.

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Keywords: *chronic kidney disease G5, community programme, conservative kidney management, interdisciplinary, model of care*

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