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Epidemiology of paediatric intensive care unit admissions, deaths and organ donation candidacy: A single-centre audit

A clinical audit of 1766 paediatric intensive care unit admissions discusses the large gap between eligible and actual organ donation by non-survivors. (See full article, p.17)

Illustration by Maria De-Castro

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EDITORIAL

Organ donation in the paediatric intensive care unit: Time for change?

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Organ transplantation remains the definitive treatment option for improving the lives of patients with end-stage organ failure. To our knowledge, the first solid organ transplantation performed in Singapore in July 1970 involved a kidney from a deceased donor.[1] Since then, rapid advancements in both transplant surgery and immunosuppressive medical therapy have enabled solid organ transplantation to better meet the increasing demands of a growing Singapore population with end-organ diseases. Yet, the supply of donor organs lags behind the demand.[2]

Singapore has a low deceased organ donation rate of 4.67 persons per million population in 2023, compared to the global average rate of 6.84.[3] Addressing the availability of donor organs becomes the crux in sustaining a successful national organ transplantation programme. Paediatric deceased donors represent a small percentage of donors, with lower donation rates than adults and further decreasing with time.[4] This is mostly due to improved paediatric safety efforts and reduced mortality.[5,6] Regardless, donor paediatric organs remain an extremely valuable resource for both adults and children.

A possible explanation for the dismal rate of deceased organ donation is the low referral rate of potential donors by intensive care units,[1,5] coupled with a disappointing conversion rate. A survey done in 2007 revealed that 69.8% of 86 referred donors did not donate because of cardiac arrest prior to the declaration of brain death, early withdrawal of life support, inability to meet brain death certification, and a lack of consent for organ donation[1] as paediatric deceased organ donation requires parental consent under the Medical (Therapy, Education and Research) Act passed by the Singapore Parliament in 1972. Even the first Singapore paediatric donation after circulatory death occurred only in 2020.[7]

In this issue of *Annals*, Low et al.[8] present a single-centre audit study of 1766 children admitted to a paediatric intensive care unit (PICU) in Singapore with a low mortality rate of 5.6% and standardised mortality ratio of 2.1. The advancements made in paediatric healthcare limits the availability of paediatric organ donors. Among the study population, 7.8% had a prolonged PICU stay of more than 2 weeks. These patients were more likely to be sicker at admission based on Pediatric Index of Mortality 3 (PIM 3) scoring, have an underlying chronic condition, be technologically dependent and have a poorer baseline functional state based on functional status scale (FSS) at admission. Comparing survivors and non-survivors, multivariate analysis revealed that the presence of comorbidities, higher PIM 3 scoring and lower functional status scale at admission were all independent and statistically significant factors associated with PICU mortality. Among the non-survivors, 76.8% were deemed ineligible for organ donation when investigators reviewed perimortem medical records (up to 72 hours before terminal event). Of the remaining 23.2% who were independently deemed to be potential organ donors, more than half were not referred for assessment as potential organ donors.

Paediatric organ donation is almost always preceded by tragedy. The death of a child goes against nature, leaving caregivers in a whirlwind of emotions. Healthcare professionals in the PICU are not spared from the harsh reality as they confront the death of a child in their care—something we know is not commonplace, based on the mortality rates of PICUs in developed countries. These emotional factors, combined with unfamiliarity in leading conversations regarding organ donation amid a multicultural and multi-ethnical backdrop of Singapore's population landscape, and the lack of a well-practised workflow[7] with the provision of a sufficiently trained organ donation coordinating

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team, this could create a general impression that paediatric organ donation is fraught with barriers and should only be considered in rare circumstances. Missed donation opportunities were primarily due to a lack of identification of potential donors and timely referral with some contributory factors, including perceived medical unsuitability and unclear disease processes leading to death.[5] Therefore, as suggested by Low et al.,[8] an independent team in charge of screening for organ donation eligibility in patients who are critically ill and have 1 or more risk factors that are associated with a higher probability of mortality (PIM 3 score, FSS, or presence of comorbidities), could be an effective method to optimise identification of potential donors. The subsequent approach for discussion of donation with the family must be thoughtfully planned and executed sensibly. Data suggest that practitioners with specialised training for the approach and consent discussions with families are associated with higher consent rates.[9,10] Other suggested ideas to improve deceased organ donation rates include having specialised teams approach families for consent for every patient whose end of life is being considered. Patients identified as possible organ donors should be referred early and routinely to the donor transplant coordinator, regardless of the perceived aetiology of the cause of death or past medical history.[9]

Organ donation is an intensely personal decision, particularly following the loss of a child. Families should never feel pressured to make such a decision, as it offers no immediate benefit to the donor. Organ donation can provide a meaningful legacy, but it is essential that families are afforded the support and information necessary to make an informed choice.

Further work needs to be done in Singapore as we move toward establishing local policy and increasing awareness and acceptance towards pediatric organ donations.

Disclosure

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

Keywords: *consent, organ donation, paediatric intensive care unit, paediatrics, PICU*

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EDITORIAL

Interventional radiology placement of totally implantable venous access devices in oncology practice

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In November 1929, Werner Forssmann, a German surgical resident, attempted the first documented central venous catheter with a 35 cm-long catheter via his left antecubital vein.[1] Although revolutionary for his time, this innovation encountered significant opposition, and he was expelled from his training programme for this unauthorised experimentation. Despite the initial censure, his idea garnered interest across the Atlantic in the US, where Andre Counard and Dickinson Richards, in the 1940s, refined his technique and used it for cardiovascular research. In 1956, Forsmann, Counard and Richards were awarded the Nobel Prize in Physiology for their work on central venous access.[2] Since then, a wide variety of central venous access options have emerged. However, totally implanted venous access device (TIVAD) is unique in that it has no exposed catheter parts. This reduces the risk of catheter-related infection, increases the longevity of the access and makes it low maintenance.[3] Infuse-A-Port was the first described TIVAD, reported by Niederhuber et al.[2] in 1982. Since then, they have been colloquially called "ports", among other names such as port-a-cath and chemoport. Among the scientifically appropriate descriptors, TIVAD, subcutaneous venous access device (SVAD) and totally implanted venous access port (TIVAP) are frequently used in medical literature. These devices have a reservoir or chamber implanted subcutaneously. A catheter connected to this reservoir is pulled through a subcutaneous tunnel and inserted into a large vein, with its tip usually placed in a central vein. The reservoir has a self-sealing silicone diaphragm that is punctured percutaneously with a non-coring needle to gain venous access. Traditionally, TIVADs were inserted by surgeons in operating theatres; however, with the transition to imaging-guided insertion, these devices are now implanted by interventional radiologists in most high-volume centres. Interventional radiology (IR) guided placement of TIVADs has been reported to be cheaper, faster and safer with higher placement success and more accurate positioning.[4]

With advances in healthcare, the incidence of treatable oncological conditions is increasing, along with the corresponding requirement for safe, reliable, long-term vascular access options. TIVADs have revolutionised modern oncologic care, providing a reliable and minimally invasive means for long-term venous access. Being entirely subcutaneous, they are aesthetically appealing and minimally interfere with the patient's quality of life (e.g. they can swim or shower normally, unlike patients with externally hanging catheter parts). A recent *Lancet* report of a randomised controlled trial by Moss et al.—comparing Hickman-type tunnelled catheters, peripherally inserted central catheters, and TIVADs for systemic anticancer treatment—found the ports to be more effective and safer than the others.[5] Most published studies on larger cohorts of patients with TIVADs are from Western centres with limited Asiacentric data in medical literature. In this issue of the *Annals*, the paper by Tashi et al.[6] has special relevance. This retrospective study from Singapore, with a large sample size of 1180 oncological patients, offers a robust dataset to analyse the safety, efficacy and complications associated with the IR placement of TIVADs. The authors report a 100% technical success rate, with most TIVADs placed in the right internal jugular vein. The mean dwell duration was 342 days, with 2.1% removed due to infection, 0.6% due to malfunction, 0.6% due to port extrusion and 0.1% at the patient's request. The procedural safety is reinforced by the low rates of major complications, such as device extrusion (0.6%), venous thrombosis (0.25%), port inversion (0.1%) and catheter-related bloodstream infections (0.25%), which are comparable to international benchmarks.

Traditionally, the reservoir of the TIVADs is sutured to the underlying pectoral fascia through the dedicated slots for anchoring sutures provided by the manufacturer. These sutures are meant to reduce the likelihood of port inversion or migration.

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Tashi et al.[6] reported a trend of decreasing usage (from 63.3% in 2019 to 27.8% in 2021) of these anchoring sutures in their practice. Their rationale for skipping this step is the unproven benefit of such sutures and the perceived reduction in procedure time. Interestingly, the single instance of flipping of the port reported in this study happened in a patient without such anchoring sutures. In a series of 534 ports placed without anchoring sutures, McNulty et al.[7] argued against the need for anchoring sutures, claiming their port flipping rate of 0.2% is comparable with other published series where the ports were anchored. However, they did not have any internal comparison in their series nor insights into specific patient characteristics or technical details from other series where ports flipped despite having anchoring sutures. Intuitively, port rotation can occur despite anchoring sutures when using absorbable sutures, loose stitching or fixation to the subcutaneous tissue instead of the pectoral fascia. Given the low probability of a properly placed port within a snug subcutaneous pocket flipping, the sample size may have to be extremely large to prove or disprove a statistically significant difference between the techniques. While one could argue on this subject ad nauseam, in our practice, we do not hesitate to spend a few additional minutes placing anchoring sutures, as they could prevent an avoidable complication.

In TIVAD implantation, the emphasis is on meticulous periprocedural asepsis, and antibiotic prophylaxis is not usually recommended.[8] In a randomised, double-blind, placebo-controlled trial of 404 patients with well-matched preoperative variables and comorbidities, there was no significant difference in surgical site infection rates. A meta-analysis of 2154 patients, specifically enquiring about the role of antibiotic prophylaxis with TIVAD insertion, did not find any significant effect on infection rates. It concluded by reminding the medical community of the hazards of unnecessary antibiotic administration, including a higher risk of allergic reactions, the development of multidrug-resistant organisms, and additional costs to the healthcare system.[10] Although Tashi et al. reported the routine use of prophylactic antibiotics in their institution, they discussed the debatable nature of this practice.

Overall, this real-world data successfully demonstrate that the radiological placement of TIVADs is a safe, effective and reliable modality for long-term venous access in oncology patients. Sharing such positive and educational experiences can potentially benefit oncology patients in Asia at large by promoting the wider adoption of TIVADs in this region. The detailed technical and contextual nuances provided in this paper could also serve as a benchmark for future reference and research.

Declaration

A/Prof (Dr) Anil has undertaken proctoring assignments as well as organised workshops for Becton Dickinson, which manufactures TIVADs. Financial renumeration towards these activities was paid to the employer.

Dr Shao Jin Ong has organised workshops for Becton Dickinson which manufactures TIVADs. Financial renumeration towards these activities was paid to the employer.

Keywords: *central venous access, interventional radiology, oncology, portacath, TIVADs*

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ORIGINAL ARTICLE

Long-term survival and clinical implications of allogeneic stem cell transplantation in relapse/refractory lymphoma: A 20-year Singapore experience

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ABSTRACT

Introduction: Allogeneic haematopoietic stem cell transplantation (allo-HSCT) is a curative option for relapse/refractory (R/R) lymphomas that have failed autologous transplantation or for high-risk lymphomas in the upfront setting. We conducted a retrospective analysis on consecutive lymphoma patients who underwent allo-HSCT over a 20-year period (2003–2022) at Singapore General Hospital and National University Hospital Singapore.

Method: A total of 121 patients were included in the study. Median age was 41 years. Diagnoses include Hodgkin lymphoma (HL, 15%), B-cell non-Hodgkin lymphoma (B-NHL, 34%), T-cell non-Hodgkin lymphoma (T-NHL, 31%) and natural killer T-cell lymphoma (NKTL, 20%). Moreover, 27% of patients had prior auto-haematopoietic stem cell transplantation (auto-HSCT), and 84% received reduced intensity conditioning (RIC). Donor types were matched sibling donor (45%), matched unrelated donor (29%), haploidentical donor (19%) and cord blood (CB, 7%).

Results: After median follow-up of 56 months, estimated 4-year progression-free survival (PFS) and overall survival (OS) for all patients were 38% and 45%, respectively. Non-relapse mortality (NRM) was 15% at day 100 and 24% at 1 year. On univariate analysis, complete remission status at transplant and RIC confers superior OS. On multivariate analysis, HL was associated with superior OS compared to NHL, whereas matched unrelated donor transplant was associated with significantly inferior OS compared to matched sibling donor.

Conclusion: Long-term curative durability was observed with allo-HSCT for patients with relapsed/refractory lymphomas. This real-world data serves as a valuable historical benchmark for future studies on lymphomas in Singapore and the Asia Pacific region.

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Keywords: allogeneic, haematology, lymphoma, refractory, transplant

CLINICAL IMPACT

What is New

- This nationwide retrospective study evaluated a 20-year dataset of patients with R/R lymphoma undergoing allogeneic transplantation.
- To authors' knowledge, this collaborative study that involves 2 national cancer centres in Singapore is the first to evaluate the efficacy and safety of allogeneic haematopoietic stem cell transplantation for R/R lymphomas in Singapore.
- It also serves as a potential benchmark for policymakers for cost and efficacy comparison analysis with more novel treatment options.
- Disease status at transplant, conditioning regimen, subtype of lymphoma and donor selection influence outcomes.

Clinical Implication

- This real-world data form a basis for future studies on R/R lymphomas in Singapore and the region.

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INTRODUCTION

Over the past few decades, a wide array of novel therapies has become available for the treatment of relapsed/refractory (R/R) lymphoma. Despite these advancements, outcomes and the durability of disease control remain poor for many patients. While autologous hematopoietic stem cell transplantation (auto-HSCT) may be appropriate for some lymphoma patients as consolidation therapy, a significant proportion of high-risk patients experience relapse after auto-HSCT. Anti-Cluster of Differentiation 19 (CD19) chimeric antigen receptor T-cell (CAR-T) therapy and bispecific T-cell engager (BiTE) therapy have revolutionised the treatment landscape for B-cell non-Hodgkin lymphoma (B-NHL). However, their utilisation is limited by factors such as resource availability, accessibility and high costs. There also remains a high relapse rate post-CAR-T, and allogeneic stem cell transplantation (allo-HSCT) remains a potential treatment option in this context. Additionally, CAR-T cell therapy and bispecific antibodies are not yet available for Hodgkin lymphoma (HL), T-cell NHL (T-NHL), and some of the less common but aggressive B-NHL subtypes.

Mamez[1], Corradini[2] and Schmitz et al.[3] (for T-cell lymphoma), Sureda[4] (for HL) and Bento[5] (for DLBCL) have explored the potential of allo-HSCT in patients who had high-risk, R/R or progressive disease after auto-HSCT. The preparative conditioning regimen, along with the potential for graft-versus-lymphoma effect, offers the possibility of disease-free survival and significant overall survival (OS) in this population. Furthermore, the use of non-myeloablative/reduced intensity conditioning (RIC) and haploidentical donors in stem cell transplantation has sparked renewed interest in allo-HSCT, as fitness and donor availability become less of a barrier. This makes it feasible for patients with high-risk lymphoma to access safer stem cell transplantation. Moreover, the graft-versus-lymphoma effect is potentially applicable to all subtypes of lymphomas. Studies have shown favourable outcomes with allo-HSCT in patients with advanced HL,[6] and there is increasing application of allo-HSCT in non-HL patients.[7]

Historically, Singapore performed its first adult allo-HSCT in 1985. Forty years later, we evaluate real-world efficacy and safety of allo-HSCT in patients with R/R lymphoma. Our primary objective was OS post-allo-HSCT. Secondary objectives included progression-free survival (PFS), non-relapse mortality (NRM) and rate of acute graft-versus-host disease (GVHD).

METHOD

This retrospective analysis included all patients who underwent allo-HSCT for lymphoma over a 20-year period (2003–2022) at 2 of the largest national transplant centres in Singapore. They were identified from medical databases after approval from the institution review board. All patients provided written informed consent for transplantation according to each local institution. The lymphoma diagnoses were based on World Health Organization 2002, 2008 and 2016 classification histologic subtype, depending on when the diagnosis was made. Staging and assessment of disease response were based on CT and PET CT referring to Cheson (2007) and Lugano (2014) criteria.[8,9] Transplants were based on physician discretion, following international bone marrow stem cell transplant society guidelines. Patient demographics, OS, PFS, NRM and factors associated with survival were examined. PFS was defined as time from date of allo-HSCT till date of disease progression or death from any cause. OS was defined as the duration of survival from the date of allo-HSCT until death. NRM is defined by the absence of progressive disease at the time of death.

Statistical methods

Using GraphPad Prism version 10.0 software (GraphPad Inc, La Jolla, US), chi-squared and Fisher's Exact two-sided tests were used to compare categorical variables, and t-test was used for continuous variables. Two-sided *P* values of <0.05 were statistically significant. The survival probabilities, PFS and OS, were calculated using the Kaplan-Meier estimator. Log-rank analysis was used to compare the different groups. Cox regression analysis was used for multivariate variable analysis.

RESULTS

Baseline demographics

A total of 121 patients were included in the study with median age of 41 years. Of these, 76 (63%) were male. Lymphoma subtypes included B-NHL (n=41, 34%), followed by T-NHL (n=38, 31%), natural killer T-cell lymphoma (NKTL) (n=24, 20%) and HL (n=18, 15%) (Table 1). Moreover, 27% of the patients had prior auto-HSCT; 60%, 22% and 16% were in complete remission (CR), partial remission (PR) or stable disease/progressive disease (SD/PD) at transplant.

Conditioning regimen

Myeloablative conditioning (MAC) was used in 14% of the patients, while the rest received RIC regimens. GVHD prophylaxis consisted of calcineurin inhibitor with 1 of the 2 from methotrexate or mycophenolate. Anti-thymocyte globulin (ATG) was administered to all patients

Table 1. Patients' characteristics.

Characteristics	Details	n (%) Total 121 (100%)
Sex	Male	76 (63)
	Female	45 (37)
Median age at transplant		41 years
Diagnosis/histological subtype	DLBCL/PMBCL	26 (21)
	PTCL	32 (26)
	NKTL	24 (20)
	Other T-NHL	6 (5)
	Other B-NHL	8 (7)
	HL	18 (15)
	CLL (Richter transformation)	7 (6)
Donor type	MSD	54 (45)
	MUD	35 (29)
	Haploidentical	23 (19)
	CB	9 (7)
Conditioning	MAC	17 (14)
	RIC	104 (86)
	Missing data	2 (2)
Previous auto-HSCT		33 (27)
Disease status at transplant	CR	73 (60)
	PR	26 (22)
	SD/PD	19 (16)
	Missing data	3 (2)
Period of transplant	Before 2010	29 (24)
	2010–2015	39 (32)
	After 2015	53 (44)

Auto-HSCT: autologous hematopoietic stem cell transplantation; B-NHL: B-cell non-Hodgkin lymphoma; CB: cord blood; CLL: chronic lymphocytic leukaemia; CR: complete remission; DLBCL: diffuse large B-cell lymphoma; HL: Hodgkin lymphoma; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; NKTL: natural killer T-cell lymphoma; PMBCL: primary mediastinal B-cell lymphoma; PR: partial remission; PTCL: peripheral T-cell lymphoma; RIC: RIC: reduced intensity conditioning; SD/PD: stable disease/progressive disease; T-NHL: T-cell non-Hodgkin lymphoma:

receiving matched unrelated grafts. Post-transplant cyclophosphamide (PTCy) or ex-vivo stem cell manipulation (alpha-beta T-cell depletion) was used in haploidentical donor transplant based on physician discretion.

Donor demographics

Matched sibling donors (MSD; n=54, 45%) were the majority followed by matched unrelated donors (MUD; n=35, 29%) in which 6 of them had 1 allele mismatched. The rest were from haploidentical (n=23, 19%) and CB (n=9, 7%) (Table 1).

Post-transplant outcome

With a median follow-up duration of 56 months, the estimated 4-year PFS and OS were 38% and 45%, respectively (Figs. 1A and 1B). Sixty-eight patients died post-transplant with the most

common cause due to lymphoma in 32 patients. NRM at 100 days and 1 year were 15% and 24%, respectively. Among all NRM, pneumonia (n=16, 44%) was the most common, followed by other infections (n=11, 31%), cerebral haemorrhage (n=4, 11%), GVHD (n=3, 8%), myocarditis (n=1, 3%) and thrombotic microangiopathy (n=1, 3%). The cumulative incidence of acute GVHD was 36% with 5 patients (4%) having grade IV GVHD.

Patients who were in CR at transplant exhibited 4-year PFS and OS of 45% and 55%, respectively, compared to PR and SD/PD; 4-year PFS 27% and 21%, 4-year OS 29% and 27%, respectively (Figs. 1E and 1F).

RIC confers significant superior PFS and OS compared to MAC with 4-year PFS and OS of 44% and 51%; 0% and 10%, respectively (Table 2) (Figs. 1G and 1H).

Regarding donor type, transplants with MSD resulted in 4-year PFS and OS 41% and 49%, respectively, while MUD transplant had 4-year PFS and OS of 29% and 44%, respectively. For haploidentical and CB donor transplants, the 4-year PFS and OS rates were 52% and 56%; 38% and 45%, respectively (Table 2; Figs. 1I and 1J).

Post-transplant outcome for HL subtype appeared the best with 4-year PFS and OS of 61% and 62%, respectively, while patients transplanted for NK-T cell lymphoma had lowest 4-year PFS and OS of 19% and 30%, respectively (Table 3; Figs. 1C and 1D).

There was a numerical trend towards improved PFS and OS in the transplants performed after 2015 (n=53) compared to those transplanted in 2010–2015 (n=39) and before 2010 (n=29) (Table 2).

Univariate analysis showed that CR status at transplant improved OS compared to PR and SD/PD (log-rank *P*=0.023). Meanwhile, RIC resulted in superior OS than MAC (log-rank P=0.011).

Multivariable analysis showed that MUD was associated with poorer OS compared to MSD with HR 3.56 P=0.004, 95% confidence interval (CI) 1.49–8.31. (Table5). Similarly, HL had superior OS when compared to B-NHL with HR 0.33 (*P*=0.025), 95% CI 0.12–0.85 (Table 5). These differences were not seen on multivariable analysis of factors affecting PFS (Table 4).

DISCUSSION

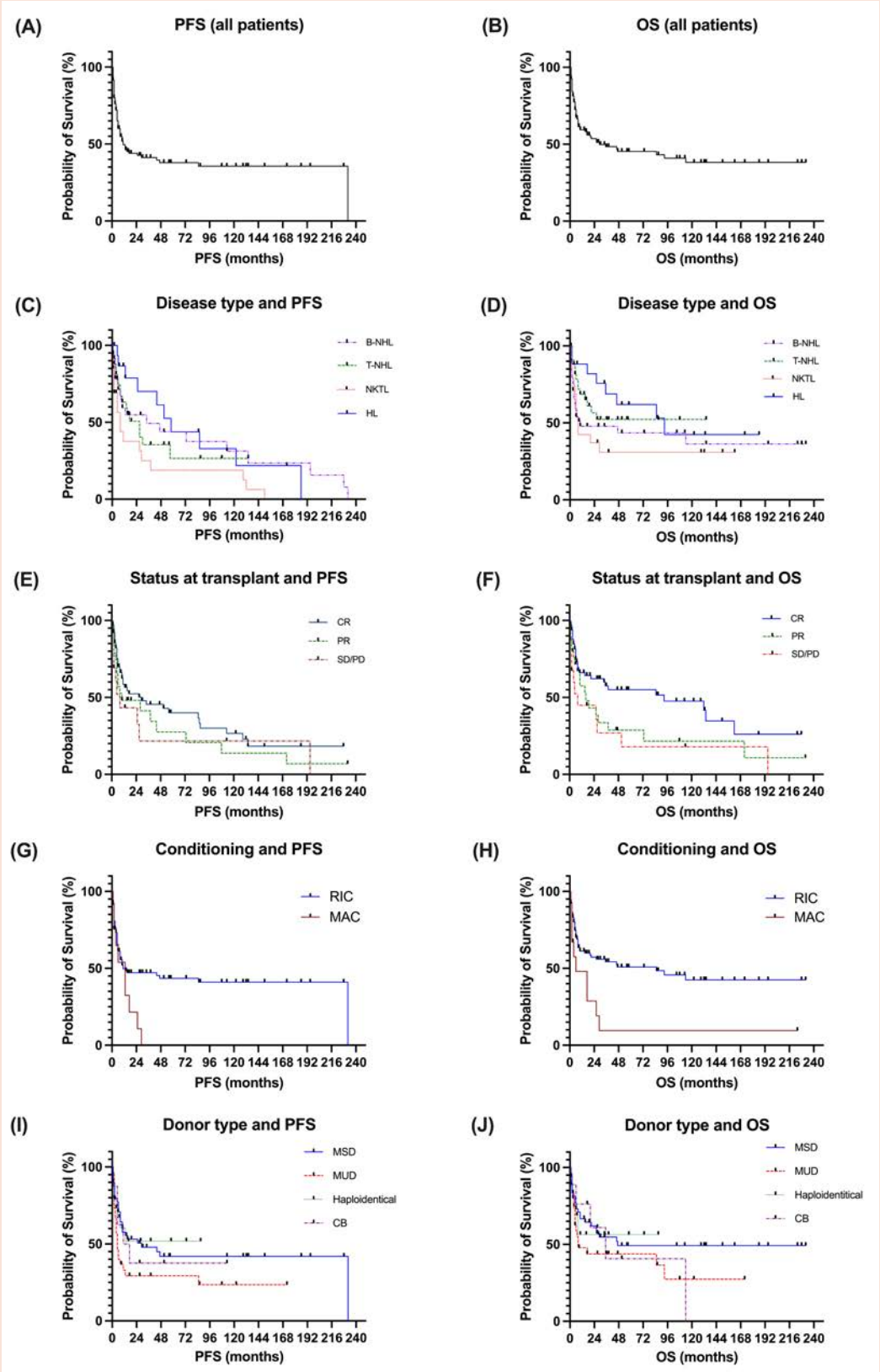
Survival outcomes and non-relapse mortality

Our study confirmed that allo-HSCT is associated with durable response and long-term survival. This was seen in 38% of patients who remained alive and disease-free while 45% remained alive at 4 years. However, allo-HSCT has significant toxicity evidenced by NRM of 24% at 1 year. This is comparable to the historical cohort reported by the European Society for Blood and Bone Marrow Transplant (EBMT) and Centre for International Blood and Marrow Transplant Research (CIBMTR) registry. Berning et al. evaluated the outcomes of allo-HSCT in patients in the EBMT cohort with R/R DLBCL and showed NRM rates of 18.8% at 1 year (patient cohort from 2010 to 2015).[10] Real-world data from the Korean Society of Blood and Marrow Transplantation registry also reported NRM rates at 1 year post-transplant of 23.4% at 1 year for patients with T-cell lymphoma.[11] In our cohort, 27 patients demised from infective complications, with pneumonia being the most common cause. Of which, 1 died of COVID-19 pneumonia during the pandemic. It is known that conditioning regimens eliminate host innate and humoral immunity. Additionally, the delayed recapitulating immune ontogeny post-transplant and the effects of GvHD contribute to this vulnerability to endogenous and exogenous pathogens.[12] It has also been shown that the outcome of COVID-19 infection in allo-HSCT recipients is uniformly poor compared to the general population.[13,14] Fortunately, the COVID-19 pandemic was deemed well-controlled in Singapore, and an early vaccination programme mitigated its impact on this highly vulnerable group. While infection has been the primary cause of NRM, the institution-specific protocols follow strict guidelines for infection prevention and monitoring. Since 2017, Singapore stem cell transplant centres have kept with the updated international recommendations for cytomegalovirus (CMV) prophylaxis; letermovir being approved and adopted for patients deemed high risk for CMV reactivation. For patients who are low-risk, pre-emptive monitoring is performed routinely and treatment instituted at the onset of significant viremia. Fungal prophylaxis is likewise incorporated in the standard protocols of each institution, and risk assessment for individual patients are assessed regularly relative to the degree and duration of neutropenia and immunosuppression. Recently, ruxolitinib has been approved for its use in steroid refractory acute GVHD, which has been effective compared to other second-line GVHD treatment. As our data span from 2003 to 2022, the benefit of effective therapies mentioned above might not reflect well in our study.[15,16]

Conditioning regime and donor selection

Patients who received RIC had improved OS compared to those who underwent MAC, regardless of age, with the median age being 41 years. This trend is consistent with findings from

Fig. 1. Kaplan-Meier curves of all patients.



