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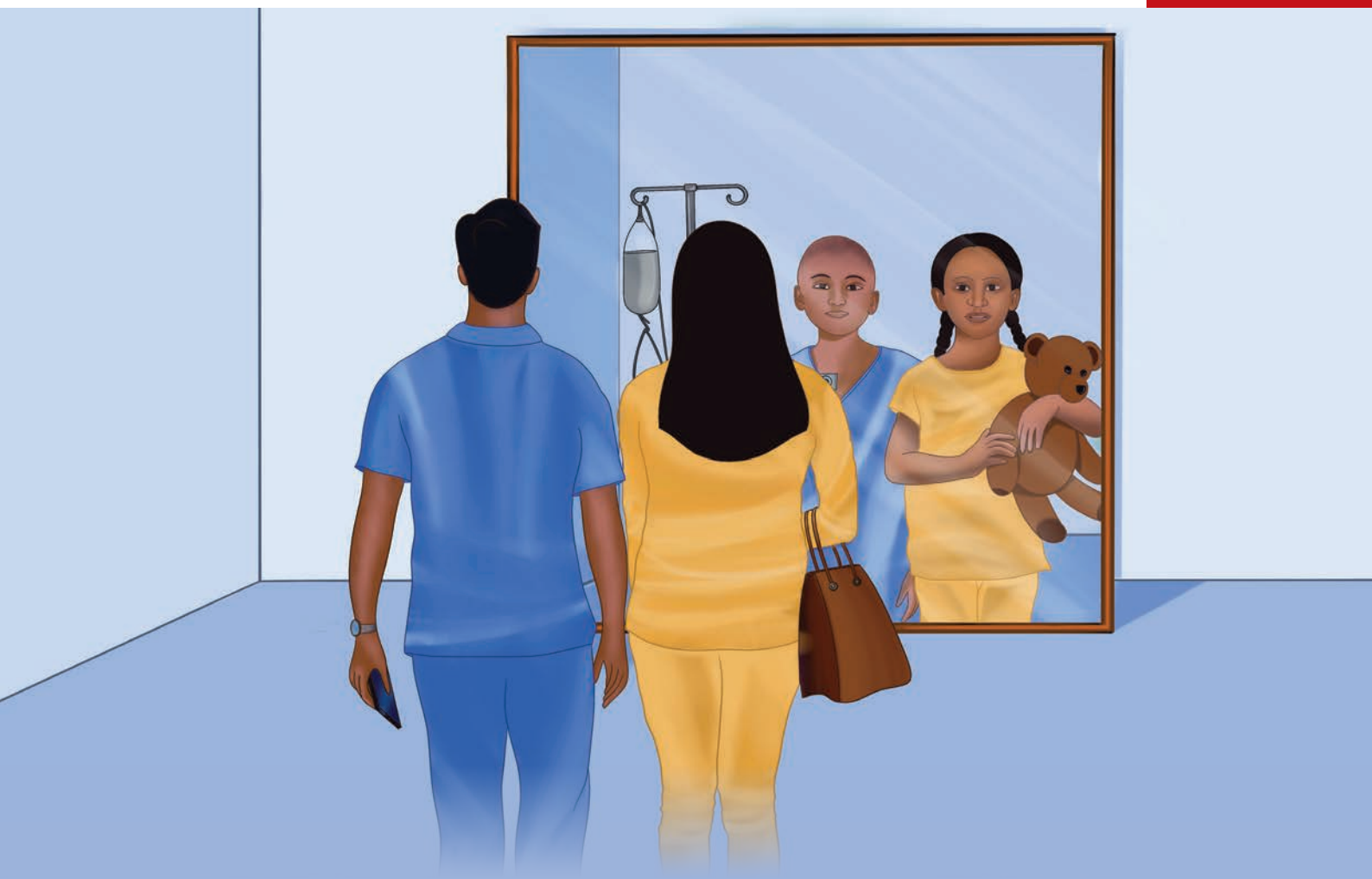

# Mental wellness and health-related quality of life of young adult survivors of childhood cancer in Singapore

Associated risk factors of psychological distress include history of psychiatric illness after cancer diagnosis and mood affected by the COVID-19 pandemic. Findings underscore the need for tailored mental health interventions to address the long-term psychological consequences of cancer survivorship. (See full article, p.530)

Illustration by Ladyfingers Co.

*Also in this issue*

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## EDITORIALS



## ORIGINAL ARTICLES



## REVIEW ARTICLE



## LETTERS TO THE EDITOR

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EDITORIAL

# Beyond survival: Addressing gaps in psychosocial support for survivors of childhood cancer

Yin Ting Cheung[1] *PhD*

I read with great interest the study conducted by Fong et al. published in this issue of *Annals*, which evaluated psychological symptoms and health-related quality of life (HRQOL) among a cohort of 143 young adult survivors of childhood cancer in Singapore.[1] Almost 1 in 4 survivors demonstrated significant psychological distress and poor mental well-being (relative to population norms) at more than 15 years post-cancer diagnosis. Other than being the first in Singapore to characterise the psychological burden experienced by survivors, the notable strengths of this study are (1) the inclusion of siblings as comparators to minimise the potential confounding effects of genetics, family environment and socioeconomic factors on the study outcomes; (2) the use of validated self-reported measures that enable cross-comparison with studies from other countries; and (3) the use of International Classification of Diseases, Ninth Edition diagnosis codes to capture clinical chronic conditions and late effects of cancer. The authors conclude their paper by calling for regular surveillance and timely interventions to improve mental health functioning and HRQOL in cancer survivorship programmes in Singapore. Taken together, this study contributes to the existing literature that highlights the unique needs that survivors of childhood cancer face as they advance to young adulthood, which include the need for ongoing psychosocial support, transition from child-centred to adult-oriented health-care systems, and age-appropriate education on their personal health risks.

There have been vast improvements in the survival rates of children with cancer due to advancements in diagnosis, treatment and supportive care. However, survivorship comes at the cost of developing a myriad of late effects and developmental challenges.[2] As a child enters young adulthood, managing the cancer survivorship experience and making important early-life transitions may be complex, with physical and psychosocial implications. Fong et al. aptly highlight the importance of routine screening of psychological distress and psychosocial challenges in long-term survivors.[1] However, a recent systematic review on mental health screening in childhood cancer survivors found that only 2 of the 30 included studies were conducted in Asian countries (China and South Korea).[3] The scarcity of published studies on this topic in Asian countries and the lack of representation of Southeast Asian groups suggest that mental health and psychosocial problems are an under-addressed topic in paediatric cancer survivorship research in the region.

Although it was unclear how mood affected by the COVID-19 pandemic was measured in the study, the authors found that this variable was significantly associated with psychological symptoms in survivors. Studies have shown how the restriction of social activities and changes in lifestyle behaviors associated with the pandemic—such as physical activity and eating habits—led to increased mental health problems in young survivors of cancer.[4] Particularly intriguing is the large proportion of overweight/obese survivors (42.0%) in the Singapore sample who were predominantly leukemia and lymphoma survivors, and therefore generally not expected to be at risk of obesity and endocrine-related late effects, unlike brain tumour survivors. This proportion seems to be descriptively higher than the overweight/obese survivors (23.3%) observed in a cohort of young adult survivors of childhood cancer in Hong Kong (mean age 24.4 years; SD 6.5 years).[5] It can be inferred from the Singapore data, as well as collective evidence from the literature, that the lack of physical activity, increased screen time, and changes in sleep habits during the pandemic may have contributed to "poorer mood" in cancer survivors. Evaluating the impact of lifestyle on survivors' mental functioning may facilitate the development of behavioral interventions. This is especially relevant in the context of Singapore, as well as other developed cities in the region, where much emphasis is now placed on ameliorating the adverse health effects of the urban environment such as sleep disturbances, a sedentary lifestyle and academic stress among children and adolescents.





[1] School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong
Correspondence: Prof Yin Ting Cheung, School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, 8th Floor, Lo Kwee-Seong Integrated Biomedical Sciences Building Area 39, Shatin, NT, Hong Kong.
Email: yinting.cheung@cuhk.edu.hk

Despite its several methodological strengths, a notable limitation of this study is the absence of a measure to assess the impact of psychological distress on survivors' life functioning outcomes. "Functional status" refers to an individual's perceived level of ability and capacity to engage in meaningful activities.[6] It is an important outcome in patients living with chronic illnesses, particularly young adult survivors of childhood cancer. To illustrate, we found that long-term survivors of childhood cancer in Hong Kong generally reported good leisure and social functioning with their peers but reduced functioning in meeting demands at work/school and at home.[5] Characterising functional outcomes trajectories in survivors during the cancer care continuum will help identify high-risk groups and the appropriate window to implement supportive interventions. Such a data- and algorithm-driven approach may guide the allocation of resources to individuals in greatest need, and the tailoring of services based on individual requirements.

Similar to published studies in some populations,[7-9] the authors did not identify differences in psychological outcomes between survivors and sibling controls. As Fong et al. employed US reference norms and not Singapore reference norms for the assessments, we are unable to determine if cancer survivors and siblings both adjusted well (or did not adjust well) psychologically after cessation of treatment. However, studies in the literature have highlighted the adverse impact of cancer diagnosis on the child's family, especially siblings, who are often regarded as "the forgotten group".[10] This is especially important as Asian cultures often emphasise strong family bonds and interdependence. Future research should investigate the longitudinal changes in psychosocial outcomes among parents and siblings, as well as the impact of the child's cancer diagnosis on family dynamics and family functioning. Such findings would guide the development of family-targeted interventions and support programmes in Singapore.

Finally, the findings of Fong et al. highlight the value of routine monitoring of patient-reported outcomes (PROs) in young cancer survivors to facilitate the early detection of psychological symptoms and timely interventions before they develop into clinical mental health conditions.[11] In particular, the time is ripe to establish and implement a PROs data collection system, related multidisciplinary services and referral pathways, as cancer survivorship has moved to the forefront of the healthcare agenda in Singapore in recent years,[12] with successful case studies and examples of care models implemented in adult cancer populations.[13,14] Similar efforts to develop integrated and coordinated care for long-term childhood cancer survivors are anticipated. Emphasis should be placed on the formal transition of care from paediatric to adult-focused survivorship services that will meet the unique medical, developmental and psychosocial challenges of young adult survivors. Although there is currently no guidance on the best transitional care model, the national resource centre on health care transition in US (Got Transition) has identified 6 core elements to improve organisational healthcare transition practices,[15] which include developing transition care policies and guides (Core Element 1), tracking progress using a registry (Core Element 2), conducting regular transition readiness assessments (Core Element 3), developing transition plan with medical summary (Core Element 4), facilitating the actual transition to adult-oriented care (Core Element 5) and confirming transfer completion (Core Element 6). A comprehensive and holistic approach to improve health and functional status in these young survivors will translate into a substantial positive impact on society.

### *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.*

***Keywords:*** *cancer, paediatrics, psychology, quality of life, rehabilitative medicine*



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EDITORIAL

# Optimising paediatric urinary tract infection diagnosis

Marcus Wing Choy Loe[1] *MD*, Jiahui Li[2,3,4] *MBBS*, Kee Thai Yeo[1,3,4] *MD*

Urinary tract infection (UTI) is the most common cause of serious bacterial illness among children and infants.[1] Up to 2% of boys and 8% of girls will develop at least 1 episode of UTI by the age of 7 years.[1,2] Of these, it is estimated that 12% to 30% will experience recurrence within a year.[3] While majority of patients recover without any long-term sequelae, UTIs can lead to severe complications such as kidney scarring and sepsis if not diagnosed and treated promptly. A very small proportion of children will develop kidney failure from UTI which is typically a result of recurrent UTIs. Known risk factors for UTI among children include female sex, age and the presence of conditions that affect urine flow, such as vesicoureteric reflux or urinary stasis (neurogenic bladder, constipation).[4] UTI typically develops due to the ascension of uropathogens that colonise the periurethral regions to the bladder (cystitis), which may ascend further up the urinary tract (pyelonephritis) and lead to bloodstream infection (urosepsis). UTIs from haematogenous spread is possible, although uncommon. Common pathogens implicated are gram-negative bacteria—primarily *Escherichia coli*; however, other pathogens such as *Klebsiella*, *Proteus* and *Enterobacter* can also be involved.



The clinical presentation of UTI, especially among infants, can be variable and is often non-specific. As such, diagnosis of UTI can be challenging, particularly among younger children, owing to the lack of localising symptoms. As such, UTI is suspected in every febrile infant with or without urinary symptoms. This is particularly important as prompt treatment of UTI significantly reduces the risk of kidney scarring if treated within 24–48 hours from the start of the febrile illness.[5] While a positive urine culture from an appropriately taken sample is the gold standard for UTI diagnosis,[6] turnaround of urine cultures can take between 24 and 48 hours which may delay decision for treatment. As such, physicians routinely commence empiric UTI treatment based on clinical symptoms and results from urinalysis.

The detection of urinary leukocyte esterase (an enzyme present in white blood cells [WBCs]) and nitrites (conversion of nitrates by bacteria) in combination with detection WBCs in urine microscopy are used to determine the likelihood of UTI among children. Previous studies have shown that the inclusion of urine microscopy for the detection of WBC among urine samples improves the sensitivity of the test due to the direct visualisation of cells in the urine sample that do not degrade over time.[7,8] In a study comparing a point-of-care urinalysis (POCT) and laboratory performed urinalysis involving 42,452 urine specimens from children presenting to the emergency department, the improved sensitivity of the laboratory-performed urinalysis (89.1% confidence interval [CI] 86.4–88.8 versus 82.5% CI 79.4–85.3) was driven by the sensitivity of WBC detection on microscopy.[8] Even so, there remains no consensus on the optimal WBC threshold to accurately predict UTIs on urinalysis, leading to variability in clinical practice and the risk of either over- or under-treatment.

In the accompanying study published in this issue of the *Annals,* researchers from KK Women's and Children's Hospital, Singapore, proposed to investigate the optimal urine WBC threshold for predicting UTIs among children being evaluated in the emergency department.[9] This prospective observational study recruited 1188 participants <18 years old over a 10-month period who were screened for suspected UTI. The authors reported that a urinalysis WBC threshold of ≥100/μL was associated with an overall sensitivity of 82.2% and a negative predictive value (NPV) of 86.2% for detecting UTI. However, an estimated 17.3% of culture-positive UTIs would be missed, particularly among nitrite-negative samples which often occur in younger children. As expected, lowering the WBC threshold to ≥10/μL increased the sensitivity and NPV to 96.5%, and 94.1%, respectively, but with an expected absolute increase in the number of urine cultures of 419 over a 12-month period and a likely increase in inappropriate antibiotics exposure.



[1] Department of Neonatology, KK Women's and Children's Hospital, Singapore
[2] Infectious Disease Service, KK Women's and Children's Hospital, Singapore
[3] Duke-NUS Medical School, Singapore
[4] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Correspondence: Assistant Professor Kee Thai Yeo, Department of Neonatology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: yeo.kee.thai@singhealth.com.sg

The study underscored the high proportion of nitrite-negative UTIs (278/460, 60.4%), particularly among infants under 1 year of age. Although majority of enteric gram-negative organisms would be able to reduce nitrates to nitrite; this conversion may not occur in young children due to their frequent bladder emptying, which limits the time needed for nitrate conversion to occur hence lack of urinary nitrite detection in young children with UTI.[10] Among the nitrite-negative samples, lowering the WBC threshold from 100/μL through to 10/μL significantly reduced the rate of missed UTIs from 17.3% to 2.2%, highlighting the potential for adjusting WBC in selected clinical context to increase the sensitivity for UTI detection. It is important to note that the current workflow in this study involves a screening point of care urinalysis (dipstick) which would reflex to a laboratory-based urinalysis if the screen is positive for leukocyte esterase or nitrite. Many clinical settings may not have the capacity or setup to conduct both tests before deciding on empiric coverage.

This study provides valuable clinical evidence that could influence clinical guidelines and practice. As noted in the current publication, various studies performed in different countries have suggested a range of optimal WBC counts for diagnosis of UTI—ranging from ≥25/μL to ≥50/μL. Interestingly, when comparing similar ranges of WBC counts in this study to the aforementioned studies in different countries, the sensitivity remains similar but the specificity is notably lower. The findings of this study also suggest that while a higher threshold (≥100/μL) may reduce the number of unnecessary urine cultures and antibiotic prescriptions, it carries a significant risk of missing UTIs, particularly in nitrite-negative cases.

The balance between sensitivity of testing for empiric UTI treatment and resource utilisation continues to present a significant dilemma in the care of children who present with undifferentiated symptoms. The results from this study provide important data that can aid the clinician in tailoring their diagnostic approach based on a patient's risk factors and clinical presentation. This is especially true among young patients that are likely to present with nitrite-negative UTIs as well as in settings where the risk of missed UTIs may result in severe consequences. The use of a lower WBC threshold may be justified in spite of the anticipated increase in urine cultures and empiric antibiotic treatment.

While further studies may be required to understand various combinations of factors that can affect diagnostic accuracy, this study's findings provide a basis for the development of algorithms that can incorporate various parameters to improve diagnostic accuracy of UTI. The ultimate goal is to facilitate more accurate and timely treatment of UTIs in children, thereby reducing the risk of complications.

### *Declaration*

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

**Keywords:** *emergency medicine, paediatrics, urinary characteristics, urinary tract infection, urinary white blood cells*

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ORIGINAL ARTICLE

# Mental wellness and health-related quality of life of young adult survivors of childhood cancer in Singapore

Francis Jia Yi Fong[1] *MBBS*, Bryan Wei Zhi Wong[1] *MBBS*, Jamie Si Pin Ong[1] *MBBS*, Beron Wei Zhong Tan[2] *BSc (Psych)*, Michaela Su-Fern Seng[3,4] *PhD*, Ah Moy Tan[3,4] *FRCP (Edin)*, Raymond Reinaldo Tanugroho[5] *MMed*

## ABSTRACT

**Introduction:** Childhood cancer survivors (CCS) are at risk of experiencing psychological distress years after completing cancer treatments. We aimed to assess the prevalence and associated risk factors affecting psychological distress and health-related quality of life (HRQOL) among CCS in Singapore, and compare with their siblings without a history of or existing cancer as control.

**Method:** We recruited 143 young adult CCS aged ≥18 years attending survivorship clinics at KK Women's and Children's Hospital in Singapore who were in remission for ≥5 years and treatment-free for ≥2 years, and 57 siblings. CCS and siblings were matched at a 1:1 ratio based on sociodemographic factors yielding 46 pairs for comparison. Among CCS participants, 79 (55.2%) were male, 86 (60.1%) had leukaemia, 29 (20.3%) had solid tumours, 15 (10.5%) had lymphoma and 13 (9.1%) had brain tumours. All participants completed the Brief Symptom Inventory-18 (BSI-18) and Medical Outcomes Short Form-36 (MOS SF-36) questionnaires from August 2021 to July 2022.

**Results:** There were 35 (24.5%) CCS who reported psychological distress in the BSI-18 Global Severity Index. Five (3.5%) and 31 (21.7%) CCS reported low HRQOL in the physical and mental composite scores, respectively. Mean scores between CCS and their siblings were not statistically significant across all domains of the BSI-18 and MOS SF-36. Associated risk factors for psychological distress and low HRQOL among CCS were history of psychiatric illness after cancer diagnosis and mood affected by the COVID-19 pandemic.

**Conclusion:** CCS reported significant psychological distress and low HRQOL although they were not statistically different from their siblings. A holistic and risk factor-centric follow-up programme can aid early detection and mitigation of psychological late effects for CCS and their families.

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**Keywords:** cancer, depression, mental health, oncology, paediatrics, psychiatry, psychology, public health, quality of life

## CLINICAL IMPACT

### What is New

- To our knowledge, this cross-sectional study is the first to investigate the prevalence of psychological distress and health-related quality of life outcomes of childhood cancer survivors (CCS) in Singapore.
- Findings highlight that a significant proportion of CCS experience psychological distress.

### Clinical Implications

- Cultural factors could be a cause for reluctance of CCS in Singapore to voice their stress, thus emphasising the need to use questionnaires as screening tools to monitor CCS' psychological wellness.
- This data can help in resource allocation for planning of survivorship programmes in Singapore.

## INTRODUCTION

Advancements in technology and cancer treatments have improved childhood cancer survival rates, with up to 85% surviving 5 years or more.[1]



[1] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2] Psychology Service, KK Women's and Children's Hospital; Children's Blood and Cancer Centre, KK Women's and Children's Hospital, Singapore
[3] Haematology Oncology Service, Department of Paediatrics, KK Women's and Children's Hospital, Singapore
[4] Duke-NUS Medical School, Singapore
[5] General Paediatrics Service, Department of Paediatrics, KK Women's and Children's Hospital, Singapore
Correspondence: Dr Michaela Su-Fern Seng and Dr Ah Moy Tan, Haematology Oncology Service, Department of Paediatrics, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Emails: michaela.seng@singhealth.com.sg, tan.ah.moy01@singhealth.com.sg
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The Malaysia-Singapore Leukaemia Study Group reported an improvement in overall 5-year survival for the past 20 years in Singapore, from 69% to 91% for acute lymphoblastic leukaemia, which is the most common type of malignancy in childhood.[2]

Despite improvement in survival rate, adult childhood cancer survivors (CCS) often experience increased psychological distress and low health-related quality of life (HRQOL) due to the late effects of the disease and treatments. Significant physical disability and chronic illnesses arising from the complications of cancer, along with intensive treatment regimens like cranial irradiation, high-dose chemotherapy and surgical resection are associated with heightened psychological distress in CCS.[3] These late effects encompass health issues arising at least 5 years post-remission and 2 years post-treatment, ranging from physical to psychological complications. The increased psychological distress, coupled with lower HRQOL, may also contribute to increased unemployment rates among CCS and increased reliance on social security assistance, posing an economic burden.[4] This problem is especially important in Asia with half of the global cancer burden as of 2022.[5]

Early detection of psychological distress is paramount to improving mental wellness and HRQOL in CCS. Existing research on this topic suggests that cultures may influence the degree of psychological distress and HRQOL of CCS. Interestingly, previous studies in Asia do not see any statistical difference in psychological distress and HRQOL between CCS and their siblings as control, contrary to findings in Europe and America.[6,7] We aimed to investigate the prevalence of psychological distress and low HRQOL among CCS in Singapore, as well as compare this with their siblings, given scarcity of such data in Southeast Asia. We also aimed to identify associated risk factors, which will help clinicians identify CCS with higher risk of having psychological distress. Additionally, since the study occurred during the COVID-19 pandemic, we wanted to know if the experience of going through a pandemic contributed to or affected the psychological distress and HRQOL of CCS.

## METHOD

### Study design

A cross-sectional, case-control study of young adult CCS attending survivorship clinics was conducted from August 2021 to July 2022 at KK Women's and Children's Hospital (KKH). KKH is the largest children's hospital in Singapore with more than 350 paediatric beds and manages the majority of childhood cancer patients in Singapore. The study aimed to assess the prevalence of and associated risk factors for psychological distress and low HRQOL among CCS in Singapore, and compare these with their siblings who have no existing or history of cancer as control. The study was approved by the SingHealth Centralised Institutional Review Board (Reference number 2021/2404).

### Study participants

#### *CCS group*

In the CCS group, 156 CCS were initially identified. Six CCS were excluded as they had neurocognitive impairment. Seven CCS did not give their consent. CCS with pre-existing psychiatric conditions before the diagnosis of cancer were excluded. A total of 143 (91.7%) CCS participants aged ≥18 years who have been in remission for at least 5 years and completed treatment for at least 2 years were recruited (Fig. 1).

Among the 143 recruited CCS participants, 86 (60.1%) patients had leukaemia, 29 (20.3%) had solid tumours, 15 (10.5%) had lymphoma and 13 (9.1%) had brain tumours. Seventeen (11.9%) patients had tumour recurrence and 2 (1.4%) patients had secondary neoplasm. There were 141 (98.6%) patients who had chemotherapy, 39 (27.3%) had radiotherapy, 60 (42.0%) had underwent surgery, and 12 (8.4%) had underwent bone marrow transplant. The mean age of diagnosis of the CCS was 7.7 (standard deviation [SD] 4.3) years and they completed treatment at the average age of 9.7 (SD 4.3) years. The average follow-up period of CCS was 16.8 (SD 6.0) years.

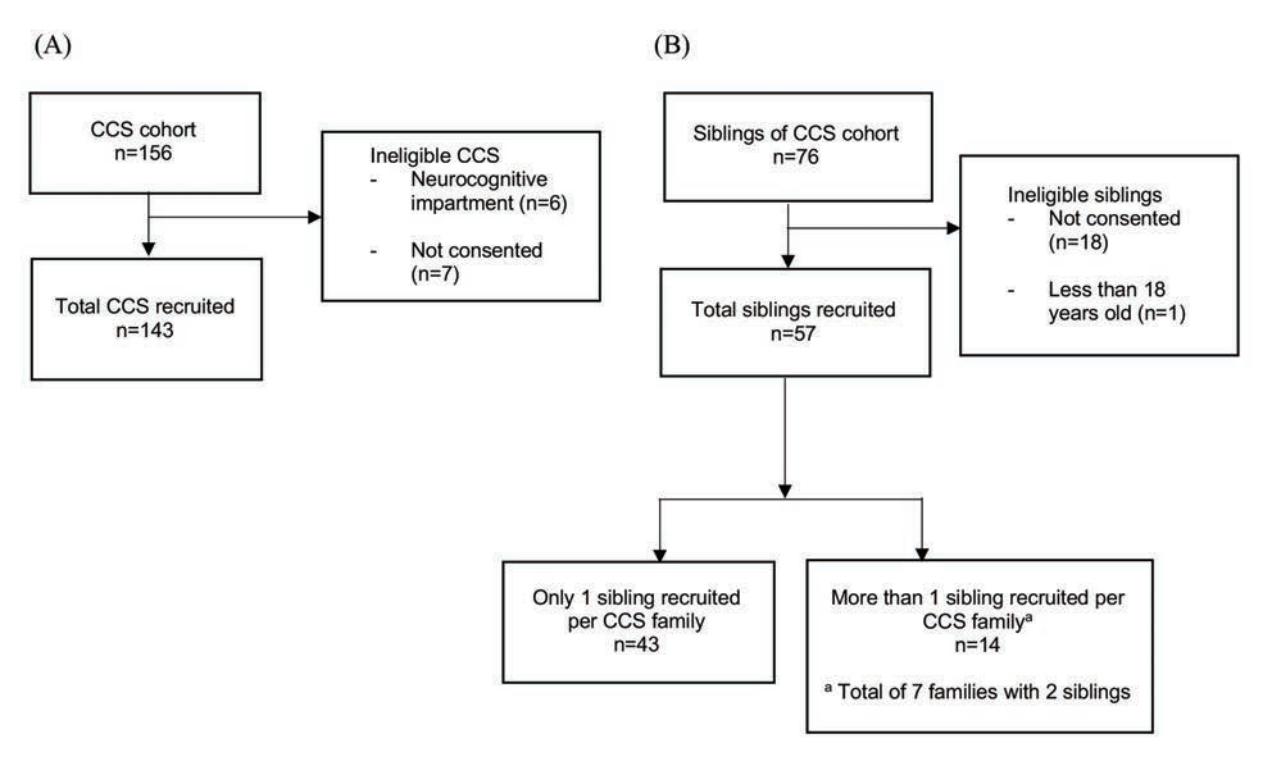
#### *Control/siblings group*

In the control group, 76 siblings of 69 CCS were initially identified and 57 (75.0%) were recruited (Fig. 1). The siblings had no history of childhood or existing cancers. Siblings were selected as the control arm in the study instead of the general population to account for potential confounders, such as different family upbringing and cultural influence.

