ANNALS

OFFICIAL JOURNAL OF THE ACADEMY OF MEDICINE, SINGAPORE

VOLUME 52
NUMBER 11
NOV 2023

Burden of antibiotic resistance in infections among very-low-birthweight infants in Singapore

A Singapore study revealed that 278 out of 2431 preterm infants had infections caused by multidrug-resistant Gram-negative bacteria. Further monitoring of antimicrobial resistance is recommended for infection prevention and control. (See full article on p.561)

Illustration by Nata Blackthorn

Also in this issue

ISSN 2972-4066

Annals, Academy of Medicine, Singapore
Volume 52 | Number 11 | November 2023

EDITORIALS

ORIGINAL ARTICLES

REVIEW ARTICLES

COMMENTARY

LETTERS TO THE EDITOR

Ann Acad Med Singap 2023;52:556-8
https://doi.org/10.47102/annals-acadmedsg.2023308

EDITORIAL

Paradigm shifts in haemophilia A therapy with emicizumab prophylaxis in Asia

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Over the past decade, the development of emicizumab, the first-in-class factor VIII (FVIII)-mimetic monoclonal antibody bispecific to activated factor IX and factor X, has ushered in a significant revolution in non-factor replacement therapy for patients with congenital FVIII deficiency or haemophilia A (HA). This groundbreaking therapy has been unequivocally supported by a series of international, multicentre, phase 3 studies, conclusively demonstrating that subcutaneous emicizumab prophylaxis can effectively and safely promote haemostasis to prevent bleeds in both paediatric and adult patients with severe or non-severe HA, with or without FVIII inhibitors.[1,2] Due to a long elimination half-life of 4–5 weeks leading to a stabilised in vivo FVIII-like activity of 20–30 IU/dL, the annualised bleeding rate (ABR) could be significantly reduced to 1.4 for treated bleeds and 2.6 for all bleeds after receiving 4 loading doses (3.0 mg/kg once a week) followed by maintenance doses (1.5 mg/kg once a week, 3.0 mg/kg every 2 weeks, or 6.0 mg/kg every 4 weeks) of emicizumab for a median follow-up time of 120 weeks in the HAVEN 1–4 studies.[1] Remarkably, 90% of patients eventually achieved 0 bleeds with 95% resolution of target joints. Furthermore, the less frequent subcutaneous injections of emicizumab meaningfully contributed to an improvement in health-related quality of life and a reduction in caregiver burden for patients with HA, particularly those with difficult venous access. Given its promising efficacy, especially in the inhibitor group for which factor replacement therapy with FVIII concentrate is contraindicated, emicizumab prophylaxis has swiftly emerged as one of the standard HA treatments worldwide, regardless of FVIII inhibitor status.

Concerning geographical disparities in Asian countries, a phase 3 study (HAVEN 5) enrolling patients aged ≥12 years with severe HA without FVIII inhibitors or severe/moderate HA with FVIII inhibitors exclusively from China, Malaysia and Thailand was separately conducted. Despite 74% of patients having target joints—higher than 61% observed in the HAVEN 1–4 studies—prophylaxis with standard-dose emicizumab for at least 24 weeks still led to excellent bleed control with the ABR of 1.0 for treated bleeds, as well as 0 treated bleeds in 61% of patients.[3] Aligning with the results from phase 3 studies, 2 retrospective studies from China and South Korea similarly showed substantial reductions in the ABR after using standard-dose emicizumab prophylaxis among paediatric and adult patients with severe/moderate HA. Zero bleeds were also achievable in 46–56% of patients in real-world settings.[4,5] As it is commonly known that several HA communities in Asia had experienced limited access to FVIII prophylaxis and treatments for HA with FVIII inhibitors,[6] resulting in a greater burden of haemophilic arthropathy and bleeding complications, these haemophilia-related morbidities can be overcome, and currently unmet needs in HA therapy may be fulfilled with emicizumab prophylaxis.

In Singapore, where 18% of patients with HA developed FVIII inhibitors, Lee et al. reported the utility of standard-dose emicizumab prophylaxis in 15 paediatric and 3 adult patients with severe HA without FVIII inhibitors or HA of any severity with FVIII inhibitors, since the introduction of emicizumab in September 2018.[7] At a median follow-up time of 22 months, the median ABR of 4.5 (3.0 in the non-inhibitor and 5.5 in the inhibitor groups) before switching treatments to emicizumab prophylaxis was absolutely suppressed to 0 in both presence and absence of FVIII inhibitors. Despite a low prevalence of target joints (11%) and a modest initial rate of 0 bleeds (22%), 0 bleeds were further induced to 83% overall and 75% in the inhibitor group. Interestingly, real-world data in a subgroup of patients aged <2 years were also described;

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2 out of 4 patients started emicizumab prophylaxis before 1 year of age, beyond the age range of participants in the HAVEN 2 study, while a phase 3 study in the infant population (HAVEN 7; NCT04431726) is still ongoing.[1] In the Singaporean cohort, 0 bleeds were achieved in 75% of infants and toddlers with HA at a median time of 18 months of emicizumab use. On safety profiles, the emicizumab regimen was well-tolerated in all age groups and did not contribute to any thrombotic adverse events.

In addition to validating its efficacy and safety in bleed control, Lee et al. demonstrated the use of emicizumab prophylaxis during surgical interventions and immune tolerance induction (ITI) for FVIII inhibitor eradication.[7] With additional doses of FVIII concentrate or recombinant activated factor VII in the perioperative periods, all procedures were successfully performed without bleeding or thrombotic complications. In 7 patients with high-titre FVIII inhibitors who underwent low-dose (86%) or high-dose (14%) ITI using FVIII concentrate, inhibitor negativity could be induced in 43% of patients without any safety concerns while on concurrent emicizumab prophylaxis. These real-world experiences provided supporting evidence for the results of the HAVEN 1–4 studies and a previous study of the ITI Atlanta protocol concomitantly using emicizumab for bleed control.[1,8] The positive outcomes suggested that standard-dose emicizumab is a valuable therapeutic option to prevent bleeds, either as a regular prophylaxis, during surgical procedures, or as an adjunct to the ITI regimen, for patients with severe or non-severe HA in Asia.

Despite its strong potential, budget constraints can be a major limitation in the implementation of standard-dose emicizumab prophylaxis in real-world practice among developing Asian countries.[6] Therefore, to be more economically compatible with local healthcare policy, the concept of reduced-dose or low-dose emicizumab prophylaxis (1.0–3.0 mg/kg/month) has been introduced.[9-11] In a case series from Malaysia, although switching emicizumab prophylaxis from standard-dose to reduced-dose regimens slightly increased bleeding rates, 44% of patients maintained 0 bleeds during a median follow-up time of 198 weeks.[9] In a study from India that evaluated the efficacy and safety of low-dose emicizumab prophylaxis in severe HA patients, with or without FVIII inhibitors, who were formerly treated with a standard-dose regimen or emicizumab-naive, at a median follow-up time of 52 weeks, no treated bleeds or thrombotic complications were reported.[10] Similarly, in another study in Thailand, even without 4 loading doses, emicizumab-naive severe/moderate HA patients with or without FVIII inhibitors still benefited from low-dose emicizumab prophylaxis, with 82% reduction in ABR from a median of 27.0 at baseline to 4.0 after prophylaxis for 1 year, with 0 bleeds achieved in 33% of patients.[11]

For a comprehensive comparison of various emicizumab regimens among Asian studies, PubMed and Embase were systematically searched from database inception to 12 September 2023, for studies in Asian countries reporting haemophilia-related clinical outcomes in patients with severe and/or non-severe HA receiving emicizumab prophylaxis. Of 58 unique records identified by the search terms "emicizumab" and "Asia", 8 studies were included after screening titles, abstracts, and full texts.[3-5,9-13] Including the latest study by Lee et al.,[7] a total of 9 eligible studies represented 171 patients with HA. Standard-dose and low-dose emicizumab regimens were applied in 6 and 4 studies, respectively. Although the median ABR during low-dose emicizumab tended to be higher than those during standard-dose emicizumab prophylaxis, a low-dose regimen significantly provided better bleed control than before or without emicizumab use.[10-12] No new safety profiles were documented in both studies of standard-dose and low-dose regimens. Based on these accumulative data, low-dose emicizumab prophylaxis could be an alternative HA treatment where the accessibility to a standard-dose regimen was limited. However, due to the small number of participants in most studies, further multicentre clinical trials or well-designed prospective studies are warranted to establish more robust evidence on the efficacy of low-dose emicizumab, compared to standard-dose emicizumab regimens.

In conclusion, emicizumab has globally shifted paradigms of prophylactic therapy for patients with HA, particularly those with FVIII inhibitors who are at the highest risk of bleeding, associated with increased morbidity and mortality. The current evidence, including, to our knowledge, the largest-to-date real-world study in Asia by Lee et al.,[7] confirms that weekly to monthly subcutaneous injections of emicizumab can contribute to effective bleed control and increase the possibility of achieving 0 or near 0 bleeds for patients with HA of any severity or FVIII inhibitor status. In Asian countries with significant budget constraints, a low-dose emicizumab regimen may be alternatively considered according to local policy and budget allotment, while its overall efficacy is anticipated. With factor replacement therapy using FVIII concentrate and non-factor replacement therapy using emicizumab, the evolution of HA therapy helps optimise treatment outcomes and promote a better quality of life for patients with HA.

Acknowledgments

The authors would like to extend their sincere gratitude to the librarian at the Faculty of Medicine, Chulalongkorn University for the assistance in retrieving full-text articles, as well as the Thai Society of Hematology, the National Hemophilia Foundation of Thailand, the Thai Hemophilia Patient Club, and Prof Ampaiwan Chuansumrit, for their contributions to promote and implement emicizumab use in Thailand.

Disclosure

All authors had no interests that might be perceived as posing a conflict or bias. No funding to be disclosed for this article.

Data availability

The supporting data are available from the corresponding author upon reasonable request.

Keywords: *emicizumab, factor VIII inhibitor, haemophilia A, healthcare rationing*

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Ann Acad Med Singap 2023;52:559-60
https://doi.org/10.47102/annals-acadmedsg.2023370

EDITORIAL

Improving management of AL amyloidosis

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In this issue of the *Annals*, Tan et al. on behalf of Singapore Myeloma Study Group presented the consensus guidelines on light chain (AL) amyloidosis.[1] This is an encouraging effort as AL amyloidosis is a rare disease, with diagnostic and therapeutic challenges. A comprehensive review examining its pathophysiology, diagnostic approach, and management by a multidisciplinary team will set the minimum bar for treatment outcomes of patients, taking into account advances in clinical management.

Amyloidosis is a disease caused by deposition of abnormal protein fibrils affecting multiple organs, such as heart, kidney, gut, etc. This causes a myriad of clinical presentation from proteinuria to life threatening/refractory heart failure. Amyloidosis remains challenging to diagnose and treat,[2] and a negative biopsy result does not exclude the diagnosis. Contributing to this is the presence of culprit plasma cells that only comprise a small fraction (a few percentages) of bone marrow population compared to myeloma where there will be a significantly increased abnormal plasma cells. The development of flow cytometry helps to identify confidently the abnormal plasma clone even at low percentage. Recent advances, such as serum free light chain analysis and mass spectrometry also help to address these limitations to confirm the diagnosis promptly and accurately. This was discussed in detail in the manuscript and can help in guiding the diagnostic process as well as in staging, which help predict the outcome of AL amyloid patient.

Meanwhile, raising disease awareness among general physicians and enabling early diagnosis are of paramount importance. Tan et al. provides guidance via an algorithm on how to work-up individuals with high suspicion of AL amyloidosis—particularly providing consensus on organ involvement, which is beneficial for all treating physicians. There are also suggestions for alternative approaches in cases where mass spectrometry analysis is not available or affordable.

In the context of various induction treatments, bortezomib-based regimens, with or without daratumumab, are recommended. Additionally, it highlights the importance of carefully selecting the right patients for autologous transplantation. However, the prognostic value of genomic markers in patients with AL amyloidosis is still under validation. For instance, consider t(11;14) in patients with AL amyloidosis, which is considered a standard prognostic marker in multiple myeloma (MM) but is associated with relatively poor outcomes in AL amyloidosis when treated with (VCD). A recent retrospective analysis further supports these findings.[3] Consequently, it is advisable to routinely screen for t(11;14) in patients with AL amyloidosis, not only due to its high incidence (at approximately 50%) but also because it influences the choice of treatment regimen. Nonetheless, an unmet need persists for treatment recommendations specific to this patient subgroup, as the VCD regimen is generally recommended. Venetoclax may offer an alternative, having shown effectiveness in MM patients, particularly those with t(11;14), as demonstrated in the phase III BELLINI study. However, this study did indicate higher mortality in non-t(11;14) patients. Furthermore, no significant difference was observed in progression-free survival (PFS) in the updated results from the phase III CANOVA study comparing venetoclax/dexamethasone and pomalidomide/dexamethasone in relapsed or refractory MM patients.[4] Therefore, further research is essential to develop more precise guidelines, moving from the current autologous transplantation or not decision towards the consideration of genetic markers, such as t(11:14), in treatment selection for AL amyloidosis patients.

The outcome for AL amyloidosis has improved significantly from diagnostic tools, treatment as well as multidisciplinary supportive care for patients. There are 3 main aspects in the management of amyloidosis—to eradicate the abnormal plasma clone rapidly; to support the affected organ until the amyloid deposit dissolves from the affected organs and to reduce the amyloid deposit in organs involved. While there are encouraging progress made in the first 2 aspects, there has yet to be significant progress in the latter.

The article by Tan et al. reviewed the treatment armamentarium for AL amyloid. Treatment of AL amyloid made first significant progress when bortezomib was used to control the abnormal

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plasma clone and to eliminate "the source" of the amyloid fibril. Following this success, further improvement was made when monoclonal antibody against plasma cells (CD38 antibody) was added to target this clone more specifically and rapidly with lesser side effects. Monoclonal antibody may even replace the role of autologous stem cells transplant in AL amyloid in future.

Remarkable medical progress was achieved in many fields to support AL amyloid patient, such as in cardiology, nephrologist, infective disease etc. These supports are important as the amyloid fibril deposit dissolve slowly from affected organs and multidisciplinary intensive support is needed. In fact, multidisciplinary approach is the key to ensure good outcome for amyloid patient.

Finally, one the remaining key challenge in amyloidosis is on how to dissolve or extract out the deposited amyloid fibril from organs rapidly to improve organ function. There are few potential medications in clinical trial that have been shown to be able to reduce the organ impairment rapidly.[5] However, these are not available in clinical practice and we hope this will make the next wave in the management of amyloid patients soon. Interestingly, doxycycline antibiotics was shown to help in dissolving amyloid fibril in mouse model as well as in trial involving a small number of participants. However, in larger trial this was not shown to have additional benefit. It is fair to say doxycycline was also not shown to increase side effects on treatment. In view of the limited agent available, it is fair to consider this as supporting medication if the patient can tolerate doxycycline without significant side effects.

AL amyloidosis is a complex disease requiring high clinical suspicion with multidisciplinary collaboration; a proper diagnostic approach; early access to supportive care for organ failure and new targeted therapy to improve outcome. The guidelines by the Singapore Myeloma Study Group provide evidence-based recommendations for use with sound clinical judgement by haematologists and other relevant specialists, in diagnosing and managing AL amyloidosis in Singapore. The group's proposed algorithm for when clinical suspicion of amyloidosis is raised, provides guidance for careful work-up of patients to ultimately lead to an early diagnosis and overall survival of patients. We have improved significantly in the management of AL amyloidosis over the past decade and are at the brink of another breakthrough for the eureka moment in treating this challenging disease.

Keywords: *AL amyloid, cancer, evidence-based, guideline, haematology*

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Ann Acad Med Singap 2023;52:561-9
https://doi.org/10.47102/annals-acadmedsg.2023190

ORIGINAL ARTICLE

Burden of antibiotic resistance in infections among very-low-birthweight infants in Singapore

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ABSTRACT

Introduction: Recent reports have described the increasing predominance of Gram-negative organisms among invasive bacterial infections affecting preterm infants. This changing pattern of infections is concerning due to the spread of antibiotic resistance among Gram-negatives.

Method: We conducted a single-centre, retrospective cohort study involving very-low-birthweight (VLBW) (<1500 grams) infants born <32 weeks gestation, with culture-proven infections (blood, urine, cerebrospinal fluid [CSF]) in the neonatal intensive care unit from 1 January 2005 to 31 October 2017.

Results: A total of 278 out of 2431 (11.4%) VLBW infants born <32 weeks gestation developed 334 infections, i.e. 52 (15.6%) early-onset infections (EOIs) and 282 (84.4%) late-onset infections (LOIs). The overall incidence decreased from 247 to 68 infections per 1000 infants over the study period, corresponding to reductions in LOI (211 to 62 infections per 1000 infants). A total of 378 bacteria were isolated, i.e. Gram-negatives accounted for 70.9% (45 of 59 [76.3%] EOI; 223 of 319 [69.9%] LOI). Specific resistant organisms were noted, i.e. Methicillin-resistant *Staphylococcus aureus* (8 of 21 *S. aureus* infections [38.1%]); Cephalosporin-resistant *Klebsiella* (18 of 62 isolates [29.0%]) and multidrug-resistant [MDR] *Acinetobacter* (10 of 27 isolates [37.0%]). MDR organisms accounted for 85 of 195 (43.6%) Gram-negative infections from the bloodstream and CSF. Based on laboratory susceptibility testing, only 63.5% and 49.3% of infecting bacteria isolated in blood were susceptible to empiric antibiotic regimens used for suspected EOI and LOI, respectively.

Conclusion: Gram-negative bacteria are the predominant causative organisms for EOI and LOI and are frequently MDR. Understanding the pattern of antimicrobial resistance is important in providing appropriate empiric coverage for neonatal infections.

Ann Acad Med Singap 2023;52:561-9

Keywords: bacteremia, Gram-negative bacilli, microbial drug resistance, nosocomial infection, premature infant

CLINICAL IMPACT

What is New

- In our setting with a high incidence of Gram-negative early- and late-onset infections among preterm very-low-birthweight infants, multidrug-resistant organisms were relatively common (47% of isolates).
- Between one third and half of all bacteria isolates in the blood were resistant to the empiric antibiotic regimen used for suspected early- and late-onset infections.

Clinical Implication

- There is a need for continued monitoring of antimicrobial resistance among infecting organisms in this high-risk population to inform infection control initiatives.

INTRODUCTION

Recent reports have described an increased predominance of Gram-negative organisms (*Escherichia coli*, *Klebsiella* species [spp]) among invasive bacterial infections in early- and late-onset neonatal sepsis in many settings.[1-5] This changing pattern of infections is particularly concerning due to the global spread of drug resistance among Gram-negatives, leading to increasingly limited therapeutic options.[6,7] The ongoing worldwide spread of antimicrobial resistance represents a major challenge in neonatal care. Previous studies have estimated that multidrug-resistant (MDR) bacteria account for approximately 30% of global neonatal sepsis mortality.[8]

Nearly half of pathogens causing neonatal sepsis were reported to be resistant to first-line (ampicillin or penicillin, gentamicin) and second-line (third-generation cephalosporin) World Health

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Organization-recommended treatments.[9,10] Of note, preterm infants admitted to the neonatal intensive care unit (NICU) are at particularly high risk of colonisation and infection with these MDR microorganisms.[11-13] There is a current dearth of local and regional data on the prevalence of antibiotic resistance and its impact on empiric antibiotic coverage among preterm, very-low-birthweight (VLBW) infants. Selection of empiric antimicrobial therapy for suspected bacterial infection or sepsis in the NICU requires knowledge of the local epidemiology of infecting organisms and their associated antibiotic resistance patterns. As such, we aim to explore the epidemiology of infecting microorganisms and their associated antimicrobial resistance in the NICU, over a 13-year period.

METHOD

Study design, setting and participants

This is a retrospective cohort study of VLBW (<1500 g) infants born <32 completed weeks gestational age over a 13-year period (1 January 2005–31 October 2017), who were admitted to the NICU at KK Women's & Children's Hospital, Singapore. Infants with major congenital anomalies, stillbirths and labour-room deaths were excluded.

Data sources

Our VLBW clinical database records maternal, perinatal and neonatal information using a standardised data collection form for all live-born infants <1500 g in the hospital.[1] We identified all VLBW infants who were born <32 weeks gestation with positive blood, urine and cerebrospinal fluid (CSF) culture results from our hospital microbiology database. We subsequently performed a data linkage with our VLBW database using unique national identification numbers (allocated to every baby born in Singapore). We included data on all infants until initial birth discharge.