(A) PFS (B) OS; various disease subtypes (C) PFS (D) OS; status at transplant (E) PFS (F) OS; type of conditioning (G) PFS (H) OS; donor type (I) PFS (J) OS

B-NHL: B-cell non-Hodgkin lymphoma; CB: cord blood; CR: complete remission; HL: Hodgkin lymphoma; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; NKTL: natural killer T-cell lymphoma; OS: overall survival; PFS: progression-free survival; PR: partial remission; RIC: reduced intensity conditioning; SD/PD: stable disease/progressive disease; T-NHL: T-cell non-Hodgkin lymphoma

Table 2. Univariate analysis of allografted patients.

Classification	n (%)	PFS		OS	
		% Patients (4-year survival)	*P* log-rank	% Patients (4-year survival)	*P* log-rank
All	121 (100)				
Status at allo-HSCTT			0.297		**0.023**
CR	73 (60)	45		55	
PR	29 (24)	27		29	
SD/PD	19 (16)	21		27	
Conditioning			0.050		**0.011**
MAC	17 (14)	0		10	
RIC	104 (86)	44		51	
Donor type			0.182		0.500
MSD	54 (44.6)	41		49	
MUD	35 (28.9)	29		44	
Haploidentical	23 (19)	52		56	
CB	9 (7.4)	38		41	
Period of transplant			0.30		0.23
Before 2010	29 (24)	30		40	
2010 to 2015	39 (32)	35		42	
After 2015	53 (44)	49		57	

Allo-HSCT: allogeneic-haematopoietic stem cell transplantation; CB: cord blood; CR: complete remission; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; OS: overall survival; PFS: progress-free survival; PR: partial remission; RIC: reduced intensity conditioning; SD/PD: stable diseases/progressive-free disease
Values in bold are statistically significant.

Table 3. Median PFS and OS of each lymphoma subtype.

Diagnosis/histological subtype	n (%)	% Patients (4-year survival, months)	Median PFS, months	% Patients (4-year survival, months)	Median OS, months
B-NHL	41 (34)	43	34	43	47
T-NHL	38 (32)	35	27	52	not reached
NKTL	24 (20)	19	8	30	8
HL	18 (15)	61	58	62	93

B-NHL: B-cell non-Hodgkin lymphoma; HL: Hodgkin lymphoma; NKTL: natural killer T-cell lymphoma; OS: overall survival; PFS: progress-free survival; T-NHL: T-cell non-Hodgkin lymphoma

Hamadani et al.,[17] who evaluated data from the observational CIBMTR database. They reported better OS among patients with R/R DLBCL who underwent RIC conditioning compared to MAC, attributable to higher rates of NRM in the MAC cohort. Similar to above studies, Kharfan et al. examined the outcome of mantle cell lymphoma and showed that RIC was superior than MAC.[18] Likewise, the use of RIC among the R/R lymphoma population was supported by a CIBMTR study in 2012 where NRM was higher after MAC, although the relapse risk was lower.[19] RIC is

Table 4. Multivariate analysis of factors influencing PFS in lymphoma patients receiving allo-HSCT.

Variable	n	HR	95% CI	P
Diagnosis				
B-NHL	41	1		Reference
T-NHL	38	0.84	0.31–2.23	0.72
NKTL	24	1.89	0.71–5.07	0.20
HL	18	1.28	0.43–3.70	0.64
Disease status at transplantation				
CR	73	1		Reference
PR	29	1.12	0.32–4.09	0.86
SD/PD	19	1.71	0.32–4.09	0.54
Donor type				
MSD	54	1		Reference
MUD	35	1.10	0.38–2.88	0.85
Haploidentical	23	0.63	0.13–2.75	0.55
CB	9	4.09	0.42–32.3	0.20
Conditioning				
RIC	102	1		Reference
MAC	17	0.64	0.19–1.83	0.43

Allo-HSCT: allogeneic-haematopoietic stem cell transplantation; B-NHL: B-cell non-Hodgkin lymphoma; CB: cord blood; CI: confidence interval; CR: complete remission; HL: Hodgkin lymphoma; HR: hazard ratio; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; NKTL: natural killer T-cell lymphoma; PFS: progress-free survival; PR: partial remission; RIC: reduced intensity conditioning; SD/PD: stable disease/progress-free disease; T-NHL: T-cell non-Hodgkin lymphoma

currently the standard conditioning regime used in allo-HCT for lymphoma.

In our cohort, MUD transplantation was associated with poorer OS on multivariable analysis. This was attributed to higher NRM in this group (34%) when compared to the rest. Castagna et al. showed that MUD was associated with poorer OS, although due to small sample size, it was underpowered to detect the difference statistically. This was in contrast to Hamadani et al.[20] who studied CIBMTR registry on mature T-cell lymphoma and showed that donor type did not significantly affect post-allo-HCT survival. Although our registry data does not contain information on the lines of treatment prior to allo-HSCT, we postulate that these patients required longer waiting time for a suitable donor. This delay might have potentially resulted in more lines of bridging therapies and therefore affected fitness level pre-transplant. The duration of donor search varies greatly depending on the ethnicity of recipient. Given the multi-ethnic population in Singapore, we noticed difficulty in looking for MUD if one is of Malay race. This was similar to the US where unrelated donor search needs to be initiated early in non-white populations.[21]

Another factor of higher NRM in MUD transplant may be related to the ATG, which is associated with delayed immune reconstitution and an increased risk of infection.[22] Our lymphoma patients were more likely to be lymphodepleted after lines of lymphoid-targeted therapies. Higher ATG dosage together with low absolute lymphocyte count (ALC) at time of ATG infusion is associated with increase fungal infection rate in recent studies.[23,24] We routinely practised weight-based ATG dosing regardless of ALC. Further local study is required to confirm this, as our registry dataset lacks information on the relationship between dosage of ATG and ALC.

Efforts to replace ATG with PTCy in MUD transplantation have not consistently shown clear survival benefits but have been associated with decreased incidences of chronic GVHD, potentially allowing for a reduction in immunosuppressant

Table 5. Multivariate analysis of factors influencing OS in lymphoma patients receiving allo-HSCT.

Variable	n	HR	95% CI	*P*
Diagnosis				
B-NHL	41	1		Reference
T-NHL	38	0.56	0.25–1.21	0.12
NKTL	24	1.08	0.51–2.27	0.83
HL	18	0.33	0.12–0.85	0.025
Disease status at transplantation				
CR	73	1		Reference
PR	29	1.02	0.41–2.61	0.98
SD/PD	19	1.680	0.41–7.82	0.49
Donor type				
MSD	54	1		Reference
MUD	35	3.56	1.49–8.31	0.004
Haploidentical	23	1.82	0.42–6.68	0.40
CB	9	2.93	0.43–17.2	0.25
Conditioning				
RIC	102	1		Reference
MAC	17	1.65	0.49–4.61	0.38

Allo-HSCT: allogeneic-haematopoietic stem cell transplantation; B-NHL: B-cell non-Hodgkin lymphoma; CB: cord blood; CI: confidence interval; CR: complete remission; HL: Hodgkin lymphoma; HR: hazard ratio; MAC: myeloablative conditioning; MSD: matched sibling donor; MUD: matched unrelated donor; NKTL: natural killer T-cell lymphoma; OS: overall survival; PR: partial remission; RIC: reduced intensity conditioning; SD/PD: stable disease/progress-free disease; tT-NHL: T-cell non-Hodgkin lymphoma

use and a consequent decrease in infective complications.[25,26] In myelodysplastic syndrome (MDS), Chalandon et al. showed that in the setting of MUD transplants, GVHD prophylaxis using PTCy, compared to ATG, resulted in better OS and PFS.[27] Among patients with R/R HL, evidence suggests the utility of PTCy specifically in the MUD and mismatch-related transplant, allowing one to postulate that PTCy can target the lymphoma itself.[28] PTCy could be an attractive GVHD prophylaxis option in MUD other than ATG, especially in lymphoma.

Interestingly, the outcome of transplants using haploidentical donors appeared comparable, if not superior, to those using MSD. This might be because haploidentical donor transplant was performed in more recent years and utilised either PTCy (n=15) or ex-vivo T-cell alpha-beta depletion (n=7) with the availability of novel GVHD prophylaxis and improvements in supportive care measures. Haploidentical donor transplantation presents an attractive option due to favourable availability.

Disease status at transplant

Our series showed that there was superior OS with better disease status at transplant. This finding is echoed by Hamadani et al. who evaluated patients with mature T-cell lymphoma from accredited EBMT and CIBMTR centres and showed improved PFS and OS in those in CR prior to allo-HSCT.[20] However, it is challenging to achieve CR pre-transplant in a significant proportion of patients with R/R high-risk lymphoma. Frontline treatment of lymphoma in Singapore was similar to National Comprehensive Cancer Network guidelines but not in the R/R setting. Although in certain parts of Asia, such as Japan and China where trials for novel therapies like valemetostat, linperlisib and golidocitinib have been made available for patients with refractory T-cell lymphomas,[29,30] access to clinical trials for our patients remains limited. This adds to the challenge of achieving CR in refractory lymphoma patients. Notably, SD/PD patients still benefitted from allo-HSCT with the effect of graft-versus-lymphoma effect evidenced by 4-year PFS

and OS of 21% and 27%, respectively. Hamadani et al. showed that certain subtypes of T-cell lymphoma are especially sensitive to graft-versus-lymphoma effect, making it possible to proceed with allo-HSCT at less than CR in those specific subtypes (e.g. angioimmunoblastic lymphoma). Balancing the benefit of CR pre-transplant against the potential risk of jeopardising fitness after multiple lines of bridging therapies has to be individualised based on disease tempo and health.[20]

Lymphoma subtype analysis

Comparing outcomes across different subtypes of lymphoma comes with caveats due to varying risks, patient demographics and disease biology. However, we observed that allo-HSCT exhibited the most promising curative potential among patients with R/R HL, with a 4-year PFS and OS of 61% and 62%, respectively. Our findings align with those of prospective phase 2 studies and retrospective reviews (GELTAMO and EBMT), where the 1-year and 4-year OS were 71% and 43%, respectively.[31]

HL patients tend to be younger, potentially resulting in better performance status, which could lead to improved tolerance of salvage regimens and, consequently, better disease control prior to allo-HSCT. Additionally, the availability of Brentuximab vedotin and PD1 inhibitors in the later era of analysis significantly contributed to achieving better responses among the relapsed subset.[32] While PD-1 blockade has helped bridge patients to allo-HSCT, it is associated with treatment-refractory GVHD.[33] Given its long half-life, it is advised to implement a wash-out period of at least 6 weeks before allo-HSCT.[34,35]

The significant proportion of the patients in our study had T-NHL, achieving 4-year PFS and OS of 35% and 52%, respectively. Our results were consistent with those reported by Schmitz et al. whose study, coordinated by the French Lymphoma Study Association and the German Lymphoma Alliance, revealed a 5-year PFS of 40% and a 3-year OS of 57% in patients with T-NHL who underwent allo-HSCT following upfront chemotherapy.[36] These comparable findings suggest to defer allo-HSCT to second-line setting as most T-NHL patients in our study received allo-HSCT at relapse.

In our study, NKTL ranks third in terms of the number of cases. In Asia, there is a higher prevalence of NKTLs compared to the West.[37] CIBMTR data on allo-HSCT in extranodal NKTLs reported 3-year PFS and OS of 28% and 34%, respectively. A Japanese registry study by Murashige et al. (2005),[38] which included 28 patients, reported 2-year OS 40%. A multicentre study by the Asia Lymphoma Study Group reported by Tse et al.[39] revealed a 5-year OS of 57%. Compared to the above, our patients exhibited inferior outcome, with a 4-year PFS and OS of 19% and 30%, respectively. This discrepancy could be attributed to a larger proportion of patients in our subgroup undergoing transplantation while not in CR (46%). There remains a significant unmet need for salvage options in R/R NKTL. PD-1 inhibitors have shown early promising activity in this subtype of lymphoma and could potentially optimise pre-transplant disease control.[40] However, the issue of hyperacute GVHD in PD-1 inhibitor post-transplantation settings necessitates careful consideration.

Among patients with B-NHL, DLBCL emerges as the most common subtype. In our study, these patients exhibited a 4-year PFS of 43% and an OS of 43.5%. These results closely align with findings from the Spanish multicentre GETH/GELTAMO study reviewed by Bento et al.,[5] where the 3-year event-free survival and OS were reported as 38% and 44%, respectively. However, other studies have demonstrated a wide range of outcomes for PFS (12–80%) and OS (28–80%), which can be attributed to the heterogeneity of the study populations, differences in conditioning regimens and variations in donor selection.[2,41,42]

Considering the prohibitive issues associated with allo-HSCT, including toxicities and donor availability, CAR-T cell therapy has emerged as a promising alternative. In patients with R/R B-cell lymphoma and high-risk cytogenetics, CAR-T cell therapy has demonstrated a 58% CR rate[43] and exhibited a 5-year PFS and OS of 31.8% and 42.6%, respectively (ZUMA-1).[44] However, the unique adverse risk of CAR-T cell therapy includes cytopenias, neurological complications and cytokine release syndrome.

Despite its effectiveness and safety, accessibility to CAR-T cell therapy remains limited in many Asian countries. Therefore, in settings where CAR-T cell therapy is unavailable or prohibited due to factors such as incipient MDS, or in patients with disease relapse post-CAR-T,[45,46] allo-HSCT may continue to offer PFS and OS benefits and serve as a reasonable alternative. There is paucity of evidence comparing the economic burden of allo-HSCT relative to CAR-T cell therapy. Each has different indications and subsequent complications which add to the cost. Traditionally, the cost of allo-HSCT has been supported by local government and private insurance policy. There were recent changes in financial policy support for CAR-T cell therapy. Unfortunately, this has not been generalised to all patients.[47] Despite the

CAR-T cell therapy advancement in B-NHL, allo-HSCT remained standard for HL, T-NHL and NKTL.

Period of transplantation

Our study showed an improved trend in terms of outcomes—both PFS and OS over the last decade. This is likely due to improvement in patient selection, deeper remission status, improved conditioning regime and supportive care peri-transplant. Over the last decades, we have seen the new supportive care in this field, including newer generation of antimicrobial, ruxolitinib for steroid refractory GVHD, letemovir for CMV prophylaxis in high-risk patients, as well as novel agents used in salvage treatment prior to allo-HSCT. Improvement in hospital and community care are other contributory factors.

Relevance of our data

Epidemiologically, there are significant geographical differences for lymphomas, especially Peripheral T Cell Lymphomas, compared to Europe and North America. In addition, the model of healthcare reimbursement and accessibility to clinical trials is different in Asia compared to western countries. As one of the largest real-world datasets looking at allo-HSCT in lymphoma in Asia, our data provides more relevant clinical outcome data for local and regional government organisations to which novel therapies can be benchmarked against for cost-effectiveness analysis for reimbursement considerations. For example, in B-NHL, the improved toxicity profile of CD19 CAR-T cell therapy and the NRM of <10% from large cohorts[43,48] compared favourably with the NRM of allo-HSCT of 24%, as demonstrated in our allo-HSCT cohort. Together with the efficacy data of CAR-T cell therapy, this has supported the use of CAR-T over allo-HSCT, and contributed to the approval for CAR-T cell therapy in Singapore. In contrast, the favourable outcomes of allo-HSCT for HL (4-year PFS and OS of 61% and 62%, respectively), comparable to outcome results worldwide, supports its use as a consolidation option for younger patients relapsing post-autologous transplant. Importantly, compared to other datasets from Japan, Korea and China,[37,38,40] results from our dataset may be more relevant and applicable to Southeast Asian countries, especially in subpopulations such as HL and T-NHL, where there is paucity of clinical trials for patients relapsing after standard of care treatment. Thus, results for our dataset will also provide an important benchmark and unique perspective for Asian-specific lymphoma treatment guidelines.

Limitation

This is a retrospective analysis that inevitably consists of physician and patient selection bias. Patients with better performance status were chosen for allo-HSCT and may not reflect the actual demographic of patients with R/R lymphoma who may have poorer fitness and difficulty in disease control. Additionally, there were some patients with missing data that could have affected the accuracy of the final analysis. Last, despite the collaboration between 2 centres, sample size remained small when performing subgroup analyses. Further evaluation in a larger cohort through collaborations with other transplant centres in the Asia-Pacific region (Singapore is part of the Asia Pacific Blood and Bone Marrow Transplant group) may help improve statistical power and provide systematic directions to standardise the role of allo-HSCT in the R/R lymphoma treatment algorithms.

CONCLUSION

Allo-HSCT is an effective treatment modality that leads to durable disease control for patients with R/R lymphoma. These real-world results form a historical benchmark for future studies of high-risk and R/R lymphomas in Singapore and in the Asia Pacific.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2015/2419) and National University Hospital Domain Specific Review Board (2010/00431).

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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ORIGINAL ARTICLE

Epidemiology of paediatric intensive care unit admissions, deaths and organ donation candidacy: A single-centre audit

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ABSTRACT

Introduction: There are limited reports on the epidemiology of paediatric intensive care unit (PICU) admissions, deaths and organ donation candidacy. We aimed to describe PICU admission characteristics and outcomes, determine risk factors for mortality, and perform an independent assessment of missed organ donation opportunities.

Method: We adopted a clinical audit design recruiting consecutive patients admitted to a single-centre multidisciplinary PICU from June 2020 to December 2023. Clinical characteristics and outcomes of survivors and non-survivors were described. Multivariable regression was performed to identify independent risk factors for mortality. Organ donation candidacy was evaluated by an independent team based on the criteria by Singapore's National Organ Transplant Unit.

Results: There were 1766 PICU admissions with mean age ± standard deviation of 5.9 ± 6.0 years. Surgical admissions accounted for 707/1766 (40%), while the most common medical admission category was respiratory (416/1766; 23.6%). The majority of 983/1766 (55.7%) had a chronic comorbidity and 312/1766 (17.6%) were dependent on at least 1 medical technology device. Mortality occurred in 99/1766 (5.6%). After adjusting for elective admissions and admission category; comorbidity with adjusted odds ratio (aOR) 95% confidence interval (CI) 3.03 (1.54–5.96); higher Pediatric Index of Mortality 3 (PIM 3) score with aOR 1.06 (95% CI 1.04–1.08); and functional status scale with aOR 1.07 (95% CI 1.00–1.13) were associated with mortality. Among non-survivors, organ donor candidacy was 21/99 (21.2%) but successful organ donation occurred in only 2/99 (2.0%).

Conclusion: In this single-centre audit, comorbidities, PIM 3 score and functional impairment were associated with mortality. Efforts are needed to improve paediatric organ donation rates.

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Keywords: children, paediatrics, paediatric intensive care units, PICU, mortality, organ donation, organ transplant

CLINICAL IMPACT

What is New

- This clinical audit identified a substantial population of children with chronic disease and medical technology dependence who were admitted to our paediatric intensive care unit (PICU).
- Presence of chronic disease, higher admission severity score and functional impairment were associated with mortality.
- Among PICU non-survivors, there was a large gap between eligibility and actual organ donation that predominantly stemmed from non-identification of potential organ donors.

Clinical Implications

- Children with chronic disease and functional impairment are vulnerable populations within our PICU, underscoring the need for research in these groups of children to improve outcomes.
- Concrete measures to improve paediatric organ donation rates may include having an independent team screen patients for eligibility when death is anticipated, involving the donor coordinator in family discussions, and establishing an operational workflow for donation after cardiac death.

INTRODUCTION

With advancements in medical care, mortality rates in critically ill patients have decreased substantially.[1,2] Contemporary studies from developed countries report paediatric intensive care mortality rates of 2–3%[3,4] in 2014 to 2019, whereas mortality in developing countries can be as high as 50%[5] as of 2024, indicating large disparities in resources,

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expertise and infrastructure between high- and low-resource countries. Other evident differences include the causes of death—sepsis, multiorgan failure and pneumonia are leading causes of mortality in developing countries,[6,7] whereas, cardiovascular disease (including congenital heart disease, cardiomyopathy and myocarditis) and neuromuscular disease (including encephalitis/encephalopathy) are more prevalent causes of death in developed countries.[3,4] Paediatric intensive care unit (PICU) registries are a useful means to track the epidemiology of PICU admissions and mortality characteristics. For example, the Virtual Pediatric Systems registry in the US,[8] the Australian and New Zealand Pediatric Intensive Care Registry (ANZPICR)[9] and the Paediatric Intensive Care Audit Network (PICANet)[10] in the UK are established PICU registries with audit, quality improvement and research aims. There is currently a lack of such registry initiatives in other parts of the world including Asia. As a result, reliable year-on-year admission characteristics and mortality data are lacking.

As most inpatient paediatric deaths occur in the PICU, identification of potential organ donors is most actively conducted in there, which is a pragmatic representation of the potential paediatric organ donor pool.[11] Besides being affected by prevailing mortality rates, organ donation in children is also diminished due to medical suitability (e.g. higher prevalence of inborn errors, of metabolism and genetic conditions compared to adults) and parental values and beliefs.[12] Singapore legislation requires parents or legal guardians of minors to give consent during an already stressful period for organ donation.[13] There are limited reports on organ donation rates and missed donation opportunities in PICUs in Singapore and globally. By leveraging a recently established paediatric ICU registry, this study aimed to (1) describe the epidemiology of PICU admissions, (2) compare characteristics of survivors and non-survivors to identify risk factors for poor outcome, and (3) explore perimortem characteristics to independently determine the number of potential organ donors over the study period.

METHOD

Study design

This study employed an audit design, extracting data from the Singapore Pediatric Intensive Care Registry (SG-PedIC). We chose to perform a clinical audit from the SG-PedIC Registry as our primary aim was to describe the epidemiology of PICU admissions, deaths and organ donation candidacy to inform regarding the current standard of care delivered in our PICU. By adopting an audit design, all consecutive PICU admissions were included. The registry routinely and prospectively collects data on patient demographics, clinical characteristics, PICU therapies and outcomes from a single-centre PICU at KK Women's and Children's Hospital. This is a tertiary, university-affiliated paediatric centre in Singapore with a multidisciplinary PICU comprising 16 beds (including medical, surgical, oncology, neurosurgical and cardiothoracic surgical subspecialties). It is also the largest paediatric hospital in Singapore, serving the majority of the local paediatric population. As this study was deemed an audit, ethics approval was waived. No generative artificial intelligence (AI) or AI-assisted technologies were used.

