



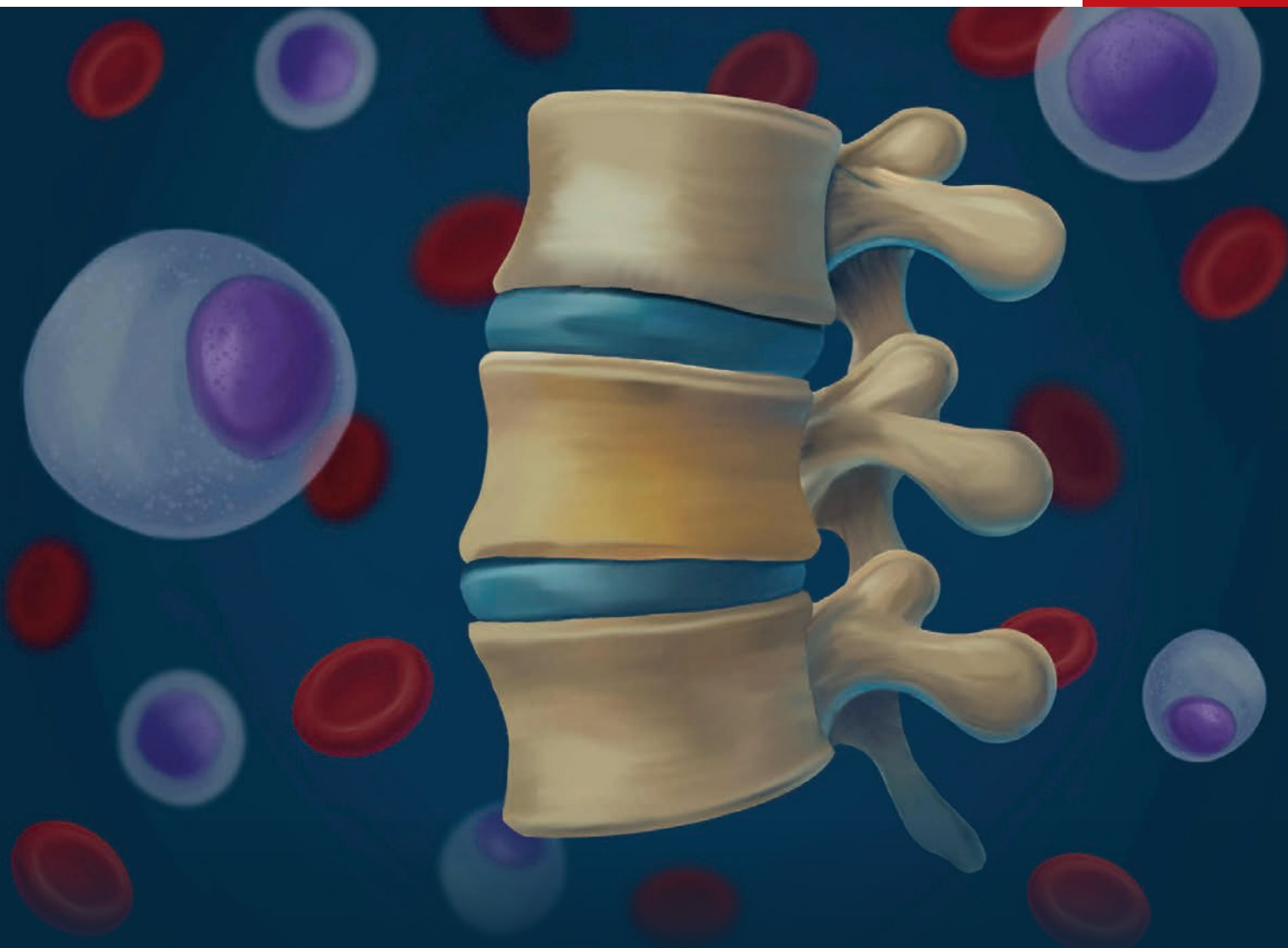
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Singapore Myeloma Study Group consensus guidelines for the management of patients with newly diagnosed multiple myeloma

The Singapore Myeloma Study Group provides consensus recommendations, incorporating key developments in diagnostics, response assessment, supportive care and definitive therapy.
(See full article, p. 561)

Illustration by Maria De-Castro

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Surviving the year: Predictors of mortality in conservative kidney management

Childhood-onset Takayasu arteritis: Unique characteristics and outcomes from a Singapore cohort

In my time: A qualitative exploration of the junior doctor experience in Singapore over the years

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Gazing into the crystal ball of mortality prediction in conservative kidney care

Charmaine Si Min Sia^{*1,2} MRCP (UK), Jia Neng Tan^{*1,2} MRCP (UK), Emmett Tsz Yeung Wong^{1,2,3} FRCP (Edin)

Since Clyde Shields became the first patient with kidney failure to undergo long-term haemodialysis in 1960, the advent of kidney replacement therapy (KRT) has provided a means of organ sustenance and life prolongation for more than 2.7 million patients with chronic kidney disease (CKD) today.¹ In the early days of dialysis, due to resource limitations, this treatment was prioritised for younger patients (defined as aged 25–45) with minimal comorbidities (i.e. “absence of long-standing hypertension and its permanent complications, particularly coronary artery disease and cerebrovascular disease”) and of “value to the community”—as determined by an Admissions Advisory Committee, nicknamed by some then as the “God Squad”.² Decades later, with advancements in medical science, improvements in dialysis technologies and increased funding support from governments worldwide, dialysis has become widely accessible. Patients considered for dialysis are getting older, multimorbid and increasingly frail.

In Singapore, patients aged ≥ 70 comprise the second largest (29%) group on KRT, accompanied by a continuous climb in the incidence of definitive dialysis.³ Experience has taught us that living with chronic organ dysfunction presents its own challenges, more so for those with CKD who are multimorbid. A systematic review in 2021 found that the survival benefit of dialysis was lost in patients older than 80 years of age and in older patients with comorbidities. Life satisfaction diminishes after dialysis initiation, with symptom burden comparable to patients on chemotherapy for advanced cancer.⁴ Nevertheless, in a carefully selected cohort of elderly patients with relatively low comorbidity burden, dialysis may still confer a meaningful survival advantage in the initial years of initiation, especially if they do not have diabetes or ischaemic heart disease.⁵

Conservative kidney management (CKM) is now widely accepted as a fourth treatment option for kidney failure, apart from haemodialysis, peritoneal dialysis and transplantation. CKM, at best, is defined as the care of people with kidney failure that focuses predominantly on providing kidney supportive care

(KSC) to promote quality of life while excluding KRT. The guiding principle is the alignment of all active therapy plans with the individual’s preferences, goals, wishes and prognosis. A patient-centred strategy aimed at minimising complications, managing symptoms, facilitating advanced care planning and integrating simultaneous palliative care, CKM has been associated with improvements in quality of life, reduction in hospitalisation rates and better symptom control.⁶ Consistent across large cohort studies and systematic reviews, the estimated median survival for older patients (age ≥ 65) on conservative management (CKD G4–5) varies internationally and substantially, depending on the estimated glomerular filtration rate (eGFR), age, comorbidity burden and care setting.⁷ More specifically, median survival estimates decline as kidney function worsens, ranging from 15 months (interquartile range [IQR] 7–34 months) when eGFR falls below 15 mL/min/1.73 m² to 8 months when it drops to ≤ 10 mL/min/1.73 m² (IQR 3–18 months).⁸ Age further influences survival, with estimates ranging from 7–41 months for those aged 70–79 and 1–37 months for those ≥ 80 years.⁹ Survival diminishes with eGFR, advancing age, increasing frailty and multimorbidity, underscoring the need for individualised prognostic estimates that reflect each patient’s unique clinical profile.¹⁰ Currently, there is no standardised definition of “conservatively managed” patients; hence, the determination of survival according to the data collection methods employed by different institutions. It has thus been challenging to predict survival reliably due to heterogeneity and paucity of data.

In this issue of the *Annals*, Teh et al. conducted a single-centre, prospective cohort study of adult patients with kidney failure on CKM.¹¹ They aimed to determine baseline predictors of mortality, apply functional assessment tools for prognostication and identify transition points to palliative care. Baseline eGFR and serum albumin were identified as significant independent multivariable predictors of 1-year mortality. The Palliative Performance Scale (PPS) was also found to be a strong predictor of survival. From

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these, the authors proposed a tailored 3-phase approach to CKM that describes the expected trajectory of kidney failure at an eGFR of ≤ 10 mL/min and encompasses suggested care goals and management aims of each phase of progression based on the eGFR and PPS scores. They proposed criteria for referral to hospice services in efforts to structure care delivery and integrate proactive, timely supportive care onboarding at an eGFR of < 5 mL/min or a drop in PPS to < 50 , which translates to a median survival of 3 months, as opposed to leaving it to individual physicians' "gut feel".

We commend the authors for a well-conducted study. While baseline predictors of mortality have been fairly extensively studied in Western cohorts, this study adds value in contextualising predictors to a Southeast Asian cohort. Serum albumin and creatinine are blood biomarkers that can be easily obtained and are routine measurements in CKD care. The PPS, a 10-point interval scoring scale, is a modification of the Karnofsky Performance Scale (KPS), which assesses a patient's functional capacity in the domains of ambulation, disease activity level, self-care, oral intake and consciousness level. Compared to the Eastern Cooperative Oncology Group scale, which only assesses ambulatory function, it provides a more nuanced assessment while being simpler to implement than its 12-point Likert scale counterpart—the interRAI Changes in Health, End-Stage Disease, Signs and Symptoms Scale. It is applicable across various healthcare settings and generalisable to a broader population with different end-of-life diagnoses.¹² The PPS is relatively simple to score once one is familiar with it. Hence, these 3 parameters can be easily used in a clinical setting to predict 1-year mortality. The authors also provide a reasonably practical framework that can be implemented and scaled for a clinical service, including the provision of timely hospice assistance or end-of-life care. The current practice and timing of hospice referrals are heterogeneous, and this framework provides a degree of objectivity to avoid placing unnecessary strain on hospice services.

This study cohort differs from other larger cohorts in various aspects, including a lower prevalence of ischaemic heart disease, a higher prevalence of cancer, higher functional independence and relatively low symptom burden. This may reflect the profile of patients who chose to pursue CKM as their treatment option while they remain relatively symptom-free, rather than the more "typical" patient with kidney failure who may be more multimorbid and have a higher symptom burden. Ironically, patients in the latter group are those who may benefit more from CKM. While we acknowledge the limitation of the time-based, observational nature of enrolment for

this study, future studies should explore differences in baseline characteristics of patients excluded from enrolment or enrolled patients who subsequently withdrew due to dialysis initiation. This would provide further insights into both medical and psychosocial-behavioural factors for this CKM model and framework in a real-world setting.

The authors assessed symptom burden and frailty indices using several scores and scales. Except for the Edmonton Symptom Assessment System Revised: Renal and Charlson Comorbidity Index, all the other measures were univariate predictors of 1-year mortality. However, none of these measures were significant, independent multivariable predictors of 1-year mortality. There may be several explanations for this observation. There may be substantial collinearity between some of these measures, which results in wide confidence intervals and loss of statistical significance. The study may also be underpowered, resulting in type II error, given the small number of events (mortality) in a small cohort relative to a large number of covariates examined. Further study validating the application of these respective scores and scales in a kidney disease model would shed additional light on both the clinical validity and utility of these measures.

Lastly, in describing early observations from their programme the authors have taken the first step in optimising personalised CKM care. In addition to the "hard" outcomes of palliative referrals, reduction in hospitalisation, etc., it would be most important to obtain patient-reported outcome measures (or PROMs) to show that KSC implemented through this CKM programme does improve the quality of life and symptom management in these patients, and fulfil their wishes of dying well. We look forward to a follow-up analysis of the longitudinal progression of outcomes.

As CKM takes on a more prominent role in integrated kidney care, a universal definition of "supportive care" is sorely needed. This will facilitate the standardisation of terminology, referencing the specific domains and tasks that KSC encompasses, and allow comparison across studies for better predictive tools and correlation with outcomes. The International Society of Nephrology has recognised this gap and has undertaken the development of consensus definitions for CKM and KSC in addition to identifying key considerations for the development of CKM programmes to promote international acceptance and inculcate global awareness.

As the biblical saying goes, "All things are permissible, but not all things are beneficial." Even as advances in dialytic therapies now offer many CKD patients a way out of imminent demise, we must

always remain cognisant that not all will reap the benefits of chronic dialysis. While medical practitioners aim to live out the maxim of *primum non nocere* (“first, do no harm”), the heart of any CKM programme lies in making the patient the main author of their own therapy. It remains our calling to help patients live well and die well.

Ethics statement

Not applicable

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: *conservative kidney management, kidney failure, mortality, nephrology, supportive care*

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The junior doctor experience in Singapore through a temporal prism

Gerald Gui Ren Sng¹ MPH, Joshua Yi Min Tung² MPH, Jia Long Chua³ MPH

Junior doctor well-being has been a pressing topic for the national healthcare system in Singapore for several years,¹ with myriad implications on mental health, quality of life and work performance, and further follow-on effects on patient care and outcomes.² Cultural factors in the workplace have been strongly implicated in junior doctor well-being and work performance. A disconnect between senior and junior staff has been suggested as a significant source of mismatched expectations and hence tension.

Anecdotally, this disconnect is often attributed to the fact that senior doctors in the public healthcare system perceive that their own experiences as junior doctors were more challenging than those of the current generation. The refrain that things were more difficult “in my time” is perhaps a familiar one to many successive generations of doctors in Singapore. The practice of medicine has indubitably changed over the last few decades. In this issue of the *Annals*, O’Hara et al. aimed to shed light on the changes in the lived experiences of junior doctors in Singapore over the generations.³ This is a novel perspective that is distinct from previous work on this topic that has tended to be cross-sectional and relevant mainly to a single time period.

In this qualitative study, the authors interviewed 30 participants across 41 years of seniority of practice. This study focused solely on a description of participants’ lived experiences, followed by a discussion of the similarities and differences across the years. In their analysis, the authors relied on thematic analysis to derive factors that “improved” or “worsened” the experience. They then constructed a model based on the socioecological model (SEM)⁴ to classify these factors based on impact at the individual, interpersonal, institutional, community and policy levels, with an overarching category of time period as a modifier. They observed a large amount of overlap between the categories, and hence chose to describe an overlapping Venn diagram-based model instead of the typical onion-layered SEM.

Unsurprisingly, marked differences in working conditions were noted across the years. O’Hara et al.

incorporated anecdotal information on working conditions obtained from their interviews, with secondary sources to illustrate working conditions in 3 time periods—1970s, 2000s and 2020s. This roughly corresponded to the 3 cohorts that participants were banded into. Working and duty hours and workload as measured by patient load appeared to decrease, but non-clinical workload appeared to increase. More significantly, complexity of care was also perceived to have increased—a finding that has not been formally reported in Singapore before. At the same time, specialist training and career opportunities became more codified, as did supervision of junior doctors. This was on a background of structural changes and 2 generation-defining pandemics. Much of the extant literature on this topic focused on both pandemics⁵; but this work helps to fill in the gaps in between.

An interesting observation is that many of the structural milestones recorded, especially from the senior cohort, were anecdotal rather than based on independent sources. At the same time, participants in the study cited tangible measures to support learning, training and rest as significant factors that improved the junior doctor experience. Furthermore, having junior doctors involved in deliberations on improving conditions seemed to be a positive experience across cohorts. This may be a reminder to policymakers and organisations that while deliberations on changes to working conditions may often take place in committee settings, such as the recent National Wellness Committee for Junior Doctors, communicating the findings and recommendations could be important both for improving participation from the junior doctors as well as future understanding by observers.

Despite significant differences in the nature and conditions of practice across the more than 2 decades of experience captured in the study, there were striking similarities in the thematic factors identified. Strong camaraderie between team members, support from seniors and mentorship were factors that improved the experience of participants from all cohorts. It is heartening to see that a culture of peer support within the medical community has persisted over the

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generations. Organisational culture has been described as a key factor contributing to job satisfaction in junior doctors previously.⁶ Arguably, this culture is an under-recognised buttress against the myriad changes in working conditions highlighted across the years. This may be a potentially valuable resource that policy-makers and organisations should tap on in their future efforts to improve wellness.

Conversely, there also remained a consistent negative undercurrent of maladaptive coping strategies to stress across the cohorts, with some sobering anecdotes of potential self-harm shared. Previous studies in the Singapore context have suggested that senior doctors are more resilient than junior doctors⁷ and hence are less burnt out, with a higher quality of life.⁸ The findings from this study across time periods remind us that the current generation of senior doctors was perhaps no different during their time as juniors from the junior doctors of today; differences in observed measures of resilience may represent both learned behaviour as well as be affected by hindsight and survivor bias.

Finally, the effect of the changing nature of practice and consequent differences in professional agency is an important finding. Participants across cohorts appeared to agree that one such change is the rise of “defensive medicine”. One participant from the senior cohort shared that it caused them to leave practice, those from the middle cohort focused on the changes to how they approached and investigated patients, while those from the junior cohort focused on the effects on their workload. As professional development and fulfilment were strong fortifying themes across cohorts, changes to practice that affect how individuals see their roles and relationship with patients could undermine junior doctors’ sense of agency and progression towards professional self-actualisation.

This study has some limitations that may limit its generalisability. The authors sampled a small selection of 30 participants; with between 8 and 11 participants in each cohort, it is possible that respondents may not necessarily be representative of the overall population of junior doctors. It is striking that participating in advocacy for junior doctors was a consistent theme identified across generations, which may suggest some degree of selection bias for participants who are more engaged about junior doctor well-being or who may have their own entrenched viewpoints on the issue. Furthermore, there is the possibility of recall bias in senior doctors who may recollect their more “extreme” experiences (whether positive or negative) more vividly. Lastly, there is the possibility of survivor bias, as doctors with extremely negative experiences may have already left the profession and are not available for recruitment.

As this study used a phenomenological approach, which is primarily descriptive, further work can be done in this area to better understand the junior doctor experience and factors affecting well-being. Other contemporary approaches towards evaluating physician well-being have utilised the job demands-resources model developed by Bakker and Demerouti,⁹ with modifications for the Singapore context.¹⁰ While this model helps to illustrate relationships between factors better than the SEM, it still lacks a temporal dimension. Future studies should incorporate a temporal element into their analysis and model-building, to allow continued relevance to the succeeding generations of junior doctors through informing adaptive workforce policies.

To conclude, this study highlights some points that may be useful to policymakers. Involving junior doctors in policy-making committees and facilitating clear communication of findings are important to ensure relevance and support buy-in. Robust mechanisms should be put in place to monitor for maladaptive coping behaviours to stress. Changes in the nature and scope of practice need to be monitored for their impact on the professional agency and consequently self-actualisation of junior doctors.

A key development is the rise of digitisation and artificial intelligence (AI) in healthcare. This study concluded in 2022, prior to the emergence of generative AI models into the zeitgeist. Even then, increasing healthcare digitisation was already seen as a key developing challenge for junior doctors in this study. Since then, the development and implementation of AI tools have become a key direction of the Ministry of Health in Singapore.¹¹ It is likely that AI tools will disrupt current clinical workflows and have a transformative impact on the junior doctor experience. Such transformation may be beneficial through a reduction in workload but may also have risks such as cognitive offloading and de-skilling. Further in-depth study is warranted to explore the effect of these technologies on both well-being and professional identity development in junior doctors in Singapore.

Ethics statement

Not applicable.

Declaration

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

Keywords: *junior doctors, lived experiences, medical education, mental health, well-being*

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Surviving the year: Predictors of mortality in conservative kidney management

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ABSTRACT

Introduction: Conservative kidney management (CKM) is a recognised treatment option for selected patients with chronic kidney disease stage 5 (CKD G5), but prognostic indicators for mortality and optimal timing for palliative care transition remain uncertain.

Method: This is a single-centre, prospective cohort study of CKD G5 patients who opted for CKM, conducted between April 2021 and September 2024, with longitudinal monitoring of Edmonton Symptom Assessment System Revised: Renal; Palliative Performance Scale (PPS); Resources Utilisation Group–Activities of Daily Living (RUG-ADL) scale; Clinical Frailty Score; Karnofsky Performance Score; and clinical and laboratory data. Primary outcomes included identifying baseline mortality predictors and validating the PPS for survival estimation. Cox proportional hazards models were used to identify independent predictors of mortality.

Results: Among 109 patients (mean age 79.8±7.3 years, 64.2% female), 62 (56.9%) died during follow-up. Multivariate analysis identified baseline estimated glomerular filtration rate (eGFR) (hazard ratio [HR] 1.32, 95% confidence interval [CI] 1.08–1.68, $P<0.01$) and serum albumin (HR 1.24, 95% CI 1.08–1.43, $P<0.01$) as predictors of 1-year mortality. Median survival varied by eGFR: 3.0 months (95% CI 0–6.2) for eGFR ≤ 5 mL/min/1.73 m², 13.0 months (95% CI 9.1–16.9) for eGFR 6–10 mL/min/1.73 m², and 20.0 months (95% CI 16.5–23.5) for eGFR >10 mL/min/1.73 m² ($P<0.01$). Subsequent PPS correlated strongly with survival, with median survival of 1.8 months for PPS <50 , 5.3 months for PPS 50–60, and 7.9 months for PPS 70–80 ($P=0.03$).

Conclusion: Baseline eGFR and serum albumin predict 1-year mortality in CKM patients. PPS offers a practical tool for identifying patients requiring palliative care transition, supporting personalised care pathways and timely integration of palliative care.

Keywords: clinical tool, conservative kidney management, mortality, nephrology, prognosis

INTRODUCTION

Conservative kidney management (CKM) has evolved from a disease-focused model to person-centred

CLINICAL IMPACT

What is New

- This study demonstrates that baseline eGFR, serum albumin and the Palliative Performance Scale (PPS) are significant predictors of 1-year mortality for patients with conservative kidney management (CKM)—an important option for patients with Chronic Kidney Disease Group Stage 5 (CKD G5) who may not benefit from dialysis. These findings emphasise the importance of personalised care pathway and timely integration of palliative care to improve patient outcome.

Clinical Implications

- A significant proportion of community dwelling older adults with CKD G5 have low symptoms.
- Risk stratification of CKM patients helps clinician to provide care in keeping with patients' preference and values. Identifying patients with short prognosis including baseline eGFR <5 mL/min/1.73 m² or persistent PPS <50 allows for a transition to palliative care or hospice seamlessly.

approach for chronic kidney disease stage 5 (CKD G5) patients.^{1,3} This transformation reflects a growing recognition that dialysis may not provide a survival advantage or improve quality of life—particularly for elderly individuals with multiple comorbidities or frailty.^{10–12,16}

Recent systematic reviews and meta-analyses have demonstrated that elderly patients with a high comorbidity burden experienced comparable survival rates between CKM and dialysis, with median survival ranging from 6 to 23 months, depending on baseline characteristics.^{6,7}

Despite the increasing adoption of CKM programmes worldwide, significant heterogeneity exists in both practice patterns and outcomes,^{6,9} highlighting the need for better prognostic indicators and standardised approaches to care delivery. Current literature

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reveals 3 critical knowledge gaps in CKM care. First, there is limited prospective data on survival predictors^{18–20} specific to CKM populations, which hampers meaningful shared decision-making between clinicians and patients and families.^{25,26,32} Second, validated tools^{2,14,21} for identifying transition points to palliative care are lacking, making it difficult to determine the optimal timing for hospice care integration. Third, the utility of palliative performance indicators for survival estimation in CKM populations remains understudied, particularly in Asian healthcare settings.

Our study addresses these gaps through 2 aims: (1) to identify baseline clinical and laboratory factors associated with 1-year mortality in CKM patients, and (2) to validate the utility of subsequent PPS in estimating survival for this population. By achieving these objectives, the authors aim to provide clinicians with practical tools for prognostication and care planning in CKM programmes.

METHOD

A prospective, single-centre cohort study was conducted from April 2021 to September 2024. The primary objective was to compare baseline characteristics associated with 1-year mortality. The secondary objective was to assess the utility of estimating survival duration based on the Palliative Performance Scale (PPS). The study was approved by the SingHealthCentralised Institutional Review Board (2021/2451) where patient consent was waived on account of service development.

Patients were referred to renal conservative care programme integrating outpatient nephrology service and community nursing.²⁸ The programme aimed to empower patients and families in shared decision-making, provide community-based reviews and interventions, identify psychosocial needs and enable timely transition to home hospice care. Additionally, community nurses initiated advance care planning discussions. Direct communication between the community nurses and the nephrologists enabled timely troubleshooting of arising issues. All the patients in the renal conservative care programme were followed up until they died.

Inclusion criteria were age ≥ 18 years, CKD G5 diagnosis with a decision to pursue CKM, and agreement with a community nursing home visit. This was a time-based enrolment observational study for a new service set-up. A total of 109 patients who met the inclusion criteria was recruited in this analysis. Patients were excluded from the analyses if they declined home visits, transferred care to another institution, initiated dialysis, were under existing home hospice care, were nursing home residents, had life expectancy of less than 1 month at enrolment, or were lost to follow-up.

Data collection

Baseline demographic, clinical and laboratory data were collected during the initial visit to renal conservative care clinic. The Edmonton Symptom Assessment System Revised: Renal (ESAS-r: Renal),^{29,30} Resource Utilisation Group–Activities of Daily Living (RUG-ADL)³¹ scale and PPS V2^{32,34,25} were obtained at the initial visit and during monthly home visits. Additional baseline factors recorded included the Charlson Comorbidity Index (CCI),³³ Clinical Frailty Score (CFS)³⁹ and Karnofsky Performance Score (KPS).¹⁸

Community nurses conducted monthly home visits, while renal conservative care clinic visits were conducted every 3 to 4 months. Patients were followed up until 30 September 2024 or the date of death, whichever occurred first.

Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation for parametric data or median with interquartile range for non-parametric data. Categorical variables were expressed as numbers and percentages.

Univariate analysis was conducted using the independent sample t-test for normally distributed data and the Mann-Whitney U test for non-parametric data. The chi-square test was used for categorical variables. Logistic regression and Cox regression were performed for multivariate analysis.

Kaplan-Meier survival analysis was conducted to estimate the survival duration by categorising the baseline eGFR into ≤ 5 , 6–10 and >10 mL/min/1.73 m². The PPS scores were stratified into <50 , 50–60 and 70–80 based on their distribution on a histogram to determine their median survival duration from the last recorded score. The independent samples Kruskal-Wallis test was used to compare median survival.

Data analysis was performed using SPSS Statistics software version 27 (IBM Corp, Armonk, NY, US).

RESULTS

Among the 109 enrolled patients, 70 (64.2%) were female, and 90 (82.6%) were Chinese. The mean age was 79.8 ± 7.3 years. The baseline estimated glomerular filtration rate (eGFR [CKD-EPI]) was 10.3 ± 2.8 mL/min/1.73 m². The primary causes of CKD G5 were diabetes mellitus (70.6%), hypertension (18.3%) and chronic glomerulonephritis (4.6%) (Table 1). Thirty patients transitioned to home hospice during the follow-up.

Patients exhibited a significant comorbidity burden, with a mean CCI of 8.5 ± 1.9 . Major comorbidities included diabetes mellitus (77.1%), ischaemic heart disease (33.0%), stroke (28.4%), dementia (23.9%), peripheral vascular disease (15.6%) and malignancy

(15.6%). Initial functional assessment indicated mild frailty, with a median CFS of 4 (interquartile range [IQR] 4–6), a KPS of 70 (IQR 60–80), a median total RUG-ADL score of 4 (IQR 4–8) and a PPS of 60 (IQR 60–70), with approximately 80% of patients maintaining independence in daily activities. Mean baseline laboratory values included haemoglobin levels of 9.6 ± 1.4 g/dL and serum albumin levels of 38.0 ± 4.9 g/L.

Initial symptom assessment revealed a relatively low burden, with a median total ESAS-r: Renal score of 1 (IQR 0–3). The most prevalent symptoms were fatigue (20.2%), pain (19.3%) and insomnia (17.4%).

Factors associated with mortality at 1 year

Among the 109 enrolled patients, 37 died within 1 year of entering the programme. Surviving patients with follow-up periods of less than 1 year were censored in the analysis.

Multivariate logistic regression analysis identified lower baseline eGFR and serum albumin levels as significant independent predictors of mortality, after adjusting for CFS, KPS, RUG-ADL and PPS (Table 2). Each 1 mL/min/1.72 m² decrease in baseline eGFR was associated with a 32% increase in 1-year mortality (HR 1.32, 95% CI 1.08–1.68, $P < 0.01$). Similarly, each 1 g/L decrease in serum albumin was associated with a 24% increase in mortality risk (HR 1.24, 95% CI 1.08–1.43, $P < 0.01$) (Table 2).

Survival analysis by baseline eGFR

At the study's conclusion, 62 patients (56.9%) had died. The median follow-up period was 10.5 months (IQR 5–17) for deceased patients and 12 months (IQR 9–22) for surviving patients in the whole cohort. Baseline kidney function had a significant impact on survival, mainly driven by eGFR < 5 mL/min/1.73 m² ($P < 0.01$). The median survival for eGFR ≤ 5 , 6–10 and > 10 mL/min/1.73 m² was 3.0, 13.0 and 20.5 months, respectively (Fig. 1).

PPS and survival duration

Among the 62 deceased patients, final PPS scores were strongly correlated with survival duration ($P = 0.03$). The median survival durations were 1.8 months for PPS < 50 , 5.3 months for PPS 50–60, and 7.9 months for PPS 70–80 (Fig. 2). These findings suggest that end-of-life care, including palliative or hospice services, should be considered when PPS drops below 50.

DISCUSSION

Our prospective cohort study provides important insights into prognostication and care delivery for CKM patients through an integrated outpatient nephrology and community nursing model. Three key findings emerged that advance current understanding of CKM care: the prognostic value of baseline parameters, the utility of functional assessment tools, and the identification of transition points for palliative care integration.

The demographic profile of our cohort (mean age 79 years, CCI 8.5) aligns with typical CKM populations but highlights notable distinctions in comorbidity patterns. Compared to the Singapore Renal Registry 2022 dialysis population,¹³ our cohort exhibited lower rates of ischaemic heart disease (33% vs 46.1%), similar rates of peripheral arterial disease (15%), but a higher prevalence of cancer (15.2% vs 8.2%). Despite significant comorbidities, most patients maintained functional independence with relatively low symptom burden, contrasting with findings from CKDopps,¹⁴ Australian Kidney Supportive Care⁴ and EQUAL cohort studies.² These disparities might reflect differences in kidney function decline rates, symptom perception and psychosocial factors across populations.³² The CCI score could be over-estimated in our cohort

Table 1. Baseline characteristics.