Variables and definitions

Early-onset infection (EOI) and late-onset infection (LOI) were defined as clinical episodes with ≥1 positive blood, urine and/or CSF culture in the presence of signs or symptoms suggestive of infection at <72 and ≥72 hours of life, respectively. Positive cultures with coagulase-negative *staphylococci* (CoNS), *Micrococcus*, *Bacillus*, *Corynebacterium* and *Propionibacterium* species were considered contaminants unless ≥2 cultures were positive for the organism and/or the infant showed signs of sepsis and received intravenous antibiotics for ≥5 days.

A separate infection episode was considered if the infant developed signs of sepsis with a positive blood, urine or CSF culture after completing at least 10 days of appropriate antibiotics. Mortality was attributed to the infection if it was designated as the primary cause of death by the attending physician and occurred within 7 days from initiation of antibiotics.[14] The empiric antibiotic regimen used during the study period were penicillin and gentamicin (EOI), and cloxacillin and gentamicin (LOI), with escalation to third-generation cephalosporin or carbapenem if clinically indicated.

Gestational age is defined as the best obstetric estimate of completed weeks based on obstetric history, clinical examination and antenatal ultrasound. An infant is small-for-gestational age (SGA) if birth weight is <10th percentile according to the Fenton growth charts.[15] Prolonged rupture of membranes (PROM) is defined as the rupture of membranes >18 hours prior to birth. Histologic chorioamnionitis is defined as the presence of inflammatory cells in the chorioamniotic membrane, umbilical cord and/or the placental disc.[16] Severe morbidities included were necrotising enterocolitis ≥ stage 2,[17] severe intraventricular haemorrhage (grades 3–4),[18] bronchopulmonary dysplasia[19] and severe retinopathy of prematurity (stages 3–5).[20]

Identification of all causative bacteria was performed using standard microbiologic methods, and antibiotic susceptibility was determined according to the Australian calibrated dichotomous sensitivity (CDS) antimicrobial susceptibility testing standards.[21] MDR Gram-negative bacteria were defined as those resistant to at least 1 agent belonging to at least 3 of the following antibiotic categories: carbapenems (imipenem, meropenem), penicillins (ampicillin, piperacillin-tazobactam), broad-spectrum cephalosporins (ceftazidime, cefepime), aminoglycosides (gentamicin, amikacin), and fluoroquinolones (ciprofloxacin).[22,23] Specific MDR bacteria of interest included (1) Methicillin-resistant *Staphylococcus aureus* (MRSA): *S. aureus* resistant to oxacillin, cefoxitin or methicillin; (2) Vancomycin-resistant *Enterococcus* (VRE): *Enterococcus* spp that is resistant to vancomycin; (3) Cephalosporin-resistant *Klebsiella* spp (CephR-Klebsiella): *Klebsiella* spp testing non-susceptible to ceftazidime, cefotaxime, ceftriaxone or cefepime; (4) Carbapenem-resistant *Enterobacteriaceae*: any *E. coli*, *Klebsiella* spp or *Enterobacter* spp testing resistant to carbapenems; (5) MDR *Acinetobacter*: any *Acinetobacter* spp testing non-susceptible to at least 1 agent in at least 3 out of 6 antimicrobial classes.[23,24] When a bacteria species has known intrinsic resistance to an antibiotic category, that specific antibiotic category was not considered in calculating the number of categories to which that bacteria species is non-susceptible. [23]

Statistical analysis

Differences in proportions between categories were tested using chi-squared test or Fisher's Exact test (where appropriate) and Mann-Whitney U test for categorical and continuous variables, respectively. Univariable and multivariable logistic regression analyses were performed to determine associated factors for the outcomes of death and death and/or severe morbidity. The following predetermined variables were included in the multivariable models: sex, birthweight, receipt of antenatal steroids, and MDR organisms. Quantitative associations from logistic regression were reported as adjusted odds ratios (AORs) with 95% confidence intervals (CIs). All tests were two-sided, and *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp, NY, US).

This study protocol was reviewed and approved by the SingHealth Centralised Institutional Review Board.

RESULTS

Over the 13-year period, 278 out of 2431 (11.4%) VLBW infants born <32 weeks gestation developed 334 episodes of culture-confirmed infections. Of these, 52 (15.6%) episodes were EOIs and 282 (84.4%) were LOIs. Five infants had both EOIs and LOIs during their admission. Another 56 infants had multiple infection episodes prior to discharge: 41 with 2 episodes, 9 with 3 episodes, and 6 with ≥4 episodes. The clinical characteristics of infants with EOIs and LOIs are shown in Table 1. Compared to infants who developed LOIs, infants with EOIs had significantly higher rates of PROM, histologic chorioamnionitis and birthweight but lower proportion of SGA. The overall incidence of infections decreased from a peak of 247 to 68 infections per 1000 infants over the study period (Fig. 1). The overall decline was mirrored by the decrease in LOI, from a peak of 211 to 62 infections per 1000 infants. The EOI incidence remained largely unchanged, ranging from 5 to 37 infections per 1000 infants.

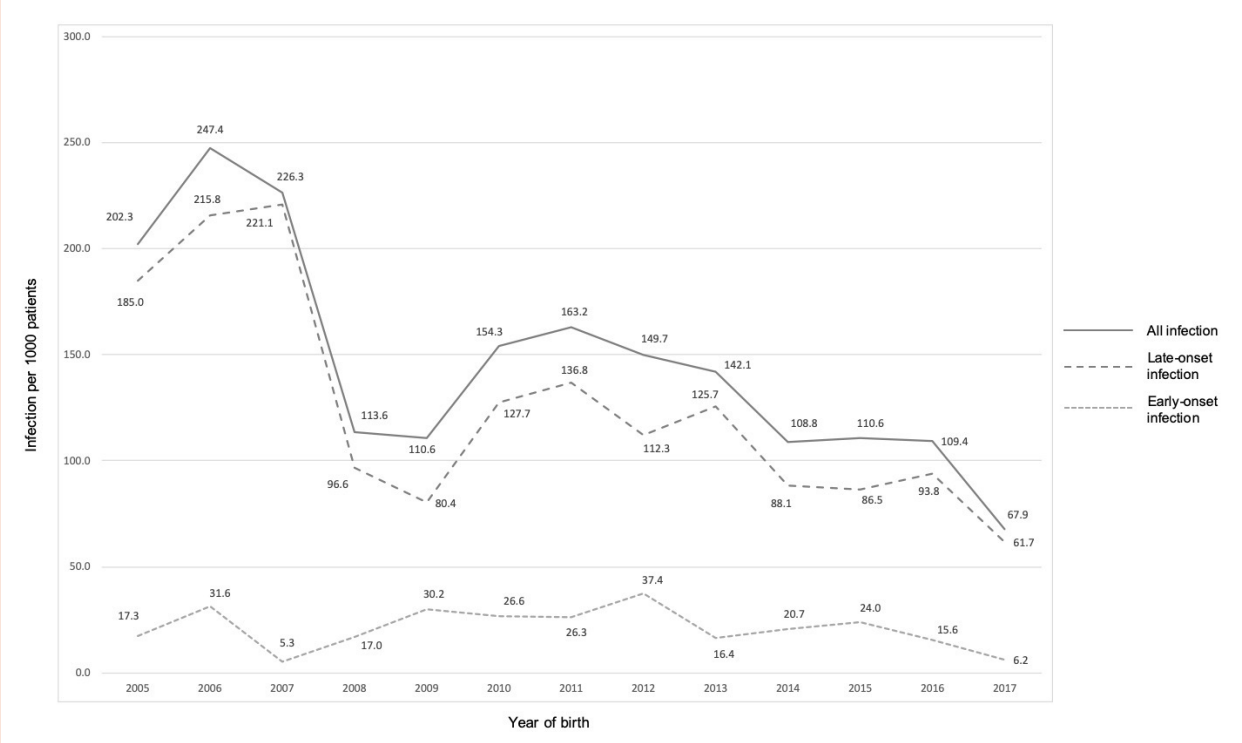
Of the 334 infections diagnosed, 275 (82.3%) were blood culture positive and 59 (17.7%) urine culture positive. All EOIs were blood culture positive infections. All 8 CSF-positive cultures were associated with blood culture positive infections, and 7 out of 8 (88%) were LOIs. Excluding 5 infants who had both episodes of EOIs and LOIs,

Table 1. Clinical characteristics of infants with early- and late-onset infections.

	EOI (n=52)	LOI * (n=231)
Median maternal age, years (IQR)	32 (29–35)	32 (27–35)
Abruptio placentae, no. (%)	8 (15.4)	40 (17.3)
Pregnancy-induced hypertension, no. (%)	5 (9.6)	45 (19.5)
PROM, no. (%)	28 (53.8)	64 (27.7) **
Antenatal steroids, no. (%)	45 (86.5)	206 (89.2)
Histologic chorioamnionitis, no. (%)	40 (76.9)	93 (40.8) **
Male sex, no. (%)	25 (48.1)	137 (59.3)
Vaginal delivery, no. (%)	27 (51.9)	112 (48.5)
Outborn, no. (%)	1 (1.9)	15 (6.5)
Median birthweight, grams (IQR)	972.5 (721.5–1184.5)	780 (650–940) **
SGA, no. (%)	4 (7.8)	55 (23.8) **
Gestational age <28 weeks, no. (%)	36 (69.2)	174 (75.3)
Median gestational age, weeks (IQR)	27 (25–28)	26 (24–27)
Multiple gestation, no. (%)	9 (17.3)	56 (24.2)
5-minute Apgar <7, no. (%)	17 (33.3)	50 (21.8)

* 5 infants had EOI and LOI during the course of their admission
** *P*<0.05 for comparisons between EOI and LOI
EOI: early-onset infection; IQR: interquartile range; LOI: late-onset infection; PROM: prolonged rupture of membrane; SGA: small-for-gestational age

Fig. 1. Trends of infections (early and late onset) in the NICU over the study period.



the rate of all-cause mortality was 36.2% for those with EOIs compared to 21.7% for those with LOIs (Supplementary Table S1). This is in contrast to the higher incidence of severe morbidity among infants who had LOIs (70.8%) compared to EOIs (37.0%).

A total of 378 organisms were isolated from 334 infections (Table 2). There was a predominance of Gram-negative infections, accounting for 70.9% of all bacteria isolated, including 45 out of 59 (76.3%) of all EOIs and 223 out of 319 (69.9%) of LOIs. *E. coli* (65 of 378, 24.2%), *Klebsiella* spp (62 of 378, 23.1%), *Enterobacter* spp (53 of 378, 19.8%), *Acinetobacter* spp (29 of 378, 10.8%) and *Pseudomonas* spp (22 of 378, 8.2%) accounted for more than 60% of all Gram-negative isolates. The dominance of Gram-negative EOI and LOI over the 13-year period was illustrated by the general trends of higher annual proportion of this subtype, ranging from 40% to 100% of EOI and from 48% to 89% for LOI (Supplementary Fig. S1).

A total of 239 infections with *S. aureus*, *E. fecalis*, *Klebsiella* spp, *E. coli*, *Enterobacter* spp and *Acinetobacter* spp were analysed for specific resistance patterns (Supplementary Table S2). The following incidences were noted: MRSA (8 of 21 *S. aureus* infections [38.1%]); cephalosporin-resistant *Klebsiella* (18 of 62 isolates [29.0%]) and MDR-*Acinetobacter* (10 of 27 isolates [37.0%]). There were no carbapenamase-resistant *Enterobacteriaceae* (*E. coli*, *Klebsiella*, *Enterobacter*; total of 172 isolates tested) or VRE (total of 16 isolates tested). MDR organisms accounted for 85 of 195 (43.6%) Gram-negative infections isolated from the blood stream and CSF (Table 3). Of these, *Enterobacter* spp and *Acinetobacter* spp infections had high rates of MDR, i.e. 91.2% and 37.0%, respectively.

Up to 63.5% and 49.3% of infecting bacteria isolated in the blood were susceptible to the empiric antibiotic regimen used for suspected EOI (benzylpenicillin and gentamicin) and LOI (cloxacillin and gentamicin), respectively (Table 4). If cloxacillin and amikacin were used for LOI, up to 70.4% of the bacteria isolated would be expected to be susceptible. There was no statistically significant difference in the proportion of resistant infecting organisms to empiric coverage between those who died (9 of 19, 47%) and those who survived EOI (9 of 33, 27.3%; P=0.1). Similarly, there was no difference in the proportion of resistance to empirical coverage between those who died (27 of 57, 47.4%) and survived LOI (89 of 174, 51.1%; P=0.6). Additionally, after adjusting for confounders, episodes of infections with MDR Gram-negative organisms were not significantly associated with increased odds of death (AOR 1.0; 95% CI 0.4, 2.4) or the combined outcome of death and/or severe morbidity (AOR 0.5; 95% CI 0.2, 1.7) (Supplementary Table S3).

Table 2. Microbial distribution of early- and late-onset infections.

Microorganism	EOI (n=59)	LOI (n=319)	Total (n=378)
Gram positive, no. (%)	14 (23.7)	96 (30.0)	110 (29.1)
CoNS	4 (28.6)	48 (50.0)	52 (47.3)
Staphylococcus aureus	1 (7.1)	20 (20.8)	21 (19.1)
Enterococcus faecalis	1 (7.1)	15 (15.6)	16 (14.5)
GBS	6 (42.9)	6 (6.3)	12 (10.9)
Others	2 (14.3)	7 (7.3)	9 (8.3)
Gram negative, no. (%)	45 (76.3)	223 (70.0)	268 (70.9)
Escherichia coli	23 (51.1)	42 (18.8)	65 (24.2)
Klebsiella spp	5 (11.1)	57 (25.6)	62 (23.1)
Enterobacter spp	5 (11.1)	48 (21.5)	53 (19.8)
Acinetobacter spp	2 (4.4)	27 (12.1)	29 (10.8)
Pseudomonas spp	5 (11.1)	17 (7.6)	22 (8.2)
Serratia marcescens	0	16 (7.2)	16 (6.0)
Elizabethkingia meningoseptica	0	6 (2.7)	6 (2.2)
Stenotrophomonas maltophilia	0	3 (1.3)	3 (1.1)
Chryseobacteriumn meningosepticum	0	3 (1.3)	3 (1.1)
Citrobacter koseri	1 (2.2)	1 (0.5)	2 (0.7)
Burkholderia cepacia	0	1 (0.5)	1 (0.4)
Flavobacterium odoratum	1 (2.2)	0	1 (0.4)
Haemophilus influenzae	1 (2.2)	0	1 (0.4)
Moraxella spp	0	1 (0.5)	1 (0.4)
Morganella morganii	1 (2.2)	0	1 (0.4)
Pantoea agglomerans	0	1 (0.5)	1 (0.4)
Proteus mirabilis	1 (2.2)	0	1 (0.4)

CoNS: coagulase-negative Staphylococcus; EOI: early-onset infection; GBS: Group B Streptococcus; LOI: late-onset infection; spp: species

Table 3. Distribution of multidrug-resistant organism among Gram-negative organisms isolated from blood and cerebrospinal fluid samples.

Microbe	No. of isolates	MDR, no. (% of isolate)
Escherichia coli	49	12 (24.5)
Klebsiella spp	48	16 (33.3)
Enterobacter spp	34	31 (91.2)
Acinetobacter spp	27	17 (63.0)
Pseudomonas spp	16	0
Serratia marcescens	8	5 (62.5)
Elizabethkingia meningosevptica	3	3 (100)
Chryseobacterium meningoseptica	3	3 (100)
Stenotrophomonas maltophilia	2	2 (100)
Proteus mirabilis	1	0
Morganella morganii	1	1 (100)
Flavobacterium odoratum	1	1 (100)
Citrobacter koseri	1	0
Burkholderia cepacia	1	1 (100)
Total	195	92 (47.2%)

MDR: multidrug resistant

Table 4. Susceptibility of bloodstream bacteria isolated during infection episodes to empiric antimicrobial combinations over the study period.

Antibiotic regimens	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Early-onset infection														
Benzylpenicillin + gentamicin, no. (% susceptible)	1 of 3 (33.3)	4 of 6 (66.7)	0 of 1 (0)	1 of 3 (33.3)	4 of 6 (66.7)	4 of 5 (80.0)	3 of 5 (60.0)	6 of 7 (85.7)	1 of 3 (33.3)	4 of 4 (100)	2 of 5 (40.0)	2 of 3 (66.7)	1 of 1 (100)	33 of 52 (63.5)
Late-onset infection														
Cloxacillin + gentamicin, no. (% susceptible)	11 of 23 (47.8)	9 of 25 (36.0)	15 of 25 (60.0)	7 of 13 (53.8)	5 of 12 (41.7)	5 of 17 (29.4)	5 of 17 (29.4)	10 of 19 (52.6)	9 of 20 (45.0)	9 of 12 (75.0)	8 of 16 (50.0)	12 of 15 (80.0)	5 of 9 (55.6)	110 of 223 (49.3)
Cloxacillin + amikacin, no. (% susceptible)	14 of 23 (60.9)	14 of 25 (56.0)	21 of 25 (84.0)	7 of 13 (53.8)	5 of 12 (41.7)	10 of 17 (58.8)	14 of 17 (82.4)	17 of 19 (89.5)	13 of 20 (65.0)	10 of 12 (83.3)	13 of 16 (81.3)	12 of 15 (80.0)	7 of 9 (77.8)	157 of 223 (70.4)

Episodes with multiple organisms are considered susceptible only if all organisms are susceptible.

DISCUSSION

Recent reports from several large cohort studies located in the US, Australia and New Zealand have revealed similar trends of stable EOI and decreasing LOI incidence among preterm, VLBW infants in the NICU.[25-28] The reported rates of neonatal sepsis ranged from 1.0% to 1.9% for EOI and from 12.2% to 24.5% for LOI,[27,28] which are consistent with our contemporaneous cohort. These reports have highlighted the increasing trend of Gram-negative EOI among VLBW preterm cohorts, with a predominance of *E. coli* over Group B Streptococcus.[27,28] The higher incidence of Gram-positive LOI, specifically CoNS, in these studies[25,28,29] is in contrast to our study and several reports from this region.[4,30-32] We observe a higher rate of Gram-negative LOI, with the most common organisms being *E. coli* and *Klebsiella pneumoniae*. Our study also illustrates a consistent trend of Gram-negative dominance for EOI and LOI in our unit through the past 13 years.

Several reasons have been proposed for this difference in microbial epidemiology, including the high antibiotic usage during the antepartum and perinatal periods.[2,7] Early life exposure can lead to alterations in neonatal mucosal colonisation, which may lead to an increased risk of Gram-negative infections.[13,33] The predominance of Gram-negative infections in this high-risk population is concerning due to the emergence of MDR Gram-negative bacteria globally, with the associated increased risk for mortality.[8,34] Preterm infants in the NICU are at particular risk for MDR infection due to high rates of MDR colonisation,[11] prolonged hospitalisation, high usage of extended spectrum antibiotics,[35] poor immune function and high usage of invasive devices.[31] Available studies from Asia, South America and Africa have reported that between 50% and 80% of infants in these settings are colonised with MDR Gram-negative bacteria with high reported rates of resistance to antibiotic such as ampicillin, aminoglycoside and third-generation cephalosporins.[31] The proportion of MDR Gram-negative organisms in our study is moderately high (47.2% of infecting organisms) compared to similarly reported MDR rates from around the region, i.e. Taiwan (18.6%)[22] and India (80–100%).[36,37]

The incidence of antibiotic resistance to empiric antibiotic regimens is important to determine in the clinical setting, as inappropriate coverage may contribute to worse outcomes. It is particularly concerning to note that our empiric regimen of benzylpenicillin and gentamicin only covered up to 64% of infecting EOI organisms in our study over the study period. Coverage with cloxacillin and gentamicin for infecting LOI organisms was lower, with only 49.3% coverage. As expected, the majority of nonsusceptibility to empiric coverage in these infections was related to Gram-negative organisms. Even so, the percentage of sepsis-related mortality (EOI 28.8%, LOI 7.5%) in our setting was within the range of reported incidence in the literature over the study period.[27, 28] Moreover, there was no difference in the proportion of resistance to empiric coverage among those infants who survived and died from EOI and/or LOI. This could be related to our unit practice of early escalation to a third-generation cephalosporin or meropenem among patients with clinical evidence of sepsis. Both of these reserve antibiotics are also still mostly effective against the common infecting Gram-negative organisms. Of note, our empiric antibiotic regimen for LOI has been changed to cloxacillin and amikacin in recent times to provide better coverage for these organisms while keeping broad spectrum antibiotic usage in check.