All consecutive patients admitted to the PICU between July 2020 and December 2023 (3.5-year period) were included in this study. Patients' characteristics including age, sex, weight, race, presence of comorbidities, admission details, Paediatric Index of Mortality 3 (PIM 3) score, PICU therapies and outcomes were extracted using a standardised case report form. The PIM 3 score that has been validated at our centre was calculated on admission to the PICU.[14,15] Comorbidities were defined according to the list of chronic complex conditions and the main system affected was reported.[16,17] The functional status scale was scored on admission to the PICU.[18] Technology dependence was defined according to the list provided by the ANZPICR.[9] Non-survivors were defined as patients who demised during in-patient admission or who were discharged directly home from the PICU for terminal extubation. Perimortem characteristics and cause of death were examined in non-survivors. In addition to routinely collected registry data, we independently identified potential organ donors based on published criteria; age (at least 2 months and above); and absence of any malignancy, disseminated infection, hepatitis C and HIV (Supplementary Table S1).[19] Patients who were diagnosed with or suspected of having inborn errors of metabolism (IEM) or other genetic conditions were excluded. Once a patient was deemed a potential organ donor, perimortem case notes (up to 72 hours before terminal event) were reviewed to determine if the medical team identified organ donation eligibility and if the topic of organ donation was broached with the patient's parents/legal guardian. Reasons for and against organ donation were identified and summarised.

Statistical analysis

The primary outcome of this audit was PICU mortality. We calculated the standardised mortality ratio by the ratio of the observed deaths to expected deaths based on the PIM 3 score at

admission. Characteristics and PICU therapies of PICU survivors and non-survivors were compared using the Student's t-test or chi-square test for continuous or categorical outcomes, respectively. Multivariable logistic regression was performed to identify independent risk factors for PICU mortality, and adjusted for baseline patient characteristics with significant univariate associations and clinical significance. Analysis was performed on STATA software version 15.1 (StataCorp, College Station, TX, US). All tests were two-tailed and *P* value <0.05 was accepted as statistically significant.

RESULTS

A total of 1766 patients were admitted to the PICU during the study period. The mean age of patients was 5.9 (±6.0) years (Table 1). Among them, 997/1766 (56.5%) were male, 946/1766 (53.6%) were Chinese and 514/1766 (29.1%) were elective admissions. Surgical admissions accounted for 707/1766 (40%) of total admissions, while the most common medical admission category was respiratory at 416/1766 (23.6%). The main sources of admission were the general inpatient ward/intermediate care unit at 550/1766 (31.1%), operating theatre at 541/1766 (30.6%) and emergency department at 487/1766 (27.6%). The majority of patients who were admitted also had preexisting comorbidities at 983/1766 (55.7%), with cardiovascular and neurological/neuromuscular comorbidities being most prevalent in our study population.

Respiratory support was the most common PICU therapy required by patients (invasive mechanical ventilation in 777/1766 [44.0%] and non-invasive respiratory support in 560/1766; 31.7%), whereas cardiovascular support was required in 484/1766 (27.4%) (Table 2). Non-survivors had increased frequency of use of all PICU support therapies, except non-invasive respiratory support. The mean length of PICU stay of our study population was 7 (±26.6) days, though 137/1766 (7.8%) patients had a prolonged PICU stay of more than 2 weeks. Patients admitted for more than 2 weeks were sicker (PIM 3 score mean standard deviation [SD] 5.4 [± 11.0]% vs. 2.6 [± 6.9]%; *P*<0.001); more likely to have an underlying chronic condition (100/137 [73.0%] vs. 884/1626 [54.4%]; *P*≤0.001); be technology dependent (48/137 [35.0%] vs. 264/1629 [16.2%]; *P*<0.001); and have a poorer functional state (functional status scale, mean [SD] 10.8 [±5.1] versus [vs] 8.2 [±3.6]; *P*<0.001). When excluding these long stayers, the mean length of PICU stay was 3.6 (±2.5) days.

Table 1. Comparison of characteristics of survivors and non-survivors admitted to the paediatric intensive care.

Patient characteristics	Total (n=1766)	Survivors (n=1667)	Non-survivors (n=99)	*P* value
Age, years	5.9 (6.0)	5.9 (5.9)	5.6 (6.0)	0.647
Age group, no. (%)				0.209
Infant (1 month to <1 year)	544 (30.8)	506 (30.3)	38 (38.3)	
Child (1 year to <10 years)	739 (41.9)	706 (42.3)	33 (33.3)	
Adolescent (10 to <18 years)	445 (25.2)	418 (25.0)	27 (27.2)	
Adult (>18 years)	37 (2.1)	36 (2.1)	1 (1.0)	
Weight, mean (SD), kg	35.8 (568.9)	36.6 (585.5)	21.8 (22.9)	0.801
PIM 3 score, mean (SD), %	2.7 (7.3)	2.3 (5.2)	12.1 (22.5)	<0.001
Male, no. (%)	997 (56.5)	946 (56.8)	52 (52.5)	0.403
Race, no. (%)				0.147
Chinese	946 (53.6)	901 (54.1)	44 (44.4)	
Malay	521 (29.5)	485 (29.1)	36 (36.3)	
Indian	147 (8.3)	135 (8.1)	12 (12.1)	
Others	150 (8.5)	144 (8.6)	7 (7.0)	
Any comorbidities, no. (%)	983 (55.7)	918 (55.2)	65 (65.6)	0.042
Neurological/neuromuscular	297 (16.8)	279 (16.7)	18 (18.1)	0.709

Table 1. Comparison of characteristics of survivors and non-survivors admitted to the paediatric intensive care. (Cont'd)

Patient characteristics	Total (n=1766)	Survivors (n=1667)	Non-survivors (n=99)	*P* value
Cardiovascular	303 (17.1)	279 (16.7)	24 (24.2)	0.054
Respiratory	104 (5.8)	96 (5.7)	8 (8.0)	0.340
Renal	27 (1.5)	25 (1.5)	2 (2.0)	0.682
Gastrointestinal	84 (4.7)	80 (4.8)	4 (4.0)	0.730
Haematology/immunology	47 (2.6)	45 (2.7)	2 (2.0)	0.683
Metabolic	66 (3.7)	63 (3.7)	3 (3.0)	0.703
Genetic/congenital	185 (10.4)	171 (10.2)	14 (14.1)	0.220
Neoplastic	180 (10.1)	169 (10.1)	11 (11.1)	0.756
Technology dependent, no. (%)	312 (17.6)	288 (17.3)	24 (24.2)	0.077
Elective, no. (%)	514 (29.1)	506 (30.4)	9 (9.0)	<0.001
Admission category, no. (%)				<0.001
Cardiac surgical	274 (15.5)	262 (15.7)	12 (12.1)	
Cardiac medical	131 (7.4)	118 (7.0)	13 (13.1)	
Trauma	48 (2.7)	40 (2.4)	8 (8.0)	
Respiratory	416 (23.6)	388 (23.3)	28 (28.2)	
Neurological	148 (8.3)	139 (8.3)	9 (9.0)	
Surgical (non-cardiac)	385 (21.8)	379 (22.7)	6 (6.0)	
Other medical diagnoses	361 (20.4)	338 (20.3)	23 (23.2)	
Admission source, no. (%)				<0.001
Operating theatre	541 (30.6)	531 (31.9)	10 (10.1)	
Emergency department	487 (27.6)	460 (27.6)	27 (27.2)	
General ward/intermediate care unit	550 (31.1)	517 (31.0)	33 (33.3)	
Neonatal department	44 (2.4)	39 (2.3)	5 (5.0)	
Inter-hospital transfers	89 (5.0)	71 (4.2)	18 (18.1)	
Others	53 (3.0)	47 (2.8)	6 (6.0)	
Admission functional status scale, mean (SD)	8.3 (3.8)	8.3 (3.7)	9.4 (4.5)	0.003
Mental status	1.1 (0.6)	1.1 (0.6)	1.3 (0.8)	0.007
Sensory functioning	1.2 (0.6)	1.1 (0.6)	1.3 (0.6)	0.037
Communication	1.2 (0.7)	1.2 (0.7)	1.4 (0.7)	0.099
Motor functioning	1.4 (1.0)	1.4 (1.0)	1.7 (1.2)	0.001
Feeding	1.6 (0.9)	1.5 (0.9)	1.8 (1.0)	0.029
Respiratory status	1.6 (1.2)	1.6 (1.2)	1.8 (1.4)	0.083

PIM 3: Pediatric Index of Mortality 3

Table 2. Comparison of intensive care therapies in survivors and non-survivors.

Intensive care therapies	Total (n=1766)	Survivors (n=1667)	Non-survivors (n=99)	*P* value
Inotrope, no. (%)	484 (27.4)	402 (24.1)	82 (82.8)	<0.001
Adrenaline	295 (16.7)	220 (13.2)	75 (75.8)	<0.001
Noradrenaline	247 (14.0)	186 (11.2)	61 (61.6)	<0.001
Milrinone	242 (13.7)	212 (12.7)	30 (30.3)	<0.001
Vasopressin	62 (3.5)	19 (1.1)	43 (43.4)	<0.001
Dopamine	32 (1.8)	21 (1.3)	11 (11.1)	<0.001
Dobutamine	12 (0.7)	7 (0.4)	5 (5.1)	<0.001
Continuous renal replacement therapy, no. (%)	43 (2.4)	20 (1.2)	23 (23.2)	<0.001
Continuous veno-venous haemodialysis	42 (2.4)	19 (1.1)	23 (23.2)	<0.001
Peritoneal dialysis	4 (0.2)	2 (0.1)	2 (2.0)	<0.001
ECMO, no. (%)	59 (3.3)	28 (1.6)	31 (31.3)	<0.001
Non-invasive respiratory support, no. (%)	560 (31.7)	533 (31.9)	27 (27.2)	0.329
Continuous positive airway pressure	455 (25.8)	443 (26.6)	12 (12.1)	0.001
Bilevel positive airway pressure	326 (18.5)	306 (18.4)	20 (20.2)	0.646
High flow nasal cannula	47 (2.7)	46 (2.8)	1 (1.0)	0.293
Mechanical ventilation, no. (%)	777 (44.0)	684 (41.0)	93 (93.9)	<0.001
Duration	3.0 (12.0)	2.4 (10.5)	13.6 (24.3)	<0.001
High frequency ventilation	51 (2.8)	29 (1.7)	22 (22.2)	<0.001
Nitric oxide	42 (2.3)	26 (1.5)	16 (16.1)	<0.001
Intracranial pressure monitor, no. (%)	45 (2.5)	38 (2.2)	7 (7.0)	0.003
ICU stay, mean (SD), days	7.0 (26.6)	6.4 (26.5)	15.6 (27.8)	<0.001
Prolonged ICU stay, no. (%)	137 (7.8)	114 (6.8)	23 (23.2)	<0.001

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit

There were a total of 99/1766 (5.6%) deaths in this population (mortality rate for each calendar year ranged 5.1–6.8% with no statistical difference between years). The standardised mortality ratio was 2.1. There were no differences in demographics between survivors and non-survivors. However, compared to survivors, non-survivors were more likely to have an underlying comorbidity (65/99 [65.6%] vs 918/1667 [55.2%]; *P*=0.042), higher PIM 3 (mean [SD] 12.1% [±22.5] vs 2.3% [±5.2], *P*<0.001), and higher admission functional status scale (mean [SD] 9.4 [± 4.5] vs 8.3 [± 3.7]; *P*=0.003). There were also differences in admission categories and source of admission between survivors and non-survivors (Table 1). In the multivariable regression model, after adjusting for elective admissions and admission category, the presence of comorbidities (adjusted odds ratio [aOR] 3.03, 95% confidence interval [CI] 1.54–5.96), PIM 3 (aOR 1.06, 95% CI 1.04–1.08) and admission functional status scale (aOR 1.07, 95% CI 1.00–1.13) were independently associated with PICU mortality (Table 3). Among the non-survivors, the main causes of death include central nervous system infarction/haemorrhage/hypertension (17/99; 17.1%) and pneumonia/chronic lung disease (15/99; 15.1%) (Table 4). There were also 30/99 (30.3%) of patients who required coroner's referral. Most deaths occurred on maximal support 38/99 (39.1%) while brain death occurred in 6/99 (6.2%) of the patients. Majority (51/99; 52.0%) of patients who died had existing limitation of care orders.

Table 3. Multivariable logistic regression for paediatric intensive care mortality.

Covariate	Univariate		Multivariate	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Comorbidities	1.55 (1.01–2.38)	0.043	3.03 (1.54–5.96)	0.001
PIM 3 score	1.06 (1.04–1.08)	<0.001	1.06 (1.04–1.08)	<0.001
Admission functional status scale	1.06 (1.02–1.11)	0.004	1.07 (1.00–1.13)	0.039
Elective	0.23 (0.11–0.46)	<0.001	0.42 (0.14–1.31)	0.134
Admission category Ref: Surgical (non-cardiac)				
Cardiac surgery	2.89 (1.07–7.81)	0.036	5.46 (1.55–19.26)	0.008
Cardiac medical	6.96 (2.59–18.71)	<0.001	3.23 (0.77–13.60)	0.110
Trauma	12.63 (4.17–38.24)	<0.001	11.09 (2.02–60.94)	0.006
Respiratory	4.56 (1.87–11.13)	0.001	2.72 (0.78–9.53)	0.117
Neurological	4.09 (1.43–11.70)	0.009	4.30 (1.07–17.35)	0.040
Other medical diagnoses	4.30 (1.73–10.68	0.002	2.99 (0.83–10.76)	0.094

aOR: adjusted odds ratio; CI: confidence interval; OR: odds ratio; PIM 3: Pediatric Index of Mortality 3

Table 4. Perimortem characteristics of non-survivors.

Perimortem characteristics	No. (%) n=99
Limitation of care order	51 (52.0)
Any CPR in ICU	37 (37.3)
CPR as terminal event	20 (20.8)
Mode of death	
Brain death	6 (6.2)
Death with maximal support	38 (39.1)
Death with therapy limited but not withdrawn	23 (23.7)
Death with therapy withdrawn (but not brain dead)	30 (30.9)
Cause of death	
CNS infarction/haemorrhage/hypertension	17 (17.1)
Pneumonia/chronic lung disease	15 (15.1)
Cardiac failure/congenital heart disease	10 (10.1)
Sepsis/multiorgan dysfunction	10 (10.1)
Pulmonary hypertension	5 (5.0)
Malignancy	4 (4.0)
Others	8 (8.0)
Coroner's referral	30 (30.3)
Organ donation	2 (2.1)

CNS: central nervous system; CPR: cardiopulmonary resuscitation; ICU: intensive care unit

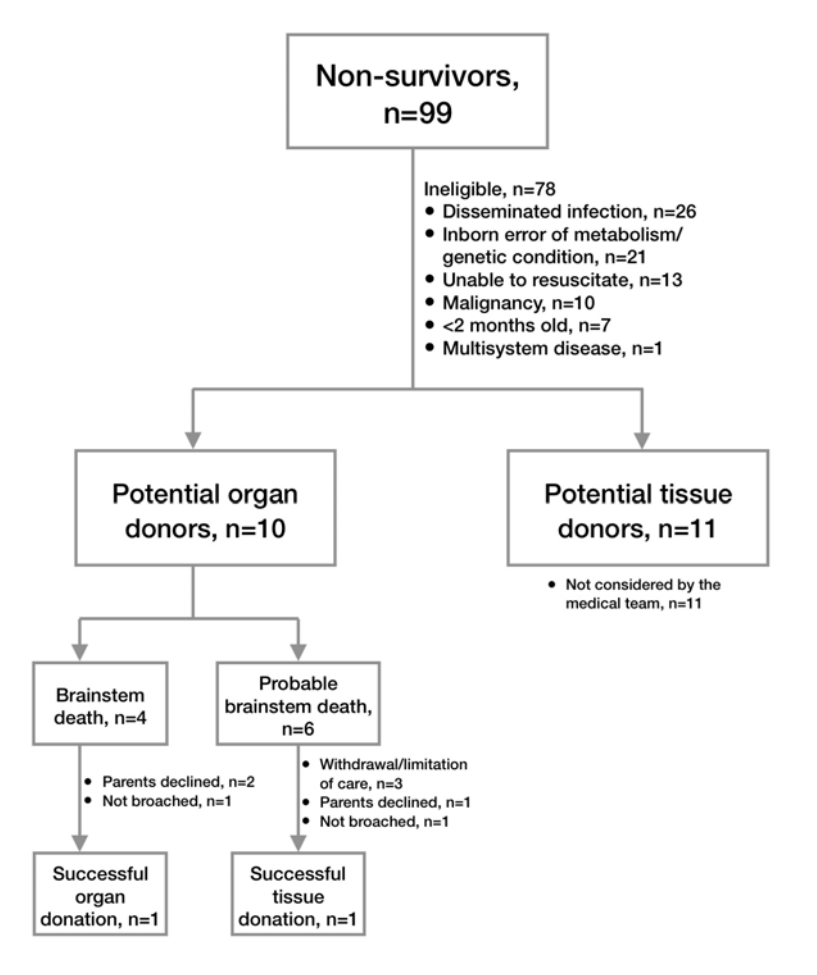
Among non-survivors, 78/99 (76.8%) were deemed ineligible for organ donation—the most common reasons for ineligibility were disseminated infection (26/78; 33.33%) and presence or suspicion of IEM/genetic conditions (21/78; 26.9%) (Fig. 1). Of the remaining 21 patients who were independently deemed to be potential organ donors, 4 met brainstem death criteria but only 1 went on to donate organs after brainstem death certification. Six patients had severe neurological prognosis with incomplete brainstem death criteria—among these only 1 went on to donate their tissue after cardiac death. The medical team did not consider the others 11/21 (52.4%) who were potential tissue donors.

DISCUSSION

In this single-centre audit of PICU admissions, we report a mortality rate of 5.6% and a standardised mortality ratio of 2.1. We identified the presence of comorbidities, higher PIM 3 score and functional impairment to be independently associated with mortality. The most common causes of death were neurological and respiratory. Of those who died, approximately 21% were eligible to donate their organs/tissue but only 2% went on to successfully donate their organs/tissue.

At 5.6%, the mortality rate reported in this study is slightly higher than those reported from developed countries including the US (1.9–3.4%),[3] Australia/New Zealand (2.6%),[20] UK (5.1%)[21] and Japan (2.1%).[4] The number of predicted deaths based on the PIM 3 score was lower, yielding a standardised mortality ratio of 2.1. This may indicate

Fig. 1. Breakdown of the organ donation process.



that PICU management and quality of care fell behind expected norms or may be contributed by deaths occurring in patients with existing limitation of care orders. However, there are additional considerations in interpreting the standardised mortality ratio. The PIM 3 score was derived from critically ill children admitted to PICUs from 2010–2011 in Australia, New Zealand, Ireland and the UK via the ANZPICR and PICANet registries, and its performance in predicting mortality may require recalibration in different regions.[15,22] Our hospital also runs an active rapid response team (intra-hospital) and transport service (inter-hospital), which provides advice to referring physicians on stabilising potential PICU candidates before transfer—this may artificially lower the PIM 3 score, which is calculated based on variables obtained once the patient is admitted to the PICU. Physiological variables for the calculation of PIM 3 may also be unavailable for some children (e.g. partial pressure of arterial oxygen), and given that PIM 3 relies on default imputation in which missing observations are given a value considered "normal" for that variable, this could have artificially lowered the score.[14] Lastly, though it is possible that a different severity of illness scores (e.g. PRISM[23]) may yield a more accurate predicted mortality rate in our unit, it was beyond the scope of the current study to compare the predictive ability of these commonly used scores in the PICU.

Higher mortality was observed in patients with existing chronic comorbidities, which is consistent with previous reports.[24] These patients may have existing organ dysfunction and/or reduced cardiopulmonary reserve, potentially increasing their risk of death[16] or may be admitted with existing limitation of care orders. Though slightly different from comorbidity per se, we observed that patients who had a higher functional status scale score (functionally impaired) also had a higher mortality rate. These patients were more likely to have a prolonged PICU stay, although the difference between these 2 groups of patients may not be clinically apparent. However, patients who were technology dependent (e.g. required long-term assisted feeding, home non-invasive respiratory

support or long-term vascular device) did not have a significantly higher mortality rate. With advances in medical care, there is likely an increasing population of patients with chronic diseases, functional impairment and technology dependence who may be admitted to PICU.[24] Data from this audit indicates that this population is vulnerable in the PICU, and further research is required to study their needs.

Despite advances in medical therapy, organ transplant remains the definitive, life-saving treatment for patients with irreversible or end-stage organ disease.[25] In Singapore, organ donation is governed by the Human Organ Transplant Act[26] and the Medical (Therapy, Education and Research) Act (MTERA),[27] and is mainly applied to adults aged 21 years old and above.[28] Paediatric organ donation may be applied for via MTERA, but it requires consent from the patient's parents/guardian and is often hindered by cultural and personal beliefs.[12] Here, we demonstrated that while 21% of our patients were deemed potential organ/tissue donors, up to 60% of these patients were not approached by the medical team. A single-centre retrospective study conducted in 2014 in the UK[29] has similarly shown that up to 54% of their neonatal patients who died were potential donors. A more recent multicentre retrospective study conducted in 2019 in the UK[30] had also reported that the majority of potential paediatric organ donors were not approached by the medical team. Both studies agree that with proper identification of potential organ donors and by approaching families respectfully, this niche group of patients may potentially augment nationwide donor pools. One concrete way to improve identification of organ donors is to have an independent team of medical staff screen patients for eligibility when death is anticipated, similar to how potential donors are screened in non-paediatric hospitals in Singapore. This differs from the current practice, in which transplant eligibility is determined by the medical team that is also in charge of the patient's treatment (a suggested workflow is provided in Supplementary Fig. S1). Once eligibility is established, family discussions should include the donor coordinator, who is a resource person on organ donation. Organ donation may be beneficial to families by providing an option to give meaning to the loss of a child's life, and if this is aligned with the values of the family, the managing team should incorporate their decision into the care plans.[12] Ideally, discussions on organ donation should be part of end-of-life care for dying patients of all ages.[12,30] Nonetheless, such conversations remain a challenge to clinicians, especially when families experience a sudden demise and such discussions may seem insensitive and even offensive, if done at the wrong time.

Organ donation after circulatory death (DCD)[31] involves initiating organ donation after circulatory death is confirmed and has been shown to increase donor pools in countries such as Spain,[32] US,[33] UK[34] and Canada.[35] This is a potential way of increasing the paediatric pool of organ donors as well as for adults.[36] Though the current legislation (i.e. MTERA) in Singapore allows for DCD and the first paediatric DCD in Singapore was reported in 2016,[37] national guidelines with an operational framework for carrying out DCD have only just been established following a pilot[38] and the guidelines were published in 2024.[39,40] Given that the largest proportion of cases with missed opportunities for tissue/organ donation in this audit were cases of DCD, we anticipate that donation rates may improve with the publication of this guideline/framework and with experience. Organ transplant in Singapore remains a sensitive issue in a relatively conservative culture. More work needs to be done to increase the awareness of the benefits of organ donation for both recipient and donor among the general public, in order to effect a change in beliefs and values even prior to an ICU encounter.[38]

Though this is to our knowledge the first audit of a large database of critically ill children in Singapore, there are several limitations. The SG-PedIC registry was initially established in a single centre but has only recently become a national-level registry that includes the only other restructured hospital admitting paediatric patients in Singapore, the National University Hospital, in 2024. As such, national-level data were not available to be included in this report and data from this single-centre audit may have limited generalisability. Another limitation of this study was that cause of death was not captured in the registry in approximately 30% of deaths that were referred to the coroners. In determining organ donation eligibility, we have taken a simplistic approach that may have reduced the number of eligible donors—we did not consider organ-specific criteria (Supplementary Table S1) and we excluded all malignancies even though some malignancies may still be considered for organ donation. Lastly, despite minimal missing quantitative data, qualitative data of communication details on organ donation between healthcare providers and patients' families may have been missed. As such, more granular details on the reasons for not considering organ donation candidacy by medical staff and the reasons for declining organ donation by parents were not available.

CONCLUSION

This single-centre audit of a multidisciplinary PICU reports a mortality rate of 5.6% and identifies the presence of comorbidities, higher PIM 3 score and functional impairment to be associated with mortality. To improve outcomes of the PICU, research is required to study the needs of patients with chronic diseases and functional impairment. We also found that close to 60% of potential organ donors were missed by the medical team indicating that more effort is needed to improve paediatric organ/tissue donation rates at our unit, which may include independent screening for eligibility, involvement of the donor coordinator in family discussions and establishing an operational workflow for donation after cardiac death.

Ethics statement

As this study was deemed an audit, ethics approval was waived.

Declaration

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Supplementary materials

Table S1. Summary of general and organ specific screening criteria.
Fig. S1. Suggested workflow and timeframe to identify potential organ donors and initiate organ donation processes.

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ORIGINAL ARTICLE

Radiologic placement of totally implantable venous access devices: Outcomes and complications from a large oncology cohort

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ABSTRACT

Introduction: Totally implantable venous access devices (TIVADs) or ports are increasingly used in oncology settings to provide long-term, easy venous access. This study reports our experience and results with 1180 cases in Singapore.

Method: Data from January 2019 to January 2022, obtained from a hospital-approved secure database application called the Research Electronic Data Capture registry, were reviewed and analysed retrospectively.

Results: A total of 1180 patients underwent TIVAD implantation with a 100% technical success rate. The mean age of the cohort was 61.9 years. The mean dwell duration was 342 days (standard deviation [SD] 223; range 3–1911). By 1 February 2022, 83% of patients were still using the TIVAD, 13.6 % underwent removal after completion of treatment, 2.1% were removed due to infection, 0.6% due to malfunction, 0.6% due to port extrusion and 0.1% at patient's request. The right internal jugular vein (IJV) was the most commonly accessed site (83.6%), followed by the left IJV (15.6%). The early post-procedure complications were pain (24.7%), bruising (9.2%), swelling (3.6%), bleeding (0.5%), fever (0.4%), itchiness (0.2%) and allergic dermatitis (0.1%). The delayed post-procedure complications were TIVAD site cellulitis (3.80%); discharge (1.10%); skin erosion with device extrusion (0.60%); malpositioned catheter (0.33%), which was successfully repositioned, catheter-related bloodstream infections (0.25%); migration of TIVAD leading to catheter dislodgement (0.25%); venous thrombosis (0.25%); fibrin sheath formation requiring stripping (0.10%) and TIVAD chamber inversion (0.10%).