### Matching sociodemographic variables for comparison between CCS and siblings

Among the 143 CCS and 57 siblings recruited, 46 pairs were matched at a 1:1 ratio based on age, sex, ethnicity, educational level and household income. Compared to their siblings, a significantly higher proportion of CCS were employed/enrolled as students, single and had chronic illnesses. On average, CCS were also significantly younger than their siblings. There were 53 (37.1%) CCS and 25 (43.9%) siblings whose moods were affected by

Fig. 1. Flowchart inclusion of (A) childhood cancer survivors (CCS) and (B) their siblings.






the COVID-19 pandemic. The sociodemographic factors of CCS and their siblings are summarised in Table 1.

Individuals with significant neurological conditions or cognitive impairment rendering them unable to complete the questionnaires independently were also excluded. The participants had to be able to read, comprehend and write their answers on the questionnaires. This assessment was done by medically trained personnel in our research team.

## Questionnaires

### *Psychological distress*

Psychological distress was measured using the Brief Symptom Inventory-18 (BSI-18), an 18-item questionnaire with a main scale (Global Severity Index [GSI]) and 3 subscales (depression, anxiety and somatisation).[8] Participants rated distress levels on a 5-point Likert scale for symptoms experienced in the last 7 days. Cumulative raw scores were converted to T scores (mean 50, SD 10). We used the BSI-18 manual published norms to calculate the T scores based on the US population, with a cut-off T score of ≥63 indicating significant psychological distress.[8] We opted for the BSI-18 due to its reliability and validity in the CCS population.[9]

### *HRQOL*

HRQOL was assessed using the Medical Outcomes Short Form-36 (MOS SF-36), a 36-item questionnaire with 8 domains representing various aspects of well-being. Domains include physical functioning, physical role limitations, bodily pain, general health perception, energy/vitality, social functioning, emotional role limitations and mental health. Each domain is measured by a scale from 0–100, with higher scores representing better HRQOL. We subsequently converted these scores into composite T scores to assess physical and mental dimensions in the form of physical health composite scores (PCS) and mental health composite scores (MCS) using the published norms.[10] Participants with T scores of ≤40 (≤1 SD) in either PCS or MCS were classified as having poor HRQOL.[11] MOS SF-36 was shown to be reliable in screening for HRQOL in CCS populations, with reliability estimates ranging from 0.89–0.94 for PCS and 0.84–0.91 for MCS.[7,10]

## Study procedures

Both BSI-18 and MOS SF-36 forms were completed by CCS who have consented to participate during their visits to the survivorship clinic using paper forms, administered by a trained member of the study group who could also address any questions

Table 1. Sociodemographic factors of childhood cancer survivors (CCS) and their siblings (non-CCS).

| Categories | CCS (n=143) | Non-CCS (n=57) | *P* value |
|---|---|---|---|
| Age, mean (SD), years | 24.46 (5.01) | 26.60 (5.78) | **0.01** |
| Male sex, no. (%) | 79 (55.2) | 24 (42.11) | 0.09 |
| **Body mass index, no. (%)** | | | |
| Underweight (<18.5 kg/m$^2$) | 17 (11.9) | 11 (19.3) | 0.08 |
| Normal (18.5–22.9 kg/m$^2$) | 66 (46.1) | 17 (29.8) | |
| Overweight/obese (≥23 kg/m$^2$) | 60 (42.0) | 29 (50.9) | |
| **Ethnicity, no. (%)** | | | |
| Chinese | 112 (78.3) | 40 (70.18) | 0.07 |
| Malay | 22 (15.4) | 13 (21.70) | |
| Indian | 9 (6.3) | 2 (3.51) | |
| Others | 0 (0) | 2 (3.51) | |
| **Highest education level, no. (%)** | | | |
| Primary/secondary | 14 (9.8) | 5 (8.77) | 0.19 |
| Pre-university/polytechnic/diploma | 72 (50.3) | 25 (43.86) | |
| Undergraduate | 45 (31.5) | 16 (28.07) | |
| Masters/postgraduate | 12 (8.4) | 11 (19.39) | |
| **Employed and/or enrolled as student, no. (%)** | 137 (95.8) | 49 (85.96) | **0.01** |
| **Household income, no. (%)** | | | |
| <SGD 20,000 | 35 (24.5) | 16 (28.07) | 0.37 |
| SGD 20,000–39,000 | 31 (21.7) | 9 (15.79) | |
| SGD 40,000–59,000 | 28 (19.6) | 7 (12.28) | |
| >SGD 60,000 | 49 (34.3) | 25 (43.86) | |
| **Marital status, married, no. (%)** | 14 (9.8) | 13 (22.8) | **0.02** |
| **Presence of chronic illness, no. (%)** | 100 (69.9) | 6 (10.53) | **<0.01** |
| **Types of late effects, no. (%)** | | | |
| Cardiovascular disease | 24 (16.8) | NA | |
| Respiratory disease | 6 (4.2) | NA | |
| Endocrine disease | 64 (44.8) | NA | |
| Neurological disease | 37 (25.9) | NA | |
| Psychiatric disease | 11 (7.7) | NA | |
| Musculoskeletal and/or orthopaedic disease | 13 (9.1) | NA | |
| **Mood adversely affected by COVID-19, no. (%)** | 53 (37.1) | 25 (43.9) | 0.37 |

NA: not available; SD: standard deviation
*P* values in bold are statistically significant.

by the participants. The recruitment of participants was not done by any healthcare professionals who were directly involved in the care of patients to avoid undue influence. Siblings of CCS who met the study criteria were sent an email inviting their participation. The email contained the online version of the same forms with an explanation of the study's purpose and the nature of participation. If there was no reply via email, siblings were contacted via telephone once a week reminding them to respond. Siblings who did not pick up the telephone after 3 attempts or declined to be included in the study were excluded. If a CCS had more than 1 sibling, we invited all their siblings to complete the survey. There was no incentive provided for participating in this study.

### Data collection and analysis

We initially identified potential risk factors affecting HRQOL and physiological distress from existing literature.[3] These factors included demographic information, such as household income, education and employment status. The education and employment status might indirectly reflect the impact of late effects on social functioning of CCS. Additionally, medical details such as chronic illnesses that developed post-cancer diagnosis were extracted from case records using International Classification of Diseases, Ninth Edition codes. Self-reported psychological distress related to the COVID-19 pandemic was also assessed by asking participants an open-ended question.

Data analysis was conducted using IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY, US). Continuous variables were presented as mean (SD), while categorical variables were expressed as proportions. Age and follow-up duration were compared using independent t-tests, while demographic differences were assessed using chi-square tests. A significance level of $P \leq 0.05$ was used. Associated risk factors ($P < 0.25$) in univariate analysis were identified for multivariate analysis via binary logistic regression, using a forward conditional method to evaluate independent contributions.

## RESULTS

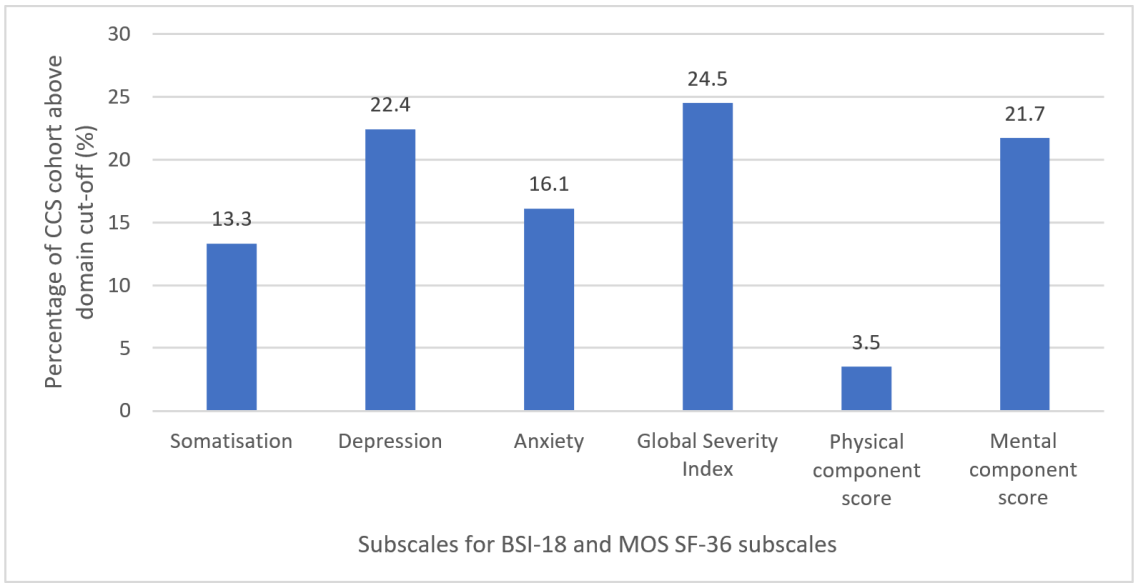
### Prevalence of psychological distress/poor HRQOL in CCS and comparison with siblings

There were 19 (13.3%) CCS who reported significant elevation in BSI-18 somatisation subscale, 32 (22.4%) in the depression subscale, 23 (16.1%) in the anxiety subscale, and 35 (24.5%) in GSI. For HRQOL, 5 (3.5%) and 31 (21.7%) CCS reported poor HRQOL in PCS and MCS, respectively. Their scores are summarised in Fig. 2.

After matching each case-control based on age, sex, ethnicity, educational level and household income to account for possible confounders, there was a final total of 46 pairs (total 92 participants) for comparison between the CCS and control groups. There was no statistical difference in the



Fig. 2. Prevalence of psychological distress and poor health-related quality of life (HRQOL) in childhood cancer survivors (CCS).




BSI-18: Brief Symptom Inventory-18; MOS SF-36: Medical Outcomes Short Form-36

mean scores across all domains of the BSI-18 and MOS SF-36 between matched CCS and control as shown in Table 2. Statistical analysis of the remaining 11 siblings did not reveal any significant difference with the 46 siblings matched to the CCS.

### Associated risk factors for psychological distress and low HRQOL in CCS

Among CCS participants, the associated risk factors for significant psychological distress were history of psychiatric illness (odds ratio [OR] 23.12, 95% confidence interval [CI] 4.38–121.98; $P<0.01$) and mood being affected by the COVID-19 pandemic (OR 3.06, 95% CI 1.29–7.30; $P=0.01$).

The associated risk factors for low HRQOL as quantified via MCS and PCS among CCS participants were a history of psychiatric illness (OR 33.07, 95% CI 5.62–194.52; $P<0.01$) and mood being affected by the COVID-19 pandemic (OR 33.07, 95% CI 5.62–194.52; $P<0.01$). The associated risk factors for significant psychological distress and low HRQOL are shown in Table 3.

## DISCUSSION

This paper examined the psychological distress and HRQOL of CCS in Singapore over a follow-up period of almost 17 years, filling the gap in the literature of psychological late effects of CCS in Southeast Asia. We showed that the number of CCS with psychological distress and low HRQOL was significant, shown in 24.5% of CCS with high GSI in BSI-18 and 21.7% of CCS with low MCS in MOS SF-36. These results were comparable with previous American, European[12-15] and Asian cohorts.[6,16] Risk factors associated with poorer BSI-18, PCS and MCS included a diagnosis of psychiatric illness and mood affected by the COVID-19 pandemic. CCS with significant psychological distress were shown to score lower in HRQOL and had a higher likelihood of developing depression, anxiety and psychotic disorders.[17] We advocate close monitoring and early referral to psychosocial services for CCS with psychiatric illness. Additionally, individuals whose moods were affected by the COVID-19 pandemic had lower scores on GSI, PCS and MCS, consistent with findings in a South African cohort.[18] Strict lockdown measures in Singapore during specific periods were associated with increased rates of clinical depression, anxiety and stress disorders.[19] A post-pandemic study is recommended to assess any changes in prevalence of psychological distress, low HRQOL and scores. Given the increasing evidence of COVID-19's long-term impact on mental health,[20] future studies should investigate its effects on the mental health of CCS, particularly considering the impact of social distancing and isolation resulting from the pandemic.

We did not find any significant differences in the degree of psychological distress and HRQOL between CCS and their siblings across all domains of the BSI-18 and MOS SF-36. Existing literature presented varied results based on geographic regions regarding psychological distress assessed by BSI-18. An American cohort exhibited an increased risk of greater psychological distress across most BSI-18 domains among CSS compared to siblings,[12] whereas a Hong Kong cohort showed no significant differences.[6] Similar contrasts in CCS and their siblings among Western and Asian cohorts were also reflected in HRQOL assessed using MOS SF-36.[6,14,16] We hypothesise that cultural differences may contribute to these disparities. For instance, Chinese cultural norms emphasise virtues of self-control and perseverance, which may lead to diminished expressions of negative emotions explicitly.[21] This cultural difference was illustrated in the US, where they found that Asian CCS were prone to suppress distressing emotions and pain related to cancer compared to non-Hispanic White CCS.[22-24] This cultural context, coupled with recent findings suggesting variations in HRQOL across nationalities and culture, underscores the importance of local studies.[25]

Another postulation that may explain differences in the extent of psychological distress among CCS cohorts is the type of coping mechanisms that CCS develop. Previous studies suggested that some CCS faced life's challenges with resilience and had a greater enthusiasm for life compared to the general population.[26] This possibly stemmed from the psychological resilience CCS cultivated while coping with the adversities during their childhood cancer treatment.[27] However, some subgroups of CCS developed maladaptive coping mechanisms, as seen in studies linking distress to negative thought suppression and low levels of optimism.[28,29] In addition, Campbell et al. found that after the end of treatment, CCS who adopted a disengagement coping mechanism were found to be positively associated with subsequent behavioural problems.[30] Thus, additional studies examining both the qualitative and quantitative aspects between the types of coping mechanisms and severity of psychological distress are required to improve our understanding on the pathogenesis of psychological distress in CCS.

Specific to our cohort, the lower representation of CCS with brain and solid tumours (9.1% and 20.3%, respectively) compared to the national

Table 2. Comparison of the mean in the Brief Symptom Inventory-18 (BSI-18) T scores and Medical Outcomes Short Form-36 (MOS SF-36) scores between matched childhood cancer survivors (CCS) and siblings.

| Subscales | CCS (SD) n=46 | Siblings (SD) n=46 | *P* value |
|---|---|---|---|
| **BSI-18 T scores** | | | |
| Somatisation | 51.72 (8.86) | 50.48 (10.12) | 0.53 |
| Depression | 55.07 (10.52) | 54.39 (9.69) | 0.75 |
| Anxiety | 51.78 (10.30) | 53.30 (9.77) | 0.47 |
| Global Severity Index | 53.83 (10.60) | 52.87 (10.93) | 0.67 |
| **MOS SF-36 scores** | | | |
| Physical functioning subscale score | 92.39 (12.46) | 85.87 (23.13) | 0.10 |
| Role physical subscale score | 91.30 (24.28) | 88.59 (23.40) | 0.59 |
| Bodily pain subscale score | 86.36 (16.56) | 81.69 (19.94) | 0.23 |
| General health subscale score | 65.76 (16.90) | 63.37 (13.95) | 0.46 |
| Vitality subscale score | 56.63 (16.40) | 51.41 (15.41) | 0.12 |
| Social functioning subscale score | 81.79 (22.00) | 79.89 (17.97) | 0.65 |
| Role emotional subscale score | 86.23 (31.09) | 74.64 (35.96) | 0.10 |
| Mental health | 67.30 (15.44) | 61.13 (17.30) | 0.07 |
| **MOS SF-36 composite T scores** | | | |
| Physical health summary component T score | 53.76 (6.62) | 52.70 (6.83) | 0.46 |
| Mental health summary component T score | 46.34 (10.34) | 43.30 (10.33) | 0.16 |

SD: standard deviation

Table 3. Multivariate analysis of associated risk factors for mental distress and low health-related quality of life (HRQOL) in childhood cancer survivors.

| Associated risk factors | Univariate odds ratio (95% CI); *P* value | Multivariate odds ratio (95% CI); *P* value |
|---|---|---|
| **Global Severity Index ≥63** | | |
| Presence of chronic illness | 2.00 (0.80–5.02); *P*=0.14 | NA |
| History of psychiatric illness | 18.25 (3.74–90.06); ***P*<0.01** | 23.12 (4.38–121.98); ***P*<0.01** |
| History of endocrine illness | 1.66 (0.77–3.58); *P*=0.19 | NA |
| Family with cancer | 2.00 (0.72–5.56); *P*=0.18 | NA |
| Mood affected by COVID-19 | 3.03 (1.38–6.64); ***P*<0.01** | 3.06 (1.29–7.30); ***P*=0.01** |
| **Medical Outcomes Short Form-36 (physical and mental composite scores) ≤40** | | |
| Highest education | 1.42 (0.83–2.42); *P*=0.20 | NA |
| History of psychiatric illness | 22.50 (4.55–111.34); ***P*<0.01** | 33.07 (5.62–194.52); ***P*<0.01** |
| Mood affected by COVID-19 | 2.40 (1.11–5.19); ***P*=0.03** | 3.18 (1.26–8.01); ***P*=0.01** |

CI: confidence interval; NA: not available

*P* values in bold are statistically significant.

registry (14.1% and 42.5%, respectively) might have influenced reported outcomes.[31] Brain and solid tumour survivors have generally exhibited poorer quality of life scores, increased psychological distress and reduced social functioning compared to leukaemia survivors.[14,32] This trend might have contributed towards the better-than-expected outcome scores of our CCS cohort.

Finally, we propose that another reason for the lack of statistical difference between the non-CCS and CCS groups could be due to the non-CCS group being equally affected by their sibling's childhood cancer diagnosis. In a large sample study by van Warmerdam et al.[33] the heightened risk of adverse mental health conditions among siblings of CCS only became evident around 15 years after diagnosis of childhood cancer. Notably, our cohort consisted of CCS and non-CCS with nearly 17 years of follow-up post-diagnosis. We too observed that a proportion of non-CCS in our cohort experienced psychological distress and lower HRQOL compared to their siblings. Therefore, future studies could explore the long-term impact of childhood cancer diagnosis of childhood cancer on both CCS and their siblings.

### Opportunity for intervention

While no statistical difference was observed between CCS and their siblings in psychological distress and HRQOL, a notable proportion of CCS still experienced psychological distress and low HRQOL, which were only detected through the questionnaires. The routine use of formal screening tools should be considered to identify at-risk individuals, with proactive psychological interventions proving effective.[34] We support the latest clinical practice guidelines from the International Late Effects of Childhood Cancer Guidelines Harmonization Group, which advocate the routine surveillance of mood disorders symptoms such as depression, anxiety and psychological distress, starting from the first follow-up visit and continuing throughout the lifespan of CCS.[35] Further evaluation by mental health professionals is advised for CCS showing indications of mental health problems, with prompt referral for diagnosis and risk assessment.

### Limitations

We acknowledge several limitations of this study. First, participants who were unable to independently fill the questionnaires due to neurocognitive impairments were excluded. While the number of participants excluded was low (n=6), there was a possibility that these participants had greater severities of late effects resulting in lower HRQOL. Future studies could include this population using caregiver-reported questionnaires for a more comprehensive representation. Second, self-reported questionnaires such as BSI-18 and MOS SF-36 may be influenced by self-report and social desirability bias, resulting in potential underestimation of distress.[30,31] Longitudinal studies with mean scores across multiple time points could improve the accuracy of such results. Third, although BSI-18 and MOS SF-36 are validated tools that are commonly used, they are generic in nature and used for screening. Future studies correlating the degree of psychological distress and HRQOL to an eventual diagnosis of psychiatric illnesses would be valuable. Finally, the limited sample size (especially in the siblings' group) stemmed from participant recruitment being confined to a single institution. Future studies can consider collaborating with a consortium of other institutions to increase the cohort size. This collaborative approach would enhance the cohort size, facilitating more robust and statistically rigorous results.

## CONCLUSION

This study explored the long-term impact of childhood cancer on psychological distress and HRQOL of CCS in Singapore. Approximately a quarter of CCS reported psychological distress and 21.7% exhibited low mental health scores in HRQOL. There were no significant differences in psychological distress and HRQOL between CCS and their siblings when demographic factors were matched. Notably, a history of psychiatric illness and mood disturbances linked to the COVID-19 pandemic was associated with poorer scores in psychological distress and HRQOL. Therefore, in light of these findings, we strongly advocate regular surveillance of psychological distress and HRQOL among CCS in order to implement timely and appropriate interventions.



### *Declaration*

*This research received funding from the National University of Singapore. 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.*

### *Ethics statement*

*The study was approved by the SingHealth Centralised Institutional Review Board (Reference number 2021/2404).*

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ORIGINAL ARTICLE

# Investigating urinary characteristics and optimal urine white blood cell threshold in paediatric urinary tract infection: A prospective observational study

Jean Nee Teo[1,2] *MRCPCH*, Yong Teck Teo[3] *MBBS*, Sashikumar Ganapathy,[1,2] Matthias Maiwald[4,5,6] *MD*, Yong Hong Ng[7] *FRCPCH*, Shu-Ling Chong[1,2] *MPH*

## ABSTRACT

**Introduction:** While the definitive diagnosis of urinary tract infection (UTI) requires a positive urine culture, the likelihood of UTI can be determined by urinalysis that includes white blood cell (WBC) count. We aimed to determine the optimal urine WBC threshold in urinalysis to predict UTIs in children presenting at the emergency department (ED).

**Method:** We performed a prospective observational study in the ED at KK Women's and Children's Hospital for children below 18 years old who underwent both urine microscopy and urine cultures, between 10 January and 7 November 2022. We assessed the various urine WBC thresholds associated with culture-proven UTIs using sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and area under receiver operating characteristic curve.

**Results:** We found a culture-proven UTI rate of 460/1188 (38.7%) among all patients analysed, and 278/998 (27.9%) among those with nitrite-negative urine samples. Among all patients, a urinalysis WBC threshold of 100/μL had a sensitivity of 82.2% (95% confidence interval [CI] 78.4–85.5) and negative predictive value of 86.2% (95% CI 83.6–88.4). Among those who were nitrite-negative, a WBC threshold of ≥100/μL resulted in a potential missed rate of 48/278 (17.3%). By lowering the WBC threshold to ≥10/μL, the potential missed cases reduced to 6/278 (2.2%), with an estimated increase in 419 urine cultures annually.

**Conclusion:** A urine microscopy WBC threshold of ≥100/μL results in a clinically significant number of missed UTIs. Implementation of various thresholds should consider both the potential missed UTI rate and the required resource utilisation.

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**Keywords:** emergency medicine, paediatrics, urinary characteristics, urinary tract infection, urinary white blood cells

## CLINICAL IMPACT

### What is New

- This study aims to determine the optimal urinalysis white blood cell (WBC) threshold associated with urinary tract infection (UTI) in the paediatric population.

### Clinical Implications

- The previous urinalysis WBC threshold of ≥100/μL may potentially miss about 17% of paediatric UTI.
- This study provides data on missed UTI rates and the corresponding increase in investigations at each urinalysis WBC threshold, to help clinicians determine the optimal threshold in their practice.

## INTRODUCTION

Urinary tract infection (UTI) is a common diagnosis in the paediatric emergency department (ED). It accounts for an estimated 5–14% of paediatric ED visits yearly in the US.[1-3] It is a common cause of serious bacterial infections in children, and the most common microorganism is *Escherichia coli* (65–75%), followed by *Klebsiella pneumoniae* (23%) and *Proteus mirabilis* (7%).[4-7] Although older children may present with specific urinary symptoms, young children may present with non-specific complaints, including fever without localising symptoms, poor feeding, vomiting or irritability, which make prompt diagnosis of UTI challenging.[1,8]



[1] Department of Emergency Medicine, KK Women's and Children's Hospital, Singapore
[2] Paediatric Academic Clinical Programme, Emergency Medicine Academic Clinical Programme, Duke-NUS Medical School, Singapore
[3] Department of Paediatrics, KK Women's and Children's Hospital, Singapore
[4] Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore
[5] Department of Microbiology and Immunology, National University of Singapore, Singapore
[6] Graduate Medical Programme, Duke-NUS Medical School, Singapore
[7] Department of Paediatrics, Nephrology Service, KK Women's and Children's Hospital, Singapore
Correspondence: Dr Jean Nee Teo, Department of Emergency Medicine, KK Women's and Children's Hospital, Singapore
Email: teo.jean.nee@singhealth.com.sg
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The gold standard for UTI diagnosis is a positive urine culture from a clean catch midstream or an in-out catheterisation urine sample, which requires 24 to 48 hours turnaround time in most places.[7,9] Therefore, physicians are required to make an informed decision on empirical treatment for UTI based first on clinical assessment and results from urinalysis, while awaiting urine culture results. While there is a clear need to avoid missing UTIs, which place patients at risk of urosepsis and long-term kidney impairment and scarring, overtreatment can result in antimicrobial resistance in the long term.[10] Moreover, prompt initiation of UTI treatment is vital because the odds of kidney scarring are 74% lower in children who receive treatment within 24 hours from the onset of fever, compared to those who receive treatment after 72 hours of fever.[5,6]

To predict UTI, physicians consider urinary white blood cell (WBC) count, urine nitrite positivity and other urinary characteristics from the urinalysis. Unfortunately, there is no international consensus on the best WBC cut-off value in urinalysis to diagnose a likely UTI for which clinicians should prescribe empirical antibiotics.

Therefore, we aimed to investigate urinary characteristics, and to determine the optimal thresholds of urine WBC and other urinalysis parameters to predict the diagnosis of UTI.