Reports on resistance to routinely used first-line antibiotics for neonatal infections vary across different geographical regions. A multicentre US NICU study of 6184 infants demonstrated that around 1 quarter of all infecting Gram-negative isolates were non-susceptible to ≥1 antibiotic, with up to 14.8% being resistant to gentamicin, 9.9% to third-generation cephalosporin or cefepime, and 0.5% (0–1.1%) to carbapenems.[33] Similar patterns of resistance were noted in a separate surveillance network study from the UK where the antibiotic resistance of *E. coli* and *Klebsiella* spp to the recommended antibiotic empiric regimen for EOI and LOI was 6–16% and 8–12%, respectively.[38] The rates of Gram-negative gentamicin resistance in our study were much higher (37% resistance) and are similar to that previously reported in 4 Asian NICUs.[4] Importantly, the rates of amikacin and cefotaxime resistance were lower in our Gram-negative isolates in comparison to that reported from regional neonatal units.[4,39-42] Carbapenem resistance is also uncommon in our setting with the only notable resistance among *Acinetobacter* spp infections. Among the Gram-positive microorganisms isolated, CoNS and *S. aureus* accounted for almost 75% of such infections. Our reported rates of MRSA infections were similar to that reported from surrounding neonatal units with rates ranging from 41% to 45%.[40,41] We did not detect any vancomycin-resistant isolates among the *Enterococcus* infections.

Our results are limited by the single-centre design of our study. However, our 13-year cohort is drawn from the largest NICU in Singapore that provides care for an estimated two thirds of VLBW infants born locally. This provides a reasonable basis from which to make important comparisons and

inferences about local and regional burden of infections and antimicrobial resistance. Lack of complete data on antenatal antibiotic exposure and device-associated infections precluded further analysis of its impact on risk of infection and resistance patterns. It is also important to note that this study is based on in vitro reporting of susceptibility to individual antimicrobial agents that does not account for the potential synergistic effect of antimicrobial combinations. Additionally, the susceptibility data were extracted from reports generated for clinical use, which may be influenced by reporting standards[21] that are used to define resistant organisms that may not be solely defined by in vitro testing.

These data provide important insights into the local and regional burden of infections among preterm VLBW infants and the NICU as well as an understanding of the general patterns of antimicrobial resistance of infecting organisms. These data can form the basis from which to develop infection control initiatives and adjustment of antimicrobial coverage in this high-risk population.

CONCLUSION

In our setting, Gram-negative bacteria are the predominant causative organisms for EOI and LOI and are frequently MDR. Understanding the pattern of antimicrobial resistance is important in providing appropriate empiric coverage for neonatal infections.

Ethics approval

This study protocol was reviewed and approved by the local institutional review board. The study was performed in accordance with the SingHealth Centralised Institutional Review Board (Reference nos. 2015/2992 and 2022/2194). It was performed in accordance with the Declaration of Helsinki. The study was granted an exemption of written consent by the ethics review board.

Conflict of interest

The authors declared no conflicts of interest.

Funding

This study received no funding.

Data availability statement

Data are available upon reasonable request from the corresponding author.

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Ann Acad Med Singap 2023;52:570-9
https://doi.org/10.47102/annals-acadmedsg.202379

ORIGINAL ARTICLE

Risk of dementia in the elderly with non-alcoholic fatty liver disease: A nested case-control study in the Republic of Korea

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is known to be associated with metabolic syndrome of which diabetes is an important component. Although diabetes is a known risk factor for dementia, studies on the association between NAFLD and dementia still produce conflicting results. This study aimed to determine whether NAFLD would be a risk factor for the development of dementia in an elderly population.

Method: This study included 107,369 subjects aged ≥60 years in the Korean National Health Insurance Service-Senior cohort, entered in 2009 and followed up until 2015. NAFLD was diagnosed by calculating fatty liver index (FLI). Subjects were screened for dementia at baseline using a Korean Dementia Screening Questionnaire, and dementia was diagnosed using ICD-10 codes. Controls were randomly selected at a ratio of 1:5 from individuals who were at risk of becoming the case subjects at the time of selection.

Results: From 107,369 subjects, 65,690 stroke- and dementia-free subjects without chronic hepatitis B or C or excessive alcohol drinking were selected for evaluation. Having NAFLD, determined by FLI, was associated with increased risk of dementia development (adjusted odds ratio [AOR] 1.493; 95% confidence interval [CI] 1.214–1.836). The increased risk of dementia in NAFLD subjects was independent of type 2 diabetes (AOR 1.421; 95% CI 1.013–1.994, in subjects with diabetes: AOR 1.540; 95% CI 1.179–2.010, in subjects without diabetes).

Conclusion: In this population-based nested case-control study, having NAFLD increased the risk of dementia in elderly individuals, independent of accompanying diabetes.

Ann Acad Med Singap 2023;52:570-9

Keywords: dementia, metabolic syndrome, non-alcoholic fatty liver disease, population-based study

CLINICAL IMPACT

What is New

- This nationwide nested case-control study assessed the risk of dementia in elderly subjects.
- Fatty liver index-defined non-alcoholic fatty liver disease (NAFLD) was associated with newly diagnosed dementia in subjects older than 60 years, independent of diabetes mellitus, a known risk factor for dementia.

Clinical Implication

- Dementia and NAFLD are frequent conditions that share underlying metabolic risk factors, and the finding of this study adds evidence that NAFLD is associated with newly developed dementia in elderly subjects.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease affecting about 25% of the general population.[1,2] NAFLD has a broad disease spectrum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH)/liver cirrhosis, resulting in increased risk of developing not only liver-related complications but also extrahepatic morbidities.[3] Common extrahepatic manifestations of NAFLD consist of cardiovascular diseases, non-liver cancers and chronic kidney disease (CKD).[4-6] It has been contemplated that increased extrahepatic complications in NAFLD might be due to metabolic derangements, such as type 2 diabetes or hypertension that are thought to have a strong association with NAFLD.[7,8]

In recent years, several reports have suggested possible links between NAFLD and impaired cognitive functions.[9-11] In a study analysing the correlation between NAFLD and total cerebral brain volume using brain magnetic resonance imaging in the cohort of Framingham Study, it was found that NAFLD is associated with smaller total cerebral brain volume independent of visceral adipose tissue and cardiometabolic risk factors.[12] In addition, a recent cohort study demonstrated that elevated liver enzymes were associated with a higher risk of

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Alzheimer's disease (AD) where NAFLD is the most frequent aetiology of abnormal liver enzyme levels.[13] On the other hand, there are studies reporting the negative association between NAFLD and cognitive function decline or dementia.[14,15]

In this study, we investigated the associations between NAFLD and the risk of dementia in an elderly population, age over 60 years, using the database of the nationwide population-based National Health Insurance Service (NHIS)-Senior cohort (NHIS-Senior) in the Republic of Korea.[16] NHIS-Senior provides nationally representative cohort data of the entire elderly population in South Korea and includes mental health screening as a major variable.

METHOD

Database

NHIS is a single-payer insurance programme that has been providing compulsory national health screening since 1996, covering almost the entire Korean population of 50 million.[17] NHIS-Senior comprises 558,147 individuals over the age of 60 years, that were randomly sampled from the 5 million examinees who received physical health examinations provided by the Korean NHIS in 2002.[18] The information in the NHIS-Senior dataset included all inpatient and outpatient medical claims data, including prescription drug use, diagnostic and treatment codes, and primary and secondary diagnosis codes. Measurements from health check-up examinations, and information on socioeconomic and demographic status were also contained. All individuals included in NHIS-Senior were followed up until 2015 unless there was death or disqualification for National Health Insurance, such as emigration.

This study was approved by the Institutional Review Board of Yonsei University Health System (3-2019-0167). Informed consent was waived, as the researchers only accessed the database for analysis purposes, and personal information was anonymised to protect individuals' privacy.

Case and control selection

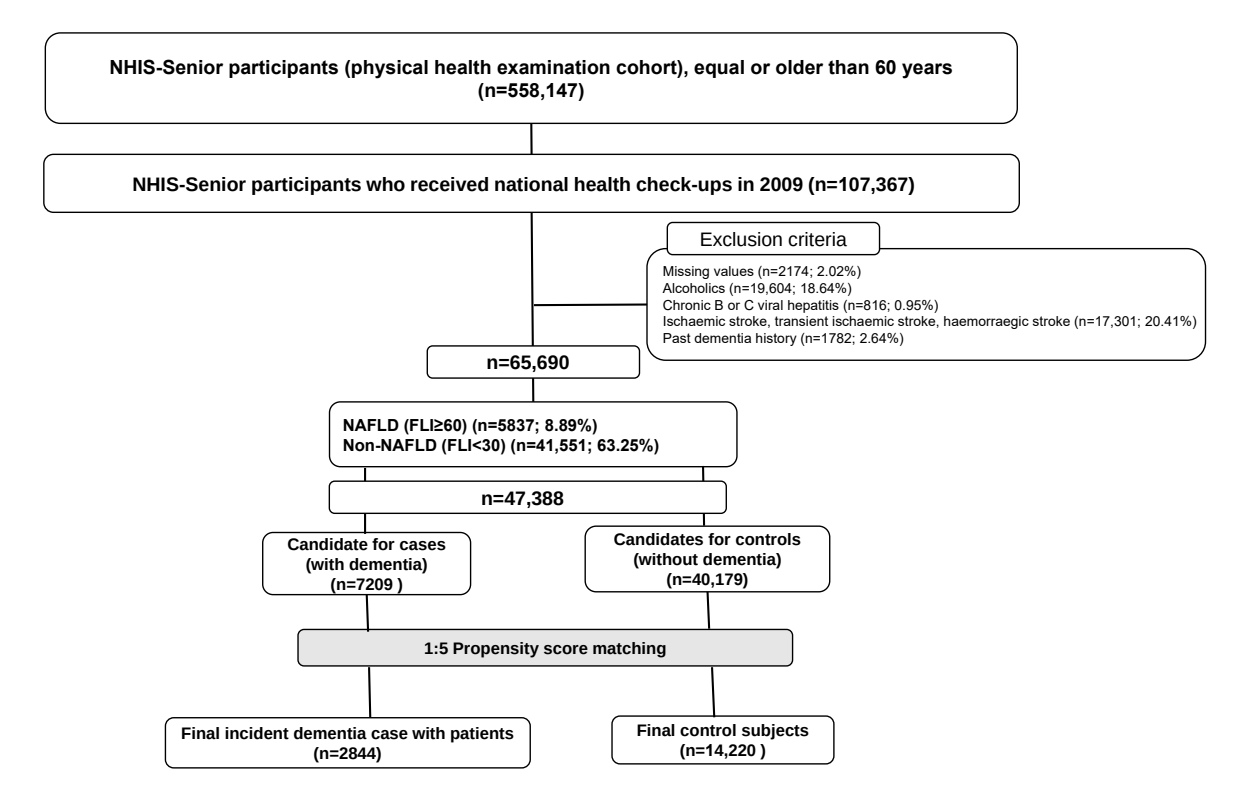
From the Korean NHIS-Senior, a total of 107,367 subjects who had a health check-up in 2009—the year when serum triglyceride (TG) level was included as a parameter in the physical health examination programme—and follow-up data were reviewed until December 2015. those, subjects who met the following criteria were excluded (n=41,677): missing data (n=2174); excessive alcohol drinking (>210 g/week for men and >140 g/week for women)[19] (n=19,604); positive serologic markers of hepatitis B or C (n=816); past history of ischaemic stroke, transient ischaemic stroke, haemorrhagic stroke (n=17,301); having dementia before or at the time of enrolment (n=1782). A total of 65,690 individuals were analysed in our study (Fig. 1). The fatty liver index (FLI) was calculated to define NAFLD. FLI was the relatively easy and accurate index that was calculated from routine measures used in clinical settings, such as body mass index (BMI), waist circumference, TG, and gamma glutamyl transferase (γGT).[20] The accuracy of FLI had been validated in identifying NAFLD with the comparable accuracy with abdominal sonography.[21] FLI was calculated according to the following formula.[20]

$$FLI = (e(0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745))/(1 + e(0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745)) \times 100$$

Similar to a previous study, the FLI cutoff of <30 was applied to predict the absence of NAFLD (specificity: 87%, negative likelihood ratio: 0.2), and FLI≥60 was used for identifying the presence of NAFLD (sensitivity: 86%, positive likelihood ratio: 0.5).[20]

The primary outcome of interest was the development of dementia, which was identified using the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Among the NHIS-Senior cases, the eligibility criteria for the dementia incidence patients were as follows: (1) first-time diagnosis of dementia (ICD F00-F03 or G30), (2) discharge diagnosis with a primary diagnosis code of dementia or confirmed at least twice in the outpatient department, and (3) no prior diagnosis of cerebrovascular disease (Fig. 1). The date of dementia diagnosis was the first date of outpatient or inpatient records with a primary diagnosis of dementia. The index date was defined as the date 1 year prior to the date of dementia diagnosis. Controls were randomly selected at a ratio of 1:5 from individuals who were at risk of becoming the case subjects at the time when the particular case subjects were selected. The subjects excluded during the case selection were also excluded from the risk set. The case and control subjects were matched based on the duration of follow-up until the age at case selection, gender, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose, hypertension, diabetes mellitus (DM), current smoking status, and economic status at index date. Since DM is known as the major risk factor for dementia,[22,23] the case and control subjects were further analysed in a subgroup analysis based on the presence of DM or absence of DM.

Fig. 1. Flow of study population.



FLI: fatty liver index; NAFLD: non-alcoholic fatty liver disease; NHIS-Senior: National Health Insurance Service

Assessment of dementia

The subjects were screened for dementia at baseline using the Korean Dementia Screening Questionnaire (KDSQ). The KDSQ consists of 3 subscales (global memory function, other cognitive function, and instrumental activities of daily living), including 15 items that can detect early changes in cognitive decline.[24] Scores for each item in the KDSQ range from 0 to 2, with a higher score indicating poorer function and a higher frequency. The KDSQ is not affected by age or educational level and has shown a sensitivity of 0.79 and a specificity of 0.80 for dementia. The KDSQ rate positive was defined as the case with the score ≥6.[25] The development of dementia was confirmed by ICD-10 codes for dementia (F00-F03, G30).

Clinical variables and biochemical measurements

We obtained information about baseline comorbidities from inpatient and outpatient hospital diagnoses. Baseline comorbidities were defined using the medical billing and prescription drug information registered before the index date. In order to increase the accuracy of diagnoses, the study was conducted based on the condition diagnosed when the patient was discharged from the hospital or diagnosed at least twice in the outpatient department, which was the same as in previous studies using NHIS.[18,26]

Hypertension was defined when blood pressure was 140/90 mmHg or higher, according to the 2020 International Society of Hypertension Global Hypertension Practice Guidelines,[27] or when taking antihypertensive medications. Diabetes was defined as a fasting blood glucose level of 126 mg/dL or currently taking diabetes medications. BMI was calculated as body weight divided by height squared (kg/m^2). An individual's standard income was based on the total amount of national health insurance premiums paid by the insured in the index year in proportion to the individual's income. Smoking status was categorised as non-smokers and past smokers into 1 group, and current smokers into another group. Blood pressure was measured using a mercury sphygmomanometer after resting for at least 10 minutes in a sitting position. Blood samples were collected as measured by a blood laboratory after an overnight fast for 12 hours. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), TG, γGT, total cholesterol, and low-density cholesterol were analysed from blood samples.

Statistical analysis

The baseline characteristics of patients with dementia and the matched cohort were compared with chi-squared tests for categorical variables and Mann-Whitney U tests for continuous variables. To analyse the association between NAFLD and risk of dementia, conditional logistic regression was performed. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were determined. Other matching variables for the nested case-control study design (i.e. confounders that were adjusted for) were... age; gender; cardiovascular disease risk factors, such as BMI, SBP, DBP, fasting blood glucose, hypertension, DM, current smoking status; and economic status. All of the confounders listed above were identified on the index date.

Although we primarily used the nested case-control design in assessing the association between NAFLD and dementia in order to avoid immortal time bias, we also assessed the association between incident NAFLD, which was entered into the models as a time-varying factor, and dementia using Cox proportional hazards regression models. The underlying time scale was the observational period and observation started on the date that participants enrolled in this study. Participants were censored at the date of dementia diagnosis, date of death or end of the study period, defined as the last date of follow-up or 31 December 2018. Covariates adjusted in multivariate analysis were identical to those adjusted in conditional logistic regression analysis from the nested case-control design.

All analyses were two-tailed, and $P<0.05$ was considered significant. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, US).

RESULTS

From the 107,306 participants in NHIS-Senior, 65,690 subjects who met the inclusion criteria were taken for NAFLD evaluation. Among 65,690 subjects, those with either NAFLD by FLI≥60 or non-NAFLD by FLI<30 were included in the analysis (Fig. 1). The final number of participants with either NAFLD or non-NAFLD was 47,388 after excluding 18,302 subjects with intermediated value evaluated by FLI. From 47,388 subjects, 7209 were diagnosed with dementia. Cases with dementia and the control subjects were matched based on the duration of follow-up until the age at case selection, gender, BMI, SBP, DBP, fasting blood glucose, hypertension, DM, current smoking status and economic status. The final number of cases was 2844, and 14,220 subjects served as the control. The baseline characteristics of the study subjects are presented in Table 1. Compared with the control group, dementia case patients had more elevated AST, γGT levels, combined NAFLD, heart failure and CKD. Naturally, dementia case patients had significantly increased KDSQ positive rates as well as KDSQ scores compared with those of the control subjects (Table 1).

Having NAFLD was significantly associated with increased risk of dementia (AOR 1.493; 95% CI 1.214–1.836) (Table 2). The association between NAFLD and development of dementia with and without DM is shown. The baseline characteristics of the 2 groups are described in Table 3. In the diabetic population, dementia case patients had significantly higher TG level and combined heart failure when other factors were not significantly different. The proportion of those with NAFLD was not different between dementia cases and the control subjects among those with DM. On the other hand, among the non-diabetic population, dementia case had increase AST, rGT levels, combined NAFLD, heart failure, myocardial infarction (MI) and CKD. However, having NAFLD was significantly associated with increased risk of dementia in both the DM group (AOR 1.421; 95% CI 1.013–1.994) and the non-DM group (AOR 1.540; 95% CI 1.179–2.010) (Table 4).

DISCUSSION

In this nationwide longitudinal nested case-control study, we evaluated 2844 dementia cases and 14,220 control cases with matching variables, including age, gender, various metabolic factors and the time of the follow-up at a 1:5 ratio, from NHIS-Senior. NHIS-Senior contains the follow-up data from 554,147 subjects over the age of 60 years, including the data from a validated dementia screening questionnaire. We found that having NAFLD, identified by FLI, a validated composite index of NAFLD, was associated with increased risk of all-cause dementia. The result was independent of having type 2 diabetes although the association tended to be stronger in those without diabetes.

The association observed in our study is in accordance with a recent Swedish cohort study showing increased dementia incidence in those with 65 years or older subjects with ICD code-defined NAFLD after a median follow-up period of 5.5 years.[28] In this study, the control group had significantly lower proportion of metabolic derangements, such as diabetes, dyslipidaemia, hypertension and obesity. After the adjustment of these metabolic factors, NAFLD patients still showed increased HR of dementia. Another cohort study from Korea, that included subjects aged 40–69 years, also indicated the association

Table 1. Baseline characteristics of dementia and matched controls.