Conclusion: TIVAD implantation via the jugular vein under radiological guidance provides a safe, reliable and convenient means of long-term venous access in oncology patients. By sharing our experience and acceptable outcomes from a large oncology cohort, we aim to increase the awareness and adoption of TIVAD usage in oncology patients, especially in Asia.

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Keywords: complications, long-term venous access, oncology, ports, totally implantable venous access device, TIVAD

CLINICAL IMPACT

What is New

- Adoption of totally implantable venous access devices (TIVADs) in oncology patients remains poor despite improved device construct and implantation techniques.
- To the best of the authors' knowledge, this study is the first from Singapore to share the experiences and results of TIVAD implantation in a large cohort.

Clinical Implications

- Radiologically guided insertion of TIVADs is a safe and reliable procedure with a high technical success rate and acceptably low complication rates.
- Apart from chemotherapy administration, TIVADs can be used for parenteral nutrition, obtaining blood samples and contrast media injections for imaging.

INTRODUCTION

Long-term intermittent venous access has proven to be indispensable for oncology patients who require frequent intravenous (IV) infusions and repeated phlebotomies apart from facing the discomfort of frequent venepuncture.[1] Totally implantable venous access devices (TIVADs) or ports are preferred to external catheters, especially in these patients, due to their low complication rates and high patient comfort and satisfaction.[2]

Historically, surgeons implant ports under general anaesthesia with venous cut-down. However, radiologically guided port placement has become increasingly popular and a routine since the first port implantation performed by Morris et al.[3] in

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1992 using interventional radiology techniques with higher technical success rates and lower complications.[4,5]

Due to the improved construct of the TIVADs currently available, apart from administering chemotherapy, it can be utilised for parenteral nutrition, withdrawing blood samples and withstanding high-pressure contrast media injections during cross-sectional imaging, which is routinely performed for oncology patients.

Although different veins at various sites can be used, the internal jugular vein (IJV) is the ideal vessel for primary venous access, with higher success rates and lower short- and long-term complication rates.[6] Hence, the most popular technique for port placement under radiological guidance is the creation of a tunnel between the venepuncture site and the port pocket in the infraclavicular region after IJV puncture. This study presents our experience and results in patients who underwent TIVAD implantation using this technique. Apart from having heterogeneous sample groups, most large cohort studies currently available are from the West, suggesting a higher adoption rate. Specific data involving the adoption rate of TIVADs and large-scale studies from Asia remain sparse. Therefore, we aim to bridge this gap and augment the adoption scale of TIVAD in Asian patients.

METHOD

The SingHealth Centralised Institutional Review Board (CIRB 2021/2357) approved this study, where the requirement for informed consent was waived due to retrospective anonymisation. Patients' data were obtained from a hospital-approved secure database application called the Research Electronic Data Capture (REDCap) registry. Data of all TIVADs placed at Singapore General Hospital from January 2019 to January 2022 were anonymised and used for this review.

Pre-procedure considerations

Written informed consent was obtained from all patients. Procedural details, including the options, advantages and expected complications, were relayed to all patients during this process. Relevant clinical histories, such as previous mastectomy and axillary dissection, prior or planned radiation therapy to the chest, presence of indwelling cardiac pacemaker and the assessment of the amount of subcutaneous tissue and condition of the skin over the infraclavicular region, were also performed. Alternative options for long-term venous access, such as peripherally inserted central catheter (PICC) or tunnelled venous catheters like Hickman, were offered to patients deemed unsuitable for TIVAD implantation.

Haemoglobin (Hb), platelet, absolute neutrophil count (ANC), international normalised ratio (INR) and partial thromboplastin time (PTT) values were obtained from all patients. The procedures were deferred if the patient has an ANC of <1500/mcL, Hb is <8.0 mg/dL, platelet is <50,000 mcL or INR and PTT are >1.5 times the normal value.

All patients were administered IV prophylactic antibiotics before the procedure: 1 g cefazolin or 600 mg clindamycin for patients with a history of penicillin allergy or 1 g vancomycin for patients with a history of methicillin-resistant *Staphylococcus aureus* infection.

Sedoanalgesia with IV midazolam and fentanyl was administered in selected cases (at operators' discretion) for patient comfort and anxiolysis, with strict continuous physiologic monitoring (with pulse oximetry, electrocardiography and non-invasive blood pressure) carried out by the nursing staff. As most TIVAD implantations were performed in an outpatient setting, patients who received IV sedation were monitored for at least 4 hours post-procedurally until they were deemed safe for discharge.

Implantation techniques

Single-lumen power that are able to withstand high-pressure contrast media injections TIVADs were implanted in the chest. IJV was the preferred venous cannulation site, followed by the external jugular vein (EJV). Smaller profile ports were usually reserved for thin cachectic patients with minimal subcutaneous fat in the infraclavicular region, with the ultimate choice left to the operator.

The following steps were universally adopted during the insertion procedure with minor technical variations between the operators: (1) Preparation. Preliminary ultrasound examination was done to assess the target veins' patency. Surgical skin preparation was performed with ChloraPrep One-Step (2% chlorhexidine gluconate/70% isopropyl alcohol; BD, Wokingham, UK) followed by sterile draping of the procedural field. Povidone iodine was used instead of ChloraPrep in cases of allergy to chlorhexidine or alcohol. (2) Venous access. Venous access was obtained under ultrasound guidance using an 18G needle. A 0.035-inch wire was introduced, and the needle was exchanged for a peel-away sheath. (3) Creation of the subcutaneous port pocket and tunnel. Subcutaneous pocket was created approximately 3 cm below the clavicle, generally

along the mid-clavicular line or slightly lateral. Ideal depth of the pocket should be 5 mm beneath the skin and superficial to the pectoral fascia. (4) Preparation and fixing of the port catheter system. The catheter was pulled through the subcutaneous tunnel with the help of a tunneller. One end of the catheter was connected to the port's exit stem. Anchoring sutures were used (at operators' choice) to anchor the port to the pectoralis fascia with non-resorbable sutures (Prolene; Ethicon, Bridgewater, NJ, US). (5) Introduction of the catheter. The other end of the catheter was trimmed to an appropriate length using fluoroscopic guidance and advanced through the peel-away sheath to the desired position under fluoroscopy. The port system was flushed and locked with 5 mL of 100 units/mL of concentrated heparin sodium solution (terminal flushing). Sodium citrate (4%) was used in patients who were hypersensitive to heparin or had a history of heparin-induced thrombocytopenia. (6) Skin closure. The port pocket was closed either with a bi-layered technique using simple interrupted deep dermal suturing with 2-0 polyglactin resorbable suture (coated Vicryl; Ethicon), followed by running subcuticular sutures with 4-0 polyglactin resorbable suture (coated Vicryl; Ethicon) with application of octyl cyanoacrylate tissue adhesive (Dermabond, Ethicon) for skin closure. However, some operators would forgo the subcuticular sutures and would close the skin with Dermabond after deep dermal suturing with 2-0 polyglactin resorbable suture (coated Vicryl). Steristrips were applied instead of tissue adhesive in cases with a history of cyanoacrylate allergy. The venotomy site was closed with Dermabond or steristrips.

A final fluoroscopic image was obtained to ensure and document the correct positioning of the system and to exclude any catheter-port dissociation or kinking.

Follow-up

A nurse clinician contacted all patients via phone on postoperative day 1 with a standardised questionnaire to check on early complications such as pain, fever, swelling, bruising and bleeding. Video consultations mostly replaced physical attendance during the pandemic, and patients were encouraged to send a photograph of their wounds, especially if there was cause for concern. Any patients who showed symptoms or signs of complications were physically evaluated at a later date.

A standardised workflow was implemented for cases where any issues or complications were encountered during the TIVAD usage. A nurse clinician would initially assess the problem and escalate to a consultant accordingly if a second opinion was required. All consultations, findings and results, including the date and reason for explantation, were recorded on the REDCap registry.

RESULTS

A total of 1180 patients underwent TIVAD implantation between January 2019 and January 2022, with a 100% technical success rate. These patients' baseline demographics are presented in Table 1. The mean dwell duration for the TIVAD was 342 days (SD 223 days; range 3–1911). At the time of data collection (1 February 2022), 83% of patients (n=980) were still using the TIVAD, i.e. in-situ, 13.6 % (n=160) had their TIVAD removed after completion of treatment, 2.1% (n=25) had their TIVAD removed due to infection, 0.6% (n=7) of the TIVAD were removed due to malfunction, 0.6% (n=7) were removed due to port extrusion and 0.1% (n=1) was removed at patient's request.

Table 1. Patients' baseline characteristics.

Characteristics (n=1180)	n	%
Age (years)		
Range	20–90	
Mean	61.9	
Sex		
Female	732	62
Male	448	38
Race		
Chinese	940	79.7
Malay	118	10.0
Indian	66	5.6
Others	56	4.7

The right IJV was the most commonly accessed site (n=986, 83.6%), followed by the left IJV (n=184, 15.6%). The left and right EJV were accessed in 6 (0.5%) and 4 (0.3%) patients, respectively. The mean number of ultrasound-guided passes for accessing the vein was 1.07±0.3, with the majority (94%) successful with a single pass.

The most common position of the catheter tip was the cavoatrial junction (58.4%), followed by the right atrium (36.8%) and then the superior vena cava (SVC) (4.8%).

Anchoring suture was utilised in 37.3 % (n=440) of the cases, with a curvilinear trend in the diminished use of anchoring suture from 63.3% in 2019 to 27.8% in 2021 (P=0.03).

Sedoanalgesia using IV midazolam and fentanyl was administered in 562 patients (47.6%). The rest (n=618, 52.4%) was performed with local anesthesia (LA) only. The range of IV midazolam administered was 0.5–5 mg, with an average dose of 1.2 mg and an SD of 2.3. For IV fentanyl, the range was 10–100 mcg, with an average dose of 15.0 mcg and an SD of 19.1.

The complications related to TIVAD implantation were divided into early (≤30 days after implantation) (Table 2A) and delayed (>30 days) (Table 2B). The most common early post-procedure complications were pain (24.7%), bruising (9.2%) and swelling (3.6%). These were treated symptomatically with analgesics and reassurances that they would resolve with time. Six patients (0.5%) presented with persistent bleeding post-procedure, which resolved with manual compression. Five patients had fevers after the procedure; they were presumed to be due to early TIVAD site infection and treated empirically with broad-spectrum oral antibiotics. One case presented with erythema and mild blistering around the site where Dermabond adhesive was applied. The vigilant attending removed the adhesive cast, and the symptoms resolved with antihistamines and steroid ointment. A patch test later confirmed that the patient had allergic contact dermatitis to the Dermabond adhesive.

Table 2A. Early (≤30-day post-implantation) complications related to TIVAD implantation.

Early related complications	n	%
Early related complications	291	24.7
Bruising	108	9.2
Swelling	42	3.6
Bleeding	6	0.5
Fever	5	0.4
Itchiness	2	0.2
Allergic dermatitis	1	0.1

Infection and failure to use TIVADs were the dominant delayed complications. The spectrum of infection ranged from TIVAD site cellulitis, which was the most common complication presenting with erythema and pain/discomfort (n=45, 3.8%), to catheter-related bloodstream infections (CRBSIs) (n=3, 0.25%). Aggressive antibiotic therapy was instituted in these cases to salvage the TIVAD system. Twenty-five (2.1%) TIVADs were removed due to infection, including those with progressive symptoms of infection, including discharge (n=13, 1.1%) despite antibiotic therapy and those with CRBSIs.

Table 2B. Delayed (>30-day post-implantation) complications related to TIVAD implantation.

Delayed related complications	n	%
TIVAD site cellulitis	45	3.80
Discharge	13	1.10
Skin erosion with device extrusion	7	0.60
Malpositioned catheter (successfully repositioned)	4	0.33
Catheter-related bloodstream infections	3	0.25
Migration of TIVAD leading to catheter dislodgement	3	0.25
Venous thrombosis	3	0.25
Fibrin sheath formation requiring stripping	1	0.10
TIVAD chamber inversion	1	0.10

TIVAD: totally implantable venous access device

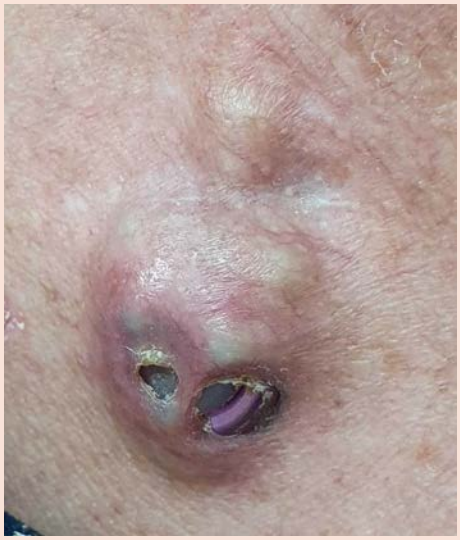
In our cohort, failure to use the TIVAD was mainly due to migration of the catheter (n=7, 0.6%) and skin erosion with extrusion of the TIVAD's septum and reservoir (n=7, 0.6%) (Fig. 1). The catheter was successfully repositioned with the aid of endovascular snares in 4 migration cases, as the tip was still intraluminal (Fig. 2). The other 3 were removed, and a new TIVAD was implanted as the catheter tip had migrated extraluminally.

Venous thrombosis around the catheter was encountered in 3 cases (0.25%). All 3 cases had significant pericatheter thrombus formation; hence, the TIVADs were explanted rather than a trial of thrombolytic agent administration. These patients were started with anticoagulation with low molecular weight heparin, and other means of venous access were obtained. One patient (0.1%) presented with the ability to infuse but could not withdraw blood (withdrawal occlusion due to ball-valve effect). Linogram confirmed the presence of fibrin sheath formation, which was successfully treated with endovascular stripping (Fig. 3). We also report a case of the TIVAD chamber inversion/flip of the TIVAD (0.1%), which happened 50 days after implantation (Fig. 4). The TIVAD was explanted for this case, and a new TIVAD was implanted on the contralateral side with anchoring sutures.

DISCUSSION

TIVAD guarantees a long-term, reliable means of venous access to oncology patients undergoing regular chemotherapy, in whom peripheral venous

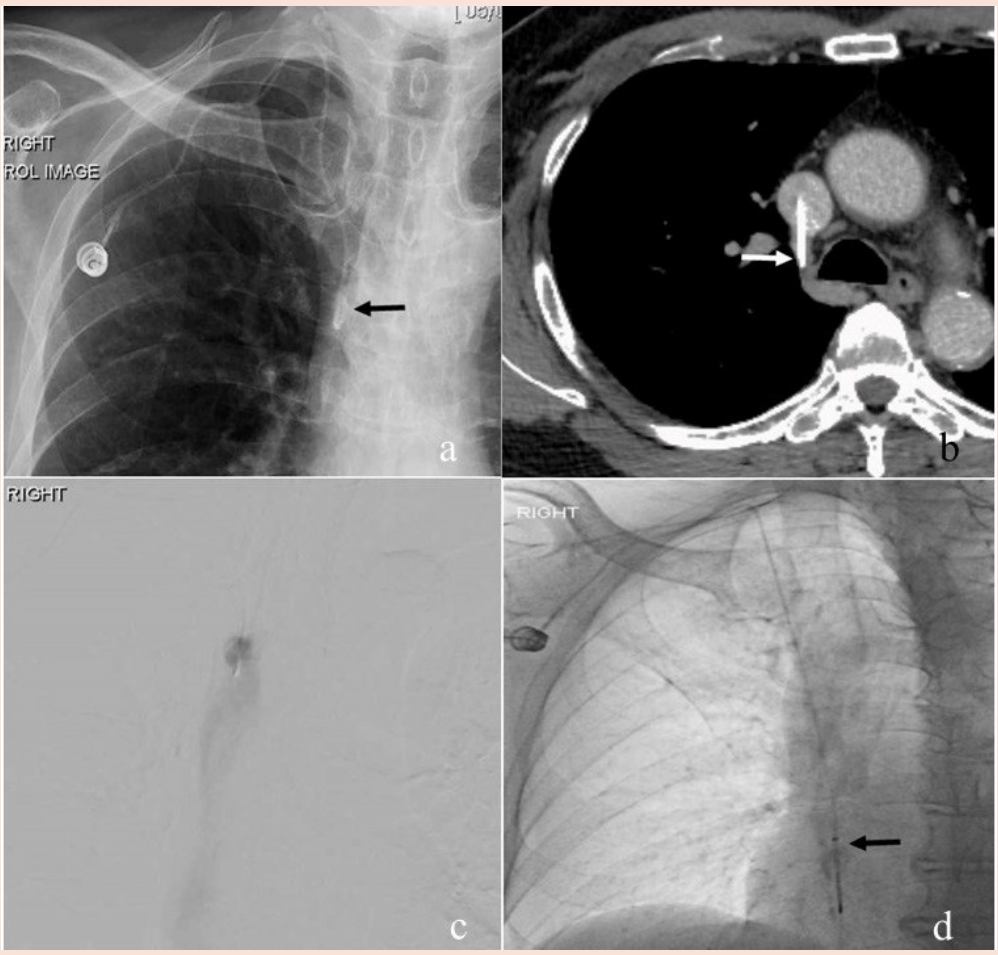
Fig. 1. Skin erosion with resultant partial exposure of the Bard PowerPort's septum and reservoir.



access often becomes increasingly difficult during the regimen. TIVAD provides better patient comfort and quality of life, offering more freedom of activity, requiring less maintenance, having a lower infection rate, longer dwell time and greater cost-effectiveness compared to external venous access catheters.[7,8]

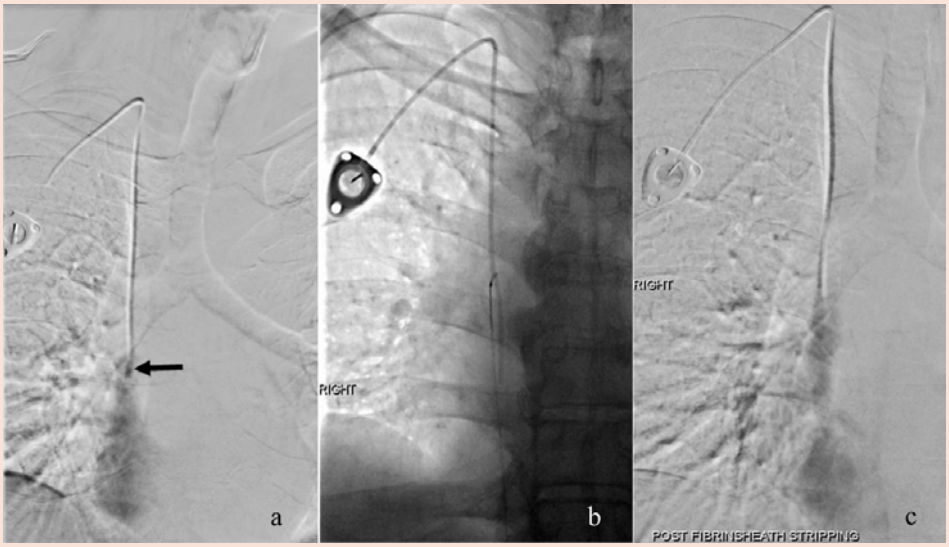
The subcutaneous pocket creation is a critical step in TIVAD implantation, and the operator must ensure that the TIVAD access site, i.e. septum, is not over the skin incision to reduce the probability of skin erosion caused by repeated punctures before adequate healing.[9] Although the reported incidence of skin erosion in literature is up to 1%,[10] this complication necessitates device explantation, as it should be considered infected even when no signs are present. The TIVAD septum should ideally be approximately 5–20 mm beneath the skin, as there is a risk of skin erosion if placed too superficial and an increased risk of difficulty in cannulation

Fig. 2. Migration of the catheter.



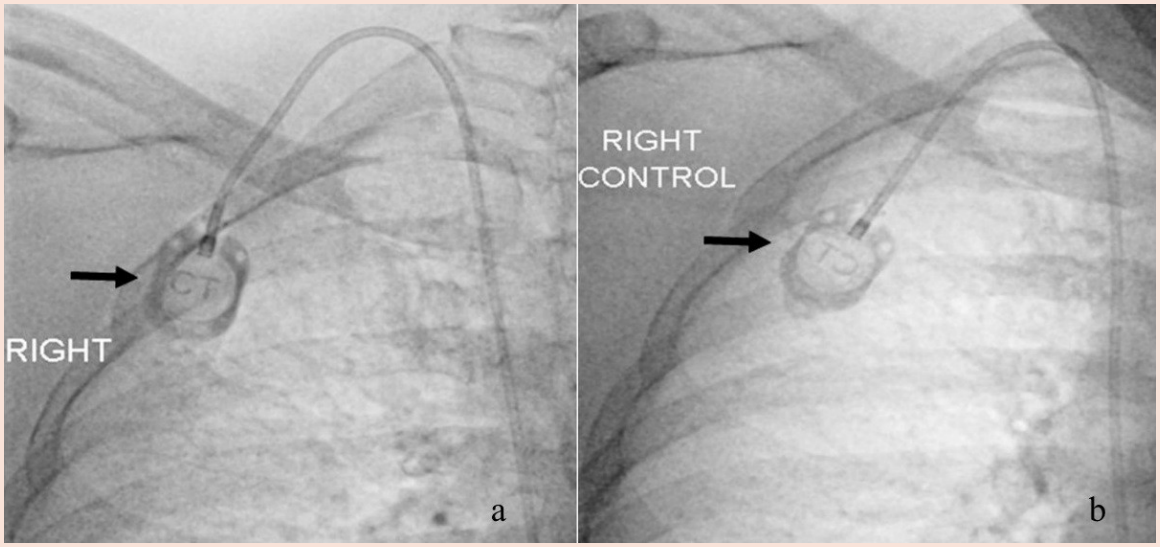
(A) The chest radiograph of a Braun Celsite Babyport shows the distal end of the catheter looping cranially and making a U-turn (arrow). (B) Contrast-enhanced computed tomography (CT) shows the catheter tip has malpositioned into the azygos vein (arrow). (C) Linogram demonstrated a patent catheter within the azygos vein, which was partially opacified. (D) The catheter tip was successfully repositioned back into the cavoatrial junction with an endovascular snare (arrow).

Fig. 3. Pericatheter fibrin sheath formation.



The patient presented with withdrawal occlusion. (A) Control linogram showed a sleeve of fibrin sheath (arrow) around the catheter with opacification of the SVC and right atrium. (B) Endovascular stripping of the fibrin sheath was performed with the aid of a loop snare catheter inserted via a right femoral venous approach. Stripping was accomplished by pulling the closed-loop snare catheter caudally. (C) Post-stripping linogram demonstrates a successful result with the disappearance of the fibrin sheath sleeve and the withdrawal occlusion.

Fig. 4. Inversion of the TIVAD chamber.



(A) Final fluoroscopic image of a Medcomp Dignity CT port. The initials "CT" were printed in reverse with radiopaque ink at the base of the TIVAD chamber (arrow) to signify that it is compatible with power injection for contrast agents. (B) On post-implantation day 50, the attending nurse could not palpate the TIVAD septum for puncture. A subsequent control radiograph demonstrated the reversal of the initials "CT" in keeping with an inversion of the TIVAD chamber. It was explanted, and a new TIVAD was inserted on the contralateral side with fixation sutures.

if placed too deep.[11] Choosing an appropriately sized device is crucial to reducing the risks of skin erosion and subsequent extrusion, as implanting a larger profile device in a thin patient may lead to overstretching of the overlying skin, which eventually thins out due to repetitive punctures.[12]

The right IJV is the most preferred site of access in our cohort. This is due to the straight course that the catheter takes from the point of venous access to the target position of the catheter tip with minimal points of contact to the vessel wall by the catheter, thereby reducing the risk of

venous thrombosis.[6,13] Additionally, jugular access precludes complications unique to subclavian venous access, like pinch-off syndrome, pneumothorax, haemothorax, thoracic duct or brachial plexus injury.[14]

The cavoatrial junction is the optimal location for the catheter's tip as it has a reduced risk of causing arrhythmias compared to the right atrium[15] and a reduced risk of catheter migration/flicking into the contralateral brachiocephalic vein (BCV), IJV or the azygos vein, which can potentially occur when the catheter tip is in the SVC. Technically, we would suggest trimming the catheter slightly longer than the target site when inserting from the left side due to the acute angulations between the left BCV and the SVC and in patients with abundant subcutaneous fat at the pocket site, as the TIVAD system will retract when the patient stands up, and the subcutaneous fat surrounding the TIVAD pocket gravitates inferiorly.[16]

Some earlier conventional techniques for TIVAD placement entail the use of anchoring sutures to prevent TIVAD inversion or rotation.[3,5] We noted a curvilinear trend in the reduced use of such anchoring sutures, with 1 case (0.1%) of port inversion and 3 cases (0.25%) of TIVAD migration leading to complete catheter dislodgement. This exceedingly low incidence of TIVAD inversion is similar to the findings described by McNulty et al.,[17] which stated an incidence ranging between 0 and 1.6% with or without suture fixation and suggested creating an optimal-sized subcutaneous pocket that snugly accepts the port to avert this issue. Sánchez LY et al. even encountered 3 cases of rotations (0.53%) despite using anchoring sutures.[18] From the authors' perspective, avoiding anchoring sutures during TIVAD explantation offers the potential advantages of shorter procedure time and less extensive dissection, as it eliminates the need to ensure complete removal of these nonresorbable sutures similar to other groups.[17]

TIVAD implantation can be performed comfortably with only LA. However, it can be associated with some discomfort and a source of anxiety in some patients. Therefore, monitored conscious sedation and IV analgesia were given for some patients.