Characteristic	
Age, years, mean (SD)	79.8 (7.3)
Sex, no. (%)	Male, 39 (35.8) Female, 70 (64.2)
Ethnicity, no. (%)	Chinese, 90 (82.6) Malay, 12 (11) Indian, 7 (6.4)
Primary renal disease, no. (%)	Diabetes mellitus, 77 (70.6) Hypertension, 20 (18.3) Chronic glomerulonephritis 5 (4.6) Polycystic kidney disease, 1 (0.9) Others, 6 (5.5)
eGFR (mL/min/1.73 m ²), mean (SD)	10.3 (2.8)
CCI, mean (SD)	8.5 (1.9)
CFS, median (IQR)	4 (4–6)
KPS, median (IQR)	70 (60–80)
ESASr: R, median (IQR)	1 (0–3)
RUG-ADL, median (IQR)	4 (4–8)
PPS, median (IQR)	60 (60–70)
Serum albumin (g/L), mean (SD)	38.0 (4.9)
Haemoglobin (g/dL), mean (SD)	9.6 (1.4)

CCI: Charlson Comorbidity Index; CFS: Clinical Frailty Score; eGFR: estimated glomerular filtration rate; ESASr:R: Edmonton Symptom Assessment System Revised: Renal; IQR: interquartile range; KPS: Karnofsky Performance Score; PPS: Palliative Performance Scale; RUG-ADL: Resource Utilisation Group–Activities of Daily Living scale; SD: standard deviation

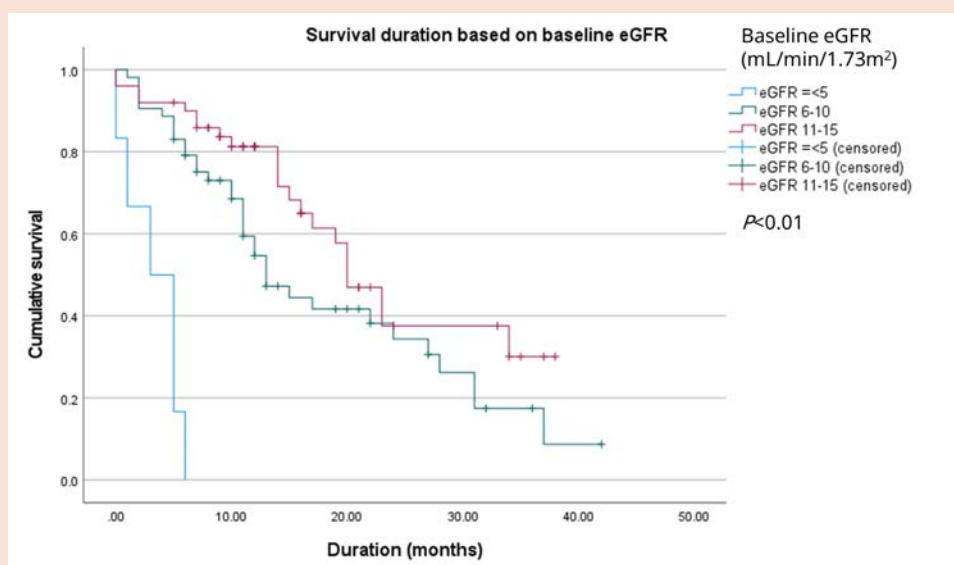
Table 2. Factors associated with mortality at 1 year.

Variables	Univariate			Multivariate
	Survive (n=53)	Deceased (n=37)	P value	95% CI
Age, years	80.8 ± 6.8	78.8 ± 8.2	0.19	0.99–1.18
CCI	8.4 ± 1.7	8.9 ± 2.0	0.21	0.78–1.49
eGFR (mL/min)	10.9 ± 2.3	8.8 ± 3.0	<0.01	1.02–1.69
Haemoglobin (g/dL)	9.7 ± 1.3	9.2 ± 1.6	0.12	0.46–1.21
Albumin (g/L)	40.1 ± 4.2	35.1 ± 5.0	< 0.01	1.12–1.60
CFS	4 (IQR 3–5.5)	5 (IQR 4–7)	< 0.01	0.46–4.00
KPS	70 (IQR 60–80)	60 (IQR 50–70)	< 0.01	0.98–1.25
ESASr:R, total, baseline	1 (IQR 0–3)	2 (IQR 0–6)	0.28	0.75–1.09
RUG-ADL, total, baseline	4 (IQR 4–6)	6 (IQR 4–10)	< 0.05	0.86–1.36
PPS, baseline	70 (IQR 60–70)	60 (IQR 50–70)	< 0.05	0.89–1.08

CCI: Charlson Comorbidity Index; CFS: Clinical Frailty Score; CI: confidence interval; eGFR, estimated glomerular filtration rate; ESASr:R: Edmonton Symptom Assessment System Revised: Renal; IQR: interquartile range; KPS: Karnofsky Performance Score; ns: non-significant; PPS: Palliative Performance Scale; RUG-ADL: Resource Utilisation Group–Activities of Daily Living scale.

Nineteen patients were excluded due to a survival duration of less than 12 months. Multivariate analysis was adjusted for age, CCI, haemoglobin, CFS, KPS, ESAS-r: Renal, RUG-ADL and PPS. Hosmer and Lemeshow test, $P=0.54$.

Fig. 1. Baseline eGFR and survival.

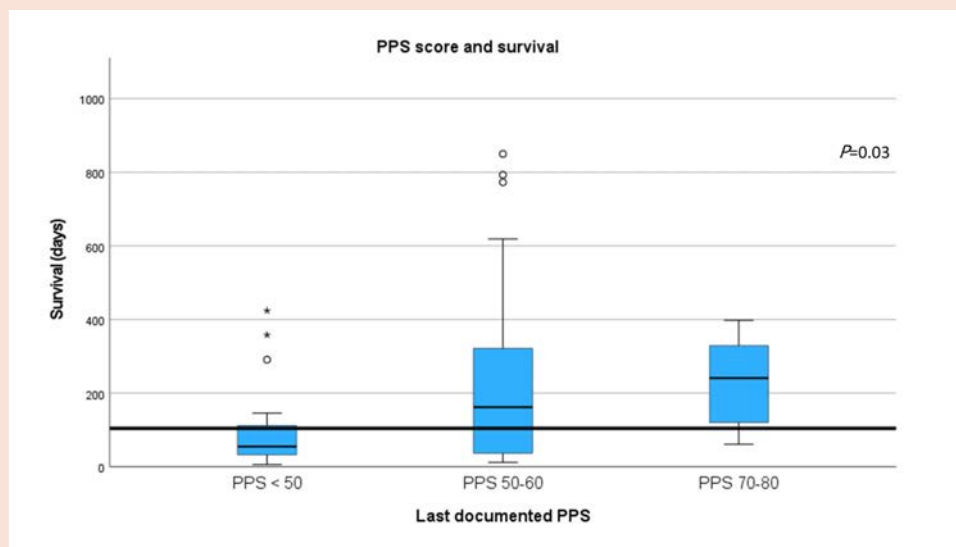


Patient count and survival rates based on initial kidney function

Month eGFR, mL/min/1.73 m ²	0	6	12	18	24	30	36	Median survival duration (months)	95% CI
≤5	6	0						3.0	0, 6.2
6–10	53	42	24	15	9	5	2	13.0	9.1, 16.9
>10	50	44	28	16	7	5	2	20.0	16.5, 23.5

CI: confidence interval; eGFR: estimated glomerular filtration rate

Fig. 2. PPS score and median survival.



° refers to statistically significant when comparing last PPS < 50 and 50–60 as well as 70–80.

* refers to significant difference between last PPS < 50 and 50–60 after adjusted by the Bonferroni correlation for multiple tests.

PPS	< 50	50–60	70–80
n=62	20	33	9
Median duration (months)	1.8 (IQR 1.1–4.2)	5.3 (IQR 1.1–11.1)	7.9 (IQR 3.1–11.2)

IQR: interquartile range; PPS: Palliative Performance Scale

because those aged ≥ 80 received 4 points, and 2 points were assigned for moderate-to-severe CKD. Despite this, these older adults had a relatively low symptom burden, and more than half were independent in activities of daily living. On the other hand, patients with significant symptoms who needed palliative care would have been referred to hospice services earlier.

Prognostic models for CKD have variable performance and limited applicability for CKM patients.^{19,20} Factors such as hypoalbuminemia,³⁷ anaemia,³⁸ symptom burden,² KPS ≤ 70 ,¹⁸ frailty¹⁵ and higher CCI³³ have been shown to be associated with mortality. Identifying baseline eGFR and serum albumin as significant predictors of 1-year mortality provides clinically valuable prognostic information. Our findings demonstrate a clear relationship between baseline kidney function and survival: median survival was 20.5 months for eGFR >10 mL/min/1.73 m², 13.0 months for eGFR 6–10 mL/min/1.73 m² and 3.0 months for eGFR ≤ 5 mL/min/1.73 m². These results align with reports of mean survival of 13–14 months for CKD G5 patients with eGFR <15 mL/min/1.73 m² in existing literature.^{4,12} Other studies^{6,7,8,10} have cited a

median survival ranging between 1 and 6 months for patients with eGFR <10 mL/min/1.73 m². The strong association between hypoalbuminaemia and mortality (32% increased risk per 1 g/L decrease) provides an additional practical prognostic marker.

Among those patients with eGFR >5 mL/min/1.73 m², the median survival was 1 year or more. Periodically monitoring this group of patients in the community is important to determine the transition to palliative care. A 2011 study reported a steep functional decline in the last few weeks of life.¹⁷ The PPS, a clinical tool used in hospice, in-patient and oncology settings,^{34,35} demonstrated a similar trend of declining performance status that was associated with poorer survival in our cohort. Based on the current study and the existing literature, patients with eGFR ≤ 5 mL/min/1.73 m², hypoalbuminaemia and a PPS score of less than 60 are likely to have survival of less than 6 months. However, CKD G5 patients in general with their high level of symptoms are likely to benefit from palliative or anticipatory care, even without a short prognosis.²³

Our findings provide several important insights into the natural history and prognostic factors in CKM

patients. These key findings emerged as the prognostic value of baseline parameters, the utility of functional assessment, and the pattern of functional decline. These findings support a 3-phase approach to CKM with the utilisation of baseline eGFR, while monitoring for any irreversible decline in functional status using PPS as follows:

The stable phase (baseline eGFR >10 mL/min, PPS >70): focuses on shared decision-making (between the clinician, patient and family to develop a goal-concordant care plan), serious illness conversation and advance care planning discussion. The management of chronic kidney disease and comorbidities, monitoring the progress using ESASr-Renal and PPS.

The transition phase (baseline eGFR <5–10, PPS 50–60): Includes symptoms surveillance and management, with supportive care. When escalation of care needs is observed without reversible factors, care should be transitioned to hospice.

The final phase (baseline eGFR <5 mL/min or a persistent drop in PPS <50 persistently): Involves the integration of end-of-life services (e.g. home/inpatient hospice), anticipatory care, family support and bereavement preparation.

This personalised approach helps patients and families align their care goals with the disease trajectory upon entering the CKM programme (Supplementary Fig. S1).

The role of community nurses in this model is crucial, facilitating shared decision-making, resolving decision conflicts and identifying patients experiencing deterioration. This approach has resulted in reduced hospital utilisation during the last 6 months of life compared to local national database studies.³⁹ About 19% of the decedents were managed in the community without hospitalisation during their last 6 months of life. Incorporating these prognostic markers into a personalised care plan could further improve the quality of CKM care.

The strengths of this study include a 3-year follow up period, an interdisciplinary approach and the implementation of a pragmatic model of care. However, limitations include a relatively small sample size, a homogeneous study population, incomplete data after transfer out from the programme, potential selection bias and the lack of a comparator arm. Additionally, the study did not assess psychosocial factors, quality of life or intercurrent illnesses that might affect survival. Future research should explore symptoms progression, the integration of quality-of-life measures and validation of predictive tools for CKM patients.

CONCLUSION

This study identifies baseline eGFR, serum albumin and the PPS score as robust predictors of survival in CKM patients, enabling a more structured approach to care delivery. The proposed 3-phase model, supported by community nursing, provides a framework for personalising care pathways and optimising resource allocation. These findings advance our understanding of CKM prognostication and support timely integration of end-of-life care services, particularly for patients with eGFR ≤5 mL/min/1.73m² or PPS <50.

Supplementary material

Fig. S1. Personalised care plan.

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Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2021/2451). Patient consent was waived as this project was part of a service development.

Declaration

This project was supported by the Tote Board Community Health Fund. All 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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Childhood-onset Takayasu arteritis: Unique characteristics and outcomes from a Singapore cohort

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ABSTRACT

Introduction: Takayasu arteritis is the most common large-vessel vasculitis in childhood, but there is a lack of literature regarding childhood-onset Takayasu arteritis (c-TAK) in Southeast Asia. We aim to describe a c-TAK cohort in Singapore and highlight a unique subset that first presents with Kawasaki-like disease (KD).

Method: A single-centre cohort study in Singapore of consecutive children diagnosed with c-TAK between 2002 and 2023 was performed. Demographic and clinical features, laboratory and angiographic findings, treatment, and outcomes were summarised. Disease activity was evaluated using the Paediatric Vasculitis Disease Activity Score and inflammatory markers.

Results: Twenty-three patients, fulfilling both the EULAR/PRINTO/PReS and ACR/EULAR 2022 criteria, were recruited. The most common clinical features at diagnosis were fever (15, 65%) and neurological symptoms (11, 48%, half of which presented with stroke), while the most prevalent angiographic pattern by Hata's classification was Type V (21, 91%). Eight children (35%) initially presented with refractory KD, and these patients were significantly younger, more male-predominant, and had higher inflammatory markers at diagnosis; all of them had coronary artery involvement, but none had intracranial vascular findings. Of the entire cohort, 16 (70%) achieved inactive disease on medications with a median duration of 6 months (interquartile range [IQR]: 4–11), and 8 (35%) achieved remission off medications with a median duration of 43 months (IQR 35–60).

Conclusion: Our c-TAK cohort has high proportions of neurological involvement and stroke. This is also the first cohort study to describe a distinct group of patients who first presented with refractory KD.

Keywords: childhood vasculitis, Kawasaki disease, paediatrics, rheumatology, Takayasu arteritis

CLINICAL IMPACT

What is New

- This is the first reported cohort of childhood-onset Takayasu arteritis (c-TAK) in Southeast Asia, showing unique characteristics including high proportion of central nervous system involvement.
- To the authors' knowledge, this study is the first to describe a distinct subgroup of c-TAK patients who initially presented with Kawasaki disease.

Clinical Implications

- Findings highlight the need to screen for large-vessel vasculitis in patients presenting with young-stroke or refractory Kawasaki disease.

INTRODUCTION

Takayasu arteritis (TAK) is the most common large-vessel vasculitis in childhood. It is characterised by

granulomatous inflammation of the aorta and its major branches, resulting in segmental stenosis, occlusion, dilatation, and/or aneurysms.¹ Compared to adult-onset TAK, childhood-onset Takayasu arteritis (c-TAK) presents with more systemic and constitutional features, has distinct vascular involvement, and is often a more refractory disease that requires greater immunosuppression.² Separate classification criteria have also been proposed for c-TAK after a joint effort between the European League Against Rheumatism (EULAR), the Paediatric Rheumatology International Trials Organisation (PRINTO), and the Paediatric Rheumatology European Society (PReS).³ Given the nonspecific systemic symptoms at initial presentation, the diagnosis of c-TAK is often difficult.^{4,5}

Kawasaki disease (KD), on the other hand, is a vasculitis that preferentially affects medium-sized arteries, particularly the coronary arteries (CA).⁶ As a result of the strong association between KD and CA aneurysms, febrile children with CA dilation or aneurysms are almost always diagnosed with KD. However, there have been case reports of children who

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were initially managed as KD and were later diagnosed with c-TAK.⁷⁻¹⁰

Notably, there is considerable variation in the incidence and characteristics of adult TAK cohorts across different geographic regions.^{11,12} Such epidemiological variability is also mirrored in c-TAK cohorts around the globe.¹³⁻²³ However, there is a paucity of literature regarding c-TAK cohorts in Southeast Asia. To address these issues, we aim to describe the clinical characteristics, radiological findings, and outcomes of our c-TAK cohort, and compare them with cohorts in other geographic regions. We also aim to describe a subset of patients with KD as the initial presentation and examine any differences in the clinical course compared with other c-TAK patients.

METHOD

Study population

Patients with c-TAK were recruited at the KK Women's and Children's Hospital, Singapore, from August 2002 to January 2023. The institution is the only children's hospital in Singapore and one of only 2 paediatric rheumatology centres nationwide, managing two-thirds or more of all referral cases. All patients were younger than 18 years at onset and were diagnosed by trained paediatric rheumatologists. The diagnosis was established based on clinical findings and angiographic images compatible with the disease, excluding other possible causes. All recruited patients fulfilled both the 2010 EULAR/PRINTO/PReS classification criteria and the 2022 American College of Rheumatology (ACR)/EULAR classification criteria.^{3,24}

Data collection

This retrospective cohort study utilised data from our prospective registry (Registry for Childhood-Onset Rheumatic Diseases).²⁵ Demographic, clinical, laboratory tests, imaging studies and treatment data were prospectively collected at diagnosis and during each follow-up visit following a standardised protocol. Arterial hypertension was defined as blood pressure >95th percentile for age and height. Blood pressure discrepancy was defined as a difference of ≥ 10 mmHg between limbs. Antinuclear antibody (ANA) was determined by indirect immunofluorescence on human cell epithelioma (Hep-2) cells substrate and defined as positive if staining reactivity was $\geq 1:160$. Antineutrophil cytoplasmic antibodies were determined using indirect immunofluorescence. Tuberculosis screening was done through both tuberculin skin tests (positive test defined as ≥ 10 mm or more regardless of age)²⁶ and the interferon-gamma release assay (IGRA). Vascular imaging studies were performed at the discretion of attending physicians, which included computed tomography angiography, magnetic reso-

nance angiography (MRA), fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan, and echocardiography studies. An arterial segment was considered affected if it demonstrates one or more of the following radiological changes: mural enhancement, thickening, or irregularity, stenosis, occlusion, dilatation, or aneurysm. The territorial distribution of lesions as defined by Hata's angiographic classification was recorded.²⁷ No patients were excluded due to incomplete data.

Outcomes

Disease activity was assessed at each visit using the validated Paediatric Vasculitis Activity Score (PVAS). PVAS is currently the only validated disease activity tool specific to paediatric vasculitis and is used as an outcome measure in paediatric vasculitis clinical trials.²⁸ Active disease was defined as PVAS ≥ 1 and/or raised inflammatory markers and/or imaging evidence of active disease, including new angiographic lesions and vessel wall inflammation by post-contrast enhancement and thickening. Partial remission was defined as a PVAS score of 0, erythrocyte sedimentation rate (ESR) <40 mm/h, C-reactive protein (CRP) <20 mg/L, and prednisolone dose ≤ 0.15 mg/kg/day or ≤ 7.5 mg/day, whichever is lower.²⁹⁻³¹ Complete remission (CR) was defined as a PVAS score of 0, ESR <20 mm/h, CRP <10 mg/L, and prednisolone dose ≤ 0.15 mg/kg/day or ≤ 7.5 mg/day, whichever is lower.²⁹⁻³¹ Clinically inactive disease on medication (CID) is defined as CR while on glucocorticoids or disease-modifying anti-rheumatic drugs (DMARDs), while clinical remission off medication (CRM) was defined as CR off all medications. Disease flare was defined as the occurrence of new c-TAK symptoms and/or an increase in inflammatory markers necessitating altered treatment and/or new or worsening angiographic lesions.³²

Statistical analyses

Non-parametric analyses were used to describe data and were shown as median (25th–75th percentiles) for continuous variables and percentages for categorical variables. Chi-squared or Fisher's Exact, Mann-Whitney U, or Kruskal-Wallis tests were applied to compare groups where appropriate. A Kaplan-Meier survival curve was constructed for median time to outcomes. All analyses were performed using Stata 18 (StataCorp, College Station, TX, US) and GraphPad Prism v7 (GraphPad Software, CA, US) with statistical significance set at $P < 0.05$.

Ethics

This study was approved by the SingHealth Centralised Institutional Review Board (CIRB 2019/2961 and 2019/2194). Informed consent was waived due to

the nature of the retrospective data review from the registry.

RESULTS

Demographic features and clinical characteristics

A total of 23 patients with c-TAK (10 females [44%], 13 Chinese [57%]) were included. The median age at diagnosis was 3.9 (0.6–11.9) years, and the median duration of follow-up was 4.0 (0.7–6.1) years (Table 1). Eight patients (35%) initially presented with clinical features of KD and were managed as such. Seven of them fulfilled the 2017 American Heart Association

Diagnostic Criteria for KD.³³ However, their disease was refractory to the first and second-line treatments (either a second dose of intravenous immunoglobulin [2 patients] or intravenous pulse methylprednisolone [4 patients], or both [2 patients]), which prompted further evaluation and eventually diagnosis of large-vessel vasculitis (referred to as the “c-TAK-KD” group herein). The median age of diagnosis of this subgroup was younger at 0.5 (0.4–1.8) years compared to the typical c-TAK group (11.4 [3.9–13.5] years, $P<0.001$). Individual characteristics of these 8 c-TAK-KD patients are summarised in Supplementary Table S3.

Table 1. Demographic, clinical and laboratory features at diagnosis.

	Total (n=23) no. (%)	Typical (n=15) no. (%)	KD (n=8) no. (%)	P value
Demographics				
Female	10 (43.5)	8 (53.3)	2 (25)	0.379
Ethnicity				
Chinese	13 (56.5)	6 (40.0)	7 (87.5)	0.121
Malay	4 (17.4)	4 (26.7)	0 (0)	
Indian	3 (13)	3 (20.0)	0 (0)	
Others	3 (13)	2 (13.3)	1 (12.5)	
Age at onset, years	3.8 (0.6–11.6)	11.4 (3.9–12.8)	0.5 (0.3–1.7)	<0.001
Age at diagnosis, years	3.9 (0.6–11.9)	11.4 (3.9–13.5)	0.5 (0.4–1.8)	<0.001
Duration from onset to diagnosis, months	1.0 (0.6–3.1)	1.0 (0.2–6.0)	1.0 (0.8–1.9)	0.975
Duration of follow-up, years	4.0 (0.7–6.1)	4.9 (0.7–6.2)	1.3 (0.2–5.0)	0.532
Clinical features				
Fever	15 (65.2)	7 (46.7)	8 (100)	0.019
Weight loss	4 (17.4)	3 (20.0)	1 (12.5)	1.000
Malaise	2 (8.7)	2 (13.3)	0 (0)	0.526
Musculoskeletal symptoms	0 (0)	0 (0)	0 (0)	NA
Neurological symptoms	11 (47.8)	10 (66.7)	1 (12.5)	0.027
Headache	6 (26.1)	6 (40.0)	0 (0)	0.058
Syncope	0 (0)	0 (0)	0 (0)	NA
Altered mental status	6 (26.1)	5 (33.3)	1 (12.5)	0.369
Meningoencephalitis	3 (13.0)	3 (20.0)	0 (0)	0.526
Seizures	3 (13.0)	3 (20.0)	0 (0)	0.526
Stroke	5 (21.7)	5 (33.3)	0 (0)	0.122
Claudication	0 (0)	0 (0)	0 (0)	NA
Pulmonary symptoms	2 (8.7)	1 (6.7)	1 (12.5)	1.000
Heart failure, cardiomyopathy	2 (8.7)	1 (6.7)	1 (12.5)	1.000

Table 1. Demographic, clinical and laboratory features at diagnosis.

	Total (n=23) no. (%)	Typical (n=15) no. (%)	KD (n=8) no. (%)	P value
Gastrointestinal symptoms	8 (34.8)	4 (26.7)	4 (50)	0.371
Eye symptoms	0 (0)	0 (0)	0 (0)	NA
Renal involvement	4 (17.4)	4 (26.7)	0 (0)	0.257
Decreased/absent pulses	0 (0)	0 (0)	0 (0)	NA
Systolic BP discrepancy in arms ≥ 20 mmHg	2 (8.7)	1 (6.7)	1 (12.5)	0.297
Bruits	4 (17.4)	4 (26.7)	0 (0)	0.257
Hypertension	9 (39.1)	7 (46.7)	2 (25)	0.543
Conjunctival injection	6 (28.1)	1 (6.7)	5 (62.5)	0.009
Mucosal changes	5 (21.7)	0 (0)	5 (62.5)	0.002
Rash	6 (26.1)	2 (13.3)	4 (50.0)	0.131
Cervical lymphadenopathy	3 (13.0)	0 (0)	3 (37.5)	0.032
Extremity changes	4 (17.4)	0 (0)	4 (50.0)	0.008
Laboratory findings				
Anaemia present	15 (65.2)	7 (46.7)	8 (100)	0.019
Haemoglobin (g/dL)	11.1 (9.7–13.1)	12.6 (10.9–13.3)	9.6 (8.9–10.7)	0.002
WBC ($\times 10^9/L$)	10.4 (7.7–15.3)	8.4 (7.2–10.4)	19.5 (15.2–36.0)	<0.001
Platelet ($\times 10^9/L$)	377 (248–532)	361 (218–463)	564 (314–718)	0.115
CRP (ng/L)	31.5 (5.4–139.1)	6.8 (1.9–33.2)	143.0 (80.8–173.9)	<0.001
ESR (mm/h)	41.5 (9.0–87.8)	31.0 (6.0–87.0)	82.0 (43.0–98.0)	0.046
ANA ≥ 160	2 (8.6) [n=17]	2 (13.4)	0 (0) [n=2]	0.860
Positive Mantoux test	4 (50) [n=8]	4 (50) [n=8]	NA	NA
Positive IGRA	1 (7.1) [n=14]	1 (6.7) [n=13]	0 (0) [n=1]	1.000

ANA: antinuclear antibodies; BP: blood pressure; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IGRA: interferon-gamma release assay; KD: Kawasaki disease; WBC: white blood cells

Musculoskeletal symptoms include arthralgia, arthritis, myalgia, back pain; gastrointestinal symptoms exclude vomiting that was due to neurological conditions. Hypertension refers to Stage 1 or 2 hypertension by American Academy of Pediatrics 2017 definition. Mucosal changes include red lips or strawberry tongue. Extremity changes include desquamation, oedema and palmar erythema. Values are presented as absolute numbers (%) or medians (25th–75th percentiles).

Overall, the most common presenting clinical features at diagnosis were fever (15 patients, 65%), neurological symptoms (11 patients, 48%), hypertension (9 patients, 39%) and gastrointestinal symptoms (38 patients, 5%, Table 1). Compared to the typical c-TAK group, the c-TAK-KD group had much higher proportion of patients with fever (8 patients [100%] versus [vs] 7 patients [47%], $P<0.001$), conjunctival injection (5 patients [63%] vs 1 patient [7%], $P=0.009$), mucosal changes (5 patients [63%] vs 0 patient [0%], $P=0.002$), cervical lymphadenopathy (3 patients [38%] vs 0 patient [0%], $P=0.032$) and extremity

changes including desquamation, oedema and palmar erythema (4 patients [50%] vs 0 patient [0%], $P=0.008$). Patients in the typical c-TAK group had more neurological symptoms (10 patients [67%] vs 1 patient [13%], $P=0.027$), of which a significant proportion presented with headache (6 patients, 40%), altered sensorium (5 patients, 33%) and stroke (5 patients, 33%).

Laboratory findings

Patients in c-TAK-KD group presented with lower haemoglobin levels (9.6 [8.9–10.7] g/dL vs 12.6 [10.9–

13.3] g/dL, $P=0.002$), higher white cell count numbers (19.5 [15.2–36.0] $\times 10^9/L$ vs 8.4 [7.2–10.4] $\times 10^9/L$, $P=0.002$), higher CRP (143.0 [80.8–173.9] mg/L vs 6.8 [1.9–33.2] mg/L, $P<0.001$) and higher ESR (82 [43.0–98.0] mm/h vs 31 [6.0–87.0] mm/h, $P=0.046$) (Table 1). Only 2 patients (8.6%) in the entire cohort had positive ANA. In terms of testing for tuberculosis, half of the patients tested had a positive tuberculin skin test, but only 1 patient (7%) had a positive IGRA; none of the patients were diagnosed with active tuberculosis.

Angiographic patterns

Twenty-one out of 23 patients (91%) had Type V angiographic patterns according to Hata's classification (Supplementary Table S1). The remaining 2, who displayed Type I and Type IV, belonged to the typical c-TAK group. Overall, the most commonly involved vascular segments cumulatively were mesenteric arteries (21 patients, 91%), abdominal aorta (20 patients, 87%), subclavian arteries (18 patients, 78%), renal arteries (17 patients, 74%), aortic arch (17 patients, 74%), carotid arteries (17 patients, 74%), followed by

descending (15 patients, 65%) and ascending aorta (13 patients, 57%) (Table 2). Not surprisingly, 100% (8 patients) of the c-TAK-KD group had CA involvement, compared to only 27% (4 patients) in the typical c-TAK group ($P=0.003$). None in the c-TAK-KD group had any intracranial artery involvement; only 1 of them had aneurysms in other medium-sized arteries (right brachial and left internal iliac arteries).

Treatment

The most commonly used immunosuppressive medications, besides glucocorticoids, were subcutaneous/oral methotrexate (MTX, 16 patients, 70%), followed by intravenous immunoglobulin (IVIg; 10 patients, 48%), intravenous cyclophosphamide (8 patients, 35%) and anti-tumour necrosis factor (aTNF, 8 patients, 35%) (Supplementary Table S2). All patients in the c-TAK-KD group received IVIg; 4 (50%) required MTX (after diagnosis of large-vessel vasculitis) and 3 (38%) required aTNF. Only 2 patients (9%) in the entire cohort received intravenous tocilizumab, and 1 of them (4%) received rituximab. Both of these patients were from the typical c-TAK group.

Table 2. Frequency of arterial territory involvement.

	Total (n=23) no. (%)	Typical (n=15) no. (%)	KD (n=8) no. (%)	P value
Intracranial arteries	6 (26.1)	6 (40.0)	0 (0)	0.363
Anterior circulation	5 (21.7)	5 (33.3)	0 (0)	0.333
Posterior circulation	3 (13.0)	3 (20.0)	0 (0)	0.606
Brain parenchymal changes (small vessels)	4 (17.4)	3 (20.0)	1 (12.5)	1.000
Pulmonary arteries	3 (13.0)	1 (6.7)	2 (25.0)	0.214
Carotid arteries	17 (73.9)	11 (73.3)	6 (75.0)	0.115
Vertebral arteries	8 (34.8)	6 (40.0)	2 (25.0)	0.437
Subclavian arteries	18 (78.3)	11 (73.3)	7 (87.5)	0.536
Ascending aorta	13 (56.5)	7 (46.7)	6 (75.0)	0.035
Aortic arch	17 (73.9)	10 (66.7)	7 (87.5)	0.066
Descending aorta	15 (65.2)	10 (66.7)	5 (62.5)	0.860
Abdominal aorta	20 (87.0)	12 (80.0)	8 (100)	0.675
Mesenteric arteries	21 (91.3)	14 (93.3)	7 (87.5)	0.462
Renal arteries	17 (73.9)	10 (66.7)	7 (87.5)	0.631
Iliac arteries	10 (43.5)	7 (46.7)	3 (37.5)	0.727
Coronary arteries	12 (52.2)	4 (26.7)	8 (100)	0.003

KD: Kawasaki disease

Values are presented as absolute numbers (%)

Outcomes

Sixteen patients (70%) in the entire cohort achieved CID with a median duration of 6 months (4–11) from treatment initiation (Table 3); a third of the cohort (8 patients, 35%) achieved CRM, with a median duration of 43 months (35–60) from treatment initiation. About a third of patients (8 patients, 35%) suffered at least 1 flare after achieving CID; the median duration from CID to flare was 13 months (4–17).

The typical c-TAK group had a higher percentage of patients achieving CID (80%) compared to the c-TAK-KD group (50%), although this did not reach

statistical significance ($P=0.182$). The c-TAK-KD group took a significantly shorter duration to achieve CID than the typical c-TAK group (Fig. 1, Table 3). The proportion of patients who achieved CRM was similar between the 2 groups (5 patients [33%] in the typical c-TAK group vs 3 patients [38%] in the c-TAK-KD group, $P=0.596$). Among the patients who achieved CID, there was a higher percentage of patients who flared in the typical c-TAK group (7 patients, 47%) compared to the c-TAK-KD group (1 patient, 13%), although this did not reach statistical significance ($P=0.176$).

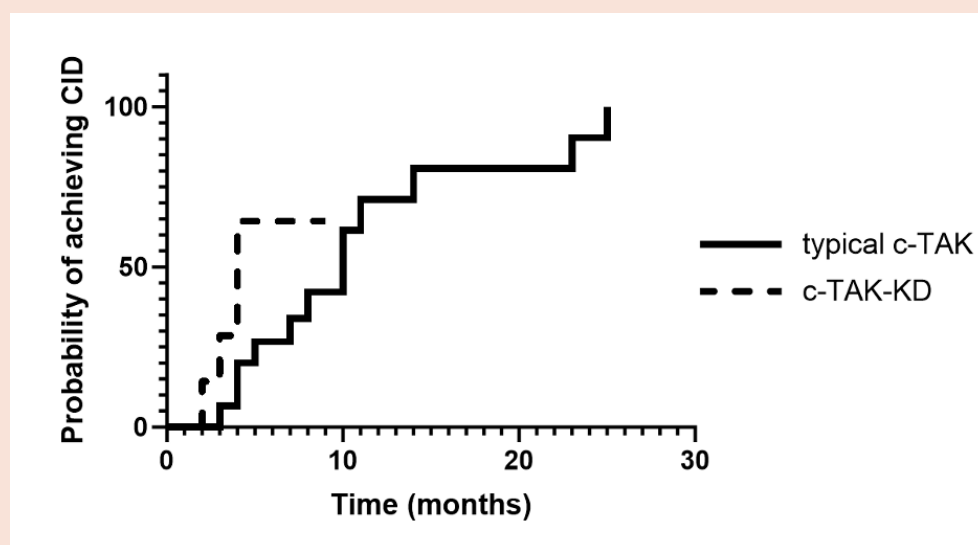
Table 3. Outcomes.