## METHOD

### *Study setting and design*

We performed a prospective observational study in the children's ED at KK Women's and Children's Hospital in Singapore over 10 months, from January 2022 to November 2022. Our centre is 1 of 2 tertiary paediatric hospitals in the country, with an annual ED attendance of about 150,000 children. This study was approved by the Centralised Institutional Review Board with waiver of informed consent (CIRB 2023/2124).

### Inclusion and exclusion criteria

We included children <18 years old, who were screened for suspected UTI. We followed existing guidelines for UTI screening, which includes patients with:

- Urinary symptoms (dysuria, haematuria, increase urinary urgency/frequency, dribbling, oliguria/anuria)
- Febrile illness with vomiting
- Febrile illness without any localising symptoms
- Increased irritability in non-verbal children
- Non-febrile infants <3 months old with non-specific or urinary symptoms including irritability, foul-smelling urine, or haematuria
- High risk of UTI (recurrent UTIs, kidney, spinal or genitourinary structural abnormalities) and symptomatic

We excluded following groups of patients:

- Children who had antibiotic pretreatment within 2 weeks of urine collection, and children who were on uroprophylaxis; in both these scenarios, the microscopy would not be accurate for interpretation and the urine culture may be falsely negative
- Cases where the urine samples were insufficient to send for both urine culture and urine microscopy
- Febrile infants <3 months old, because this is a high-risk group that would be hospitalised and subsequently receive extensive investigations
- High risk of UTI but asymptomatic (likely asymptomatic bacteriuria)

### Testing procedures

At the children's ED, the first-line screening test is the urine dipstick (Combur 10 Test Strips, Roche Diagnostics, Rotkreuz, Switzerland). If the initial urine dipstick was ≥2+ positive for leukocyte esterase and/or positive for nitrite, a midstream or in-out catheterisation urine sample was collected and sent to the hospital's laboratory for urinalysis, including urine microscopy. As part of this study, we required that urine samples be concurrently sent for urine culture. Midstream urine samples were collected by the respective caregivers after being taught the proper method of collection by the attending physicians and/or nurses, while in-out catheterisation urine samples were performed by physicians.

Urinalysis was performed on uncentrifuged urine samples at the hospital's Clinical Chemistry Laboratory. Urine was first tested using Combur 10 Test Strips (Roche Diagnostics) that were read on a Cobas u 411 urine analyser (Roche Diagnostics). When the test strip results for either red blood cells (RBCs), WBCs, nitrite or protein were positive, urine microscopy was performed on Kova Glasstic slides (Kova International, CA, US), and cells were manually counted by the lab personnel. Urine cultures were performed at the hospital's microbiology laboratory. During office hours, fresh urine was plated onto blood and MacConkey agar using calibrated 1 µL plastic loops; agar plates were incubated at 35°C overnight. After office hours, urine was inoculated at the ED onto Uricult Trio dipslides (Orion Diagnostica, Espoo, Finland), which consist of cystine-lactose-electrolyte-deficient (CLED), MacConkey and *Escherichia coli* media, before it was sent to the laboratory to be incubated at 35°C overnight.

In our institution, at the time of study, we were using a WBC threshold of ≥100/μL in a mid-stream or in-out catheterisation urine microscopy sample to initiate treatment for UTI, empirically with a course of cephalexin, while awaiting the urine culture result.[11]

### Data variables and definitions

We collected information on patient demographics, presenting symptoms including urinary symptoms or symptoms commonly associated with UTI, and significant past medical history including previous UTI, and kidney, spinal or genitourinary structural abnormalities.

We obtained the following information from ED urine dipstick screening: leukocyte, erythrocyte and protein semiquantitative counts. Laboratory urine microscopy and urinalysis results were documented for RBCs and WBCs as cells per microliter, as well as the presence (or absence) of microorganisms and nitrite positivity.

In our study, we defined UTI as the presence of a uropathogen in urine by culture, with at least 50,000 colony-forming units (CFUs)/mL in catheterised urine samples as per the revised 2011 American Academy of Paediatrics guideline; or >105 CFU/mL in clean-catch midstream urine samples as per the 2012 Italian Society of Paediatric Society, the 2015 European Association of Urology and European Society for Paediatric Urology guidelines, and the 2016 Urological Association of Asia and Asian Association of Urinary Tract Infection and Sexually Transmitted Infection guidelines.[10,12,13] In the case of growth of dual uropathogens, we considered a diagnosis of UTI when both the uropathogens had significant growth as defined above.

Nitrite-positivity, irrespective of the urine WBC counts, is specific for UTI.[12] Therefore, we performed a sensitivity analysis among those with nitrite-negative UTIs.

### Statistical analysis

We described continuous variables using mean with standard deviation (SD) or median with interquartile range (IQR), depending on normality. Categorical variables were described using frequencies and percentages. We compared children with a diagnosis of UTI to those without a diagnosis of UTI. We used either t-test or Wilcoxon rank sum test for continuous data depending on normality, and chi-square test for categorical data. We took statistical significance at $P<0.05$. All $P$ values were based on 2-tailed tests. We reported the area under receiver operating characteristics (AUC) curves using point estimates with 95% confidence intervals (CIs). The optimal WBC threshold corresponded with the point nearest to the upper left corner of the AUC box, therefore providing the values of highest sensitivity and specificity. At each threshold, we evaluated performance using sensitivity, specificity, negative and positive predictive values, and positive and negative likelihood ratios. Among those with nitrite-negative urine, we performed a subanalysis on infants, defined as <1 year old because this group tends to present with non-specific symptoms. Statistical analysis was performed using SPSS version 26 (IBM Corp, Armok, NY, US).

## RESULTS

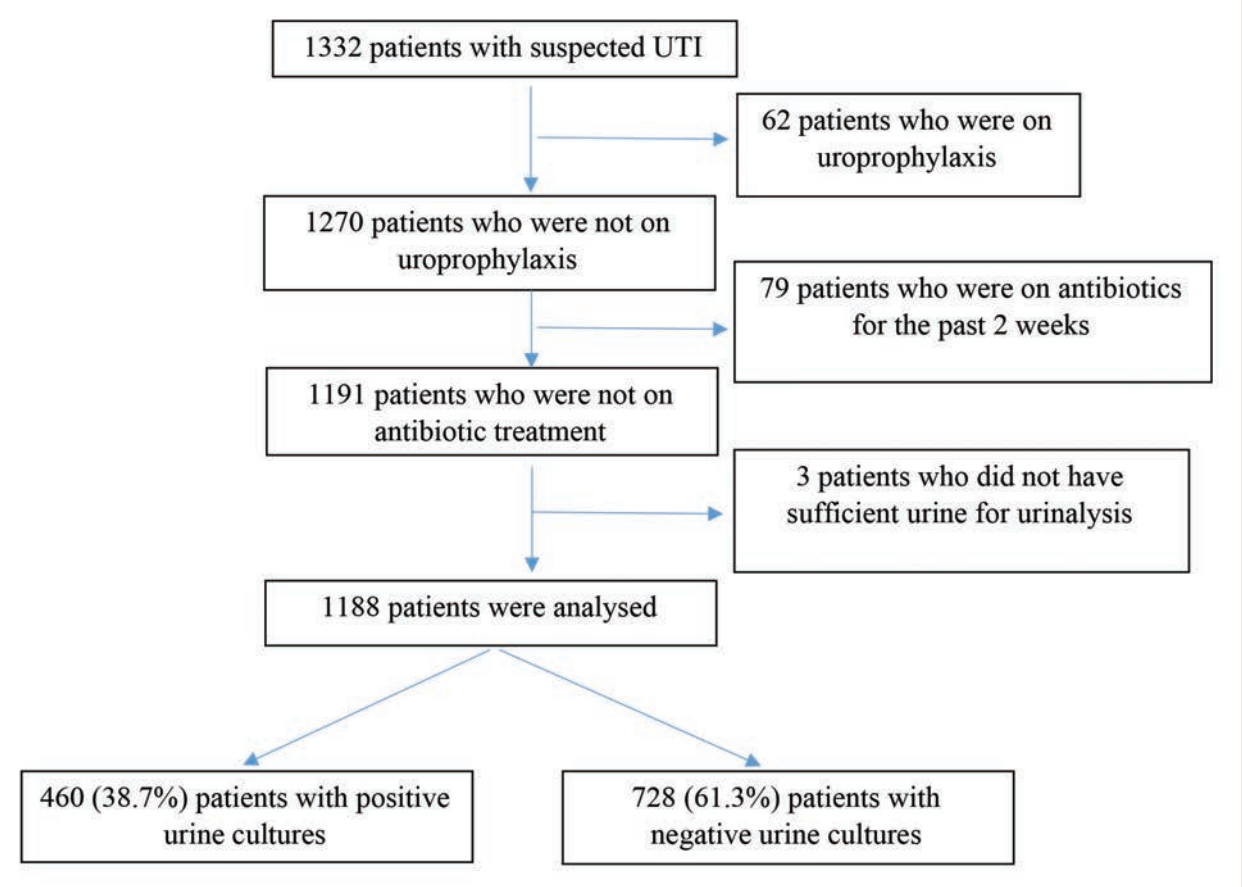
A total of 1188 urine samples from 1188 patients were analysed. Among them, 460 (38.7%) were diagnosed with UTI (Fig. 1). Our patients had a median age of 3 years (IQR 1.0–6.0) and a median weight of 14.3 kg (IQR 9.8–22.6). There was a greater number of males in the group with UTI compared to the group without (164/460, 35.7% versus [vs] 162/728, 22.3%, $P<0.001$) (Table 1). Among infants ≤3 months old, this male predominance was more marked (29/38, 76.3% vs 9/38, 23.7%). Those with a significant past medical history such as previous UTI and structural abnormalities were at higher risk of getting a UTI.

Children with UTIs had significantly higher WBC and RBC on urine microscopy compared to those without (median WBC were 604 WBC/μL [IQR 170–2000] vs 27 WBC/μL [IQR 4–129], $P<0.00$; and median RBC were 27 RBC/μL [IQR 10–70] vs 7 RBC/μL [IQR 0–28], $P<0.001$) (Table 2). There was a significantly higher proportion of those with raised urine protein, as well as presence of urine nitrite and microscopically visible microorganisms among children with UTIs compared to those without UTIs (Table 2). The urine WBC had an AUC of 0.83 (95% CI 0.81–0.86) in the prediction of UTI, while urine RBC had an AUC of 0.69 (95% CI 0.66–0.72).

Among the 460 patients with positive urine culture results, 446 (97%) had a single uropathogen, and 14 (3%) had 2 uropathogens, with significant growth that fulfilled the diagnosis of UTI as defined above (Table 3). The top 3 most common microorganisms found were *Escherichia coli* (80%), *Proteus mirabilis* (10%) and *Klebsiella pneumoniae* (5.2%). Thirty-one (7%) of the microorganisms were positive for extended-spectrum beta-lactamases (ESBLs).

Among the 460 culture-proven UTIs, 278 urine specimens were nitrite negative, among which 113/278 (40.6%) were <1 year old. The AUCs of various WBC thresholds in all patients with UTI, and in patients with nitrite-negative UTI are

Fig. 1. Flow chart for study population.






shown in Fig. 2(A) and Fig. 2(B). A urinalysis WBC threshold of 100/μL had an ROC of 0.76 (95% CI 0.73–0.79) and 0.77 (95% CI 0.74–0.80) for all patients and nitrite-negative patients, respectively. Among all patients, a urinalysis WBC threshold of 100/μL had a sensitivity of 82.2% (95% CI 78.4–85.5) and negative predictive value (NPV) of 86.2% (95% CI 83.6–88.4) (Table 4). By lowering the threshold to 10/μL, we could achieve a sensitivity of 96.5% (95% CI 94.4–98.0) and a NPV of 94.1% (95% CI 90.6–96.3). Among nitritenegative urine samples, thresholds of 100/μL, 50/μL and 10/μL would have missed 48/278 (17.3%), 35/278 (12.6%), and 6/278 (2.2%) UTIs, respectively (Table 5[A]). At the same time, lowering the threshold from 100/μL would result in an estimated annual increase in 130 (for a threshold of 50/μL) and 419 (for a threshold of 10/μL) urine cultures, respectively, with the same number of children being started on empirical antibiotics (Table 4). Among infants with nitrite-negative UTI, a urinalysis WBC threshold of 100/μL had a sensitivity of 78.8% (95% CI 70.1–85.9) and NPV of 77.1% (95% CI 69.8–83.1). By lowering the threshold to 10/μL, we could achieve a sensitivity of 96.5% (95% CI 91.2–99.0) and a NPV of 92.7% (95% CI 82.6–97.2) (Table 5[B]). Among these samples, thresholds of 100/μL, 50/μL and 10/μL would have missed 24/113 (21.2%), 17/113 (15.0%), and 4/113 (3.5%) UTIs, respectively.

In our study, 247 out of 460 patients (53.7%) with UTI had kidney imaging on follow-up, while 213 of them (46.3%) either declined kidney imaging or were lost to follow-up. Among those who had kidney imaging, 26/247 (10.5%) had abnormal structures, including solitary or duplex kidneys, pelvicalyceal dilatation, dilated ureters, or small kidneys. Among children with recurrent UTIs for whom micturating cystourethrogram (MCUG) had been performed, 10/12 (83.3%) had vesicoureteral reflux.

## DISCUSSION

We performed a prospective observational study to examine urinary characteristics and to evaluate the optimal WBC threshold in predicting UTI. The UTI prevalence was 38.7% in this study population, and the most common organisms were *Escherichia*

Table 1. Baseline characteristics of study population.

| Variable | No UTI n=728 | UTI n=460 | *P* value |
|---|---|---|---|
| Age in years, median (IQR) | 3.0 (1.0–7.0) | 1.0 (0.7–5.0) | <0.001 |
| Age ≤3 months, no. (%)[a] | 38 (5.2) | 38 (8.3) | - |
| Age >3 months to 2 years, no. (%) | 258 (35.4) | 241 (52.4) | - |
| Age >2 years to 8 years, no. (%) | 315 (43.3) | 136 (29.6) | - |
| Age >8 years to 18 years, no. (%) | 117 (16.1) | 45 (9.8) | - |
| Male sex, no. (%) | 162 (22.3) | 164 (35.7) | <0.001 |
| Presence of past medical history, no. (%) | | | <0.001 |
| Kidney/spinal/genitourinary structural abnormality | 30 (4.1) | 9 (2.0) | - |
| Previous UTI + structural abnormality | 11 (1.5) | 20 (4.4) | - |
| Fever >37.5°C vs afebrile, no. (%) | | | <0.001 |
| Febrile | 449 (61.7) | 366 (79.6) | - |
| Afebrile | 279 (38.3) | 94 (20.4) | - |
| Urinary symptoms, no. (%) | 275 (37.8) | 207 (45.0) | 0.044 |
| Dysuria | 180 (65.5) | 132 (63.8) | - |
| Haematuria | 39 (14.2) | 18(8.7) | - |
| Increased urinary frequency | 27 (9.8) | 10 (4.8) | - |
| Smelly urine | 15 (5.5) | 46 (22.2) | - |
| Urinary urgency | 14 (5.1) | 1 (0.5) | - |
| Vomiting (%) | 31 (4.3) | 103 (22.4) | <0.001 |
| Loose stools, no. (%) | 5 (0.7) | 29 (6.3) | <0.001 |
| Abdominal pain or tenderness, no. (%) | 113 (15.5) | 62 (13.5) | 0.333 |
| Presence of penile or per vagina complaints, no. (%) | 23 (3.2) | 13 (2.8) | 0.744 |

IQR: interquartile range; UTI: urinary tract infection
[a] Infants ≤3 months old with febrile illness were excluded in the study.

*coli*, *Proteus mirabilis* and *Klebsiella pneumoniae*. We reported the performance of various urinary WBC thresholds ranging 10–100/μL, the number of missed UTIs at each threshold, as well as the corresponding number of urine cultures that would be required.

The diagnosis of UTI requires a confirmatory urine culture, which is available only after 24–48 hours in most settings. A point-of-care urine dipstick is usually first performed, with a sensitivity of between 83–93%.[1,6,10,14] If the urine dipstick fulfils the criteria for a possible UTI, the urine sample will then be sent to the laboratory for analysis. Therefore, urinalysis is key for early decision-making. Urinalysis has a reported sensitivity of predicting a likely UTI between 75–85%.[15] The optimal WBC threshold in predicting likely UTI is a topic of debate in the literature. Adult UTI studies in the Netherlands and Belgium reported the optimal cut-off to be in the range of 20–74 WBC/μL.[16,17] In the paediatric population, studies in different countries have reported a range of WBC diagnostic thresholds: ≥25/μL in Taiwan (sensitivity 79%, specificity 87%); ≥35/μL in Belgium (sensitivity 99.5%, specificity 80.6%); and ≥50/μL in girls of all ages and boys under 3 years old, and ≥10/μL in boys above 3 years old in Germany.[12,14,18] In our study, we found that our institution's existing threshold of urinary WBC ≥100/μL had the highest AUC (0.761, 95% CI 0.733–0.789), but sensitivity and negative predictive value were only moderate (83.4% and 91.7%, respectively).

Table 2. Laboratory-tested urine microscopy and urinalysis findings.

| Variable | No UTI n=728 | UTI n=460 | *P* value |
|---|---|---|---|
| Urine microscopy red blood cells (per μL), median (IQR) | 7 (0–28) | 27 (10–70) | <0.001 |
| Urine microscopy white blood cells (per μL), median (IQR) | 27 (4–129) | 604 (170–2000) | <0.001 |
| Urine protein, no. (%) | | | <0.001 |
| Negative | 95 (13.0) | 9 (2.0) | - |
| 1+ | 583 (80.1) | 323 (70.5) | - |
| 2+ | 30 (4.1) | 87 (19.0) | - |
| 3+ | 12 (1.6) | 33 (7.2) | - |
| 4+ | 8 (1.1) | 6 (1.3) | - |
| Urine nitrite positive, no. (%) | 8 (1.1) | 180 (39.3) | <0.001 |
| Presence of microorganisms in urine microscopy, no. (%) | | | <0.001 |
| Negative | 373 (51.2) | 31 (6.7) | - |
| Occasional or few | 318 (43.7) | 189 (41.1) | - |
| 1+ | 26 (3.6) | 104 (22.6) | - |
| 2+ | 11 (1.5) | 84 (18.2) | - |
| 3+ | 0 (0) | 52 (11.3) | - |



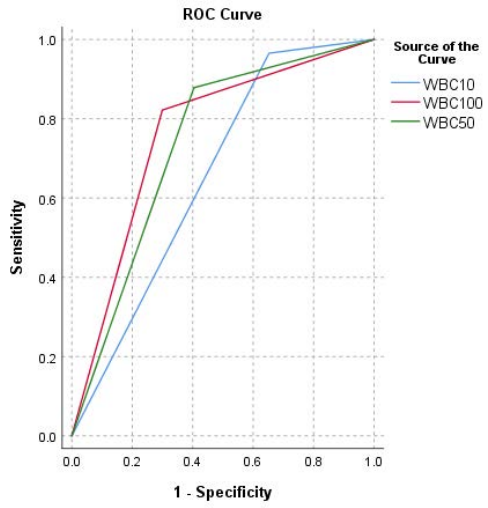
Table 3. Positive urine culture findings.

| Variable | UTI n=460 |
|---|---|
| Number of uropathogens | |
| Single uropathogen, no. (%) | 446 (97) |
| 2 uropathogens, no. (%) | 14 (3) |
| Species of microorganisms, no. (%) | |
| Escherichia coli | 371 (80) |
| Enterococcus faecalis | 4 (0.08) |
| Enterobacter cloacae | 1 (0.02) |
| Klebsiella pneumoniae | 24 (5.2) |
| Proteus mirabilis | 48 (10) |
| Others | 27 (5.8) |
| Extended-Spectrum Beta-Lactamase positive microorganisms, no. (%)[a] | |
| Yes | 31 (7) |
| No | 429 (93) |

[a] ESBL microorganisms reported as per Calibrated Dichotomous Susceptibility guidelines, which are resistant to ampicillin, ceftazidime, ceftriaxone, cefotaxime and cefepime.

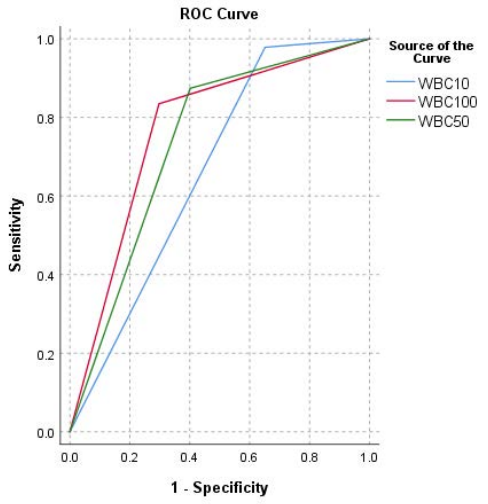
Fig. 2. Area under receiver operative characteristic curve (AUC) comparing different white blood cell thresholds in culture-proven urinary tract infection.

(A) AUC for all 1188 patients.




| UFEME WBC thresholds | AUC (95% confidence interval) |
|---|---|
| **WBC ≥ 100 (μL)** | **0.76 (0.73–0.79)** |
| WBC ≥ 90 (μL) | 0.76 (0.73–0.79) |
| WBC ≥ 80 (μL) | 0.75 (0.73–0.78) |
| WBC ≥ 70 (μL) | 0.75 (0.72–0.78) |
| WBC ≥ 60 (μL) | 0.74 (0.72–0.77) |
| **WBC ≥ 50 (μL)** | **0.74 (0.71–0.77)** |
| WBC ≥ 40 (μL) | 0.73 (0.70–0.76) |
| WBC ≥ 30 (μL) | 0.72 (0.69–0.74) |
| WBC ≥ 20 (μL) | 0.69 (0.66–0.72) |
| **WBC ≥ 10 (μL)** | **0.66 (0.63–0.69)** |

(B) AUC for all 988 patients with nitrite negative urine samples.




| UFEME WBC thresholds | AUC (95% confidence interval) |
|---|---|
| **WBC ≥100 (μL)** | **0.77 (0.74–0.80)** |
| WBC ≥ 90 (μL) | 0.77 (0.74–0.80) |
| WBC ≥ 80 (μL) | 0.76 (0.73–0.79) |
| WBC ≥ 70 (μL) | 0.75 (0.72–0.79) |
| WBC ≥ 60 (μL) | 0.75 (0.72–0.78) |
| **WBC ≥ 50 (μL)** | **0.74 (0.71–0.77)** |
| WBC ≥ 40 (μL) | 0.73 (0.70–0.76) |
| WBC ≥ 30 (μL) | 0.72 (0.69–0.75) |
| WBC ≥ 20 (μL) | 0.70 (0.67–0.73) |
| **WBC ≥ 10 (μL)** | **0.66 (0.63–0.70)** |

ROC: receiver operative characteristic; UFEME: urine full examination, microscopic examination; WBC: white blood cell

Apart from WBC count, presence of nitrite in the urinalysis is also one of the parameters to predict the diagnosis of UTI. Presence of nitrite, while helpful, may be falsely negative, because most Gram-negative enteric microorganisms need approximately 4 hours to convert dietary nitrate to nitrite.[6,10,14] This is relevant especially for infants who empty their bladders rapidly.[6] Furthermore, studies have shown that besides enterococcal UTI which usually produce nitrite-negative urine results, 96% of nitrite-negative UTI were due to more common gram-negative uropathogens, such as *Escherichia coli* (84%).[19] In our study, we presented the performance of the various urinalysis WBC thresholds in the overall population as well as in those with nitrite-negative urine samples.

Our study builds on the above literature by performing a sensitivity analysis of nitrite-negative urine samples. Among all children with nitrite-negative urine microscopy, we found that a WBC threshold of ≥100/μL missed 17.3% of UTI. By lowering the WBC threshold to ≥10/μL, the missed cases would be reduced to <5%, with a sensitivity of 97.8% and a negative predictive value of 97.7%, but with a specificity of only 34.9%. Infants require more care,

Table 4. Comparing different white blood cell thresholds (all patients) in culture-proven urinary tract infections (n=1188).

| UFEME WBC threshold to diagnose UTI | Sensitivity (%) [95% CI] | Specificity (%) [95% CI] | NPV (%) [95% CI] | PPV (%) [95% CI] | Negative Likelihood Ratio [95% CI] | Positive Likelihood Ratio [95% CI] | Absolute total number of cultures over 10 months | Absolute increment in cultures (standardised to 12 months) |
|---|---|---|---|---|---|---|---|---|
| WBC ≥100 (μL) | 82.2 [78.4–85.5] | 70.0 [66.6–73.3] | 86.2 [83.6–88.4] | 63.4 [60.6–66.1] | 0.25 [0.21–0.31] | 2.74 [2.44–3.09] | 622 | Reference |
| WBC ≥90 (μL) | 83.3 [79.5-86.6] | 68.9 [65.5–72.3] | 86.7 [84.1–88.9] | 62.9 [60.2–65.6] | 0.24 [0.20–0.30] | 2.68 [2.3-–3.0] | 637 | 18 |
| WBC ≥80 (μL) | 83.7 [80.0–86.9] | 66.9 [63.4–70.3] | 86.7 [84.0–88.9] | 61.5 [58.8–64.0] | 0.24 [0.20–0.30] | 2.53 [2.26–2.82] | 654 | 39 |
| WBC ≥70 (μL) | 84.8 [81.2–87.9] | 65.1 [61.5–68.6] | 87.1 [84.4–89.4] | 60.6 [57.9–63.1] | 0.23 [0.19–0.29] | 2.43 [2.18–2.70] | 673 | 61 |
| WBC ≥60 (μL) | 86.1 [82.6–89.1] | 62.6 [59.0–66.2] | 87.7 [84.9–90.0] | 59.3 [56.8–61.7] | 0.22 [0.18–0.28] | 2.30 [2.08–2.55] | 698 | 91 |
| WBC ≥50 (μL) | 87.8 [84.5–90.7] | 59.6 [55.9–63.2] | 88.6 [85.7–90.9] | 57.9 [55.5–60.2] | 0.20 [0.16–0.26] | 2.17 [1.98–2.39] | 731 | 130 |
| WBC ≥40 (μL) | 90.0 [86.9–92.6] | 55.8 [52.1–59.4] | 89.8 [86.9–92.1] | 56.2 [54.1–58.4] | 0.18 [0.14–0.24] | 2.03 [1.87–2.22] | 771 | 179 |
| WBC ≥30 (μL) | 91.7 [88.8–94.1] | 51.2 [47.5–54.9] | 90.7 [87.8–93.1] | 54.3 [52.3–56.3] | 0.16 [0.12–0.22] | 1.88 [1.74–2.04] | 816 | 233 |
| WBC ≥20 (μL) | 93.9 [91.3–95.9] | 44.8 [41.1–48.5] | 92.1 [88.9–94.4] | 51.8 [50.1–53.5] | 0.14 [0.09–0.20] | 1.70 [1.59–1.82] | 879 | 308 |
| WBC ≥10 (μL) | 96.5 [94.4–98.0] | 34.7 [31.3–38.3] | 94.1 [90.6–96.3] | 48.3 [46.9–49.7] | 0.10 [0.06–0.16] | 1.48 [1.40–1.56] | 971 | 419 |

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; UFEME: urine full examination, microscopic examination; UTI: urinary tract infection; WBC: white blood cell

Table 5. Comparing different white blood cell threshold (nitrite negative) in culture-proven urinary tract infections.