Characteristics	Cases (n=2844)	Controls (n=14,220)	*P* value
Age at case selection, years	72.5 ± 3.6	72.4 ± 3.6	0.548
Male sex, no. (%)	649 (22.8)	3245 (22.8)	>0.999
BMI, kg/m^2	22.9 ± 2.5	22.9 ± 2.4	0.337
NAFLD[a], no. (%)	192 (6.8)	784 (5.5)	**0.009**
Economic status, no. (%)			>0.999
Low	487 (17.1)	2435 (17.1)	
Middle	688 (24.2)	3440 (24.2)	
High	1669 (58.7)	8345 (58.7)	
Current smoker, no. (%)	78 (2.7)	390 (2.7)	>0.999
Hypertension[b] no. (%)	1742 (61.3)	8710 (61.3)	>0.999
SBP, mmHg	128.0 ± 14.5	128.2 ± 13.2	0.385
DBP, mmHg	77.1 ± 9.5	77.2 ± 9.0	0.836
Fasting glucose, mg/dL	96.0 ± 12.5	95.9 ± 12.1	0.751
Total cholesterol, mg/dL	200.2 ± 39.2	200.0 ± 37.5	0.777
LDL cholesterol, mg/dL	121.4 ± 39.3	121.5 ± 40.6	0.916
TG, mg/dL	125.1 ± 72.4	122.3 ± 67.9	0.058
AST, U/L	25.2 ± 12.7	24.6 ± 10.0	**0.032**
ALT, U/L	20.2 ± 14.5	19.7 ± 12.8	0.095
γGT, U/L	23.8 ± 34.9	21.6 ± 22.5	**0.001**
Creatinine, mg/dL	0.96 ± 0.90	0.95 ± 0.94	0.589
Heart failure, no. (%)	345 (12.13)	1220 (8.6)	**<0.001**
CKD or ESRD, no. (%)	33 (1.2)	77 (0.5)	**<0.001**
History of MI, no. (%)	64 (2.3)	251 (1.8)	0.079
Malignancy, no. (%)	217 (7.6)	1088 (7.7)	0.969
Cognitive function[c]			
KDSQ positive rate, no. (%)	83 (27.9)	278 (15.7)	**<0.001**
KDSQ score	2.0 ± 2.1	1.4 ± 1.7	**<0.001**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; ESRD: end-stage renal disease; KDSQ: Korean Dementia Screening Questionnaire; LDL: low-density lipoprotein; MI: myocardial infarction; NALFD: non-alcoholic fatty liver disease; SBP: systolic blood pressure; TG: triglyceride; γGT: γ glutamyl transferase
Values are expressed as means ± standard deviation or no. (%).
Bold values represent statistical significance.
Case and control subjects were matched based on the duration of follow-up until the age at case selection, gender, cardiovascular disease risk factors (e.g. BMI, SBP, DBP, fasting blood glucose, hypertension, diabetes mellitus, current smoking status) and economic status.
[a] NAFLD was defined as having fatty liver index ≥60, a fatty liver prediction model based on BMI, waist circumference, TG and γGT.
[b] Hypertension was defined as SBP≥140 mmHg, DBP≥90 mmHg or receiving antihypertensive drugs.
[c] KDSQ includes 5 items. Each item on the KDSQ is scored from 0 to 2, with a higher score indicating poorer function and a greater frequency. The KDSQ rate positive was defined as the case with the score ≥6.

Table 2. Relationship between dementia and non-alcoholic fatty liver disease.

Liver status[a]	Cases (n=2844)	Controls (n=14,220)	Crude	Adjusted[b]
	No. (%)	No. (%)	OR (95% CI)	OR (95% CI)
Non-NAFLD	2652 (93.3)	13,436 (94.5)	1.00	1.00
NAFLD	192 (6.8)	784 (5.5)	1.372 (1.125–1.673)	1.493 (1.214–1.836)

CI: confidence interval; NAFLD: non-alcoholic fatty liver disease; OR: odds ratio
[a] NAFLD was defined as having fatty liver index (FLI) ≥60, a fatty liver prediction model based on body mass index (BMI), waist circumference, triglyceride and γ glutamyl transferase. Non-NAFLD was defined as having FLI<30.
[b] Adjusted for age, gender, BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose, hypertension, diabetes mellitus, current smoking status and economic status.

Table 3. Baseline characteristics of dementia and matched controls in diabetes mellitus and non-diabetes mellitus groups at index date[a].

Group	Diabetes mellitus			Non-diabetes mellitus		
Characteristics	Cases (n=746)	Control (n=3730)	*P* value	Cases (n=2098)	Control (n=10,490)	*P* value
Age at case selection, years	72.0 ± 3.2	72.0 ± 3.2	0.736	72.6 ± 3.7	72.6 ± 3.7	0.614
Male sex, no. (%)	144 (19.3)	720 (19.3)	>9.999	505 (24.1)	2525 (24.1)	>9.999
BMI, kg/m^2	23.5 ± 2.3	23.5 ± 2.3	0.659	22.7 ± 2.5	22.7 ± 2.4	0.385
NAFLD[b]	77 (10.3)	325 (8.7)	0.161	115 (5.5)	459 (4.4)	**0.027**
Economic status, no. (%)			>9.999			>9.999
Low	119 (16.0)	595 (16.0)		368 (17.5)	1840 (17.5)	
Middle	161 (21.6)	805 (21.6)		527 (25.1)	2635 (25.1)	
High	466 (62.5)	2330 (62.5)		1203(57.4)	6015 (57.4)	
Current smoker, no. (%)	735 (98.5)	3675 (98.5)	>9.999	67 (3.2)	335 (3.2)	>9.999
Hypertension[c], no. (%)	593 (79.5)	2965 (79.5)	>9.999	1149 (54.8)	5745 (54.8)	>9.999
SBP, mmHg	128.6 ± 13.8	128.6 ± 13.2	0.937	127.8 ± 14.7	128.1 ± 13.3	0.341
DBP, mmHg	76.8 ± 9.5	76.8 ± 8.9	0.953	77.3 ± 9.5	77.3 ± 9.0	0.836
Fasting glucose, mg/dL	101.7 ± 16.2	101.6 ± 15.9	0.861	94.0 ± 10.1	93.9 ± 9.6	0.772
Total cholesterol, mg/dL	196.9 ± 41.4	196.7 ± 38.4	0.911	201.4 ± 38.3	201.1 ± 37.1	0.787
LDL cholesterol, mg/dL	117.5 ± 46.1	117.9 ± 39.4	0.820	122.8 ± 36.4	122.8 ± 41.0	0.969
TG, mg/dL	135.6 ± 88.2	126.8 ± 71.2	**0.011**	121.3 ± 65.4	120.7 ± 66.6	0.680
AST, U/L	24.8 ± 8.7	24.6 ± 10.7	0.720	25.3 ± 13.9	24.6 ± 9.8	**0.030**
ALT, U/L	21.0 ± 10.7	21.0 ± 15.6	0.912	19.9 ± 15.7	19.2 ± 11.6	0.059
γGT, U/L	25.0 ± 27.5	23.4 ± 26.4	0.133	23.4 ± 37.2	20.9 ± 20.9	**0.003**
Creatinine, mg/dL	0.99 ± 0.95	0.97 ± 0.98	0.375	0.96 ± 0.90	0.94 ± 0.94	**0.029**
Heart failure, no. (%)	119 (15.9)	408 (10.9)	**<0.001**	226 (10.8)	812 (7.7)	**<0.001**
CKD or ESRD, no. (%)	11 (1.5)	45 (1.2)	0.548	22 (1.0)	32 (0.3)	**<0.001**
History of MI, no. (%)	24 (3.2)	116 (3.1)	0.878	40 (1.9)	135 (1.3)	**0.027**
Malignancy, no. (%)	60 (8.0)	330 (8.9)	0.477	157 (7.5)	758 (7.2)	0.678

Table 3. Baseline characteristics of dementia and matched controls in diabetes mellitus and non-diabetes mellitus groups at index date.[a] (Cont'd)

Group	Diabetes mellitus			Non-diabetes mellitus		
Characteristics	Cases (n=746)	Control (n=3730)	*P* value	Cases (n=2098)	Control (n=10,490)	*P* value
Cognitive function[d]						
KDSQ positive rate, no. (%)	27 (29.7)	79 (16.0)	**0.002**	56 (27.0)	199 (15.5)	**<0.001**
KDSQ score	2.1 ± 2.1	1.5 ± 1.7	**0.011**	2.0 ± 2.1	1.4 ± 1.7	**<0.001**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; ESRD: end-stage renal disease; KDSQ: Korean Dementia Screening Questionnaire; LDL: low-density lipoprotein; MI: myocardial infarction; NALFD: non-alcoholic fatty liver disease; SBP: systolic blood pressure; TG: triglyceride; γGT: γ glutamyl transferase
Values are expressed as means ± standard deviation or no. (%).
Bold values represent statistical significance.
Case and control subjects were matched based on the duration of follow-up until the age at case selection, gender, cardiovascular disease risk factors (e.g. BMI, SBP, DBP, fasting blood glucose, hypertension, diabetes mellitus, current smoking status) and economic status.
[a] The index date was defined as the date 1 year prior to the date of dementia diagnosis.
[b] NAFLD was defined as having fatty liver index ≥60, a fatty liver prediction model based on BMI, waist circumference, TG and γGT.
[c] Hypertension was defined as SBP≥140 mmHg, DBP≥90 mmHg or receiving antihypertensive drugs.
[d] KDSQ includes 5 items. Each item on the KDSQ is scored from 0 to 2, with a higher score indicating poorer function and a greater frequency. The KDSQ rate positive was defined as the case with the score ≥6.

Table 4. Relationship between dementia and non-alcoholic fatty liver disease according to diabetes mellitus.

	With diabetes mellitus				Without diabetes mellitus			
	Cases (n=746)	Controls (n=3730)	Adjusted*	*P* value	Cases (n=2098)	Controls (n=10,490)	Adjusted*	*P* value
	No. (%)	No. (%)	OR (95% CI)		No. (%)	No. (%)	OR (95% CI)	
Non-NAFLD	669 (89.68)	3405 (91.3)	1.00	0.042	1983 (94.5)	10,031 (95.6)	1.00	0.002
NAFLDa	77 (10.3)	325 (8.7)	1.421 (1.013–1.994)		115 (5.5)	459 (4.4)	1.540 (1.179–2.010)	

CI: confidence interval; NAFLD: non-alcoholic fatty liver disease; OR: odds ratio
[a] NAFLD was defined as having fatty liver index (FLI) ≥60, a fatty liver prediction model based on body mass index (BMI), waist circumference, triglyceride and γ glutamyl transferase.
* Adjusted for age, gender, BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose, hypertension, diabetes mellitus, current smoking status and economic status.
In the Cox proportional hazards regression model, NAFLD was the risk factor for dementia, compared to non-NAFLD in the overall, DM, and non-DM population (adjusted hazard ratio [HR] 1.239 [95% CI 1.129–1.360], 1.229 [95% CI 1.070–1.412], 1.227 [95% CI 1.080–1.395]), respectively (Table 5).

between dementia and NAFLD identified by the hepatic steatosis index from calculation using ALT/AST ratio, BMI, gender and diabetes.[29] The control group from the Korean study also showed significantly lower metabolic disorders, and the multivariable analysis adjusting these metabolic factors still produced increased HR of dementia development in NAFLD patients. However, the association between NAFLD and dementia is still under dispute, and some studies claimed the lack of association. A study using primary data from Germany suggested that ICD code-defined NAFLD/NASH patients failed to demonstrate increased risk of dementia compared with those without NAFLD/NASH diagnosis.[14] In this German study, the NAFLD/NASH group and the control group showed no significant differences in the proportion of metabolic derangements such as diabetes, hyperlipidaemia and hypertension. Another study from Sweden compared biopsy-proven NAFLD with the control group and suggested no association between NAFLD and dementia.[30] As the investigators of this Swedish study discussed in the article, there were insufficient clinical and biochemical information on the control group. Since NAFLD is highly prevalent and tends to be underdiagnosed, the control group could have not been truly the control group. In addition, the German study defined NAFLD/NASH by ICD code, having the possibility that those who failed to be assessed for NAFLD/NASH might have been included in the control group, affecting the dementia event outcome. Considering that defining exposed (NAFLD) and unexposed (non-NAFLD) groups is an important process in an observational study evaluating the association

Table 5. Hazard ratios for dementia risk factors in the Cox regression model.

Overall		
	HR (95% CI)	***P***
Age	**1.101 (1.096–1.106)**	**<0.001**
Male sex	**0.782 (0.740–0.827)**	**<0.001**
BMI	**0.961 (0.951–0.970)**	**<0.001**
Hypertension	**1.154 (1.097–1.213)**	**<0.001**
Diabetes	**1.177 (1.118–1.239)**	**<0.001**
High economic status	**0.934 (0.880–0.990)**	**0.0228**
Smoking	**1.142 (1.043–1.251)**	**0.0043**
NAFLD[a]	**1.493 (1.214–1.836)**	**0.001**
Subjects with type 2 diabetes		
Age	**1.094 (1.085–1.102)**	**<0.001**
Male sex	**0.799 (0.728–0.876)**	**<0.001**
BMI	**0.966 (0.951–0.981)**	**<0.001**
Hypertension	**1.144 (1.043–1.255)**	**0.0044**
High economic status	**0.900 (0.816–0.992)**	**0.0343**
Smoking	**1.203 (1.028–1.406)**	**0.0343**
NAFLD[a]	**1.094 (1.085–1.102)**	**<0.001**
Subjects without diabetes		
Age	**1.104 (1.098–1.110)**	**0.0017**
Male sex	**0.773 (0.721–0.828)**	**<0.001**
BMI	**0.957 (0.946–0.969)**	**<0.001**
Hypertension	**1.158 (1.090–1.230)**	**<0.0001**
Smoking	**1.122 (1.002–1.255)**	**0.0452**
NAFLD[a]	**1.104 (1.098–1.110)**	**<0.001**

BMI: body mass index; CI: confidence interval; HR: hazard ratio; NAFLD: non-alcoholic fatty liver disease
[a] NAFLD was defined as having fatty liver index (FLI) ≥60, a fatty liver prediction model based on BMI, waist circumference, triglyceride and γ glutamyl transferase. Non-NAFLD was defined as having FLI<30.
Bold values represent statistical significance.

between a risk factor and an outcome of interest, the underdiagnosed NAFLD subjects that might have been included in the control group could have altered the outcome result. To our best knowledge, all the currently published observational studies on the association between NAFLD and dementia used event-based cohort design where the event being having NAFLD and the outcome being occurrence of dementia.[14,28-31] On the other hand, we applied the nested case-control method, the case being dementia event, in an effort to minimise immortal time bias. However, case-control observational studies also have some limitations, particularly selection bias.[32] Nevertheless, it has been generally believed that when cases and controls are selected from the same source, the likelihood of selection bias tends to be diminished. In our study, the case and control subjects were selected from a population-based cohort.

We used NHIS-Senior, which comprises individuals over the age of 60 years that were randomly sampled from the 5 million examinees who received physical health examinations provided by the Korean NHIS.[18] Unlike the general

NHIS cohort, individuals included in NHIS-Senior were screened for dementia using KDSQ, the primary screening tool for cognitive dysfunction.[24] Those with the possibility of having dementia with KDSQ positive rate are to be further evaluated and diagnosed for dementia.

Apart from the possible sampling bias mentioned above, this study has several other limitations that need to be further addressed in future studies. Although NHIS-Senior is convenient and useful for clinical research, information on the results of specific medical evaluations other than those related to health examinations cannot be assessed. Moreover, NAFLD could only be operationally defined using FLI. However, it has been validated that FLI could identify NAFLD comparable with ultrasonography.[21] In the clinical milieu where NAFLD often fails to receive medical attention, defining NAFLD using a validated prediction model would compensate for the underestimation of the disease. Another limitation is that we could not fully control other possible dementia risk factors, such as educational level, accompanying hearing loss, depression, physical activity level and medication that might affect cognitive functions. In addition, pathophysiological mechanisms between NAFLD and dementia cannot be demonstrated in this observational study. There are studies demonstrating that NAFLD patients have increased risk of carotid atherosclerosis as well as increased carotid intima media thickness that may result in cognitive impairments.[33-35] Another previous investigation suggested that NAFLD and dementia may have a common aetiological mechanism of oxidative stress and inflammation.[36] Among the subtypes of dementia, studies on the pathogenesis of AD produced a growing body of evidence linking AD and insulin resistance, which is the major pathogenesis behind NAFLD.[37,38] A study on the protein–protein interaction analysis of AD and NAFLD identified that both disease entities shared 189 genes related with carbohydrate metabolism, fatty acid metabolism and interleukin-17 signalling pathways.[39] Moreover, brain amyloid burden is known to be an important pathology of AD, and it has been reported that liver dysfunction resulted in decreased peripheral amyloid-β clearance.[40,41] In our study, 79.6% of dementia patients had AD. When NAFLD was associated with AD only, it also demonstrated a significant risk (data not shown). Further studies on the pathophysiology are needed to give solutions for NAFLD and dementia.

CONCLUSION

This nationwide study used a database where dementia was screened out using a dementia screening questionnaire (KDSQ) and evaluated whether having NAFLD was associated with the occurrence of dementia in individuals with age over 60. Our results support that NAFLD was associated with an increased risk of dementia, independent of accompanying DM.

Acknowledgement

This study used data from the Korean National Health Insurance Service (NHIS) (NHIS-2019-2-272) and made clear that all results were not related to NHIS.

Financial support

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2021R1H1A2093347).

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Ann Acad Med Singap 2023;52:580-9
https://doi.org/10.47102/annals-acadmedsg.2023100

ORIGINAL ARTICLE

Real-world data on the use of emicizumab in patients with haemophilia A with and without inhibitors in Singapore

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ABSTRACT

Introduction: Emicizumab is a bispecific monoclonal antibody that mimics the function of factor VIII by binding to factor IXa and factor X to achieve haemostasis in haemophilia A. The long half-life and subcutaneous mode of administration makes emicizumab a compelling treatment option for bleeding prophylaxis. There is still limited real-world data on its use and management considerations, especially during surgical procedures. The objective of the study is to describe the real-world experience of emicizumab in a cohort of adult and paediatric haemophilia A patients in Singapore, including its use in the periprocedural setting.

Method: This was an observational study conducted at the 2 main haemophilia treatment centres in Singapore. All haemophilia A patients who commenced treatment with emicizumab before 1 July 2022 were recruited.

Results: A total of 18 patients with haemophilia A were included in this study. Ten (55.6%) patients had active inhibitors. The median annual bleeding rate for all patients before emicizumab use was 4.5 events (interquartile range [IQR] 2.8–8.3) compared with 0 events (IQR 0–0) after emicizumab was commenced (P=0). There were no adverse events of venous or arterial thrombosis, thrombotic microangiopathy, or death. A total of 6 procedures in 5 patients were performed during the study period with no major bleeding complications.

Conclusion: Emicizumab effectively protects against bleeding in haemophilia A patients with and without inhibitors, including in children less than 12 years old. More studies are required to address clinical nuances, such as periprocedural management and the role of immune tolerance in patients with inhibitors on emicizumab.

Ann Acad Med Singap 2023;52:580-9

Keywords: emicizumab, haemophilia A, haemostatic agent, inhibitor, prophylaxis

CLINICAL IMPACT

What is New

- This study adds real-world data on the effectiveness of emicizumab in protecting haemophilia A patients with and without inhibitors, including in children less than 12 years old, against bleeding.

Clinical Implication

- This data can guide policymaking to improve the accessibility of this effective but costly treatment option to haemophilia A patients in Singapore.

INTRODUCTION

Haemophilia A is an X-linked hereditary bleeding disorder caused by pathogenic genetic variants, which results in a deficiency of factor VIII (FVIII).[1] The mainstay of treatment is FVIII replacement, which can be administered as prophylaxis or on-demand.[2] While FVIII replacement has greatly improved outcomes in people with haemophilia A, they still face multiple challenges.

The most serious complication of haemophilia A management is the development of inhibitors, which are alloantibodies directed against infused factors. Individuals who develop inhibitors will not be able to use FVIII replacement for the treatment of bleeding or for prophylaxis, and have an increased risk of bleeding.[3] For patients without inhibitors, the high frequency of intravenous administration of FVIII, usually 3 times a week, results in problems with venous access and need for indwelling catheters.[4,5] Extended half-life products can decrease the frequency of FVIII administration; however, the reduction may be modest.[6] Novel agents for the treatment of haemophilia A are required to address these issues.

Emicizumab is a bispecific monoclonal antibody that mimics the function of FVIII by binding to factor IXa and factor X to achieve haemostasis

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in haemophilia A.[7] Initial trials demonstrated impressive efficacy in preventing bleeding episodes in patients with haemophilia A with inhibitors, both in the adult and paediatric population.[7,8] Similar results were seen in patients with haemophilia A without inhibitors.[9,10] This enabled regulatory approval for routine prophylaxis to prevent or reduce bleeding episodes in patients with haemophilia A with or without FVIII inhibitors of all age groups.[11,12]

Emicizumab is an alternative treatment option for people with haemophilia A. It serves the unmet need of providing prophylaxis against bleeds in patients with inhibitors and enables treatment at a lower frequency and via an easier route of administration for those without inhibitors. Yet, more data are required to demonstrate the efficacy, safety profile and nuances around the use of emicizumab in the real-world setting. This is especially so in the periprocedural setting, where there is much more heterogeneity in management.