	Total (n=23) no. (%)	Typical (n=15) no. (%)	KD (n=8) no. (%)	P value
Achieved CID	16 (69.6)	12 (80.0)	4 (50.0)	0.182
Months from treatment initiation to CID	6.0 (4.0–10.8)	9.0 (4.3–13.3)	3.5 (2.3–4.0)	0.013
Achieved CRM	8 (35.0)	5 (33.3)	3 (37.5)	1.000
Months from treatment initiation to CRM	42.5 (34.5–60.0)	45.0 (39.5–65.0)	33.0 (2.0–NA)	0.393
Flare after CID	8 (35.0)	7 (46.7)	1 (12.5)	0.176
Months from CID to first flare	13.0 (3.5–17.0)	11.0 (3.0–17.0)	17.0 (17.0–17.0)	0.500
No new involvement on follow-up MRI	6 (26.0)	4 (26.7)	2 (25.0)	1.000
Contrast enhancement on MRI resolved	2 (8.6)	2 (13.3)	0 (0)	0.526

CID: clinically inactive disease (while on medication); CRM: clinical remission off medication; KD: Kawasaki disease; MRI: magnetic resonance imaging

Values are presented as absolute numbers (%) or medians (25th–75th percentiles).

Fig. 1. Kaplan-Meier curves of achieving inactive disease on medication (CID).



CID: clinically inactive disease (while on medication); c-TAK: childhood-onset Takayasu arteritis; c-TAK-KA: c-TAK with initial presentation as Kawasaki disease

The radiological course of the disease did not seem to mirror the clinical course in our cohort completely. Out of all patients, only 6 patients (26%) showed no new area of involvement in the follow-up MRA (Table 3). Even fewer patients (2, 9%) achieved resolution of previously noted contrast enhancement in at least one follow-up MRA.

All 8 patients in the c-TAK-KD group developed coronary changes, among which 5 (62.5%) had medium- to giant aneurysms (Supplementary Table S3). In 4 (50%) of the 8 patients, the coronary changes eventually returned to normal on follow-up 2D echocardiogram, with a median duration of 5.5 (1.5–29.0) months. Among those with coronary aneurysms (5 patients), 2 (40%) patients had medium-sized aneurysms, and both achieved normalisation of their coronary arteries on follow-up. Three (60%) patients had giant aneurysms; 1 passed away from myocardial infarction, another had a persistent giant aneurysm at the end of follow-up, whereas the third had partial resolution with a moderate aneurysm at the end of follow-up. The remaining patients had only coronary dilatations, all of whom had normalisation of coronary arteries except for 1 who passed away from non-cardiac cause.

DISCUSSION

To our knowledge, our study is the first to analyse a c-TAK cohort in Southeast Asia with unique clinical characteristics. This study is also the first to describe 2 distinct groups of patient types: typical c-TAK and c-TAK-KD, that initially presented with KD features.

At first glance, our cohort seemingly deviated from previous studies regarding female preponderance (43.5% vs 64–79%),^{32,34–43} as well as the age of onset (median 3.8 years vs 9.2–16 years). This is in part due to skewing by the c-TAK-KD subgroup, who presented at a younger age and trended towards a male preponderance (Table 1); excluding that, the typical c-TAK cohort had sex distribution and age of onset closer to previous cohorts. Expectedly, all c-TAK-KD patients had an initial presentation of fever, and most had multiple KD features, which were otherwise absent in most typical c-TAK patients. They also had significantly higher inflammatory markers at presentation, as opposed to the typical c-TAK patients, who tended to present at a convalescent rather than an inflammatory stage. This group of patients was initially managed with IVIg for KD, but was refractory despite second-line treatment (either second dose of IVIg or pulse methylprednisolone, or both), requiring further immunosuppressants, and eventually found to have angiographic evidence of large-vessel vasculitis. It is unknown if this group of patients constitutes a distinct clinical entity, but all of them still fulfilled the EULAR/PRINTO/PReS and ACR/EULAR classification

criteria for TAK.^{3,24} Kierzkowska et al. reported a 7-month-old female infant with an initial diagnosis of refractory KD who was later found to have abdominal aorta aneurysms.⁷ Lee et al. described a 4-year-old female with initial KD features and coronary aneurysms whose further imaging revealed diffuse aortitis.⁸ Shimura and colleagues also reported a 2-year-old boy with initial incomplete KD but had rapid deterioration, leading to death. Autopsy results indicated multiple sites of large-vessel stenosis, resulting in cerebral and renal infarctions.⁹ All 3 cases presented with an acute inflammatory state and fulfilled the criteria for KD diagnosis, but the diagnosis of c-TAK was only ascertained when the course of illness was atypical and further evaluations revealed other large vessel involvement. A recent report by Jin et al. described 10 patients with infantile-onset TAK (onset before 3 years old), more than half of whom were initially diagnosed and treated with KD, leading to significant morbidity and mortality.¹⁰ In patients with KD of an atypical course, a differential diagnosis of c-TAK should be considered, especially when patients are refractory to both first and second-line treatments.

Excluding the c-TAK-KD group, our typical c-TAK patients also differed from other cohorts in their clinical characteristics. Paediatric patients have been known to present with non-specific symptoms at a higher frequency than adults.^{2,34,43,44} However, our patients did not often present with constitutional symptoms like weight loss (3 patients, 20%) or malaise (2 patients, 13%). Comparatively, c-TAK cohorts in both the West and East Asia regions have significantly higher proportions of patients presenting with these constitutional symptoms (Fig. 2). Notably, our c-TAK patients also presented less often with hypertension (7 patients, 47%) compared to previously reported studies (57–100%).^{37,41} However, this did not preclude using the EULAR/PRINTO/PReS classification of c-TAK despite hypertension being one of the features listed. All our patients fulfilled both the EULAR/PRINTO/PReS and ACR/EULAR 2022 classification criteria.

None of our patients presented with claudication. In contrast, all cohorts in the current literature described patients presenting with claudication (Fig. 2). Apart from the UK cohort, all other cohorts, including West and East Asian cohorts, had more than 20% of the patients presenting with claudication.^{32,34–43} This is despite a relatively high proportion of patients with arterial involvement of the subclavian and iliac arteries (Table 2). On the other hand, our cohort of patients had a significantly higher proportion of patients presenting with stroke (33% vs 0–18%), all of whom had involvement of their intracranial arteries. This highlights c-TAK as an important differential diagnosis for ischaemic stroke in young patients with central nervous system (CNS) arteriopathies, in addition to

infectious, cardiac, metabolic, haematologic and genetic causes.⁴⁵ Evaluation of the aorta and its major branches should be considered in these cases.

In terms of angiographic patterns, the majority of our patients presented with Type V (21 patients, 91%), which is generally comparable to other cohort studies, although the latter did not have such overwhelming percentages (25–76%, Fig. 3).^{35,40} In addition, the most commonly involved territory in the entire cohort was the mesenteric arteries, followed by

the abdominal aorta. Looking at differences among the subgroups, the c-TAK-KD patients had no intracranial involvement, and unsurprisingly, all had involvement of the CA. Interestingly, the c-TAK-KD group had a significantly greater involvement of the ascending aorta than the typical c-TAK group (6 patients [75%] vs 7 patients [47%], $P=0.035$).

Even though most patients in our cohort were ethnically Chinese, the clinical characteristics were markedly different from various reports from

Fig. 2. Comparison of clinical features across major published cohorts of childhood-onset Takayasu arteritis (excluding patients with initial presentation as Kawasaki disease).

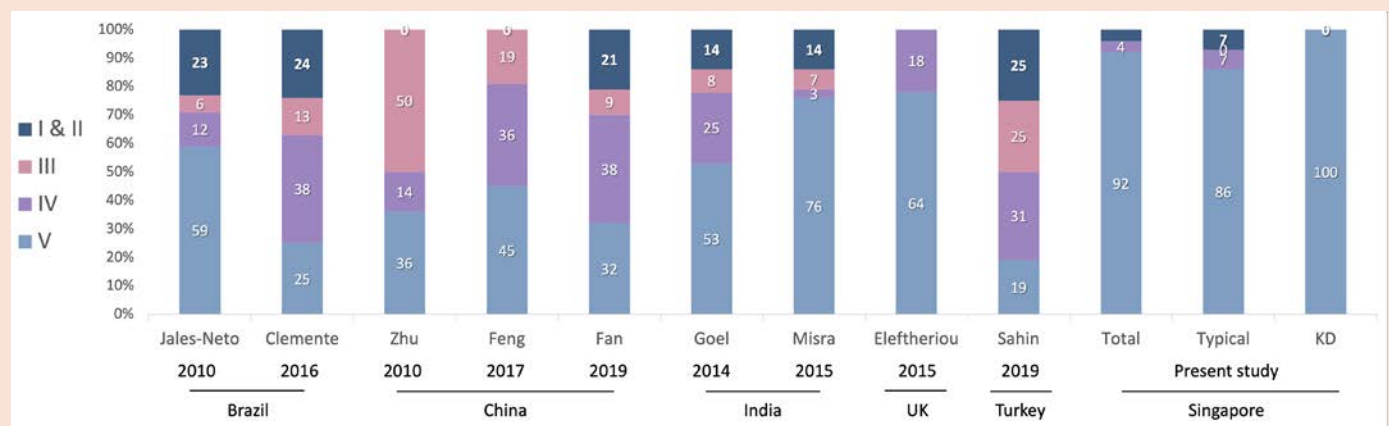
Cohort	Jales-Neto 2010	Clemente 2016	Zhu 2010	Feng 2017	Fan 2019	Goel 2014	Misra 2015	Szugye 2014	Eleftheriou 2015	Aeschlimann 2017	Sahin 2019	Present study
Country	Brazil		China			India		USA	UK	Canada	Turkey	Singapore
Fever	41	78 ^a	29	45	13	45	86	14	36	19	44	46.7
Weight loss	59		36	NA	NA	5	24	48	36	30	19	20.0
Malaise	NA		NA	NA	NA	53	24	38	NA	48	50	13.3
MSK sx	41	65	43	NA	NA	3	17	14	9	19	44	0
Neuro sx	NA	70	64	27	45	NA	34	24	36	NA	NA	66.7
Stroke	18	NA	0	NA	NA	8	7	0	18	11	13	33.3
Claudication	59	37	29	9	23	40	41	14	9	22	38	0
Pulmonary	12	54	21	NA	34	28	NA	19	27	15	0	6.7
Cardiac	18	18	29	9	25	20	14	5	27	NA	6	6.7
GI sx	29	58	64	45	NA	23	NA	NA	9	15	31	26.7
Eye sx	29	21	21	NA	NA	18	20	10	NA	15	13	0
Renal	NA	NA	7	27	NA	33	14	NA	9	NA	25	26.7
Rash	NA	NA	NA	NA	NA	NA	14	0	9	NA	NA	13.3
HTN	65	85	93	100	70	73	76	57	73	70	63	46.7

MSK sx: musculoskeletal symptoms (which include arthralgia, arthritis, myalgia and back pain); Neuro sx: neurological symptoms (which include headache, syncope, altered mental status, seizures, etc.); Pulmonary: dyspnea or other pulmonary symptoms; Cardiac: heart failure or cardiomyopathy; GI sx: gastrointestinal symptoms (not including vomiting from neurological involvement); Eye sx: ophthalmological symptoms; HTN: hypertension

^a Percentage of all constitutional symptoms.

Values are presented as percentages.

Fig. 3. Comparison of angiographic classification types across major published cohorts of childhood-onset Takayasu arteritis.



KD: Kawasaki disease

China,^{10,16,17,23} from presenting symptoms to angiographic types (Figs. 1 and 2). This again echoes the epidemiological variability of c-TAK across populations and geographic regions, highlighting the uniqueness of our Southeast Asian cohort.

TAK is commonly seen in East Asia, where the prevalence of *Mycobacterium tuberculosis* (TB) infection is high, with various studies showing an association between TB infection and TAK.^{46,47} Half of our patients who had testing had a positive Mantoux test, but only 1 (7%) had positive IGRA testing. This discrepancy could be due to the nationwide Bacilli Calmette-Guerin vaccination at birth. In addition, autoantibodies and autoreactive T cells against human 60kDa heat shock protein (HSP) are involved in the pathogenesis of TAK, and these have been shown to cross-react with the mycobacterial 65kDa HSP, causing a false-positive Mantoux result.⁴⁸ Nevertheless, none of our patients had active TB infection.

There is no recognised evidence-based recommendation for c-TAK treatment thus far. As such, there is a variation of preferred immunosuppressive agents for c-TAK in institutions worldwide. Treatment decisions for patients in our cohort were made at the discretion of the attending rheumatologists, although references were drawn from existing adult large-vessel vasculitis management guidelines by EULAR and ACR. Other than the obvious use of IVIg for c-TAK-KD, MTX was the most commonly used non-steroidal immunosuppressive agent in our cohort, which corresponds with the majority of previously published studies. This is compared to mycophenolate mofetil in an Indian study and azathioprine in a Turkish cohort.^{39,43} In our cohort, MTX was followed by cyclophosphamide in the typical c-TAK group (7 patients, 47%) and infliximab in the c-TAK-KD group (3 patients, 38%). Notably, the outcomes were not significantly different between the typical c-TAK and c-TAK-KD groups. Both groups had similar rates of achieving CRM during treatment, although the former trended towards a higher flare rate after inactive disease.

Previous studies of KD showed that close to 25% of patients developed CA lesions if not treated with IVIg.⁶ In comparison, patients in our c-TAK-KD cohort universally developed some degree of coronary lesions. Five (63%) of them received timely administration of the first dose of IVIg (Day 3 to 7 from fever onset); despite this, 4 developed medium- to giant coronary aneurysms (Supplementary Table S3). This observation, together with findings of large-vessel involvement, suggests that they are a clinically distinct group from the “run-of-the-mill” KD patients.

Lastly, although many of our patients achieved CID, the resolution of radiological features did not seem to correspond. Only 2 (9%) of our patients had a resolution of enhancement on MRA. However, the rest of

the patients remained asymptomatic throughout their follow-up, suggesting a discrepancy between MRA findings and disease activity. In 1 meta-analysis, the reported utility of vessel wall thickening and enhancement by MRA to detect active disease in TAK varied across studies.⁴⁹ Sartorelli et al. found that MRA had a 50% concordance with clinical assessment of disease activity and that vessel wall enhancement did not predict stenosis at follow-up in 2 years.⁵⁰ Kato et al. compared 2 groups of TAK patients with active and inactive diseases, respectively, and showed that late gadolinium enhancement on MRA was useful in detecting the distribution of vessel wall involvement but was unable to accurately assess disease activity.⁵¹ An MRA scoring system with a combination of abnormal findings was proposed, but this was not validated in c-TAK cohorts.⁵² These findings emphasised the limitation of MRA imaging for disease monitoring in c-TAK and cautioned against the sole dependence on MRA to guide treatment.

This study is not without limitations. The sample size is small, but to our knowledge, this is the largest study on c-TAK to date in a Southeast Asian paediatric population. We acknowledge the potential for referral bias in this single-centre study; however, our centre—being the only children’s hospital in Singapore, with the biggest paediatric rheumatology clinic—helps to ensure its representativeness of the local population. Although we use a validated instrument (PVAS) to measure disease activity, other measurement tools exist.^{53,54} There is ultimately no universally accepted disease activity measure for childhood TAK yet. We had the availability of repeat MRA imaging in most patients, but FDG-PET scans were not routinely performed in our institution. Hence, we cannot compare and correlate findings between both imaging modalities. Lastly, we describe a distinct group of c-TAK-KD patients, but due to the small sample size, we could not match the patients with typical c-TAK for a more robust comparison between the 2 groups.

CONCLUSION

Our c-TAK cohort has unique characteristics compared to the Western and East Asian cohorts. It also highlights the heterogeneity in demographic, clinical, and angiographic characteristics of c-TAK in different geographic locations. The high proportion of CNS involvement and stroke in our cohort prompts c-TAK as an important differential diagnosis in young patients with stroke. Our observation of a distinct group of patients who initially presented with KD features has not previously been described. Early recognition of these entities and anticipating disparate treatment outcomes are essential to help reduce morbidity of our c-TAK patients through timely immunosuppression. Future studies would benefit from a longer follow-up

duration and larger sample size to better understand this subgroup of c-TAK patients.

Supplementary material

Supplementary Table S1. Angiographic classification type.

Supplementary Table S2. Treatment.

Supplementary Table S3. Clinical characteristics and treatments of c-TAK-KD patients.

Ethics

The SingHealth Centralised Institutional Review Board (2019/2961 and 2019/2194) approved this study and waived the need for informed consent due to the nature of retrospective data review from the registry.

Declaration

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

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In my time: A qualitative exploration of the junior doctor experience in Singapore over the years

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ABSTRACT

Introduction: Despite efforts to improve junior doctors' working conditions, burnout, distress and disillusionment persist, with implications for patient outcomes. This qualitative study analysed factors shaping the lived experiences of junior doctors in Singapore and their changes over time, thereby seeking to inform improvements to working conditions.

Method: Thirty purposively sampled respondents who were junior doctors in Singapore between 1975 and 2022 were interviewed. Respondents were grouped into 3 cohorts: (1) junior, (2) middle and (3) senior. Employing the framework method of qualitative analysis, open coding was performed with reference to the individual, interpersonal, institutional, community and policy levels of the socioecological model (SEM).

Four themes emerged: (1) inherent challenges of junior doctorship, (2) exacerbating factors, (3) alleviating factors and (4) responses of junior doctors to their experiences. Codes were reconstructed into a modified SEM, demonstrating trickle-down effects of interpersonal or structural forces on the individual doctor and pertinent factors evolving with time.

Results: Across cohorts, respondents echoed mental and physical challenges. While senior cohort doctors recounted higher patient-to-doctor ratios and longer working hours, junior cohort doctors cited new difficulties. These include a hostile medicolegal landscape, patients' increasingly complex needs and expectations, and higher administrative loads. Amid these difficulties, alleviating factors included good workplace relationships alongside institutional interventions. Doctors responded differently to their challenges. Some externalised difficulties through expression and advocacy; others internalised them, whether into fulfilment or distress.

Conclusion: While some facets of junior doctorship have improved with time, new challenges that warrant consideration are emerging. Junior doctors should be centred, listened to and empowered in shaping improvements to working conditions.

Keywords: burnout, junior doctors, medical education, mental health, qualitative research

CLINICAL IMPACT

What is New

- To the best of the authors' knowledge, this exploratory qualitative study is the first to examine the lived experiences of junior doctors in Singapore over several decades.
- Findings demonstrate factors in the junior doctor experience that have impacted junior doctors in Singapore from the 1980s to the present day.

Clinical Implications

- Through first-hand accounts from doctors themselves, this study lends deep insight to policymakers and senior management seeking to improve the experiences of junior doctors in Singapore, with notable downstream effects on patient safety.

INTRODUCTION

Junior doctor well-being is a prominent global issue.¹ Navigating the formative years of a career requiring expertise and high-stakes decisions, junior doctors are challenged considerably. These pressures impact patient outcomes and workforce retention.¹ Despite interventions intended to improve working conditions,² distress and disillusionment prevail.¹ COVID-19 spotlighted these concerns in the public eye.³ However, in the post-COVID era, junior doctor well-being remains under-addressed.⁴

Junior doctors in Singapore include house officers (recently-graduated doctors serving their year-long housemanship) and medical officers (either undergoing initial years of training in residency or non-specialty tracks, or rotating every 6 months via the national Medical Officer Posting Exercise).⁵ To pay subsidised tuition fees, graduates from local medical schools are

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bonded to the public healthcare system for 4–5 years following housemanship.⁶

Previous local studies have quantified junior doctor well-being and stress via survey instruments.^{2,7–9} These addressed specific contexts including COVID-19,⁹ individual specialties⁷ and institutions.² Recent qualitative study examines junior doctors' experiences in Singapore's public healthcare system¹⁰ via a priori framework concerning job demands and satisfaction. Singapore's healthcare landscape, cultural perceptions and institutional frameworks have evolved significantly.¹¹ Thus far, no local studies have explored junior doctors' experiences open-endedly across time.

This qualitative study aims to analyse the factors shaping the junior doctor experience in Singapore and their changes over time. It interprets junior doctors' experiences in their own words, capturing the interplay of environmental and individual forces. It also seeks to elicit variables promoting well-being or distress in Singapore's junior doctors, exploring how and why these have evolved. Through this, the aim of this study is to encourage systemic change towards a more conducive environment for junior doctors, thereby improving patient safety.

METHOD

This qualitative study comprised semi-structured interviews with doctors who graduated from 1980 to 2021 and became junior doctors in Singapore's public healthcare system thereafter. This study was approved by the National University of Singapore Institutional Review Board (2022-248) and reported according to the 2014 Standards for Reporting Qualitative Research.¹²

Theoretical approach

The framework method of qualitative analysis was adopted, which was formalised in 1994¹³ and has since been widely used in health research.¹⁴ This method was chosen because it allowed both a data-driven (inductive) and theory-driven (deductive) analytical approach.¹⁴

Our starting point was the socioecological model (SEM) first described by Bronfenbrenner in 1979.¹⁵ Widely featured in public health research, the SEM influences health interventions and demonstrates reciprocal relationships between individuals and environments.¹⁶ The interview guide was designed to centre on the lived experiences of junior doctors, and having respondents walk through their junior doctorship.

Our team comprised junior doctors and medical students. Cognisant of possibly prioritising our own narratives over participants, this risk was mitigated through regularly discussing the authors' relationships with the data, with close oversight from the principal

investigator, a senior clinician-educator. Simultaneously, identifying with this study afforded a critical lens for data collection and analysis.

Participant recruitment, data collection and data processing

Inclusion criteria required participants to be over 21 years old and to have worked as a junior doctor in Singapore's public healthcare system between 1975 and 2022. For recruitment, a junior doctor was defined as a house officer or medical officer. During interviews, participants could self-define "junior doctor."

Employing purposive sampling, participants were recruited online through a form circulated via the Singapore Medical Association. Forty responses were received, among which 9 respondents were subsequently uncontactable and 1 withdrew, leaving 30 participants. The participants were grouped into 3 time-based cohorts that reflect significant policy changes in Singapore's healthcare system: (1) senior cohort (1980–1999 graduates), (2) middle cohort (2000–2014 graduates) and (3) junior cohort (2015–2021 graduates). Policy changes that were considered included healthcare digitisation in the early 2000s, as well as duty hour mandates and the revision of remuneration in the mid-2010s.

Online interviews were conducted by 4 team members between September and November 2022. Verbal consent was sought in lieu of written consent, and interviewees could disable their video feeds for privacy. Study team members were briefed to identify signs of participant distress and alert the principal investigator if needed; participants were reminded of their ability to withdraw at any time. Interviews were audio-recorded, anonymised, and then transcribed using artificial intelligence (AI). AI-generated transcripts were manually corrected and proofread by medical student volunteers with direct reference to audio recordings. Participants were reimbursed with a SGD20 shopping voucher.

Data analysis

Our coding approach was both deductive and inductive. The layers of the SEM (from individual to policy) formed the skeleton of a coding frame, with an additional category representing factors that evolved over time. Open coding¹⁷ was performed by 5 team members and key codes were categorised into the coding frame skeleton. The coding frame was iteratively revised through discussion to resolve any inter-coder disagreement before consolidating overarching themes and generating a modified SEM. Thematic saturation was assessed through iterative team discussions regarding the emergence of new themes within each cohort. There was consensus

that code saturation had been achieved within each cohort, with no new meaningful codes generated after 11, 11 and 8 interviews within the senior, middle and junior cohorts, respectively.¹⁸ Thus, no additional participants were recruited.

RESULTS

Among the 30 participants interviewed, 11, 11 and 8 doctors were from the senior, middle and junior cohorts, respectively. Participant characteristics are presented in Supplementary Appendix S1. Across all cohorts, most respondents worked in tertiary care, although 4 middle cohort doctors practised in primary care. Most senior cohort doctors were senior consultants who had experience in both private and

public institutions; most middle cohort doctors were consultants, with a few resident physicians. Most junior cohort doctors were either medical officers or residents, with one locum.

System differences across generations

Participants surfaced key differences in junior doctors' work from day-to-day responsibilities to the broader sociocultural climate. These were corroborated with secondary sources^{19,20} and summarised in Fig. 1.

Key themes elicited were (1) the junior doctor experience as inherently challenging, (2) exacerbating factors, (3) alleviating factors and (4) responses of junior doctors to their experiences. These themes are discussed sequentially.

Fig. 1. Data gathered from interviews and secondary sources about the objective working conditions in each cohort of doctors' respective experiences.

1970s ————— 2000s ————— 2020s —————>			
	Senior cohort	Middle cohort	Junior cohort
On-call system	30 to 36-hour call system - No restriction to number of calls per month, reports of up to 11 calls per month	- Majority 30 to 36-hour call system - Maximum of 8 calls per month	- Majority 30-hour call system - Minority with 24-hour call system or night float system - Between 4–8 calls per month
Day-to-day duties	Significant time spent on ward-based procedures (e.g. venepuncture, cannula setting)	Mix of administrative work (physical and digital) and ward-based procedures (e.g. venepuncture, cannula setting)	Significant time spent on digital documentation and patient/family communication
Patient load (day time)	Generally 20–40 patients per junior doctor during day time	Generally 10–20 patients per junior doctor during day time, but at times up to 30–40 patients	
Health records	Physical case notes	Mix of physical and electronic health records	Majority electronic health records
Supervision	Expected to perform complex procedures under minimal supervision (e.g. chest tube insertion, lumbar puncture)		Close supervision required for procedures; less experience with complex or uncommon procedures
Specialist training and career options	- BST versus (vs) AST system - Most non-specialist trainees would opt for general practice	- Transition towards residency system - Introduction of alternative career options to general practice vs specialist training (e.g. resident physician track)	- Residency system - Introduction of further alternative career options (e.g. hospital clinician scheme)
Medical decision-making	More paternalistic model of medicine	Shared decision-making with increasing health literacy	
Goals/priorities	- Professional development - Skill acquisition	Professional development, often directed towards selection for residency	- Work-life balance - Professional development, directed towards varied career end-points
Milestones	1978: Introduction of bond for doctors¹⁹ 1980s: Work-to-rule collective action (anecdotal) 1987: MOH Holdings established¹⁹ 1990s: Doctors paid for calls (anecdotal)	2000s: More nurses accredited for ward-based procedures²⁰ 2003: SARS 2000s–2010s: Transition to electronic medical records 2010s–2020s: Rise of blogs/social media	2010s–2020s: Rise of social media accounts 2019–2021: COVID-19 pandemic

AST: Advanced Specialist Training; BST: Basic Specialist Training; MOH: Ministry of Health; SARS: severe acute respiratory syndrome

Table 1. The junior doctor experience as inherently challenging.

Layer of modified SEM	Sub-theme	Quote
Individual Impression of work as a junior doctor	Perceived role as a junior doctor	"I think my role was largely to make sure all the changes were done. [...] Keep patients alive as much as we could. Keep relatives happy and the patients happy." – Participant M7, middle cohort
		"The way I thought about it is that we are the workhorse and we are the buffers. Anything, we will try to, you know, take as much as possible, and just let a few things get escalated." – Participant M8, middle cohort
Interpersonal Impact of relationships on self	Navigating hierarchy	"The thing about [being a] junior doctor is that you're constrained by being junior. So a lot of times, plans from seniors, you don't really agree [...] it's not best practice; but a lot of times [we just] sort it out, just do it because the senior says so. Then there is a feeling of powerlessness, I guess, because you're still beholden to the powers above you." – Participant J8, junior cohort
		"Just because, you know, 'I'm a registrar or consultant, I say this, therefore, just shut up and do it.' I think that was one of the hardest for me to deal with because they can be wrong, right?" – Participant M3, middle cohort
		"Housemanship is a very arbitrary construct. You were at the bottom of the food chain." – Participant S5, senior cohort
Individual Impression of work as a junior doctor	Steep learning curve	"On call, sometimes the MO (medical officer) is busy, the reg (registrar) is away, you can't possibly call the consultant [...] you are really alone to make a decision. And you do not know enough, you do not know if this is within your role, is this really expected of you. Sometimes that's really tough." – Participant M4, Middle Cohort
		"One of the first realisations as a houseman is that you realise a lot of stuff that you learned in medical school didn't really equip you for the day to day working as a doctor." – Participant S6, senior cohort
		"[As a medical officer], I felt at least I needed to be a little bit more independent in decision-making, which would be different from being a house officer, where there was always a medical officer to turn to and say, 'I don't know what to do.'" – Participant S7, senior cohort
Individual Impression of work as a junior doctor	High stakes; reckoning with mistakes and limitations	"I guess the first low point was my first patient [who] died. That was really quite a terrible experience after up till now it's still in my mind; I still have his name in my mind, I still know exactly what happened I know which ward, which bed [...] the first death is what you will never forget." – Participant S3, senior cohort
		"Well, I think the main thing that made it traumatic was first of all [...] you actually were dealing with medicine. You are dealing with people in pain, you're dealing [with] people who are, you know, who are frightened and they were worried. You're dealing with some children who, you knew were terminal, and you know, the pain and, and it's really there in front of you." – Participant S6, senior cohort
		"There's also difficulty when, when you make certain mistakes and the consequences [...] hopefully they don't have lasting impact, but some of them do. And trying to learn from that and move on is sometimes can be, can be a struggle. Yeah, because it can potentially be like something that comes back to haunt you, you know, if a similar situation comes up." – Participant J7, junior cohort
		"[Things feel] a bit futile at times. [...] When a patient [accumulates] a certain cluster of comorbidities, or they have a certain social circumstance tied in with those comorbidities, no matter what you do for them—and you can give them the correct treatment... y'all do everything correctly, evidence-based, and you get them well and out the hospital... but within a few weeks [or] a month or so, you probably see them back in the hospital again." – Participant J7, junior cohort
Individual-institutional Physical and mental demands of being a junior doctor	Fatigue and stress	"Ahhh, the mental stress, I suppose, and the physical stress. I have friends who are on calls they get migraines and vomiting in the toilets. [...] You're so tired, you haven't eaten, you haven't peed, you haven't showered, you haven't brushed your teeth. But you just have to keep going because there's this whole list of things that needs to be done." – Participant M6, middle cohort

Table 1. The junior doctor experience as inherently challenging. (Cont'd)

Layer of modified SEM	Sub-theme	Quote
		I think by the time you get to about 12[pm] to 2[pm], 12[pm] to 3[pm], that's the time when it's like a big struggle to stay awake. And that's when a lot of mistakes happen [...] But there're pharmacists also counter checking your work. So that's a bit of a safeguard. And of course, the nurses will also look through the meds and make sure that it makes sense for the plan. – Participant J7, junior cohort
Individual–institutional Physical and mental demands of being a junior doctor	Impact on patient care	"If you're rushed, you're just thinking about the next thing that needs to be done, the next thing that's waiting for you are the next call that's going to come and all that [...] Whereas if you really have that time to sit and talk, [and] just spend that time interacting [with that] patient or that family member, then yeah, it makes a big difference. Yeah." – Participant M11, middle cohort The whole year I was just on survival mode. [...] It's a shame because I feel that your housemanship year [is] actually a very good opportunity for you to learn to relearn a lot of basics, [because in medical school, you never] really fully grasp all these concepts [like] clerking a patient and doing all the procedures until you are forced to do it, especially at night, but it's a pity because the schedule was back then it was so packed that I didn't feel like I had time to really sit down and reflect on my cases to learn." – Participant M9, middle cohort
Individual–institutional Relationships outside of work	Sacrifice and compromise	"Hardly ever saw anybody because we were doing 1 in 3 [calls]. So as I used to say, no social life for the duration of the traineeship." – Participant S4, senior cohort "Family? I think I'm non-existent to them." – Participant M4, middle cohort "I mean, in that period of time, I got married as well. So it's like that. I remember what my boss told me at that time, 'Okay, you're great, you got a 1-week honeymoon, take any more time and I'll have to cancel your posting.' He was kidding of course, but that having been said, it was a rule that in a posting the most you can get off is 1 week." – Participant S2, senior cohort

SEM: socioecological model

Theme 1. The junior doctor experience as inherently challenging.