**(A) In all age groups (n=998).**

| UFEME WBC threshold to diagnose UTI | Sensitivity (%) [95% CI] | Specificity (%) [95% CI] | NPV (%) [95% CI] | PPV (%) [95% CI] | Negative Likelihood Ratio [95% CI] | Positive Likelihood Ratio [95% CI] | Number of missed UTI/ Total number of UTI (nitrite negative) (%) |
|---|---|---|---|---|---|---|---|
| WBC ≥100 (μL) | 83.4 [78.6–87.6] | 70.3 [ 66.8–73.6] | 91.7 [89.4–93.5] | 52.0 [ 48.9–55.1] | 0.23 [0.18–0.31] | 2.85 [2.52–3.23] | 48/278 (17.3) |
| WBC ≥90 (μL) | 84.2 [79.3–88.3] | 69.2 [65.6–72.5] | 91.8 [89.6–93.7] | 51.3 [48.3–54.3] | 0.23 [0.17–0.30] | 2.73 [2.42–3.08] | 44/278 (15.8) |
| WBC ≥80 (μL) | 84.9 [80.1–88.9] | 67.1 [63.5–70.5] | 92.0 [89.6–93.9] | 49.9 [47.0–52.8] | 0.23 [0.17–0.30] | 2.58 [2.30–2.89] | 42/278 (15.1) |
| WBC ≥70 (μL) | 85.6 [80.9–89.5] | 65.3 [61.7–68.8] | 92.2 [89.8–94.0] | 48.8 [46.0–51.6] | 0.22 [0.16–0.30] | 2.47 [2.21–2.76] | 40/278 (14.4) |
| WBC ≥60 (μL) | 87.1 [82.5–90.8] | 62.8 [59.1–66.3] | 92.6 [90.2–94.5] | 47.5 [44.8–50.1] | 0.21 [0.15–0.28] | 2.34 [2.11–2.60] | 36/278 (12.9) |
| WBC ≥50 (μL) | 87.4 [82.9–91.1] | 59.9 [56.2–63.5] | 92.5 [89.9–94.4] | 45.7 [43.2–48.2] | 0.21 [0.15–0.29] | 2.18 [1.97–2.41] | 35/278 (12.6) |
| WBC ≥40 (μL) | 89.9 [85.8–93.2] | 55.9 [52.3–59.6] | 93.5 [90.9–95.4] | 44.1 [41.9–46.4] | 0.18 [0.13–0.26] | 2.04 [1.86–2.24] | 28/278 (10.1) |
| WBC ≥30 (μL) | 92.5 [88.7–95.3] | 51.5 [47.8–55.2] | 94.6 [92.1–96.4] | 42.4 [40.4–44.4] | 0.15 [0.10–0.22] | 1.91 [1.76–2.07] | 21/278 (7.5) |
| WBC ≥20 (μL) | 94.9 [91.7–97.2] | 45.0 [41.3–48.7] | 95.9 [93.2–94.5] | 40.0 [38.3–41.7] | 0.11 [0.07–0.19] | 1.73 [1.61–1.85] | 14/278 (5.0) |
| WBC ≥10 (μL) | 97.8 [95.4–99.2] | 34.9 [31.4–38.5] | 97.7 [94.9–98.9] | 36.7 [35.4–38.0] | 0.06 [0.03] | 1.50 [1.42–1.59] | 6/278 (2.2) |

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; UFEME: urine full examination, microscopic examination; UTI: urinary tract infection; WBC: white blood cell

Table 5. Comparing different white blood cell threshold (nitrite negative) in culture-proven urinary tract infections. (Cont'd)

**(B) In infants <1 year old (n=234).**

| UFEME WBC threshold to diagnose UTI | Sensitivity (%) [95% CI] | Specificity (%) [95% CI] | NPV (%) [95% CI] | PPV (%) [95% CI] | Negative Likelihood Ratio [95% CI] | Positive Likelihood Ratio [95% CI] | Number of missed UTI/ Total number of UTI (nitrite negative) (%) |
|---|---|---|---|---|---|---|---|
| WBC ≥100 (μL) | 78.8 [70.1–85.9] | 66.9 [57.8–75.2] | 77.1 [69.8–83.1] | 68.9 [62.9–74.5] | 0.32 [0.22–0.46] | 2.38 [1.82–3.12] | 24/113 (21.2) |
| WBC ≥90 (μL) | 79.7 [71.0–86.6] | 66.1 [56.9–74.5] | 77.7 [70.3–83.7] | 68.7 [62.7–74.1] | 0.31 [0.21–0.45] | 2.35 [1.80–3.07] | 23/113 (20.4) |
| WBC ≥80 (μL) | 81.4 [73.1–88.1] | 64.5 [55.3–72.9] | 78.8 [71.2–84.8] | 68.2 [62.4–73.4] | 0.29 [0.19–0.43] | 2.29 [1.77–2.96] | 21/113 (18.6) |
| WBC ≥70 (μL) | 82.3 [74.0–88.8] | 60.3 [51.0–69.1] | 78.5 [70.5–84.8] | 65.9 [60.5–71.0] | 0.29 [0.19–0.45] | 2.07 [1.64–2.63] | 20/113 (17.7) |
| WBC ≥60 (μL) | 84.1 [76.0–90.3] | 60.3 [51.0–69.1] | 80.2 [72.2–86.4] | 66.4 [61.0–71.4] | 0.26 [0.17–0.41] | 2.12 [1.68–2.68] | 18/113 (15.9) |
| WBC ≥50 (μL) | 84.9 [77.0–90.9] | 59.5 [50.2–68.3] | 80.9 [72.7–87.1] | 66.2 [60.9–71.1] | 0.25 [0.16–0.40] | 2.10 [1.67–2.64] | 17/113 (15.0) |
| WBC ≥40 (μL) | 87.6 [80.1–93.1] | 56.2 [48.9–65.2] | 82.9 [74.4–89.1] | 65.1 [60.1–69.8] | 0.22 [0.13–0.37] | 2.00 [1.62–2.48] | 14/113 (12.4) |
| WBC ≥30 (μL) | 90.3 [83.3–95.0] | 52.9 [43.1–62.0] | 85.3 [76.4–91.3] | 64.2 [59.5–68.6] | 0.18 [0.10–0.33] | 1.92 [1.57–2.34] | 11/113 (9.7) |
| WBC ≥20 (μL) | 93.8 [87.7–97.5] | 47.9 [38.8–57.2] | 89.2 [79.8–94.6] | 62.7 [58.5–66.8] | 0.13 [0.06–0.27] | 1.80 [1.51–2.15] | 7/113 (6.2) |
| WBC ≥10 (μL) | 96.5 [91.2–99.0] | 42.2[33.2–51.5] | 92.7 [82.6–97.2] | 60.9 [57.1–64.5] | 0.08 [0.03–0.22] | 1.67 [1.43–1.95] | 4/113 (3.5) |

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; UFEME: urine full examination, microscopic examination; UTI: urinary tract infection; WBC: white blood cell

as we would have missed 21.2% of UTI with a WBC threshold of ≥100/μL, and this number would also be lowered to <5% with a WBC threshold of ≥10/μL. Overall, a urinary WBC threshold of ≥10/μL would result annually in an estimated 419 extra urine specimens for urine culture with the same number started on empirical antibiotics.

We recognise that the decision on which WBC threshold to adopt should take into account both the number of missed UTIs as well as the additional resources required, including the number of urine cultures and patients started on empirical antibiotics. While a low WBC threshold will result in fewer missed UTI cases, there will also be a larger number of patients who are over-investigated and over-treated. After analysing the different WBC thresholds, a cross-disciplinary team in our hospital discussed and determined that lowering the WBC threshold to ≥50/μL would reduce the number of missed UTIs, while balancing an acceptable increase in the number of urine cultures being performed by the laboratory with a corresponding increase in number of patients started on empirical antibiotic treatment. By presenting the number of missed UTIs and corresponding increase in number of urine cultures at each urinary WBC threshold, our data serves to inform such decision-making in other outpatient contexts.

Of note, clinicians do not rely solely on the urinary WBC count in predicting UTI. Other parameters in the urinalysis which are useful in predicting UTI would be the presence of nitrite and micro-organisms. In addition to that, the patient's profile is also an important factor in predicting the likelihood of UTI. Infants have a higher rate of missed UTI compared to the overall paediatric population at all WBC thresholds, and WBC must be carefully reviewed together with patient's presentation as well as other urinary characteristics. In our study, boys appeared at higher risk of UTI, especially among infants, which is consistent with the literature.[6] Other risk factors include urinary symptoms, vomiting, abdominal or flank pain, increase the likelihood of UTI by 2–6 fold.[1,5] Therefore, for patients who have these symptoms, or infants who present with fever without any localising source, physicians should have a low threshold to suspect a UTI. In particular, among children with recurrent UTIs, especially in those who present with no other localising source of fever, physicians should send urine cultures and initiate empirical antibiotics as they have increased risk of kidney scarring.[20]

The strength of this study is that it was carried out in a large children's ED. We were able to obtain urine samples from 1188 patients who had a wide range of urinary WBC values. We recognise the limitations of our study. We excluded febrile infants <3 months old because they are directly hospitalised with further investigations done as inpatient. Future studies should include this population to understand the urinary characteristics and optimal urinary WBC threshold for UTI diagnosis, because they usually present with vague symptoms and largely have nitrite-negative urine samples.[21] Based on clinical workflow, we only analysed urine samples that were screened positive via urine dipstick with a result of leukocyte esterase of 2+ and above. It is possible that we may have missed UTIs among those whose urine dipstick had <2+ leukocyte esterase. Our study did not allow us to directly compare the diagnostic performance of urinary dipstick leukocyte esterase and/or nitrite versus urinary microscopy WBC and/or nitrite in predicting UTI in the paediatric population. Also, among patients with insufficient urine samples for whom we were not able to submit urine for both urinalysis and urine culture, we may potentially have missed UTIs. In addition, urinalysis was performed on uncentrifuged urine. We did not take into account whether the concentration of urine may have affected the analysis of urine WBC. In future, analyses may be useful that look at urine concentration measured by way of osmolality in relation to the various urine WBC thresholds. Finally, this is a single-centre study, and validation in other centres is required to understand if our findings can be generalised.



## CONCLUSION

We conclude that a urine microscopy WBC threshold of 100/μL results in a clinically significant number of missed UTIs. Adopting lower urinary WBC thresholds requires a value-judgement on overall resource utilisation including additional urine cultures and empirical antibiotics. It is also important for the clinicians to keep a high clinical index of suspicion for UTI if patients have risk factors for UTI.

### 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.*

### *Ethics statement*

*This study was approved by the local ethics board with waiver of informed consent (Centralised Institutional Review Board CIRB 2023/2124, Singapore).*

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ORIGINAL ARTICLE

# Predictors of early removal of intragastric balloon due to intolerance: Insights from a multiethnic Asian cohort

Amadora Choo[1] *MRCS*, Eugene Lim[1] *FRCS*, Alvin Eng[1] *FRCS*, Weng Hoong Chan[1] *FRCS*, Ravishankar Asokkumar[2] *MRCP*, Jeremy Tan[3] *FRACS*, Ai Shan Tan,[3] Agnes Chong,[3] Yumni Binte Md Shahrin,[3] Xuan Wang,[3] Phong Ching Lee[4] *MRCP*, Chin Hong Lim[1] *FRCS*

## ABSTRACT

**Introduction:** Intolerance frequently limits the use of intragastric balloons (IGBs) in the treatment of obesity. This includes refractory nausea, vomiting and abdominal discomfort. Our study aims to identify predictors of balloon intolerance and early removal, which will help to guide patient selection for this intervention and peri-procedure care.

**Method:** We conducted a retrospective cohort study of 54 consecutive patients who underwent IGB insertion from July 2017 to July 2022 in a single tertiary institution in Singapore. Forty-seven (87.0%) patients completed therapy, while 7 patients (13.0%) had early removal of the balloon due to intolerance. Characteristics of both groups were compared.

**Results:** Multivariate analysis revealed significant associations between early balloon removal and both depression ($P$=0.012) and anxiety ($P$=0.001) after adjusting for age, sex, ethnicity, height, nulliparity, balloon type and volume. Univariate analysis revealed that anxiety was the main risk factor ($P$=0.004, odds ratio 9.111, 95% confidence interval 1.624–51.124), while depression was no longer a significant predictor.

**Conclusion:** Identifying predictors of balloon intolerance and early removal can enhance patient selection and improve peri-procedural care. In patients with a history of depression or anxiety, it is important to ensure adequate counselling and preparation prior to balloon insertion.

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**Keywords:** *early removal, elipse, intolerance, intragastric balloon, obesity, orbera, spatz, weight loss*

## CLINICAL IMPACT

### What is New

- Our study identified depression and anxiety as significant predictors of intragastric balloon intolerance and early removal.

### Clinical Implications

- Peri-procedural support is crucial for patients with depression and anxiety, including counselling on physiological changes and setting realistic treatment goals.
- Optimising psychiatric comorbidities prior to intragastric balloon insertion and involving families in the process are also beneficial.
- One can also consider admitting these patients for monitoring and intravenous anti-emetics after balloon insertion, rather than performing it as an ambulatory procedure.

## INTRODUCTION

Obesity, affecting over 2.1 billion people globally, is an escalating health crisis with serious economic consequences.[1] It is associated with multiple comorbidities including type 2 diabetes mellitus (T2DM), hypertension, coronary artery disease, stroke, sleep apnea, osteoarthritis and even certain cancers.[2] In the US alone, USD190 billion per year is spent on the treatment of obesity and obesity-related complications.[3] When compared with normal weight individuals, obese patients are responsible for 46% higher inpatient costs, 27% more outpatient visits and 80% higher spending on prescription medications.[4]

Clinically significant weight loss of 5–10% from baseline can substantially reduce cardiovascular risk factors and improve obesity-related comorbidities, such as obstructive sleep apnea, non-alcoholic fatty liver disease and the prevention or delay in development of type 2 diabetes.[5] Lifestyle interventions, including a low-calorie diet, increased



[1] Department of Upper Gastrointestinal & Bariatric Surgery, Division of Surgery, Singapore General Hospital, Singapore
[2] Department of Gastroenterology & Hepatology, Division of Medicine, Singapore General Hospital, Singapore
[3] Department of Dietetics, Singapore General Hospital, Singapore
[4] Department of Endocrinology, Division of Medicine, Singapore General Hospital, Singapore
Correspondence: Dr Lim Chin Hong, Department of Upper Gastrointestinal & Bariatric Surgery, Singapore General Hospital, 20 College Road, Singapore 169856.
Email: lim.chin.hong@singhealth.com.sg

physical activity and behaviour modification, is the first line for weight loss. Unfortunately, physiologic adaptations to weight loss result in increased appetite, decreased resting metabolic rate and consequently weight regain. As a result, most patients fail to achieve sustained weight loss with lifestyle interventions alone.[6] Pharmacotherapy is an important adjunct to lifestyle and behavioural modifications, and even in patients post-bariatric surgery. However, while glucagon-like peptide-1 (GLP-1) agonists have been shown to be effective in weight loss, its cost has deterred its usage as a first-line therapy. Furthermore, there are also misconceptions about the safety of obesity pharmacotherapy. For example, in Singapore, a survey of the public who attended an obesity forum revealed that 65.1% believed that weight loss medications are dangerous, and only 20.6% thought they were effective for weight loss.[7]

Metabolic-bariatric surgery (MBS) is the most effective treatment for severe obesity and its metabolic complications, with the percentage of excess weight loss ranging from 60% to 87% in randomised controlled trials.[8] Yet, only 1% of patients who quality for MBS undergo the procedure as it is associated with peri-operative risks.[9]



Intragastric balloon (IGB) therapy has been proposed as a less invasive and reversible approach to weight loss that bridges the gap between lifestyle interventions or pharmacotherapy and MBS. It is a space-occupying device that is either inserted endoscopically or swallowed, which results in gastric distention, delayed gastric emptying, increased satiety and consequently reduced intake.[10] IGBs vary in terms of material, duration of therapy, balloon volume, adjustability, method of insertion and removal. Currently, the 3 IGBs approved by the United States Food and Drug and Drug Administration are the Obalon, Orbera and ReShape balloons. Additional balloons approved for use in Europe include the Elipse, End-Ball, Heliosphere BAG, Lexbal, MedSil and Spatz3. Orbera, one of the oldest IGBs still in use, is composed of silicon, filled with 400 to 700 mL of saline and inserted endoscopically into the stomach for up to 6 months. ReShape balloon is similarly inserted endoscopically for up to 6 months and filled with approximately 750 to 900 mL of saline. Both the Obalon and Elipse balloons are swallowed and do not require endoscopy for insertion; however, Elipse is the only IGB that is removed via natural excretion. Spatz3 balloon is unique as its volume can be adjusted.[11]

IGBs have been shown to be safe and effective for treating obesity and its metabolic complications, producing an initial weight loss between 6% and 15%, which is superior compared to 1% to 5% with lifestyle modifications alone.[12] Nonetheless, it is difficult to achieve sustained weight loss with the IGBs, as weight regain is expected to occur after removing the balloon. Furthermore, intolerance of the IGB also limits its use. As the balloon rapidly fills with fluid within the stomach, unwanted symptoms may develop. Nausea and vomiting are the most common symptoms of intolerance, the duration and severity of which vary between individuals. Profuse vomiting with poor intake may also result in dehydration and electrolyte imbalance. Other symptoms of intolerance include abdominal pain, cramps as well as heartburn.[13] The incidence of early removal of IGB due to intolerance ranges from 0.44% to 20% across several studies worldwide.[13–36] Many studies have evaluated the safety and efficacy of IGBs, but few have scrutinised the predictors of intolerance and early removal. Our study aims to identify predictors of early removal of IGB due to intolerance, which will help to guide patient selection and peri-procedural care.

## METHOD

We conducted a retrospective cohort study on 54 consecutive patients who underwent IGB insertion between July 2017 and July 2022 at the Singapore General Hospital. Indications for IGB insertion in our institution include patients with obesity (body mass index [BMI] ≥27.5 kg/m$^2$) who do not qualify, decline or are unsuitable for MBS and who have been unsuccessful in achieving or maintaining weight loss despite dietary and lifestyle modifications. Contraindications to IGB insertion include patients with large hiatal hernia (larger than 5 cm), active ulcers in the stomach or duodenum, upper gastrointestinal bleeding, prior gastric surgeries, coagulopathy, severe liver disease, those who are pregnant or desire to become pregnant, or have any contraindications to undergo oesophagogastroduodenoscopy. All patients received standardised pre-procedure counselling, including informational handouts provided during clinic visits. All patients were evaluated at our weight management unit by a multidisciplinary team consisting of endocrinologists, surgeons, dieticians, physiotherapists, psychiatrists or psychologists prior to commencement of IGB therapy. We optimise the management of any existing psychiatric disorders through medication or therapy to ensure patient is stable prior to the procedure. Post-procedure, our psychologist will continue follow-up and support patients if needed.

Three types of IGB were used in our institution, the Orbera365, Elipse and Spatz3 balloons. The Orbera365 system (Apollo Endosurgery, Austin,

TX, US) is a spherical balloon that is filled with 400–700 mL of saline. It is inserted and removed endoscopically and can remain in the stomach for up to 12 months.[10] Elipse (Allurion Technologies, Wellesley, MA, US) is the first swallowable gastric balloon that does not require endoscopy or sedation for insertion or removal. The balloon is contained in a capsule and once in the stomach, the capsule dissolves and the balloon is filled with 550 mL of fluid via a catheter. The catheter is dislodged from the balloon once filling is completed and withdrawn through the patient's mouth. The balloon self-deflates after 4 months and is naturally excreted.[37] Spatz3 Adjustable Balloon System (Spatz Medical, Great Neck, NY, US) is a silicone spherical IGB with a catheter that allows adjustments. It is inserted endoscopically and filled with 400 to 700 mL of saline. The volume can be adjusted downwards to improve tolerability or upwards to improve weight loss. It has an implantation duration of up to 12 months before it is removed endoscopically.[12] The type of balloon was chosen after a discussion with the patient based on the method of insertion, need for endoscopic removal, adjustability, cost and duration of implantation.

All Elipse balloons were inserted without sedation or anesthesia. The Orbera365 and Spatz3 balloons were inserted endoscopically under sedation (i.e. IV Midazolam). In the first post-procedure day, all patients were commenced on our post-MBS protocol, which included small quantities of clear fluids, progressing to a full liquid diet by the afternoon. Patients will stay on liquid diet for 1 week and gradually progress to stage 3 diet (soft food) under the supervision of our dietician. For anti-emesis, oral Aprepitant (125 mg on night before deployment day, 80 mg daily for 2 days) was prescribed in combination of Ondansetron 4 mg (3 times per day) and Metoclopramide 10 mg (3 times per day) for 5 days. For balloon intolerance, patients were offered option of admission for intravenous Dexamethasone 4 mg (4 times per daily) and intravenous hydration to avert early removal if possible. Patients were reviewed by our multidisciplinary team at 2 weeks post-procedure, followed by review at 1 month, 3 months, 6 months and subsequently annually. Fig. 1 illustrates a typical patient's journey prior to IGB insertion and post-procedure follow up.

Our study aims to identify clinical predictors of early removal of IGB due to intolerance. Intolerance referred to patients who experienced accommodative symptoms such as nausea, vomiting, abdominal discomfort or cramps that were severe enough to warrant early removal. Early removal referred to patients who had the balloon removed before the intended treatment duration was completed, i.e. less than 4 months for Elipse and less than 12 months for Orbera365 and Spatz3 balloons. Variables of interest were identified based on clinical observation and literature review. These include the type of balloon, balloon volume, length of stay following IGB insertion, age, sex, ethnicity, height, nulliparity, presence of psychiatric disorder such as anxiety or depression, use of antidepressants or antipsychotics, presence of T2DM and whether proton pump inhibitor was prescribed. This information was retrieved from a prospectively collected database that was kept for all patients who underwent IGB insertion at our institution.

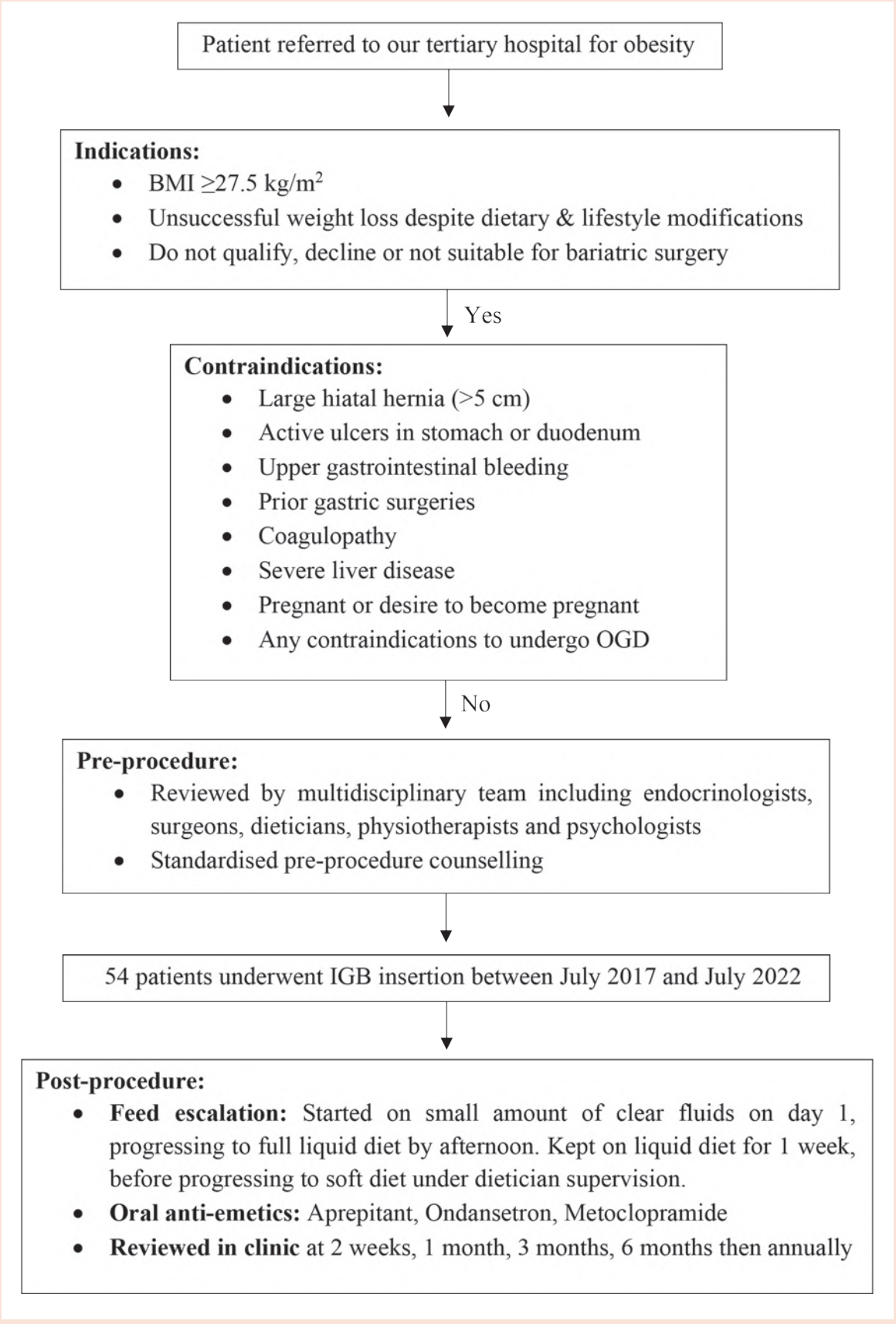
### Statistical analysis

All categorical variables were given as percentages (%) of subjects affected, and normally distributed continuous variables were presented as the mean ± standard deviation (SD). Patients were divided into those who had early removal and those who completed therapy. Characteristics of these 2 groups were compared using Student's t-test for continuous variables or chi-square test for categorical variables. When analysing the relationship between multiple independent and dependent variables, a linear and logistic regression model was used. $P<0.05$ was taken to indicate statistical significance. All analyses were performed using Stata version 16 software (Lakeway Drive, TX, US).