Singapore is a small island nation in the Asia-Pacific with a small but high-needs haemophilia population with a prevalence of 10.31 per 100,000 males, with an inhibitor rate of 17.9%.[13]

The recent HAVEN 5 study evaluated prophylactic emicizumab for haemophilia A in the Asia-Pacific region in a randomised controlled study.[14] This provides very limited data from the Asia-Pacific region. In this study, we describe real-world data on the use of emicizumab in Singapore in paediatric and adult populations.

METHOD

This was an observational study conducted at 3 public hospitals in Singapore—Singapore General Hospital (SGH) and KK Women's and Children's Hospital (KKH). The study received Institutional Review Board approval from both centres. SGH is the largest adult tertiary hospital in Singapore, and adults with haemophilia A were recruited from the centre, while KKH is the largest paediatric hospital in Singapore, and children with haemophilia A were recruited from this centre. Data collection was performed retrospectively from the Blood Disorder Registry at SGH and from the Bleeding Disorders Registry at KKH. Data were analysed in July 2022. Emicizumab was first used in September 2020 at SGH and in September 2018 at KKH. All haemophilia A patients who commenced emicizumab before 1 July 2022 were included in the study.

Data collection included demographics, baseline haemophilia A history (inhibitor, prophylaxis, immune tolerance induction [ITI], bleeding events) 1 year before emicizumab initiation and post-emicizumab data (emicizumab dosing regime, inhibitor, concurrent prophylaxis or ITI, bleeding events, side effects) 1 year after emicizumab initiation. Patients' minor bleeding episodes were recorded by the patients or caregivers, and documented in the electronic medical records during clinic visits, while more severe bleeding episodes were reviewed by our specialty nurses or haematologists before getting documented in the electronic medical records. Stable patients were reviewed in clinics every 6 months. Patients with higher frequency of bleeds were reviewed more frequently. Annualised bleeding rates (ABRs) were calculated to account for variable follow-up periods. Data were collected from patients undergoing invasive procedures, including procedure type, products used before and after procedures, and bleeding or thrombotic complications during or after surgery. Monitoring of FVIII replacement and inhibitor titres were performed by a bovine-based FVIII chromogenic assay while patients were on emicizumab.

Group comparisons between patients with and without inhibitors were performed with Mann-Whitney U test and Fisher's Exact test. Bleeding data (median ABR, proportion of patients with 0 bleeding events, and proportion of patients with target joints) pre- and post-emicizumab were compared using Wilcoxon sign-rank test and McNamar test. A P value of <0.05 was considered statistically significant. The bleeding outcomes for patients less than 12 years old were analysed as a separate cohort. Statistical analysis was performed using SPSS version 20.0 software (SPSS Inc, Chicago, IL, US).

RESULTS

Eighteen patients were included in the analysis. Their demographic data are presented in Table 1. The median age at the initiation of emicizumab was 6.3 years old (range: 0.08–49.0)—15 were children with a median age of 5 years (range: 0.08–17.5), while 3 patients were adults with a median age of 43 years (range: 21.0–49.0). The median duration of emicizumab prophylaxis was 21.5 months (range: 3.0–46.0). All except 1 patient was male, and 16 (88.9%) patients had severe haemophilia A. Twelve (66.7%) patients were on prophylaxis before emicizumab initiation, with 11 receiving factor VIII prophylaxis and 1 receiving recombinant activated factor VII (rFVIIa) prophylaxis. Ten (55.6%) patients had active inhibitors before initiating emicizumab. Among the patients with active inhibitors, the median inhibitor titre before emicizumab initiation was 9.3 BU (interquartile range [IQR] 6.52–21.3 BU) and all had high-responding inhibitors. Three (37.5%) patients were receiving ITI before emicizumab initiation.

The 2 most common indications for initiating emicizumab prophylaxis were the presence of inhibitors (8 patients) and frequent bleeds in haemophilia A patients without inhibitors (6 patients). Patients were switched from FVIII prophylaxis if the ABR was 2 or more while on FVIII

Table 1. Demographics.

Characteristics	Patients with no inhibitors (n=10)	Patients with inhibitors (n=8)	*P* value
Median age of starting emicizumab (IQR), years	7.9 (2–16.1)	4.1 (1.9–35.5)	0.929
0 to <2 years, no. (%)	2 (20)	2 (25)	
2 to <6 years, no. (%)	2 (20)	3 (37.5)	
6 to <12 years, no. (%)	3 (30)	0 (0)	
12 to <18 years, no. (%)	2 (20)	1 (12.5)	
>18 years, no. (%)	1 (10)	2 (25)	
Sex, no. (%)			
Male	10 (100)	7 (87.5)	0.444
Race, no. (%)			
Chinese	4 (40)	7 (87.5)	0.199
Malay	3 (30)	1 (12.5)	
Indian	1 (10)	0 (0)	
Others	2 (20)	0 (0)	
Severity, no. (%)			
Mild	0 (0)	1 (12.5)	0.245
Moderate	0 (0)	1 (12.5)	
Severe	10 (100)	6 (75)	
Reason for switching to emicizumab, no. (%)			
Inhibitor	0 (0)	8 (100)	NA
Frequent bleed	6 (60)	0 (0)	
Venous access issues	3 (30)	0 (0)	
Parental/patient request	1 (10)	0 (0)	
Pre-emicizumab			
Prophylaxis prior to emicizumab, no. (%)			
FVIII	8 (80)	2 (25)	0.057
rFVIIa	0 (0)	1 (12.5)	
On demand therapy	2 (20)	5 (62.5)	
ITI before emicizumab, no. (%)	NA	3 (37.5)	NA
Median exposure days to FVIII (IQR) at the onset of inhibitors	NA	24 (10–39)[a]	NA
Median inhibitor titres before emicizumab, BU, years (IQR)	NA	9.3 (6.5–21.3)	NA
High-responding inhibitor, no. (%)	NA	8 (100)	NA
Post-emicizumab			
Median duration of emicizumab, months (IQR)	22 (7.0–32.5)	21 (10.5–23.3)	0.562
Median exposure days (IQR) to emicizumab	38 (23.3–51.3)	41 (11.5–66.8)	0.859

Table 1. Demographics. (Cont'd)

Characteristics	Patients with no inhibitors (n=10)	Patients with inhibitors (n=8)	*P* value
Emicizumab regime, no. (%)			
Weekly	0 (0)	1 (12.5)	0.331
2-weekly	7 (70)	3 (37.5)	
3-weekly	0 (0)	1 (12.5)	
4-weekly	3 (30)	3 (37.5)	
Concurrent FVIII with emicizumab, no. (%)			
Currently ongoing	1 (10)	NA	NA
Never had	4 (40)		
Previously had	5 (50)		
Concurrent ITI with emicizumab, no. (%)			
Currently ongoing	NA	6 (75)	NA
Never had		1 (12.5)	
Previously had		1 (12.5)	
Median latest inhibitor titre (IQR), BU	0 (0)[b]	5.2 (0.4–57.5)	NA

FVIII: factor VIII; ITI: immune tolerance induction; IQR: interquartile range; NA: not applicable; rFVIIa: recombinant activated factor VII
[a] n=7; 1 missing value as 1 patient had developed inhibitors more than 30 years ago, the exposure days to FVIII could not be determined.
[b] n=8; 2 missing values as 2 patients had not had inhibitors checked since starting emicizumab.

prophylaxis. The 5 patients without inhibitors, who were switched to emicizumab, had ABRs ranging from 2 to 14. The 1 patient without inhibitors, who was started on emicizumab without prior FVIII prophylaxis, was a 4-week-old neonate who had 2 episodes of subdural haemorrhage. All patients were started on the initiation regime of emicizumab 3 mg/kg once weekly for 4 weeks. In the paediatric population, 10/15 (66.7%) were on a 2-weekly 3 mg/kg regime, 1 was on a weekly 1.5 mg/kg regime and 1 was on a 3-weekly 4.5 mg/kg regime, while all adult patients were on a 4-weekly 6 mg/kg regime. Given the wide range of body weights in the paediatric subgroup and the standardised dosing in each vial of emicizumab, different frequencies of emicizumab administration are required to achieve the most cost-effective use of emicizumab in this subgroup. Only 1 patient had ongoing concurrent FVIII administration among patients with no inhibitors. Most patients (n=6) with inhibitors had ongoing ITI with emicizumab prophylaxis.

Bleeding outcomes

The median ABR for all the patients before emicizumab prophylaxis was 4.5 events (IQR 2.8–8.3) compared to 0 events (IQR 0–0) after emicizumab was commenced (*P*=0.000) (Table 2). When stratified into patients with and without inhibitors, the improvement in median ABR after commencing emicizumab remained statistically significant for both groups. The median ABR in patients without inhibitors prior to emicizumab was 3.0 events (IQR 0.8–10.3) compared with 0 events (IQR 0–0) on emicizumab (*P*=0.012). In patients without inhibitors, the median ABR prior to emicizumab was 5.5 events (IQR 4.0–8.0) compared with 0 events (IQR 0–2.3) on emicizumab (*P*=0.011).

There was a higher proportion of patients with 0 bleeding events in the first 6 months after commencing emicizumab compared to the 6 months before commencing emicizumab (83.3% versus vs 22.2%, *P*=0.001) (Table 2). When stratified into patients with and without inhibitors, the increase in proportion of patients with 0 bleeds after commencing emicizumab was seen in both groups but only remained statistically significant in patients without inhibitors (non-inhibitor group: from 30% to 90%, *P*=0.031; inhibitor group: from 12.5% to 75%, *P*=0.063). There was no statistically significant difference in the proportion of patients with target joints before and after the commencement of emicizumab.

We performed a separate analysis on the bleeding outcomes in patients under 12 years old because this age cohort has the least published data (Table 3). There were 12 patients in this age group, with 5 having active inhibitors. Similar to the overall analysis, the median ABR was lower (4 events lowered to 0 events, *P*=0.003), and the proportion of patients with 0 bleeding events was higher (8.3% increased to 91.7%, *P*=0.002) after the commencement of emicizumab. A similar trend was preserved when stratified into patients with and without inhibitors.

Four children were initiated on emicizumab when they were less than 2 years old, and 2 of them had active inhibitors (Table 3). The other 2 children had no inhibitors and were started on emicizumab prophylaxis after spontaneous intracranial haemorrhage events. All had improved ABR (median ABR improved from 4 pre-emicizumab to 0 post-emicizumab), and 3 had 0 bleeding events after emicizumab commencement.

Of the 10 patients without inhibitors, only 1 had emicizumab commenced before 50 exposure days (EDs) to FVIII. Emicizumab was initiated at 12 EDs to FVIII when the patient was 4 weeks old. FVIII administration was continued once a week until 25 EDs and inhibitors to FVIII were monitored regularly. No inhibitors to FVIII were detected during the period of follow-up.

Procedural outcomes

A total of 6 procedures in 5 patients were performed during the study period (Table 4). All except 1 were minor procedures (3 port removals, 1 wisdom tooth extraction, 1 circumcision). There were 2 procedures done on the same patient with active inhibitor for which periprocedural rFVIIa was given. The remaining procedures were done in patients with no active inhibitors, and periprocedural FVIII replacement was given. There were no significant bleeding or thrombotic events documented.

Concurrent ITI with emicizumab prophylaxis

There were 7 patients who were on concurrent ITI therapy and emicizumab (Table 5). Four patients had ITI therapy prior to the initiation of emicizumab, the other 3 were started on ITI while on emicizumab. Low-dose ITI regimes were started for most patients. We had 1 case where a low-dose regime (50 IU/kg every other day [EOD]) was stepped up to a higher dose regime (150 IU/kg EOD) in light of bleeding manifestations. Emicizumab was started after the step-up, and the ITI dosing was decreased back to a low-dose regime after bleeding symptoms improved. Three out of 7 patients achieved eradication of inhibitor while on concurrent therapy.

Safety

None of the 18 patients discontinued emicizumab. They were not screened for anti-emicizumab drug antibodies as per standard clinical practice. There was no loss of clinical efficacy to emicizumab as a clinical surrogate. There was also no patient who developed inhibitors to FVIII while receiving emicizumab. There were no adverse events of venous or arterial thrombosis, thrombotic microangiopathy or death.

DISCUSSION

Our study has demonstrated similar effectiveness of emicizumab in people with haemophilia A to those reported in clinical trials.[15] Patients with and without inhibitors experienced an improvement in median ABR after the commencement of emicizumab. Both groups in our study had an increase in the proportion of patients with 0 bleeding events over 6 months after the commencement of emicizumab. Although the difference was not clinically significant in the inhibitor group, it is likely due to the small sample size.

The efficacy and safety of emicizumab across a broad population of adults with haemophilia A, with or without FVIII inhibitors, have been demonstrated in the HAVEN clinical trials: HAVEN 1 (NCT02622321), HAVEN 3 (NCT02847637) and HAVEN 4 (NCT03020160).[7-10] Only the HAVEN 2 (NCT02795767) trial investigated emicizumab prophylaxis in children below 12 years old with haemophilia A but was limited to children with inhibitors.[8] Of the 88 children recruited, only 8 children were less than 2 years old. Published data on the safety and efficacy of emicizumab prophylaxis among paediatric patients with no inhibitors and in the infant/toddler group are still limited.

The HOHOEMI study reported good clinical efficacy of emicizumab in 13 paediatric severe haemophilia A patients without inhibitors.[16] In this study, only 3 out of 13 children were aged less than 2 years. Barg et al. described a cohort of 40 paediatric previously treated patients, of whom 18 had inhibitors, and 22 had no inhibitors (9 children were less than 1 year old) with a low ABR and no safety concerns after commencing emicizumab.[17] In another study by Barg et al., they described the effective use of emicizumab prophylaxis in reducing bleeds in 11 infants and toddlers with inhibitors (7 were under the age of 2 years).[18] McCary et al. reported on a cohort of 49 previously treated

Table 2. Overall bleeding data.

Bleeding data	All patients (n=18)			Patients without inhibitors (n=10)			Patients with inhibitors (n=8)		
	Pre-emicizumab	Post-emicizumab	*P* value	Pre-emicizumab	Post-emicizumab	*P* value	Pre-emicizumab	Post-emicizumab	*P* value
Median ABR (IQR)	4.5 (2.8–8.3)	0 (0)	0.000	3 (0.8–10.3)	0 (0)	0.012	5.5 (4–8)	0 (0–0.8)	0.011
Zero bleeding events in 6 months, no. (%)	4 (22.2)	15 (83.3)	0.001	3 (30)	9 (90)	0.031	1 (12.5)	6 (75)	0.063
Presence of target joint, no. (%)	2 (11.1)	0 (0)	0.500	1 (10)	0 (0)	1.000	1 (12.5)	0 (0)	1.000
Subpopulation: Children less than 12 years old									
	All patients (n=12)			**Patients without inhibitors (n=7)**			**Patients with inhibitors (n=5)**		
	Pre-emicizumab	Post-emicizumab	*P* value	Pre-emicizumab	Post-emicizumab	*P* value	Pre-emicizumab	Post-emicizumab	*P* value
Median ABR (IQR)	4 (3–7.8)	0 (0)	0.003	3 (2–14)	0 (0)	0.027	4 (4–7)	0 (0–0.5)	0.042
Zero bleeding events in 6 months, no. (%)	1 (8.3)	11 (91.7)	0.002	1 (14.3)	7 (100)	0.031	0 (0)	4 (80)	0.125

ABR: annualised bleeding rate; IQR: interquartile range

Table 3. Bleeding data for infants/toddlers less than 2 years old.

Case	Age at emicizumab first dose	FVIII ED prior to emicizumab	Inhibitor status	FVIII ED prior inhibitor onset	Rationale for emicizumab	Maintenance regime	Duration of follow up after emicizumab	Bleeding events since emicizumab	Adverse events since emicizumab
1	4 weeks	12	No	NA	SDH and SAH during neonatal period	2-weekly	14 months	Nil	Nil
2	8 months	39	Yes	24	High-responding inhibitor titres	2-weekly	35 months	ABR 1	Nil
3	12 months	58	No	NA	SDH and IPH bleed at 10 months	2-weekly	21 months	Nil	Nil
4	21 months	24	Yes	24	High-responding inhibitor titres	4-weekly	4 months	Nil	Nil

ABR: annualised bleeding rate; FVIII ED: factor VIII exposure day; IPH: intraparenchymal haemorrhage; NA: not applicable; SAH: subarachnoid haemorrhage; SDH: subdural haemorrhage

Table 4. Summary of surgical procedures.

Surgical procedure	Inhibitor status	Inhibitor level prior operation	Preoperative FVIII	Postoperative FVIII	Preoperative bypass agent	Postoperative bypass agent	Postoperative bleeding
Port removal	Yes	360 BU	Nil	Nil	2 mg (0.09 mg kg) rFVIIa given at induction	2 mg (0.09 mg/kg) rFVIIa given once postoperative	Nil
Port removal	Yes	Not detected	750 U (80 U/kg) given once at induction	750 U (80 U/kg) given every 8 hours and gradually reduced	Nil	Nil	Nil
Port removal	No	NA	3500 U (50 U/kg) given once at induction	3500 U (50 U/kg) given every 8 hours and gradually reduced	Nil	Nil	Nil
Circumcision	Yes	9.5 BU	Nil	Nil	3 mg (0.09 mg/kg) rFVIIa given at induction	3 mg (0.09 mg/kg) rFVIIa given once postoperative	Nil
Burr hole drainage	Yes	Not detected	750 U (80 U/kg) given once at induction	750 U (80 U/kg) given every 8 hours and gradually reduced	Nil	Nil	Nil
Wisdom tooth extraction	No	NA	2000 U (60 U/kg) prior procedure	2000 U (60 U/kg) Daily x 3 days	Nil	Nil	Nil

NA: not applicable; FVIII: factor VIII; rFVIIa: recombinant activated factor VII

Table 5. Summary of patients on emicizumab and immune tolerance induction (ITI).

Patient	Age of initiating emicizumab (years)	Prior initiation of emicizumab			ITI regime while on emicizumab	ITI duration while on emicizumab (months)	Total duration on ITI (months)	Current status	Last inhibitor titre (BU) as of July 2022
		Peak inhibitor titre (BU)	Last inhibitor titre (BU)	ITI regime					
1	0.7	5.5	5.5	50 U/kg FVIII 3x/week	50 U/kg FVIII 3x/week	2	3	Maintenance ITI with 30 U/kg FVIII 1x/week	0.25
2	1.75	11	8.5	Nil	30 U/kg FVIII 2x/week	4	4	Active ITI	26
3	2.25	8	8	30 U/kg FVIII 2x/week	30 U/kg FVIII 2x/week	19	9	Maintenance ITI with 30 U/kg FVIII 1x/week	0.4
4	2.5	10	10	Nil	25 U/kg FVIII 1x/week	13	13	Active ITI	32.5
5	5.75	3300	1200	100 U/kg FVIII daily	50 U/kg FVIII 3x/week	17	33	Stopped ITI after 33 months	345
6	13	24	24	50 U/kg FVIII 3x/week	50 U/kg FVIII 3x/week	25	25	Active ITI	3.5
7	49	26	11.5	Nil	150 U/kg FVIII EOD	6	6	Maintenance ITI with 50 U/kg EOD	Negative

EOD: every other day; FVIII: factor VIII; ITI: immune tolerance induction

patients with no inhibitors aged less than 12 years (10 were under the age of 2 years) with a very low ABR achieved on emicizumab and an excellent safety profile.[19] Mason et al. described 4 cases of previously untreated aged less than 2 years in whom emicizumab was safe and effective in preventing bleeds.[20] Our study adds to the current pool of real-world data, demonstrating the effectiveness and safety of emicizumab use for prophylaxis in children with and without inhibitors, under 12 years of age and within our subpopulation of children under 2 years of age.

Similar to the case series of 4 patients by Mason et al. and the case report by Bush et al., our study shows that early initiation of emicizumab prophylaxis in infants with severe haemophilia A and intracranial haemorrhage in the absence of inhibitors is effective in preventing subsequent bleeds.[20,21] The subcutaneous mode of administration for emicizumab makes it appealing for use in younger children, including infants, as it allows the initiation of prophylaxis at an earlier age when venepuncture can be very challenging in the absence of a central venous access device.