Table 1 summarises key quotations from participants about inherent difficulties to being a junior doctor. Across cohorts, participants described challenges arising from their duties and perceived role in the healthcare team. Duties were largely ward-based: attending ward rounds, performing bedside procedures, documenting progress and communicating with families and other professionals. To most, their responsibilities were to execute plans (referred to as "doing changes") and minimise escalation to seniors. Some described administrative duties as "not very meaningful," while others lamented following orders they sometimes disagreed with.

On the flipside of this hierarchy lay another inherent challenge of junior doctoring—the steep learning curve. Key milestones included transitioning from student to house officer, and then to medical officer. Several participants across cohorts recounted feeling underprepared for their roles. Often, distress arose when participants had to function alone, whether due to emergencies or barriers in reaching seniors for help—real or perceived. Exacerbating these were the high stakes of medical decision-making, the narrow margin for error and the emotional intensity of the job.

One last challenge partially inherent to junior doctoring was its physical and mental demands. Long working hours and on-call duties were oft-cited stressors. Some respondents cited how fatigue compromised patient care and safety. Many participants described spending their junior doctor years in "survival mode" and making various "sacrifice[s]." Participants recognised that rigour was necessary for them to learn; simultaneously, some considered its extent unwarranted.

Theme 2. Exacerbating factors that made the junior doctor experience more challenging.

Table 2 details key interview excerpts regarding factors compounding the inherent challenges at work. Several participants raised concerns about manpower and patient loads, describing workplaces as running at or over capacity. Acknowledging recent institutional efforts to improve working conditions, participants observed barriers or gaps in implementation, including institution-to-institution variations and entrenched workplace norms.

Another issue, especially among middle and junior cohort doctors, was the heavy administrative load which some found disproportionately high compared to overseas. Alongside this were grievances concerning inefficiencies of the electronic medical records system.

Table 2. Exacerbating factors that made the junior doctor experience more challenging.

Layer of modified SEM	Sub-theme	Quote
Institutional Operational factors in healthcare institutions	Manpower, patient load and running at capacity	"It was very, very stressful. When someone was on leave, you're either pre-call, post-call or on call. So you're constantly doing calls." – Participant S10, senior cohort
		"Interviewer: With that doctor–patient ratio, did you have the bandwidth and the time to treat [your patients] as well as you wanted to? Respondent: Unfortunately, the answer [...] is no. You're just busy trying to settle your urgent changes. And like I always have to say, save one sinking <i>sampan</i> (Malay word for rowboat) at a time. It perpetually felt like things were on fire and you just had to put out the fire one at a time." – Participant M9, middle cohort
		"When I was studying overseas, in [the] UK, discharge issues [weren't] that common. I mean, patients wanted to go back home; that was the aim. [Here, a] lot of patients don't want to go back home, they are either home alone, or they don't have the support at home [...] The waiting time for like nursing homes, community hospitals is very long [...] which makes it difficult for junior doctors to try and offload the admissions and the patients in the hospital." – Participant J1, junior cohort
		"Sometimes I feel like [patients] just need someone to talk to. A lot of them keep coming in for, you know, 'I have pain in my back, I have pain in my back, I have pain in my back.' But everyone just says, 'okay, X-ray's normal, X-ray's normal, MRI is normal.' [...] But there must be a reason why they keep obsessing over it. [...] [In internal medicine,] every complaint has an origin, but [doctors] don't have enough time to address every single one of them. Because sometimes we have 20 patients [to round]. You can't spend that much time speaking to them. You know, it's tough, it's tough. Another issue is when you also get a text saying, 'bed occupancy rates is 120%, please discharge patients.' Which is like, how are you supposed to deal with that?" – Participant J3, junior cohort
		"I felt like maybe the media or the ministry itself portrayed that it was a COVID-related surge that caused a break in the healthcare system. But I mean, those of us who were in the system before, I think many colleagues could testify that it was already overflowing before. [...] Maybe not, not breaking yet, but there was close to overload before. Not entirely new to COVID [but] COVID probably did push it over the edge at the end." – Participant J2, junior cohort
Policy System-level rules and workflows	Unenforced policy	"Although <redacted: national employer of junior doctors> now is trying to get doctors to not see new patients after 24 hours, meaning to say we can work for like 30 hours but like the 6 [hours] past 24 hours we shouldn't be seeing any new patients according to the latest <redacted: employer> guidelines if I'm not wrong. [But] I think due to manpower shortages [...] most of the time, I mean like 90–95% of the time, we still have to run clinics or be in [the operating theatre] post-call [...] If you [were to] try and enforce [24-hour calls instead of 30-hour calls] with a lack of manpower on the ground, then the person that ultimately suffers is the patient. Let's say I go post-call sharp at 8 am sharp, then there's not enough MOs to provide coverage. See, then yeah, ultimately [it's] the patient's care that will be compromised." – Participant J5, junior cohort
		"Every clinic in [my list] right now [...] So, two o'clock is first appointment. 2:05 is the next one. Third appointment's 2:05. Fourth appointment's 2:05. Fifth appointment is 2:10. So [multiple] appointments are 2:05 to 2:10. Does that mean each patient gets less than 2 minutes?" – Participant J3, junior cohort
		"The culture of each hospital, the workload is all very different. And I feel like <redacted: national employer of junior doctors> as an overarching, organisational body, I felt like they were very ill equipped to deal with the differences." – Participant M9, middle cohort
		"But I think that there are a lot of so-called cultural things that in the practice of medicine, in the hospitals. So for example, the rounding before your MO, and rounding before your registrar, preparing those team lists, exiting late, making sure you finish all the changes before you go. I think those are cultural things." – Participant M5, middle cohort

Table 2. Exacerbating factors that made the junior doctor experience more challenging. (Cont'd)

Layer of modified SEM	Sub-theme	Quote
		"[As a resident, we were supposed to] log in hours, honestly, and of course, unsurprisingly, when I log in my hours, it always exceeded, there was always an alert because I always exceeded. So in the end, what happened was instead of the residency, so instead of coming to find out, you know, why am I reaching my hours all the time, this is a thing that should be looked into, things like that, they basically just told me to lie about my working hours, they told me to not log in more than what would exceed the hours you see. So I told her I was logging in my honest hours, and they just didn't care. They just asked me to not more than x number of, regardless of the true working hours." – Participant M10, middle cohort
Institutional Operational factors in healthcare institutions	Administrative load of junior doctors	"When I was meeting fellow junior doctors from other countries, they were allowed to do much more from what our local doctors are allowed to do. [What Singaporean doctors do instead], a lot of it is administrative work, isn't it? Like ordering medicine, taking history, organising scan, all those things are actually not, not very meaningful, learning wise. You'd be probably better if you spent that time learning how to do procedures under supervision." – Participant M5, middle cohort
		"Our healthcare system is very reliant on the compliance and the confidence of our medical profession. Yeah. So, for example, if let's say an operating theatre needs to be closed, and there are already patients there: in the UK, what happens is that there's a clerk who will rearrange everything. Slot the patient elsewhere, rearrange the anaesthesia review, financial counselling, and all that. In Singapore, you don't have that. Everything is up to the doctor." – Participant J4, junior cohort "I'm not trying to say we are damn great and do what, but it's like, you go through 5 years or 6 of med school and train, and then you end up filling forms and taking bloods, which can be taught in one day and you can start working you know? Some of my classmates, to earn extra money, they become phlebotomists on the weekend and you actually earn more than an on-call houseman." – Participant S11, senior cohort
Policy System-level rules and workflows	Electronic medical records	"The huge benefit of the computer system is that it brings information with it, but that is also its downfall, because there's so much information to sift through and to look through that sometimes that can make things even more complicated than it really is.... How did we even come up with 'pre-clerking'? [It's] because we have to go to the computer system to pick up all the information. [...] And because there are so many computer systems nowadays, this like, you have to look through every single one." – Participant J7, junior cohort
		"Can you see how inefficient it is? And unfortunately, I have to say the poor junior officers have to bear [the brunt of this] inefficiency [...] And who has put this in place? [...] They spend thousands and thousands and thousands, hundred thousands or millions of dollars on all these IT systems which sometimes crash or they're on maintenance. You know, and then who has to scramble? The poor junior doctor [...] But all the IT that I've seen. They don't work in favour of the doctor. [...] In fact, this comment by a medical officer recently, she said, you know, it's faster to handwrite when the system was down [...] This was just recently, I can tell you, a few months ago, because the system was under maintenance. How can you have a system that [is] under maintenance from five o'clock in the morning to one o'clock?" – Participant S7, senior cohort
Society/community Scope and nature of medical practice	Increasing complexity	"Globally speaking, we're talking about ageing population, much more elderly, much more complex, both medically [and] socially as well [...] [People have] smaller families, no caregiver, heavily dependent on foreign worker, which may or may not work out. [There are] long queues for nursing homes because there's no caregiver available. [...] Very often, [families are] asking the medical team to play a coordinating role in this and it can be very difficult to tie all these <inaudible> together into one plan." – Participant J6, junior cohort
		"The treatments are a lot more complex. For example, you only had sulfonylureas, metformin and insulins back then. There's no DPP4, there were no SGLT[-2 inhibitor]s, for example. There's no acarbose even, for diabetes, so the complexity in terms of drug decision making, in terms of the interactions, in terms of the complexity of choosing the right treatment, among the panoply of options, has gone up tremendously." – Participant S9, senior cohort

Table 2. Exacerbating factors that made the junior doctor experience more challenging. (Cont'd)

Layer of modified SEM	Sub-theme	Quote
		"We are doing a lot more than what we could do [previously]. The scope of medicine has expanded, things that used to be done in certain limited locations are expanded. For example, polyclinics have an ultrasound, where it was used to be only a tertiary hospital thing. We can do a lot more lab tests than what we did [before]..." – Participant M4, middle cohort
Society/community Patients and families	Expectations and attitudes	"But nowadays, you know, it's, it's never so straightforward. I mean, sometimes, yes, there are still family members who have implicit trust with the healthcare system and don't really question anything. But more [often] what actually happens is that there's a lot more questioning, nitpicking, I guess. Yeah. And, and Dr. Google always wants to have a say in these situations." – Participant J7, junior cohort "The workplace is increasingly hostile in terms of interactions with patients." – Participant S9, senior cohort "In my first week [...] I was told by the patient [that they would] report me to SMC, they were going to stop me, they were going to report me to Zaobao (local Mandarin newspaper). [...] When I was an MO (medical officer), [...] there was this patient's family who was very unreasonable. [...] They somehow got my private phone number, [and were] calling me at weird hours of the day. [...] I think they posed as a doctor and got my phone number. They were just calling me at all times of the day to try and scold me, and they wanted really unreasonable things. Like they wanted the on-call doctor to come and give their patient a foot massage. Like 11 plus, 12 plus at night." – Participant M8, middle cohort "I am a GP now and I do like to engage my patients. [But] some patients actually can be quite combative. They can actually believe the videos or whatever that they see on the internet, which says things like, '10 things your doctor doesn't want you to know', you know, or 'your doctor is actually secretly trying to kill you', you know, that sort of thing." – Participant S11, senior cohort
Society/community Patients and families	Expectations and attitudes	"Updating families is probably one of the changes that does occupy most of the time. Each phone call depends on how the patient is, how critically ill they are. One phone call can take an average of half an hour. And also some families requested to be updated, like more family members request to be updated for the same patient. So that can take some time." – Participant J1, junior cohort
Society/community Scope and nature of medical practice	Defensive medicine	"The practice of medicine has become, definitely, more defensive than [when] I first knew it. Everything is like because of medical, legal, [...] you can sue for anything now. Especially, I think it's just something that's imparted in from the (United) States, right. So definitely a lot more defensive than before. Therefore, that's why a lot of ancillary work has been done, like documentation, everybody is like running a lot of other things, tests additional stuff, just to make sure you don't miss out that 1%, that could come back and haunt you." – Participant M3, middle cohort "Sometimes patients suspected doctors are trying to make money and then the doctors are suspecting the patients are trying to sue them. So then it becomes a very unhealthy relationship." – Participant M7, middle cohort "Defensive medicine is not helpful to anyone, not to patients, to society, or public healthcare expenditure. [...] When these [medical lawsuits] become public, whether it's warranted or not, there's always a court of public opinion. So the media tends to publish the names of the doctors, everything, even before a conclusion has been made. And I think that's not good. [...] Yeah, our public healthcare expenditure is exploding." – Participant J4, junior cohort "I [spend] more time documenting, and I have to be a lot more careful when I document. [...] More time spent documenting means less time, for example, physically seeing the patient or compromising on time for the next patient, and things like that, especially in a clinic setting whereby we have to finish seeing the patients by a certain time." – Participant J5, junior cohort "The medical legal climate is very different. And I don't mind saying it's mainly because of the medical legal climate that I've decided to stop working." – Participant S7, senior cohort

Table 2. Exacerbating factors that made the junior doctor experience more challenging. (Cont'd)

Layer of modified SEM	Sub-theme	Quote
Interpersonal Impact of relationships on self	Workplace bullying	"We just get totally trashed by our registrar in particular... they were extremely, extremely, unreasonably demanding. [...] The registrar would expect, like absolute perfection for everything, even for things that shouldn't matter. So for example, for the team list, that we print out for the team every morning, I remember once that she actually completely ripped the HO's (house officer's) apart, just because the lines—the columns that are outlining the boxes of the details on the team list—just because the lines were of different thickness. [...] Then the other things that they will pick on are like your seniors' coffee orders, you know, the <i>kopi o kosong</i> (Singaporean term for black coffee) and everything for each person, every single coffee order, their breakfast order had to be, you know, perfectly done and listed. [...] The attacks became very personal... to a point where it's not unusual to have vulgarities thrown at us. We not only [had] vulgarities thrown at us, but physical objects—we have the patient folders being thrown at us directly. And in the operating theatre, you have scalpels being thrown at you." (In a later part of the same interview) "So [a mentor from a different department] actually tried to help me ask for help from my team senior but in the end what I got was more backlash, so I got bullied even more and got more crap thrown my way, and things got worse and eventually I couldn't take it [...] I really couldn't take it and at one of the exit rounds, I just went off to toilet and then I stole, before I went to the toilet I stole <redacted: medication> from drug stores and I tried to inject myself." – Participant M10, middle cohort "[Redacted: department], I shall not name which hospital, wasn't as friendly. Every day, every day I feel like we are taking an exam every day, we are afraid that the consultants would throw files at us and make us cry." – Participant M4, middle cohort "But last time, generally there's a lot of blaming culture on the junior doctors, because the seniors they always get away with their own—the consultants, not the reg—they get away of things, then they also don't like to blame each other during the M&M (morbidity and mortality discussion), so every time it's the fault, the slip-up will chunk all the MOs (medical officers) or sometimes the reg (registrar)." – Participant S11, senior cohort
		"I thought that was the strength of the MOPEX (Medical Officer Posting Exercise) system in that every 6 months you can choose something else. So you can try you know radiology, psychiatry, anything that you choose. But it didn't really work out in that sense, because a lot of the times you actually don't really get what you chose." – Participant J2, junior cohort "A lot of us feel that it's very, that we feel that the bond is just to trap us in our system, for very practical reasons. Because they don't want us to just get our full registration and leave and go [to the] private [sector], you see, they know that we will do that. [...] And it's not, it doesn't make sense that you know, that our local medical school fees are actually that expensive and governments are subsidising you. That was what we were told." – Participant M10, middle cohort "It produces a lot of doctors that are quite sour. [...] The moment their bond ends, they leave." – Participant S11, senior cohort "My year was the first year with a proper bond. [...] Some people felt there was like 'slavery' and so on. Because you know, not much, not that much pay compared to what you earn outside. And, of course, long hours and not being able to get or choose the postings that you want, and so on, so forth. So of course, it's something that cuts both ways, your employment is guaranteed, but you have very little control over it." – Participant S2, senior cohort "I think there are more options in terms of specialisation, but there's also much more competition.... Because in old days, we wouldn't write papers or participate in this kind of research, unless you are either a very senior MO trainee, or you're a registrar." – Participant S6, senior cohort "I was posted to <redacted: department> 3 times against my will." – Participant M8, middle cohort
Individual Policy relating to actual or anticipated career trajectory	Feeling trapped, sour or stagnant	

Table 2. Exacerbating factors that made the junior doctor experience more challenging. (Cont’d)

Layer of modified SEM	Sub-theme	Quote
Individual Policy relating to actual or anticipated career trajectory	Concerns about remuneration	“There were postings where I worked consecutively for 3 to 4 weekends, so that means like, I think the record was 27 days consecutively. Yeah so when you factor all those things together, then you realise, hey, you know, perhaps we should be a bit more fairly remunerated for our time. – Participant J4, junior cohort
		“You can’t even, you know, speak about stuff, if you’ve got a ridiculous mortgage. When I try to inspire younger people to say, “oh, do a bit of academic work, do teaching, do research...”, [They’d say], ‘sorry, I don’t have time or you know, I have to go private practice because my wife doesn’t work with 3 children.’ That’s astounding. That’s outrageous.” – Participant S5, senior cohort
		“It’s only when I started working then I realised for the amount of salary I’m getting and the pay, it’s really a pretty bad deal...and also [when] you compare to what your friends who are non-medical are making then the [disgruntlement] kind of comes in.” – Participant M9, middle cohort
Individual Impression of work as a junior doctor	International medical graduates’ experiences	“It took a lot to adjust to [the] Singapore hospital system. I mean, just I mean, just the fact that, you know, the computer system is totally new. And, you know, acronyms. Yeah, the way things are done, and [even] the patient demographic is so different. Right, right. And, yeah, I guess [the] culture as well.” – Participant J7, junior cohort
		“The patients are a lot sicker. There’s a lot more patients [...] [My experience overseas] was a breeze compared to what we’re doing here...” Participant M8, middle cohort

SEM: socioecological model

At a societal level, junior and middle cohort respondents described facing increasingly complex patient care, driven by an ageing population with multiple comorbidities alongside evolving caregiving norms. Treatment advancements further complicated clinical decision-making. Participants identified a shift towards shared decision-making, compounded by internet-driven public access to medical information. While beneficial, this demands effort in explaining medical decisions and combatting misinformation. Several participants even recounted “hostile” behaviours from patients and next-of-kin.

Hostility also came from colleagues, especially seniors. While hierarchy was unavoidable, abuse of this hierarchy led to distress. Anecdotes from senior and middle cohort doctors were harsher, ranging from verbal abuse to physical intimidation. For one respondent, severe workplace bullying contributed to an attempted suicide.

The last set of exacerbating factors concerned careers and finances. Several participants described feeling trapped by their bond or pushed into departments they were uninterested in through the medical officer posting system. Concerns surfaced regarding remuneration amid rising living costs and increasingly competitive specialist training. Additionally, overseas-trained doctors highlighted difficulties transitioning to work in Singapore.

Theme 3. Alleviating and protective factors that improved the junior doctor experience.

Table 3 details factors that ameliorated the difficulties that participants encountered as junior doctors. Many participants found motivation in witnessing patient recovery, expressions of gratitude or meaningful interactions. Participants appreciated having room to learn from mistakes and grow in clinical competence. Some drew spiritual meaning from their work, while others found support from loved ones or hobbies.

Camaraderie among junior doctors was a common source of strength, with shared struggles cementing lasting friendships. Support from supervisors, nurses and allied health staff was also frequently mentioned. Nurturing seniors were a critical protective factor. Notably, these accounts came more frequently from senior and middle cohorts.

At the institution and policy levels, many participants expressed satisfaction with simply using employment entitlements: taking leave, having feedback considered, or leaving punctually post-call. However, several participants qualified that these entitlements were not guaranteed or varied between departments. Some participants in formal training programmes appreciated departmental efforts to prioritise their learning. Others shared how their department’s discretion or concern benefited them. In contrast,

Table 3. Alleviating factors that improved the junior doctor experience.

Layer of modified SEM	Sub-theme	Quote
Individual Impression of work as a junior doctor	Successfully treating patients or contributing to their care	"Actually seeing your patients going home, especially the ones you've been taking care of for some time, like 1 month plus... You, you sort of see them facing issue after issue [...] When you finally get to discharge them back home or to some other disposition, it is quite rewarding and fulfilling. And sometimes you can just see the gratitude that patients do express." – Participant J1, junior cohort
		"You know, when they come in, they're like, oh, 'I'm so sick' [and they're] delirious. [...] Then on the day of discharge, they are inviting you to go for a beer. [...] These are things which are fulfilling and things that I look forward to." – Participant J7, junior cohort
		"That was fulfilling: that you were actually able to do something that was actually positive for patient care. You picked up the pneumo[thorax], then you ask your MO, you set the chest tube—there's a sense of achievement when setting a chest tube. Yeah, you picked up the pneumo and saved this guy from like, having a worsening tension pneumo right. So I thought that was really, really helpful." – Participant S9, senior cohort
		"Well, patient interaction. I always find it very satisfying when I empower patients with the knowledge of their own conditions, and help them down the patient journey." – Participant J4, junior cohort
Individual Institutional development as a doctor	Growth and learning	"I guess it's like, the idea that there was, there was growth, there was growth and development as a doctor. You came in as someone who's basically, you know, supernumerary you weren't terribly useful [...] and so and you can see yourself sort of developing [or] acquiring skills and acquiring some degree of clinical acumen. And I think that kept me going, in the sense that I could see that I was not the same person..." – Participant S6, senior cohort
		"I think for me [it] was the process of learning. As a junior, people will look out for you [or] they will check in on you, make sure you're doing the right thing. And therefore, [I felt] safe to do things, to make mistakes." – Participant M4, middle cohort
Individual Personal values, priorities and aspirations	Religion as a grounding force	"The biggest [thing that kept me going] was my faith. I'm a Christian, we believe that being called, being in [the] medical profession, it's God's calling, and that He would give me, God would give me the strength to be able to do what he wants me to do." – Participant M4, middle cohort
		"What kept me going? Hmm...maybe also, like some of the writings, the writings of the Baha'u'llah kept me going like, you know, the betterment of the world can be accomplished through pure and goodly deeds, commendable and seemly conduct..." – Participant M7, middle cohort
Individual Impression of work as a junior doctor	Enjoying the (hard) work	"It sounds sadistic or whatever, but there was actually a lot of joy in working hard. You come out all ready to work hard, and they really make you work damn, damn hard. If all the hard work [had] been on more productive tasks, it would be even better.... Most of us don't have problems working a bit hard when you need to, even though our mental health, everything, suffers a bit. But we do get the joy." – Participant S11, senior cohort
		"Yeah, it was fun. It was fun. It was really fun. Yeah, a lot of procedures, accompanying patients to scans, accompanying patients to ICUs, is fun" – Participant M6, middle cohort
Interpersonal Healthcare team	Camaraderie	"What were my main motivators? I think, for me, it was a team like really, really the people around me. I was very affected by people around me. So I've had very good team[s], no matter what I knew we would get through this together because everybody was suffering. And we were all pulling the weight. So that really got me through one of the hardest postings." – Participant M3, Middle Cohort
		It's me versus 38 [patients] today, and, you know, the changes, everybody came in and helped me do changes. And it was good. So I think it's yeah, the workload was horrible, but because everybody was working together, it wasn't that bad." – Participant M8, middle cohort

Table 3. Alleviating factors that improved the junior doctor experience. (Cont'd)

Layer of modified SEM	Sub-theme	Quote
Interpersonal Senior colleagues	Journeying alongside and mentoring junior colleagues	"I was very grateful that my MO stepped down and did some work. They clerked the case for me, [would] draw blood for me. And that really helped a lot, that I was not left alone to flounder. [...] That helped motivate me to say, 'Well, in order to be like them I need to get me to be as good as them, if not better.'" – Participant S3, senior cohort
		"(In a particular department), seniors focused a lot on our understanding, rather than just doing the work. I remember there were times where I made a wrong decision, [the] consultant would ask me, 'why did you do that?' [They] spent time to teach me [why] the decision wasn't so good. And because there was a lot of collaboration, the consultants would really listen to us during ward rounds; ward rounds [were] a discussion, rather than just following instructions." – Participant M4, middle cohort
		"The one that would that was a bit hard to enforce was the '1 in 7 rest days' (1 rest day every 7 days). Because [it] was actually sort of left to the teams [to enforce]. I know sometimes it was hard to get 1 day off in 7, but the registrars, to their credit, they tried to, they tried to give us that." – Participant J2, junior cohort
		"I remember this particular case [where] I actually couldn't figure out what was wrong with this patient [and] the patient didn't turn out so well. [By] the time the registrar was informed, she (the patient) was actually very, very ill. [...] [The registrar] had a private word with me [and] I never felt that I would be left on my own. [...] He actually worked out with me, [on] what we would say in the (morbidity and mortality) report." – Participant S7, senior cohort
		"Certain departments, the registrar will come around at 11 o'clock at night and say, let's all go out for supper. And we all go out into his car for supper. Yeah, but not every department [would] do that. Yeah. Yeah. And then now, I think the departments are too big. [...] I don't think that happens anymore." – Participant S7, senior cohort
Interpersonal Friends and family	Supportive presence of loved ones	"I really don't go home, but I feel, I mean I had a wonderful family who was very supportive of me, they message me, make sure I'm okay. I come home late and rush to work, I've always got a room to sleep in peacefully, very, very good support." – Participant M4, middle cohort
		"I guess the first thing I would say life outside of work? Even with less time but just whatever time you have with family and friends... I think that's what gets me going." – Participant J8, junior cohort
Institutional Employee and trainee management	Tangible measures to support learning, training and rest	"I will say my (residency) programme [is] quite good in terms of how they structured the postings, essentially making sure [...] we did most of our out-postings before our exams, to make sure that we got sufficient breadth of exposure before certain exams [...] and also making sure that the postings that we were in, like leading up to the exams, were ones that you can take leave in..."
		"(Later on in the same interview) The most helpful ones were things like, the extra off days that we got along the way. I think any time off is always very useful as a wellness initiative." – Participant M11, middle cohort
		"I think leave regulation was actually fairly well enforced. They did ask us to clear leave, which is pretty good. I think most, most people [didn't] get shortchanged for their leave." – Participant J2, junior cohort
		"[Some of] my rights will probably be to be able to go post call a certain time, I think that is generally quite well protected." – Participant M2, middle cohort
Institutional Employee and trainee management	Responding to needs and suggestions	"In particular, the good thing is that the Department of <redacted> is very—they do listen to us. If we do decide to suggest any changes, they're quite welcome to that." – Participant J1, junior cohort
		"After my first houseman posting at <redacted: hospital>, I actually requested for a lighter posting. Because I had some...my own medical problems. I had to see a psychiatrist and all that. And so <redacted: national junior doctor employer> was actually quite nice. They, they told me, yeah, let's try to give you a lighter posting. So they sent me to <redacted; hospital>, which is generally known to have lighter postings. And so that helped a lot. And I was very grateful for <redacted: national junior doctor employer> to do that." – Participant M7, middle cohort

Table 3. Alleviating factors that improved the junior doctor experience. (Cont'd)

Layer of modified SEM	Sub-theme	Quote
		"(As overseas medical graduates) But overall, I felt like we were taken care of. I mean, <redacted: national employer of junior doctors>. As a PGY-1 (post-graduate year 1 doctor), <redacted: national employer of junior doctors> did have like regular meetings, like I think at the 6th month mark and the end of the year, to sort of meet up with us, check up on us." – Participant J1, junior cohort
Institutional Employee and trainee management	Accounts of historical management of junior doctors as trainees and employees	"When we were going to take our clinical exams, we had to arrange our own tutorials. So the training programme, the, well, the professor's—the senior tutors, were not the ones who arranged these for us. We had to go and ask around. [...] So we had to go to the different hospitals, arrange all these sessions with them..." – Participant M1, middle cohort
		"I remember going down to the department one day before I was supposed to start work and sort of said, hello. And everybody said, well, okay, here you go. And then you [were] just tossed [into the] deep end [...] there was really no systematic kind of training programme for housemen. We were given the handbook of the department if you were lucky [...] the teaching was really very disorganised." – Participant S6, senior cohort
		"And I guess, you know, at the time, there was not much welfare per se, you know, they didn't think very much about how we will cope." – Participant S10, senior cohort

SEM: socioecological model

senior cohort anecdotes revealed less institutional regard for junior doctors' well-being or training.

Theme 4. Responses of junior doctors to their experiences.

Table 4 details the ways in which participants responded to their circumstances as junior doctors. Many respondents viewed junior doctorship as a rite of passage, which allowed them to develop requisite hard and soft skills. Despite the growth, most participants across cohorts agreed that the stress imposed was not completely warranted. A participant characterised this period as "one of the most traumatic experiences of my life"; many felt amazed that they managed to "survive".

Respondents reacted in varied ways—some weathered the difficulties, others left their places of practice, and others escalated their concerns to authorities or vowed to improve things for their juniors. A notable minority suffered severe repercussions on their mental well-being.

Among the few respondents who expressed their concerns more openly, one ran a blog about their experiences; another recounted a 1980s work-to-rule collective action that preceded salary improvements; one wrote to the Ministry of Manpower and their employer regarding their contract; and another joined their Residents' Welfare Committee. Among the respondents, some felt disillusionment about the possibility of change, including concerns around speaking out. In contrast, some individuals believed that coping with hardship was a personal prerogative.

Modified socioecological model (SEM)

A modified SEM was conceptualised (Fig. 2), encapsulating interconnected relationships between the individual level and interpersonal, institutional, community and policy levels. Instead of concentric circles, the modified SEM's layers create a Venn diagram, with the individual layer in the middle. This centres the junior doctor's lived experience and demonstrates trickle-down effects from other SEM layers. Furthermore, certain factors, which defy categorisation into a single layer, are situated between layers. The key factors within the SEM correspond with the salient sub-themes presented in Tables 1–4.

Encapsulating the modified SEM is a time period bubble highlighting how each junior doctor's experience is situated within its unique time context.

DISCUSSION

Thematic analysis juxtaposed factors that worsened or improved the junior doctor experience, serving as a call to action to reduce exacerbating factors, enhance alleviating factors, and consider and mitigate inherent challenges. The modified SEM pinpoints the layers of stakeholders to engage in improving the junior doctor experience.

Comparisons between cohorts: Objectively different circumstances

Senior cohort experiences were characterised by long working hours, frequent overnight duties, heavy patient loads, minimal structured training or supervision and an entrenched culture that neglected well-

Table 4. Responses of junior doctors to their experiences.