## RESULTS

Fifty-four consecutive patients who underwent IGB insertion in a single tertiary institution in Singapore between July 2017 and July 2022 were included in our study. Thirteen patients (24.1%) experienced symptoms of intolerance including nausea, vomiting and abdominal pain, to varying severities. Eight patients (14.8%) required readmission for intravenous hydration and anti-emetics due to persistent vomiting and abdominal pain. Five of these patients experienced improvement in symptoms with medical therapy and eventually completed therapy. One patient had downsizing of the Spatz3 balloon volume from 700 mL to 500 mL and eventually completed therapy. The other 2 patients had requested for early removal of IGB during the admission due to persistent symptoms. A further 5 patients also had early removal of IGB due to intolerance symptoms, but they were not keen for a trial of admission to hospital for symptomatic treatment first. Out of 54 patients in our study, a total of 7 patients (13.0%) had early removal of the balloon due to

Fig. 1. Flowchart illustrating a typical patient's journey prior to IGB insertion and post-procedure follow-up.




BMI: body mass index; IGB: intragastric balloon; OGD: oesophagogastroduodenoscopy

intolerance while 47 (87.0%) patients completed therapy.

The mean duration of therapy was 263.5 days in those who completed therapy, and 7 days in the early removal group. Consequently, those who had the balloon removed early achieved less weight loss of 4.4 ± 3.6 kg compared to 11.7 ± 6.7 kg in those who completed therapy. The average length of stay post-procedure was comparable between the 2 groups (Table 1).

Table 2 compares the baseline characteristics of patients who had early IGB removal with those who completed therapy. There were no significant differences between the 2 groups in terms of age, sex, ethnicity, type of IGB or balloon volume. The pre-operative weight, BMI and height of patients in both groups were also similar, suggesting that these factors were not statistically significant predictors of intolerance and early removal. Among those who received the Spatz3 adjustable balloon, 3 patients experienced intolerance where 2 opted for the balloon to be removed while 1 had the balloon downsized from 700 mL to 500 mL and eventually completed 12 months of therapy. Another 5 patients had their balloon volume increased for weight stagnation.

Table 1. Effects of treatment.

| | Early removal (n=7) | Completed therapy (n=47) | *P* value |
|---|---|---|---|
| Nadir weight (kg ± SD) | 91.4 ± 18.5 | 86.2 ± 18.5 | 0.490 |
| Weight loss (kg ± SD) | 4.4 ± 3.6 | 11.7 ± 6.7 | 0.008* |
| Procedure duration (min ± SD) | 25 ± 7.6 | 29.2 ± 5.1 | 0.060 |
| Length of stay (day ± SD) | 1.6 ± 1.1 | 1.8 ± 1.5 | 0.661 |
| Duration of therapy (day ± SD) | 7 ± 7.3 | 263.5 ± 21.4 | <0.000* |

SD: standard deviation



Table 2. Baseline characteristics.

| | Early removal (n=7) | Completed therapy (n=47) | *P* value |
|---|---|---|---|
| Age (year ± SD) | 36.3 ± 13.1 | 38.5 ± 12.1 | 0.658 |
| Sex, no. (%) | | | |
| Male | 2 (28.6) | 15 (31.9) | 0.862 |
| Female | 5 (71.4) | 32 (68.1) | |
| Ethnicity, no. (%) | | | 0.459 |
| Chinese | 3 (42.9) | 22 (46.8) | |
| Malay | 3 (42.9) | 7 (14.9) | |
| Indian | 1 (14.3) | 12 (25.5) | |
| Others | 0 | 6 (12.8) | |
| Balloon type, no. (%) | | | 0.741 |
| Orbera365 | 1 (14.3) | 4 (8.5) | |
| Spatz | 2 (28.6) | 23 (48.9) | |
| Elipse | 4 (57.1) | 20 (42.6) | |
| Balloon volume, no. (%) | | | 0.892 |
| 400–500 cc | 1 (14.3) | 11 (23.4) | |
| 500–600 cc | 5 (71.4) | 26 (55.3) | |
| 600–700 cc | 1 (14.3) | 10 (21.3) | |
| Pre-operative weight (kg ± SD) | 95.8 ± 18.9 | 97.9 ± 19.9 | 0.800 |
| Height (cm ± SD) | 162.3 ± 10.0 | 164.5 ± 8.6 | 0.529 |
| Pre-operative BMI (kg/m$^2$ ± SD) | 36.7 ± 8.6 | 36.0 ± 6.3 | 0.799 |

BMI: body mass index; SD: standard deviation

Table 3 compares several clinical parameters, such as nulliparity, depression, anxiety, use of antidepressants or antipsychotics, presence of T2DM or the use of proton pump inhibitors, among those who had early removal and those who completed therapy. On univariate analysis, we found that anxiety disorder was associated with risk of early removal ($P$=0.004, odds ratio 9.111, 95% confidence interval 1.624–51.124). Logistics regression was used to estimate the relationship between a dependent variable and independent variables. After adjusting for age, sex, ethnicity, height, nulliparity, balloon type and volume, multivariate analysis revealed significant associations between early balloon removal and both depression ($P$=0.012) and anxiety ($P$=0.001).

## DISCUSSION

Intragastric balloons act as an artificial bezoar that occupies space in the stomach, resulting in early satiety, reduced food intake and consequently weight loss.[44] Unlike MBS, they are reversible and do not alter gastrointestinal anatomy. In a meta-analysis of 5 randomised controlled trials[38-42] with a total of 903 patients (506 in the IGB group and 397 in the control group), Kotinda et al. showed that the mean percentage of excess weight loss difference between the groups was 17.98% ($P$<0.00001), significantly in favour of the IGB group over sham and lifestyle intervention.[12] Studies have also examined the sustainability of weight loss following balloon removal. In a randomised sham-controlled study with crossover at 3 months, Genco et al. showed that the group that had the balloon inserted for 3 months continued to lose weight at a greater rate in the 3 months following balloon removal, compared to the group that started out without a balloon for 3 months.[42] Beyond weight loss, IGBs also induce significant decrease in hepatic steatosis, insulin resistance and improvement in other obesity-associated comorbidities.[19]

While IGBs are safe and effective, its use is limited by intolerance.[43] Table 4 summarises the current literature on the experience with IGB worldwide, where the incidence of early removal due to intolerance varies between 0.44% and 20%. However, data on predictors for intolerance has been relatively scarce, with only 2 prior studies reporting on such predictors in the Caucasian population. The first study by Vargas et al. in the US[24] showed that the use of selective serotonin or serotonin-norepinephrine reuptake inhibitors (SSRI/SNRI) at time of balloon placement was associated with increased odds of early removal before 8 weeks. The second study by Luisa de-Castro et al. in Spain[21] showed that intolerance was more frequent in females and in patients who complained of digestive symptoms beyond the first month. Our study represents the first and only study of these predictors in an Asian population.

In fact, our study showed that the early removal rate for intragastric balloons was significantly higher in the Asian population (13%) compared to Caucasian populations, which is consistent with the paper by Ganesh et al.[16] The only other study conducted specifically in an Asian patient cohort found that 20% of patients required early balloon removal due to refractive nausea and epigastric discomfort, and concluded that intragastric balloons are poorly tolerated by Asian patients even when lower volumes are infused into the balloon to compensate for the smaller Asian stature. Insights into the predictors of early IGB failure in an Asian population represent an important addition to the limited existing literature in this field. By identifying the key predictors of early balloon failure in this population, clinicians



Table 3. Predictors of early removal of intragastric balloon due to intolerance (univariate analysis).

| | Early removal (n=7) | Completed therapy (n=47) | Odds ratio | 95% confidence interval | *P* value |
|---|---|---|---|---|---|
| Nulliparous, no. (%) | 3 (60.0) | 21 (65.6) | 0.786 | 0.114–5.425 | 0.807 |
| Depression | 1 (14.3) | 10 (21.3) | 0.617 | 0.066–5.731 | 0.671 |
| Anxiety | 4 (57.1) | 6 (12.8) | 9.111 | 1.624–51.124 | 0.004* |
| Other psychiatric disorders | 0 | 5 (10.6) | 0.515 | 0.026–10.320 | 0.665 |
| Antidepressants | 2 (28.6) | 5 (10.6) | 3.36 | 0.511–22.104 | 0.207 |
| Antipsychotics | 1 (14.3) | 5 (10.6) | 1.400 | 0.139–14.120 | 0.775 |
| Type 2 diabetes mellitus | 0 | 9 (19.2) | 0.270 | 0.014–5.159 | 0.385 |
| Proton pump inhibitor | 3 (42.9) | 19 (40.4) | 1.105 | 0.222–5.509 | 0.903 |

Table 4. Summary of experiences with intragastric balloons in terms of the incidence and predictors of early removal due to intolerance.

| Study | Type of IGB | Country | Sample size | Incidence of early removal of IGB due to intolerance, no. (5) | Reason for intolerance of IGB | Predictors of intolerance of IGB |
|---|---|---|---|---|---|---|
| Roman et al. (2004)[14] | BioEnterics Intragastric Balloon (BIB) | France | 176 | 15 (8.5%) | Vomiting, abdominal pain | Not applicable |
| Genco et al. (2005)[15] | BIB, now known as Orbera | Italy | 2515 | 11 (0.44%) | Psychological intolerance | Not applicable |
| Ganesh et al. (2007)[16] | BIB | Singapore | 20 | 4 (20%) | Refractory nausea, retching, epigastric discomfort | Higher early removal rate among Asian patients despite lower volume of balloon filling compared to the Caucasian experience with BIB |
| Imaz et al. (2008)[17] | BIB | Meta-analysis of 17 studies including 2 RCTs | 3442 | 104 (3.0%) | Voluntary removal, nausea, vomiting, abdominal pain, dehydration | Not applicable |
| Dastis et al. (2008)[18] | BIB | Switzerland | 100 | 14 (14%) | Nausea, vomiting, bdominal pain | Not applicable |
| Forlano et al. (2010)[19] | BIB | Italy | 130 | 6 (4.6%) | Nausea, vomiting, abdominal pain | Not applicable |
| Lopez-Nava et al. (2011)[20] | BIB | Spain | 714 | 31 (4.3%) | Psychological intolerance, gastroparesis | Not applicable |
| Luisa de-Castro et al. (2013)[21] | BIB and Heliosphere Bag balloon | Spain | 91 | 12 (13.2%) | Psychological intolerance, persistent vomiting | Intolerance more frequent in females ($P$=0.03) and in patients who complained of digestive symptoms beyond the first month ($p$=0.001) |
| Ghoneim et al. (2014)[22] | BIB | Egypt | 101 | 3 (3%) | Not mentioned | Not applicable |
| Mitura et al. (2015)[13] | Orbera | Poland | 57 | 1 (1.7%) | Persistent vomiting, dehydration, electrolyte imbalance | Not applicable |
| Silva et al. (2018)[23] | Orbera | Portugal | 51 | 7 (13.7%) | Abdominal pain, nausea, vomiting | Not applicable |

Table 4. Summary of experiences with intragastric balloons in terms of the incidence and predictors of early removal due to intolerance. (Cont'd)

| Study | Type of IGB | Country | Sample size | Incidence of early removal of IGB due to no. (%) | Reason for intolerance of IGB | Predictors of intolerance of IGB |
|---|---|---|---|---|---|---|
| Vargas et al. (2018)[24] | Orbera | Minnesota (Mayo clinic's database) | 321 | 54 (16.6%) | Symptoms necessitating early balloon removal include: vomiting (36%), nausea (21%), abdominal pain (8%), troublesome gastroesophageal reflux (8%) and a combination of above symptoms (4%) | Use of selective serotonin or serotonin-norepinephrine reuptake inhibitors (SSRI/SNRI) at time of balloon placement was associated with increased odds of early removal before 8 weeks. Aprepitant use appeared to be protective. |
| Fittipaldi-Fernandez (2020)[25] | Orbera | Brazil | 5874 | 357 (6.1%) | Not mentioned | Not applicable |
| Neto et al. (2017)[26] | Orbera, Medicone, Silimed, Spatz, Helioscopie | Brazil | 41,866 | 928 (2.2%) | Not mentioned | Not applicable |
| Schwaab et al. (2019)[27] | Orbera (non-adjustable) and Spatz3 (adjustable) | Brazil | 470<br>326<br>Orbera<br>144<br>Spatz3 | 30 (6.4%)<br>22 (6.7%) Orbera<br>8 (5.6%) Spatz3 | Not mentioned | Higher incidence of early removal due to intolerance for non-adjustable balloons |
| Machytka et al. (2017)[28] | Elipse | US | 34 | 2 (5.9%) | Not mentioned | Not applicable |
| Al-Subaie et al. (2017)[29] | Elipse | Kuwait | 51 | 5 (9.8%) | Not mentioned | Not applicable |
| Alsabah et al. (2018)[30] | Elipse | Kuwait | 135 | 8 (5.9%) | Nausea, vomiting, abdominal pain | Not applicable |
| Jamal et al. (2019)[31] | Elipse | Kuwait | 112 | 6 (5.4%) | Nausea, vomiting, abdominal pain | Not applicable |
| Ienca et al. (2020)[32] | Elipse | 19 international centres across Europe and Middle East | 1770 | 52 (2.9%) | Not mentioned | Not applicable |
| Taha et al. (2021)[33] | Elipse | Egypt | 96 | 3 (3.1%) | Repeated vomiting | Not applicable |
| Machytka et al. (2014)[34] | Spatz3 | Czech Republic and Manchester | 77 | 3 (3.9%) | 1 due to GERD, 2 not mentioned | Not applicable |
| Abu Dayyeh et al. (2021)[35] | Spatz3 | US | 187 | 31 (17%) | Not mentioned | Not applicable |
| Ibrahim et al. (2019)[36] | MedSil | Egypt | 86 | 7 (8.1%) | Nausea, vomiting, abdominal pain | Not applicable |

GERD: gastroesophageal reflux disease; IGB; intragastric balloon; RCTs: randomised controlled trials

can make more informed decisions about patient suitability and tailor their approaches to achieve the best possible results.

While Vargas et al.[24] found that the use of SSRI/SNRI was significantly associated with balloon intolerance and early removal, our study did not find this association to be statistically significant ($P$=0.195). A possible explanation could be that the presence of underlying depression or anxiety that necessitated the use of SSRI/SNRI may have been a confounder to the results in Vargas et al. Similar to how depression, anxiety and stress are associated with functional dyspepsia and irritable bowel syndrome,[44] we postulate that these psychiatric disorders contribute to visceral hypersensitivity via complex brain-gut neural pathways, resulting in an increased perception of bloating and nausea following IGB insertion.

In terms of the type of IGB, Al-Subaie et al. reported that patients with the Elipse balloon experienced higher symptom severity immediately after insertion, possibly due to an underestimation of the symptoms since the insertion is procedureless.[29] However, Elipse was found to be rapidly tolerated after the first 72 hours, and Alsabah et al. postulated that its thin polymer film design makes it better tolerated in the stomach compared to the rigid designs of other balloons.[30] On the other hand, Spatz3 is an adjustable IGB, where the volume of saline within the balloon can be reduced to improve tolerance. In a retrospective review of 165 consecutive patients who underwent Spatz3 balloon insertion, Usuy et al. showed that downward adjustments of balloon volume alleviated early intolerance in 80% of patients.[45] In our study, 1 patient with Spatz3 had the balloon downsized from 700 mL to 500 mL for persistent nausea and vomiting, and eventually completed 12 months of therapy. Overall, our results nonetheless found that there was no statistically significant association between the type of balloon ($P$=0.741) or balloon volume ($P$=0.892) on intolerance and early removal. Other factors—including age, sex, ethnicity, pre-operative weight, BMI, height, nulliparity, T2DM and the use of proton pump inhibitors—were not significant predictors of intolerance and early removal.

A limitation of our study is its small sample size, which reduces its statistical power and increases the possibility of a type 2 error. With 3 different IGBs with different proposed dwell times (4 versus 12 months) and different methods of insertion and management (2 with fixed volumes and 1 adjustable), it may be difficult to conclusively tease out the factors for intolerability. Furthermore, as a retrospective review of a single-centre experience, this limits the generalisability of our findings and larger confirmatory studies are needed. With a larger sample size, it may be possible to do a case-matched control study to investigate the incidence and factors for intolerance across the various IGBs. Nonetheless, our study hopes to be hypothesis-generating as there is currently no data available on predictors for early removal of intragastric balloon. Given that depression and anxiety are significantly associated with balloon intolerance and early removal, we hope that this information will help to guide patient selection and pre-procedure counselling. In patients with pre-existing depression or anxiety, peri-procedural support is imperative. This includes counselling them on the physiological changes to be expected post-procedure, clarifying the role of the intragastric balloon and to set realistic treatment goals. It is also equally important to adequately optimise the patient's underlying psychiatric comorbidities prior to IGB insertion. Involving families in process has also been shown to be beneficial, especially for adolescent patients. It may also be worthwhile to admit these patients for close monitoring and IV anti-emetics after balloon insertion rather than performing it as an ambulatory procedure.



## CONCLUSION

In conclusion, while IGBs are a promising, less-invasive alternative to MBS in the treatment of obesity and its metabolic complications, intolerance is a problem especially in Asian populations where the rates of early balloon removal are significantly higher than in Caucasian populations. Identifying patients at risk of intolerance and early removal enables the healthcare team to implement necessary countermeasures, reducing this risk and increasing the success of IGB therapy. It allows clinicians to make informed decisions about patient suitability and tailor their approach to achieve best possible results for each patient.

### *Declaration*

*No funding was received for this work. 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.*

### *Ethics statement*

*Formal consent is not sought as this is a retrospective study that does not use any identifying data.*

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REVIEW ARTICLE

# 2023 guidelines on the management of psoriasis by the Dermatological Society of Singapore

Hazel H Oon[1] *MD*, Chris Tan[2] *MBBS*, Derrick Chen Wee Aw[3] *MBBS*, Wei-Sheng Chong[1] *MBBS*, Hong Yi Koh[4] *MBBS*, Ying-Ying Leung[5,6] *MD*, Kar Seng Lim[7] *MBBS*, Jiun Yit Pan[1] *MBBS*, Eugene Sern-Ting Tan[1] *MBBS*, Ki Wei Tan[8] *MBBS*, Siew Nee Tham[4] *MBBS*, Colin Theng[9] *MBBS*, Su-Ni Wong[10] *MBBS*

## ABSTRACT

**Introduction:** Psoriasis is a multisystem, chronic, inflammatory dermatological disease. In routine clinical practice, the management of psoriasis varies significantly. The current study aimed to develop a set of practice guidelines relevant to dermatology practice in Singapore.

**Method:** The Psoriasis Therapeutic Guidelines Workgroup, comprising members of the Dermatological Society of Singapore with a subspecialisation in psoriasis, was convened to develop the guidelines. Clinical questions on selected topics were generated and refined by the workgroup. A literature search using PubMed was performed on their assigned topics from June 2013 to December 2023. The articles were included and graded based on the level of evidence.

**Results:** The guidelines address topics ranging from clinical assessment to practical considerations in the management of mild, moderate and severe psoriasis, including delivery of care, referrals to specialists and adherence to treatment. The recommended therapies include phototherapy, methotrexate, acitretin, cyclosporine; apremilast; topical corticosteroids, calcipotriol, topical calcineurin inhibitors; and biologics (i.e. adalimumab, infliximab, secukinumab, ixekizumab, ustekinumab, etanercept) either in combina-tion or as monotherapy. Common therapeutic concerns relating to biologic use were addressed. Recommendations on generalised pustular psoriasis, palmoplantar pustular psoriasis and psoriatic arthritis were also made. Patients on systemic therapy would receive appropriate vaccine counselling. Therapeutic implica-tions in special populations, such as pregnant/lactating women, children, the elderly, those undergoing surgery and those suffering from specific infections and cancer were addressed.

**Conclusion:** These guidelines were developed for dermatologists, family physicians, rheumatologists and other specialists to support their selection of appropriate management options.

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**Keywords:** biologic therapy, ethnicity, psoriasis, psoriatic arthritis, therapy

## CLINICAL IMPACT

### What is New

- The Dermatological Society of Singapore has developed guidelines for the management of psoriasis, which is currently managed in diverse ways.
- The guidelines cover aspects of clinical assessment and treatment across severity levels.

### Clinical Implications

- The guidelines emphasise the management of pustular and palmoplantar psoriasis, psoriatic arthritis and psoriasis in special populations.
- It also provides a comprehensive framework for dermatologists and promotes standardised patient care.
- Furthermore, the guidelines discuss the indications and selection of biologic therapy in the management of psoriasis.



[1] National Skin Centre, Singapore
[2] Division of Dermatology, National University Hospital, Singapore
[3] Department of Dermatology, Sengkang General Hospital, Singapore
[4] TSN Dermatology Skin Specialist Clinic, Singapore
[5] Department of Rheumatology and Immunology, Singapore General Hospital, Singapore
[6] Duke-NUS Medical School, Singapore
[7] The Dermatology Practice, Singapore
[8] Department of Dermatology, Changi General Hospital, Singapore
[9] The Skin Specialists & Laser Clinic, Singapore
[10] Dr SN Wong Skin, Hair, Nails & Laser Specialist Clinic, Singapore
Correspondence: Dr Hazel H Oon, National Skin Centre, 1 Mandalay Road, Singapore 308205.
Email: hazeloon@nsc.com.sg

## INTRODUCTION

Psoriasis is a chronic multisystem, autoimmune and inflammatory dermatological condition. It usually persists throughout one's lifetime, and spontaneous remission is rarely seen. As per the World Health Organization (WHO), the global prevalence of psoriasis is about 0.09%–11.4%.[1]

Psoriasis may be linked to other serious diseases, such as depression, psoriatic arthritis (PsA), diabetes and heart disease. PsA is a common comorbidity occurring concurrently with psoriasis. According to WHO, the global prevalence of PsA is about 1.3%–34.7%.[1] The treatment of psoriasis should address both psychosocial and clinical manifestations of the disease. Several innovative therapies are available for psoriasis, ranging from topical treatment to oral systemic therapy and novel biologic treatments. The treatment regimen is chosen based on the extent of the disease, relevant comorbidities and the effect of the disease on patients' quality of life.

The primary goal of this study is to provide evidence-based guidelines for managing different types of psoriasis, with a focus on plaque psoriasis.

### Target group

These guidelines have been developed for dermatologists, family physicians, rheumatologists and other specialists to enhance their understanding of psoriasis and support their decision-making in selecting the most appropriate management option. With the advent of new biologics, these guidelines will also help dermatologists decide on the appropriate indication and selection of biologic therapy. The guidelines are not meant to be a didactic algorithm for the treatment of psoriasis. They should be individualised for each patient and used in conjunction with the personal experience of the prescribing physician.

## METHOD

The Psoriasis Therapeutic Guidelines Workgroup comprises 12 dermatologists from the Dermatological Society of Singapore (DSS). They subspecialise in psoriasis and accepted the invitation of the DSS Executive Committee to participate in this workgroup. The aim was to develop a set of practice guidelines for clinicians in Asia, particularly in Singapore, in an easy-to-read format while incorporating more recent literature.

Clinical questions on selected topics were created and refined by the workgroup based on clinical experience as well as feedback on the main concerns of patients with psoriasis and members of the Psoriasis Association of Singapore. A literature search using PubMed was performed by the workgroup members on their assigned topics. Journal articles published from June 2013 to December 2019 were included and graded based on the level of evidence. Subsequently, key articles and references up to December 2023 were reviewed,[2-14] including changes in biologics on the subsidised drug list of the Ministry of Health, Singapore.[15]

These guidelines were based on the first edition of the DSS Psoriasis Management Guidelines, published on 30 June 2016. Therapeutic guidelines existing worldwide, especially the joint American Academy of Dermatology (ADD)-National Psoriasis Foundation (NPF) 2019 guidelines for the management of psoriasis along with an emphasis on awareness and attention to comorbidities; the 2019 joint ADD-NPF guidelines of care in managing psoriasis with biologics; the joint American College of Rheumatology-NPF 2018 guidelines for the management of PsA;[16] the 2017 National Institute for Health and Care Excellence guidelines for the management of psoriasis;[17] the 2009 Canadian guidelines and 2016 Addendum to the Canadian guidelines; the 2017 British Association of Dermatologists guidelines; and the 2017 European S3-Guideline on the systemic treatment of psoriasis vulgaris, were used as references for developing the current guidelines. References were also made to the regional psoriasis therapeutic guidelines and the National Skin Centre psoriasis guidelines in Singapore.

The draft guidelines and evidence were reviewed in a series of workgroup meetings. Consensus was obtained, defined as a minimum of 90% agreement, on guidelines that lacked sufficient evidence from the literature.

Guidelines reflect considerations of benefits and harms, side effects and risks. Social values, psychological aspects and preferences were identified in consultation with patients in public and private healthcare clinics, as well as with members of patient support group, the Psoriasis Association of Singapore.

Expert panel members were invited from different public and private healthcare institutions to ensure a balance of views, equity, feasibility and acceptability. The experts were dermatologists with subspecialisation in psoriasis and special expertise in cutaneous infections and photodermatology. In addition, a rheumatologist, YY Leung, provided input for drafting the section on PsA.

While formulating the guidelines, the experts also considered the costs of biologics and the availability of medication assistance funds. However, they recognised that not all patients would be eligible for funding, and some would seek care as private patients.

The modified Delphi method was used for formulating the guidelines. The workgroup adopted the Scottish Intercollegiate Guidelines Network grading system for the grade of recommendations and level of evidence, presented in Supplementary Table S1.[18] Two key opinion leaders in the field of psoriasis reviewed the guidelines critically. The document was vetted and approved by the entire panel of authors. Statements were accepted when a unanimous agreement was reached. The entire process was completed in 3 rounds. Printed copies of the guidelines were distributed to the members of the DSS.

The guidelines will be updated 5 years after publication. A description of the method followed to develop the guidelines is provided in Supplementary Fig. S1. The guidelines are presented in Supplementary Tables S2 and S3.[19-30]

## RESULTS

In addition to addressing the clinical assessment and management of various severities of psoriasis, the guidelines provide detailed recommendations for handling specific subtypes, such as pustular and palmoplantar psoriasis. The scope also includes subgroups of PsA, ensuring comprehensive coverage of the disease spectrum. Moreover, the guidelines offer insights into managing psoriasis in special populations, such as children, pregnant women and individuals with malignancies, recognising the unique challenges and considerations these groups may face in treatment and care. Overall, these guidelines offer a thorough framework for healthcare providers to deliver effective and tailored management strategies for individuals with psoriasis across different manifestations and circumstances.