Post-procedure pain and minor bruising/ecchymosis around the implantation site are usually expected and will resolve with time. Minor haematomas have been reported in up to 8%.[19] However, the presence of palpable haematoma is more significant as it can lead to difficulties in needling the TIVAD due to the inability to palpate the TIVAD septum. It can also potentially lead to issues with wound healing due to the increased tension in the pocket caused by the accumulation of blood, which also increases the likelihood of abscess formation.[11] Hence, palpable haematomas causing tension at the incision site warrant evacuation by reopening the incision. Therefore, meticulous haemostasis before closure of the TIVAD pocket is paramount to prevent this complication.

A technique employed to minimise bleeding during pocket creation involves using a local anaesthetic combined with a vasoconstrictor, usually adrenaline. Although this reduces the amount of lignocaine needed to get the desired anaesthetic effect, it has effectively reduced bleeding at the operative site. This combination has effectively reduced bleeding and facilitated a safe and efficient surgical experience.[20]

Several studies have investigated the timing of initial chemotherapy administration after TIVAD insertion. A recent study published in the Korean Journal of Clinical Oncology found that chemotherapy administration within 2 days of implantation was safe.[21] Currently, our institution allows TIVAD usage as early as the day following the procedure, provided there are no complications. The duration between TIVAD insertion and the first access for chemotherapy was recorded for 52.6% of the cohort, with a mean duration of 3.4 days and an SD of 2.1. There have been reports of poor wound healing in patients receiving antineoplastic agents targeting the vascular endothelial growth factor (VEGF) signalling pathway. As VEGF-mediated angiogenesis in wound healing mainly occurs 4–14 days after administration, an interval of 14 days has been suggested between administration of VEGF-targeted therapy and TIVAD placement.[22]

The use of prophylactic antibiotics before the implantation of the TIVAD remains controversial. Although these procedures are generally considered clean surgeries, some studies have suggested that prophylactic antibiotics may reduce the risk of surgical site infections.[23] However, other studies have found that the prevalence of surgical site infections following TIVAD implantation is low and that prophylactic antibiotics are unnecessary.[24,25] Nezami et al.,[26] a study in a large cohort of 5967 patients, concluded that prophylactic antibiotics did not prevent short-term implantation-related infection; however, there was a statistically significant risk of infection when TIVADs were placed in an inpatient setting. This was thought to be due to an increased frequency of TIVAD access and a more pathogenic hospital ecosystem.

At Singapore General Hospital, prophylactic antibiotics are routinely administered during TIVAD implantation procedures, which is still perceived as the standard of care. Implantation is avoided in patients with neutropenia (ANC <1500/mcL).[27] Although we should strive to achieve an ideal outcome with a 0% infection rate, our reported infection rate is still low, 3.8% for TIVAD site cellulitis and 0.25% for CRBSIs. These are comparable to the reported incidence of TIVAD-associated infection in literature, ranging from 0.6% to 27%.[28] Besides prophylactic antibiotics and neutrophil counts, we believe that there are other clinical factors, such as diabetes mellitus; type and stage of malignancy, i.e. haematological malignancy; microbial colonisation at the insertion site; and type of chemotherapy used, may play a role in TIVAD-related infection. We hope that a dedicated trial with a detailed subgroup analysis of these factors can be considered as a prospective study in the future.

Catheter-related thrombosis is a known complication of long-term venous access. In an extensive series of 51,049 cancer patients with TIVAD insertion, 1.81% of the patients developed venous thrombosis.[29] Unfortunately, cancer patients have an increased risk of developing venous thrombo-occlusive disease due to their underlying prothrombotic state, with a host of them receiving potentially venotoxic medications, which can lead to endothelial damage. Other factors for increased risk of venous thrombosis are the type of central venous catheters used, insertion into the subclavian vein, longer catheter dwell time, catheter-to-vein ratio and post-insertion care of the catheter system.[30] A systematic review and meta-analysis have also shown that TIVADs are associated with a decreased risk of thrombosis compared to PICCs or external catheters like Hickman catheters.[32]

Our group did not encounter other complications, such as accidental arterial puncture, air embolism, pneumothorax or haemothorax, due to the routine and meticulous use of ultrasound and fluoroscopic guidance during these procedures.

Study limitations

There are some limitations to our study. The patient cohort was from a single tertiary academic institution with a dedicated interventional radiology service and a high volume of TIVAD referrals, which may limit the generalisation of the results. Procedures were performed by a large number (>20) of consultants (with experience varying from <1 year to >25 years) and supervised trainees with a diverse range of skills and knowledge, which can influence the outcome. Further statistical analysis beyond descriptive statistical analysis was not performed due to the low incidence of complications, which limits the capability of this study despite the large sample size.

CONCLUSION

TIVAD or port inserted via the jugular vein under radiological guidance is a safe, convenient and reliable means of long-term venous access, with an acceptable rate and severity of complications and a low rate of device explantation due to these complications.

We aim to increase the awareness and adoption of TIVAD in oncology patients, particularly in Southeast Asia, by sharing these findings and favourable outcomes, and look forward to more robust TIVAD studies from Asia.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (CIRB 2021/2357).

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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REVIEW ARTICLE

Consensus guidelines for the management of treatment-naïve chronic lymphocytic leukaemia in Singapore (2024)

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ABSTRACT

Introduction: Chronic lymphocytic leukaemia (CLL) has a heterogeneous disease course and a variable prevalence across populations. Appropriate management for achieving optimal outcomes requires consideration of multiple factors, including disease-related factors like genomic alterations, patient characteristics and fitness, availability and access to treatments, and logistics/cost. This review aims to provide comprehensive and pragmatic recommendations for the management of treatment-naïve (TN) CLL that are relevant to Singapore's clinical context.

Method: Clinical consensus statements were developed by an expert panel of haematologists from Singapore through a 2-round modified Delphi process. Statements were drafted using recent evidence-based guidelines and published literature. Panel members reviewed draft statements, provided anonymised feedback and proposed modifications where relevant. A physical meeting was held to facilitate discussion, voting and endorsement of the final consensus statements.

Results: The final consensus included 15 statements covering major TN CLL patient subsets. The recommendations highlight the importance of molecular testing for key biomarkers, where available/accessible, to guide initial therapy. Due to the superior efficacy of targeted agents (Bruton's tyrosine kinase inhibitors [BTKis] and B-cell lymphoma 2 inhibitors [BCL2is]) these are favoured over standard chemotherapy or chemotherapy-immunotherapy, especially for patients with del(17p) or *TP53* mutation, and less fit patients.

Conclusion: These consensus statements provide practical recommendations for the current management of TN CLL patients in Singapore and similar healthcare systems based on up-to-date evidence. Regular updates to treatment guidelines are important to ensure responsiveness to emerging evidence and evolving clinical practices and to improve patient outcomes and quality of life.

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Keywords: BTKi, chronic lymphocytic leukaemia, management, treatment algorithm, treatment-naïve

CLINICAL IMPACT

What is New

- This comprehensive, up-to-date clinical consensus for treatment-naïve chronic lymphocytic leukaemia in Singapore emphasises a balanced approach to therapy selection, integrating patient preferences, side-effect profile, cost, accessibility and logistics for informed decision-making.

Clinical Implications

- These recommendations offer a practical treatment algorithm that aligns with Singapore's healthcare system.
- Treatment decision-making requires consideration of multiple factors and this should be recognised when adapting recommendations for different resource settings.

INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is a lymphoid neoplasm characterised by clonal expansion of mature B-lymphocytes and has a characteristic immunophenotypic pattern. CLL prevalence varies considerably across populations. Although CLL is the most common leukaemia in adults in Western

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countries (25–30% of all leukaemia cases), it is much less common among individuals of Asian and Middle Eastern ancestry.[1,2] As most CLL patients are older adults, with median age of onset ranging from 65 to >70 years,[3,4] many will have coexisting conditions that increase their risk of morbidity and mortality from treatment. When selecting the optimal regimen for an individual patient, these factors and other disease and patient-related features (e.g. clinical/disease characteristics, symptoms, genetic risk factors and fitness) should be considered.[5,6]

In Singapore, an estimated 20–30 new cases of CLL are diagnosed annually.[7] Patients may receive treatment at public or private institutions, including specialised haematology centres. Singapore's healthcare system offers a mix of insurance-paid, subsidised, co-pay and self-paying options for patients; thus, treatment decision-making involves consideration of several factors, including availability/access to approved or investigational drugs, companion diagnostics, the experience of the specific treatment centre or team, financial considerations and patient preferences. In terms of access to important diagnostic tests for CLL, this is relatively uniform across the public and private sectors. Financing of outpatient cancer treatment in Singapore is determined by a drug's local approval status, and its inclusion in the Ministry of Health's Cancer Drug List (CDL) based on evaluations of its clinical effectiveness and cost-effectiveness.[8] Patients can receive subsidised access to drugs included in the CDL. With a complex and rapidly evolving treatment landscape, clinicians require practical guidance incorporating up-to-date and emerging clinical evidence. Guidelines from various sources are available but may have greater or lesser applicability to local clinical populations and health systems.[5,6,9,10] This clinical consensus from a panel of experts in Singapore seeks to offer pragmatic recommendations for the management of treatment-naïve (TN) CLL, considering factors relevant to the local clinical population and healthcare setting. Although the panel's recommendations were developed for a primary audience of haemato-oncologists in the Singapore setting, the practice discussed here may be relevant to specialists practising in similar healthcare settings or systems.

METHOD

Two-round modified Delphi process for consensus generation

A modified Delphi process was used to generate consensus for the management of TN CLL. This consensus aims to provide guidance on contemporary treatment options for TN CLL, with consideration of specific patient subpopulations and important clinical outcomes, including but not limited to treatment efficacy. The expert panel comprised 8 haematology oncology specialists with extensive experience in CLL, practising in Singapore's public healthcare institutions (with all 3 public healthcare administrative clusters represented) or in private specialist centres. The modified Delphi process consisted of 2 rounds. A set of provisional statements on CLL management was developed based on a targeted review of recent clinical guidelines for CLL management and available published literature. A steering committee provided guidance and input for drafting the consensus statements and revising them based on the panel's feedback.

The evidence base for these recommendations includes pivotal studies on CLL management, as identified in recent evidence-based guidelines (European Society for Medical Oncology [ESMO], Canadian evidence-based guidelines for CLL [2022 update], and National Comprehensive Cancer Network [NCCN] Guidelines version 3.2023).[10-13] Literature relevant to first-line CLL treatment was considered, including primary and follow-up publications for key trials. An adapted version of the evidence grading system employed for the Pan-Asian adapted ESMO clinical practice guidelines for non-small-cell lung cancer[14] was used to define the level of evidence available for each statement proposed (I: at least 1 large randomised controlled trial of good methodological quality—low potential for bias—or meta-analyses of well-conducted randomised trials without heterogeneity; II: small randomised trials or large randomised trials with a suspicion of bias—low methodological quality—or meta-analyses of such trials or of trials with demonstrated heterogeneity). Following the development of this consensus in 2023, updates to guidelines from ESMO and NCCN (2024) became available and are summarised in Supplementary Table S1.[15,16]

The 17 statements covered 5 major areas: (1) general principles of management for TN CLL; (2) treatment of patients with deletion 17p [del(17p)] or tumour protein 53 *(TP53)* mutation; (3) treatment of fit, immunoglobulin heavy chain *(IGHV)* mutated patients without del(17p) or *TP53* mutation; (4) Treatment of unfit, *IGHV*-mutated patients without del(17p) or *TP53* mutation; and (5) treatment of *IGHV*-unmutated patients without del(17p) or *TP53* mutation.

Data collection and consensus classification

In round 1, the statements and supporting evidence were presented to panel members for input. Responses were collected anonymously using an

electronic survey form. Panel members were asked to respond within 2 weeks, with email reminders as required. For each statement, panel members rated their level of agreement on a 5-point Likert scale: (1) "accept completely"; (2) "accept with minor changes"; (3) "accept with major changes required"; (4) "reject with major changes required"; (5) "reject completely". If panel members selected options 2–5, they were asked to elaborate on the reasoning for their response and their suggestions for modifying the statement and could propose the addition of other relevant supporting references. A statement was deemed to have achieved consensus when ≥80% of the panel voted "1" or "2" (accept completely or with minor changes). Statements that did not achieve consensus in round 1 were modified based on panel members' input and presented for discussion and voting in round 2.

Round 2 consisted of a moderated face-to-face meeting in Singapore on 26 October 2023. The round 1 voting results and the panel's consolidated input on the statements were presented. This was followed by a moderated discussion to clarify the clinical reasoning for different viewpoints and provide opportunities for alignment. Statements that did not achieve consensus in round 1 were refined after the discussion and presented for a final round of voting and endorsement by the panel members.

RESULTS AND DISCUSSION

Seventeen provisional statements were presented for the panel's input and voting in round 1. Consensus was reached on 14 out of 17 statements (82.3%) in round 1. The 3 statements that did not reach consensus were presented for discussion and refinement before the final voting process in round 2. After discussion, the panel agreed to omit 1 statement from consideration for the consensus. The remaining 2 statements were refined based on the panel's input, and consensus was reached on both modified statements (2 out of 2, 100.0%) during round 2. Overall, consensus was achieved on 15 statements (≥80% voted "1" or "2" to accept completely or with minor changes). The final consensus statements are shown in Table 1. The corresponding algorithm for TN CLL is illustrated in Fig. 1. The following sections cover the clinical reasoning and supporting evidence for the final consensus statements.

General principles of treatment

Early-stage and asymptomatic CLL

CLL is a heterogenous disease with a variable clinical course. A subset of CLL patients can live with their disease without needing any active treatment over the course of their life, while other patient subsets require treatment and exhibit poor overall survival (OS) and progression-free survival (PFS) even with multiple therapeutic interventions.[17] Only 5% of CLL patients require treatment at diagnosis.[17] Table 2 provides an overview of the suggested clinical workup for newly diagnosed CLL in routine practice settings, as per iwCLL criteria.[18] For most patients, active surveillance (i.e. watchful waiting) is considered appropriate until there are signs of active disease, as defined by iwCLL criteria.[18] In line with iwCLL criteria, the authors recommend initiating treatment only for symptomatic patients.[18] For asymptomatic patients or those not meeting iwCLL treatment criteria, any concurrent conditions, such as autoimmune haemolytic anaemia or immune thrombocytopenia, should be investigated and addressed prior to considering CLL-specific therapy. All international guidelines support this approach of watchful waiting in asymptomatic disease.

Several clinical trials have sought to address whether active treatment with monotherapy or combinations offers meaningful benefit for early-stage asymptomatic patients with CLL, particularly those at a higher risk of disease progression. These include trials of fludarabine monotherapy (CLL-1),[19] fludarabine, cyclophosphamide and rituximab (FCR; CLL7)[19] and ibrutinib (CLL12).[20] However, none of these trials demonstrated OS benefit with active treatment versus (vs) active surveillance for asymptomatic early-stage CLL in patients with high-risk genetic profiles, i.e. *TP53* mutation or del(17p). With the continuing development of additional novel targeted agents, there has been interest in re-evaluating the benefits of early therapeutic intervention. Several phase II/III trials comparing early intervention using newer targeted agents with watchful waiting are ongoing, including acalabrutinib-venetoclax (PreVent-ACaLL, NCT03868722),[21] acalabrutinib with or without obinutuzumab (NCT03516617)[22] and venetoclax-obinutuzumab (EVOLVE, NCT04269902).[23] Considering the available evidence, the authors favour the current standard approach of monitoring early-stage asymptomatic patients with CLL until there is evidence of disease progression and/or symptoms[18] (see statement 1 in Table 1).

Pre-treatment testing

Due to the heterogeneous characteristics of CLL, pre-treatment testing of molecular biomarkers is considered valuable for guiding patient counselling, prognosticate disease and subsequent disease management.[9,18] Cytogenetic aberrations (assessed using fluorescence in situ hybridisation, or FISH) and the somatic hypermutation (SHM) status of the *IGHV*

Table 1. Final list of consensus statements.

Statement no.	Statement	Level of evidence[a]	Evidence	% agreement (voted "1" or "2")[b]	Consensus achieved in
General principles of treatment					
1	For treatment-naïve CLL patients who do not meet the iwCLL 2018 criteria for initiation of therapy, a watchful waiting approach is recommended.	I	CLL12, iwCLL guidelines 2018	100.0%	Round 1
2	Besides FISH testing for del(17p), it is important to evaluate *TP53* and *IGHV* mutational status to guide appropriate treatment choices.	N.A.	iwCLL guidelines 2018, NCCN CLL/SLL guidelines version 3.2023, ESMO guidelines, ERIC recommendations	100.0%	Round 1
3	In general, and where equally available, novel targeted agents are preferred over CIT. CIT may be a reasonable option for patients who are fit, *IGHV*-mutated, without del(17p) or *TP53* mutation after appropriate counselling on increased risk of acute haematological toxicity, infection and small increased risk of secondary myeloid malignancies. *Note: applies to all subpopulations; subpopulation-specific statements included under respective sections*	I	CLL14, E1912, ELEVATE-TN, Alliance A041202, ECOG ACRIN	100.0%	Round 1
4	In general, where novel agents are to be used, the choice between continuous (e.g. BTKi therapy) or time-limited therapy (e.g. V+O or upcoming combinations) should be based on careful consideration of factors including genomic alterations, side-effect profile, patient preferences, comorbidities and medications, logistics and cost, as well as physician judgement.	N.A.	NCCN CLL guidelines version 3.2023	100.0%	Round 1
5	Where continuous treatment is selected, second-generation BTKis (acalabrutinib or zanubrutinib) may be preferred to first-generation BTKis (ibrutinib) based on their side effect profile. Where acalabrutinib is selected, it can be used alone or combined with obinutuzumab. *Notes:* *This statement applies to the following subpopulations:* *- patients with del(17p) or TP53 mutation* *- unfit, IGHV-mutated patients without del(17p) or TP53 mutation* *- IGHV-unmutated patients without del(17p) or TP53 mutation*	II	ELEVATE-TN, SEQUOIA, NCCN CLL/SLL guidelines version 3.2023, ESMO guidelines 2020 *Note: No head-to-head comparisons in the TN setting.*	100.0%	Round 1

Table 1. Final list of consensus statements. (Cont'd)

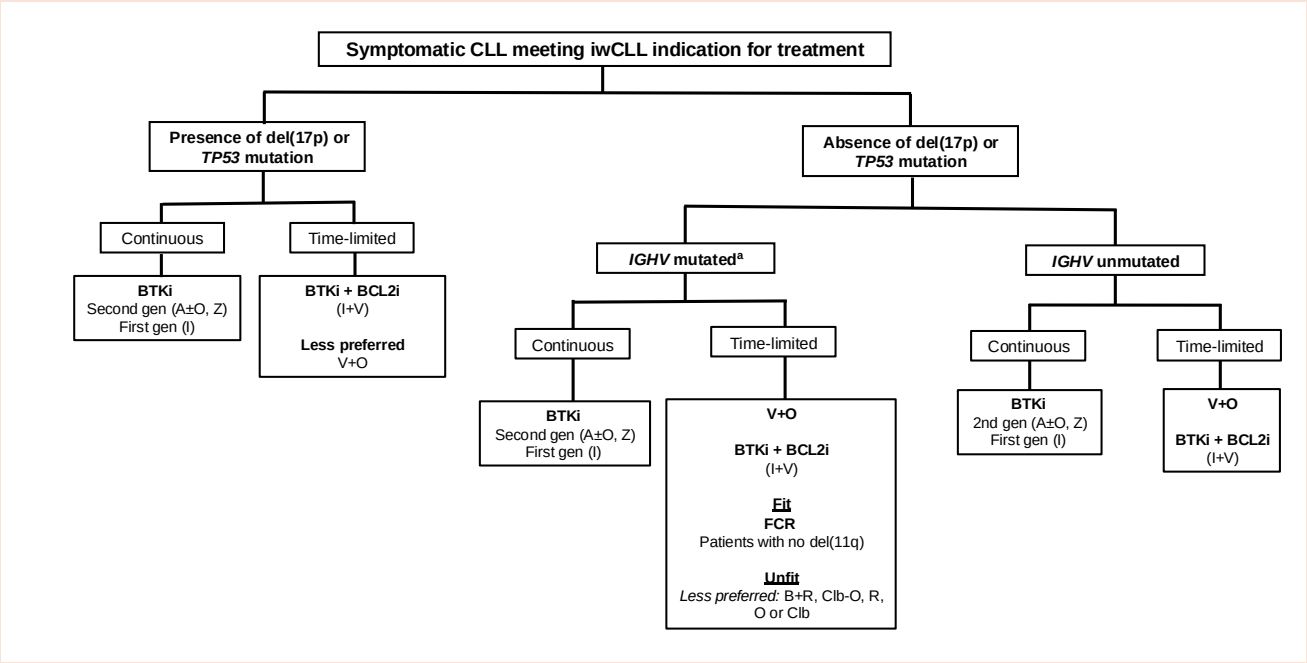
Statement no.	Statement	Level of evidence[a]	Evidence	% agreement (voted "1" or "2")[b]	Consensus achieved in
Treatment in patients with del(17p) or *TP53* mutation					
6	Novel targeted agents (within either continuous or time-limited treatment regimens) are recommended for patients with del(17p) or *TP53* mutation; the choice of novel agent(s) should be based on careful consideration of factors including patient preferences, side effect profile, comorbidities and medications, logistics and cost, as well as physician judgement.	I	iLLUMINATE, CLL14	100.0%	Round 1
7	For time-limited treatment for young patients with del(17p) or *TP53* mutation, a BTKi+BCL2 inhibitor combination may be considered, accepting heightened risks of hypertension and low but not insignificant risk of cardiac arrhythmia. *Note: The only currently approved combination is I+V in Singapore, Europe and Canada. More evidence on other BTKi+BCL2i combinations are expected as survival data from ongoing trials mature (e.g. A+V±O: AMPLIFY, Z+V: SEQUOIA).*	I	CAPTIVATE	100.0%	Round 1
8	Time-limited V+O combination is less preferred for patients with del(17p) or *TP53* mutation, but may be an option for patients preferring time-limited treatment, after careful counselling of higher risk of progression after time-limited treatment.	I	CLL14, CLL14 follow-up	100.0%	Round 1
Treatment in *IGHV*-mutated patients without del(17p) or *TP53* mutation					
9	Recommended treatment options for fit, *IGHV*-mutated patients without *TP53* mutation, del(17p) are single agent BTKi (first gen), FCR [patients with no del(11q)], V+O or BTKi+BCL2 inhibitor combination, the choice of which should be based on careful consideration of factors including patient preferences, side effect profile, comorbidities and medications, logistics and cost, as well as physician judgement, after appropriate counselling on high rates of haematological toxicity, infection, and small increased risk of secondary myeloid malignancies.	I	CLL8, CLL13 (GAIA), RESONATE-2, ECOG, ALLIANCE, E1912 and E1912 long-term follow-up	87.5%	Round 1
10	If CIT is selected, FCR is the preferred CIT regimen in fit patients without *TP53* mutation, del(17p) or del(11q) and *IGHV* mutated.	I	CLL10, CLL8 and follow-up data	100.0%	Round 2

Table 1. Final list of consensus statements. (Cont'd)

Statement no.	Statement	Level of evidence[a]	Evidence	% agreement (voted "1" or "2")[b]	Consensus achieved in
12	If time-limited treatment is selected, V+O or I+V is the preferred treatment option in unfit, *IGHV*-mutated patients without del(17p), or *TP53* mutation.	I	CLL14	100.0%	Round 1
13	After V+O or I+V, the next preferred time-limited treatment options for unfit, *IGHV*-mutated patients without del(17p), or *TP53* mutation include B+R, Clb+O, single-agent rituximab, single-agent obinutuzumab or single-agent chlorambucil.	I	RO5072759 [GA101], CLL14, GAGE, CLL5, Rituximab Phase II trial, NCCN CLL/SLL guidelines Version 3.2023	100.0%	Round 2
Treatment in *IGHV*-unmutated patients without del(17p) or *TP53* mutation					
14	Novel targeted agents (continuous or time-limited) are recommended for *IGHV*-unmutated patients without *TP53* mutation, or del(17p); the choice of novel agent(s) should be based on careful consideration of factors including patient preferences, side effects, comorbidities and medications, logistics and cost, as well as physician judgement.	I	RESONATE-2, ELEVATE-TN, SEQUOIA, CLL 14 and follow-up data, GLOW	100.0%	Round 1
15	If time-limited treatment is selected, V+O or I+V combination is preferred for *IGHV*-unmutated patients without del(17p) or *TP53* mutation.	I	CLL14	100.0%	Round 1

[a] Level of evidence: I — Evidence from at least 1 large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity; II — Small randomised trials or large randomised trials with a suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
[b] Level of agreement: 1 — "accept completely", 2 — "accept with minor changes"
A: acalabrutinib; B: bendamustine; BCL2: B-cell lymphoma 2; BTKi: Bruton's tyrosine kinase inhibitor; C: cyclophosphamide; CIT: chemoimmunotherapy; Chl: chlorambucil; CLL: chronic lymphocytic leukaemia; ESMO: European Society for Medical Oncology; ERIC: European Research Initiative on CLL F: fludarabine; FISH: fluorescence in situ hybridisation; I: ibrutinib; IGHV: immunoglobulin heavy chain gene; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; O: obinutuzumab; R: rituximab; R1: Round 1; R2: Round 2; SLL: small lymphocytic lymphoma; TN: treatment-naïve; TP53: tumour protein p53; V: venetoclax; Z: zanubrutinib

Fig. 1. Algorithm for treatment-naïve CLL.