Layer of modified SEM	Sub-theme	Quote
Individual Reflections on being a junior doctor	Rite of passage/formative experience	"You kind of have to go through that training to figure out what you want to do with your life" – Participant M2, middle cohort
		"But even if even if, let's say I went to HO (house officer) and then I left immediately after HO I just wouldn't feel confident in the private sector or doing locum." – Participant J2, junior cohort
		"I would say there will be some aspects [of being a junior doctor] that were not quite worth it. Yeah, but like some of the time pressure and some of the stress and all that, I would say [it was] not really worth it. But I would say overall, it's something that has helped me grow and helped me change and made me who I am." – Participant M11, middle cohort
		"I think it's made me who I am." – Participant J2, junior cohort
Individual Society/community Action and advocacy	Resolving to make things better/paying it forward	"Maybe some of it was necessary, otherwise, it wouldn't have been possible for you to make such a drastic transition in such a narrow; such a short period of time." – Participant S6, senior cohort
		"Even though the experience was very tough, I learned things from it. Like I learned how to care for patients in crunch. I know how to manage long patient lists. I know what kind of senior I don't want to be." – Participant M8, middle cohort
		"Just remember that, when your time comes to be on top, you think about your times and resolve to make it better for the next... rather than say, 'we went through it, so what's your problem?' That's not the way of looking at it." – Participant S2, senior cohort
		"I also hope that the juniors down the road, like you, right, would have a better experience... because sometimes I felt the environment was too discouraging [and] not helpful for personal growth." – Participant M7, middle cohort
Individual Reflections on being a junior doctor	Extent of difficulty encountered	"I always felt like I did it because I had no other choice [...] just because we went through it, does not justify, you know, perpetuating this toxic culture for the future generations." – Participant M9, middle cohort
		"I think it probably is one of most traumatic experiences of my life" – Participant S6, senior cohort
		"My classmate attempted suicide. She almost succeeded, if not for the fact that someone—she tried to off herself in the call room by injecting herself with [redacted: high-alert medication], it was only by sheer luck that one of our colleagues had to recover something from the call room, barged in and found her comatose and CPR her back and she survived. I'm not kidding." – Participant S9, senior cohort
		"I felt like I wasn't good enough to other house officers, I felt that I wasn't efficient enough. I wasn't as good at multitasking, you know. [...] It took me a very long while to realise that I'm not 100% fault-free for sure. But there were really a lot of things that went wrong with that posting in that department that were out of my control and that shouldn't [have] happened." – Participant M10, middle cohort
		"You know, not eating for like 12 hours, straight, things like that, it probably builds character. But again, I think you've got to make sure that it doesn't affect your welfare as well. Because I did come across other HOs who didn't take it so well. They do suffer from anxiety, depression. So it really depends... whether it's all worth it at the end." – Participant J1, junior cohort
		"I think it was just this sense of like how we're being exploited? The long hours, the low salary, just the stress of it all, the continuity. If you do this for 1 day a week, I think it's fine. But if you do it every single day without a proper break, it's really very taxing." – Participant M9, middle cohort

Table 4. Responses of junior doctors to their experiences. (Cont'd)

Layer of modified SEM	Sub-theme	Quote
Individual Institutional Relationship with one's place of practice	Leaving their places of practice	"I prefer the outpatient setting [...] even then I also chose to leave [...] Because the numbers were too overwhelming, the time given is too short, you can't really do a good job. [...] I found going into primary care in private practice so much more fulfilling because you really develop relationships with the patients." – Participant S8, senior cohort
		"There were also health reasons and [...] I actually asked to take no-pay leave, but that was not granted unfortunately. [...] And so I had to choose between like deteriorating health and continue to work versus breaking the bond. So after discussing with family and all that decided to go with breaking the bond." – Participant M7, middle cohort
		"Pull [factors] [were] like, I just have quite a lot of family overseas [...]. I think part of that is my own aspiration [...] that I always kind of wanted to do residency overseas." – Participant J2, junior cohort
		"So I have a few friends that did decide to leave for like private practice, or go to GP, family medicine, things like that. I think it is <inaudible> individual experience and interest. Some of them didn't get their first choice, so [they] decided to choose an alternative path. A lot of them also decided to start a family early on, and wanted more of their work life balance." – Participant J1, junior cohort
Individual Society/community Action and advocacy	Concrete actions taken by junior doctors	"Before us, we—I think the housemen, MOs (medical officers), didn't get any night duty allowances. But if you look back in the history, somewhere around the 80s, early-to-mid 80s, there was actually a small sort of a strike, small work-to-rule kind of thing over allowances, among other things, and after that, we got something like, I can't remember the sums, but we got paid for the first, like, 4 night calls, a certain amount..." – Participant S2, senior cohort
		"(Regarding a meeting with the manpower ministry that they managed to secure) It was actually an open meeting, I think people were actually talking about it. There were, I think 40 or 50 participants at the town hall. And I remember it was quite well received... that the nurses [were] there as well. [...] I think many doctors are not that keen to risk their residency or ruin their reputation in the eyes of the faculty. So I don't think it was very popular at the time to form a union among my friends, so we didn't, I didn't go [down] that route. I just went directly to <redacted: manpower ministry> as a concerned citizen." – Participant M5, middle cohort
		"I raised, like 10 or 13, points to HR (human resources) of <redacted: national employer of junior doctors> to, to ask them about all these things that are not mentioned in [our] employment contract, even though there are some resources on the MOM website that stipulate that these things need to be stated. So I think, I think we just discussed the shortcomings with <redacted: national employer of junior doctors> HR. And I think they gave a reply to all the points. And I'm not sure [whether] they looked into it after that, because, yeah, I remember after we, I think they revise the pay from time to time." – Participant M5, middle cohort
		"I used to blog when I was an MO. And the, it's very interesting because when I blogged it was during SARS and that time blogging and social media were quite non-existent... so I was the only local doctor blogging..." – Participant M1, middle cohort
		"I think only recently, with like social media becoming more influential, <redacted: national employer of junior doctors> is finally like, getting all this news from junior doctors about our welfare, especially like call systems and all that can be improved. Okay, I mean <redacted: national employer of junior doctors> did recently, I think last year, to try and improve our welfare. Like they did increase the call pay—but that's only a small amount of improvement that can be done. Yeah." – Participant J1, junior cohort
		"(Regarding experiences on the Residents' Welfare Committee) The only thing that did probably had to be escalated to <redacted: national employer of junior doctors>, [...] I think it was a bit about financial compensation when you're working on public holidays. So certain hospitals... wouldn't compensate you for coming back on a public holiday to work. But I think that that was brought up to the, this was in <redacted hospital>. So that was brought up to the Chief [of the] Medical Board. And I think they eventually discussed with [redacted: government ministry]. And they did agree to reimburse us, financially compensate us, if we do come back to work on a public holiday." – Participant J1, junior cohort

Table 4. Responses of junior doctors to their experiences. (Cont’d)

Layer of modified SEM	Sub-theme	Quote
		“They put me in a few other committees to look at junior doctor welfare, gave me a lot of free rein [with] what I want to do with junior doctors, and if I now put my foot down and say no, my MOs (medical officers) are not doing this, [the senior management] really don’t do this. [...] You need [a] junior doctor voice there to tell [the senior doctors] what the junior doctors actually need. I think <redacted: healthcare cluster> now has a junior doctor committee or something. Yeah. And I was looking at the list, right? A lot of them are quite senior people. Yeah, these people aren’t junior at all.” – Participant M8, middle cohort
Individual Policy Relationship towards policies and structures in place	Coping with the state of affairs	“The prevailing attitude then was that suck it up and stop whining.” – Participant S9, senior cohort
		“If you’re unhappy with something, you can’t really escalate it [...] There was a lot of ‘This is the way it is. You know, last time I had it worse,’ that kind of thing. So you just felt like you can’t really complain much.” – Participant M8, middle cohort
		“I don’t really feel that the policy level is going to help much honestly, because I think that we will always be overworked, there will always be work for junior doctors to do. Maybe it’s pessimistic [to think] we’re not going to change much even if there’s anything, any further welfare[related] policies implemented. But it’s more of individuals, how we cope with this work ourselves. The system is not designed to benefit individual doctors, more designed to keep the system going and rooted in many years or so called in tradition, that you know, junior doctors are supposed to bear the grunt of the work and so on.” – Participant J8, junior cohort

SEM: socioecological model

being. Moreover, 36-hour calls—up to 11 per month— or having 30 inpatients per doctor were common. In contrast, junior cohort doctors had relatively shorter working hours, fewer overnight duties and improved doctor-patient ratios. Call shifts were 24 or 30 hours long, usually 4–7 times per month; having to manage 30 inpatients day-to-day was not the norm. Middle cohort doctors were at a transition point: 36-hour calls were phased out, stricter regulations around off-days were implemented, structured training programmes were established, and electronic medical records were introduced. These experiences correlate with policies since the 2010s, including 80-hour-weekly limits, some institutions establishing night float systems,²¹ and the transition to electronic medical records from the early 2000s.

Although junior and middle cohort doctors generally experienced lighter absolute patient loads and hours, present-day conditions exert a significant toll on physical and mental well-being. Crucially, conditions remain poorer or only on par with international standards in high-income countries.²² For example, the Australian Medical Association’s 2016 National Code of Practice recommends that shifts be a maximum of 14 hours long.²³ Singapore’s 80-hour work limit mirrors the US,²⁴ and it is far from the 48-hour weekly limit in the UK, where resident doctors follow the European Working Time Directive by default.²⁵ While Singapore does not enforce protected rest time at work, both the UK and Australia

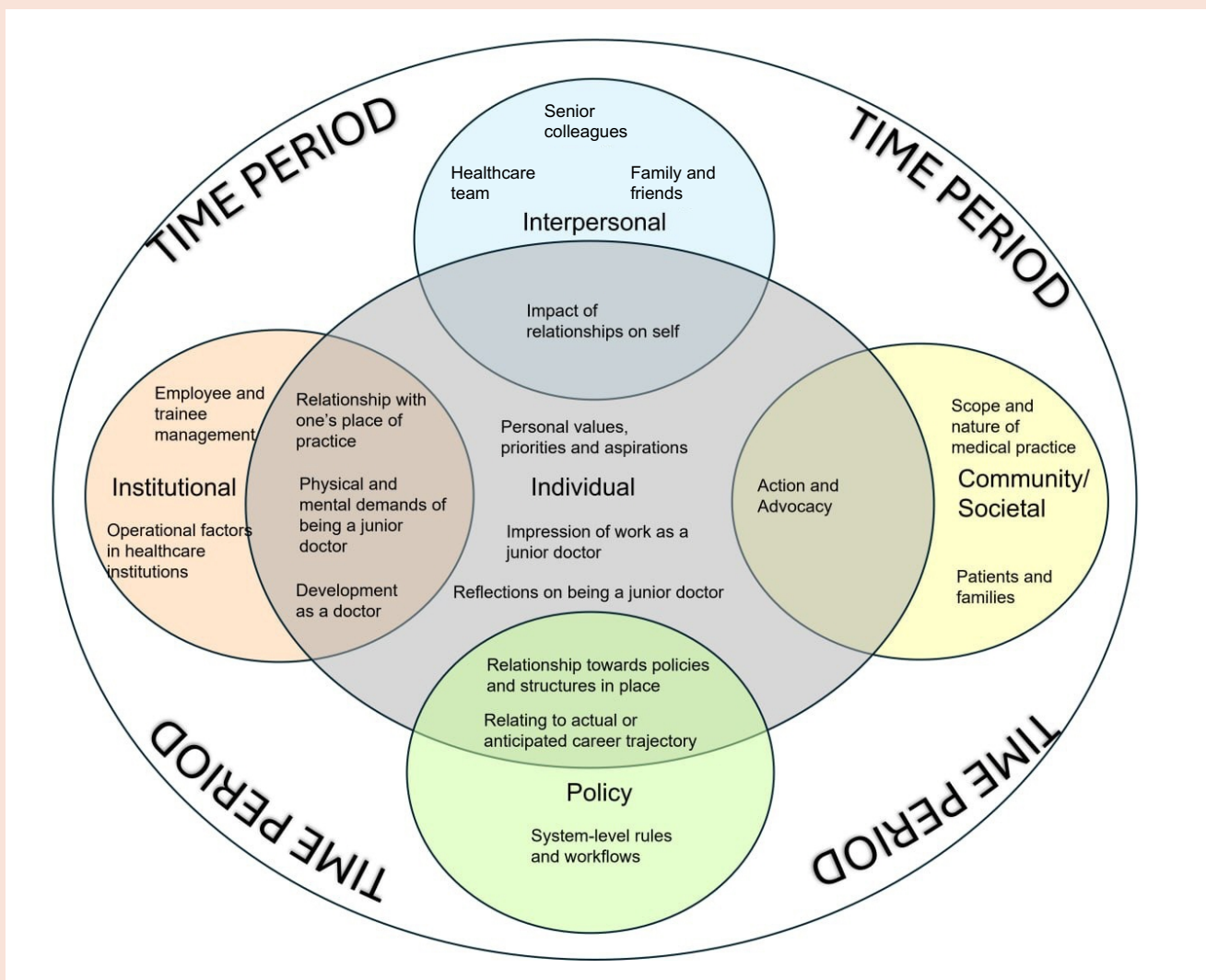
have explicit recommendations or requirements for rest.

For junior and middle cohort doctors, new challenges have emerged, such as healthcare digitisation,²⁶ a hostile medicolegal climate and defensive medicine,²⁷ increasingly complex medical care²⁸ and evolving patient expectations. Traditionally defined by a fear of malpractice litigation, defensive medicine encompasses “self-protective” decisions that physicians make, stemming from a “fear of patient dissatisfaction” or “overlooking a severe diagnosis”, among others.²⁹ Defensive medicine promotes unnecessary investigations, interventions and specialist referrals, alongside a tendency to avoid patients or procedures deemed riskier.³⁰ This trickles down to both patients and doctors alike: more tests need to be paid for (and interpreted), and more consultations must be attended (and documented). Many middle and junior cohort doctors recounted juggling extensive medical documentation while being sandwiched between the demands of both seniors and patients. Some also felt “trapped” in these circumstances by their 5-year bond, a feature unique to countries with mandatory service requirements like Singapore.

Comparisons between cohorts: Subjectively similar experiences

It is this interplay of improvements, setbacks and the inherent challenges of junior doctorship that may have contributed to most respondents looking back

Fig. 2. Modified socioecological model (SEM) constructed as a Venn diagram.



"Time Period" denotes each junior doctor's experience within its unique time context.

at their experiences with similar sentiments despite different contexts. Distress pervaded all cohorts. Still, many felt fulfilled "coming out on the other side" of these years. Some doctors externalised this through writing or advocacy. Conversely, others internalised their distress, sometimes harming themselves—notably, 2 separate accounts of attempted suicide surfaced during our interviews. Junior doctors' distress warrants urgent action.

Efforts to improve the junior doctor experience

Significant steps have been taken to improve junior doctors' experiences in Singapore: workgroups have been established, remuneration has improved, and efforts are underway to reduce consecutive work hours. Simultaneously, doctors and students are increasingly advocating for themselves through various

platforms including social media. Our findings highlight the need to centre junior doctors in improving working conditions, empowering them to be involved without fear of penalisation.

This study raises several potential suggestions for local and international institutions. Workplaces should proactively foster relationships that support junior doctors, such as peer-to-peer, interprofessional and senior-to-junior support. Simultaneously, disruptive behaviour and abuse—whether from patients and next-of-kin or colleagues—should not be tolerated. Working hours and remuneration should match international gold standards; well-intentioned policies must be properly enforced. Institutions with overnight calls may consider alternative night-duty systems such as night floats. Careful watch must be kept on junior doctors' administrative burdens³¹ and on priori-

tising structured professional development for all. Within and outside the medical community, active efforts should be made to mitigate defensive medicine.

As echoed by many participants, improving junior doctors' experiences is not only a meaningful end in itself, but is crucial for patient safety through reducing attrition, burnout and errors.³² The economic costs of burnout have been quantified previously and should not be underestimated.³³ Amid disillusionment, many participants still found deep fulfilment from their work—this sense of purpose must be safeguarded.

Strengths, limitations and future research

The merit of this study lies in its ability to delve deep into the lived experiences of current and former junior doctors across generations in Singapore. This study captures evolving challenges that may be missed in single-time-point studies. While these findings may not be entirely generalisable to an international audience, a key strength is precisely the specificity of the analysis to Singapore's junior doctors.

This study has limitations. AI transcription may have compromised accuracy, which was mitigated through manual proofreading. While purposive sampling enabled exploration of experiences across cohorts, hindsight bias in the senior cohort may be present, further amplified by its smaller size. Future studies may consider recruiting more senior participants. Given the shared backgrounds of participants with the study team, reflexivity bias and social desirability bias are worth considering. Reflexivity bias was mitigated through inter-coder reflection, alongside consolidating and corroborating themes with objective data. Selection bias is another limitation, with certain profiles, such as those with advocacy interests or with distressing experiences more likely to self-select. Rather than representing a comprehensive scope of doctors in Singapore, this study forms the basis for future studies to evaluate junior doctors' experiences in specific domains identified from our qualitative inquiry.

Future research may explore solutions to emerging issues, from defensive medicine to healthcare digitisation. Studies with longer time horizons could also follow a fixed cohort of junior doctors via qualitative longitudinal research methods,³⁴ investigating the influence of evolving contextual factors across time.

CONCLUSION

This study uniquely demonstrates Singaporean junior doctors' experiences over the past decades. Despite material improvements to working conditions, further development is warranted. Emerging challenges

also call for thoughtful solutions that consider their implications for junior doctors.

Supplementary material

Appendix S1. Participant characteristics.

Ethics statement

This study was approved by the National University of Singapore Institutional Review Board (2022-248).

Declaration

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Singapore Myeloma Study Group consensus guidelines for the management of patients with newly diagnosed multiple myeloma

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ABSTRACT

Multiple myeloma (MM) is the second most common haematologic malignancy and remains incurable. Significant advances have been made in both supportive care and definitive therapy for MM, leading to marked improvements in survival and quality of life. The availability of potent novel agent-based induction regimens, as well as methods to assess deeper levels of response, has transformed the landscape of MM therapy. Balancing therapeutic efficacy against toxicities and cost-effectiveness remains a key challenge to be addressed. Here, the Singapore myeloma study group provides consensus recommendations on the management of newly diagnosed MM, incorporating key developments in diagnostics, response assessment, supportive care and definitive therapy.

Keywords: cancer, guideline, haematology, multiple myeloma, Singapore

CLINICAL IMPACT

What is New

- The management of multiple myeloma has seen major advances in the last decade, resulting in improved clinical outcomes.
- The array of diagnostic and treatment modalities available presents a challenge for physicians in delivering high-quality and cost-effective care.

Clinical Implications

- The Singapore Myeloma Study Group provides updated recommendations on the holistic management of patients with newly diagnosed myeloma.
- The guideline highlights data from Singapore studies and provides recommendations based on landmark trials adapted to Singapore.

INTRODUCTION

Multiple myeloma (MM) is the second most common haematologic malignancy worldwide and remains incurable.^{1,2} Approximately 100 to 120 people per year are diagnosed with MM in Singapore. Therapeutic advances with novel agents have changed the treatment landscape; while once largely untreatable, patients with MM now have a higher likelihood of entering remission with prolonged survival. The guidelines produced by the Singapore Myeloma Study Group (SMSG) are evidence-based recommendations for the diagnosis and management of MM.³ These guidelines are intended for medical and allied health

staff caring for patients with MM. They are not meant to be prescriptive and are intended to be used in conjunction with sound clinical judgment. The guidelines focus on the management of newly diagnosed patients and are divided into 5 sections:

- Diagnosis, staging and risk stratification of MM
- Supportive care in patients with MM
- Response assessment and monitoring
- Management of transplant-eligible patients
- Management of patients ineligible for autologous stem cell transplantation

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METHOD

The SMSG performed a review of key English language literature from inception until December 2024, including MEDLINE and Cochrane Library, and proceedings of major meetings from the American Society of Hematology, American Society of Clinical Oncology, European Hematology Association and the International Myeloma Working Group (IMWG). The literature search focused on MM and included diagnosis, risk stratification, response assessment and management as the key components. Recommendations were formulated based on evidence from randomised controlled trials (RCTs) whenever possible. The strength of the recommendations was evaluated based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) nomenclature. The GRADE criteria are available at <http://www.gradeworkinggroup.org>, and the GRADE level of evidence is indicated in the text for all recommendations including those that were based on less robust study designs.⁴ Members of the study group proposed and drafted the content of assigned sections of the guideline. All members then reviewed and approved the recommendations in their final form. Key recommendations from IMWG^{5,6} and British Society for Haematology⁷ have also been incorporated into the current guideline.

These findings were summarised into a draft, and the SMSG revised and proposed recommendations in situations where there were insufficient published data. The SMSG suggests the IMWG guidelines as a reference for readers looking for more details on specific aspects of the management of MM. The SMSG recommends that patients be considered for enrolment in high-quality clinical trials whenever feasible and appropriate.

Section 1. Diagnosis, staging and risk stratification of MM

Background

MM forms part of a spectrum of clonal plasma cell disorders and is typically preceded by monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM).⁵ MGUS and SMM are defined by specific levels of monoclonal protein and clonal bone marrow plasma cells in the absence of organ involvement (called myeloma defining events), and these patients may progress to develop MM at varying rates.⁸ The current approach for the management of these patients is observation until the onset of organ involvement.^{9,10}

Diagnosis of symptomatic MM as defined by IMWG criteria

The diagnosis of MM requires monoclonal plasma cells in the bone marrow ($\geq 10\%$) or biopsy-proven bony

or extramedullary plasmacytoma with any 1 or more of the following myeloma-defining events denoted by the acronym “SLiM-CRAB”.^{5,11}

- **S:** Clonal bone marrow plasma cell percentage $\geq 60\%$
- **Li:** Involved/uninvolved serum free light chain ratio ≥ 100
- **M:** >1 focal lesion ≥ 5 mm in size on magnetic resonance imaging (MRI) studies
- **C:** Hypercalcaemia (> 2.75 mmol/L or >0.25 mmol/L above the upper limit of normal)
- **R:** Renal dysfunction (creatinine clearance <40 mL/min or serum creatinine >177 mmol/L).
- **A:** Anaemia (haemoglobin <10 g/dL or >2 g/dL below the lower limit of normal)
- **B:** Bone disease: One or more osteolytic lesions on bone imaging

It is noteworthy that the presence of a monoclonal paraprotein in the serum is not a requirement for the diagnosis of MM. The IMWG has also revised the definition of plasma cell leukaemia with a cutoff of 5% for the percentage of plasma cells in the peripheral blood in patients who fit the other diagnostic criteria for MM.¹²

Recommendations

1.1 Screening for monoclonal proteins

Although the presence of a monoclonal protein is not mandatory for the diagnosis of MM, approximately 97% of patients with MM have a monoclonal protein.⁵ The finding of a monoclonal protein is also a frequent cause of referrals from other medical specialists who screen patients for monoclonal gammopathies. Serum immunofixation (IFE) is mandatory to confirm monoclonality and the serum free light chain assay (SFLC) is important in the diagnosis of patients with light chain MM who may have CRAB features but have a negative IFE. SFLC is also relevant for the prognostication of patients with MGUS and the identification of patients with high-risk SMM who may be either reclassified as MM or have a very high short-term risk of progression to MM and require closer monitoring. The SMSG recommends using the new reference ranges for SFLC based on the latest IMWG update.¹³

The SMSG recommends that serum protein electrophoresis (SPEP), IFE and SFLC be used as screening tests for a monoclonal protein. When SPEP, IFE and SFLC are available, screening for a monoclonal protein in the urine adds limited diagnostic or prognostic information, and the authors do not recommend its routine use. The SMSG recommends using SPEP, IFE and SFLC in the format of a “screening panel” for the convenience of clinical and laboratory staff. Twenty-four-hour urinary protein quantification

is helpful in the evaluation of suspected amyloid light-chain amyloidosis or monoclonal gammopathies of renal significance.¹⁴ However, spot urine IFE, M-band quantification or urine FLC are not recommended.

Recommended investigations: Screening for monoclonal proteins (GRADE 1C)

1.1.1 Serum protein electrophoresis

1.1.2 Serum immunofixation

1.1.3 Serum free light chain study

1.2 Investigations for confirmation of diagnosis and risk stratification

Bone marrow aspiration and trephine biopsy (BMAT) are mandatory for the diagnosis of MM, and immunohistochemical assessment of light chain restriction on the trephine specimen is recommended to confirm plasma cell clonality.⁵ Flow cytometric immunophenotyping is not mandatory for the diagnosis of MM, but may be considered on a case-by-case basis, especially if a B-cell lymphoproliferative disorder is part of the differential diagnosis.¹⁵ BMAT is especially important in the 3% of patients with non-secretory MM who present with CRAB features and no evidence of a monoclonal protein on the screening investigations described above. A full blood count (FBC), serum creatinine and corrected calcium are essential to confirm the presence of anaemia, renal impairment and hypercalcaemia. Quantification of the serum M protein by densitometry is recommended at diagnosis to provide a baseline quantitative estimation for subsequent response assessment. Immunoglobulin quantification by turbidimetry is recommended in patients with immunoglobulin A, immunoglobulin M or immunoglobulin D paraproteins, which may not be reliably quantified by M protein densitometry.¹⁶

A whole-body skeletal survey (SKS) was the previous standard imaging modality used to screen for lytic skeletal lesions. Whole-body low-dose computed tomography (WBLDCT), whole-body MRI and positron emission tomography (PET) scans have since emerged as more sensitive techniques. In a multicentre study, the IMWG compared SKS and whole-body CT scans of 212 patients with monoclonal gammopathies. They found that WBLDCT identified bone lesions in 25.5% of patients who had a negative SKS.¹⁷ In a cohort of 52 patients with a variety of monoclonal gammopathies, 12 patients (23%) were shown to be positive for osteolytic lesions on WBLDCT despite a negative SKS. These results confirm the increased sensitivity of WBLDCT compared with SKS.¹⁸ WBLDCT is hence recommended by the IMWG and the Asian Myeloma Network consensus as the minimal requirement to screen for bone lesions.^{19,20} If WBLDCT is negative,

and no other myeloma-defining events are present, the IMWG recommends the use of whole-body MRI as an alternative.¹⁹ PET-CT may also be an alternative to WBLDCT or whole-body MRI if the relevant imaging technique is contraindicated or unavailable.¹⁹

An MRI of the spine is specifically indicated if there is a clinical suspicion of spinal cord compression. Whole-body MRI is also recommended for all patients diagnosed with SMM, as finding more than 1 focal lesion >5 mm on MRI will lead to them being reclassified as MM.¹¹ PET-CT maybe an alternative for this purpose if whole-body MRI is not available or contraindicated.²¹ MRI or PET-CT are also important tools in distinguishing truly solitary bone plasmacytoma from MM by identifying additional occult bone lesions.¹⁹ Specifically, a whole-body MRI is recommended for solitary bone plasmacytoma, while a PET scan is recommended for extramedullary plasmacytoma.¹⁹

It is noteworthy that when the clinical suspicion is MM, the above imaging (WBLDCT/MRI/PET-CT) should all be performed without any intravenous contrast due to the risk of contrast nephropathy.²² The lack of contrast does not affect the imaging efficiency in discerning MM bone or marrow lesions when recommended imaging techniques are employed (for example, fluorodeoxyglucose [FDG] PET without contrast or diffusion-weighted MRI without gadolinium). The Asian Myeloma Network's imaging guidelines for myeloma provide more information on each of these modalities and alternatives in resource-constrained situations.²⁰

Risk stratification and staging

Risk stratification of MM has traditionally been based on the international staging system (ISS) where albumin and β 2-microglobulin (β 2M) were used to generate the prognostic score.²³ Genetic information obtained through bone marrow karyotyping and fluorescent in situ hybridisation (FISH) is also an important prognostic factor.²⁴ Specifically, the presence of t(4; 14), 17p13(del), t(14; 16), t(14; 20), 1p loss and 1q gain have been shown to carry an adverse prognosis.²⁴ These can all be detected by FISH performed on CD138-enriched plasma cells from the bone marrow. Conventional metaphase karyotyping has low yield (informative karyotypes in less than 30% of patients) and an inability to detect some prognostically relevant abnormalities such as t(14;16).²⁵ Although it is useful in the absence of FISH, the utility of metaphase karyotyping in the presence of FISH is limited.

The revised international staging system (R-ISS) that incorporates the prognostic value of the ISS, genetics and lactate dehydrogenase (LDH) has been revised since the publication of the previous guideline.^{26,27} The latest International Myeloma Society (IMS)/

IMWG risk stratification defines high-risk MM by the presence of specific combinations of chromosomal abnormalities and/or high $\beta 2M$ (>5.5 mg/dL) with normal creatinine (Table 1).⁶ The SMSG proposes using the updated IMS/IMWG risk stratification as the current standard for staging and prognostication. The SMSG recommends the following investigations for diagnosis, risk stratification and pretreatment evaluation.

Table 1. International Myeloma Society/International Myeloma Working group criteria for high-risk myeloma.

Del(17p) and/or TP53 mutation
One of these translocations—t(4;14) or t(14;16) or t(14;20)—co-occurring with +1q and/or del(1p32)
Monoallelic del(1p32) along with +1q, or biallelic del(1p32)
High $\beta 2M$ (>5.5 mg/dL) with normal creatinine (<1.2 mg/dL)
$\beta 2M$: $\beta 2$ -microglobulin

Recommended investigations for confirmation of diagnosis and risk stratification

1.2.1 Blood investigations (GRADE 1C)

1.2.1.1 Serum M protein quantification (in addition to SPEP/SFLC and IFE)

1.2.1.2 FBC, serum electrolytes and renal function assessment including urea/creatinine and corrected calcium

1.2.1.3 Serum $\beta 2M$, albumin and LDH

1.2.2 Bone marrow investigations (GRADE 1C)

1.2.2.1 Bone marrow aspirate and trephine biopsy

1.2.2.2 FISH myeloma panel including the following probes: fibroblast growth factor receptor 3/multiple myeloma SET domain t(4;14), MAF-B t(14;20) and MAF-C t(14;16) translocations, and copy number changes for 17p, 1q and 1p

1.3 Imaging

1.3.1 WBLDCT as the minimum first line screening modality (GRADE 1B).

1.3.2 Non-contrasted diffusion-weighted whole-body MRI or non-contrasted FDG PET-CT to be considered if WBLDCT is not conclusive or unavailable (GRADE 1C).

1.3.3 Whole-body MRI is the modality of choice when evaluating patients with SMM for

high-risk biomarkers, which may result in upstaging to active MM (GRADE 1B). PET-CT is an alternative if whole-body MRI is not feasible (GRADE 2B).

1.3.4 Whole-body PET-CT scan if there is suspected extramedullary disease (GRADE 1B).

Recommendations for pretreatment evaluation (GRADE 1C)

The pretreatment evaluation suggested below is recommended for all patients with newly diagnosed MM. The protocol for financial assessment and assistance may vary between institutions.

- (1) Height, weight and body surface area to be recorded
- (2) Urine human chorionic gonadotrophin test for females of childbearing age
- (3) Liver function tests
- (4) Viral serologic screen: hepatitis B surface antigen, anti-hepatitis B core antibody (polymerase chain reaction for hepatitis B deoxyribonucleic acid [DNA] would be required if the core antibody is positive), anti-hepatitis C virus and human immunodeficiency virus serology
- (5) Glucose-6 phosphate dehydrogenase quantification
- (6) Dental assessment
- (7) 25-OH vitamin D level
- (8) Red cell phenotyping if CD38 monoclonal antibody therapy is planned
- (9) Pre-chemotherapy counselling according to institutional protocol
- (10) Financial assessment and referral to social worker if necessary

Section 2. Supportive care in patients with MM

Supportive care is essential to ensure that patients remain minimally affected by the complications of MM and its treatment. The SMSG proposes the following recommendations for supportive care in conjunction with references made to published guidelines.²⁸⁻³⁰

2.1 Hypercalcaemia

Osteoclast-mediated bone destruction in MM may lead to hypercalcaemia, which can present with a variety of clinical manifestations.³¹ Hydration with intravenous normal saline is usually adequate for mild hypercalcaemia ($Ca^{2+}=2.6$ to 2.9 mmol/L), while bisphosphonates are recommended for moderate to severe hypercalcaemia ($Ca^{2+} >2.9$ mmol/L),³² ideally after dental clearance. Steroids such as dexamethasone, along with intravenous (IV) hydration, can help resolve even moderately severe hypercalcaemia

promptly and can also be used as first-line treatment (GRADE 1C recommendation).

Zoledronic acid was found to be superior to pamidronate in the treatment of malignancy-related hypercalcaemia (GRADE 1B recommendation),³³ while denosumab is an option for hypercalcaemia refractory to zoledronic acid.²⁹ However, the use of bisphosphonates in patients with renal dysfunction needs careful consideration, in discussion with renal physicians, due to the potential for further kidney damage. Close monitoring of renal function, appropriate dose modification and use of a slow infusion of pamidronate are suggested (due to slightly lower renal risk compared to zoledronate).²⁹ Calcitonin can also be considered as an adjunctive therapy in hypercalcaemia refractory to bisphosphonates or when bisphosphonates are contraindicated (GRADE 2C recommendation).³⁴ Close monitoring of fluid balance is crucial, and expectant diuresis should also be considered (GRADE 2C recommendation).³² Prompt initiation of definitive antimyeloma treatment, is of vital importance in conjunction with these supportive measures.