## DISCUSSION

Psoriasis encompasses various subtypes, each presenting distinct clinical features and treatment considerations. Additionally, managing psoriasis requires attention to comorbidities, such as hepatitis, tuberculosis (TB), human immunodeficiency virus (HIV) and malignancies, which may influence treatment decisions and overall disease outcomes. Special considerations, such as pregnancy and adherence management, further highlight the complexity of psoriasis care and the need for tailored approaches to ensure optimal outcomes for patients.

### Management of moderate and severe psoriasis

#### *Phototherapy*

Phototherapy is the recommended second-line therapy for patients with psoriasis involving >10% of the body surface area (BSA). Both ultraviolet B (UVB) and psoralen + ultraviolet A (UVA) are effective in clearing psoriasis when delivered 2 to 3 times a week in the clearance phase until minimal residual activity. The treatment is then reduced to once weekly or fortnightly during the maintenance phase before cessation.

#### *Conventional systemic therapy*

About 20% of patients with psoriasis experience moderate-to-severe symptoms and are considered suitable for systemic therapy.[31] Severe disease is defined as Psoriasis Area and Severity Index (PASI) ≥10, BSA ≥10% or Dermatology Life Quality Index (DLQI) ≥10 (the rule of 10s). The disease in high-impact areas is associated with significant psychological or functional disability (e.g. major parts of the scalp, genitals, palms, soles and intertriginous areas). A summary of recommendations for managing moderate-to-severe psoriasis using phototherapy and systemic therapy is presented in Table 1.[31,32]

#### *Biologics and their use in special situations*

Biologics are employed as either standalone treatments or in conjunction with other systemic or topical medications for psoriasis management.[31] A summary of recommendations for the management of moderate-to-severe psoriasis using biologics and in special situations is provided in Table 2.[5,31-35]

### Management of pustular psoriasis

Pustular psoriasis, a rare, systemic, immunemediated dermatological disorder, affects both children and adults. It is classified into generalised and localised pustular psoriasis depending on whether the pustules are widespread or localised. A summary of treatment recommendations for generalised pustular psoriasis and palmoplantar pustular psoriasis is presented in Table 3. Moreover, a multicentre study involving Asian patients revealed that intravenous spesolimab enhanced outcomes while managing flares of generalised pustular psoriasis.[4]

### Practical considerations in psoriasis

#### *Delivery of care and social and psychological aspects of psoriasis*

Psoriasis is associated with several comorbidities, and PsA has arguably the most well-known association with psoriasis. Other comorbidities are also associated with psoriasis, such as cardiovascular disease (CVD) and metabolic syndrome (MetS) and its components, including obesity, hypertension, diabetes mellitus and dyslipidaemia.

Table 1. Summary of recommendations for the management of moderate-to-severe psoriasis: phototherapy and systemic therapy.[31,32]

| **Summary of recommendations for treatment with phototherapy** | |
|---|---|
| **Phototherapy regimens** | **Level, grade** |
| Topical/bath PUVA | Level 2++, B |
| Excimer light | 2+, C |
| PUVA + acitretin | Level 1+, B |
| NBUVB | Level 1+, A |
| UVB + MTX | Level 1+, A |
| UVB + acitretin | Level 1+, A |
| UVA + biologics | Level 2+, C |
| UVB + apremilast | Level 2+, C |
| **Summary of recommendations for treatment with systemic therapy** | |
| Treatment modality is guided by severity, impact on QoL and the presence of cutaneous psoriasis elsewhere and psoriatic arthritis. | GPP |
| MTX* is an inexpensive and effective drug for both psoriatic arthritis and psoriasis and can be combined with phototherapy. | 1+, A |
| Acitretin* is not immunosuppressive and may be used effectively as<br>monotherapy or<br>combined with phototherapy | <br>2+, B<br>1+, A |
| Cyclosporine* is a fast-acting and highly effective drug for psoriasis. | 1+, A |
| Hydroxyurea may be considered for chronic plaque psoriasis and generalised pustular psoriasis with >20% BSA in patients with adverse events or comorbidities, precluding the use of conventional oral systemics and biologics. | 3, C |
| Apremilast is not immunosuppressive and is an effective systemic agent for the management of plaque psoriasis, psoriatic arthritis and palmoplantar psoriasis. | 1+, A |
| The primary aim of systemic treatment is to achieve clearance of psoriasis. If the primary aim is not achievable, the next aim should be to improve the extent of disease and QoL of patients by achieving the following treatment targets: PASI reduction by 75% (with newer biologics, PASI reduction by 90% or PGA 0/1 may be achieved in highly motivated patients) or DLQI <5 or DLQI reduction by a minimum of 5 points. | 4, D |
| Definition of standard systemic therapy: cyclosporine 2–5 mg/kg/day for 12 weeks; MTX 15–25 mg weekly for 12 weeks; acitretin 25–50 mg daily for 12–24 weeks and definition of adequate response to therapy: PASI reduction by 75% or DLQI <5 or DLQI reduction by at least 5 points. | 4, D |
| **Systemic treatment in erythrodermic psoriasis**<br>(1) Cyclosporine: for unstable cases, because of its rapid onset of action<br>(2) Acitretin or MTX in less acute disease | <br>2+, B<br>2+, B |

*Systemic agents commonly used in Singapore.
BSA: body surface area; DLQI: Dermatology Life Quality Index; GPP: good practice points; MTX: methotrexate; NBUVB: narrow-band ultraviolet B; PASI: Psoriasis Area and Severity Index; PGA: physician global assessment; PUVA: Psoralen + UVA; QoL: quality of life; UVA: ultraviolet A

### *Indications for referral to specialists*

A patient should be referred to a dermatologist when: (1) the patient presents with a complex disease, i.e. an extensive disease that is likely to require systemic treatment, with BSA >10%; (2) the disease is associated with significant psychological distress, e.g. DLQI >5 or less than a 5-point reduction compared with baseline after treatment; (3) the patient is unsatisfied with the current level of control; (4) the patient exhibits suboptimal response to primary care management, i.e. less than 75% reduction in BSA involvement or PASI; or (5) the patient develops significant adverse effects to topical medications, e.g. skin atrophy, striae, hirsutism

Table 2. Summary of recommendations for biologics in the management of moderate-to-severe psoriasis and in special situations.[5,31-35]

| Recommendations | Level/grade |
|---|---|
| **Pre-biologic evaluation** | |
| Pre-biologic assessments include:<br>Disease severity<br>• PASI (or BSA and PGA)<br>• DLQI<br>Exclude contraindications<br>Cardiovascular<br>• 2D echocardiography if heart failure based on NYHA class III/IV (anti-TNFs)<br>Neurologic<br>• Exclude demyelination in personal or first-degree relatives in the family history (anti-TNFs)<br>Infections<br>• Exclude active or chronic infections<br>Tuberculosis<br>• Screen for active or latent TB by clinical and diagnostic investigations<br>Malignancy<br>• Refer to primary care physicians for age- and sex-appropriate cancer screening if indicated<br>**Tests**<br>• FBC, creatinine, LFT, HBsAg, HBsAb, and HBcAb, anti-hepatitis C IgG and CXR<br>• IGRA (e.g. T-SPOT®.TB or QuantiFERON®-TB Gold). Mantoux test may be more difficult to administer and interpret and less reliable in patients already on immunosuppressants.<br>• HIV screening if clinical suspicion of HIV exists<br>• Urine pregnancy test (if at risk)<br><br>**Financial counselling and assessment**<br>Patients must be informed regarding the cost of the biologic therapy.<br>When the cost of therapy is an issue, subsidised patients in restructured hospitals who meet the medical criteria for biologics under SDL or MAF should be assessed for financial assistance.<br>SDL biologics: adalimumab biosimilar and infliximab biosimilar<br>MAF biologics: secukinumab and ixekizumab | 4, C |
| **Monitoring on biologics** | |
| An IGRA is conducted annually. If too costly or not available, CXR can be considered as an alternative. | GPP |
| FBC and LFT at 4 weeks (2 weeks for infliximab) and then 3–6 monthly | 2+, B |
| Creatinine: 6 monthly | 2+, B |
| Hepatitis B, Hepatitis C, HIV, periodic urine pregnancy test, if at risk | 2+, B |
| **Switching from nonbiologic systemic therapy to biologic therapy in the management of moderate-to-severe psoriasis** | |
| **General considerations**<br>• When switching due to safety reasons, a washout period is desirable until the safety parameter is stabilised or normalised.<br>• An overlap period or a direct transition may be considered if the switch is due to a lack of efficacy.<br>• An approved induction dose must be used when initiating biologic therapy. | 3, D |
| Switching from acitretin<br>• It does not need a washout period.<br>• Contraception must be continued in women of childbearing age for 3 years. | 3, D |
| **Switching from cyclosporine**<br>• It does not require a washout period.<br>• A brief overlap period along with biologic therapy (such as for 2–8 weeks) could be considered to reduce the risk of rebound in partial responders. However, the dose of cyclosporine should be tapered at the earliest. | 3, D |
| **Switching from MTX**<br>• It does not require a washout period.<br>• MTX to be used concomitantly or may be overlapped with approved biologics. | 3, D |

Table 2. Summary of recommendations for biologics in the management of moderate-to-severe psoriasis and in special situations.[5,31-35] (Cont'd)

| Recommendations | Level/grade |
|---|---|
| **Switching between biologics** | |
| **General considerations** | |
| • It is generally recommended to fully optimise a biologic before switching to another. | |
| • In cases where efficacy is lost over time (secondary non-responders) or the patients do not respond adequately (do not achieve a minimum of PASI75) by the end of the induction phase (primary non-responders), switching must be performed with considerations to dose adjustments. | |
| • A washout period is necessary when safety concerns are the reason for switching until the safety parameter is stabilised or normalised. | |
| • A washout period is unnecessary when the reason for switching is a lack of efficacy; a switch can be made to the new biologic when the next dose of the original therapy is scheduled. | |
| • A maintenance dose must follow after the approved induction dose for the new biologic. | 3, C |
| • Patients failing to respond to a biologic may respond to another biologic (even if the biologic belongs to the same class as the previous one, e.g. anti-TNF). | 4, D |
| • If a response is achieved to the biologic therapy, then a standard therapy must be rationalised (e.g. dose reduced or stopped). | 4, D |
| • MTX and acitretin (limited data for the latter) do not show increased toxicity when combined with anti-TNFs. | |
| **How to stop biologics?** | |
| Biologics may be stopped abruptly if required. | 4, D |
| Continuous therapy is more efficacious and associated with less development of antidrug antibodies (with associated loss of efficacy and side effects). | 3, C |
| **Biologic therapy in special situations** | |
| **Surgery** | |
| • The risk of a psoriatic flare needs to be balanced with the advantage of postoperative infection prevention achieved by stopping the treatment. | 4, D, GPP |
| • When wound healing is optional and there is no sign of infection, then biologics may be restarted postoperatively. | 4, D, GPP |
| **Retreatment after stopping biologics** | |
| • Continuous therapy is more efficacious than interrupted therapy, but situations may arise where patients need to interrupt treatment and restart again later. | 4, D, GPP |
| • Etanercept, adalimumab, ustekinumab, secukinumab, guselkumab and risankizumab: most patients regain their initial response on retreatment. | |
| **Drug interactions** | |
| • In patients on immunosuppressives, biologics should be used with great caution and concomitant use should be avoided if possible. | 4, D, GPP |
| **Pregnancy** | |
| • Patients planning conception should discuss with their dermatologist the benefits versus risks of continuing biologic treatment during pregnancy. Certolizumab pegol has minimal placental permeability and is the safest and preferred biologic treatment option throughout pregnancy. | |
| • Certolizumab is an unregistered therapeutic product in Singapore and if required, drug approval should be obtained via the special access route. Other biologics may be used with caution in pregnancy, with TNF-alpha inhibitors as the preferred class. | 4, D, GPP |
| • If TNF-alpha inhibitors or other biologic therapies (excluding certolizumab) are given after week 22 of pregnancy, live vaccines, such as BCG, should be delayed until the infant is more than 6 months old. | |

2D: two dimensional; BCG: Bacillus Calmette-Guerin; BSA: body surface area; CXR: chest X-ray; DLQI: Dermatology Life Quality Index; FBC: full blood count; GPP: good practice points; HBcAb: Hepatitis B core antibody; HBsAb: Hepatitis B surface antibody; HBsAg: Hepatitis B surface antigen; HIV: human immunodeficiency virus; IgG: immunoglobulin G; IGRA: interferon-gamma release assay; LFT: liver function test; MAF: medication assistance fund; MTX: methotrexate; NYHA: New York Heart Association; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; SDL: standard list; TB: tuberculosis; TNF: tumour necrosis factor

Table 3. Summary of treatment recommendations for generalised pustular psoriasis, palmoplantar pustular psoriasis and impetigo herpetiformis.

| Recommendations | Generalised pustular psoriasis (level, grade) | Palmoplantar pustular psoriasis (level, grade) | Impetigo herpetiformis (level, grade) |
|---|---|---|---|
| Topical corticosteroids | 3, D | 2+, C | NA |
| Topical calcipotriol | 3, D | NA | NA |
| Topical tacrolimus | 3, D | NA | NA |
| Phototherapy | 2+, C | 2+, C | NA |
| MTX | 2+, C | 2+, C | NA |
| Acitretin | 2+, C | 1+, A | NA |
| Cyclosporine | 2+, C | 1+, A | 3, D |
| Adalimumab | 2+, C | 2+, C | 3, D |
| Infliximab | 2+, C | 2+, C | 3, D |
| Secukinumab | 2+, C | NA | 3, D |
| Ixekizumab | 2+, C | NA | 3, D |
| Ustekinumab | NA | 2+, C | NA |
| Guselkumab | 2+, C | 1+, A | NA |
| Etanercept | 3, D | 1+, A | NA |

MTX: methotrexate; NA: not applicable



and steroid-induced acne. Referral to a dermatologist might also address the need for urgent in-patient care—when the patient presents with generalised pustular psoriasis, erythrodermic psoriasis or acute unstable psoriasis.[36]

## Addressing poor adherence to treatment

The presence and extent of adherence should be routinely monitored by questioning the patients directly. The top 3 causes of poor adherence to topical agents for psoriasis management are low efficacy, time consumption and inadequate cosmetic characteristics.[37] Some of the strategies to improve adherence are listed below.

Patients should be provided with information about psoriasis, such as through patient information leaflets or websites, including resources like the Psoriasis Association of Singapore (http://www.psoriasis.org.sg/), DSS (https://www.dermatology.org.sg/education/ psoriasis/) and NPF (https://www.psoriasis.org/). The social impact of psoriasis should be recognised, which may include addressing emotional and psychological aspects alongside physical symptoms. Patients should be informed about the potential side effects of topical therapies. Frequent and regular follow-up visits are highly recommended, especially in the initial stage of treatment, to monitor progress, adjust the treatment plan as needed and address any concerns or issues that may arise.[38]

## Considerations in PsA

PsA, affecting approximately 20% of those with psoriasis, is a chronic inflammatory condition marked by substantial morbidity and a notable impact on quality of life.[2] Screening tools and diagnostic approaches are crucial in the effective management of PsA, facilitating early identification and appropriate referral to rheumatologists.

### *Screening tools*

Screening tools for PsA have been developed to help dermatologists identify patients for referral to rheumatologists. The Psoriasis Epidemiology Screening Tool (PEST)[39] was chosen, as it can be completed rapidly by patients and has good sensitivity.

### *Diagnosis*

There is a lack of serum biomarkers and specific laboratory tests for PsA. Erythrocyte sedimentation rate, fibrinogen levels and C-reactive protein may not always be increased, even in individuals with active disease.[40] Rheumatoid factor and anti-cyclic

citrullinated peptide antibodies are absent in about 95% of patients with PsA. If present, it is desirable to use clinical features and imaging features for differentiating PsA from rheumatoid arthritis.[41] Human leukocyte antigen (HLA)-B*27 can identify patients with psoriasis more prone to develop PsA or for the early diagnosis of PsA when inflammatory back pain is present.[42]

### *Imaging features*

Destruction of cartilage and bone along with new pathological bone formation is the hallmark of PsA on a radiograph.[41] This simultaneous joint destruction and formation is unique to PsA.

- Spondylitis and sacroiliitis in PsA can mimic ankylosing spondylitis (AS). However, the development of non-marginal syndesmophytes, unilateral sacroiliitis and asymmetry of syndesmophytes may distinguish PsA from AS.
- Ultrasonography may be performed to check for enthesitis.
- Magnetic resonance imaging may provide information on bone marrow edema in axial and peripheral structures, such as entheses, synovitis and focal erosions.

### *Referral to a rheumatologist*

Early identification and treatment of PsA can prevent irreversible joint damage. As primary care providers for patients with psoriasis, dermatologists play a pivotal role in providing holistic treatment nd, where appropriate, organising multidisciplinary care.

The following clinical features may predict more severe disease outcomes in PsA, and co-management with a rheumatologist may be considered:[43] female sex, older age at diagnosis, obesity, smoking history, longer disease duration, higher baseline disease activity (≥5 affected joints and/or elevated inflammatory markers), presence of dactylitis or nail involvement, and worse baseline physical function.

The treatment for PsA encompasses conventional step-up strategies, initially utilising topical therapies for psoriasis and conventional synthetic disease-modifying antirheumatic drugs for arthritis. However, it also includes accelerated treatment pathways, where biologic DMARDs or targeted synthetic DMARDs may be employed as first-line therapy, if accessible and deemed appropriate.[2]

A summary of recommendations for PsA screening, referral and management is presented in Table 4.[44-46]

## Psoriasis in special populations and comorbidities

### *Pregnant and lactating women*

Topical medication is usually the preferred treatment for psoriasis in pregnant and lactating women. As medications pass through the placenta and are found in breast milk in varying concentrations, they should be used with caution. Common psoriasis treatments, the descriptions of their use in pregnancy and lactation, their effects on fertility, and their earlier United States Food and Drug Administration (USFDA) categories are elaborated in Supplementary Table S2.[19-30]

Adalimumab and certolizumab may be acceptable in pregnancy, with certolizumab being the preferred biologic and safe in lactation. They may be given after consideration of the risk–benefit ratio and should be individualised.[35] If TNF-alpha inhibitors or other biolo-gic therapies (excluding certolizumab) are given after week 22 of pregnancy, live vaccines such as Bacillus Calmette-Guerin (BCG) should be delayed till after the infant is more than 6 months of age.[47]

### *Children*

Psoriasis affects around 1% of children and most commonly occurs during adolescence. Chronic plaque psoriasis is the most observed presentation in children, with sites such as the scalp, elbows and knees or skinfolds (i.e. those behind the ears, armpits and groin) being the most affected. Children with psoriasis may present with comorbidities, such as obesity, MetS and PsA.[48] Factors that are taken into account when selecting suitable treatments for psoriasis in the paediatric population are the safety profile, dosing schedule and approval of the drug in the paediatric population.

Methotrexate (MTX), cyclosporine (CyA) and acitretin, although not USFDA-approved for paediatric psoriasis, can be considered for shortterm and intermittent usage.

Combining biologics with topical corticosteroids, with or without a vitamin D analogue, is a safe option for treating moderate-to-severe plaque psoriasis in children.

Adalimumab has been approved by Singapore's Health Sciences Authority (HSA). Children aged ≥4 years and weighing ≥30 kg are initially administered a dose of 40 mg at week 0, followed by a maintenance dose of 40 mg every 2 weeks. For children weighing between 15 kg and 30 kg, the initial dose is 20 mg at week 0, followed by a maintenance dose of 20 mg every 2 weeks.[9,48]

Table 4. Summary of recommendations for psoriatic arthritis screening, referral and management.[44-46]

| Recommendations for PsA: Screening and referral | Level, grade |
|---|---|
| All patients with psoriasis should be assessed initially and then at least annually for signs and symptoms of PsA. | GPP |
| Patients with clinical predictors of worse PsA outcomes warrant more intense monitoring and treatment, including multidisciplinary care, to prevent the development of irreversible joint damage. | GPP |
| The choice of therapy should be individualised and take into consideration the chief PsA domain affected and the severity of cutaneous psoriasis. | GPP |
| **Treatment recommendations: Non-pharmacological therapies** | |
| Patient education, physical therapy, exercise, weight loss and smoking cessation are the essential and integral components of PsA management.<br>Patients with active PsA must be recommended to utilise some form of or a combination of occupational therapy, exercise and physical therapy. Low-impact exercise is preferred over high-impact exercise. | 2+, D |
| **Treatment recommendations: Pharmacological therapies** | |
| Pharmacological therapies may be classified as: | |
| csDMARDs: e.g. MTX (Level 2+, C), sulfasalazine (Level 1−, C), leflunomide (Level 2+, C) and cyclosporine (Level 2−, D) | 2+, C |
| bDMARDs: e.g. biological agents targeting cytokines, such as TNF, IL-12/23, IL-17A and IL-23 | 1+, A |
| Biologic DMARDs have higher levels of evidence compared with conventional synthetic DMARDs and are more effective, especially for axial PsA. | 1+, A |
| PDE-4 inhibitor: e.g. apremilast | 1+, A |
| Others: NSAIDs and glucocorticosteroids (intra-articular or systemic)<br>NSAIDs and intra-articular corticosteroids are useful in the treatment of PsA symptoms. | 1−, B |
| Systemic corticosteroids should only be used sparingly at the lowest dose necessary for short durations. | 1−, C |
| **Treatment recommendations according to different domains for PsA** | |
| **Peripheral arthritis**<br>• NSAIDs may be used for symptomatic relief for patients with mono/oligoarticular disease (≤4 joints) and the absence of risk factors for poor prognosis (e.g. dactylitis or joint damage).<br>• Intra-articular corticosteroids may be used as an adjunctive therapy. Systemic corticosteroids should only be administered, if absolutely necessary, for short periods of time and at the minimum dose required for efficacy (commonly <7.5 mg/day) to reduce adverse effects, including psoriasis flare upon stopping the treatment.<br>• Where there is polyarthritis (>4 joints) or the presence of poor prognostic factors, csDMARDs or bDMARDs should be used as first-line therapy or after only a short course of NSAIDs (<2 weeks). If axial or entheseal involvement is prominent, early use of bDMARDs is suggested as csDMARDs are not effective in such conditions.<br>• Among the csDMARDs, MTX is highlighted for its wide experience of use and demonstrated efficacy in control arms of multiple clinical trials of PsA. Other csDMARDs, such as leflunomide and sulfasalazine, have limited efficacy in skin psoriasis.<br>• If there is inadequate response or intolerance to an initial csDMARD or bDMARD, co-management with a rheumatologist should be considered. | 1−, B |
| **Axial PsA**<br>• NSAID monotherapy is used as first-line therapy, and the duration of treatment may be prolonged (up to 12 weeks, provided there is symptom relief by 4 weeks).<br>• csDMARDs are generally ineffective in axial disease. In the event of inadequate response to NSAIDs, it is recommended that a bDMARD be considered, which in current practice is usually a TNF inhibitor or an IL-17 inhibitor. | 1−, C |
| **Enthesitis**<br>• NSAIDs and local corticosteroid injections are first-line therapies. csDMARDs are generally not efficacious. A bDMARD may be used in case of inadequate response, intolerance or contraindication to NSAIDs. | 2++, C |
| **Dactylitis**<br>• csDMARDs and bDMARDs may be used in dactylitis. NSAIDs have not demonstrated efficacy. | 1−, C |

bDMARD: biological disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; DMARD: disease-modifying antirheumatic drug; GPP: good practice points; IL: interleukin; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; PDE-4: phosphodiesterase-4; PsA: psoriatic arthritis; TNF: tumour necrosis factor

Secukinumab has demonstrated high efficacy in alleviating skin symptoms and enhancing the health-related quality of life in paediatric patients (aged 6 to 17 years)[3] with severe chronic plaque psoriasis while maintaining a favourable safety profile.[49] For plaque psoriasis treatment in paediatric patients aged 6 years and above, the subcutaneous administration of the drug dose based on weight is recommended. Injections should be given at weeks 0, 1, 2, 3 and 4, followed by every 4 weeks thereafter. Patients weighing less than 50 kg (when dosing) should receive a dose of 75 mg. Patients weighing 50 kg or more (when dosing) should receive a dose of 150 mg, which may be increased to 300 mg monthly.[49,50]

Ixekizumab, which targets interleukin (IL)-17A selectively, can be used in paediatric patients (aged 6 to <18 years) with moderate-to-severe psoriasis.[51] It shows a similar safety profile to that of adults. Patients weighing over 50 kg should receive a recommended dose of 160 mg (2 80 mg injections) at week 0, followed by a dose of 80 mg every 4 weeks. Patients weighing between 25 kg and 50 kg are recommended a dose of 80 mg at week 0, followed by a dose of 40 mg every 4 weeks.[51,52] Ustekinumab can be administered subcutaneously (60 kg: 0.75 mg/kg/dose; 60 kg to ≤100 kg: 45 mg; 100 kg: 90 mg) at weeks 0 and 4, and then every 12 weeks, in children aged 12 to 17 years for the treatment of psoriasis.[21,53,54]

### *Elderly*

Comorbidities, such as hyperlipidaemia, hypertension and type 2 diabetes, are more common in elderly patients. Therefore, the utilisation of systemic therapies may be restricted in this population. Drug interactions can also occur between psoriasis drugs, and concomitant medications can precipitate or aggravate psoriasis.[55,56]

The primary goals are to clinically control the disease with safe and tolerable treatment modalities, satisfy patients' expectations and improve their quality of life. Topical corticosteroids and topical vitamin D analogues are first-line treatments for mild psoriasis under appropriate guidance.[55] Caution must be exercised with topical corticosteroids due to their known cutaneous side effects.[55]

Narrow-band UVB, acitretin, MTX and biologics are advised as first-line treatment options in elderly patients with extensive psoriasis. Newer IL-23 and IL-17 therapies with higher efficacy are other promising options for the elderly.[56]

Dermatological drugs mainly excreted by the kidneys (e.g. MTX) may be eliminated more slowly in the elderly. Therefore, it is desirable to consider a dose reduction. MTX is also hepatotoxic, and caution must be exercised while prescribing this drug in the elderly.[55] In case of extensive disease, CyA is preferred as a second-line systemic treatment.[55]

Despite the availability of many effective systemic treatments for psoriasis, deciding the treatment approaches for specific populations with psoriasis, such as patients with TB, HIV, hepatitis, malignancies or surgical patients, can be challenging. These groups are typically not included in clinical trials, and very few up-to-date reviews on psoriasis management in these populations are available.