Treatment should be initiated for symptomatic patients who meet iwCLL criteria. For patients with a high-risk profile—e.g. del(17p)/*TP53* mutation, unmutated *IGHV*—regimens containing active targeted agents should be prioritised. The choice of treatment regimen should be based on careful consideration of a range of factors including genomic alterations, side-effect profile, patient preference, comorbidities and medications, logistics and cost, as well as physician judgement.

[a] A subset of IGHV-mutated patients (stereotyped B-cell receptor (BCR) Subset 2) exhibit an aggressive clinical course and poor prognosis and should be treated similarly to patients with high-risk genetic profiles, i.e. *TP53* mutation or del(17p).

A: acalabrutinib; B: bendamustine; BCL2i: B-cell lymphoma 2 inhibitor; BTKi: Bruton's tyrosine kinase inhibitor; Clb: chlorambucil; CIRS: Cumulative Illness Rating Scale; CLL: chronic lymphocytic leukaemia; CrCl: creatinine clearance; gen: generation; I: ibrutinib; IGHV: immunoglobulin heavy chain gene; iwCLL: International Workshop on Chronic Lymphocytic Leukaemia; O: obinutuzumab; R: rituximab; V: venetoclax; Z: zanubrutinib

gene (assessed using Sanger sequencing or next-generation sequencing) are important biomarkers that provide both prognostic and predictive information in CLL.[18,24-26] Patients with del(17p) or *TP53* mutation show poor responses to chemoimmunotherapy (CIT) but respond better to targeted agents.[18,27-29] In general, patients with unmutated *IGHV* (defined as <2% somatic hypermutation relative to the germline sequence) have a poorer prognosis than those with mutated *IGHV* due to faster tumour cell regrowth kinetics.[9,30] An exception is the B-cell receptor (BCR) stereotyped subset 2, representing 3% of CLL cases; although appearing *IGHV*-mutated in terms of SHM status, this subset is characterised by an aggressive clinical course and a poor prognosis.[31,32]

The authors acknowledge the key factors of availability, accessibility and affordability in facilitating the uptake of molecular testing. A recent Asian consensus highlighted that resources for *IGHV* mutation testing are scarce in several Asian countries.[9] As *IGHV* mutational status does not change over time, *IGHV* mutational testing can be done at the time of diagnosis. In contrast, cytogenetic testing should be conducted pre-treatment, as these aberrations may accumulate over the course of the disease[18] (see statement 2 in Table 1).

Patient fitness

Patient fitness has been an important consideration for treatment selection, notably in the context of chemotherapy and CIT regimens. In clinical trials, the Cumulative Illness Rating Scale (CIRS) and creatine clearance (CrCl) are often used in combination to define patients' fitness to receive CIT.[33,34] Fit patients are commonly defined as those aged <65 years with a CIRS score <6 and CrCl ≥70 mL/min.

In real-world practice, the assessment of fitness has evolved from focusing on chronological age to considering the patient's physical condition and comorbidities. As such, comprehensive geriatric assessments and frailty indices may support a more nuanced evaluation of fitness and may be helpful in specific cases. That said, the CIRS remains practical and highly relevant in clinical settings as a well-established, standardised approach and judgements based on the CIRS and CrCl criteria are easily aligned with clinical trial data.

Table 2. Overview of clinical workup for newly diagnosed chronic lymphocytic leukaemia in routine practice settings.

	Recommendations (as per iwCLL 2018 guidelines)[18] and notes
Diagnosis	
Blood tests	CBC with different count • (≥5×10^9/L B lymphocytes in the peripheral blood for at least 3 months)
Immunophenotyping	Flow cytometry analysis of peripheral blood to confirm • Expression of CD19, CD20, CD23 • CD5 co-expression • Expression of kappa or lambda immunoglobulin light chains
Before treatment	
Medical history and physical examination	• Complete physical examination, including evaluation of lymph nodes, liver and spleen • Performance status (ECOG) • Comorbidities
Laboratory studies	• CBC with differential count • Serum chemistry (liver and kidney function) • Serum immunoglobulin levels • Direct antiglobulin test • Infectious disease status (e.g. cytomegalovirus, hepatitis B virus or hepatitis C virus)
Imaging	• Chest radiograph
Other tests	
Cytogenetics and molecular genetics studies	• Interphase FISH tests for del(13q), del(11q), del(17p), trisomy 12 in peripheral blood lymphocytes • *TP53* mutation analysis • *IGHV* mutational status

CBC: complete blood count; CLL: chronic lymphocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; FISH: fluorescence in situ hybridisation; iwCLL: International Workshop on CLL; TP53: tumour protein p53; IGHV: Immunoglobulin heavy chain gene

Treatment with novel targeted agents

Multiple studies have demonstrated the superior efficacy of novel targeted agents for TN symptomatic CLL, and these agents are now considered the standard of care in several healthcare systems.[5,6,10,11,35] Targeted agents Bruton's tyrosine kinase inhibitors (BTKis, such as ibrutinib, acalabrutinib and zanubrutinib) and B-cell lymphoma 2 inhibitors (BCL2is, such as venetoclax).[36] CIT, the previous standard of care, may be a reasonable treatment option under certain circumstances, as discussed in later sections. However, CIT would not be considered for subgroups expected to show poor response to CIT, including patients with del(17p), *TP53* mutations and the BCR stereotyped subset 2 (i.e. poor prognosis CLL subset characterised by *IGHV3-21* gene expression with a short immunoglobulin heavy chain complementarity determining region 3, and a progressive phenotype regardless of *IGHV* mutational status[37]). Pivotal randomised controlled trials (RCTs) of frontline therapies for CLL are summarised in Table 3. Most of these RCTs enrolled patients aged ≥65 years or unfit patients aged ≥18 years to <65 years, except for ALLIANCE A041202, which included only patients aged ≥65 years.[38]

Clinical trials of first-generation (i.e. ibrutinib) and second-generation BTKis (i.e. acalabrutinib and zanubrutinib) have demonstrated the superior efficacy of these targeted agents over standard CIT regimens for TN CLL. In the E1912 trial, the ibrutinib-rituximab combination demonstrated superior PFS (hazard ratio [HR] 0.35, 95% confidence interval [CI] 0.22–0.56) and OS (HR 0.17, 95% CI 0.05–0.54) compared with the FCR regimen in fit, young patients (<70 years) with TN CLL without del(17p).[39] In the ALLIANCE A041202 trial, ibrutinib alone (HR 0.39, 95% CI 0.26–0.58) and ibrutinib-rituximab (HR 0.38, 95% CI 0.25–0.59) both demonstrated superior PFS to bendamustine-rituximab (BR) in TN CLL patients ≥65 years; however, the OS duration was similar across the treatment arms.[40] Notably, the incidence of grade ≥3 hypertension and atrial fibrillation adverse events (AEs) was significantly higher with ibrutinib-containing regimens than with CIT (P<0.05) in ALLIANCE.[40] The ELEVATE-TN trial showed that acalabrutinib, with or without obinutuzumab, significantly prolonged PFS vs obinutuzumab-chlorambucil in elderly and generally less fit patients (CIRS score >6 or reduced creatinine clearance).[38] No cardiac AEs were reported with acalabrutinib-containing regimens in ELEVATE-

Table 3. Pivotal studies for treatment-naïve CLL.

Study	Population[a]	Design	PFS benefit for experimental arm?	OS benefit for experimental arm?
Alliance A041202 (phase 3)[40]	Fit, older patients (>65 years), del(17p) allowed	BR vs Ibru vs IR	YES, IR superior 2-year PFS rate: 74% (BR) vs 87% (I) vs 88% (IR)	NO 2-year OS rate: 95% (BR) vs 90% (I) vs 94% (IR)
CLL5 (phase 3)[66]	Treatment-naïve, ≥65, Binet stage C, ECOG 0–2	F vs Clb	NO 19 months for F vs 18 months for Clb	NO 46 months for F vs 64 months for Clb
CLL8 (phase 3)[29]	Treatment-naïve, physically fit, age 30–80, CD20+	FC vs FC+R	YES, FC+R superior 3-year PFS rate: 65% (FCR) vs 45% (FC)	NO not reached for FCR vs 86.0 months for FC
CLL10 (phase 3)[76]	Treatment-naïve, physically fit, age 30–80, no del(17p)	FCR vs BR	YES, FCR superior PFS 41·7 months BR and 55·2 months	NO
CLL12 (phase 3)[20]	Treatment-naïve, Binet stage A, ECOG 0–2	Observational: no treatment Treatment: I vs placebo	YES 3-year PFS rate: 80.9% (Ibru) vs 28.5%	-
CLL13 (GAIA) (phase 3)[57]	Fit, no *TP53* aberrations	CIT: FCR or BR V combinations: VR vs VO vs VO+I	YES, VO+I most superior 3-year PFS rate: 90.5% (VO+I) vs 87.7% (VO) vs 80.8% (VR) vs 75.5% (CIT)	NO 3-year OS rate: 95.3% (VO+I) vs 96.3% (VO) vs 96.5% (VR) vs 95.0% (CIT)
CLL14 (phase 3)[47]	Unfit (CIRS >6 or CrCl <70)	VO vs Clb-O	YES, VO superior 3-year PFS rate: 82% (VO) vs 50% (Clb-O)	NO 24-month OS rate 92% (VO) vs 93% (Clb-O)
CAPTIVATE (phase 2)[55]	Treatment-naïve, ≥70 years	I+V	YES 24-month PFS rate 95%	YES 24-months OS rate 98%
E1912 (phase 3)[39,59]	Fit, no del(17p)	FCR vs I+R	YES, IR superior 3-year PFS rate: 73% (FCR) vs 89% (IR)	YES 3-year OS rate: 92% (FCR) vs 99% (IR)
GAGE[77]	Treatment-naïve CLL	O 1000 mg vs 2000 mg	YES, but not superior	-
ELEVATE-TN (phase 3)[38,41]	Unfit (CIRS >6 or CrCl <70)	A vs A+O vs Clb-O	YES. A+O superior Estimated 24-month PFS rate: 93% (A+O) vs 87% (A) vs 47% (Clb-O)	YES Estimated 24-month OS rate: 95% (A+O) vs 95% (A) vs 92% (Clb-O)

Table 3. Pivotal studies for treatment-naïve CLL. (Cont'd)

Study	Population[a]	Design	PFS benefit for experimental arm?	OS benefit for experimental arm?
FLAIR (phase 3)[58]	Treatment-naive, fit to receive FCR, age 18-75, WHO performance status ≤2, and treatment required from iwCLL criteria	I+V vs I vs FCR	YES. I+V superior to FCR. Estimated 3-year PFS rate: 97.2% (I+V) vs 76.8% (FCR)	YES 3-year OS rate: 98.0% (I+V) vs 93.0% (FCR)
GLOW (phase 3)[48]	≥65 years OR CIRS >6	I+V vs Clb-O	YES, I+V superior Estimated 30-month PFS rate 80.5% (I+V) vs 35.8% (Clb-O)	NO
HDMP+R[78]	Treatment-naïve	HDMP+R	YES PFS 30.5 months	YES 3-years OS rate 96%
iLLUMINATE (phase 3)[61]	Unfit (CIRS>6 or CrCl<70) or *TP53* del/mut	I+V vs Clb-O	YES Estimated 30-month PFS rate 79% (I+V) vs 31% (Clb-O)	NO Estimated 30-month OS rate: 86% (I+V) vs 85% (Clb-O)
RESONATE-2 (phase 3)[60]	≥65 without del(17p)	I vs Clb	YES 5-year PFS rate: 70% (I) vs 12% (Clb)	YES 5-year OS rate: 83% (I) vs 68% (Clb)
Rituximab (phase 2)[65]	Treatment-naïve	R	YES 1- and 2-year PFS rates were 62% and 49%, respectively	YES
RO5072759 [GA101] (phase 3)[64]	Treatment-naïve, CIRS >6	Clb-O vs Clb vs Clb-R	YES, Clb superior Median PFS 26.7 months (Clb-O) vs 11.1 months (Clb) vs 16.3 months (Clb-R)	YES OS rate 9% (Clb-O) vs 20% (Clb) vs 15% (Clb-R)
SEQUOIA (phase 3)[42]	Untreated, ≥65 years, ECOG 0–2	Z vs BR	Median PFS not reached in either arm. Z showed longer PFS.	NO Estimated 24-month OS rate 94·3% (Z) vs 94·6% (BR)

[a] Fit patients are defined as those aged <65 years with a CIRS score <6 and CrCl ≥70 mL/min

A: acalabrutinib; B: bendamustine; Clb: chlorambucil; CLL: chronic lymphocytic leukaemia; CIT: chemoimmunotherapy; CrCl: creatine clearance; CIRS: Cumulative Illness Rating Scale; C: cyclophosphamide; ECOG: Eastern Cooperative Oncology Group; F: fludarabine; HDMP: high-dose methylprednisolone; FCR: fludarabine + cyclophosphamide + rituximab; I: ibrutinib; iwCLL: International Workshop on CLL; PFS: progression-free survival; O: obinutuzumab; OS: overall survival; R: rituximab; V: venetoclax; WHO: World Health Organization; Z: zanubrutinib

TN.[38] The efficacy and safety of acalabrutinib, with or without obinutuzumab, were maintained at 6 years of follow-up. Estimated 72-month PFS rates were 78% for acalabrutinib-obinutuzumab, 62% for acalabrutinib monotherapy and 17% for obinutuzumab-chlorambucil.[41] The median OS was not reached in any treatment arm and was significantly longer on acalabrutinib-obinutuzumab vs obinutuzumab-chlorambucil.[41] The SEQUOIA study demonstrated superior PFS for zanubrutinib vs BR in TN CLL patients >65 years, with the rates of grade ≥3 cardiac events being similar across treatment arms.[42] BTKis carry a possible risk for cardiac toxicity, as noted in studies on ibrutinib, although this risk is lower with second-generation agents (e.g. acalabrutinib, zanubrutinib). Clinicians should weigh the risks and benefits accordingly. Recent analyses, including a 3-year real-world study, reported a more favourable cardiovascular safety profile including lower rates of atrial flutter, hypertension and sepsis in patients treated with acalabrutinib vs ibrutinib.[43] Safety analyses using FDA Adverse Event Reporting System (FAERS) data highlighted that ibrutinib carries a higher incidence of severe cardiovascular events, notably atrial fibrillation, cardiac failure, pericardial effusion or haemorrhage, underscoring the need for careful patient selection and toxicity monitoring with long-term therapy.[44,45]

Similarly, BCL2i-containing regimens were superior to CIT comparator regimens in TN CLL patients with coexisting conditions. In the CLL14 study, unfit patients with CIRS score >6 venetoclax-obinutuzumab for a fixed duration of 1 year demonstrated a significantly lower risk of progression than those receiving chlorambucil-obinutuzumab (HR 0.35, 95% CI 0.23–0.453).[46] The reduced risk of progression with venetoclax-obinutuzumab was maintained at 2 years after treatment cessation (HR 0.31, 95% CI 0.22–0.44).[47] Several trials, including CAPTIVATE and GLOW, have assessed the effects of combining a BCL2i with a BTKi.[48,55] In GLOW, treatment with a fixed-duration combination of venetoclax plus ibrutinib significantly reduced the risk of progression compared with chlorambucil-obinutuzumab (HR 0.22; 95% CI 0.13–0.36; $P<0.001$).[48]

Targeted agents are now generally preferred over CIT because of their superior efficacy (see statement 3 in Table 1). In higher-risk TN CLL patients, i.e. unmutated or with del(17p) or *TP53* mutation, CIT is generally not recommended, given the significantly inferior outcomes compared with BTKi or BCL2i-based therapy. CIT may be considered for TN CLL patients who are fit and have low-risk disease, i.e. mutated *IGHV*, without del(17p) or *TP53* mutation, after careful consideration of side-effects side effects associated with CIT—such as increased risk of acute haematolo-gical toxicity and infection, and a small increased risk of secondary myeloid malignancies.[49,50]

Important considerations for selecting initial therapy in CLL include genetic risk, side-effect profile, clinical characteristics in a patient (overall fitness/performance, organ function, comorbidities), patient preference (e.g. if there is a choice between continuous or time-limited therapy, or method of administration, such as intravenous injections), cost, accessibility and logistical concerns. Additionally, physician and centre experience managing treatment-related side effects may influence treatment selection. Resource availability at the system level, including access to specific drugs and diagnostic tests, may also be a relevant consideration. Treating physicians should consider all these aspects and carefully counsel their patients to support informed decision-making as appropriate within their local context (see statement 4 in Table 1).

Treatment in patients with del(17p) or *TP53* mutation

The presence of *TP53* aberrations or del(17p) has historically been associated with poor prognosis,[27,29] with a median PFS of 11.3 months on FCR therapy.[51] The introduction of small-molecule inhibitors (BTKis and BCL2is) significantly improved PFS among previously untreated patients with del(17p) or *TP53* mutation,[38,40,46] and these targeted agents are now considered the standard of care for this patient subset.

A pooled analysis of 4 trials (PCYC-1122e, RESONATE-2, iLLUMINATE and E1912) included 89 patients with del(17p) or *TP53* mutation receiving single-agent ibrutinib (n=45) or ibrutinib in combination with an anti-CD20 antibody (n=44). In this analysis, median PFS was not reached at 4 years of follow-up, and the estimated 4-year PFS and OS rates were 79% and 88%, respectively.[52] Direct comparisons between continuous BTKi therapy vs time-limited targeted agent-based combinations are not available as the head-to-head trials are ongoing (e.g. CLL17/NCT04608318). However, there are indications that continuous BTKi therapy may confer longer PFS than time-limited regimens. While exercising caution in drawing inferences from cross-trial comparisons, at 76.4 months of follow-up in the CLL14 study for 10% of patients with del(17p) or *TP53* mutation,[46] patients treated with fixed-duration venetoclax-obinutuzumab had a median PFS of 51.9 months.[53] The 5-year PFS for del(17p) or *TP53* mutated patients was 40.6%, and the approximate 4-year estimated PFS was 52%.[54] Other highly-anticipated readouts include longer-term follow-up data for ibrutinib-venetoclax

time-limited treatment regimens. Several factors are relevant when choosing between continuous BTKi-based therapy and time-limited therapy with venetoclax combinations. Time-limited therapy can potentially produce complete responses[42] and allows for treatment-free intervals, which some patients may prefer. With finite treatment duration, there may be reduced risk of toxicity and potentially lower drug-related costs. However, these potential advantages must be weighed against additional requirements for safety monitoring (risk of tumour lysis syndrome) and dose ramp-up, which have logistical implications.

Available evidence indicates that second-generation BTKis are as effective as ibrutinib for the del(17p) or *TP53*-mutated patient subset. ELEVATE-TN randomised patients to receive acalabrutinib monotherapy, acalabrutinib-obinutuzumab, or obinutuzumab-chlorambucil.[38] A pre-specified subgroup analysis of ELEVATE-TN showed that the PFS benefit with acalabrutinib therapy was consistent across subgroups, including patients with del(17p) and *TP53* mutation (14% of patients).[38] As for zanubrutinib, Arm C of the SEQUOIA trial includes patients with del(17p13.1) receiving zanubrutinib monotherapy.[42] At the 24-month follow-up, the PFS and OS rates for Arm C were 88.9% and 93.6%, respectively.[42] Given the accruing evidence for both first- and second-generation BTKis, continuous BTKi therapy is preferred over time-limited regimens for patients with del(17p) or *TP53* mutation[42, 52] (see statement 6 in Table 1).

Although continuous therapy is preferred in *TP53* patient group, a BTKi + BCL2i time-limited regimen could be considered in the case of cardiac or bleeding concerns. Evidence supporting the use of venetoclax-BTKi combinations for patients with del(17p) or *TP53* mutation has been limited, as trials have included few of these patients. However, the ongoing CAPTIVATE trial includes patients with del(17p) or *TP53* mutation (17% of patients with known mutational status).[55] A follow-up analysis of CAPTIVATE data estimated the 4-year PFS and OS rates in this patient population at 63% and 96%, respectively.[56] In the venetoclax-obinutuzumab arm of CLL14, the grade ≥3 AE rates were 78.8% for all AEs, 52.8% for neutropenia and 6.6% for vascular AEs (i.e. hypertension and hypotension).[46] Of note, the incidence of grade ≥3 tumour lysis syndrome was lower with venetoclax-obinutuzumab than with chlorambucil-obinutuzumab (1% vs 3%).[46] In view of the available evidence, a BTKi-BCL2i combination is preferred over a combination of BCL2i plus an anti-CD20 monoclonal antibody for patients with del(17p) or *TP53* mutation who prefer time-limited treatment (see statements 7 and 8 in Table 1). However, it should be noted that the follow-up of trials using BTKi and BCL2i combination regimens are relatively short.

Treatment in fit, *IGHV*-mutated patients without del(17p), *TP53*

The choice of treatment for TN CLL patients with mutated *IGHV* depends on their age, physiological fitness, presence of comorbidities, and FCR eligibility. As discussed above, younger patients (<65 years) with a CIRS score of <6 and CrCl ≥70 mL/min are considered fit to receive a more intensive CIT regimen in clinical trials.[33,34] In clinical practice, physicians may consider older patients (≥65 years) with good functional capacity or without comorbidities fit for treatment. Notably, the clinical trials discussed in this section included a substantial proportion of fit older patients, including 41% of patients in the E1912 trial,[39] 84% of those in ELEVATE-TN,[38] and 34% of patients enrolled in GAIA (CLL13).[57]

For several years, fixed-duration CIT or chemotherapy was the standard treatment for previously untreated fit patients. FCR therapy in TN CLL was associated with significant PFS benefit over FC across several prognostic subgroups, including patients with mutated *IGHV*.[51] A 5.9-year follow-up analysis of the CLL8 trial confirmed significant OS and PFS benefit with FCR over FC across several prognostic subgroups, including patients with mutated *IGHV* (HR [progression] 0.47, 95% CI 0.33–0.68; HR [death] 0.62, 95% CI 0.34–1.11).[51] Median PFS and OS were not reached among *IGHV*-mutated patients who received FCR.[51] In CLL10, frontline FCR therapy was associated with a higher PFS rate than BR at 31.7 months of follow-up. Although patients aged ≤65 years derived significant PFS benefit from FCR in CLL10, there was no significant PFS difference between FCR and fludarabine-cyclophosphamide (FC) for physically fit older patients aged >65 years (median PFS not reached vs 48.5 months; *P*=0.172).

Some studies have demonstrated the superiority of ibrutinib-based therapy over FCR in unselected CLL patient populations, including E1912 and FLAIR. Approximately 29% of patients in E1912 and 33.1% of those in FLAIR had mutated *IGHV*.[39,58] Although the planned interim analysis for E1912 (ibrutinib-rituximab vs FCR) showed a similar 3-year PFS rate in both treatment arms for patients with mutated *IGHV* (87.7% vs 88.0%; HR 0.44, 95% CI 0.14–1.36),[39] a long-term follow-up analysis (median follow up of 70 months) showed a significantly better 5-year PFS rate with ibrutinib-rituximab vs FCR (83% vs 68%; HR 0.27, 95% CI 0.11–0.62).[59] In FLAIR, a randomised trial (minimal residual disease-guided therapy comparing ibrutinib

monotherapy with ibrutinib-venetoclax for up to 6 years vs FCR), ibrutinib-venetoclax therapy showed significantly higher efficacy than standard FCR.[58] After a median follow-up of 44 months, the 3-year PFS rate was 97.2% for ibrutinib-venetoclax vs 76.8% for FCR (HR [progression] 0.13, 95% CI 0.07–0.24), with OS benefit (HR 0.31, 95% CI 0.15–0.67), in the overall trial population.[58] However, the PFS results in the *IGHV*-mutated subgroup did not favour ibrutinib-venetoclax over FCR at the time of the analysis (HR 0.54, 95% CI 0.21–1.38). The OS results favoured ibrutinib-venetoclax in *IGHV*-unmutated patients (HR 0.23, 95% CI 0.06–0.81) but not in *IGHV*-mutated patients (HR 0.61, 95% CI 0.20–1.82).[58] It remains to be seen how and whether longer follow-up will impact these results as in the E1912 trial.

The GAIA trial showed that venetoclax-based combinations (venetoclax-rituximab vs venetoclax-obinutuzumab vs venetoclax-obinutuzumab-ibrutinib) were superior to CIT (FCR or BR) in physically fit patients with TN CLL. At 38.8 months of follow-up, among patients with unmutated *IGHV*, PFS rates were 86.6% in the venetoclax-obinutuzumab-ibrutinib group, 82.9% in the venetoclax-obinutuzumab group, 76.4% in the venetoclax-rituximab group and 65.5% in the CIT group, as compared with 96.0%, 93.6%, 87.0% and 89.9%, respectively, in patients with mutated *IGHV*. In the prespecified subgroup analysis, this benefit of venetoclax-obinutuzumab therapy with or without ibrutinib was observed in all groups except for those with mutated *IGHV*, trisomy 12, normal karyotype and intermediate CLL-IPI scores. OS rates at 3 years were comparable across all treatment arms.[57] Overall grade ≥3 SAEs were numerically higher in the venetoclax-obinutuzumab-ibrutinib arm compared with CIT or other venetoclax arms.[57]

Based on available evidence, first-generation BTKi-based or venetoclax-based regimens or FCR are reasonable options for fit patients with mutated *IGHV*. Expected toxicity profiles, medical comorbidities, patient preference, cost, accessibility and logistical concerns all play an important role in guiding treatment decisions (see statements 9 and 10 in Table 1). As for FCR, the availability of data on long-term outcomes of BTKi-based and venetoclax-based therapy trials will help clarify their comparative "curative" potential in this patient subset.