2.2 Renal complications

Renal impairment is associated with an increased risk of mortality in patients with MM³⁵ and occurs as a result of light chain cast nephropathy.³⁵ There is a pressing need to curtail further worsening of renal function and possibly reverse renal injury to avoid the need for long-term renal replacement therapy in these patients. While adequate hydration, management of hypercalcaemia and the avoidance of nephrotoxic agents are important, early institution of anti-myeloma treatment may reverse renal complications in up to 50% of patients.³⁶

Three RCTs evaluated high cut-off (HCO) dialysis compared to standard dialysis in patients with suspected light chain cast nephropathy.^{37–39} None of these studies conclusively demonstrated the superiority of HCO over standard dialysis. A meta-analysis including 2 of the aforementioned clinical trials, as well as 3 retrospective cohort studies, showed that although HCO dialysis resulted in faster clearance of free light chains, there was no significant benefit in terms of renal recovery.⁴⁰

With regard to plasmapheresis (PLEX), 3 RCTs^{41–43} evaluated PLEX compared to standard MM treatment in light chain cast nephropathy with mixed results and no clear demonstration of superior renal recovery. While a meta-analysis of 147 patients with MM-related renal impairment suggested an improved renal outcome in patients treated with chemotherapy and PLEX rather than chemotherapy alone.⁴⁴ Taken together, there is currently insufficient evidence to support the routine use of HCO dialysis or PLEX in all patients with suspected light chain cast nephropathy.

These interventions may be considered on a case-by-case basis for patients with severe renal injury, in discussion with nephrologists (GRADE 2C recommendation).

2.3 Anaemia

Anaemia is a frequent complication of MM and may significantly impair quality of life.^{45,46} A thorough clinical evaluation to exclude other causes of anaemia such as haematinic deficiency or blood loss is required. Erythropoiesis stimulating agents (ESAs) were once recommended for the management of anaemia in patients with cancer; however, studies have shown an increased risk of thrombotic events and increased mortality.^{47–49} The SMSG therefore recommends ESAs in MM only if the anaemia does not respond adequately to definitive MM therapy (GRADE 2C recommendation),⁵⁰ especially when there is associated renal dysfunction. The additional thrombotic risk of immunomodulatory therapy is an important consideration in weighing the risk/benefit of the use of ESAs.⁵¹ If ESAs are deemed necessary, the aim of therapy is to increase the haemoglobin to a level at which symptoms of anaemia are addressed and transfusion is avoided (GRADE 2C recommendation).⁵⁰ Erythropoietin alpha or beta and darbepoetin, as well as the equivalent biosimilar agents, are acceptable options (GRADE 2C recommendation).^{48,50} ESAs should be discontinued if no response (increase in haemoglobin by at least 1–2 g/dL) is observed after 6 to 8 weeks (GRADE 1B recommendation).⁵⁰

2.4 Bone disease and related complications

Osteolytic bone lesions occur in up to 80% of patients with newly diagnosed MM,²⁹ and can result in pain, pathologic fractures and spinal cord compression.⁵² The management of bone disease in MM can be divided into bone directed medical therapy and the management of acute skeletal events.

2.4.1 Bone-directed therapy and maintenance of bone health

Treatment of vitamin D deficiency is a crucial aspect of bone health maintenance.²⁹ The SMSG recommends the measurement of 25 hydroxyvitamin D levels in all patients at diagnosis. Vitamin D and calcium replacement is indicated in patients with vitamin D deficiency and/or those who are on bisphosphonate treatment (GRADE 1A recommendation). Vitamin D or calcium replacement is contraindicated in patients with hypercalcaemia until normalisation of serum calcium levels.²⁹

All patients with symptomatic MM, regardless of the presence of bone lesions, should be treated with a bisphosphonate—the first choice being zoledronic

acid (GRADE 1A recommendation).²⁹ Beyond bone health, zoledronic acid has been shown to have antimyeloma activity, with improvements in overall survival (OS) seen in patients on treatment.⁵³ Pamidronate at a monthly dose of 30 mg is an option in patients with a creatinine clearance <30 mL/min. The minimum duration of bisphosphonate therapy is 12 months at monthly dosing (GRADE 1B recommendation). For patients achieving a very good partial response (VGPR) or better, reduction in the frequency of bisphosphonate therapy to every 3 months for the next year can be considered.^{29,54} Discontinuation of bisphosphonate after 2 years of therapy can be considered if the response of VGPR or better is maintained, and bisphosphonates should be restarted at the time of relapse to prevent new skeletal events.²⁹

Denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand, was shown in a Phase III randomised trial to be at least of equivalent efficacy to zoledronic acid.⁵⁵ These findings remained consistent in a subgroup analysis of Asian patients,⁵⁶ supporting the broader application of denosumab across ethnic groups. Denosumab is a reasonable alternative to bisphosphonates and may be a consideration in patients with creatinine clearance <30 mL/min, albeit with close monitoring²⁹ (GRADE 1B recommendation). The potential rebound effect on osteoclasts when denosumab is discontinued is an important consideration. Administration of a bisphosphonate 6 months after discontinuation of denosumab has been proposed as a means to overcome the rebound effect,²⁹ but further studies are required to define the optimal strategy to mitigate this effect. The risk of serious hypocalcaemia associated with denosumab can be reduced by commencing it after vitamin D is replete.

Given the risk of medication-related osteonecrosis of the jaw (MRONJ) with both bisphosphonates and denosumab, all patients should undergo dental assessment prior to initiating these agents and at least annually while on treatment²⁹ (GRADE 1C recommendation). Bone-directed therapy should be paused prior to dental procedures and restarted 4 to 6 weeks after the procedure, depending on the state of the dentition and urgency of need for anti-resorptive therapy.⁵⁷ Prompt referral to an oral-maxillofacial surgeon is required if patients develop symptoms suggestive of MRONJ.⁵⁷

2.4.2 Management of fractures

Long bone fractures may require surgical stabilisation⁵⁸ and consideration of subsequent radiotherapy⁵⁹ (GRADE 1B recommendation). Local radiotherapy with 8 Gy in a single fraction has been shown to be an effective and safe dose for pain control.⁶⁰ Use of cross-sectional imaging can help identify areas of

imminent fracture (large or unstable lytic lesions) that should prompt an orthopaedic opinion to consider preemptive surgical management, helping to reduce fracture associated morbidity and healthcare/rehabilitation costs.⁵⁸ Kyphoplasty or vertebroplasty are also options for painful vertebral compression fractures.^{61,62} The presence of neuro-logical symptoms and spinal stability is a key deciding factor in the optimal management of vertebral fractures. A dedicated bone disease directed multidisciplinary team comprised of spinal/orthopedic surgeons, interventional radiologists, haematologists, radiation oncologists and pain management specialists, could be invaluable in making individualised management decisions.

2.4.3 Management of spinal cord compression

If there is any clinical suspicion of spinal cord compression, an urgent MRI scan of the spine should be performed, and orthopaedic/spinal surgeon consulted about the need for immediate surgical intervention⁶³ (GRADE 1A recommendation). Corticosteroid therapy should be commenced as soon as possible in addition to spinal nursing. Radiotherapy is appropriate for spinal cord compression due to plasmacytomas while surgery should be considered if the spinal cord is unstable or if the compression is due to retropulsed bone fragments.⁶³

2.5 Infective complications

The combination of MM-related hypogammaglobulinaemia and treatment-related immunosuppression increases the susceptibility to and severity of infections in MM patients.³² Infections are an important cause of mortality in patients with MM, and the risk is highest during the first 3 months after diagnosis.³⁰

Antiviral prophylaxis using acyclovir is recommended for patients receiving proteasome inhibitors or monoclonal antibodies, while both antiviral and *Pneumocystis jirovecii* pneumonia prophylaxis is recommended for patients receiving high-dose steroids^{30,64,65} (GRADE 4C recommendation). For patients who are seropositive for the hepatitis B core antibody, seronegative for hepatitis B surface antigen and have no detectable viral load, prophylactic antiviral therapy based on institutional protocols is recommended^{30,66} (GRADE 4C recommendation). Consultation with hepatology is recommended for patients with active hepatitis B. The routine use of antibacterial and antifungal prophylaxis in MM patients cannot be recommended given the equivocal evidence supporting their use at the time of publication.⁶⁷ An exception to this is the neutropenic phase of the stem cell transplant where fluoroquinolone prophylaxis should be considered (GRADE 4C recommendation). Management of neutropenic fever should be carried out according to institutional protocols.

The recommendation regarding intravenous immunoglobulin (IVIG) has been updated based on data questioning the efficacy of prophylactic IVIG at reducing infection rates in the modern era.^{68,69} Rather than recommending IVIG replacement in all patients with hypogammaglobulinaemia and infection, the SMSG suggests IVIG replacement in a selected group of patients—specifically for those with serum IgG less than 400 mg/dL and recurrent or severe infections with encapsulated bacteria despite adequate antimicrobial prophylaxis and immunisation³⁰ (GRADE 2A recommendation). IVIG as post-exposure prophylaxis in patients who are exposed to varicella, hepatitis A and herpes zoster may be considered on a case by case basis³⁰ (GRADE 2B recommendation).

2.5.1 Immunisations

Although immune paresis associated with MM may lead to impaired responses to vaccination, they do confer a benefit of reducing the frequency of infections and resulting hospitalisations.^{70,71} The seasonal influenza and pneumococcal vaccines have been used widely for MM patients and have a favourable safety profile.⁷² Patients with MM should receive inactivated vaccines rather than live vaccines in view of their immunocompromised status³⁰ (GRADE 2B recommendation). The SMSG recommends using the influenza vaccine annually, and the *Streptococcus pneumoniae* vaccine (PCV13) followed by PPSV23 based on institutional protocols (GRADE 2B recommendation). Vaccination against other encapsulated organisms like *H. influenzae* as well as the inactivated shingles vaccine and COVID-19 vaccinations can also be considered following institutional/national guidelines⁷³ (GRADE 2B recommendation). Patients should also undergo revaccinations post autologous stem cell transplant according to international guidelines/institutional protocols^{72,74} (GRADE 2B recommendation).

2.6. Thrombotic complications

The risk of venous thromboembolism (VTE) in MM is dependent on patient, disease and treatment related factors.⁷⁵ VTE is more common in newly diagnosed patients with more extensive disease, and immunomodulator based therapy increases thrombotic risk, especially in combination with immobility, steroids or chemotherapy.^{51,76,77} The risk of VTE with proteasome inhibitor/immunomodulator based triplet combinations has been reported at 2–5%.^{78–80} Although there is no prospective RCT data supporting the use of thromboprophylaxis in MM, retrospective analyses of VTE incidence in published RCT cohorts provide adequate grounds for its implementation.^{81,82} There are also no head-to-head comparisons between the various thromboprophylactic agents (low molecular

weight heparin versus aspirin versus target-specific oral anticoagulants). The SMSG proposes the following recommendations with reference to the risk assessment model suggested by the IMWG (Table 2).⁵¹

- Consider aspirin prophylaxis for all MM patients treated with immunomodulator-based combinations (GRADE 2B recommendation).
- For all MM patients treated with immunomodulator-based combinations with 2 other risk factors, consider low molecular weight heparin (LMWH) prophylaxis (GRADE 2B recommendation).
- Rivaroxaban or apixaban prophylaxis may be considered on a case-by-case basis (GRADE 2C recommendation).

It is noteworthy that the incidence of VTE in Asian MM patients treated with immunomodulators may be lower than that of their western counterparts.^{83,84} There is hence a need for VTE prediction scores developed and validated in Asian patients. More recently developed predictive models including IMPEDE-VTE⁸⁵ and SAVED⁸⁶ are promising options which need to be evaluated further in the Asian context. Our recommendations should be applied bearing in mind the individualised risk/benefit ratio for thromboprophylaxis.

Recommendations

A multidisciplinary approach is crucial to ensure holistic supportive care and maximise the benefits from treatment. Our recommendations for supportive care under the domains of hypercalcaemia, anaemia, renal impairment, bone disease, infection and thrombosis are presented in Table 3.

Section 3. Response assessment and monitoring

3.1 Response definitions

Standard response assessment for MM relies on paraprotein quantification using M protein densitometry and the SFLC assay in light chain disease.⁸⁷ Bone marrow studies are required for confirmation of complete response (CR) and stringent CR.⁸⁷ The SMSG recommends following the uniform response criteria defined by the IMWG,⁸⁷ summarised in Table 4 (GRADE 1A recommendation). There have been significant developments in the field of response assessment for MM since the publication of the previous guideline. These pertain to the concepts of minimal residual disease and imaging which are discussed below.

3.2 Minimal residual disease (MRD) assessment

The use of potent targeted drug combinations has resulted in deep responses for patients with MM, prompting the evolution of techniques to detect clonal plasma cells at levels beyond the resolution

Table 2. Risk factors for venous thromboembolism in multiple myeloma patients.

Individual factors	Obesity	BMI ³ 30 kg/m ²
	Comorbidities	Cardiac disease
		Renal disease
		Diabetes mellitus
		Blood clotting disorders/previous VTE
		Acute infection
		Immobilisation
	Surgical issues	General surgery/anaesthesia
		Trauma
	Medications	Erythropoietin
Myeloma related	Disease factors	Hyperviscosity
	Therapy related	High-dose dexamethasone (>480 mg dexamethasone equivalent per month)
		Doxorubicin
		Multiagent chemotherapy

VTE: venous thromboembolism

Table 3. Summary of recommendations for supportive care of patients with multiple myeloma.

Domains	Recommendations for supportive care	
Hypercalcaemia		
Mild hypercalcaemia	IV N/S	Monitor fluid status.
Moderate-severe hypercalcaemia	IV N/S	Monitor fluid status.
CrCl >30 mL/min	IV zoledronic acid 4 mg over 15 min	Suggested dose adjustment for renal impairment: - CrCl 50 to 60 mL/min: reduce dose to 3.5 mg - CrCl 40 to 49 mL/min: reduce dose to 3.3 mg - CrCl 30 to 39 mL/min: reduce dose to 3.0 mg - CrCl <30 mL/min: use is not recommended To consider IV pamidronate if significant renal impairment.
CrCl <30 mL/min	IV pamidronate 30 mg over 4–6 hours	There is limited pharmacokinetic data in patients with CrCl <30 mL/min. - Suggested dose for CrCl <30 mL/min and extensive bone disease: 90 mg (or consider reduced dose) over 4–6 hours. - Consider reduced initial dose if renal impairment pre-existing.
Refractory hypercalcaemia	SC calcitonin 4 units/kg every 12 hours	
	SC denosumab 120 mg 4 weekly	Suggest monitoring calcium levels prior to each dose; dental clearance is recommended prior to initiation of therapy.
Renal impairment		
All patients with renal impairment	Optimise hydration	
	Avoid nephrotoxic agents	
	Definitive treatment for MM	Bortezomib-based therapy is recommended.
Requiring renal replacement therapy with high SFLC	Consider plasmapheresis or HCO dialysis	Consider on case-by-case basis.

Table 3. Summary of recommendations for supportive care of patients with multiple myeloma. (Cont'd)

Domains	Recommendations for supportive care	
Hypercalcaemia		
Anaemia		
Hb <10 g/L	Erythropoietin	To consider erythropoietin stimulating agents if anaemia does not respond to definitive MM therapy. Consider stopping therapeutic trial if no response after 6–8 weeks.
Skeletal complications		
Spinal cord compression	Consider surgical intervention/RT IV dexamethasone	
Bone protection	Monthly zoledronic acid	See above for dosage adjustment for CrCl.
Infective complications		
Antimicrobial prophylaxis		
• Bortezomib	Acyclovir prophylaxis	
• High-dose steroid	Co-trimoxazole prophylaxis	NA
Management of hypogammaglobulinaemia	IVIg	To consider in patient with serum IgG less than 400 mg/dL and recurrent or severe infections despite adequate antimicrobial prophylaxis and immunisation.
Thromboprophylaxis		
Newly diagnosed MM treated with thalidomide/lenalidomide	PO Aspirin 100 mg OM	
MM patients treated with thalidomide/lenalidomide in combination with steroids/chemotherapy	PO Aspirin 100 mg OM	
MM on thalidomide/lenalidomide with 2 other risk factors	LMWH at prophylactic dose	

CrCl; creatinine clearance; Hb: haemoglobin; HCO: high cut-off ; IgG: immunoglobulin G; IV: intravenous; IVIg: intravenous immunoglobulin; LMWH: low molecular weight heparin; MM: multiple myeloma; N/S: normal saline; PO: by mouth; RT: radiotherapy; SC: subcutaneous; SFLC: serum free light chain assay; OM: every morning

of light microscopy.⁸⁸ The IMWG recommends MRD assessment via next-generation flow cytometry (NGF) or next-generation sequencing (NGS) using variable-diversity-joining rearrangement also known as V(D)J rearrangements to identify clonal plasma cells.⁸⁷ MRD negativity is defined by the IMWG as the absence of phenotypically aberrant plasma cells using a validated NGF or NGS technique with a sensitivity of at least 1 in 10⁵ nucleated cells.⁸⁹ MRD positivity has been established as an important adverse prognostic factor in MM, with MRD negativity even proposed to overcome adverse cytogenetic risk.^{90,91}

While the prognostic value of MRD is clear, the optimal methodology for MRD assessment in routine clinical practice remains uncertain. The EuroFlow 8-colour NGF panel was validated on patients treated in the PETHEMA/GEM2012MENOS65 trial⁹¹ and is recommended as the standard NGF platform by

the IMWG.⁸⁷ Other centres have also developed multiparametric flow cytometry panels reporting equivalent sensitivity⁹² although their use is not as widespread as that of the EuroFlow panels. NGS platforms have shown similar levels of sensitivity to NGF and have the advantage of requiring a smaller number of cells⁸⁸. NGS is however more costly, requires a longer turnaround time, a baseline sample and significant bioinformatics support.⁸⁸

A number of clinical trials have explored MRD-based adaptation of therapy in newly diagnosed MM.^{93,94} These trials have demonstrated the feasibility of applying MRD-adapted treatment protocols as well as the value of attaining MRD negativity, especially in patients with high cytogenetic risk MM. The optimal time point at which to assess MRD, however, remains to be determined. While the prognostic impact of MRD pre-maintenance⁹⁵ has been established, the

Table 4. International Myeloma Working Group definitions of response categories.

Response sub-category	Response criteria
Sustained MRD-negative CR	MRD negativity in the bone marrow by NGF and/or NGS, and by imaging as defined below, confirmed on at least 2 time points 1 year apart. The duration of negativity can be described based on subsequent evaluations, e.g. MRD-negative at 3 years.
MRD- and imaging-negative CR	MRD negativity in the bone marrow by NGF and/or NGS, in addition to resolution of all areas of PET tracer uptake detected at baseline to less than the mediastinal blood pool SUV or to less than the surrounding normal tissues.
Flow MRD-negative CR	Absence of phenotypically aberrant clonal plasma cells by NGF on a bone marrow aspirate using the EuroFlow standard operating protocol for MRD detection in MM, with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher.
Sequencing MRD-negative CR	Absence of clonal plasma cells by NGS on a bone marrow aspirate in which the presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing using the LymphoSIGHT (Sequentia/Adaptive) platform (or validated equivalent method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher.
Stringent CR	CR as defined below plus • Normal SFLC ratio • Absence of phenotypically aberrant PC by MPFC
CR	• Negative IFE on serum and urine • Disappearance of any soft tissue plasmacytomas • ≤5% bone marrow PC
VGPR	• Serum and urine M-protein detectable by IFE but not on SPEP; or • ≥90% reduction in serum M-protein plus reduction in 24 hr urine M-protein by ≥90% or to <100 mg/24 hr
PR	• ≥50% reduction of serum M-protein and reduction in 24 hr urinary M-protein by >90% or to <200 mg/24 hr
Stable disease	• Not meeting criteria for CR, VGPR, PR or PD
Progressive disease	• >25% increase in serum M-protein in 3 months (absolute increase must be >5 g/L) • >25% increase in urine M-protein in 3 months (absolute increase must be >200 mg/24 hr) • >25% increase in the difference between involved and uninvolved SFLC levels (applicable only to patients without measurable serum and urine M-protein (absolute increase must be >100 mg/L) • >25% increase in bone marrow plasma cell percentage (absolute percentage must be >10%) • Development of new bone lesions or soft tissue plasmacytoma • Development of hypercalcaemia

CR: complete response; DNA: deoxyribonucleic acid; hr: hour; IFE: immunofixation electrophoresis; MM: multiple myeloma; MPFC: multiparameter flow cytometry; MRD: minimal residual disease; NGF: next-generation flow cytometry; NGS: next-generation sequencing; PC: clonal plasma cells; PD: progressive disease; PET: positron emission tomography; PR: partial response; SFLC: serum free light chain; SPEP: serum protein electrophoresis; SUV: standardised uptake value; VGPR: very good partial response

PRIMER study suggests that pre-transplant MRD negativity may not have the same prognostic value.⁹⁶

MRD assessment from bone marrow samples fails to account for patchy marrow involvement as well as spatial heterogeneity of the tumour cells⁹⁷ that are typical in MM. The invasive nature of bone marrow sampling and the associated costs means that MRD assessment at multiple time points may be unacceptable for some patients. Although peripheral blood-based MRD monitoring platforms are being developed, these are not ready for clinical application at the time of publication.⁹⁸ Importantly, bone marrow-based or blood-based MRD assessment does not take into account extramedullary disease.⁸⁷

3.3 Imaging for response assessment

Since the previous SMSG guideline, evidence has emerged on the value of sensitive imaging techniques to detect progression of bone lesions and extramedullary disease.^{19,99} As suggested by the IMWG, a WBLDCT should be considered before the initiation of maintenance therapy as a baseline if it was not performed at diagnosis. A repeat WBLDCT can be considered at the point of serologic relapse, or if there are clinical symptoms suggestive of new bone lesions¹⁹ If there is a suspicion of extramedullary relapse, or the patient had PET imaging at diagnosis, PET would be the recommended modality of imaging at relapse.¹⁹ The finding of new bone lesions during

an otherwise biochemical relapse may help decision-making regarding initiation of treatment.

As mentioned in section 3.2, currently available modalities for assessment of MRD fail to account for extramedullary disease. The combination of bone marrow MRD assessment using NGF/NGS with sensitive imaging to document the absence of extramedullary disease is therefore attractive. The adverse prognostic value of FDG avid lesions on post-treatment PET has been demonstrated in prospective clinical trials.^{21,100} The IMWG defines the “imaging plus MRD-negative” status as the achievement of MRD negativity by NGF/NGS plus disappearance or reduction in standard uptake value (SUV) of all FDG avid lesions seen on the baseline 18F-FDG-PET-CT. Whole-body MRI and WBLDCT have limited value in the setting of imaging MRD assessment or detection of extramedullary disease.

Although the rationale for a composite MRD assessment is strong, there remain many unanswered questions. Specifically, at what time points and how often should the MRD assessments be done, and should all modalities be used at each time point? Most importantly, there is currently insufficient data to support guiding treatment decisions based on MRD results alone and this is strongly discouraged outside of a clinical trial context.

Recommendations

- The SMSG recommends following the current IMWG consensus criteria for response assessment⁸⁹ (GRADE 1A).
- PET imaging is recommended for patients with non-secretory MM and to assess extramedullary disease/plasmacytomas (GRADE 1B).
- The SMSG does not recommend routine assessment of MRD outside of clinical trials. If MRD assessment is used on a case-by-case basis, we recommend NGF using the EuroFlow-8 colour panel. The rationale for this recommendation is that the expertise to conduct this analysis is available locally, in addition to the faster turnaround time and lower cost compared to NGS (GRADE 2C).
- The SMSG strongly discourages starting new therapy/changing therapies based on MRD results alone (GRADE 2C).

Section 4. Management of transplant-eligible patients with MM

4.1 Background and definition of transplant eligibility

High-dose melphalan followed by autologous stem cell transplant (ASCT) has been shown to prolong progression-free survival (PFS) in several large RCTs. The key RCTs supporting the use of ASCT in

the modern era are the IFM2009,⁸⁰ EMN02 H95¹⁰¹ and DETERMINATION¹⁰² trials. In this section, the authors discuss the evidence base for management of transplant eligible patients with MM and provide recommendations on the optimal treatment options.

4.2 Choice of induction therapy

4.2.1 Proteasome inhibitor/immunomodulator-based triplet combinations

A meta-analysis of Phase III RCTs comparing bortezomib and non-bortezomib containing induction regimens showed a superior response rate and PFS for the bortezomib containing regimens.¹⁰³ The combination of bortezomib with thalidomide and dexamethasone (VTD) was shown to be superior to bortezomib/cyclophosphamide/dexamethasone (VCD) in terms of response rates pre ASCT.¹⁰⁴ Bortezomib, lenalidomide, dexamethasone (VRD) has been proposed as the optimal choice of proteasome inhibitor-based triplet combination.^{105,106} Although there are no RCTs directly comparing VRD with VTD, an integrated analysis of 4 RCTs suggested superior response rates with VRD compared to VTD pre pre-ASCT.¹⁰⁷ While carfilzomib-based triplet regimens have been studied in the first-line setting for transplant eligible patients,^{108,109} the only RCT that compared KRD with VRD was not able to show a significant PFS benefit over VRD.⁷⁹ It is noteworthy however that this study did not include patients with high cytogenetic risk MM. Among the triplet regimens, the SMSG recommends VRD as the first choice, with VTD as an alternative option.

4.2.2 Daratumumab-based quadruplet combinations

Daratumumab (DARA) is an anti-CD38 human immunoglobulin G kappa monoclonal antibody, which induces apoptosis of malignant plasma cells via a variety of mechanisms.¹¹⁰ DARA-based quadruplet regimens have been evaluated as induction therapy pre-ASCT in the CASSIOPEIA (DARA-VTD), GRIFFIN (DARA-VRD) and PERSEUS (DARA-VRD) trials.¹¹¹⁻¹¹³ All 3 RCTs showed a benefit for DARA-VTD and DARA-VRD (DVRD) over VTD and VRD, respectively, in terms of stringent complete response rate and PFS.^{111,112} Importantly, the DARA-based quadruplets in all 3 trials resulted in superior rates of MRD negativity, which has emerged as an important predictor of long-term outcomes.^{114,115} The superiority of DARA-based quadruplets (with regard to response rates and PFS) over standard triplet induction regimens has been confirmed in systematic reviews and meta analyses.^{116,117} Given the excellent results obtained with DARA-based quadruplet therapy, the SMSG recommends that DARA-VTD or DARA-VRD be considered as options for pre-ASCT induction. The recommended regimens for induction therapy

are summarised in Table 5, and dose adjustments for toxicity are summarised in Appendix S1.

Table 5. Options for induction therapy in transplant-eligible patients with newly diagnosed multiple myeloma.

Triplet regimens	Quadruplet regimens
Bortezomib/lenalidomide/ dexamethasone (preferred option)	Daratumumab-VTD
Bortezomib/thalidomide/dexamethasone	Daratumumab-VRD

VRD: bortezomib/lenalidomide/dexamethasone; VTD: bortezomib/thalidomide/dexamethasone

Recommendation

- The SMSG recommends VRD, DARA-VTD or DARA-VRD as the preferred regimens for induction therapy pre ASCT (GRADE 1A).

4.3 Number of cycles of induction and response before stem cell harvest

The depth of response pre-transplant correlates with event-free survival and overall survival, with patients in CR having the best outcome.^{118,119} The minimum response required before proceeding to ASCT is a partial response (PR). If a PR is not achieved after 4 cycles of induction therapy, a further 2 cycles should be considered. If a PR is not achieved after 6 cycles or there is progressive disease at any time point during induction, a change of therapy is recommended^{120,121} (GRADE 1B recommendation).

4.4 Mobilisation chemotherapy and stem cell collection

High-dose cyclophosphamide (CY) at 4–7 g/m² with granulocyte colony-stimulating factor (GCSF) has been shown to be effective for haematopoietic progenitor cell (HPC) mobilisation.¹²² Vinorelbine 25 mg/m² in combination with cyclophosphamide 1500 mg/m² (i.e. VINO-Cy) was shown to be comparable to high-dose cyclophosphamide mobilisation in retrospective analyses and has less haematologic toxicity.^{121,123,124} Pegylated GCSF may also be an equally effective and more convenient alternative to conventional GCSF.¹²⁵

The use of lenalidomide and CD38 monoclonal antibodies can limit the harvest, especially if the patient has had multiple cycles of treatment. However, timing the harvest in relation to these agents and the use of plerixafor have enabled safe and effective collection of CD34-positive cells in adequate quantities in these patients. In general, based on prospective trials using the above agents in combination, the quantum of CD34-positive cells collected has been lower and use of rescue plerixafor higher in DARA-containing arms. Given the current cost of plerixafor, rescue use of plerixafor seems the most economical

approach in the Singapore context, although preemptive use to enable higher quantum collection possibly with reduced number of apheresis sessions and associated hospital stay remains a good strategy.¹²⁶

4.5 The SMSG recommends one of the following mobilisation protocols (GRADE 1B):

- Vinorelbine 25 mg/m² on day 1, cyclophosphamide 1500 mg/m² on day 2 with pegylated GCSF 6 mg on Day 4. Or
- Cyclophosphamide 1500 mg/m² on day 1 and 2 and conventional GCSF 10 mcg/kg/day from day 5 onwards.

An HPC collection adequate for 2 SCTs should be the target, this is conventionally accepted to be greater than 5×10^6 per kg/body weight.¹²⁷

4.6 Conditioning regimen and early versus delayed ASCT

Melphalan 200 mg/m² is the standard conditioning regimen for ASCT in MM.^{106,128} While the addition of bortezomib¹²⁹ or busulfan¹³⁰ to melphalan conditioning has been studied, these trials have not shown conclusive clinical benefits. Dose modification of melphalan is recommended in some situations, such as in renal dysfunction and in patients >70 years of age.¹³¹ Indeed, there is data suggesting that the outcomes with melphalan 140 mg/m² and 200 mg/m² are comparable in patients who have achieved VGPR or better with induction therapy.¹³²

The IFM2009¹³³ and DETERMINATION¹⁰² trials demonstrated that patients having ASCT in first remission enjoyed a markedly improved PFS when compared to the non-ASCT arm with VRD induction and lenalidomide maintenance therapy. The lack of an OS benefit in these trials has however triggered the debate as to whether delayed transplant is a reasonable alternative. Furthermore, there is no guarantee that patients will retain their performance status and fitness for ASCT if they choose to wait until relapse. Importantly, access to therapies at relapse in the Singapore context is different to their availability in the countries where these trials were conducted. Given the marked PFS benefit and the challenges of demonstrating an OS benefit in MM (due to the potent salvage options available), the SMSG recommends ASCT in first remission as the standard.

Recommendations

- Melphalan 200 mg/m² remains the standard conditioning regimen (GRADE 1A recommendation).
- Delayed ASCT maybe considered on an individualised basis if there are personal or logistic reasons that prevent a patient from having ASCT in first remission (GRADE 2A recommendation).

4.7 Single versus double ASCT

A randomised study by the Intergroupe francophone du myélome showed that tandem ASCT results in an OS benefit for patients who achieved less than a VGPR after their first ASCT.¹³⁴ This study was however conducted in the pre-novel agent era. Several trials have since evaluated the relative efficacy of single versus tandem ASCT in newly diagnosed MM following novel agent containing induction therapy.^{135–137} A long-term follow-up analysis of patient-level data from 3 Phase III trials comparing single versus tandem ASCT using bortezomib-based induction regimens demonstrated that the greatest benefit was for patients with high-risk cytogenetics and a suboptimal response to induction therapy.¹³⁸

Recommendation

- Double ASCT should be discussed as an option and considered in patients who have achieved less than VGPR after first ASCT, especially in patients with high-risk disease (GRADE 2C).