### *TB*

Patients with psoriasis on treatment with immunosuppressant medications are at a high risk of activating latent TB infection (LTBI). However, acitretin is well-tolerated in patients with LTBI.[10]

The gap between the initiation of biologic therapy for psoriasis and the development of clinical signs of TB or the confirmation of TB diagnosis may range from 3 to 12 months.[57] If the screening result or TB status is unclear or LTBI is suspected, therapy with biologics should not be initiated without consultation with a relevant physician (e.g. physicians specialising in infectious or respiratory diseases). The 2 preferred regimens for the treatment of TB infection in adults are rifampicin daily for 4 months (4R), or isoniazid daily for either 6 or 9 months (6H/9H).[58] Treatment with a biologic may be initiated as early as possible, typically 1 month after initiating prophylaxis for TB. If there is a suspicion of TB reactivation that is justified or a new infection during biologic therapy, the interferon-gamma release assay and chest X-ray should be repeated.

Treatment with TNF-α inhibitors and ustekinumab can be considered in individuals with LTBI after appropriate TB prophylaxis.[59] The risk of TB reactivation in patients with psoriasis and LTBI remains less with the use of IL-17 or IL-23 inhibitors. Hence, in cases where concerns about TB reactivation arise, prioritising IL-17 or IL-23 inhibitors over TNF-α inhibitors is recommended.[6]

### *HIV infection*

Fundamental therapy of HIV with antiviral medications, such as highly active antiretroviral therapy (HAART), may have additional beneficial effects on dermatological lesions, such as complete or nearly complete symptom clearance in up to 90% of patients with HIV-associated psoriasis. Immunocompetent HIV patients may be treated with nearly all the therapeutic agents that can be used in an HIV-negative psoriasis patient provided there are no adverse interactions with HAART, if any. Treatment options include topicals (Level 1+,

A), phototherapy (Level 2+, B), retinoids (Level 3, B), MTX (Level 4, D), CyA (Level 4, D) and biologics (Level 3, B).

## Hepatitis

### *Hepatitis B*

Screening should be done for Hepatitis B surface antigen (HBsAg) before starting the treatment with MTX, CyA and biologics in patients with psoriasis; screening for anti-HB antibodies is recommended. Patients should not be managed with immunosuppressive therapies in the acute hepatitis stage. However, treatment with biologics may be considered in patients presenting with resolved or chronic hepatitis under close supervision and in consultation with a gastroenterologist.

#### ***Recommendations for HBsAg-positive patients with psoriasis***

It is advisable to avoid administering biologics to patients who are positive for HBsAg. Topicals, phototherapy, acitretin and apremilast should be considered. The screening for hepatitis B and C is not required for the initiation of apremilast, but drug cost and access may be prohibitive. Considerations for starting oral agents and biologics should be in consultation with gastroenterology. Input is required for choice of drug due to individual risk of liver fibrosis (e.g. acitretin),[60] hepatitis B reactivation risk, comorbidities and initiation of prophylaxis if indicated. Inactive HBV carriers (HbsAg-positive, HBcAb-positive, HBV DNA<2000 IU/mL, acceptable transaminases) may be started on biologics with lower risk of HBV reactivation under prophylactic anti-HBV therapy.[61] Antiviral therapy is suggested to commence either at the same time or 1 to 2 weeks before biologics.[7] Reactivation of the HBV typically manifests during immune reconstitution, necessitating the continuation of antiviral therapy for 6 to 12 months following the cessation of immunosuppression.[61] Prophylaxis is recommended with close monitoring through laboratory tests, including assessments of liver function and HBV DNA viral load.

Among HBsAg-positive patients, acitretin, apremilast,[61] IL-17 inhibitors and IL-23 inhibitors[60] are considered low-risk for HBV reactivation (<1%) but still require monitoring for viral reactivation with transaminases and HBV DNA.[61] Higher potency TNF inhibitors (infliximab, adalimumab, certolizumab[62]) are considered high risk for reactivation (>10% risk level); ustekinumab,[63] etanercept[62] and cyclosporine[61] are moderate risk (1%–10%). While the use of MTX and CyA is contraindicated or relatively contraindicated in most guidelines, acitretin may be used along with monitoring of LFTs.

#### ***Recommendations for anti-HBc-positive patients with psoriasis***

Before initiating treatment with CyA and biologics in patients with past hepatitis B exposure (anti-HBc-positive, HBsAg-negative patients), screening for HBV DNA load is recommended. The risk of reactiva-tion for anti-HBc-positive, HBsAg-negative and HBV DNA-negative patients is lower than for HBsAg-positive patients. Such patients treated with TNF-α inhibitors, ustekinumab and CyA are associated with a moderate risk of HBV reactivation and should be monitored with transaminases and HBV DNA. MTX, acitretin or apremilast are associated with a minimal risk of reactivation and thus do not necessitate anti-HBV therapy. Patients on biologics and cyclosporine should be offered gastroentero-logy review with the option of antiviral prophylaxis on a case-by-case basis.

### ***Hepatitis C***

About 80% of patients with acute hepatitis C may develop chronic hepatitis C infection, defined as detectable viral replication for at least 6 months. [60] Liver enzymes could be normal in around 50% of patients with chronic hepatitis C. Recommendations for the management of these patients include serology before the initiation of treatment with MTX, acitretin, CyA and biologics and consultation with a gastroenterologist. Oral direct-acting antivirals are safe and effective treatment against hepatitis C and have high rates of sustained virological response.[64] Apremilast and IL-17 inhibitors seem to have a favourable safety profile for psoriasis. However, data are scarce, including data on the safety of IL-23 inhibitors in patients with hepatitis. MTX should be avoided in patients with chronic hepatitis. CyA use in chronic hepatitis is not well established.[57,59]

### ***MetS (hypertension/hyperlipidaemia/diabetes mellitus/obesity)***

Beyond dermatological symptoms, systemic inflammation observed in psoriatic patients contributes to the phenomenon known as the psoriatic march. This suggests that inflammatory processes extending from the skin to systemic levels in psoriatic patients may trigger immune-mediated changes, leading to significant comorbidities, such as metabolic disorders (including obesity, hypertension and dyslipidaemia) and CVDs.[11]

The occurrence of MetS is potentially 3-fold higher among individuals with psoriasis than in the overall populace, potentially influencing the preferred treatment options for specific patients.[8]

Multiple studies have identified a strong association between psoriasis and CVD. The American Heart Association and the American College of Cardiology have classified psoriasis as a condition that enhances the risk of atherosclerotic CVD. Annual metabolic screening for blood glucose or glycated haemoglobin, lipid levels, blood pressure and obesity (body mass index and/or waist circumference) should be included as part of the dermatological follow-up for patients with psoriasis. In addition, patient education regarding the cardiovascular risks associated with psoriasis should be provided during their follow-up appointments. Patients with diagnosed metabolic disorders or smoking should be advised on risk factor modification and to attain treatment targets.[8]

### *Malignancy*

As several systemic therapies indicated in psoriasis are associated with an elevated risk of de novo or reactivated malignancies, caution is needed while choosing a therapeutic option for patients with a history of solid tumours. The staging and type of cancer, the burden of psoriasis, and the risk of recurrence of melanoma skin cancer and non-melanoma skin cancer (NMSC) have been recently diagnosed. Phototherapy (UVB 308 nm, UVB 311 nm), topical therapy and/or therapy with acitretin are recommended.[57] Preventative effects are observed with acitretin on NMSC. Thus, they are preferred in patients with an elevated risk for skin cancers. If possible, it is desirable to avoid CyA and MTX in this kind of setting.[65] It is also advised to avoid biologics in patients with a recent or recurrence of malignancy unless the likelihood of cure is high (including adequately treated NMSC) and/or the malignancy was diagnosed and managed more than 5 years ago. If the malignancy is less than 5 years post-remission, biologics should be considered in consultation with an oncologist.

### *Surgery*

The likely advantage of postoperative infection prevention by the discontinuation of psoriasis treatment needs to be balanced with the risk of a psoriatic flare (Level 4, Grade D, good practice

Table 5. Summary of treatment recommendations in patients with comorbidities and on delivery of care, and social and psychological aspects of psoriasis.[36,66,67]

| **Recommendations for patients with psoriasis with a risk of comorbid conditions** | **Level, grade** |
|---|---|
| Psoriatic arthritis should be considered in all patients with cutaneous psoriasis. Patients with signs and symptoms suspicious of psoriatic arthritis must be completely evaluated for psoriatic arthritis. | 3, B |
| Patients with psoriasis must be screened actively for cardiovascular risk factors. | 2–3, B |
| Patients with moderate-to-severe psoriasis should have their obesity status determined according to the national guidelines. | 2–3, B |
| Patients with psoriasis should be actively screened for metabolic syndrome and its components by an appropriate healthcare professional according to the national guidelines. | 2–3, B |
| **Recommendations for patients with psoriasis with comorbid conditions** | |
| Obese and overweight patients with psoriasis should be counselled regarding weight loss and the impact of weight on psoriasis severity as well as on the treatment response. | 2–3, D |
| Acitretin and MTX should be used with caution in patients with psoriasis having liver disease. | 4, D |
| Patients with IBD must avoid interleukin-17 inhibitor therapy. | 1–3, C |
| Lifestyle interventions, such as smoking cessation and weight loss, should be encouraged in patients with psoriasis who are current smokers or are obese. A referral for smoking cessation or weight management programmes may be considered if appropriate. | 4, D |
| **Recommendations on delivery of care and social and psychological aspects of psoriasis** | |
| Patients with acute unstable psoriasis, erythrodermic psoriasis and generalised pustular psoriasis should be urgently referred to a dermatologist for consideration of inpatient management. | 4, D (GPP) |
| Patients must be provided clear instructions regarding the use of topical agents and therapeutic education to improve adherence. | 1+, A |
| Patients with psoriasis should be followed up regularly and frequently, especially in the initial stages of treatment. | 2+, C |

GPP: good practice points; IBD: inflammatory bowel disease; MTX: methotrexate

Table 6. Treatment recommendations for children with psoriasis.[48]

| Topical treatments and phototherapy: Treatment recommendations |
|---|
| • An ointment of tacrolimus 0.1% may be recommended as an off-label use monotherapy for paediatric psoriasis of the genital region and the face. |
| • A combination of betamethasone dipropionate 0.064% and calcipotriol 0.005% is recommended in patients ≥12 years of age for scalp and body psoriasis. |
| • Calcipotriol may be recommended as an option for the management of childhood plaque psoriasis. However, its application is not recommended in large body surface areas. |
| • Rotational therapy with topical corticosteroids, tar-based therapies, emollients, topical calcineurin inhibitors and topical vitamin D analogues can be considered to avoid the adverse effects of continuous long-term steroid-based therapy. |
| • Coal tar preparations when combined with other topical therapies or as monotherapy may be used. |
| • Narrow-band UVB may be recommended as an option to manage guttate psoriasis and moderate-to-severe paediatric plaque. |
| **Nonbiologic systemic treatments: Treatment recommendations** |
| • MTX may be the recommended systemic therapy effective in managing moderate-to-severe plaque psoriasis and other subtypes in children. |
| • Cyclosporine may be the recommended effective systemic therapy in moderate-to-severe plaque psoriasis in children. However, during treatment, it is recommended to monitor the blood pressure routinely. |
| • Acitretin may be recommended as an effective, non-immunosuppressive systemic therapy for children with extensive guttate or moderate-to-severe psoriasis vulgaris and pustular psoriasis. However, caution should be exercised while administering long-term acitretin therapy to children because of the decreased bone mineral density, formation of periosteal bone, calcification of anterior spinal ligaments, hyperostosis resembling diffuse idiopathic skeletal hyperostosis, and potential risk of premature epiphyseal closure. |
| **Biologic therapy: Treatment recommendations** |
| • Adalimumab 0.8 mg/kg (maximum, 40 mg) may be administered at weeks 0 and 1 and every other week, off-label, to effectively manage adolescents and children with moderate-to-severe psoriasis. |
| • Infliximab 3.3–5 mg/kg may be administered at weeks 0, 2 and 6 and then every 8 weeks in combination with MTX or as monotherapy, for off-label use, in the case of severe plaques or pustular psoriasis in the paediatric population. |
| • Alternative biologics include ustekinumab, secukinumab, ixekizumab and etanercept. |

MTX: methotrexate; UVB: ultraviolet B



points). In the case of minor surgeries, such as those involving skin or dental structures, any treatment that is systemic may be continued. Before major surgeries, it is desirable to discontinue treatment with systemic immunosuppressives and restart in the absence of postoperative infection.[21] Stopping biologics, in consultation with the surgeon, should also be considered. If there is an intent for the biologics to be eliminated from the system, it should be stopped for at least 2 to 5 half-lives before the surgery and each patient profile and associated morbidity must be considered.[21]

Table 5 presents the summary of recommendations for patients with psoriasis with a risk of comorbidities and patients with psoriasis with comorbid conditions, as well as delivery of care and social and psychological aspects of psoriasis.[36,66,67] Table 6 presents the summary of treatment recommendations for children with psoriasis.[48]

## Considerations for vaccination

While on treatment with systemic immunosuppressants/biologics, vaccination requires special care. Vaccine counselling is an essential component of the treatment plan for psoriasis. Patients should be up-to-date on all immunisations, as recommended by local guidelines.[68]

The following groups should not receive live vaccines:[30] (1) patients on systemic immunosuppressants/biologics, and (2) infants up to 6 months of age whose mothers had received biologic treatment beyond 22 weeks of gestation (except certolizumab).[47]

If live vaccination is needed, then it should be administered after stopping the biologics therapy for at least 3 half-lives. Live attenuated zoster vaccine should not be given while on biologics. The recombinant zoster vaccine (SHINGRIXÔ), an inactivated vaccine, can be given while on biologics. In general, systemic immunosuppressants/biologic treatment can be started at least 4 weeks after the administration of a live vaccine.[36] Recommendations on when to administer live vaccines based on biological half-life are given in Supplementary Table S3.[30]

Inactivated vaccines can be given while on systemic immunosuppressants/biologics and, where possible, may be given at least 2 weeks before initiation for an optimal immune response. Response to vaccines is normal or slightly impaired while

on systemic immunosuppressants/biologics.[36] Live vaccines are to be avoided during systemic immunosuppressants/biologic treatment, including measles–mumps–rubella vaccination, varicella, rotavirus, BCG, yellow fever, oral typhoid and oral polio.[53]

## Limitations of guidelines

These guidelines represent the best evidence at the time the project commenced. The field of therapeutics for psoriasis is rapidly advancing, and the findings from forthcoming studies may necessitate altering the recommendations mentioned in this report.

Treatment should be tailored to individual patients and their specific circumstances. It may be necessary to deviate from these guidelines in specific patients or in special circumstances. Adherence to guidelines may not serve as a defence in a negligence claim. Similarly, deviation from the recommendations should not be considered as negligence.

These guidelines take into consideration the financial implications of treatment, medical assistance and funding. However, there may be changes in these schemes, the clinical evidence surrounding these medications, and side effect profiles when more data emerge.

Guidelines are based on a literature search until December 2019, supplemented with key updates till 31 December 2023. However, newer biologics (guselkumab, risankizumab and spesolimab) and oral deucravacitinib were not included as they received HSA approval after the 2019 literature review and not included as part of the consensus voting and discussion. Published data beyond this date may be a topic for consideration in future guidelines.

## CONCLUSION

The practical guidelines developed by the members of the DSS Psoriasis Therapeutic Guidelines Workgroup outline evidence-based recommendations in an easy-to-read format. This can help prescribing dermatologists in achieving good outcomes when managing their patients.

### *Supplementary materials*

*Table S1. SIGN grading system: 1999–2012.*[18]

*Table S2. Common topical and nonbiologic systemic psoriasis medications and description for their use along with their earlier FDA categories.*[19-30]

*Table S3. Recommendations on when to administer live vaccine based on half-lives of biologics.*[30]

*Fig. S1. Flowchart explaining the process followed in formulating the guidelines.*

### *Declaration*

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LETTER TO THE EDITOR

# Assessing the accuracy and consistency of generative pretrained transformers in assigning Eastern Cooperative Oncology Group performance status

Chun En Yau[*1], Qihuang Xie[*2], Ren Yi Jonas Ho[3] *MRCP*, Chun Yi Yau[1] *MBBS*, Elaine Guan[1], Dawn Yi Xin Lee[4], Xinyan Zhou[1], Gerald Gui Ren Sng[5] *MRCP*, Joshua Yi Min Tung[6] *MRCS*, Andrew Fu Wah Ho[7,8] *PhD*, Ryan Shea Ying Cong Tan[**9,10] *MRCP*, Daniel Yan Zheng Lim[**3,11] *MRCP*

Dear Editor,

The Eastern Cooperative Oncology Group (ECOG) is a commonly used performance status (PS) scale in oncology. It influences cancer treatment decisions and clinical trial recruitment. However, there can be significant inter-rater variability in ECOG-PS scoring, due to subjectivity in human scoring and innate cognitive biases.[1,2] We propose that generative pretrained transformers (GPT), a foundational large language model (LLM), can accurately and reliably score ECOG-PS.

We used 16 fictional scripts (Supplementary Table S1, Set 1) from studies by Datta et al. and Azam et al., both of which assessed the inter-rater reliability of ECOG-PS scoring by oncology health professionals.[2,3] We used the OpenAI Action Programming Interface to query the GPT-3.5-turbo model with the scripts. A standardised prompt (I would like you to assume the role of an oncologist. You will review the patient case history that I give you and score the ECOG score) was used. No further instructions were provided. We queried GPT-3.5-turbo with 16 scenarios sequentially. Each scenario was reassessed for 50 iterations, and all outputs were captured and documented precisely. For the 12 scenarios from Datta et al., the most appropriate ECOG score for each vignette was decided in the original study through consensus rating among the 3 oncologists who designed the vignettes. Any discrepancy in the ratings was resolved through feedback and discussion. For the scenarios from Azam et al., the original study did not provide a gold standard ECOG score for each of the 4 vignettes. Thus, the most appropriate ECOG score was determined by an author of the current study, RSYCT, a consultant oncologist. We did an initial qualitative appraisal of the interpretability and validity of the responses. We then quantitatively assessed the accuracy (percentage correct ECOG-PS) and consistency (Fleiss' kappa[4]) of the responses. GPT's scores were compared with human scores using the Mann-Whitney U test. The cut-off for statistical significance was set at $P<0.001$ (after Bonferroni correction).

Since GPT pretraining data used text corpora before 2021, there is a possibility that the original vignettes were included as pretraining data. Thus, we also assessed GPT responses to modified versions of the vignettes. We created 2 new sets of vignettes (Supplementary Table S1, Sets 2–3), with 1 set paraphrasing the script and another modifying numerical values. We ensured that the textual and numerical changes did not change the overall ECOG-PS for both sets.

Qualitatively, GPT yielded clear, comprehensible answers in response to all scripts. A single valid ECOG-PS was assigned for all the scenarios. Although unprompted, GPT further justified the ECOG-PS assigned in all cases. All script responses were reviewed qualitatively and summarised (Supplementary Table S2).

Notably, it demonstrated the ability to distinguish between a patient's functional ability for activities of daily living and their ability to perform work





[1] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2] Department of Pharmacy, National University of Singapore, Singapore
[3] Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore
[4] School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, United Kingdom
[5] Department of Endocrinology, Singapore General Hospital, Singapore
[6] Department of Urology, Singapore General Hospital, Singapore
[7] Department of Emergency Medicine, Singapore General Hospital, Singapore
[8] Pre-Hospital and Emergency Research Centre, Duke-NUS Medical School, Singapore
[9] Division of Medical Oncology, National Cancer Centre, Singapore
[10] Duke-NUS Medical School, Singapore
[11] Medicine Academic Clinical Programme, Duke-NUS Medical School, Singapore
* Joint first authors
** Joint last authors
Correspondence: Dr Daniel Yan Zheng Lim, Department of Gastroenterology and Hepatology, Singapore General Hospital, Outram Road, Singapore 169608.
Email: limyzd@gmail.com
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activities, which is important in differentiating ECOG-PS scores of 1 and 2. Furthermore, some responses displayed a level of inference of how a patient's symptoms might impact function, as shown in Supplementary Fig. S1, in which ascites and pedal oedema were inferred to contribute to limited mobility. Hallucination was observed in a few cases. This included a few instances of misinterpretation of the prompt. For instance, 1 case in which the patient's work activity of running a store was not considered, and she was given a score of ECOG-PS 3 (Supplementary Fig. S2).

GPT scored ECOG-PS correctly more often than human raters (Table 1). The difference in performance was statistically significant in 7 scripts (44%). Ten scripts (63%) had ≥90% correct scores. GPT had excellent consistency, with Fleiss' kappa of 0.785 on Datta et al.'s scripts and 0.739 on Azam et al.'s. Conversely, human raters had less consistency, with kappa of 0.167 on Datta's scripts (Azam et al. did not report a kappa value). There was no substantial difference between the GPT responses on the original scripts (Set 1) and the modified scripts (Sets 2–3) for most cases (Supplementary Tables S3–S4). For the cases with a difference in performance, there were more correct responses on the variant scripts. Only patient 5 in Azam et al. had a decline in performance on the variant scripts. The consistency of GPT on variant scripts remained excellent (Fleiss' kappa: set 2 Datta et al., 0.776; set 3 Datta et al., 0.771; set 2 Azam et al., 0.843; set 3 Azam et al., 0.665).

To the authors' knowledge, this is the first study to examine whether GPT can be used to determine the ECOG-PS and compare its performance to human raters. Our results show that GPT performs ECOG-PS scoring more accurately and consistently than human raters in fictional patient scripts. GPT performed comparably to human raters on Set 1 in cases 2, 4, 7, 8, 9, 10 and 12. It also had significantly more correct responses in cases 1, 3, 5, 6 and 11 than human raters who had considerable experience in oncology (mean = 4.4 ± 4.2 years, >80% having at least 1 year of experience in Datta et al.).

Apart from assigning ECOG-PS with greater accuracy, our results demonstrate that GPT can consistently determine ECOG-PS with high inter-rater reliability across 3 sets of fictional scripts (kappa >0.7). Our results also suggest a good basic performance level of GPT that could be improved with task-specific fine-tuning.

Important limitations of this study include the fact that GPT is a general language model not specifically trained for ECOG-PS scoring. At the time of writing, newer models such as GPT-4-turbo had not been released, and they were not assessed in this study. The quality information on ECOG in the underlying pretraining data of GPT is not public and cannot be independently verified. However, the relatively good performance in this study suggests that GPT processes this area of medicine well. Another limitation is that ECOG scores are subjective assessments dependent on the experience and opinion of the rater. While we have attempted to assign the most appropriate ECOG score by using consensus scoring and expert opinion from an experienced oncologist, they remain subjective measures of PS. Currently, only the zero-shot prompting technique was experimented. However, if necessary, LLM effectiveness may be enhanced through various prompting techniques and fine-tuning. Some prompting techniques that can be explored in future work range from in-context learning examples,[5] to more intricate methods like the chain-of-thought,[6] and even a prompting technique (MedPrompt) that yielded comparable performance in answering medical school examination questions to LLM pretrained on medical text.[7] We also recognise that our study was performed on a small set of fictional patient scenarios. Future work should examine scoring on actual patient clinical notes with concurrent human evaluation (including clinicians across the spectrum of experience and practices) to better assess the capabilities of LLMs. With more refinements to LLM algorithms, training data and interpretability, LLM-determined clinical scoring may become even more consistent and can be used as a useful adjunct to counterpoise human bias for such scoring in the future.



### *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. Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this research.*

***Keywords:*** *cancer, ChatGPT, ECOG, large language model, performance status*

Table 1. Comparison of GPT and human rater responses on original scripts provided in Datta et al. and Azam et al. [2,3]

| Source | Patient | ECOG PS | | | | | Most common ECOG PS | Suggested answer[a] | Accuracy (% correct) | *P* value[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | | | | |
| Datta et al. | 1 | 12 | 45 | 14 | 1 | 0 | 1 | 2 | 19.4 | Ref |
| GPT | | 0 | 2 | 48 | 0 | 0 | 2 | 2 | 96.0 | <0.001* |
| Datta et al. | 2 | 3 | 14 | 35 | 20 | 0 | 2 | 3 | 27.8 | Ref |
| GPT | | 0 | 0 | 50 | 0 | 0 | 2 | 3 | 0.0 | 0.632 |
| Datta et al. | 3 | 6 | 10 | 21 | 30 | 5 | 3 | 2 | 29.2 | Ref |
| GPT | | 0 | 13 | 37 | 0 | 0 | 2 | 2 | 74.0 | <0.001* |
| Datta et al. | 4 | 11 | 28 | 30 | 3 | 0 | 2 | 2 | 41.7 | Ref |
| GPT | | 0 | 48 | 2 | 0 | 0 | 1 | 2 | 4.0 | 0.003 |
| Datta et al. | 5 | 3 | 22 | 23 | 22 | 2 | 2 | 2 | 31.9 | Ref |
| GPT | | 0 | 0 | 20 | 30 | 0 | 3 | 2 | 40.0 | <0.001* |
| Datta et al. | 6 | 0 | 1 | 0 | 17 | 54 | 4 | 3 | 23.6 | Ref |
| GPT | | 0 | 0 | 3 | 46 | 1 | 3 | 3 | 92.0 | <0.001* |
| Datta et al. | 7 | 1 | 12 | 24 | 31 | 4 | 3 | 2 | 33.3 | Ref |
| GPT | | 0 | 0 | 50 | 0 | 0 | 2 | 2 | 100.0 | 0.001 |
| Datta et al. | 8 | 1 | 15 | 20 | 31 | 5 | 3 | 2 | 27.8 | Ref |
| GPT | | 0 | 0 | 45 | 5 | 0 | 2 | 2 | 90.0 | 0.033 |
| Datta et al. | 9 | 8 | 41 | 21 | 2 | 0 | 1 | 1 | 56.9 | Ref |
| GPT | | 0 | 49 | 1 | 0 | 0 | 1 | 1 | 98.0 | 0.02 |
| Datta et al. | 10 | 21 | 39 | 7 | 5 | 0 | 1 | 1 | 54.2 | Ref |
| GPT | | 0 | 49 | 0 | 0 | 1 | 1 | 1 | 98.0 | 0.09 |
| Datta et al. | 11 | 1 | 2 | 24 | 39 | 6 | 3 | 3 | 16.7 | Ref |
| GPT | | 0 | 0 | 0 | 49 | 1 | 3 | 3 | 98.0 | <0.001* |
| Datta et al. | 12 | 0 | 26 | 31 | 12 | 3 | 2 | 1 | 36.1 | Ref |
| GPT | | 0 | 3 | 47 | 0 | 0 | 2 | 1 | 6.0 | 0.248 |
| Azam et al. | 1 | 4 | 18 | 25 | 1 | 0 | 2 | 2 | 54.3 | Ref |
| GPT | | 0 | 0 | 50 | 0 | 0 | 2 | 2 | 100.0 | <0.001* |
| Azam et al. | 2 | 0 | 2 | 28 | 8 | 0 | 2 | 2 | 56.0 | Ref |
| GPT | | 0 | 20 | 30 | 0 | 0 | 2 | 2 | 60.0 | <0.001* |
| Azam et al. | 3 | 0 | 1 | 12 | 33 | 1 | 3 | 3 | 66.0 | Ref |
| GPT | | 0 | 0 | 2 | 48 | 0 | 3 | 3 | 96.0 | 0.004 |
| Azam et al. | 4 | 0 | 1 | 7 | 19 | 14 | 3 | 3 | 38.0 | Ref |
| GPT | | 0 | 0 | 1 | 49 | 0 | 3 | 3 | 98.0 | 0.088 |

ECOG: Eastern Cooperative Oncology Group; GPT: generative pretrained transformers; PS: performance status
[a] based on the original description by Datta et al.
[b] Mann-Whitney U-test for differences in score distribution

***Supplementary materials***

*Fig. S1. Example prompt and response from GPT.*

*Fig. S2. A response with erroneous score by GPT.*

*Table S1. Set 1 (original vignettes by Datta et al. and Azam et al.), Set 2 (vignettes with variation in language) and Set 3 (vignettes with variation in numeric values).*

*Table S2. Qualitative summary of GPT's responses (compiled from Sets 1, 2 and 3).*

*Table S3. Comparison of GPT responses for Sets 1, 2 and 3 using the patient vignettes provided in Datta et al.*

*Table S4. Comparison of GPT responses for Sets 1, 2 and 3 using the patient vignettes provided in Azam et al.*

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LETTER TO THE EDITOR

# Evaluating the role of technology in disseminating education to patients with chronic kidney disease

Hui Boon Tay[1] *MRCP*, Terina Ying Ying Seow[1] *MD*, Chun Fan Lee[2] *PhD*, Lee Ying Yeoh[1] *FRCP*

Dear Editor,

The optimal management of chronic kidney disease (CKD) requires lifestyle changes and adherence to long-term medications. Knowledge is a component of health literacy and is needed for self-management. Limited health literacy can lead to negative outcomes, such as adverse clinical events and mortality.[1]

Using technology to improve patients' knowledge and self-management skills through websites or mobile applications is an attractive option. It may engage patients better[2] and is an efficient mode of delivery from a systems point of view. However, for it to be used effectively, patients need to have the necessary electronic health literacy skills. Electronic health (eHealth) literacy has been defined as the ability to seek, find, understand and appraise health information from electronic sources, and apply the knowledge gained to address or solve a health problem.[3] We aimed to evaluate eHealth literacy and receptiveness to education via electronic means among CKD patients.