Treatment in unfit, *IGHV*-mutated patients without del(17p) or *TP53* mutation

Several targeted agents have been investigated for the treatment of unfit patients with mutated *IGHV*. In the ALLIANCE study, ibrutinib with or without rituximab was superior to BR with respect to PFS in unfit older patients (note that *IGHV* mutation status was not reported).[40] Both RESONATE-2 and iLLUMINATE assessed the efficacy of ibrutinib-containing regimens in FCR-ineligible older patients. Up to 44% of the patients in RESONATE-2 had mutated *IGHV*; in this study, ibrutinib therapy was associated with significantly longer PFS (HR 0.16, 95% CI 0.09–0.28) and OS (HR 0.16, 95% CI 0.05–0.56) compared with chlorambucil. The PFS benefit with ibrutinib was consistently demonstrated across prespecified subgroups, including patients with mutated *IGHV* (HR 0.15, 95% CI 0.05–0.43).[60] Similarly, iLLUMINATE demonstrated PFS benefit with ibrutinib-obinutuzumab over chlorambucil-obinutuzumab (HR 0.25, 95% CI 0.16–0.39) at 45 months of follow-up. PFS benefit with ibrutinib-obinutuzumab was also observed in patients with mutated *IGHV* (HR 0.20, 95% CI 0.07–0.59).[61]

Clinical trials of second-generation BTKis (ELEVATE-TN and SEQUOIA) have enrolled FCR-ineligible older patients aged ≥65 years or unfit younger patients aged ≥18 years. Of 535 patients in ELEVATE-TN randomised to acalabrutinib or acalabrutinib-obinutuzumab or obinutuzumab-chlorambucil, there were 338 patients (63.1%) with unmutated *IGHV* and 191 (35.7%) patients with mutated *IGHV*.[38] Acalabrutinib-obinutuzumab significantly improved PFS vs obinutuzumab-chlorambucil in both *IGHV*-mutated patients (HR 0.15, 95% CI 0.04–0.52) and *IGHV*-unmutated patients (HR 0.08, 95% CI 0.04–0.16).[38] In SEQUOIA, PFS in *IGHV*-mutated patients who received zanubrutinib-rituximab was not significantly different from that in BR-treated patients (HR 0.67, 95% CI 0.36–1.22).[42]

The results of CLL14 support a role for BCL2i-containing regimens in treating older or unfit younger patients with mutated *IGHV*. In CLL14, 39% of patients with known mutation status had mutated *IGHV*.[62] In this *IGHV*-mutated subset, fixed-duration venetoclax-obinutuzumab significantly improved PFS relative to chlorambucil-obinutuzumab (HR 0.36, 95% CI 0.19–0.68) at 4 years of follow-up.[62] In GLOW (26% with mutated *IGHV*), PFS was significantly longer with fixed-duration ibrutinib-venetoclax than with chlorambucil-obinutuzumab (HR 0.233, 95% CI 0.065–0.839) at 27.7 months, although with higher rates of cardiac toxicity related to ibrutinib.[48]

Less intensive chemotherapy or CIT regimens for treatment-naïve unfit patients include bendamustine-rituximab,[63] chlorambucil-obinutuzumab,[64] single-agent rituximab,[65] obinutuzumab or chlorambucil.[66] As for fit *IGHV*-mutated patients, treatment selection for unfit patients should also consider expected toxicity profiles, presence of comorbidities, patient preference, cost, availability and logistical concerns (see statements 11–13 in Table 1).

Treatment in *IGHV*-unmutated patients without del(17p)

The presence of unmutated *IGHV* is consistently associated with poor prognosis in CLL, and it is one of the biomarkers included in the CLL-IPI.[30,67,68] As for other patient subsets, including those with mutated *IGHV*, targeted therapies have shown notable efficacy for unfit patients with unmutated *IGHV*, and are thus recommended (see statements 14 and 15 in Table 1). Across trials of targeted agents, the proportions of patients with unmutated *IGHV* (known mutational status) were 44% in RESONATE-2, 58% in iLLUMINATE, 63% in ELEVATE-TN and 51% in SEQUOIA.[38,42,60,61] In RESONATE-2, single-agent ibrutinib therapy significantly improved PFS vs chlorambucil (HR 0.13, 95% CI 0.06–0.31) at 18.4 months follow-up in older patients with unmutated *IGHV*.[60] Similarly, among patients with unmutated *IGHV* in E1912, ibrutinib-rituximab showed superior 3-year PFS compared with FCR (90.7% vs 62.5%; HR 0.26, 95% CI 0.14–0.50).[39] In a 48-month analysis of iLLUMINATE data, PFS outcomes in unfit patients with unmutated *IGHV* favoured ibrutinib-obinutuzumab over chlorambucil-obinutuzumab (HR 0.17, 95% CI 0.10–0.29). Similar trends have been noted with second-generation BTKi therapy in unfit patients with unmutated *IGHV*. In ELEVATE-TN, the 24-month PFS rate was higher in patients receiving acalabrutinib-obinutuzumab than those receiving obinutuzumab-chlorambucil (91% vs 31%; HR 0.08, 95% CI 0.04–0.16).[38] This was maintained at 6 years of follow-up, with the PFS rates in the *IGHV*-unmutated subgroup being 75% (acalabrutinib-obinutuzumab), 60% (acalabrutinib monotherapy) and 5% (obinutuzumab-chlorambucil).[41] In the SEQUOIA study, zanubrutinib treatment was associated with improved PFS vs BR (HR 0.24; 95% CI 0.13–0.43) at 26.2 months follow-up.[42]

BCL2i-containing regimens have shown superior PFS to standard CIT in patients with unmutated *IGHV*. In CLL14 (60% *IGHV*-unmutated patients), PFS outcomes at 24 months strongly favoured venetoclax-obinutuzumab over chlorambucil-obinutuzumab in patients with unmutated *IGHV* (HR 0.22, 95% CI 0.12–0.38).[46] In GLOW (52% *IGHV*-unmutated patients), PFS was also significantly longer with ibrutinib-venetoclax compared with chlorambucil-obinutuzumab (HR 0.269, 95% CI 0.148–0.488) at 27.7 months follow-up.[48]

CONCLUSION

The clinical consensus developed through this modified Delphi process offers practical guidance for clinicians managing TN CLL patients in Singapore and similar healthcare systems. The recommendations made for different patient subsets are based on a range of factors, from biomarker profiles to comorbidities, fitness and treatment preferences. For early-stage asymptomatic CLL patients, active surveillance is recommended, along with pre-treatment molecular biomarker testing to guide treatment selection. In general, targeted agents are prioritised over chemotherapy/CIT, especially for unfit patients, while chemotherapy/CIT may remain relevant for selected patients, e.g. young/fit and without del(17p) or *TP53* mutations. Although the use of targeted agents has improved outcomes in patients with del(17p) or *TP53* mutation, more effective regimens are needed to extend survival and preserve quality of life. Emerging strategies such as minimal residual disease (MRD)-guided adaptive approaches offer a promising way to tailor treatment duration to improve outcomes.[58] Although discussed in recent guideline updates,[15,16] MRD-guided approaches are not considered sufficiently mature for routine adoption; moreover, these assessments require specialised flow cytometry capabilities and expertise that may not be widely available—an important practical consideration.[11] However, once adequately validated in clinical trials, MRD-guided approaches could help rationalise treatment choices and duration.

While this clinical consensus focuses primarily on guiding frontline management, it is relevant to consider the potential implications of initial treatment selection for subsequent therapy in the relapsed/refractory setting. Patients who relapse after treatment with a novel agent (BTKi or BCL2i) may show a response to an agent of the other class. Patients achieving remission on time-limited regimens (BCL2i combinations) can be re-treated if their remission lasted 3–5 years, while treatment with a BTKi remains an option irrespective of the duration of remission.[10,11] On the other hand, patients relapsing after treatment with covalent BTKis (e.g. ibrutinib, acalabrutinib, zanubrutinib) are unlikely to respond to another covalent BTKi, and require alternatives such as BCL2i-based therapy. As more patients receive targeted agents earlier in the disease course, options to overcome resistance or intolerance will be increasingly important. Emerging options include non-covalent BTK inhibitors, such as pirtobrutinib, which have demonstrated promise in re-establishing BTK inhibition and clinical responses.[69,70,71] Of note, ongoing pirtobrutinib trials have recruited Asian participants; these include head-to-head studies with covalent BTKis (NCT05254743, BRUIN-CLL-314).[72] Such studies should provide valuable Asian-specific CLL outcome data, which have hitherto been very limited. Other agents like nemtabrutinib and vecabrutinib are being studied in ongoing trials, although resistance to non-covalent BTKis is also emerging.[73,74] BTK protein

degraders may represent another emerging option in cases of BTKi resistance.[75]

The main motivation of this consensus is to promote clinical practice improvement and standardisation, based on the best available evidence. As an additional benefit, the exercise of regularly updating clinical guidelines facilitates consultation and dialogue among funders, regulatory bodies, local experts and national societies. These interactions are important to guide selection and implementation of appropriate interventions, which may include tiered pricing or expanded access programmes, depending on the characteristics of the health system. Effective collaboration among all stakeholders is critical for securing appropriate access to effective therapies, and achieving sustainable improvement in outcomes for patients and healthcare systems. Moving forward, regular updates will ensure these clinical recommendations remain responsive to emerging evidence and clinical practice.

Supplementary Material

Supplementary Table S1. Comparison of recommendations for first-line treatment with NCCN (ver 3.2024), ESMO CPG interim update (2024) and BSH (2022) guidelines.

Ethics statement

These consensus guidelines did not involve the collection or analysis of patient data. As such, ethics review and patient informed consent were not applicable.

Declaration

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COMMENTARY

Navigating the evolving landscape in the prescribing of medications for insomnia in Singapore: Principles and considerations from a psychiatrist's perspective

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ABSTRACT

There are significant challenges for medical practitioners who have to navigate complex clinical, legal, ethical and administrative considerations in the prescription of controlled medications in the treatment of insomnia. This commentary examines the changing landscape and reframing of risks associated with the use of benzodiazepines and Z-drugs in light of recent legal precedents based on Singapore's frameworks of the Singapore Medical Council's Ethical Code and Ethical Guidelines, and the Prescribing of Benzodiazepines Guidelines (MOH Clinical Practice Guidelines 2/2008). The recent ruling from the Court of Three Judges has shone a spotlight on rigorous justification in instances where there is deviation from established treatment guidelines and thorough risk-benefit analysis, particularly when considering off-label use of medications, which is not uncommon in the clinical setting. While the risks of long-term prescription of benzodiazepines should never be discounted, preservation of a patient's functioning and current quality of life should also be taken into consideration in the risk-benefit analysis. The complexities of transitioning patients from sedative hypnotics to alternative medications are also addressed, with an advocation for licensed medications with established safety profiles.

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Keywords: benzodiazepines, insomnia, medico-legal, psychiatry, Z-drugs

INTRODUCTION

The risks of prescribing benzodiazepines and Z-drugs for insomnia are well recognised by regulators, where the prescribing of such medications in contravention of guidelines has been the subject of regulatory action.[1,2] Medical practitioners involved in the prescription of such medications need to grapple with complex clinical, legal, ethical and administrative considerations that may not be apparent at first glance. Consider, for example, a well-informed patient who has been visiting a succession of doctors for insomnia where evidence of a substance use disorder is lacking. This patient has been prescribed with numerous benzodiazepines, including midazolam which he/she perceives to be the most efficacious. The patient may reference the National Drug Formulary (Singapore), and argue that midazolam, a short-acting but highly addictive benzodiazepine, is indicated in the short-term treatment of severe insomnia, and contend that the non-prescription of this medica-tion is detrimental to his/her well-being. When presented with clinical practice guidelines for prescribing of benzodiazepines, one may quote the statement of intent of the guideline in that recommendations are not intended to serve as a standard of medical care and that every physician is ultimately responsible for an individualised approach with each patient.[2] Such a consultation is unlikely to end on a productive note, where practitioners now also need to take into consideration the recent legal developments that have been now enshrined in Singapore case law.[3] In this commentary, we will discuss salient points with regard to these developments, and provide practical prescribing considerations in accordance with relevant principles.

Recent legal developments delivered by the Court of 3 Judges

The Court of 3 Judges, in the delivery of the judgment for Ang Yong Guan v Singapore Medical Council and another matter, set out that while the Singapore Ministry of Health (MOH) guidelines set forth a presumptive standard of care, departures from this may be permissible in individual cases. These instances should be justified or supported by good reasons. The same applies to the standards derived from the package inserts and product monographs of the different medicines prescribed. While this seems to favour the argument of the patient illustrated in the example, it was emphasised that the same burden falls upon the medical practitioner, with no distinction made

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between general practitioners or psychiatrists. There was also an emphasis in the judgement on treating the underlying condition that resulted in the patient's persistent use of benzodiazepines, instead of simply leaving it to any specialist to continue the prescription of benzodiazepines beyond the stipulated time limit of 8 weeks.

The judgment stressed that the psychiatrist does not have free reign to disregard the standards set out simply by virtue of being a specialist, and remains obliged to justify any departures from the presumed standards. Such justifications include considering why the guidelines exist and the relevant risks. Beyond considering the rationale behind that standard and conducting a risk-benefit analysis of each prospective departure, it would be essential as well to demonstrate that the psychiatrist had then come to an objectively defensible conclusion that the departure wasjustified under those circumstances.

Awareness of the current ethical framework for off-label drugs

Following clinical guidelines rather than deviating from them is a choice that most clinicians consider safe. However, there may be unrecognised pitfalls when generalising international guidelines to any local setting, given the need to also take into account local guidelines and regulations. Non-pharmacological methods (e.g. cognitive behavioral therapy for insomnia) are the first-line treatment options but here we limit our discussion to pharmacological options to highlight the challenges that clinicians can face when it comes to prescribing. In addition, many medications are used on an off-label basis in insomnia, and this may not be explicitly mentioned or discussed during patient consultations.[4] In addition, the patients' consent to such use must be obtained if they are able to do so. However, the validity of such consent would be questioned if a patient was not informed that the medication was being used off-label. It is also important to note that off-label prescribing encompasses any modification of dosage regimen, administration route, pharmaceutical form, different indications, different age groups and different categories of patients beyond the licensing of these medications.[5] To illustrate an example of what would be considered off-label prescribing in Singapore, some patients may prefer a lower dose of 2.5 mg of lemborexant (where there is evidence that this dose may sufficiently treat insomnia while minimising next morning residual sleepiness), instead of the licensed dose of 5–10 mg daily.[6]

While off-label prescribing may benefit different categories of patients, there are serious repercussions should due care not be carried out.[5] The Singapore Medical Council's Ethical Code and Ethical Guidelines (SMC ECEG) requires medical practitioners, when using off-label drugs, to justify that it is in the patients' best interests.[7] To elaborate, the SMC ECEG also mandates an assessment of the risks and benefits of such use, which is not endorsed by all jurisdictions around the world.[8] In the treatment of insomnia, international guidelines include those by the American Academy of Sleep Medicine or the British Association for Psychopharmacology.[4,9] However, these guidelines recommend benzodiazepines and Z-drugs, in contrast to Singapore guidelines. Medical practitioners may then be inclined to consider other medications mentioned in such guidelines, such as trazodone. However, not all medical practitioners may be well-equipped to counsel patients regarding off-label use of medications, as well as adequately document their provision of medical advice.[10] In the Singapore setting of multidisciplinary and team-based care in restructured hospitals, good documentation and communication between different team members is important to maintain good continuity of care. Inadequate disclosure by a prior team member regarding off-label use of medication with subsequent revelation by other team members may lead to negative patient experience, a rupture in the therapeutic alliance and medico-legal issues, particularly if adverse effects from such use emerge.

Going back to basics: Start first with licensed medications with clinical evidence for safety and value!

Currently, there are efforts internationally to contain spiralling healthcare costs via standardisation. Factors such as variations in clinical practice with a lack of standardisation has been shown to increase cost unnecessarily and impact the quality of care.[11] While off-label prescribing is not uncommon in the treatment of insomnia, the lack of strong evidence for this practice adds to significant variation in clinical care with subsequent implications for safety and costs.[4] One potential contributor to this variation is the perception of the concept of off-label prescribing among patients. In a study to understand public perceptions of approved versus off-label use for COVID-19-related medications via an analysis of 609,189 tweets on social media,[12] the authors found varied perceptions and stances on off-label versus U.S. Food and Drug Administration-authorised drug use across different stages of

COVID-19.[12] These variations, in addition to the legal and ethical need to discuss off-label prescribing vis-à-vis the aforementioned court judgment, will invariably impact consultation times and therefore costs as well.

One potential solution is to prioritise licensed medications for insomnia in care pathways for the management of insomnia. To our knowledge, the only 2 medications in Singapore currently licensed for the treatment of insomnia are lemborexant and melatonin (prolonged release), which been shown to be efficacious and safe.[13,14] These medications lack the clinical, ethical and legal risks associated with addictive medications like benzodiazepines or Z-drugs. Lemborexant, an orexin receptor antagonist, is indicated for the treatment of adult patients with insomnia- characterised by difficulties with sleep onset and/or sleep maintenance—with no restrictions on duration of use.[15] Melatonin (prolonged release) is indicated for short-term treatment of primary insomnia in patients who are aged 55 or over.[16] As both are currently not subsidised by MOH, further cost-effectiveness studies may justify their inclusion in the Standard Drug List.[15,16]

For patients already on benzodiazepines and Z-drugs, medical providers need to exercise caution with regards to their continued prescription beyond 8 weeks. This may involve a thorough assessment regarding the underlying factors that resulted in the patient's continued use of benzodiazepines.[3] When prescribing of benzodiazepines and other hypnotics, it would be prudent for medical practitioners to begin with an endpoint in mind as the Administrative Guidelines issued by MOH in 2008 suggested that patients who were already on high-dose and/or long-term benzodiazepines initiated by their specialists should be referred back to these specialists for further management.[17]

Medical providers could consider facilitating patients' transition from sedative-hypnotics to other medications. A recent 2024 study has reported a significant number of successful transitions from Z-drugs and other hypnotics to lemborexant with no serious treatment-emergent adverse events, bearing in mind however that this was an open-label multicentre study involving 90 patients.[18] Studies have also looked at melatonin in a similar manner.[19] If patients still need to be continued on benzodiazepines or Z-drugs for a duration beyond that endorsed in existing guidelines, medical practitioners should endeavour a nuanced risk-benefit analysis, taking into consideration the preservation of a patient's functioning and current quality of life against potential side effects. Ultimately, clinicians need to balance many requirements including clinical and legal obligations with the need to provide patient-centred care for the best possible outcomes. In so doing, value-based outcomes are improved, and truly more care is achieved.

Declaration

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LETTER TO THE EDITOR

Knowledge and attitudes towards sarcopenia among healthcare professionals

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Dear Editor,

Sarcopenia is the age-related loss of skeletal muscle mass as well as muscle strength and/or performance.[1] Sarcopenia is an important public health issue as it has a significant impact on patient health outcomes, and personal and social economic outcomes. It leads to increased adverse outcomes such as increased risks of falls, fractures, postoperative complications, disability and increased mortality.[2] It is associated with many chronic diseases such as heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes and cognitive impairment.[2,4] The prevalence of sarcopenia is expected to dramatically increase in the next few decades, especially in ageing populations.[6]

Sarcopenia was recognised as a disease by the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) with the code M62.84 in 2016. Yet, many clinicians and healthcare professionals remain unaware of the condition and uncertain about diagnostic tools and management strategies.[6]

We conducted a study to describe the current knowledge and practice regarding sarcopenia among healthcare professionals and to identify potential gaps, if any. A structured survey was crafted and modified based on a previous study.[7] Key survey results are shown in Table 1.

From 1 February to 1 August 2023, an online survey was completed by 108 healthcare professionals across 3 public hospitals in Singapore. An online survey link was sent to healthcare professionals from the institutions inviting them to participate in an anonymous survey via the FormsSG digital survey platform. This study received ethics approval from the National Healthcare Group Domain Review Board (2022/00781).

There was a total of 108 respondents. Majority of the respondents were nurses (56%) and doctors (36%). The rest of the allied health professionals respondents were therapists, dieticians and pharmacists. The majority of doctors were from internal medicine (40%) and geriatric medicine (35%). The remaining were from family medicine (7.5%), gastroenterology (5%), endocrinology (5%), dermatology (2.5%), palliative medicine (2.5%) and rehabilitation medicine (2.5%).

First, a set of questions were on participants' attitudes regarding sarcopenia. Overall, most healthcare professionals strongly agreed that the recognition and management of sarcopenia was important. However, only 22.20% of participants diagnosed sarcopenia within the past 3 months. Common reasons cited for not diagnosing sarcopenia included lack of tools for diagnosis, and feeling that they are not the ones responsible for the diagnosis of sarcopenia.

Second, we assessed participants' knowledge on sarcopenia. Only 13% (n=14) identified sarcopenia as a disease, and this was similar for both allied health professionals (13%, n=9) and doctors (12.5%, n=5). The majority of respondents correctly agreed that sarcopenia can be prevented (65.7%, n=71). We wanted to assess participants' knowledge on diagnostic criteria of sarcopenia too, and the majority of participants correctly identified the following determinants in the diagnosis of sarcopenia: muscle mass (88.89%, n=96, muscle strength (86.11%, n=93) and physical performance (77.78%, n=84). However, there was also a high percentage of respondents who selected clinical impression (50.93%, n=55), nutritional status (63.89%, n=69), (body mass index (BMI; 53.70%, n=58) and frailty criteria (57.41%, n=62) as part of diagnostic criteria for sarcopenia, even though current guidelines only recommend usage of muscle mass, muscle strength measurements and physical performance.[1]

Third, we aim to assess current practice for diagnosis and management of sarcopenia. Based on the Singapore Clinical Practice Guideline for

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Table 1. Key survey results.

Survey item	Overall	Allied health professionals	Doctors	*P* value[a]
	n=108	n=68	n=40	
How confident are you in identifying sarcopenia? (5 = extremely confident, 4 = very confident, 3 = neutral, 2 = somewhat confident, 1 = not at all)[b]	2.7 ± 1.0	2.6 ± 1.0	2.9 ± 1.0	*P*=0.086
How important is sarcopenia in the overall management of a patient? (5 = extremely important, 4 = very important, 3 = somewhat important, 2 = minimal importance, 1 = not important)[b]	4.1 ± 0.7	4.2 ± 0.7	3.9 ± 0.7	***P*=0.005**
It is important to recognise sarcopenia in a patient and ensure that appropriate management is instituted. (5 = strongly agree, 4 = agree, 3 = neutral, 2 = disagree, 1 = strongly disagree)[b]	4.4 ± 0.6	4.4 ± 0.6	4.2 ± 0.6	***P*=0.046**
Have you diagnosed sarcopenia in your practice in the previous 3 months? Yes, %	22.20% (n=24)	11.76% (n=8)	40.00% (n=16)	***P*=<0.001**
If sarcopenia was not diagnosed in the previous 3 months, what were the reasons for not diagnosing sarcopenia?				
I am not responsible for diagnosing sarcopenia	48.15% (n=52)	61.76% (n=42)	25.00% (n=10)	
I do not have tools to diagnose sarcopenia	43.52% (n=47)	45.59% (n=31)	40.00% (n=16)	
I do not work with adults 60 years old and older	1.90% (n=2)	2.90% (n=2)	0 (n=0)	
Others: Have not discovered sarcopenia in practice	0.90% (n=1)	1.50% (n=1)	0 (n=0)	
Others: Lack of time and resources to diagnose and manage	0.90% (n=1)	0	2.50% (n=1)	
Others: Not a clinical priority in my department	1.80% (n=2)	0	5.00% (n=2)	
Others: Not sure how to. No protocol on how to diagnose or who to refer to.	0.90% (n=1)	1.50% (n=1)	0 (n=0)	
Have you received any sarcopenia-related education in the past year? Yes, %	32.40% (n=35)	29.40% (n=20)	37.50% (n=15)	*P*=0.388
Sarcopenia is recognised as a…				***P*=0.023**
Disease	13% (n=14)	13% (n=9)	12.50% (n=5)	
Syndrome	32.40% (n=35)	22% (n=15)	50% (n=20)	
Condition	43.50% (n=47)	51% (n=35)	30% (n=12)	
Not sure	11.10% (n=12)	13% (n=9)	7.50% (n=3)	
Did you use clinical impression to diagnose sarcopenia in your practice? Yes, %	38.90% (n=42)	26.47% (n=18)	60.00% (n=24)	***P*=<0.001**

Table 1. Key survey results. (Cont'd)

Survey item	Overall	Allied health professionals	Doctors	*P* value[a]
	n=108	n=68	n=40	
Did you use muscle mass to diagnose sarcopenia in your practice? Yes, %	9.30% (n=10)	4.41% (n=3)	17.50% (n=7)	***P*=0.023**
Did you use muscle strength to diagnose sarcopenia in your practice? Yes, %	19.40% (n=21)	19.11% (n=13)	20.00% (n=8)	*P*=0.911
Did you use physical assessment to diagnose sarcopenia in your practice? If yes, %	25.00% (n=27)	23.50% (n=16)	27.50% (n=11)	*P*=0.645
Did you use nutrition to diagnose sarcopenia in your practice? Yes, %	22.20% (n=24)	25.00% (n=17)	17.50% (n=7)	*P*=0.37
Did you use body mass index to diagnose sarcopenia in your practice? Yes, %	16.70% (n=18)	17.65% (n=12)	15% (n=6)	*P*=0.722
Did you use frailty criteria to diagnose sarcopenia in your practice? Yes, %	28.70% (n=31)	32.35% (n=22)	22.50% (n=9)	*P*=0.274
Is there a protocol for diagnosis of sarcopenia at your workplace?				*P*=0.298
No	37% (n=40)	32.35% (n=22)	45% (n=18)	
Yes	5.60% (n=6)	7.35% (n=5)	2.50% (n=1)	
Not sure	57.40% (n=62)	60.29% (n=41)	52.50% (n=21)	
Is there a protocol for management of sarcopenia at your workplace?				*P*=0.147
No	38% (n=41)	33.82% (n=23)	45% (n=18)	
Yes	4.60% (n=5)	7.35% (n=5)	0% (n=0)	
Not sure	57.40% (n=62)	58.82% (n=40)	55% (n=22)	

Values are shown in mean ± standard deviation for continuous variables or in % for categorical variables. *P* values ≤0.05 are in bold.
[a] *P* value was calculated by Student's t-test for continuous variables and chi-square test for categorical variables. Comparison was made between allied health professionals and doctors for the calculation of *P* value.
[b] Mean scores were obtained.