4.8 Role of consolidation therapy

While older studies reported a PFS benefit for bortezomib or lenalidomide as consolidation therapy,^{139,140} the patients in these trials did not receive a proteasome inhibitor/immunomodulator based induction which is considered standard today. Since the publication of the previous SMSG guideline, 2 large RCTs have evaluated post-ASCT consolidation therapy. The STAMINA trial compared 4 cycles of VRD consolidation against tandem ASCT and single ASCT followed by continuous lenalidomide maintenance.¹⁴¹ The EMN02/H095 trial compared VRD consolidation with no consolidation in patients who had undergone either bortezomib/melphalan/prednisolone (VMP) or single/double ASCT followed by lenalidomide maintenance.¹⁴² Neither trial demonstrated a PFS or OS benefit for consolidation therapy. While consolidation therapy has been employed in RCTs evaluating DARA-based quadruplet induction, none of them included a randomisation at consolidation.^{113,143,144}

Recommendation

- There is inadequate evidence to recommend the routine administration of consolidation therapy, although it may be considered on a case-by-case basis for patients not achieving at least a VGPR post-ASCT, using the same regimen used for induction therapy (GRADE 2C).

4.9 Maintenance therapy post-autologous stem cell transplantation

Lenalidomide maintenance has been shown to prolong PFS and OS post-ASCT,¹⁴⁵ in 4 key RCTs.^{139,146–148} All 4 trials showed a significant PFS benefit in favour of

lenalidomide with the CALGB 100104 and MRC XI trials also showing an OS benefit. The OS benefit was confirmed by a meta-analysis including patients from all the trials except MRC XI,¹⁴⁹ establishing lenalidomide as the standard of care for post-ASCT maintenance therapy.

Although the evidence base for thalidomide maintenance is not as strong as that for lenalidomide, it remains an option for patients who cannot tolerate lenalidomide.¹⁵⁰ Single-agent bortezomib maintenance has only been assessed in 1 prospective trial where the standard arm was treated with vincristine, doxorubicin, dexamethasone induction, ASCT and thalidomide maintenance.¹⁵¹ While bortezomib-based maintenance is frequently used in high-risk MM, this recommendation is not supported by RCT data.^{152,153} Close monitoring for peripheral neuropathy is crucial if bortezomib or thalidomide are used for maintenance therapy.³²

Ixazomib presents an alternative maintenance option based on the TOURMALINE MM-3 study,¹⁵⁴ which showed a modest PFS benefit in favour of ixazomib over placebo. DARA was investigated as maintenance therapy in the second randomisation of the CASSIOPEIA trial where PFS was significantly longer in the DARA maintenance group than the observation group.¹⁴³ DARA could therefore be considered in patients who are unable to receive lenalidomide maintenance. Although there are no RCTs comparing lenalidomide, ixazomib and DARA maintenance against each other, a recent meta-analysis suggests that lenalidomide remains the preferred option.¹⁵⁵

The optimal duration of maintenance therapy remains an area of uncertainty. Although the key trials evaluating lenalidomide employed continuous maintenance until progression,^{139,145,147,156} long-term toxicities including second primary malignancies are an important concern. Ongoing trials are evaluating the role of individualised maintenance therapy based on response to treatment, especially MRD adapted approaches,¹⁵⁷ which may be incorporated into future treatment algorithms. Based on currently available data, maintenance therapy for 2 years is considered an acceptable standard, with consideration of extended duration in individuals with manageable toxicity profiles.¹⁵⁸

Recommendation

- The SMSG recommends lenalidomide maintenance as the standard of care for standard risk patients (GRADE 1A), while for high-risk patients, lenalidomide- and/or bortezomib-based therapy can be considered (GRADE 2C). We do not recommend the routine use of DARA maintenance

given the lack of clear evidence at the present time that it is superior to lenalidomide.

- Bortezomib, thalidomide or ixazomib maintenance maybe considered on an individualised basis when lenalidomide maintenance is not tolerated or contraindicated (GRADE 2B).
- The SMSG suggests 2 years of maintenance therapy as the standard duration, with consideration of longer duration on a case-by-case basis depending on toxicities (GRADE 2C).

4.10 Role of allogeneic transplant

Allogeneic SCT (allo-SCT) is currently the only curative therapy available for MM, however it is associated with a high transplant-related mortality (TRM) of 20–30%.¹⁵⁹ The high TRM, together with the exponentially increasing treatment options in MM was the reason for allogeneic SCT falling out of favour in the last decade. However, with the move from more myelosuppressive regimens to more immunosuppressive, reduced intensity regimens in conditioning, better supportive therapy, earlier allo-SCT and less prior chemotherapy the TRM has been reduced. Long-term survival was achieved in 10–25% of the patients and the plateau in survival curve was observed in 1 study.^{160,161}

Recommendation

- Given the plethora of agents currently available, allo-SCT would be considered investigational in the upfront setting; however in selected young, fit patients with ultra-high-risk myeloma at first relapse, it may be an appropriate consideration (GRADE 3C).

Section 5. Management of patients ineligible for autologous stem cell transplantation

5.1. Patient selection

The determination of transplant eligibility and fitness for treatment should be based on a comprehensive functional assessment rather than age alone. Geriatric assessment is of increasing importance in MM, and comprehensive frailty evaluation has become a standard of care to optimise the safety of treatment and minimise the impact on quality of life.¹⁶² Stratification of patients by frailty enables treatment to be tailored to individual patients' tolerance of therapy. The IMWG frailty score is the current standard for geriatric assessment in MM, incorporating age, comorbidities and functional measures.¹⁶³ Frailty scoring systems used or being developed in MM are summarised in Table 6.

Recommendation

- The SMSG suggests using the IMWG frailty score, while awaiting further validation of the newer frailty scoring systems (GRADE 2B).

5.2. Induction therapy for transplant ineligible patients

Many of the currently used transplant-ineligible induction regimens build on the lenalidomide/dexamethasone (Rd) backbone established by the FIRST trial, which showed the superiority of Rd to the prior standard of melphalan/prednisolone/thalidomide (MPT).¹⁸³ It is noteworthy that this effect was more apparent for continuous therapy with Rd compared to time-limited Rd given for 18 months.¹⁸³ The VRD regimen was compared against RD for transplant ineligible MM patients in a randomised study (SWOG S0777), which resulted in VRD becoming a standard of care induction regimen.¹⁸⁴ It is noteworthy, however, that the population included in this trial was younger than the typical transplant-ineligible population in the Singapore context.

DARA-based induction therapy in transplant-ineligible patients was first evaluated in the ALCYONE trial, which demonstrated a PFS and OS benefit for DARA+VMP over VMP.¹⁸⁵ The MAIA trial compared the DARA/lenalidomide/dexamethasone (DRd) regimen in a continuous fashion against Rd.¹⁸⁶ DRd resulted in a marked PFS benefit over Rd (median PFS not reached for DRd versus 34.4 months for Rd (hazard ratio [HR] 0.53, 95% confidence interval [CI] 0.43–0.66; $P < 0.0001$)).¹⁸⁶ Notwithstanding the caveats of the MAIA study,¹⁸⁷ the remarkable results have led to DRd being considered one of the standard of care regimens in transplant-ineligible MM patients.

CD38 monoclonal antibody-based quadruplet induction has been investigated in the IMROZ and BENEFIT trials (Isatuximab-VRD),^{188,189} and the ongoing CEPHEUS trial (DARA-VRD),¹⁹⁰ with MRD negativity as the primary end point. All 3 trials have shown superiority of the quadruplets with regard to efficacy, with a favourable toxicity profile. It is however noteworthy that these trials did not enrol frail patients, hence the use of these regimens may be limited to a subset of fit, transplant-ineligible patients.

Isatuximab-VRD and DARA-VRD are currently not approved for induction therapy in transplant-ineligible patients but may become viable options in the near future. Recommended treatment protocols for induction therapy are summarised in Table 7 and dose adjustments based on frailty status and toxicity are summarised in Table 8 and Appendix S1. Doublet regimens such as bortezomib, dexamethasone¹⁹¹ and RD¹⁸³ are also reasonable options in frail patients. It is noteworthy that dexamethasone-sparing induction regimens are under active investigation¹⁹² and may become an option for frail patients in the future.

If a triplet regimen is being used, SMSG recommends induction therapy for 8–9 cycles until a response plateau. Subsequently, options include continuing the triplet until disease progression or stepping down to

Table 6. Comparison of the frailty scoring systems in multiple myeloma.

Score	Reference	Variables	Frailty/outcome groups defined	Validation
Fried phenotype	Fried ¹⁶⁴	• Unintentional weight loss • Weakness • Poor endurance and exhaustion • Slowness • Low physical activity	• Frail group (≥3 frail criteria) • Intermediate-frail (1–2 criteria)	• No internal validation cohort
Clinical frailty index	Rockwood ¹⁶⁵	• Modified Mini-Mental State Examination • Cumulative Illness Rating Scale • History of falls, delirium, cognitive impairment or dementia • CSHA definition of frailty • CSHA Frailty Index • CSHA Function Scale	• Very fit • Well • Well, with treated comorbid disease • Apparently vulnerable • Mildly frail • Moderately frail • Severely frail	• Longitudinal follow-up of original cohort
Hematopoietic cell transplantation-specific comorbidity index	Sorró ¹⁶⁶	• Atrial fibrillation or flutter, sick sinus syndrome or ventricular arrhythmias • Coronary artery disease, congestive heart failure, myocardial infarction or EF ≤50% • Crohn's disease or ulcerative colitis • Diabetes requiring treatment with insulin or oral hypoglycaemics but not diet alone • Transient ischaemic attack or cerebrovascular accident • Depression or anxiety requiring psychiatric consult or treatment • Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN • Patients with a body mass index > 35 kg/m² • Infection requiring continuation of antimicrobial treatment after day 0 • SLE, RA, polymyositis, mixed CTD or polymyalgia rheumatica • Peptic ulcer requiring treatment • Serum creatinine >2 mg/dL, on dialysis, or prior renal transplantation • DLco and/or FEV1 66–80% or dyspnoea on slight activity • Prior solid tumour treated at any time point in the patient's history, excluding nonmelanoma skin cancer • Heart valve disease except mitral valve prolapse • DLco and/or FEV1 ≤65% or dyspnoea at rest or requiring oxygen • Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	• 0 • 1–2 • >2	• Internal validation; training (n=708), validation (n=347). • External validation in multiple studies^{167,171}
International Myeloma Working Group	Palumbo ¹⁷²	• Age • CCI • IADL • ADL	• Fit • Intermediate-fit • Frail	• No internal validation cohort • External validation by 125 patients in a single institution¹⁷³

Table 6. Comparison of the frailty scoring systems in multiple myeloma. (Cont'd)

Score	Reference	Variables	Frailty/outcome groups defined	Validation
Simplified Frailty scale	Facon ¹⁷⁴	- Age - CCI - ECOG	- Non frail - Frail	- Retrospective analysis of the patients in the Phase III FIRST trial - External validation in a population-based cohort¹⁷⁵
Revised myeloma comorbidity index	Engelhardt ¹⁷⁶	- Age - eGFR - Lung disease - Karnofsky Performance Status - Frailty - Cytogenetics	- Fit - Intermediate-fit - Frail	- Internal validation; training (n=552) and validation (n=249) - External validation¹⁷⁷
Myeloma risk profile	Cook ¹⁷⁸	- Age - Performance status - C-reactive protein - International Staging System	- Low risk - Medium risk - High risk	- Internal validation with the NCRI Myeloma XI study [NCRI-XI, n=1852] and externally validated using the MRC Myeloma IX study [MRC-IX, n=520]) - External validation in prospective and retrospective studies^{179, 180}
Mayo Clinic Frailty	Milani ¹⁸¹	- Age - Performance status - NT-BNP	- I - II - III - IV	No external validation studies
Carolina Frailty Index	Guerard ¹⁸²	- IADL - Physical function - Comorbidities - Number of daily medications - Vision - Hearing - Nutrition - Mental health - Social activity - Measure of physical function and cognition	- Robust - Pre-frail - Frail	No external validation studies

ADL: activities of daily living; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CCI: Charlson Comorbidity Index; CSHA: Canadian Study of Health and Aging; CTD: connective tissue disease; DLco: diffusion capacity of lung; eGFR: estimated glomerular filtration rate; ECOG: Eastern Cooperative Oncology Group; EF: ejection fraction; FEV1: forced expiratory volume in 1 second; IADL: instrumental activities of daily living; IMWG: International Myeloma Working Group; MRC: Medical Research Council; NCRI: National Cancer Research Institute; NT-BNP: N-terminal pro-B-type natriuretic peptide; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ULN: upper limit of normal

maintenance therapy. This decision should be guided by the disease risk stratification, depth of response to treatment, toxicities, financial circumstances and patient preference.^{193,194}

Recommendations

- The SMSG recommends DRd or VRD as preferred induction regimens, while RD or VD can be considered for frail patients (GRADE 1A).
- Continuous therapy or de-escalation to single-agent maintenance after 8–9 cycles are both reasonable strategies (GRADE 2C).

5.3 Maintenance therapy

Lenalidomide maintenance has shown consistent PFS benefit across clinical trials and is considered the standard of care for maintenance therapy.^{156,195} Notably, for intermediate-fit elderly patients treated with Rd, stepping down to lenalidomide maintenance was shown to be comparable to continuous Rd with regard to efficacy and avoided the additional toxicities of continuous Rd.¹⁹⁶ Thalidomide maintenance has also been shown to prolong PFS but peripheral neuropathy can be a limiting factor; furthermore, a

network meta-analysis suggested that lenalidomide maintenance maybe superior to thalidomide.^{197,198} Hence, thalidomide should only be considered if lenalidomide maintenance is not tolerated.

Ixazomib maintenance was compared to placebo in transplant ineligible patients in the TOURMALINE-MM4 trial where the ixazomib arm showed a modest PFS benefit (median 17.4 months for ixazomib versus 9.4 months for placebo (HR 0.659, 95% CI 0.542–0.801; $P < 0.001$).¹⁹⁹ A recent meta-analysis also suggested that lenalidomide maintenance is superior to ixazomib maintenance.¹⁵⁵ There is no evidence supporting the use of bortezomib maintenance in the transplant ineligible setting. The SMSG therefore proposes lenalidomide as the standard of care, while bortezomib-based maintenance can be considered on a case-by-case basis for patients with high-risk MM, based on extrapolation from the transplant-eligible patient data.

Recommendations

- SMSG recommends lenalidomide as the preferred maintenance option for transplant-ineligible patients (GRADE 1A).

Table 7. Frontline treatment options for transplant-ineligible multiple myeloma patients.

Fit	Daratumumab, lenalidomide, dexamethasone Bortezomib, lenalidomide, dexamethasone
Frail	Bortezomib, lenalidomide, dexamethasone with dose reduction Bortezomib, dexamethasone Lenalidomide, dexamethasone
Unfit	VD or RD tailored according to patient frailty with appropriate dose attenuation

RD: lenalidomide, dexamethasone; VD: bortezomib, dexamethasone

Table 8. Dose adjustments in elderly patients with multiple myeloma.

Drug	Initial/standard dose	Reduced dose	Further reduction if required
Dexamethasone ^a	40 mg/day D1, 8, 15, 22 every 28 days	20 mg/day D1, 8, 15, 22 every 28 days	10 mg/day D1, 8, 15, 22 every 28 days
Thalidomide	100 mg ON	50 mg ON	50 mg EON
Lenalidomide (used with dexamethasone)	25 mg D1–21 every 28 days	15 mg D1–21 every 28 days	10 mg D1–21 every 28 days
Bortezomib ^b	1.3 mg/m ² D1, 8, 15, 22 every 28 days	1.0 mg/m ² D1, 8, 15, 22 every 28 days	0.7 mg/m ² D1, 8, 15, 22 every 28 days
Cyclophosphamide	500 mg once weekly	300 mg weekly	200 mg weekly

(Adapted from Palumbo A, Mina R. Management of older adults with multiple myeloma. *Blood Rev* 2013;27:133-42.)

EOD: every other day; EON: every other night; ON: at night

^a Dexamethasone should be commenced at the reduced dose (20 mg once weekly) in patients above the age of 70 years.

^b To consider using bortezomib 1.3 mg/m² twice weekly on D1, 4, 8, 11 every 3 weeks in selected patients who require rapid reduction of paraprotein levels.

- Thalidomide or ixazomib maintenance can be considered as alternatives when lenalidomide is not tolerated (GRADE 2B).
- The SMSG suggests 2 years of maintenance therapy as the standard duration, with consideration of longer duration on a case-by-case basis depending on toxicities (GRADE 2C).

Supplementary material

Appendix S1. Drug toxicity and dose adjustments for induction and maintenance therapy in multiple myeloma.

Ethics statement

Not applicable as no study participants were involved.

Declaration

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

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Systemic disconnects in musculoskeletal healthcare across the care continuum

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ABSTRACT

Musculoskeletal disorders are a leading cause of disability, particularly among the elderly. Despite growing awareness, care for these conditions remains episodic and poorly integrated across the care continuum. This is driven by 3 key systemic disconnects: between biomedical and psychosocial care, between reactive and preventive approaches, and between research, practice and policy. These disconnects have led to fragmented, short-term responses, resulting in suboptimal outcomes and missed opportunities for early intervention, functional preservation and long-term independence, especially for the ageing population. Addressing them requires a shift in approach that incorporates psychosocial assessment into routine care, prioritises preventive strategies that build intrinsic capacity, and supports investment in implementation science, capacity building and cross-sector collaboration. Ultimately, musculoskeletal healthcare must be treated as a core element of chronic disease management, integrated within a broader framework that addresses non-communicable diseases rather than treating it in isolation. Moreover, a holistic, person-centred approach is essential—one that integrates preventive care, rehabilitation and social support, backed by policies that promote long-term, coordinated care. This comprehensive approach, which aligns all stakeholders, can help prevent avoidable outcomes, enhance patient autonomy and reduce societal costs.

Keywords: aged, chronic disease, health policy, musculoskeletal diseases, patient-centred care

INTRODUCTION

Globally, musculoskeletal disorders are the second leading cause of non-fatal disability, affecting more than 1.63 billion people.¹ Conditions such as osteoarthritis, osteoporosis, sarcopenia, low back pain and other degenerative disorders are particularly prevalent among the elderly and are often intertwined with multimorbidity, disability and social vulnerability.² Although these conditions are recognised as predictors of adverse outcomes and despite growing awareness of their complexity, care remains episodic,

acute-focused and poorly integrated across the primary-to-tertiary continuum, especially in developing countries where occupational risks and longer workweeks exacerbate musculoskeletal disability-adjusted life years.³ This struggle stems from 3 critical systemic disconnects: a disconnect between biomedical and psychosocial intervention strategies, a disconnect between reactive/episodic and preventive care, and a disconnect between research, practice and policy. Each of these disconnects have led to fragmented, short-term responses that contributes to suboptimal outcomes and missed opportunities for early intervention, functional preservation and long-term independence of the ageing population.

Disconnect 1: Biomedical versus psychosocial interventions

Clinical assessments and treatment protocols for chronic musculoskeletal conditions typically emphasise anatomical, biomechanical and physiological factors. This approach, while essential for diagnosis and medical management, often neglects the social, emotional and environmental determinants of health that significantly influence recovery and long-term function.⁴ Modern healthcare systems invest significantly in uncovering the molecular and cellular underpinnings of disease. Cutting-edge studies delve deep into genomics, proteomics and metabolomics to better understand disease pathways. However, equivalent attention is rarely paid to psychosocial dynamics, such as the influence of depression, anxiety, caregiver support or socioeconomic status on recovery and function. This biomedical skew leaves a crucial gap in delivering truly comprehensive, patient-centred care. To close this gap, healthcare systems must embrace a broader paradigm, one that embeds psychosocial assessment into routine musculoskeletal care. This includes integrating validated tools for mental health screening, deploying social prescribing models to connect patients with community resources, evaluating built environment barriers to physical activity, and designing behavioural change interventions that support sustained lifestyle improvements.⁵⁻⁸

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Several validated instruments are available to support comprehensive psychosocial assessment. Psychological factors such as fear of movement, balance confidence, coping, self-efficacy and catastrophising can be evaluated using tools like the Tampa Scale of Kinesiophobia, the Fear-Avoidance Beliefs Questionnaire, the Activities-specific Balance Confidence Scale, the Pain Catastrophizing Scale, and the Pain Self-Efficacy Questionnaire.^{9,10} Social factors, including social support and isolation, may be measured with instruments such as the Lubben Social Network Scale, the Multidimensional Scale of Perceived Social Support and the Patient-Reported Outcomes Measurement Information System social health measures.¹¹ This list includes instruments locally validated in Singapore and is illustrative, not exhaustive, as many others remain validated in different contexts. The integration of these tools into routine assessment should not be seen as optional but as essential. Embedding such multidimensional strategies within musculoskeletal care pathways enhances the responsiveness of services to real-world needs and contributes to improved patient engagement, satisfaction and clinical outcomes.

Disconnect 2: Reactive versus preventive care

A second, equally pressing disconnect is the one between reactive and preventive care, which results in delayed interventions—particularly concerning for the elderly—as they miss the window for preserving function and independence.¹² Current models still prioritise short-term fixes, addressing musculoskeletal disorders only after patients present with significant pain, disability or injury. This reactive approach limits the scope of meaningful intervention, burdens healthcare systems with preventable complications and loss of function. Yet, musculoskeletal deterioration is not an inevitable consequence of ageing—it is modifiable. Preventive interventions have shown clear benefits in delaying or even reversing its progression. Multicomponent intervention programmes that include exercise, balance training, nutritional support, weight management, cognitive stimulation and social engagement have demonstrated the potential to build intrinsic capacity, preserve muscle strength, maintain joint mobility and sustain overall physical function, thereby slowing musculoskeletal decline.^{13,14} For such preventive models to succeed, they must be integrated into primary care and community health frameworks, tailored to local cultural and socioeconomic contexts, and made accessible to people across all stages of life. A life course approach to musculoskeletal health, starting in early adulthood and continuing into older age, can help build resilience, lower the risk of disabling conditions and support

healthy ageing.¹⁵ Moving the focus upstream from treatment to prevention is not only a clinical necessity but also an ethical responsibility, aligned with the values of equity, dignity and sustainable healthcare.

Disconnect 3: Research versus practice and policy

The third critical gap is the misalignment between research findings, real-world clinical practice and policy implementation. While the body of evidence on effective interventions for musculoskeletal disorders continues to grow, the translation of this knowledge into everyday healthcare settings remains slow and inconsistent.¹⁶ Academic research is often conducted in controlled environments with carefully selected populations, which limits generalisability. Meanwhile, clinical settings face constraints such as workforce shortages, time limitations and lack of resources, making it difficult to apply evidence-based practices consistently. On the other hand, group-based interventions, although offering advantages such as scalability, cost-effectiveness and peer support, remain underutilised due to factors such as perceived lower effectiveness and cultural preferences, which can be addressed through targeted education and awareness efforts.¹⁷ Policies that acknowledge these burdens of musculoskeletal disorders are a welcome start.¹⁸ However, many of these policies lack enforceable strategies, adequate funding or alignment with frontline practice realities. Bridging this gap requires investment in implementation science, clinical decision support systems, workforce capacity building and cross-sector collaboration. Real-world models such as care pathways designed to promote evidence-based and guideline-driven care, show how systematic approaches can drive systems-level change and inform practice.¹⁹ These models can be scaled and adapted to diverse health system contexts when supported by policies that incentivise integration, promote preventive care and prioritise patient-reported outcomes. Strategic collaboration across sectors such as healthcare, urban planning, social services and education can also help break down the silos that hinder coordinated care.

Towards a unified musculoskeletal care ecosystem

Addressing the global burden of musculoskeletal disorders among the elderly requires a radical reimagining of care models—one that brings together primary care, occupational health and safety, hospital services, rehabilitation, social support, community engagement and supportive cross-sector policies into a seamless, person-centred ecosystem. Emerging technologies such as artificial intelligence, predictive analytics and precision health can support this transformation by enabling early identification

of risk, personalised care planning and real-time monitoring of outcomes. However, technology alone is not the solution. The deeper transformation lies in redefining musculoskeletal healthcare as a core element of chronic disease management and ageing policy.²⁰ Musculoskeletal health should not be dealt with in isolation but integrated within the broader continuum of strategies addressing non-communicable diseases. This approach can reduce redundancies, streamline services and ensure timely interventions, ultimately improving patient autonomy and reducing the long-term societal costs of disability. To realise this vision, governments and institutions must align funding mechanisms, workforce development and policy frameworks around a shared commitment to prevention, integration and person-centred care. It is essential to bring together all stakeholders, including researchers, doctors, physiotherapists, occupational therapists, psychologists, social workers, administrators and policymakers, so they understand the disconnects and actively work together towards solutions. The time to bridge these systemic disconnects in musculoskeletal care continuum is now, not only for improved outcomes but to sustainably support the growing ageing population.

Ethics statement

Not applicable as no study participants are involved.

Declaration

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

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Transcatheter aortic valve in transcatheter aortic valve: Clinical characteristics and outcomes

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Dear Editor,

Transcatheter aortic valve implantation (TAVI) is an efficacious treatment for aortic stenosis (AS).^{1,2} With more TAVI performed in younger patients, concerns about durability/treatment once index prostheses degenerate have arisen.³ We examined data to evaluate clinical characteristics of patients with TAVI bioprosthetic valve dysfunction (BVD) and treatment with transcatheter aortic valve (TAV)-in-TAV at a tertiary cardiac centre.

TAVI patients at the National Heart Centre, Singapore, were included in a registry (CIRB 2014-2165). We retrospectively searched the registry from 2009–2024 to identify BVD requiring TAV-in-TAV. Clinical outcomes and severe BVD were assessed according to Valve Academic Research Consortium (VARC)-3 definitions.⁴ We limited this study to severe BVD from structural deterioration requiring TAV-in-TAV in aortic position.

During the study period, 692 TAVI were performed: 654 for native aortic valves and 38 in failed surgical aortic valves (TAV-in-SAV). Index prostheses included supra-annular self-expanding valves (SEV) (44%), balloon-expandable valves (BEV) (47%), intra-annular SEV (7%) and others (2%). Ten patients required TAV-in-TAV for BVD. Nine patients had index and repeat valvular interventions in our centre. One patient (case 6) had index procedure in another hospital and underwent TAV-in-TAV in our centre. Complete follow-up records were available for 96% of study patients. No patients had BVD and refused reintervention or were found unsuitable for TAV-in-TAV based on multi-detector computer tomography (MDCT).

Table 1 shows data on index TAVI and TAVI-in-TAVI procedures. Index TAVI was performed for native AS in 8 patients, native aortic regurgitation (AR) in 1 patient, and SAV replacement (SAVR) AR in another patient. Index TAVI valves were SEV (60%) and BEV (40%) and accounted for 1.7% of the total SEVs and 1.3% of the total BEVs in the registry, respectively. Index procedures

were successful. None had moderate or severe patient prosthesis mismatch (PPM): index effective orifice area (iEOA) of $\leq 0.85 \text{ cm}^2/\text{m}^2$ and $\leq 0.65 \text{ cm}^2/\text{m}^2$. Post-index TAVI AR was predominantly trivial.

Mean time from index procedure to reintervention was 70.0 months (SEV: 67.0 months; BEV: 74.5 months). Modes of BVD were regurgitation (50%) and restenosis (50%). Modes of SEV BVD were restenosis (16.7%) and regurgitation (88.3%). Mode of BEV BVD was restenosis (100%). Four had BVD within 5 years of index procedure.

MDCT was performed for all TAV-in-TAV patients. No hypo-attenuated leaflet thromboses were found. TAV-in-TAV prostheses were sized using index TAVI internal diameters. Risks of coronary occlusion were assessed. All patients were found to have either adequate valve-to-coronary distance (VTC) $>4 \text{ mm}$ or patent coronary artery bypass grafts (CABG) with low risk of coronary occlusion. Similarly, all patients had sufficient valve-to-sinotubular junction (VTSTJ) $>4 \text{ mm}$, patent CABG conduits, or coronary risk plane below the sinotubular junction.

All BEV BVD were treated with SEV. Of 6 patients with SEV BVD, 2 received SEV and 4 received BEV. All reinterventions were successful with resolution of regurgitation and restenosis (mean aortic gradient of 12.0 mmHg post-reintervention). One patient with BEV BVD treated with SEV had moderate PPM with iEOA of $0.70 \text{ cm}^2/\text{m}^2$. No patient had severe PPM. None had mortality, coronary occlusion, pacemaker implantation or stroke during TAV-in-TAV hospitalisation. Four patients died at 6, 28, 54 and 70 months after TAV-in-TAV from non-cardiac-related mortality.

Long-term durability of TAVI is uncertain. Low-risk TAVI trials showed non-inferior durability compared to SAVR of up to 5 years.^{1,2} However, long-term results are not available.