A cross-sectional survey of 100 male and 100 female outpatients with CKD attending renal clinics at Sengkang General Hospital was conducted from February to June 2022. All patients attending the clinics were screened for eligibility and informed consent was obtained. Patients included in the study had to have a diagnosis of CKD and understand English or Chinese. The survey comprised questions on use of technology, assessment items from the validated eHealth Literacy Scale (eHEALS) and questions on patient preference of modality for CKD education. eHEALS is an 8-item scale used to measure knowledge, comfort and perceived skills at finding, evaluating and applying electronic health information to health problems,[4] and was used to assess participants' eHealth literacy in this study. The cut-off score indicating adequate eHealth literacy has varied in literature, with the score of ≥26 used in some Singapore studies on patients with chronic diseases and notably, the score of ≥32 in a previous study on CKD patients.[5-8] Survey questions on the use of technology and patient preference of modality for CKD education were drafted in English by the investigators, piloted among staff and translated into Chinese. The options of education modalities included a renal coordinator in person, a renal coordinator by video consult, leaflet, website or mobile application. Patients were allowed to select all options that they preferred and were asked to indicate which their top choice was of the selected options. Demographic data, cause of CKD, relevant past medical history, dialysis dependence, details of renal visits, renal function, haemoglobin A1C and body mass index readings were also extracted from electronic medical records. Study data were collected and managed using electronic data capture tools hosted at Sengkang General Hospital. The study protocol was approved by the SingHealth Institutional Review Board (CIRB Ref No: 2021/2636) and all participants provided written informed consent.

Logistic regression was used to model receptiveness of education via electronic means, to age, education level, eHEALS score and use of internet on the phone. Factors adjusted for included sex, ethnicity, cause of CKD, diabetes, hypertension, heart disease, and exposure to renal coordinator education. Taking into consideration the Bonferroni correction, $P<0.01$ was taken as the threshold of significance.

In total, 200 renal patients with a median age of 56.5 (interquartile range [IQR] 44.5–68) years were surveyed. Patient characteristics are summarised in Table 1. Median estimated glomerular filtration rate (eGFR) was 30 mL/min/1.73 m$^2$ (IQR 14–54) with 51% of patients in CKD stages 1–3. There were 22.5% patients who were on dialysis at the time of the study, while 38.5% were not aware of their diagnosis of CKD. The median eHEALS score was 29 (IQR 24–32), and 194 (97%) participants had mobile phones with 158 (79%) using the internet on them. Email use was noted for 137 (68.5%) participants.



[1] Department of Renal Medicine, Sengkang General Hospital, Singapore
[2] Centre for Quantitative Medicine, Duke-NUS Medical School, Singapore
Correspondence: Dr Hui Boon Tay, Department of Renal Medicine, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886.
Email: tay.hui.boon@singhealth.com.sg
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Table 1. Patient characteristics of the renal cohort surveyed (n=200).

| Patient characteristics | |
|---|---|
| Age, median (IQR), years | 56.5 (44.5–68) |
| Sex, no. (%) | |
| Male | 100 (50) |
| Female | 100 (50) |
| Ethnicity, no. (%) | |
| Chinese | 122 (61) |
| Malay | 48 (24) |
| Indian | 21 (10.5) |
| Others | 9 (4.5) |
| Education level, no. (%) | |
| Up to Primary | 37 (18.5) |
| Secondary | 87 (43.5) |
| Tertiary | 75 (37.5) |
| Did not report | 1 (0.5) |
| Employment status, no. (%) | |
| Employed | 106 (53) |
| Professional | 65 (32.5) |
| Non-professional | 38 (19) |
| Unemployed | 36 (18) |
| Retired | 58 (29) |
| Cause of chronic kidney disease, no. (%) | |
| Diabetes | 85 (42.5) |
| Hypertension | 34 (17) |
| Glomerulonephritis | 48 (24) |
| Polycystic kidney disease | 4 (2) |
| Others | 29 (14.5) |
| Comorbidities, no. (%) | |
| Diabetes | 106 (53) |
| Hypertension | 169 (84.5) |
| Heart disease | 52 (26) |
| Dialysis, no. (%) | 45 (22.5) |
| Haemodialysis | 36 (18) |
| Peritoneal dialysis | 9 (4.5) |
| Clinic visit type, no. (%) | |
| New case | 14 (7) |
| Follow up | 186 (93) |
| Renal coordinator counselling, no. (%) | |
| Done | 78 (39) |
| Not done | 122 (61) |
| eGFR (mL/min/1.73 $m^2$), median (IQR) | 30 (14–54) |
| CKD stage, no. (%) | |
| 1 | 20 (10) |
| 2 | 24 (12) |
| 3 | 58 (29) |
| 4 | 44 (22) |
| 5 | 53 (26.5) |
| Data not available | 1 (0.5) |
| eHEALS score, median (IQR) | 29 (24–32) |

CKD: chronic kidney disease; eHEALS: eHealth Literacy Scale; eGFR: estimated glomerular filtration rate; IQR: interquartile range

The top modality preferred for CKD education was for education by a renal coordinator in person (66.5%). Overall, 94 (47%) participants were receptive to education by electronic means (website or mobile application), though only 19.5% chose it as their top choice. Education by leaflet was the least popular choice (2%).

Older participants were less likely to be receptive to education by electronic means (odds ratio [OR] 0.95, 95% confidence interval [CI] 0.91–0.98, *P*=0.003). Participants with higher eHealth literacy were more likely to be receptive to education by electronic means (OR 1.14, 95% CI 1.05–1.23, *P*=0.001). Education level and internet use on phone were not associated with receptiveness to education by electronic means.

Our study findings on eHealth literacy with a median eHEALS score of 29 are similar to those from a study on digital health literacy among adults living in the community in Singapore,[7] which reported a mean eHEALS score of 29.4. As eHEALS scores of ≥26–32 have been used in other studies to indicate adequate eHealth literacy,[5-8] this may be considered adequate, though higher scores would be ideal. Participants reported high access to technology and were generally receptive to education by electronic modes, though they still preferred face-to-face education.



Other studies have shown similar preference for in-person counselling despite high electronic and internet accessibility, especially among older adults.[9] In-person education may allow for more effective question-and-answer communication, with visual and auditory interaction and cues adding to its effectiveness. Although entirely remote, unsupervised electronic-based programmes have been successful,[10] this would likely apply to highly motivated participants. Many unsupervised digital learning is often at best partially consumed.[2] Most patients do not wish for remote programmes to completely replace in-person interaction, although they are not averse to them as complementary modes.

Moving forward, an integrated method such as in-person counselling enhanced by the use of use of electronic media or a mixture of remote and face-to-face sessions may be acceptable to patients, and result in a more effective mode of education. As almost all our patients possessed mobile phones and had internet access, any educational material should be optimised for mobile phones.

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***Keywords:*** *chronic kidney disease, eHEALS, eHealth, electronic health, nephrology, patient education, technology*

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LETTER TO THE EDITOR

# Evolving landscape of sports injuries and recommendations on injury preventions: A retrospective analysis in Singapore

Jade Chee*[1] *MMed (FM) (S'pore)*, Francis Jia Yi Fong*[2] *MBBS*, Mingchang Wang[1] *FCFP (S)*, Lee Yee Han Dave[1] *FRCS (Tr&Ortho)*

Dear Editor,

Sports have become increasingly integral to the daily lives of Singaporeans. According to the National Sport and Exercise Participation Survey, the percentage of Singaporeans exercising weekly rose from 54% in 2015 to 73% in 2023.[1] While this surge in sports activities brings numerous health benefits, it also results in a corresponding increase in sports-related injuries, which incur significant healthcare costs. Countries worldwide estimate spending between USD 1.58 billion and 2.4 billion dollars annually on the treatment of these injuries.[2]

In light of these trends, evidence-based injury prevention strategies are essential. Continuous monitoring of injury patterns is necessary for developing effective prevention measures, ultimately reducing the prevalence and economic burden of sports injuries. The recent COVID-19 pandemic has notably shifted exercise routines, with many individuals turning to home-based exercises and outdoor activities such as running and cycling.[3] This change in exercise habits has altered the landscape of sports injuries, presenting an opportunity to explore how specific injury patterns correlate with different sports and to identify commonly associated injuries within popular sports.

Our study, conducted at the National University Hospital, Singapore, retrospectively analysed patients presenting with sports-related injuries for the first time between March 2019 and February 2021. The study aimed to provide insight into recent changes in injury patterns among paediatric and adult patients, thereby guiding healthcare resource allocation and enhancing the understanding of sports injuries. Ethical approval was obtained from the National Healthcare Group Domain Specific Review Board (DSRB Reference Number: 2022/00230).

A total of 10,432 medical records were reviewed, with 2000 records meeting the study's criteria for inclusion. The analysis revealed significant findings related to the evolving landscape of sports injuries in Singapore (Table 1).

First, there was a notable increase in injuries associated with individual sports such as climbing, gym workouts and cycling from March 2020 to February 2021, compared to the previous year. In contrast, injuries resulting from team sports such as football decreased significantly during the same period. This shift likely reflects changes in sports participation patterns due to pandemic-related restrictions, which limited team sports activities and led to a rise in individual sports participation.

In terms of injury type, the study found a significant increase in back injuries, particularly among individuals who engaged in gym workouts and swimming. Multivariate analysis revealed that gym and swimming activities were associated with higher risks of back injuries, whereas football had a lower risk. The increase in back injuries among gym-goers may be attributed to the use of weight-training machines, which can restrict the range of motion and reduce the engagement of stabilising back muscles, potentially leading to injury.[4] Similarly, certain swimming techniques, such as hyperextension of the spine or poor body balance may contribute to the increased risk of back injuries.[5]

Additionally, the study observed a decrease in anterior cruciate ligament (ACL) injuries, particularly in non-contact ball sports and martial arts. This decline may be linked to the reduction in team sports participation during the pandemic. However, multivariate analysis identified team-based ball sports, especially football and basketball, as being associated with higher risks of ACL injuries. The mechanisms underlying ACL injuries in these sports often involve high-impact rotational landing, valgus loading forces on the knees, and external rotation of the knee, all of which are common in non-contact team-ball sports.[6]

Shoulder labral injuries also saw a significant increase, with gym workouts and climbing sports being particularly associated with higher risks.





[1] Department of Orthopaedic Surgery, National University Hospital, Singapore
[2] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
* Joint first authors
Correspondence: Dr Francis Fong Jia Yi, Yong Loo Lin School of Medicine, National University of Singapore, 10 Medical Dr, Singapore 117597.
Email: e0474171@u.nus.edu
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Table 1. Multivariate analysis of sports associated with back, anterior cruciate ligament (ACL) and shoulder labral injuries.

| | Injury of interest, no. (%) | Other injuries, no. (%) | Risk, mean (95% confidence interval) | *P* value |
|---|---|---|---|---|
| **Sports associated with higher risk of back injury** | | | | |
| Gym | 30 (13.6) | 190 (86.4) | 5.95 (3.60–9.83) | **<0.01** |
| Other sports | 38 (2.6) | 1432 (97.4) | | |
| Swimming | 5 (31.3) | 11 (68.8) | 11.62 (3.92–34.46) | **<0.01** |
| Other sports | 63 (3.8) | 1611 (96.2) | | |
| **Sports associated with lower risk of back injury** | | | | |
| Football | 3 (1.2) | 244 (98.8) | 0.26 (0.08–0.84) | **0.01** |
| Other sports | 65 (4.5) | 1378 (95.5) | | |
| **Sports associated with higher risk of ACL injury** | | | | |
| Football | 75 (30.4) | 172 (69.6) | 3.29 (2.40–4.51) | **<0.01** |
| Other sports | 169 (11.7) | 1274 (88.3) | | |
| Basketball | 44 (27.0) | 119 (73.0) | 2.45 (1.68–3.57) | **<0.01** |
| Other sports | 200 (13.1) | 1327 (86.9) | | |
| Other ball sports | 38 (21.0) | 143 (79.0) | 1.68 (1.14–2.47) | **0.01** |
| Other sports | 206 (13.7) | 1303 (86.3) | | |
| Martial arts | 24 (29.6) | 57 (70.4) | 2.65 (1.62–4.37) | **<0.01** |
| Other sports | 220 (13.7) | 1389 (86.3) | | |
| **Sports associated with lower risk of ACL injury** | | | | |
| Gym | 12 (5.5) | 208 (94.5) | 0.31 (0.17–0.56) | **<0.01** |
| Other sports | 232 (15.8) | 1238 (84.2) | | |
| Running | 17 (6.4) | 353 (95.4) | 0.23 (0.14–0.39) | **<0.01** |
| Other sports | 227 (17.2) | 1093 (82.8) | | |
| Cycling | 1 (2.8) | 35 (97.2) | 0.17 (0.02–1.22) | **0.05** |
| Other sports | 243 (14.7) | 1411 (85.3) | | |
| **Sports associated with higher risk of shoulder labral injury** | | | | |
| Gym | 31 (14.1) | 189 (85.9) | 3.19 (2.04–4.98) | **<0.01** |
| Other sports | 72 (4.9) | 1398 (95.1) | | |
| Climbing | 8 (26.7) | 22 (73.3) | 5.99 (2.60–13.81) | **<0.01** |
| Other sports | 95 (5.7) | 1565 (94.3) | | |

*P* values in bold are statistically significant

These injuries are often caused by unfavourable positions during common gym exercises or repetitive upper-limb movements on vertical terrain, as seen in climbing. The rise in shoulder labral injuries may be attributed to the growing popularity of high-intensity fitness trends such as high-intensity interval training, which have been linked to increased knee, ankle and shoulder injuries, especially among amateurs lacking sufficient flexibility, mobility, core strength and muscle conditioning to perform these exercises safely.[7]

Based on these findings, we propose several preventive measures targeting specific injuries. For back injuries, core strength and trunk stabilisation exercises involving the transverse abdominal and lumbar multifidus muscles should be emphasised.

Studies have shown that such exercises can reduce the incidence of back injuries in sports such as swimming and gym workouts.[8] Healthcare professionals, including gym instructors, physicians and physiotherapists should consider incorporating trunk stabilisation exercises into rehabilitation routines for patients with lumbar injuries. Additionally, improper exercise execution is a common cause of back injuries in gym workouts, highlighting the importance of correcting form and technique to prevent injuries, particularly among beginners.

For the prevention of ACL injuries, there is strong evidence supporting the effectiveness of injury prevention programmes, especially in non-contact ball sports. Successful programmes, such as the Fédération Internationale de Football Association (FIFA) 11+ programme, emphasise plyometrics, strengthening, flexibility, agility and feedback.[9] These programmes have demonstrated success in reducing the risk of soccer-related injuries and should be advocated through targeted online infomercials by health agencies to promote awareness and risk reduction.

For shoulder injuries, warm-up routines that emphasise internal rotation range of motion, external rotator muscle strength and scapular muscle strength have been shown to reduce the likelihood of injuries. While these measures have primarily been studied in athletes participating in overhead sports, we suggest that individuals engaged in gym workouts or climbing activities could also benefit from such practices. Strengthening the rotator cuff and scapular muscles can enhance shoulder joint stability, reducing the likelihood of shoulder injuries.[10]

Our study's strengths lie in its large cohort size, rigorous methodology and focus on first-visit presentations, providing a comprehensive overview of the demographics of sports injuries. However, the study's scope was limited to a single tertiary centre, and future multicentre cohort studies would enhance the overall understanding of the demographic landscape of sports injuries in Singapore. Additionally, the study could have been strengthened by collecting information on patients' demographics and the specific mechanisms of injury, which would provide a better understanding of how certain injuries are commonly obtained, allowing for more targeted interventions.

This study highlights the evolving landscape of sports injuries in Singapore, emphasising the importance of continuous monitoring and the implementation of targeted injury prevention strategies. By understanding these shifts, authorities and healthcare professionals can better anticipate future trends, implement effective public health interventions, and reduce the prevalence of sports injuries and associated healthcare costs. Hospitals and allied health services, such as sports medicine practitioners and physiotherapists, should be prepared to handle the changing demographic of patients presenting with sports injuries.

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LETTER TO THE EDITOR

# Facing death alone: An exploration of terminally ill individuals living alone in palliative care

Paul Bashyam[1] *MCouCFT*, Ching Sian Yap[1] *BA (Hons) Philosophy*, XiangYi Chen[1] *BSocSci*, Zhi Zheng Yeo[1] *MPH*

Dear Editor,

Home palliative care clinicians provide end-of-life care for patients from diverse social and economic backgrounds. They include patients who live alone—a single-person household.[1] Auon et al. found that 7–12% of patients under palliative care lived alone for more than a year.[3] Demographic trends increasingly highlight this group to be a growing population with pressing concerns (e.g. the number of single-person households in Singapore has almost doubled between 2012 and 2022).[2] With the greying population, the trend of patients living alone is expected to grow.

Understanding the characteristics and behaviours of patients living alone is important for clinicians to better identify their needs and provide appropriate and timely care. Coordination between healthcare and social service providers can also be strengthened. However, information about this group remains fragmented and insufficiently documented. Hence, we aimed to conduct an exploratory study on the prevalence and service experience of terminally ill patients who live alone.



A systematic retrospective review of electronic medical records was conducted for patients who were deceased or discharged between December 2021 and May 2022. Of the 1412 patients, 1079 (76.4%) had their living and care arrangements documented. These patients were then categorised by whether they lived: (1) alone, (2) with family members, (3) with only 1 family member or (4) with non-family members. Statistical tests (i.e. chi-squared, Fisher's Exact and t-tests) were performed to test for demographic differences between patients living alone and those living with family who represented the typical patient archetype supported by home palliative care.

Table 1 summarises the results of the analyses. Among 52 patients, 4.8% lived alone, 62.9% lived with family members and 32.3% stayed with 1 family caregiver or with non-family.

Compared to patients who lived with family, patients who lived alone were not significantly different in terms of sex, age, disease type and number of contacts with the clinical team ($P \geq 0.05$). However, there were significant differences ($P < 0.05$) by (1) race: more Chinese patients tended to live alone than other ethnicities; (2) marital status: patients who lived alone were more likely to be widowed, divorced/separated or single. Interestingly, 19% of patients were married, but their spouses did not stay in the same household and were not present; (3) means test categories: nearly 80% of patients were means tested to be eligible for subsidies of up to 80% of expenses; (4) death/discharge location: patients were more likely to be discharged or deceased in locations other than their own homes; and (5) length of stay in home palliative care: patients received support for a shorter period.

In addition, a narrative review of medical and social work case notes of 2 patients who lived alone was conducted to describe their service experience. Initially, the patients were resistant towards the home palliative care service, exhibiting avoidant behaviours and refusing visits. They also did not regularly update on their health conditions, leading to untimely care rendered. While the number of contacts they received did not differ from patients who have family support, clinicians often documented that they faced difficulties engaging the patients.

Throughout their illness trajectory, patients demonstrated a strong desire to maintain independence. Safety concerns often conflicted with their preference to remain at home and to decline healthcare or social work support. They rejected clinical advice to be admitted into care facilities and would request to remain at home. Mobility aids were accepted as their conditions deteriorated.

Clinicians needed to exercise continual efforts to engage with the patients while respecting their preferences to stay at home alone. This eventually fostered rapport building, and patients eventually became more receptive to more frequent contacts with care providers.

As the patients' conditions deteriorated, they gradually explored alternative care arrangements through consultations with the clinicians. The



[1] HCA Hospice Limited, Kwong Wai Shiu Hospital, Singapore
Correspondence: Mr Paul Bashyam, Psychological Services, HCA Hospice Limited, 705 Serangoon Road, #03-01 Block A @ Kwong Wai Shiu Hospital, Singapore 328127.
Email: paulb@hcahospicecare.org.sg

Table 1. Demographics data of loner patients.

| Demographics | Staying alone (n=52) | Staying with family (n=679) |
|---|---|---|
| Sex, no. (%) | | |
| Male | 26 (50) | 317 (46.6) |
| Female | 26 (50) | 362 (53.3) |
| Age, mean (SD), years | 75.8 (13.8) | 74.9 (13.5) |
| Race, no. (%) | | |
| Chinese | 44 (84.6) | 493 (72.6) |
| Malay | 5 (9.6) | 135 (19.9) |
| Indian | 1 (1.9) | 31 (4.6) |
| Others | 2 (3.8) | 20 (2.9) |
| Disease, no. (%) | | |
| Cancer | 35 (67.3) | 522 (76.8) |
| Non-cancer | 17 (32.7) | 157 (23.1) |
| Marital status,[a] no. (%) | | |
| Married | 10 (19.3) | 449 (66.1) |
| Widowed | 19 (36.5) | 169 (24.9) |
| Divorced/separated | 11 (21.1) | 23 (3.4) |
| Single | 12 (23.1) | 38 (5.6) |
| Means test category,[ab] no. (%) | | |
| 0% | 9 (17.3) | 19 (28.3) |
| 15–30% | 2 (3.9) | 77 (11.3) |
| 40–50% | 0 | 21 (3.1) |
| 55–60% | 1 (1.9) | 129 (19.0) |
| 75–80% | 40 (76.9) | 260 (38.3) |
| Length of stay in home hospice,[a] mean (SD), days | 112 (113.9) | 125 (180.2) |
| Contacts with clinical team | | |
| Median no. of phone calls | 9 | 10 |
| Median no. of home visits | 6 | 7 |
| Death/discharge location,[a] no. (%) | | |
| Hospital | 11 (21) | 202 (29.8) |
| Nursing home or hospice | 26 (50) | 44 (6.5) |
| Others/blank | 4 (7.7) | 24 (3.5) |
| Own home | 11 (21.2) | 409 (60.2) |

SD: standard deviation
[a] Significant at $P<0.05$
[b] Used as a measure of socioeconomic status by evaluating an individual's or household's financial means, including income and assets, to determine eligibility for medical and healthcare subsidies.

patients also sought out estranged relationships for reconciliation or closure. They were more likely to share information about themselves due to closer rapport with the clinicians.

The patients desired a good death. They wished to live independently and to reconcile with estranged relationships. Their measure of a good death was not determined by the place where they spent their last days, but how and with whom they spent the days with.

Patients who live alone constitute a small but significant proportion of patients in home palliative care. Our study observed that these patients may be more socially isolated or disadvantaged, whether by choice or by circumstance. Financial struggles appeared to be a common challenge; more than 80% were found to be eligible for substantial subsidies. Moreover, they are often estranged from families and friends. The absence of informal support at home compounded by poor care coordination and safety surveillance[4] makes this group of patients vulnerable. This reveals the urgency for socioeconomic support where scheduled and regular visits can act as a safety net.

Patients who live alone demonstrate a strong preference for independence and tendency to reject support from clinicians. This presented a challenge to healthcare workers who must balance the tension of safeguarding safety and respecting patients' autonomy. Regular attempts at engagement without imposing instructions on patients have shown to help develop rapport and trust with them, increasing their likelihood to accept clinical advice and support in future.

Findings highlight other factors that influence patients' living arrangement. For example, there is a higher proportion of Chinese patients who lived alone compared to other ethnic groups, suggesting differences in cultural values that shape a patient's living and care arrangements.

The results suggest the need for an empathetic approach that is sensitive to patients' desire for autonomy and tailored care that addresses their unique health, psychological, emotional and cultural needs. Due to limited studies conducted on values and cultural factors influencing care preferences of patients who live alone, this study highlights the importance of further research to explicate the psychosocial and cultural complexities of this patient group. We intend to explore the experiences and needs of these patients in greater depth, and share findings that can enable providers to better support more patients like them in future.

### *Declaration*

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

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**ANNALS, ACADEMY OF MEDICINE, SINGAPORE**
81 Kim Keat Road, #11-00 & #12-00 NKF Centre, Singapore 328836
Email: annals@ams.edu.sg | Website: https://www.annals.edu.sg