Early initiation of emicizumab prophylaxis before 50 EDs to FVIII puts these patients at a prolonged risk of FVIII inhibitor development that may subsequently occur when patients are re-exposed to FVIII after a bleed. One option will be to expose the patient to FVIII up to approximately 50 EDs. Our centres had initiated emicizumab in only 1 patient without inhibitors before 50 EDs. We opted to continue FVIII exposure until 25 EDs before discontinuing regular FVIII administration and had documented no FVIII inhibitor development during the study follow-up period. Several upcoming clinical trials on emicizumab use in previously untreated patients (PUPs), i.e. the HAVEN 7 (NCT04431726); the Emicizumab PUPs and Nuwiq ITI Study (NCT04030052); and The Hemophilia Inhibitor Prevention Trial (NCT04303559), will help provide further guidance in this aspect.

Our centres adopt a more conservative approach in periprocedural management for haemophilia A patients on emicizumab undergoing surgical procedures. Our study reported more minor surgical procedures being given preoperative and postoperative factor replacement (either FVIII or rFVIIa) compared with other studies. Previous real-world studies on emicizumab reported no or a single additional factor replacement given for minor procedures.[19,22,23] There is a wide variation in practice regarding periprocedural factor replacement. The reported surgical experience from the HAVEN 1–4 studies has also concluded that emicizumab alone provides adequate coverage for patients undergoing minor procedures, with over 90% having no postoperative bleeds without additional factor administration.[22] However, increasing real-world data have shown that centres are still using periprocedural replacement strategies. Multiple observational studies have reported that the majority of patients undergoing minor procedures like port removal still receive pre-operative doses of factor replacement.[18,19] Although reducing the amount of periprocedural factor administration would decrease cost, there are no clear guidelines for optimal periprocedural dosing in children with haemophilia on emicizumab prophylaxis. Our centres have chosen a conservative approach to minimise surgical bleeding, even in minor procedures.

The concomitant use of ITI and emicizumab in patients with inhibitors were not studied in the initial HAVEN studies. The AKATSUKI study will prospectively evaluate the use of emicizumab during and after ITI, and we await the emerging data.[24] For now, we have limited real-world data to understand the efficacy and safety of combined therapy. While emicizumab offers good bleeding prophylaxis, ITI remains as an important option for inhibitor eradication and restoration of haemostatic response to allogenic factor VIII, especially in the paediatric population with a higher risk of traumatic bleeds. Our findings mirror other small case series on the safe use of ITI and emicizumab without thrombotic complications.[25] In addition, there are emerging data to suggest that emicizumab may enhance ITI responses.[26] The optimal dosing of ITI is also not clear. For our patients, we used a lower dose ITI regime, taking into account patient preferences for less frequent infusions and cost considerations. This is lower than the ITI doses published so far with the Atlanta protocol using dosages of 50–100 IU/kg 3 times per week.[25]

Limitations of this study include the short study period, small sample size, and retrospective data collection from the adult centre. Due to the retrospective nature of data collection for the 3 adult patients, bleeding events that were not documented in the medical record may not have been included. However, this likely would be similar before and after emicizumab, and hence would have been accounted for when comparing each patient's ABR pre- and post-emicizumab.

CONCLUSION

In conclusion, this study shows that emicizumab effectively protects against bleeding for haemophilia A patients with and without inhibitors,

including in children less than 12 years old, with a reduction in ABR and minimal periprocedural bleeding symptoms following periprocedural factor replacement. However, many questions on the use of emicizumab remain. These questions include whether early initiation of emicizumab will mask or delay inhibitor development, whether there is a role of concomitant FVIII replacement to prevent inhibitor development, and whether there is a role for ITI in patients with inhibitors on emicizumab. There is also a need for guidelines on the optimal dosing for periprocedural factor replacement in haemophilia A patients on emicizumab. Large, prospective studies will be necessary to answer these questions and provide more guidance in using this novel therapy.

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Ann Acad Med Singap 2023;52:590-600
https://doi.org/10.47102/annals-acadmedsg.2022414

ORIGINAL ARTICLE

Clinical utility of PET/MRI in multiple myeloma

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ABSTRACT

Introduction: This study aimed to evaluate the clinical utility of positron emission tomography/magnetic resonance imaging (PET/MRI), especially in comparison with PET/computed tomography (CT), which has been widely used in clinical practice in multiple myeloma.

Method: F-18 fluorodeoxyglucose PET/MRI and PET/CT studies were done at baseline and when at least a partial response to treatment was achieved. These were done for newly-diagnosed myeloma patients who have not had more than 1 cycle of anti-myeloma treatment, or for relapsed and/or refractory myeloma patients before the start of next line of therapy.

Results: PET/MRI correlated significantly with PET/CT, in terms of number of lesions detected, standardised uptake value (SUVmean and SUVmax, both at baseline and post-treatment. PET/MRI and PET/CT correlated with survival at baseline, but not post-treatment.

Conclusion: In this study, PET/MRI was more sensitive in detecting early disease and disease resolution post-treatment, compared with PET/CT. However, PET/MRI was less sensitive in detecting lesions in the ribs, clavicle and skull.

Ann Acad Med Singap 2023;52:590-600

Keywords: cancer, diagnostic radiology, haematology, multiple myeloma, nuclear medicine, oncology

CLINICAL IMPACT

What is New

- This study showed that PET/MRI correlated well with PET/CT in multiple myeloma.
- PET/MRI was more sensitive in detecting early disease and disease resolution post-treatment, compared with PET/CT, though less sensitive in detecting lesions in the ribs, clavicle and skull.

Clinical Implications

- Given that PET/MRI is more sensitive in detecting early disease compared with PET/CT, it can be a better modality for diagnostic evaluation of myeloma.

INTRODUCTION

Multiple myeloma (MM) is a haematological malignancy characterised by abnormal accumulation of malignant plasma cells and is associated with anaemia, renal impairment, hypercalcemia and bone lesions. A sensitive method to detect bone lesions is crucial as it could determine the decision to start treatment. In this era, the International Myeloma Working Group (IMWG) consensus recommends low-dose whole-body computed tomography (CT) over the conventional skeletal survey, in view of its increased sensitivity in detecting osteolytic bone lesions.[1]

More advanced imaging techniques, such as positron emission tomography/computed tomography (PET/CT) and whole-body magnetic resonance imaging (MRI), are even more sensitive and able to determine not only bone destruction, but also disease burden and disease activity. In particular, focal lesions could only be detected by MRI and PET scans. These focal lesions are different from the osteolytic lesions where bone destruction has occurred—a process that can be detected by CT alone or conventional skeletal survey.[1]

Studies have also shown that residual lesions on PET/CT and MRI were related to poorer outcomes.[2-4] Imaging modality has also been incorporated into the MM response assessment criteria by the IMWG, in which the imaging plus minimal residual disease (MRD)-negative response category requires both MRD and PET/CT negativity.[5]

MRI has excellent soft tissue contrast[6] and can evaluate abnormal infiltration in the tissue, including bone marrow, with high sensitivity, while PET-imaging evaluates the tissue metabolic activity to assess the viability of the focal lesions.[1,7] Thus, MRI and PET provide complementary evaluation for increased sensitivity in MM imaging. This

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study aimed to evaluate the role of PET/MRI, which combines the benefits of both MRI and PET-imaging, especially in comparison with PET/CT that has been widely used in clinical practice.

METHOD

Study design and patients

Newly-diagnosed MM patients who have not had more than 1 cycle of anti-myeloma treatment, or relapsed and/or refractory MM patients before the start of next line of therapy, were recruited. PET/MRI and PET/CT studies were done at baseline and when at least a partial response to treatment as defined by IMWG,[5] was achieved. All patients gave written informed consent. The study protocol was approved by the institutional ethics review board (Study Reference Number: 2015/00254).

Image acquisition

Participants underwent a single F-18 fluorodeoxyglucose (FDG) injection, followed by dual-imaging protocol including a whole-body PET/CT, followed by a PET/MRI scan. The baseline scans were done with 186 ± 4.53 MBq (5.02 ± 0.12 mCi) F-18 FDG injection, while the post-treatment scans were done with 188.90 ± 4.20 MBq (5.10 ± 0.11 mCi) F-18 FDG injection. Eight subjects had both baseline and end-of-treatment scans, while 4 subjects only had baseline scans performed. All reconstructed PET images were converted to standardised uptake value (SUV) images using the measured activity concentration, injected dose and body weight: SUV=tissue concentration [MBq/kg]/(injected dose [MBq]/body weight [kg]) .

PET/CT scan was performed on a Biograph mCT (Siemens Healthcare, Germany) 60 min post-injection from the skull base to the knees, with an imaging duration of 5 min per bed position. The PET images were reconstructed into 400 x 400 matrix size with voxel size of 2.04 x 2.04 x 2.03 mm^3 using three-dimensional ordinary Poisson ordered-subset expectation maximisation (OP-OSEM3D) algorithm, with resolution modelling and point-spread-function and time-of-flight correction, and using 3 iterations and 21 subsets. Low-dose CT protocol (120 kVp, 150 mA, pitch 1.5, careDose) was utilised for attenuation correction of the PET data and image fusion.

Simultaneous PET/MRI scan was then performed on Biograph mMR (Siemens Healthcare, Germany), approximately 1 hour after the PET/CT scan, from skull to mid-thigh. Magnetic resonance (MR) images were acquired with 3T whole-body MRI and shielded whole-body gradient coil system, with the respective imaging parameters for the different MR sequences in Table 1. The PET images were reconstructed into 344 x 344 matrix size with voxel size of 2.01 x 2.01 x 2.03 mm^3 using OP-OSEM3D. Similarly, all corrections were applied, with resolution modelling using 3 iterations and 24 subsets. For attenuation correction, a Dixon volume interpolated breath-hold examination sequence was performed to generate the attenuation map used during the data reconstruction.

Table 1. Imaging parameters for MR sequences.

Imaging parameters	T1-weighted	T2-weighted	DWI
TR (ms)	660	2000	17,300
TE (ms)	8.8	86	74
TI (ms)	Nil	240	180
Flip angle (°)	140	160	Nil
Matrix size	384 x 256	320 x 320	134 x 134
Field of view (mm)	450	450	430
Slice thickness (mm)	4	4	5
Inter-slice gap (mm)	0	0	0
Bandwidth (kHz)	310	781	2332

DWI: diffusion-weighted imaging; MR: magnetic resonance; TE: echo time; TI: inversion time; TR: repetition time

Image analysis

Image analysis was performed by 2 nuclear medicine radiologists by viewing the images in the transaxial, coronal and sagittal planes.

Osseous foci presenting with significant F18 FDG uptake above that of blood pool and adjacent uninvolved marrow, and unlikely to be attributed to a benign aetiology (e.g. degenerative change, inflammation or trauma) were considered as positive for MM. Extra-osseous foci were also evaluated in the same manner for extra-osseous involvement of MM. Quantitative evaluation was performed using SUVmax and SUVmean computed from volumes of interest (VOI) placed over the foci of increased F18 FDG uptake. A reference SUVmax for each patient was obtained from the marrow at the iliac ala that demonstrated no MM lesions, as well as the right hepatic lobe.

Morphologically, lesions that did not show significant FDG-avidity but demonstrated morphological features compatible with MM were also considered positive for MM. A measurable lucent marrow lesion was defined as a lesion of more than 5 mm in diameter on CT images, or lesion appearance on MRI with low T1 signal or exhibiting restricted diffusion on high b-value

diffusion-weighted imaging (DWI). Lesion characterisation was based on both functional (PET) and morphological (MRI/CT) criteria.

Four main patterns of bone marrow FDG uptake were identified: (1) normal FDG distribution with no abnormal focal FDG uptake to indicate MM involvement; (2) focal FDG-avid bone lesions identified and consistent with MM involvement; (3) diffusely increased, intense FDG uptake within the marrow without focal lesions but suspicious for extensive marrow disease infiltration; and (4) mixed pattern of focally FDG-avid bone lesions on a background of diffusely increased FDG uptake within the marrow.

Statistical analysis

Statistical analysis was done using the RStudio version 1.2.5042 software (RStudio, Boston, MA, US) on Mac OS Catalina version 10.15.5 (Apple Inc, Cupertino, CA, US). The statistical evaluation was performed using the Spearman's rank for correlation analysis, and Kaplan-Meier with log-rank test for survival analysis. All reported *P* values were evaluated at the conventional 5% significance level.

RESULTS

Baseline characteristics

From April 2016 to Jan 2019, a total of 40 whole-body F-18 FDG PET/CT and PET/MRI scans of 12 patients were conducted. Of the 12 patients in this study, 10 patients were newly diagnosed MM patients, 1 patient was newly-diagnosed with amyloid light-chain (AL) amyloidosis and 1 patient was a relapsed MM patient.

The demographics of the patients are presented in Table 2.

Radiological findings and correlation

All 12 patients underwent PET/CT and PET/MRI studies at baseline, and 8 out of 12 patients underwent post-treatment PET/CT and PET/MRI studies. Of the 4 patients who did not undergo post-treatment studies, 2 were due to the logistic issue of time unavailability and 2 died. Although the patients were planned to have the baseline imaging done at baseline or within cycle 1 of MM treatment, 2 of the enrolled patients (patients ID 9 and 10, Table 1) had their scans done during cycle 2 of MM treatment due to difficult logistic arrangements.

Table 2. Patient demographics.

Patient ID	Age	Sex	Disease	Presence of lytic lesion (skeletal survey)	ISS Stage	High-risk FISH	R-ISS Stage
1	46	Male	Newly diagnosed MM	Yes	1	No	1
2	60	Female	Newly diagnosed MM	Yes	1	Yes (17p del)	2
3	60	Male	Newly diagnosed MM	Yes	2	No	3
4	59	Female	Newly diagnosed MM	Yes	2	No	2
5	59	Male	Newly diagnosed MM	Yes	3	No	2
6	65	Male	Newly diagnosed MM	Yes	3	No	3
7	63	Female	Newly diagnosed MM	No	2	No	2
8	61	Female	Newly diagnosed MM	Not available	2	No	2
9	73	Male	Relapsed MM	Not available	3	Yes t(4;14)	3
10	65	Female	Newly diagnosed MM	Not available	2	No	2
11	54	Male	Newly diagnosed MM	Yes	2	No	2
12	54	Male	AL amyloidosis[d]	No	2	No	2

AL amyloidosis: immunoglobulin light chain amyloidosis; FISH: fluorescence in situ hybridisation; ISS: International Staging System; MM: multiple myeloma; R-ISS: Revised International Staging System; t(4;14)=translocation (4;14); 17p del: deletion 17p

Both PET/CT and PET/MRI images were of adequate diagnostic quality. Based on the evaluation of FDG marrow uptake pattern, at baseline, 2 patients demonstrated normal FDG distribution, 3 patients demonstrated focal FDG-avid bone lesions, 4 patients demonstrated diffuse bone marrow disease infiltration and 3 patients demonstrated a mixed pattern (Table 3). Maximal intensity projection images of the 4 patterns of bone marrow FDG uptake are shown in Fig. 1.

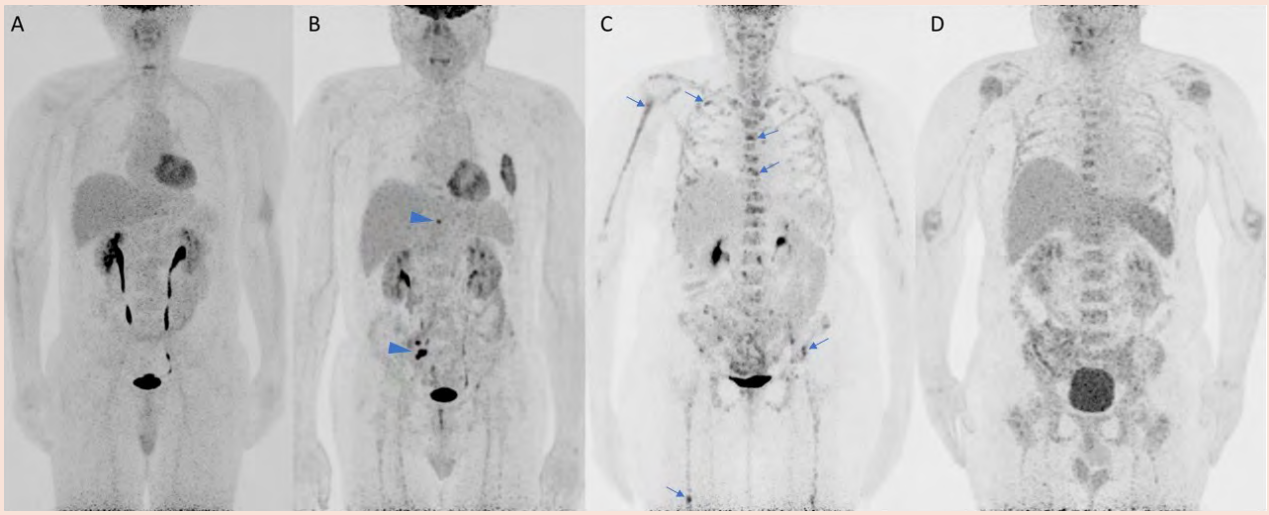
Post-treatment scans of the 8 patients demonstrated resolution of the abnormal patterns (patterns 2, 3 and 4) of marrow FDG uptake in 6

Table 3. Bone involvement pattern.

Patient ID	Pre-treatment FDG-uptake pattern	Pre-treatment morphological pattern	Post-treatment FDG uptake pattern	Post-treatment morphological pattern
1	Mixed, predominantly diffuse with focal lesions	MRI: focal lesions CT: mottled appearance with focal lytic lesions	FDG uptake resolved	MRI: focal lesions resolved CT: no change
2	Predominantly diffuse also involving long bones	MRI: diffuse marrow replacement CT: innumerable lytic lesions	FDG uptake resolved, especially in long bones	MRI: marrow lesions resolved CT: innumerable lytic lesions, more sclerosis
3	Focal lesions Some FDG-avid lesions are not seen on MRI or CT	MRI: focal lesions, some lesions not FDG avid CT: lytic lesions	Not done	Not done
4	Diffuse marrow uptake	MRI: diffuse marrow change with focal lesions CT: innumerable lytic lesions	Diffuse marrow uptake resolved	MRI: resolved CT: lytic lesions are less in number, new areas of sclerosis likely treated disease
5	Diffuse marrow uptake, no focal lesions except at T12/L1 fractures	MRI: diffuse marrow replacement CT: mottled appearance, no focal lytic lesion	FDG uptake resolved	MRI: resolved, fatty conversion CT: no change
6	Innumerable lesions	MRI: Diffuse marrow replacement CT: innumerable lytic lesions	Died	
7	Diffuse mild marrow uptake Focal extraosseous right axillary node	MRI: diffuse marrow replacement, no focal lesions CT: no focal lytic lesion	FDG uptake resolved Extraosseous right axillary node resolved	MRI: resolved CT: no change
8	Mixed Focal on diffuse	MRI: diffuse marrow replacement, DWI multiple focal lesions CT: lytic lesions	Not done	Not done
9	Mixed Focal on diffuse	MRI: innumerable focal lesions, DWI same CT: innumerable lytic lesions	Died	
10	No FDG avid lesions Insufficiency fractures with FDG uptake	MRI: multiple T1-hypointense lesions with no FDG-avidity, DWI shows multiple lesions with no FDG-avidity CT: multiple fractures, no focal lytic lesions	FDG unchanged, normal	MRI: overall less vertebral involvement by T1-hypointense and DWI intense lesions. CT: unchanged
11	Focal right humerus	MRI: dominant right humerus lesion, several tiny lesions on MRI (right iliac wing) too small for PET CT: dominant right humerus, innumerable lytic lesions.	FDG uptake resolved but many more sites of extraosseous nodal disease	MRI: both the lesions at the right humerus and the right iliac bone resolved CT: unchanged
12	Normal	No lesions on MRI or CT	Normal scan	No lesions on MRI or CT

CT: computed tomography; DWI: diffusion-weighted imaging; FDG: fluorodeoxyglucose; MRI: magnetic resonance imaging; PET: positron emission tomography

Fig. 1. F-18 fluorodeoxyglucose (FDG) positron emission tomography maximum-intensity-projection images demonstrating (A) normal FDG distribution, (B) focal FDG-avid lesions, (C) focal FDG-avid lesions on a background of diffusely increased marrow FDG uptake, and (D) diffuse pattern of increased marrow FDG uptake.