Sarcopenia,[8] diagnosis is made via presence of low muscle mass and muscle function. Muscle mass can be measured by dual x-ray absorptiometry (DXA). Muscle strength can be measured via grip strength, and physical performance can be measured by gait speed, 5 times sit-to-stand test or short physical performance battery test. However, only 9.30% (n=10) for the diagnosis used muscle mass to diagnose sarcopenia, and 19.4% (n=21) used muscle strength for the diagnosis of sarcopenia. Interestingly, 22.2% (n=4) of respondents used nutritional status for diagnosis of sarcopenia. Also, 16.17% (n=18) of respondents used BMI and 28.70% (n=31) used frailty criteria in the diagnosis of sarcopenia, even though they are not part of the recognised diagnostic criteria for sarcopenia. Only 5.6% (n=6) for the diagnosis indicated that there was a protocol for diagnosis of sarcopenia, and only 4.6% (n=5) indicated the existence of a protocol for the management of sarcopenia in their institutions.

With the rise in research for sarcopenia and increased resources for diagnosis and management of sarcopenia, there should be a corresponding increase in awareness of this disease. Based on this survey, the majority of respondents demonstrated

a positive attitude towards sarcopenia. However, there is significant heterogeneity in how sarcopenia is being diagnosed. Less than 20% (n=21) of participants used muscle strength and mass for the diagnosis of sarcopenia, even though it was included in a standardised diagnostic criteria put forth by the Asian Workgroup for Sarcopenia and Singapore clinical practice guidelines.[9,8] Interestingly, up to 38.9% (n=42) of participants uses clinical impression for the diagnosis of sarcopenia, despite presence of standardised guidelines. This can lead to risks of misdiagnosis and undertreatment, especially in patients who may appear to have larger body habitus due to obesity or fluid overload states. Obesity and sarcopenia are not mutually exclusive entities.

In addition, there is a low rate of diagnosis for sarcopenia (22.2%) despite awareness of the disease. Sarcopenia can lead to adverse outcomes such as falls, fractures, disability and increased mortality. Similar to this study, a survey of healthcare professionals across Asia (in 2022) revealed that approximately 99.3% were aware of sarcopenia; and yet only 42.4% of them had screened for sarcopenia, while 42.9% diagnosed sarcopenia.[10] This shows that the gap between awareness and diagnosis of sarcopenia is not unique to Singapore, but we may be falling behind in screening and diagnostic rates compared to rest of Asia. More work needs to be done to improve the screening and diagnosis rates for sarcopenia. Just having an awareness of sarcopenia is insufficient.

Possible strategies involve improving access to diagnostic tools such as bioelectrical impedance analysis or DXA machines. From this survey, 48.15% (n=52) of participants felt they did not have the tools for the diagnosis of sarcopenia. The most common equipment used in hospitals are dynamometers for testing of hand grip strength. Other equipment such as the bioelectrical impedance analysis machine or DXA machine may not be readily available. Investment in these machines and education of staff on the interpretation of results will bridge this gap. Second, it is important to increase efforts in educating healthcare professionals on sarcopenia within each hospital, to streamline diagnostic processes. Third, implementing protocols involving multidisciplinary teams in the screening, diagnosis and management of sarcopenia is crucial. Doctors and allied healthcare play an important role in screening patients on the ground, and subsequently liaising with dieticians and physiotherapists for targeted interventions, tailored to the individual. Based on this survey, only 5.6% (n=6) of participants are aware of a protocol for sarcopenia diagnosis in their workplace. Perhaps a case finding approach can be performed, with administration of SARC-F (strength, assistance walking, rise from a chair, climb stairs and falls) questionnaires and grip strength or functional assessment offered to older adults in the clinic setting. This can be a good start to increase the screening and diagnostic rates. Fourth, creation of an Agency for Care Effectiveness clinical guideline on sarcopenia in Singapore may be useful for dissemination of information to clinicians on the ground.

There is a need to emphasise that sarcopenia is an important chronic disease, much like diseases such as hypertension or diabetes. Those with sarcopenia have higher odds of hospitalisation, and have increased hospital costs of around USD2315.70 (SGD 3,172.50) per person annually based on a cross-sectional study in US,[3] on top of increased fall risks, fractures and disability. Proper interventions can lead to early identification of sarcopenia and reduce downstream complications, reduce healthcare costs and improve quality of life for older adults.

Overall, based on this survey, there is generally low adherence to Singapore clinical practice guidelines on sarcopenia, especially on screening and diagnosis of the disease. This inevitably results in reduced diagnosis or misdiagnosis, and inability to institute management early. Patient care is therefore affected, as we are not able to reduce risk of downstream effects such as falls, fractures, disability and increased postoperative complications. Sarcopenia is still relatively underdiagnosed and undertreated in tertiary hospitals. Institution of protocols for screening, diagnosis and management of sarcopenia in hospitals and community is needed. As suggested above, future efforts can be focused on education of healthcare professionals on the importance of sarcopenia detection, increasing accessibility to tools for the diagnosis of sarcopenia, and perhaps even direct efforts at the public health level to increase the public awareness of sarcopenia.

Ethics statement

This study has been approved by National Healthcare Group (NHG) Domain Specific Review Board (2022/00781).

Declaration

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LETTER TO THE EDITOR

Exploring the perspectives of child health strategy stakeholders on resilience and well-being in children and youths in Singapore: A qualitative study

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Dear Editor,

Resilience has been defined as the capacity of a dynamic system to adapt well to potential threats, while mitigating the negative impact of behavioural and physiological changes due to chronic stress, and the resumption of positive functioning thereafter. Resilience enables one to adapt positively to adversities in life and allows the transformation of toxic stress to tolerable stress. The factors associated with resilience are homogeneous across studies, which are individual attributes such as self-regulation and problem-solving skills, relational attributes such as secure attachment relationships, and connections to school and community. This is relevant to the Singaporean context, as the Singapore Mental Health Study conducted from 2016 and 2018 revealed that 1 in 5 youths, aged between 18 and 34 years old have a mental disorder.[5] Mental disorders were also reported to be the largest contributor to disease burden for Singaporeans aged 10 to 34 years old, peaking for 15 to 19 year-olds, for whom it represented 25.8% of total disability-adjusted life years (DALYs). In 2020, suicide is the leading cause of death for those aged 10 to 29 years old. Parent-child relationships are the focus of resilience studies in how they shape a child's resilience to bounce back after encountering adversities. Parental influence is key to the resilience and well-being of the child and family systems.

The single most common finding of children with adverse childhood experiences with good outcomes in life is the presence of at least one stable and committed relationship with an adult who is their parent or caregiver. A highly responsive caregiver with consistent "serve and return" interactions with the child stimulates brain development in the cognitive, executive, social and emotional domains. This happens when a child attempts to communicate their needs, and the parent or caregiver responds appropriately to the child's signals and needs. The supportive relationship enhances positive experiences and adaptive skills in children, which forms the basis of resilience-building. There is little data regarding the framework of resilience-building and well-being in children and youths. The understanding of how resilience can be built provides opportunities for designing more upstream measures to improve a child's life outcomes—through enhancing capacity and resilience-building. Our study is timely as there is increasing focus in the area of resilience and well-being in children and youths as upstream measures to prevent mental health issues.

We conducted a qualitative study based on the interpretative approach to understand the different perspectives of child-health strategy stakeholders on resilience and well-being, and explore enablers and challenges in resilience-building and well-being in children and youth aged between 0 and 18 years in Singapore.

We carried out 16 in-depth semi-structured interviews in Singapore between December 2021 and April 2022, both virtually and on-site. Participants were identified as potential child-health stakeholders if they were parents or caregivers to children and/or youths, or had worked with them for at least 1 year, and invited for the interview via purposive sampling. Further respondents were recruited via snowball sampling. A conceptual framework based on Walt and Gilson's Triangle Framework and Socio-Ecological Model was used for the interview guide. Both inductive and deductive analyses were used to identify themes and subthemes from the data. QSR NVivo 12 software (Lumivero, CO, US) was used for analysis.

The study involved participants with an average of 18 years of experience working with children in the public sector. The cohort was diverse, including

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parents, youths, educators, school counsellors, paediatricians, psychiatrists, psychologists and social workers.

Data triangulation was carried out through having comparable groups of stakeholders. Recruitment of participants was stopped when data saturation was reached. The Consolidated Criteria for Reporting Qualitative Studies (COREQ) checklist was used to ensure the study design, data collection and analysis were comprehensive.

Table 1 encapsulates the key enablers and challenges identified across various domains impacting the resilience and well-being of children and youths.

Our key and most consistent finding is that having parents with good socio-emotional skills helped children build resilience and well-being as the adults were attuned to their child's emotional needs and were able to cope with their tantrums. The children were described as having developed ways to express themselves appropriately and built emotional and mental health literacy to cope with life's challenges. This provides children with an emotionally safe environment to emulate their parents and gain intrapersonal and interpersonal relational skills for resilience-building. Positive parental role-modelling during adversities also influence how children perceive and deal with future challenges.

The main challenge is the lack of time in modern-day parenting to invest in socio-emotional literacy and parenthood skills to support their children and enhance their relationships. Our data suggests that individual resilience is shaped by family behaviour and practices. These results are consistent with our literature review.

Singapore has progressed rapidly from a third-world country to a first-world society. To keep up with the rising cost of living, family units are getting smaller, where dual-income parents are common. With less time invested in the parent-child relationship—because both parents work—quality family time is affected, and family bond and identity suffer. The social fabric significantly weakens with bearings on future generations. This is exacerbated by excessive use of screen time, which impairs social connection and relationships. Unregulated excessive screen time diminishes sleep efficiency and duration, impacts socio-emotional development, language, cognitive and executive functions, which worsens intrapersonal and interpersonal skills, with impact on mental health. The COVID-19 pandemic amplified this, increasing social isolation and leading to worsening relational and communication skills, with a rise in mental health issues.

The Singapore government has recognised the importance of maternal and child health, resilience and well-being. The development and implementation of various programmes such as KidSTART and the formation of multi-ministry and cross-agency taskforces, with active public engagement and consultations, show that the government is taking proactive steps towards upstream preventive measures. Despite the positive steps made by the government, major areas of concern from the study were identified: the Singaporean identity and values; lack of time and support in modern-day parenting; unregulated excessive screen time; and lack of human resources, expertise and funding for programmes targeting children and youth.

In the pursuit of success—often defined by Singaporean societal standards to be academic and achievement-focused—there is cultural and societal separatism, with a loss in sense of community. A strong family unit forms the basis of a community, where there is shared identity that can confer purpose to one's being and is an important contributor to life satisfaction. This is important in the formation of a child's identity and sense of belonging. However, it is acknowledged that as children enter various life transitions, they struggle with forming their personality while still belonging to a shared identity, and may find it difficult to conform. With the influence of social media and the pressure to fit in, children may lose their sense of self, leading to mental health issues. This can be mitigated with better socio-emotional literacy.

Being a pragmatic society with good governance, funding to initiate or sustain various programmes in promoting health and socio-emotional literacy need to be substantiated with data and evidence. While recognised as necessary, this is reported as a barrier for existing programmes. Current manpower in schools, healthcare and community organisations is often stretched with increased workload but inadequate funding and resources to meet programmes' goals, leading to burnout. It is important to reconsider the support structure for such programmes prior to scale-up.

Our data's key recommendation is for family health to be considered as an expansion from maternal and child health. We recommend that family health, which includes family and parental resilience, take on a Life Course Health Development model, looking at the family structure, family decision-making processes and communication, family cognitions and health-related behaviours. Parental role-modelling in relational skills within a stable marriage, cognitive processes, socio-

Table 1. Summary of key findings and recommendations.

Themes according to Socio-Ecological Model	Sub-themes identified from the main themes	Enablers	Challenges	Quotes	Recommendations
Individual	• Temperament • Sense of identity • Sense of self • Sense of belonging • Sense of purpose • Emotional security • Exposure to adversities and trauma • Intrapersonal relational skills • Growth mindset	• Clear sense of self and purpose • Sense of belonging • Adaptability	• Adverse childhood experiences • Lack of self-identity	*"A sense of belonging to somewhere. If they don't feel belonging to the, the home, they would find a sense of belonging and identity with their friends or with some external things. And sometimes it's not healthy, that kind of attachment." [IDI007]*	• Early childhood mental and socio-emotional health literacy can be introduced as early as possible by parents
Interpersonal	• Interpersonal relationships • Interpersonal relational skills • Parenting styles	• Secure relationships • Consistent and responsive caregiving • Good socio-emotional and mental health literacy • Positive parental role-modelling	• Lack of parental socio-emotional and mental health literacy • Lack of time in modern parenting • Excessive screen time • COVID-19	*"When the child has a tantrum, it's to […] have the socio-emotional skills to cope with it so that the child learns that 'I can express big feelings.'" [IDI003]* *"It's very obvious to us when we go for dinners. Everybody is in their own world, in the community of isolation […] They think they're having communal activity." [IDI005]*	• Recognise any early warning signs of mental health issues in children and youths
Community	• Involvement of organisations in the community in the care of child	• Multiple programmes available Schools: • Peer support programmes in school • Co-curricular activities • Triple P Programme (an evidence-based programme that equips parents with techniques to promote their children's—aged up to 16 years—psychological, social and emotional competence. It is built on a tiered system that provides different degrees of parental support.)	• Lack of trained personnel • Increased workload and burnout in existing manpower • Lack of participation of parenting programmes by vulnerable groups	*"Lack of manpower. […] the same small group of people being stretched too thin to do too many things. Not just in terms of the things that they need to do, but because it's so mentally taxing. […] it just decreases the efficiency […] and what they can actually do if they had more reserves." [IDI011]*	• Introduce socio-emotional literacy curriculum at the preschool level • Increase publicity and awareness regarding parenting programmes and the importance of community • Carry out needs analysis to understand factors leading to decrease in uptake and participation, i.e. through focus group discussions of relevant stakeholders

Table 1. Summary of key findings and recommendations. (Cont'd)

Themes according to Socio-Ecological Model	Sub-themes identified from the main themes	Enablers	Challenges	Quotes	Recommendations
		Community: • Parenting programmes including Triple P Programme • KidSTART programme (an upstream programme supporting pregnant mothers and children aged 0–6 years from low income families to give their children a good start in life in Singapore) • Youth Mental Well-being Network (a local network that develops ground-up projects ranging from enhancing youths' emotional resilience to strengthening peer support within the family, workplace and community) • Passionate programme drivers such as National Youth Council, volunteers, grassroot leaders, etc.		*"I think the first thing is the […]buy-in from the parents. So a lot of programs, I think, […] whether a young person accesses it really, is largely determined by the parents approval or enthusiasm. And I don't blame them. Sometimes it's because, you know, […] they also need to, I think support families. They've long working hours. […] so I think […] we should try to break, improve this accessibility as far as possible. Because also sometimes I think that they may not recognise there's a need for this." [IDI012]*	• Collaboration amongst healthcare workers to be equipped with anticipatory guidance and advice for parents and children
Societal	• Cultural and societal expectations and standards	• Gracious and nurturing society • Increasing acceptance of importance of mental well-being • Government rrecognises the need for resilience and well-being building	• Societal and cultural expectations • High academic pressure • Fear of missing or losing out mindset • Singaporean definition of success appears to be academic and achievement-focused	*"What do we want […] to be known for? Is it […] top [scores]? Are those the things are important to our population, our society?" [IDI005]*	• Workplace child-care support • Increase scope of maternal and child health to family health, that includes family resilience • Increase awareness regarding national insurance plan coverage for mental health and well-being services

emotional literacy and health behaviour has a large influence on the child's growing years.

The spotlight on child and maternal health and well-being, and mental health in recent years, brings an opportunity to reassess the nation's priorities and evaluate the root causes of issues of concern such as rising youth mental health problems. Going upstream into resilience-building and promoting well-being can stem these. Further studies need to be undertaken to understand the gaps and priorities of Singaporean families prior to the design and implementation of strategies to improve family and individual resilience and well-being.

Supplementary Materials

Supplementary Appendix 1: Interview Guide
Supplementary Appendix 2: COREQ Checklist

Ethics statement

Ethics approval was obtained from the National University of Singapore Institutional Review Board. (Reference Code: NUS-IRB-2021-721).

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: *family health, mental health, paediatrics, parent-child relationship, public health, resilience*

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LETTER TO THE EDITOR

Improving school teachers' self-efficacy and knowledge on food allergy and management of anaphylaxis using a virtual multidisciplinary workshop

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Dear Editor,

Children with food allergies are at risk of inadvertent allergic reactions that range from mild to potentially life-threatening anaphylaxis, even with appropriate dietary avoidance.[1] This risk is often increased in community settings such as schools via accidental exposure to allergens during learning activities or meal times. A quarter of children were found to have their first allergic reaction on school grounds.[2] Studies of self-reported reactions have shown that 16–18% of school-aged children with known food allergy experienced an allergic reaction in school.[3] In Singapore, the prevalence of self-reported food allergy among children aged 11–30 months could be as high as 5%. Food allergies can contribute to reduced quality of life and barriers to participation in day-to-day activities.[4] Therefore, it is crucial that all schools are prepared to effectively prevent and manage food-related allergic reactions.

Previous studies have identified several deficits in food allergy and anaphylaxis management in school settings.[5-7] These include failures in recognising allergic signs and in implementing timely management plans. Anaphylaxis requires prompt action to prevent complications, and delayed treatment with adrenaline is a major risk factor for morbidity and mortality.[8] Gaps in schools' food allergy policies, procedures and protocols may intensify anxiety among parents, and can affect the child's health, well-being and educational outcomes.

The aim of this study was to assess the effectiveness of a virtual multidisciplinary educational workshop in improving the self-efficacy and knowledge of school teachers, in the management of food allergic reactions in school. Participation in this workshop is voluntary and non-obligatory. Data were collected from workshops conducted between June 2021 and June 2022.

The 2-hour long workshop was delivered via the Zoom online meeting platform by paediatric allergists, allergy specialist nurses and dietitians from the Paediatric Allergy Service of KK Women's and Children's Hospital, Singapore. It consisted of 2 components. The theoretical session included didactic lectures on prevention of accidental allergen exposure, recognition and treatment of allergic reactions and roles of all stakeholders based on recommendations in published guidelines. These were followed by a hands-on session requiring participants to perform a return demonstration using an autoinjector training device.

Anonymous online questionnaires were administered to participants before and after the workshop (Supplementary Table S1). The post-intervention questionnaire was administered immediately after the workshop. The School Personnel Self-Efficacy-Food Allergy and Anaphylaxis Questionnaire (S.PER.SE-FAAQ),[9] a validated instrument, was used to assess participants' self-efficacy in managing students with food allergy. It consisted of 8 questions and comprised 2 main factors: anaphylaxis management and food allergy management. Answers were on a scale from 1 ("Cannot do at all") to 5 ("Highly certain can do"). To objectively assess their theore-tical knowledge, participants were also presented with 2 clinical vignettes of food-allergic children who experienced a mild reaction versus anaphylaxis in school (Supplementary Fig. S1). Four possible options for action and treatment were proposed and they were asked to choose the best answer. The study with waiver of informed consent was approved by the SingHealth Centralised Institutional Review Board (reference number 2021/2165).

A total of 444 participants attended the 4 workshops, with no repeat attendees. Most of the participants were women (92.3%) and working in preschools (67.6%). Two-thirds of the participants

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had not attended any prior training on the administration of adrenaline auto-injectors (AAI) though three-quarters did know of or had looked after children with food allergy. This highlights the discordance in the current knowledge and abilities of our teachers, with what they are expected to do, i.e. care for children with food allergies. Approximately 27% of the teachers were aware of their students carrying an AAI. Most of them (81.3%) had not managed a student with acute food allergic reaction and none of them had administered an AAI before.

Overall, there was a significant improvement in total mean self-efficacy scores (standard deviation), from 28.8 (0.31) pre-workshop to 34.8 (0.21) post-workshop (P<0.005). Self-efficacy of all individual factors improved significantly (Table 1). Participants had the lowest confidence in recognising anaphylaxis symptoms and administering drugs before the workshop. However, these 2 factors showed the greatest improvement post-workshop. The proportion of participants who answered Question 1 (mild allergic reaction scenario) correctly improved from 41.9% to 58.1% (P<0.001) and from 36.0% to 64.0% (P<0.001) for Question 2 (anaphylaxis scenario) post-workshop. The results for Question 1 were less ideal compared to Question 2, though there was still a significant improvement post-workshop. In this scenario, a known egg-allergic child developed oral itch, facial rashes and lip swelling after ingestion of a slice of cake. Most of the incorrect answers were conservative options, such as asking the student to drink plenty of water or bringing the student to the sick bay for observation. These conservative options may not be ideal (compared to the best answer of prompt administration of antihistamines), but it may reflect the restrictions placed on teachers by school policies where teachers may not be allowed to administer medications to students without explicit and written consent from the parents and/or the child's physician. This underscores the importance of engaging school management in closing this gap, to advocate for better awareness and child safety.

Our study is, to our knowledge, the first reported educational intervention for school teachers that

Table 1. Self-efficacy scores pre- and post-workshop.

Question	Pre-workshop, mean (SD)	Post-workshop, mean (SD)	Pre- and post-workshop difference (95% CI)	*P* value
Assure a safe school setting for students with food allergy (FAM)	3.85 (0.94)	4.39 (0.65)	0.54 (0.43–0.64)	<0.005
Put in place a personalised care plan for the management of students' food allergy (FAM)	3.76 (0.96)	4.31 (0.72)	0.55 (0.44–0.66)	<0.005
Manage a student at risk of allergic reactions to food (AM)	3.61 (0.93)	4.37 (0.67)	0.76 (0.65–0.86)	<0.005
Recognise anaphylaxis symptoms (AM)	3.18 (1.02)	4.30 (0.674)	1.12 (1.00–1.23)	<0.005
Co-work with other professionals and families in food allergy management at school (FAM)	3.72 (0.94)	4.35 (0.69)	0.63 (0.52–0.74)	<0.005
Manage allergens avoidance (e.g. reading labels, avoiding contaminations) (FAM)	3.82 (0.97)	4.38 (0.68)	0.56 (0.44–0.66)	<0.005
Guarantee full participation to all school activities to students with food allergy (e.g. attending school trips) (FAM)	3.70 (0.99)	4.31 (0.73)	0.61 (0.49–0.72)	<0.005
Administer drugs (e.g. adrenaline auto-injector) to a student having a severe and sudden reaction (AM)	3.19 (1.16)	4.44 (0.69)	1.25 (1.12–1.37)	<0.005
Total FAM SE (Scoring scale 5–25)	18.8 (4.00)	21.7 (3.01)	2.89 (2.43–3.35)	<0.005
Total AM SE (Scoring scale 3–15)	10.0 (2.66)	13.1 (1.85)	3.12 (2.82–3.42)	<0.005
Total SE (Scoring scale 8–40)	28.8 (0.31)	34.8 (0.21)	6.01 (5.28–6.74)	<0.005

AM: anaphylaxis management factor; CI: confidence interval; FAM: food allergy management factor; SD: standard deviation; SE: self-efficacy

was conducted virtually. The use of telehealth and tele-education has been dramatically accelerated during the SARS-CoV-2 pandemic and these platforms have brought us new opportunities to deliver patient education.[10] Prior to the pandemic, our hospital conducted these workshops physically and the number of participants was limited by the size of training ground as well as teachers' availability to travel to the training venue. From 2021, we adapted by converting the training curriculum to an online platform and arranged for autoinjector training devices to be couriered to schools. This has seen an increase in participation numbers, translating to better training efficiency. The results of this study demonstrated that virtual multidisciplinary workshops that include hands-on practice with an AAI training device are efficacious in improving the self-efficacy and knowledge of school teachers, and in the management of food allergy and anaphylaxis.

Our study also showed that the majority of teachers lacked prior training despite caring for children with food allergy, highlighting the need for a coordinated national strategy to facilitate education of school staff in allergy management. Lack of follow-up data from this study limits our understanding of the long-term efficacy of this training modality. Re-evaluation of workshop participants to assess practical real-life application of knowledge and AAI skills is presently being considered. In conclusion, we believe that such an outreach programme plays an important role in patient advocacy, enabling schools to provide children and their families the support and information needed to create a safe and inclusive school environment for food-allergic children.

Disclosure

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript. The authors did not receive any financial support for this study. No generative artificial intelligence (AI) or AI-assisted technologies have been used.

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Keywords: *anaphylaxis, food allergy, paediatrics, self-efficacy, virtual workshop*

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