NOTION trial compared SEV versus SAVR treatment of low-risk AS patients. Ten-year results were reassuring with BVD lower after SEV versus

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Table 1. Clinical, imaging, procedural and outcome data of index TAVI and TAVI-in-TAVI procedures.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Index TAVI procedural data										
Aortic valve morphology	Tricuspid	Tricuspid	Tricuspid	Tricuspid	Tricuspid	Tricuspid	Tricuspid	Bioprosthetic valve	Tricuspid	Tricuspid
TAVI indication	AS	AS	AS	AS	AS	AS	AS	AR	AS	AR
Access	TF	TF	TF	TF	TF	TF	TF	TF	TF	TF
Anaesthesia	GA	GA	GA	GA	GA	Unknown	GA	GA	LA	LA
TAVI platform	Sapien XT	Sapien XT	Sapien	Corevalve Evolut R	Sapien	Corevalve Evolut R	Corevalve	Corevalve Evolut R	Corevalve Evolut Pro	Corevalve Evolut R
TAVI Size (mm)	23	26	23	29	23	34	26	23	26	34
Pre-dilation balloon size (mm)	20	20	20	20	20	Unknown	18	Nil	18	23
Post-dilation balloon size (mm)	Nil	Nil	Nil	Nil	Nil	Unknown	Nil	Nil	20	Nil
In-hospital complications	No	No	No	No	No	No	No	No	No	No
Post-index TAVI echocardiogram										
Aortic valve area (cm ²)	1.8	2.1	1.5	2.4	1.8	Unknown	1.9	2.3	2.2	2.2
Indexed EOA (cm ² /m ²)	1.1	1.2	1.0	1.5	1.1	Unknown	1.2	1.3	1.3	1.2
Aortic MPG (mmHg)	18	13	12	8	16	Unknown	14	4	7	13
AV peak velocity (cm/s)	298	240	260	200	240	Unknown	270	128	183	259
LVEF (%)	61	62	66	46	67	Unknown	69	45	60	59
Aortic regurgitation	Trivial	Mild	Trivial	Trivial	Trivial	Unknown	Trivial	Trivial	Trivial	Trivial
Patient clinical characteristics during TAV-in-TAV										
Age, years	88	61	81	104	78	84	81	86	78	73
Sex	Female	Female	Female	Male	Female	Male	Male	Male	Male	Male
Symptoms	Dyspnoea	Dyspnoea/ chest pain	Nil	Dyspnoea	Dyspnoea	Dyspnoea	Nil	Nil	Dyspnoea	Nil

Table 1. Clinical, imaging, procedural and outcome data of index TAVI and TAVI-in-TAVI procedures. (Cont'd)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
NYHA class	II	II	I	II	II	II	I	I	III	I
STS score	2.0	8.7	2.1	22.5	1.2	2.7	2.6	20.5	2.0	3.7
High risk features	Porcelain aorta	Patent LIMA	Porcelain aorta	NA	Porcelain aorta	Patent LIMA	Porcelain aorta	Patent LIMA	NA	Porcelain aorta
Smoking history	N	N	N	N	N	N	N	N	N	N
Hypertension	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Dyslipidaemia	Y	Y	N	N	Y	Y	Y	Y	Y	N
Diabetes mellitus	N	Y	N	N	Y	N	N	Y	N	N
Previous PCI	N	Y	N	Y	Y	Y	N	N	Y	Y
Previous CABG	N	Y	N	N	N	Y	N	Y	N	N
Previous SAVR	N	N	N	N	N	N	N	Y	N	N
Previous PPM	N	N	N	Y	N	N	N	N	N	Y
Dialysis	N	Y	N	N	N	N	N	N	N	Y
Time from index TAVI (months)	85	24	85	43	104	57	109	44	75	74
Pre-TAV-in-TAV echocardiogram										
Aortic valve area (cm ²)	0.9	0.7	0.7	1.4	0.6	2.1	0.9	1.8	2.5	1.7
AVA indexed (cm ² /m ²)	0.5	0.4	0.6	0.9	0.3	1.2	0.6	1.0	1.5	1.0
Aortic MPG(mmHg)	40	47	40	5	40	9	45	11	8	10
AV peak Velocity (cm/second)	410	460	416	157	410	230	406	214	193	214
LVEF (%)	70	62	62	64	60	60	61	60	62	43
Transvalvular AR	Mild	Mild	Trivial	Severe	Mild	Severe	Trivial	Severe	Severe	Severe
TAV-in-TAV indication	AS	AS	AS	AR	AS	AR	AS	AR	AR	AR

Table 1. Clinical, imaging, procedural and outcome data of index TAVI and TAVI-in-TAVI procedures. (Cont'd)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Pre-procedural MSCT										
Aortic annulus area (mm ²)	252	384	316	405	282	471	325	275	358	405
Aortic annulus perimeter (mm ²)	57.0	69.8	64.5	74.0	60.4	77.2	64.0	59.0	66.0	72.0
Average annular diameter (mm ²)	17.8	22.1	20.6	23.8	19	24.3	20.5	18.6	20.6	26.0
LM height (mm)	9.7	13.4	18.5	12.4	12.3	10.0	14.0	9.9	12.2	13.3
RCA height (mm)	11.6	17.1	16.5	13.2	13.4	12.0	15.0	14.0	17.9	18.1
Average SOV width (mm)	28.8	33.1	27.1	33.0	28.0	42.0	30.0	29.0	30.0	37.0
STJ diameter (mm)	26.0	28.0	26.0	35.0	20.3	35.9	27.0	32.0	25.0	30.4
VTC (mm)	6	NA s/p CABG	LM and RCA above XT	9	5	NA s/p CABG	RCA 4, LM 6	9	5	9
VTSTJ (mm)	Index TAVI below STJ	NA s/p CABG	Index TAVI below STJ	6	Index TAVI below STJ	NA s/p CABG	3	NA s/p CABG	3	6
Procedural characteristics										
Access	TF	TF	TF	TF	TF	TF	TF	TF	TF	TF
Anaesthesia	GA	GA	LA	GA	GA	LA	LA	LA	LA	LA
Transcatheter heart valve	Corevalve evolut R	Corevalve evolut Pro	Corevalve evolut R	Corevalve evolut R	Corevalve evolut R	Sapient 3	Sapient 3	Corevalve evolut FX	Sapient 3	Sapient 3
Valve size (mm)	23	26	23	29	23	29	23	23	23	23
Pre-dilation	N	N	N	N	N	N	N	N	N	N
Post-dilation	N	N	N	N	N	N	N	N	N	N
Cerebral embolic protection	N	N	N	N	N	Y	N	N	N	N
In-hospital complications	N	N	N	N	Y-Vascular	N	N	N	N	N

Table 1. Clinical, imaging, procedural and outcome data of index TAVI and TAVI-in-TAVI procedures. (Cont'd)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Post-TAV-in-TAV echocardiogram										
Aortic valve area (cm ²)	1.7	1.2	1.2	2.6	1.6	1.7	1.9	1.6	1.5	2.2
Indexed EOA (cm ² /m ²)	1.0	0.7	0.9	1.6	0.9	0.9	1.2	0.9	0.9	1.3
Aortic MPG (mmHg)	15	9	15	5	12	9	15	10	11	10
AV peak velocity (cm/s)	259	217	267	164	220	196	254	187	227	217
LVEF (%)	63	60	64	60	67	40	63	57	56	35
AR	Nil	Mild	Mild	Nil	Mild	Trivial	Trivial	No	No	Trivial
Follow-up data										
Duration of mortality from TAV-in-TAV (months)	70	54	NA	NA	28	NA	NA	6	NA	NA
Age at time of mortality (years)	94	66	NA	NA	81	NA	NA	86	NA	NA
Cause of mortality	Pneumonia	Limb gangrene	NA	NA	Intestinal bleed	NA	NA	Intracranial Bleed	NA	NA

AR: aortic regurgitation; AS: aortic stenosis; AV: aortic valve; CABG: coronary artery bypass surgery; EOA: effective orifice area; GA: general anaesthesia; LA: local anaesthesia; LCC: left coronary cusp; LIMA: left internal mammary artery; LM: left main; LVEF: left ventricular ejection fraction; MDCT: multi-detector computer tomography; MPG: mean pressure gradient; N: no; NA: not available; NYHA: New York Heart Association; NCC: non-coronary cusp; PCI: percutaneous coronary intervention; PPM: permanent pacemaker; RCA: right coronary artery; RCC: right coronary cusp; SAVR: surgical aortic valve replacement; SOV: sinus of Valsalva; s/p: status post; STJ: sinotubular junction; STS: Society of Thoracic Surgeons; TAV: transcatheter aortic valve implantation; TAVI: transcatheter aortic valve implantation; TF: transfemoral; VTC: valve-to-coronary; VTSTJ: valve-to-STJ; Y: yes.

SAVR. Nevertheless, no conclusion about long-term durability was made as only 36% of cohort was alive at 10 years.⁵

Our study found 10/692 patients (1.4%) required TAV-in-TAV for BVD. Four had early BVD within 5 years of index procedure. Causes of early BVD include young age at index TAVI procedure (case 2), post-dilatation of index TAVI (case 9), TAVI in degenerated surgical valve replacement (case 8) and end-stage renal failure (case 2 and case 10).

BVD was predominantly AR in SEV and exclusively restenosis for BEV. SEV has thinner porcine leaflets (0.28–0.35 mm) sutured in supra-annular position; BEV has thicker bovine leaflets (0.34–0.55 mm) in intra-annular position. In-vitro studies found lower leaflet stress for SEV compared to BEV.⁶ Differences in leaflet thickness and stress may explain susceptibility of SEV to tears and AR, while BVD in BEV was due to restenosis.

Treatment using TAVI for severe BVD includes TAVI explant or TAV-in-TAV. Higher 1-year mortality was found with explant compared to TAV-in-TAV (32.4% versus [vs] 15.4%; $P=0.001$).⁷ TAV-in-TAV will likely be the mainstay treatment for BVD.

MDCT is essential for TAV-in-TAV procedures to reduce periprocedural risks, optimise haemodynamics and maintain coronary access. Ease of coronary access is determined by index TAVI valve leaflets, which are pushed circumferentially by the new TAVI prosthesis to create a neoskirt covered stent. Particularly for tall-framed SEV with supra-annular leaflets, neoskirt will be high and hinder future coronary access. MDCT were reviewed to determine coronary occlusion risk by considering index TAVI (BEV vs SEV), index TAVI depth, coronary heights, sinus of Valsalva and sinotubular junction widths. MDCT allows projection of virtual valves to simulate TAV-in-TAV implantation and neoskirt heights at various implantation depths. Measurements of VTC and VTSTJ determine coronary obstruction risks and need for coronary wire protection or leaflet modification techniques, e.g. BASILICA/UNICORN.^{8,9} VTC/VTSTJ >4 mm suggests low-risk of coronary occlusion. When coronaries are located above neoskirt risk-plane, there is low risk of coronary occlusion whereas risk is high if coronaries are below risk-plane.

In our study, no patients had VTC < 4mm or had patent CABG grafts. None required coronary wire protection or leaflet modification.

SEV were implanted in all BEV BVD patients to optimise haemodynamics. Of the 6 SEV patients, 2 were treated with implantation of another SEV. One of these patients had patent CABG grafts, hence coronary access was not a consideration, and optimal

haemodynamic result was sought with SEV-in-SEV. Second patient was 104 years old with adequate VTC/VTSTJ. Decision was for SEV-in-SEV to optimise haemodynamics with little concern for coronary access because of patient's age.

Four patients with BVD of SEV were treated with BEV to maintain neoskirt risk-plane below coronary ostia. Upper edges of BEV were positioned in these patients below left-main to maintain coronary access, yet compromising optimal results by allowing leaflet overhang. Long-term outcome of this strategy is unknown.

No major complications occurred during TAV-in-TAV hospitalisation. There was good symptom relief. There were no patients with 30-day major adverse events, including death, myocardial infarction, stroke and major bleeding. Four patients died 6, 28, 54 and 70 months post-reintervention from non-cardiac mortality.

In conclusion, our retrospective study identified 10 TAVI patients (1.4%) with BVD occurring at a mean of 70 months post-index TAVI. TAV-in-TAV procedure was a safe/efficacious BVD treatment with careful pre-procedural planning.

Ethics statement

All patient consent were obtained for the study and approved by the SingHealth Centralised Institutional Review Board (2014-2165).

Declaration

Dr Ewe See Hooi has received speaker fees from Philips Healthcare and GE Healthcare. Dr Jonathan and Dr Kay Woon Ho are proctors for Medtronic and Edwards Lifesciences. The remaining 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: aortic stenosis, bioprosthetic valve dysfunction, cardiology, transcatheter valvular intervention, valvular heart disease

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Family outcomes of the novel ECHO framework implemented in Singapore's early intervention programme

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Dear Editor,

About 200 million children in the world live with disability. Good quality early intervention (EI) improves the trajectory for developing life capabilities towards better adult outcomes for these children.¹⁻² High quality EI is a priority among nations. In Singapore, developmental and behavioural disabilities increased by nearly 5 folds between 2004 and 2019.³⁻⁴ With increasing public expenditure on EI services, outcome-based reporting is paramount to improve public accountability, service and policy development.⁵ Hence, the national Enabling Masterplan for disability development in 2012 to 2016 recommended the development and implementation of a common child and family outcomes measurement system for EI.⁶ In Singapore, EI services are structured along a continuum of support needs, ranging from Learning Support and Development Support programmes for children with lower support needs, to inclusive preschools for those with moderate needs, and Early Intervention Programme for Infants and Children (EIPIC) for children requiring moderate-to-intensive support.³ The Early Childhood Holistic Outcome (ECHO) project piloted a common child and family outcomes measurement system and an EI service framework for EIPIC in 2014 to 2018. This article reports the outcomes of families enrolled in Project ECHO from January 2016 to December 2017. To our knowledge, this is the first study in Singapore that demonstrates the effectiveness of EIPIC in improving family outcomes.

Project ECHO adopts a cohort methodology to measure child and family outcomes prospectively. Family outcomes (FO) were measured at entry (pre-intervention) and at first review follow-up (post-intervention) as part of the EIPIC standard service delivery, outcome monitoring and programme evaluation processes. The SingHealth Centralised Institutional Review Board approved the project (2014/099/E). Consent for data usage was obtained from families who were enrolled into 4 Thye Hua Kwan (THK) EIPIC centres from January 2016 to December

2017. FO were measured using the Family Outcome Survey-Revised (FOS-R), a validated 5-point Likert scale (1 lowest, 5 highest), with psychometric validity previously established in the Singapore population.⁷ Parents completed the English or Chinese versions of FOS-R. For this study, the FO data of families whose children remained in the THK EIPIC for at least 3 months post-enrolment were extracted for analysis. Data analysis was performed using STATA 14.2 (StataCorp, College Station, TX, US), with clinical and demographic data summarised using standard descriptive statistics. We tested the normality of FO rating distribution using the Shapiro-Wilk test and compared the entry and follow-up FO ratings using the non-parametric Wilcoxon signed-rank test in view of the largely non-normal distribution and pre-post nature of FO ratings.

Among the entry cohort from January 2016 to December 2017 (n=563), survey response rate was 52.9% (n=298). At follow-up, 218 families remained in the study cohort and 141 responded to the survey (follow-up survey response rate was 64.7%). The entry clinical and demographic profiles of the children and families in the study cohort were comparable to the general EIPIC cohort in Singapore,⁵ with 60.1% Chinese, 78.2% male, mean EIPIC entry age of 47.2 months (range 12–84 months), and the majority having a primary diagnosis of autism spectrum disorder (56.0%) and global developmental delay (33.9%). Among the parents, 67.2% of fathers and 60.4% of mothers had post-secondary or higher educational qualifications, though the majority of families were of low-to-middle income (79.9%).

The mean duration of first review was 10.5 months (standard deviation [SD] 3.2, range 6–16 months). At entry, the mean domain FO ratings ranged 3.51–3.82 (Table 1). At follow-up, there were statistically significant improvements in the mean ratings of all 5 domains, ranging 3.78–4.00 ($P<0.05$).

The highest ratings at entry and follow-up were found in the FO1 domain (understanding your child's

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strength, needs and abilities). The greatest improvement was in the FO2 domain (knowing your rights and advocating for your child), despite it being charting the lowest mean entry score.

The lowest-rated items at entry and follow-up were: knowing the options available when the child leaves the programme (A8), ability to talk to other families with children with similar needs (A16) and the

Table 1. Family outcome ratings at entry and at follow-up.

Family outcomes		Entry (n=298)	Follow-up (n=141)	P value
		Mean rating	Mean rating	
Family outcome 1: Understanding your child's strengths, needs and abilities		3.82	4.00	0.0016 ^a
A1.	We know the next steps for our child's growth and learning.	3.51	3.81	0.0011 ^a
A2.	We understand our child's strengths and abilities.	3.78	3.98	0.0829
A3.	We understand our child's delays and/or needs.	3.95	4.05	0.3572
A4.	We are able to tell when our child is making progress.	4.01	4.16	0.0252 ^a
Family outcome 2: Knowing your rights and advocating for your child		3.51	3.79	0.0006 ^a
A5.	We are able to find and use the services and programs available to us.	3.47	3.72	0.0241 ^a
A6.	We know our rights related to our child's special needs.	3.47	3.78	0.0007 ^a
A7.	We know who to contact and what to do when we have questions or concerns.	3.57	4.11	<0.0001 ^a
A8.	We know what options are available when our child leaves the ditto.	3.12	3.43	0.0035 ^a
A9.	We are comfortable asking for services & supports that our child and family need.	3.91	3.92	1.0000
Family outcome 3: Helping your child develop and learn		3.54	3.81	0.0035 ^a
A10.	We are able to help our child get along with others.	3.50	3.77	0.0156 ^a
A11.	We are able to help our child learn new skills.	3.55	3.81	0.0153 ^a
A12.	We are able to help our child take care of his/her needs.	3.67	3.89	0.0689
A13.	We are able to work on our child's goals during everyday routines.	3.44	3.77	0.0041 ^a
Family outcome 4: Having support systems		3.61	3.78	0.0336 ^a
A14.	We are comfortable talking to family and friends about our child's needs.	3.68	3.81	0.4630
A15.	We have friends or family members who listen and care.	3.84	3.93	0.4809
A16.	We are able to talk with other families who have a children with similar needs.	3.37	3.69	0.0100 ^a
A17.	We have friends or family members we can rely on when we need help.	3.62	3.72	0.0591
A18.	I am able to take care of my own needs and do things I enjoy.	3.56	3.73	0.0348 ^a
Family outcome 5: Accessing the community		3.75	3.89	0.0041 ^a
A19.	Our child participates in social, recreational or religious activities that we want.	3.11	3.45	0.0003 ^a
A20.	We are able to do things we enjoy together as a family.	3.95	3.97	0.3222
A21.	Our medical and dental needs are met.	3.70	3.80	0.0459 ^a
A22.	Our child care needs are met.	3.80	3.96	0.1173
A23.	Our transportation needs are met.	3.88	4.03	0.0597
A24.	Our food, clothing and housing needs are met.	4.06	4.14	0.1128

^a P values are statistically significant.

child's participation in social, recreational or religious activities that the family wants (A19), despite some improvement observed at follow-up.

This is the first report providing concrete evidence on the effectiveness of Singapore's EIPIC programme in improving family outcomes. The measurable improvement in families' knowledge, awareness rights, advocacy skills and broader well-being in this study demonstrates the utility of FOS-R for service quality monitoring and benchmarking in EIPIC. However, gaps remained in helping families better understand post-EIPIC options, connecting with other caregivers and improving community inclusion. These are potential areas for EIPIC providers to improve on when supporting families in EI.

The high cohort attrition and low survey response rate in this study may subject our results to biases. However, our study cohort's entry FO ratings were comparable to a previous Singapore cross-sectional study using FOS-R,⁷ suggesting that our results are adequately comparable with the rest of the EIPIC population. It is interesting to note that this study's FO ratings were higher than those of a study in Japan,⁸ but lower than those reported in the US.⁹ The follow-up duration was short in this study, though it is encouraging that statistically significant improvements were still observable. Further studies with a bigger cohort size and longer follow-up duration will be helpful to ascertain if these improvements were sustained or further enhanced. Reasons for prematurely exiting EIPIC programme and the association between improvement in FO and child outcomes should also be further studied.

With the success of project ECHO, the ECHO Framework was nationally scaled up in 2019 to 2024 in Singapore.¹⁰ However, this phase only focused on implementation of the Global Child Outcomes measurement system. Our study results not only add to the body of literature demonstrating effectiveness of EI in improving family quality of life, but these findings may also support local and regional EI providers and policymakers to enhance outcome-based accountability by holistically monitoring family quality of life using FOS-R prospectively.

Ethics statement

SingHealth Centralised Institutional Review Board approved the project (2014/099/E).

Declaration

Lien Foundation funded the pilot ECHO project. The funders did not have any role in study design, data

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

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We would like to acknowledge the immense contribution of the late Prof Lim Sok Bee towards the success of Project ECHO and the eventual national adoption of the ECHO Framework within the EIPIC programme in Singapore. We also acknowledge Louise Clarke and Choy Mian Yee for their work in the conception, study design, data acquisition and result interpretation stages of the project. Finally, Louise Clarke and Dr Teoh Wei Qin also reviewed the manuscript and provided valuable inputs and suggestions.

Keywords: early intervention, family, outcome, paediatrics, quality of life

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STAT: Enhancing confidence in clinical data analysis

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Dear Editor,

Access to statistical and graphical tools is fundamental to all clinical research for data analysis.¹ However, subscription-based models and complex functionality of existing statistical software that require formal training are barriers to access, specifically for junior clinicians and healthcare professionals, including early-career researchers and healthcare professionals from low- to middle-income countries.¹⁻⁴ Although Microsoft Excel is used, it can be prone to errors due to autoformatting and difficulty in performing analysis on large datasets.^{5,6} While open-source statistical programmes like Jamovi and BlueSky Statistics have become available, they do not provide data visualisation, creating a gap in this area for healthcare professionals.^{1,7}

We aimed to develop a user-friendly, publicly available web-based data analysis tool with statistical and data visualisation functions called STAT, which can enhance the confidence of healthcare professionals in clinical data analysis.

The STAT webtool was created using the Streamlit (<https://www.streamlit.io>) platform. An interactive and user-friendly version of the tool is publicly available at <https://statapp.streamlit.app/>. STAT was coded using Python 3.7, utilising the latest version of statistical packages SciPy, Researchpy, scikit-learn and scikit_posthocs, and data visualisation packages Chart Studio, Matplotlib, seaborn and SigFig. The concept of STAT spurred from the fact that healthcare professionals engaged in clinical research frequently need to undertake certain statistical analyses and data visualisation. Yet, the existing resources do not sufficiently support this need. Accordingly, we selected (1) statistical tools based on descriptive statistical measures and measures of association most commonly used to analyse healthcare data, and (2) common data visualisation tools that were not provided in the current freely available statistical software (Supplementary Appendix S1).^{7,8} STAT is also

optimised for structured, tabular datasets, relying on the most familiar, standard format (Supplementary Appendix S1). The codes, files and instructions on running STAT have been uploaded to a GitHub repository (<https://github.com/kuanrongchan/STAT>).

To assess the user experience and their confidence in clinical data analysis using STAT, the participants were recruited as below. The webtool was made freely available at <https://statapp.streamlit.app/> and publicised in the medical and research community of National University Health System (NUHS) via email and social media, inviting them to attend the workshop to learn the STAT tool (Fig. 1A); the target audience included doctors, allied health professionals such as nurses and research staff. NUHS is a tertiary healthcare institution closely affiliated with the National University of Singapore (NUS). The training session was recorded and is made freely available on YouTube (<https://youtu.be/k2GU7M3xxKE>). The study was approved by the NUS Institutional Review Board (NUS-IRB-2023-554). Detailed methodology is provided in Supplementary Appendix S1.

A total of 95 participants, aged 22–63 years, participated and filled in both pre- and post-learning questionnaires. Only 10% of participants had non-clinical qualifications, and the majority of participants did not have experience using data analysis software other than Microsoft Excel (Supplementary Table S1).

After the practice data analysis, the majority (71.6%, $n=68$) found the STAT webtool was easy to use (Fig. 1B) and they would recommend it to others for clinical data analysis (98.9%, $n=94$) (Fig. 1C). Comparing pre- and post-workshop user confidence levels for clinical data analysis, the STAT webtool workshop significantly improved user confidence ($P<0.0001$) (Fig. 1D).

The authors also intended to understand whether prior knowledge of data analysis programmes or profession affected the outcomes. Hence, a comparison of participants with and without prior knowledge

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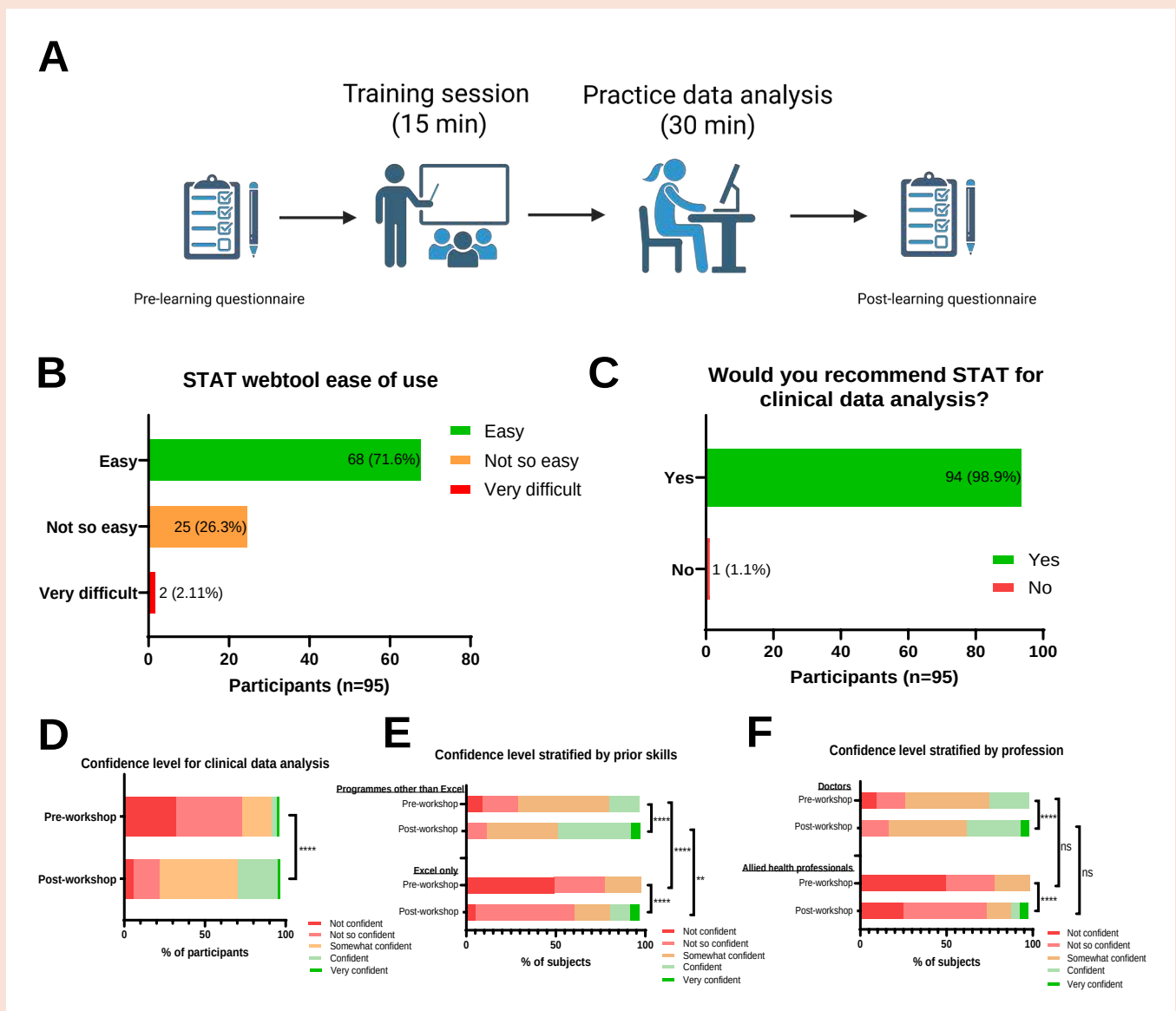
of data analysis programmes other than Microsoft Excel ($n=52$ and $n=34$, respectively) was performed. Also compared were the experience of doctors ($n=35$) versus allied health professionals ($n=51$).

As expected, those with knowledge of programmes other than Excel had greater confidence before being introduced to STAT. However, participants had a significant improvement in confidence regardless of whether they had knowledge of programmes other than Excel (Fig. 1E). Profession had no bearing on

pre- and post-training confidence in clinical data analysis; doctors and allied health professionals both had a significant improvement in confidence (Fig. 1F).

Most of the participants evaluated in our study indicated that the tool was easy to use, with improved confidence in data analysis using STAT. The 10-minute accompanying YouTube tutorial that mimics the training session in our study, has capability to facilitate learning for prospective users at their own pace, without the need for formal training. Compared to

Fig. 1. Workflow of the STAT webtool workshop and participants' post-workshop feedback.



(A) STAT Webtool workshop activity flow. Created in <https://BioRender.com>. (B) Participants' feedback recorded post-workshop for STAT's ease of use. (C) Participants' feedback recorded post-workshop on whether they would recommend STAT for clinical data analysis. (D) Confidence level of participants ($n=97$) performing clinical data analysis increased after the workshop ($P<0.0001$), compared to before the workshop. (E) Confidence levels for clinical data analysis before and after the workshop, stratified by prior skills (those who used programmes other than Microsoft Excel and those who only used Microsoft Excel). (F) Confidence levels for clinical data analysis before and after the workshop, stratified by profession (doctors and allied health professionals).

other open-source solutions—such as Jeffreys's Amazing Statistics Program, BlueSky Statistics software and Statistics Open for All—our webtool is maintained online and does not require local installation to deploy. This is one of the key advantages since it means it can be whitelisted for use on hospital computers. Healthcare institutions usually have strict data security policies to ensure that patient data do not leave internal servers. Such requirements typically preclude the possibility of programme installation by users that are not pre-approved by the in-house IT team.⁷ Alternatively, there is also flexibility of local installation that allows it to be run without internet access. Finally, it is capable of handling large datasets, as it is executed through the Python programming language.

In the knowledge-to-action cycle of continual improvement in healthcare, knowledge is first created through robust research conducted on clinical datasets; this could be in the form of observational studies such as cohort studies, or interventional studies such as randomised controlled trials.⁹ Thereafter, evidence is implemented and then outcomes evaluated; this is often done in the form of implementation studies and clinical audits. Robust analysis and clear visualisation of clinical data underlie all the steps in this cycle. Unlike R, IBM SPSS or STATA, which require advanced expertise in data analysis or subscription, STAT improves access to data analytics for busy healthcare professionals. In fact, being agnostic to actual context of the input dataset, STAT has broad applicability across different industries where simple and efficient data analysis needs to be performed by non-analysts.

The age distribution of our study participants, between 26.3 and 36.4 years, may limit the extrapolation of findings to researchers outside of this range. However, this limitation may not affect our overarching goal of improving confidence in data analysis for early-career healthcare professionals.

In conclusion, the STAT tool developed in the study has potential to empower healthcare professionals to perform clinical data analysis, visualisation and statistical comparisons.

Supplementary materials

Appendix S1. Methods.

Appendix S2. User feedback questionnaire.

Table S1. STAT study participant (n=95) demographics, profession, non-clinical qualifications and prior experiences with statistical applications.

Table S2. Complete the following descriptive table.

Table S3. Test for correlations between age, baseline SBP and post-treatment SBP, stratified by smoking status.

Table S4. Discover univariate predictors for clinically significant decrease in SBP (i.e. more than 5 mmHg).

Table S5. Dataset used for the hands-on activity. Information about 250 participants, their blood pressure before and after treatment, and subject demographics.

Fig. S1. STATApp flowchart of analysis that could be done after data have been imported.

Ethics statement

This study was approved by the NUS Institutional Review Board (NUS-IRB-2023-554) on 18 August 2023 and conducted in accordance with the Declaration of Helsinki.

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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Keywords: biostatistics, data analysis, healthcare professionals, statistics, webtool

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"Machine learning to risk stratify chest pain patients with non-diagnostic electrocardiogram in an Asian emergency department": Correspondence

Erkan Boğa¹ MD

Dear Editor,

I read with great interest the recent article by Lin et al. on machine learning-based risk stratification of chest pain patients with non-diagnostic electrocardiograms in an Asian emergency department (ED).¹ The implementation of the myocardial-ischaemic-injury-index (MI³) algorithm offers significant potential to improve early triage and disposition decisions in busy ED environments.

The reported sensitivity (98.9%) and negative predictive value (99.8%) of MI³ for excluding type 1 myocardial infarction (MI) at 30 days are highly promising, particularly in resource-limited and overcrowded emergency settings.² When compared to conventional strategies such as the 99th percentile troponin cut-off or the European Society of Cardiology 0/2-hour algorithm, MI³ either matched or outperformed these benchmarks, highlighting its potential to reduce unnecessary admissions and improve patient flow.

However, several aspects merit further reflection. The model's performance with only baseline troponin data showed excellent accuracy but was limited in its ability to identify low-risk patients, classifying only 8.5% as such. In real-world practice, reliance on single troponin measurements is often unavoidable due to delayed presentations and ED congestion.^{2,3} Enhancing the model's discriminatory capacity in this context would increase its clinical applicability.

A noteworthy limitation is the algorithm's dependency on the Abbott ARCHITECT STAT high-sensitivity troponin I assay. Many institutions, including mine, use alternative platforms such as high-sensitivity troponin T. Cross-platform validation of MI³ or development of platform-agnostic models, is essential before widespread adoption can occur.⁴ The inconsistency in performance metrics across different assays underscores this need.

Clinician trust and interpretability remain central issues. Although MI³ requires only age, sex and troponin levels—making it more objective than tools like HEART—it remains a "black-box" system for many users.⁵ Improving model transparency and integrating

explainable artificial intelligence (AI) methods could enhance clinician acceptance, especially in non-academic and high-turnover environments.⁶

Lin et al. raise an important point about the financial burden of unnecessary admissions. The potential for cost savings by identifying low-risk patients early is significant. Nevertheless, this remains speculative without formal cost-effectiveness analysis.¹ Future research should explore the economic implications of MI³ implementation using real-world data from diverse healthcare systems.⁷

Additionally, the generalisability of MI³ to multi-ethnic populations needs further investigation. Although the authors note the underrepresentation of Asian populations in prior studies, subgroup analyses by ethnicity could reveal performance discrepancies. This is especially relevant in regions like Singapore with diverse demographics.⁸ Such analyses may inform whether model recalibration is needed for specific subpopulations.

I concur with the authors that AI tools should not replace clinical judgement. However, structured training and integration with clinical decision support systems could standardise use and mitigate the risk of overreliance or inappropriate application.⁹ Electronic medical record-based integration would also facilitate seamless adoption and adherence to protocolised care.

In summary, Lin et al. contribute valuable evidence supporting machine learning integration in acute cardiovascular care. To realise the full potential of tools like MI³, efforts should focus on improving single-sample performance, expanding cross-platform compatibility, enhancing interpretability and generating local economic data. I look forward to future implementation studies that address these real-world challenges.

Ethics statement

Not applicable. This manuscript is a commentary on a previously published study and does not involve original research on human subjects; therefore, Institutional Review Board approval was not required.

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Keywords: cardiology, chest pain, emergency medicine, machine learning, risk stratification

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