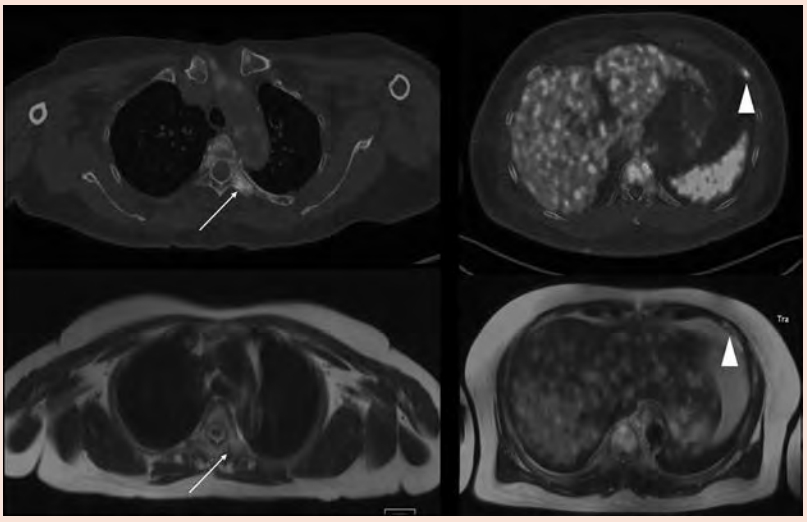


patients, while 2 patients with normal distribution of FDG on baseline scans had no discernible change on their post-treatment scans.

A total of 80 lesions were identified with PET/MRI and a total of 95 lesions were identified with PET/CT. For the number of lesions detected, PET/MRI correlated significantly with PET/CT, both at baseline and post-treatment with r=0.84 (P<0.001) and r=0.79 (P=0.019), respectively. However, there were some observable disparities. The largest disparity of lesions detected with PET/CT that was not detected on PET/MRI occurred for patient 2. In this patient, the majority of the lesions detected on PET/CT had relatively low FDG-avidity, with SUVmax and SUVmean values equal to or below the reference liver SUVmax and SUVmean (Fig. 2). One important caveat to note is that the PET/CT and PET/MRI scans were performed sequentially after a single F-18 FDG injection leading to different uptake periods.

In patient 4, both PET/MRI and PET/CT demonstrated a mixed pattern of focal FDG-avid bone lesions on a background of diffusely increased marrow FDG uptake. In addition, there was a focal FDG-avid left cervical level V lymph node that was initially deemed indeterminate. On post-treatment scans,

Fig. 2. Fused positron emission/computed tomography (PET/CT) (top) and PET/magnetic resonance (MR) (bottom) images demonstrating fluorodeoxyglucose-avid lesions at the left transverse process of T4 (arrows) and the left 10th rib (arrowheads), which have an SUVmax and SUVmean equal to that of the liver on PET/CT but lower than the liver on PET/MR, accounting for the disparity in detection of bone lesions in this patient.

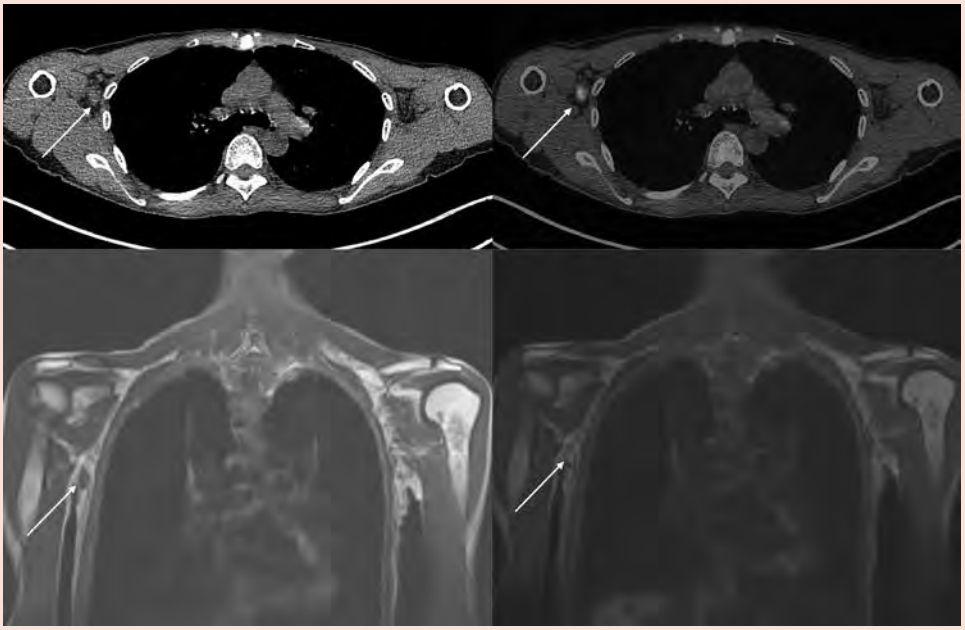


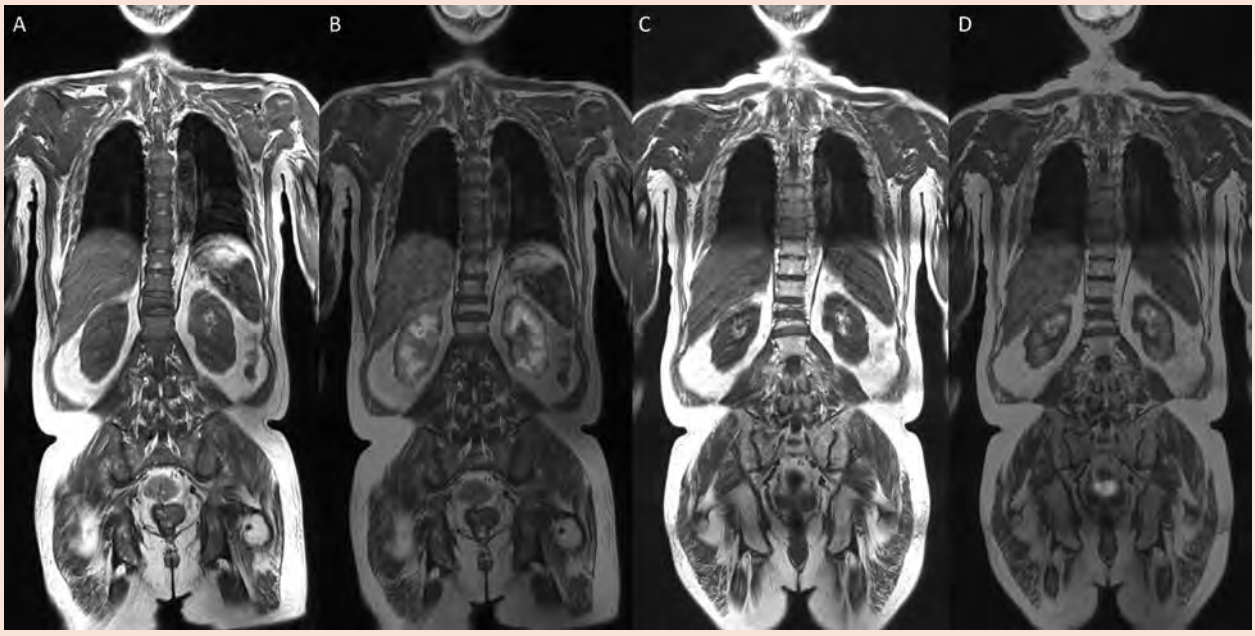
both PET/MRI and PET/CT showed a decrease in the number and FDG-avidity of bone lesions, but a discordant increase in the FDG-avidity of the left cervical level V lymph node. It was concluded that the lymph node was unlikely to represent a site of extramedullary disease. This might have contributed to the slight increase in SUV on the post-treatment scans.

For patient 7, both PET/MRI and PET/CT demonstrated a diffuse pattern of FDG uptake in the marrow without any focal signal abnormalities on MRI or lytic lesions on CT. In addition, both PET/MRI and PET/CT identified an enlarged and FDG-avid right axillary lymph node that was deemed to be a possible site of extramedullary disease. On post-treatment scans, both PET/MRI and PET/CT showed resolution of the diffuse pattern of FDG uptake in the marrow as well as resolution of the right axillary lymphadenopathy (Fig. 3).

For patient 10, neither PET/MRI or PET/CT detected any FDG-avid bone lesions that were deemed as positive for MM involvement. Furthermore, there

Fig. 3. Top: Both axial positron emission tomography/computed tomography (PET/CT) and coronal PET/magnetic resonance (MR) demonstrate the FDG-avid lymph node in the right axilla, suspicious for a focus of extramedullary myelomatous disease. Bottom: (A) Pre-treatment coronal T1-weighted MR and fused PET/MR images demonstrate a diffuse hypointense marrow signal in the spine with (B) diffusely increased FDG uptake. (C) Post-treatment scans demonstrate restoration of normal signal intensity on T1-weighted MR images (D) as well as resolution of the diffusely increased FDG uptake.





were multiple vertebral compression fractures that did not demonstrate significant FDG-avidity, as well as evidence of prior healed fractures in the pubic rami and left femoral neck. Hence, these changes were deemed to be more likely attributable to insufficiency fractures from osteoporosis (Fig. 4).

For patient 11, PET/MRI detected more lesions than PET/CT (5 versus 3, respectively). In this patient, several tiny lesions were observed in the right iliac bone on MRI, which were probably too small for PET detection and demonstrated no abnormality on CT imaging (Fig. 5). Incidentally, both PET/MRI and PET/CT demonstrated FDG-avid lymphadenopathy, predominantly above the diaphragm. Post-treatment PET/MRI and PET/CT showed metabolic resolution of the dominant lesion at the right humerus, although there was an increase in the number and FDG-avidity of lymphadenopathy, which also progressed to involve the pelvic nodal stations. Due to the discordance of these findings, the FDG-avid lymphadenopathy was deemed unlikely to be related to MM.

Patient 12 had primary AL amyloidosis with low level plasma cells in the bone marrow and did not have any bone lesions.

Quantitative evaluation of SUVmax and SUVmean derived from VOIs drawn around MM lesions was performed. The SUVmax and SUVmean analysis for both PET/CT and PET/MRI studies are summarised in Table 4.

The SUVmean and SUVmax of the positive lesions at baseline on PET/MRI and PET/CT showed significant correlations of r=0.83 (P=0.001) and r=0.82 (P=0.002). Similarly, the SUVmean and SUVmax of the positive lesions post-treatment on PET/MRI and PET/CT showed significant correlations of r=0.84 (P=0.018) and r=0.84 (P=0.018), respectively. For baseline scans, the average SUVmean and SUVmax were 2.85 and 4.96 for PET/CT, and 2.14 and 3.37 for PET/MRI. For post-treatment scans, the average SUVmean and SUVmax were 1.75 and 3.06 for PET/CT, and 2.14 and 3.37 for PET/MRI.

Clinical correlation

Baseline

For the evaluation of the number of lesions, we divided the patients into 6 groups (group 1= 0 lesion, group 2: 1–3 lesions, group 3: 4–6 lesions, group 4: 7–9 lesions, group 5: 10–12 lesions and group 6: 22–24 lesions). We excluded the 1 relapsed MM patient from this survival analysis.

For the evaluation of SUVmean and SUVmax, we divided the patients into 9 groups, consisting of group 1: no lesion, group 2: SUV 0.1–1.9, group

Fig. 4. F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) maximum-intensity-projection image demonstrates normal FDG distribution in this patient. Sagittal fused PET/magnetic resonance (MR) image demonstrates compression fractures of the lumbar vertebrae (arrowheads) without significant FDG uptake. Axial fused PET/MR and T1-weighted MR images demonstrate linear hypointense signal at both sides of the sacral promontory with mildly increased FDG uptake (arrows). These lesions were deemed to be more likely attributable to insufficiency fractures secondary to osteoporosis than myelomatous disease involvement.

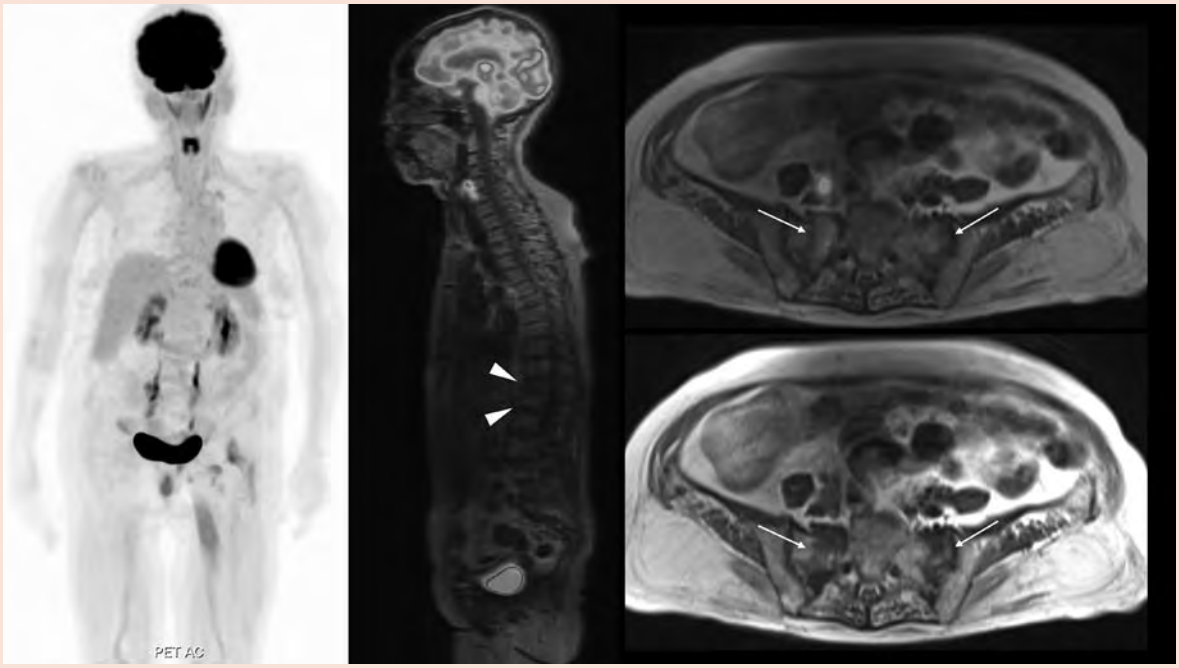
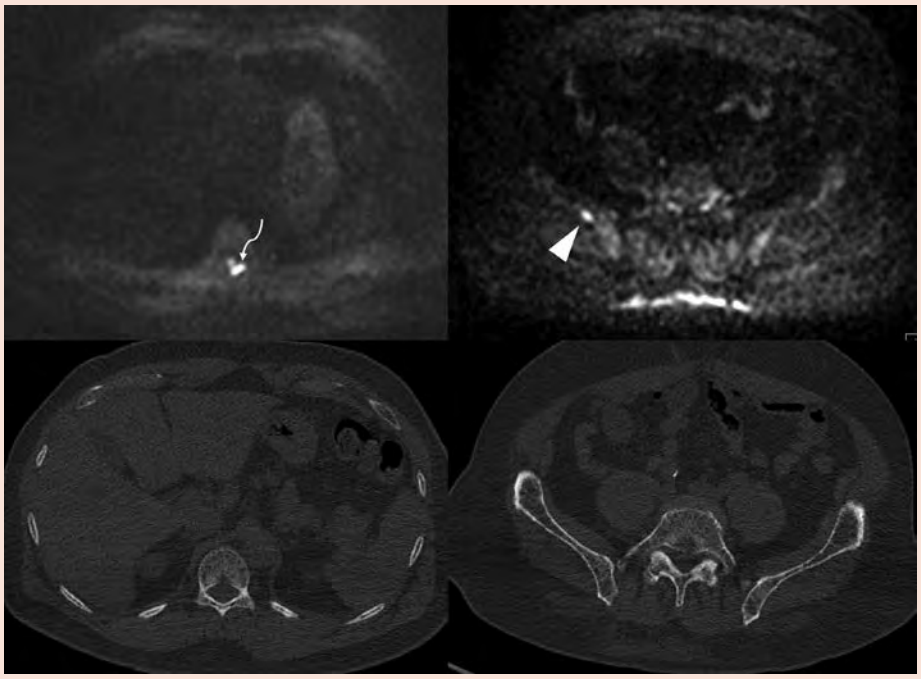
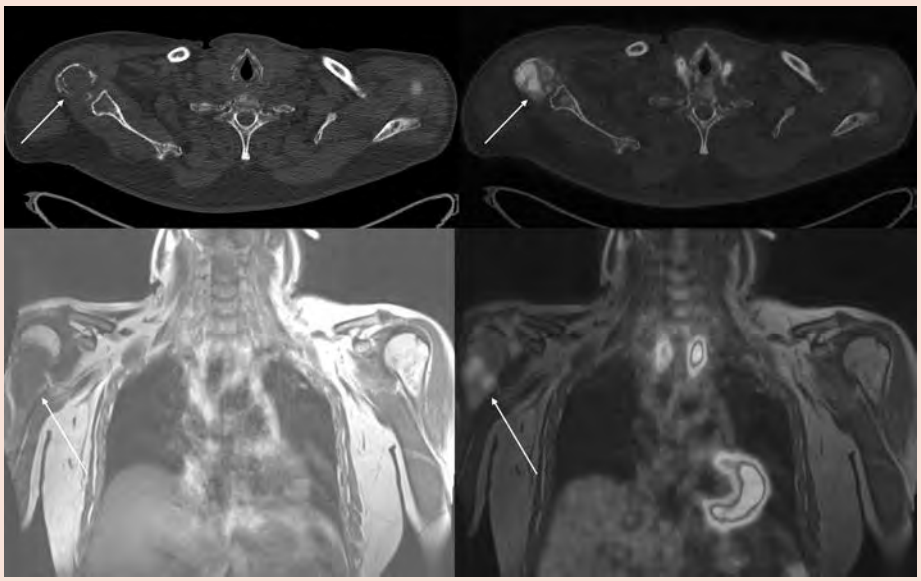


Fig. 5. (A) Diffusion-weighted imaging (DWI) in this patient demonstrated tiny lesions at the left lamina of T11 (arrow) and the right iliac wing (arrowhead) with no lytic change on the corresponding CT images. (B) Both axial positron emission tomography/computed tomography (PET/CT) and coronal PET/magnetic resonance (MR) demonstrate the dominant fluorodeoxyglucose-avid lesion involving the proximal right humerus (arrows) with lytic destruction of bone on CT imaging and a markedly hypointense marrow lesion on T1-weighted MR images.

(A)



(B)



3: SUV 2–2.9, group 4: SUV 3–3.9, group 5: SUV 4–4.9, group 6: SUV 5–5.9, group 7: SUV 6–6.9, group 8: SUV 7–7.9, and group 9: SUV 8 and above.

On the survival analysis, the number of lesions on PET/MRI at baseline correlated significantly with progression-free survival (PFS) (P=0.02) and overall survival (OS) (P=0.04). The number of lesions on PET/CT at baseline correlated significantly with PFS (P=0.02), but not for OS (P=0.08). Both the SUVmean and SUVmax on the baseline PET/MRI correlated significantly with PFS (P=0.02 and P=0.02 respectively). On the other hand, both the SUVmean and SUVmax at baseline PET/CT did not show significant correlation with PFS (P=0.2 and P=0.1, respectively). The SUVmean and SUVmax of both baseline PET/MRI and PET/CT did not show significant correlation with OS (P=0.8 and P=0.8 for PET/MRI and P=0.8 and P=0.9 for PET/CT).

Table 4. Number of lesions and standardised uptake value (SUV)mean and SUVmax on positron emission tomography (PET/CT) and PET/magnetic resonance imaging (MRI).

(A) Baseline scans.

Patient	PET/CT			PET/MRI		
	No. of lesions	SUVmean	SUVmax	No. of lesions	SUVmean	SUVmax
1	8	3.1	5.6	4	1.7	2.8
2	8	2.9	4.4	1	3.2	4.4
3	6	4.2	7.1	5	3.5	5.7
4	10	2.4	4.0	9	1.6	2.4
5	2	3.8	6.6	2	2.8	4.8
6	22	2.7	4.4	22	1.7	2.3
7	1	2.6	4.4	1	1.7	2.7
8	6	5.6	9.7	6	4.5	7.2
9	12	3.0	6.3	11	2.6	4.1
10	Not avid	Not avid	Not avid	Not avid	Not avid	Not avid
11	3	4.0	7.2	5	2.4	4.0
12	0	0	0	0	0	0

(B) Post-treatment scans.

Patient	PET/CT			PET/MRI		
	No. of lesions	SUVmean	SUVmax	No. of lesions	SUVmean	SUVmax
1	1	1.9	3.7	1	0.8	1.4
2	3	2.3	4.0	0	0	0
3	-	-	-	-	-	-
4	3	2.5	4.5	3	1.2	1.9
5	0	0	0	0	0	0
6	-	-	-	-	-	-
7	0	0	0	0	0	0
8	-	-	-	-	-	-
9	-	-	-	-	-	-
10	Not avid	Not avid	Not avid	Not avid	Not avid	Not avid
11	10	7.3	12.3	10	3.1	4.9
12	0	0	0	0	0	0

Post-treatment

We divided the patients into 2 groups based on the presence and absence of positive lesions.

Survival analysis showed that the presence and absence of positive lesions on both PET/MRI and PET/CT post-treatment did not correlate significantly with PFS (P=0.3 and 0.4, respectively). The OS analysis could not be performed as all patients with post-treatment scans available are still alive. Both the SUVmean and SUVmax on the post-treatment PET/MRI did not correlate significantly with PFS (P=0.3 and P=0.3, respectively). The

SUVmean and SUVmax on post-treatment PET/CT did not correlate significantly with PFS (P=0.5 and P=0.5, respectively) as well.

DISCUSSION

To our knowledge, our study is the first to compare changes in PET/MRI in MM pre- and post-treatment along with survival correlation, and the second to compare the utility of PET/MRI and PET/CT in MM.

Our study showed that PET/MRI is not inferior to PET/CT. For detection of positive lesions, PET/MRI has significant correlation with the lesions on PET/CT. The SUVmean and SUVmax on PET/MRI also had good correlation with those of PET/CT, both at baseline and post-treatment. Similar findings were also noted in a previous study that showed significant correlation between these 2 modalities.[8]

With superior lesion contrast in the marrow and soft tissue, MRI could detect MM lesions presenting as marrow signal abnormalities, before bone destruction could be identified on CT. Hence, PET/MRI is the more sensitive imaging technique compared with PET/CT, especially in early disease.[7] Also, MRI has far superior sensitivity for diffuse marrow infiltration, which is potentially morphologically undetectable on CT imaging.[8,9] This finding is in keeping with a previous study, which reported that MRI showed abnormalities in 30% patients with negative PET/CT scan, especially of the diffuse pattern.[10] Similarly, another study also reported that whole-body MRI showed significantly more extensive disease than whole-body multidetector CT (MDCT), with many false-negative MDCT findings being found in cases with diffuse marrow infiltration, which might not necessarily be associated with the destruction of trabecular or cortical bone.[11]

However, although PET/MRI is sensitive for lesions in the vertebrae and pelvis, it is less sensitive for lesions in the ribs, clavicles and skull. This would explain why PET/MRI detected fewer lesions than PET/CT in patients 1 and 2, both of whom had most lesions involving the ribs. Interestingly, a systematic review that compared modern and conventional imaging techniques in MM reported that modern imaging techniques, including CT, MRI and FDG-PET detected fewer lesions in the skull and ribs, and recommended that additional conventional X-ray of the ribs and skull be performed if clinically relevant. For MRI, this mainly concerned lesions of the ribs; with a study reporting a 4.3 times higher detection of rib lesions by X-ray. FDG-PET or FDG-PET-CT and CT missed lesions in the ribs (by 7–33%) and skull (by 4–9%).[12]

In the post-treatment setting, PET/MRI has the added benefit of evaluating treatment response.[13] Along with FDG-PET, which is known to be useful in the assessment of treatment response,[14] the MRI component complements metabolic changes detected on FDG-PET. Changes in morphological findings on MRI correlate with response to therapy. Morphological evidence of treatment response on MRI includes complete resolution of signal abnormalities, replacement of myeloma lesions with fatty marrow signal or a conversion of a diffuse pattern of marrow infiltration into a pattern of focal lesions in patients with a partial response. In some of our patients with diffuse marrow involvement at baseline, post-treatment MRI images demonstrated restoration of the normal marrow signal. In patients with focal disease, post-treatment MRI demonstrated fatty conversion of myeloma lesions. Many of these lesions remained lytic on CT images. Although no dedicated studies have been published, PET/MRI might be useful in the diagnosis and disease monitoring of oligosecretory and nonsecretory MM.[13]

Both SUVmax and SUVmean of MM lesions were significantly higher on PET/CT than on PET/MRI. This might be contributed by the additional waiting time between PET/CT and PET/MRI acquisitions, which were obtained sequentially in all patients. This would result in lesions demonstrating relatively lower FDG-avidity being more difficult to be identified on PET/MRI than on PET/CT. A similar study that compared both modalities, with PET/CT performed sequentially followed by PET/MRI, showed similar results.[8]

Compared with PET/CT, PET/MRI has the additional benefit of minimising ionising radiation exposure to the patient. However, PET/MRI is not without problems. MRI is contraindicated in patients with metallic implants or implantable devices that are not MRI-compatible. MRI is also far more time-consuming compared with CT, and in patients with significant bone pain or claustrophobia, the shorter scan acquisition time achievable in PET/CT would be preferred.

In terms of clinical correlation, at baseline, the number of focal lesions on both PET/MRI and PET/CT showed significant clinical correlation with PFS. In addition, PET/MRI has an additional significance of clinical correlation with OS. This is in keeping with the results of previous studies, which showed that the number of focal lesions was associated with survival.[15-17] However, contrary to the result of previous studies, on post-treatment scans, both the evaluation of PET/MRI and PET/CT did not correlate significantly with PFS.[3,4] This might be partly related to the small number of patients who had post-treatment scans, and the unrelated changes that might affect the SUVs as described

earlier. Another study showed that PET/MRI could predict bone marrow abnormalities and correlated with known biochemical prognostic markers.[18]

Functional MRI sequences (DWI) were obtained for some patients, including patients 5 (post-treatment only), 7 (post-treatment only), 8, 9, 10, 11 and 12. In these patients, PET/MRI detected an equal number of, or more lesions compared to PET/CT. In particular, functional MRI identified 2 bony lesions in patient 11, which were missed on PET/CT. If functional MRI sequences were routinely performed, it is likely that we would be able to detect more bony lesions, such as in the ribs, which were missed on conventional MRI sequences.

One limitation of our study is that PET/MRI was performed later than PET/CT after a single FDG injection, which might make the SUV values for PET/MRI less reliable. It might have been better if an independent injection was administered prior to each scan. Another limitation of our study is the small number of patients recruited. However, even with this small number of patients, significant correlation could be detected.

In conclusion, PET/MRI correlates well with PET/CT, with PET/MRI being more sensitive in detecting early disease compared with PET/CT. PET/MRI at baseline correlates with clinical outcomes and could identify disease resolution better than PET/CT. The cost-effectiveness of PET/MRI should be explored.

Acknowledgements

This project is supported by the National University Cancer Institute, Singapore Centre Grant Seed Funding Grant for WJC. WJC is also supported by National Medical Research Council Singapore Translational Research Investigatorship. This research is partly supported by the National Research Foundation Singapore and the Singapore Ministry of Education under the Research Centers of Excellence initiative as well as the RNA Biology Center at the Cancer Science Institute of Singapore, National University of Singapore, as part of funding under the Singapore Ministry of Education's Tier 3 grants, grant number MOE2014-T3-1-006.

Disclosure

No relevant conflicts of interest to disclose.

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Ann Acad Med Singap 2023;52:601-24
https://doi.org/10.47102/annals-acadmedsg.2023101

REVIEW ARTICLE

AL amyloidosis: Singapore Myeloma Study Group consensus guidelines on diagnosis, treatment and management

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ABSTRACT

AL amyloidosis is the most common form of systemic amyloidosis. However, the non-specific nature of presenting symptoms requires the need for a heightened clinical suspicion to detect unexplained manifestations in the appropriate clinical setting. Early detection and treatment are crucial as the degree of cardiac involvement emerges as a primary prognostic predictor of survival in a patient with AL amyloidosis.

Following the diagnosis of AL amyloidosis with appropriate tissue biopsies, prompt treatment with a bortezomib, cyclophosphamide and dexamethasone-based first-line induction with or without daratumumab should be initiated. The goal of treatment is to achieve the best haematologic response possible, ideally with involved free light chain <20 mg/L, as it offers the best chance of organ function improvement.

Treatment should be changed if patients do not achieve a partial response within 2 cycles of treatment or very good partial response after 4 cycles or after autologous stem cell transplant, as achievement of profound and prolonged clonal responses translates to better organ response and long-term outcomes. Early involvement of multidisciplinary subspecialists such as renal physicians, cardiologists, neurologists, and gastroenterologists for optimal maintenance and support of involved organs is recommended for optimal management of patients with AL amyloidosis.

Ann Acad Med Singap 2023;52:601-24

Keywords: AL amyloidosis, cancer, guideline, haematology, myeloma, rare diseases, renal disease

CLINICAL IMPACT

What is New

- First in Asia guideline highlighting the diagnosis, treatment and management of AL amyloidosis.
- The goal of treatment should be to achieve the best hematologic response rapidly as it offers the best chance of organ function improvement.

Clinical implications

- Early diagnosis, tailored treatment strategies to achieve profound and rapid involved light chain responses, and collaboration among specialists is key in managing AL amyloidosis effectively.

Amyloidosis refers to disorders characterised by the deposition of insoluble amyloid fibrils, which are pathogenic,[1] resulting in organ dysfunction. Amyloidoses differ in the protein precursor undergoing aggregation and downstream target organs implicated. Consequently, clinical manifestations are varied, from localised amyloidosis in Alzheimer's disease, to systemic amyloidosis such as immunoglobulin light chain amyloidosis (AL), reactive amyloidosis (AA) and transthyretin amyloidosis (ATTR). The most common form of systemic amyloidosis is amyloid fibrils derived from immunoglobulin light chains, designated as AL amyloidosis, produced by underlying neoplastic plasma cells or B-cell clones.

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In this guideline, we will focus on AL amyloidosis. These guidelines are developed as a consensus by the Singapore Myeloma Study Group (SMSG) to provide evidence-based recommendations for diagnosing and managing AL amyloidosis in the local Singapore context. The recommendations are not intended to be prescriptive and should be used with sound clinical judgment by haematologists and other relevant specialists with experience in managing patients with AL amyloidosis.

The following topics will be outlined: (1) epidemiology and pathophysiology; (2) diagnosis, staging and risk stratification; (3) treatment; (4) supportive care; and (5) drug toxicity and dose adjustments.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Epidemiology

The epidemiology of AL amyloidosis has not been well characterised as it is a rare disease. Incidence has remained stable, with 9.7–14.0 cases per million person-years.[2] A similar population-based cohort study in Taiwan showed that the crude annual incidence of AL amyloidosis was 8.46 per million in 2016 and 8.31 per million population in 2019.[3] However, prevalence has increased, and in a population-based study in the US, the prevalence of AL amyloidosis was 15.5 cases per million in 2007 and 40.5 in 2015.[2] This increase is likely due to a significant improvement in overall survival over time.

The mean age of AL amyloidosis in patients is approximately 63 years, doubling in individuals >65 years compared with those aged 35–54 years.[4]

Pathophysiology

Disorganisation of normal protein structure leads to abnormal interactions, which can result in disease. The amyloid fibrils in AL amyloidosis are composed of misfolded immunoglobulin light chains that form proteolysis-resistant beta-pleated sheets, resulting in extracellular deposition of amyloid and end-organ impairment. Immunoglobulin light chains can be produced by atypical clonal B lymphocytes or more commonly, clonal plasma cells. Somatic mutations of the variable chain of such a clonally produced free light chain and disruption of homeostasis of the naturally existent chaperone pathways responsible for the metabolism of such extracellular proteins are often the key pathogenetic mechanisms.[6]

As such, underlying plasma cell dyscrasia is often the precursor for AL amyloidosis. The relative risk of AL amyloidosis is 8.8 in patients with monoclonal gammopathy of undetermined significance (MGUS) compared with those without. In 5–7% of patients with AL amyloidosis, an IgM-producing clone with MGUS or Waldenstrom's macroglobulinemia characteristics is responsible for the pathology. Rarely, AL amyloidosis is associated with non-lymphoplasmacytic lymphoproliferative disorders such as marginal zone lymphoma and chronic lymphocytic leukemia.[7]

The material that constitutes the deposits determines the properties and behaviours and consequently, the manifestations of amyloid disease. The critical concentration required for nucleation and formation of deposits varies depending on the stability of light chains. The accumulation of amyloid deposits in parenchymal tissue leads to cumulative tissue damage, which results in organ dysfunction and eventually, organ failure.[8] Therefore, early diagnosis of AL amyloidosis and administration of effective therapy that can produce a rapid and profound reduction of the amyloid precursors are critical to stop fibril growth and disease progression. Amyloid deposits are generally resistant to degradation, but slow natural clearance of amyloid deposits by endogenous chaperone pathways can occur.

DIAGNOSIS, STAGING AND RISK STRATIFICATION

For the optimal treatment of AL amyloidosis, the initial evaluation must be comprehensive. Confirmation of diagnosis, establishing the extent, sites and severity of disease involvement and its clinical consequences, as well as detailed assessment of any potential co-morbidities likely to affect treatment choices, are essential before commencing treatment.

Clinical manifestations

The clinical presentation of AL amyloidosis depends on the number and nature of the organs affected. Most patients have 2 or more organs involved at diagnosis, but about a third have only 1 organ affected.[9] The diagnosis of systemic AL amyloidosis is often delayed as initial symptoms may be non-specific (e.g. fatigue/unintentional weight loss, with the median time from symptom onset to diagnosis being 6–10 months.[10] The incidence, symptoms of organ involvement, diagnostic findings and consensus criteria for determining organ involvement by AL amyloidosis are highlighted in Table 1. As the presenting symptoms are often related to end-organ dysfunction in this multisystem disease, and advanced amyloidosis carries a high risk of mortality even with treatment, a high index of suspicion to investigate an unexplained manifestation in the appropriate clinical setting can lead to an early diagnosis of AL amyloidosis and ultimately lead to improvement of overall survival of patients.

Some examples of such clinical scenarios are patients with unexplained diastolic cardiac dysfunction, heart failure with preserved ejection fraction, especially with disproportionally higher N-terminal pro-brain natriuretic peptide (NT-proBNP) values, or patients requiring incrementally reduced anti-hypertensives due to pseudo "normalisation" of blood pressure caused by visceral neuropathy. Hepatomegaly with or without splenomegaly and associated elevated alkaline phosphatase is a common presentation to gastroenterologists and general physicians. Screening for serum free light chains (FLC) by nephrologists in patients with proteinuria and diabetes where blood sugars have been well-controlled can also assist in the early diagnosis of AL amyloidosis. Although periorbital purpura and macroglossia are pathognomonic symptoms of AL amyloidosis, it only occurs in 10–15% of patients.[11]

Patients being followed up for MGUS or smouldering multiple myeloma (SMM) need to be assessed for clinical features of AL amyloidosis and investigated appropriately while also being monitored for disease progression to multiple myeloma (MM).

Suspicion of amyloidosis often starts with a consistent clinical syndrome, imaging findings suspicious of amyloidosis (e.g. on echocardiogram), or rarely an incidental tissue biopsy with amyloid deposit. Potential clinical scenarios that should raise a suspicion of amyloidosis are discussed and presented in Table 1.[12-14]

Occasionally, a diagnosis of amyloidosis on tissue biopsy might be noted incidentally where there has not been a clinical suspicion of amyloid disease. Careful work-up of such patients is required as localised forms of AL amyloidosis have been recognised. This includes localised AL amyloidosis, in which light chain deposits are localised to only skin, upper aerodigestive tract, genitourinary tract or soft tissues without any evidence of a monoclonal protein in either serum, urine or clonal plasma cells in the bone marrow. Localised AL amyloidosis is thought to arise from the FLC production by polyclonal plasma cells in the affected area. Recognition of this entity is essential since its treatment involves either observation, surgery or local radiotherapy rather than systemic chemotherapy.[12]

Approach to diagnosis and confirmation of sub-type

The diagnosis of AL amyloidosis requires the following: (1) presence of a clinical syndrome consistent with amyloidosis; (2) tissue biopsy with histological confirmation of amyloid deposits; (3) evidence of monoclonal LC restriction by amyloid typing of the tissue; and (4) presence of an underlying monoclonal plasma cell disorder (of the same isotype).

In circumstances where clinical suspicion of amyloidosis is raised, a proposed algorithm for the patient's work-up is outlined in Fig. 1.

Given that the diagnostic work-up can be time and resource-consuming and expensive, the extent of these investigations should be decided on the merit of the individual patient's clinical presentation by an experienced haematologist, carefully balancing the possible benefits of an early diagnosis and the consequences of delaying or missing a potential diagnosis of AL amyloidosis in discussion with other relevant specialities and taking the patient's perspectives into account.

The first diagnostic step is checking serum and urine immunofixation, protein electrophoresis and serum FLC assay. This comprehensive panel can identify >95% of AL amyloidosis patients.[10] If the above shows a clear presence of monoclonal protein or FLC, bone marrow aspiration and biopsy are the next essential steps to confirm the presence of monoclonal plasma cells or B lymphocytes to quantify them by morphology, flow cytometry and trephine biopsy. Additionally, trephine biopsy is a surrogate site to demonstrate tissue amyloid deposits by Congo red staining. Unlike in MM, the median clone size of plasma cells in bone marrow is relatively low at <10%[16]. Hence, a good-quality aspirate and biopsy are crucial to positively identify a clonal population of plasma cells. In a patient with AL amyloidosis, if plasma cells are >10% (or with any CRAB features, i.e. hypercalcaemia, renal dysfunction, anaemia and destructive bone lesions; or MM defining events as per International Myeloma Working Group's definition), additional imaging (low-dose computed tomography [CT] or positron emission tomography-CT) must be performed to confirm that it is not secondary AL amyloidosis with concurrent MM. The prognosis of such patients is worse and more like MM, and should be managed as per the myeloma treatment paradigm. Bone marrow also allows for prognostication using fluorescence in situ hybridisation (FISH)-based cytogenetic evaluation of clonal plasma cells. Genomic prognostication in AL amyloidosis differs from that of MM, with markers considered good prognosis in MM having relatively poor outcomes in AL amyloidosis.

If a monoclonal protein and their source in terms of clonal plasma cells or lymphocytes in bone marrow are confirmed, the next step would be to confirm the presence of amyloid deposits with a tissue biopsy. Depending on the clinical situation, these interventions are performed concurrently to avoid time delay and allow prompt therapy initiation.

Table 1. Most common presenting symptoms/signs, incidence, diagnostic findings and consensus criteria of AL amyloidosis depending on organ involvement.[13]

Organ	Incidence (%)	Clinical manifestations	Investigations and diagnostic findings	Consensus criteria for involvement[14,15]
Heart	60–75	Exertional dyspnoea Orthopnoea Paroxysmal nocturnal dyspnoea Lower limb oedema Pleural effusions Arrhythmias	ECG • Disproportional QRS voltage to the degree of LV hypertrophy on imaging, conduction system disease, atrial fibrillation, pseudo infarct pattern TTE • LV hypertrophy (mean left ventricular wall thickness >12 mm), thickened valves and interatrial septum • Diastolic dysfunction with preserved LVEF, reduced GLS/ apical sparing pattern on GLS, increased RV wall thickness MRI • Subendocardial late gadolinium enhancement; elevated ECV/T1; abnormal myocardial nulling	• Mean left ventricular wall thickness on echocardiography >12 mm, no other cause found • NT-proBNP >39 pmol/L in the absence of renal failure or atrial fibrillation
Kidney	50–70	Lower limb oedema Anasarca Uraemia	Proteinuria, typically nephrotic range Acute kidney injury Hypercholesterolaemia Hypothyroidism Hypercoagulability	• 24-hr urine protein >0.5 g/day, predominantly albumin
Liver	20	Right upper quadrant tenderness Early satiety Weight loss	Hepatomegaly Isolated increase in alkaline phosphatase Coagulopathy due to coagulation factor deficiency[a]	• Hepatomegaly with total liver span >15 cm in the absence of heart failure, or • Alkaline phosphatase >1.5 times upper limit of normal
Gastrointestinal tract	10	Diarrhoea Weight loss Malabsorption Hematochezia or melena		• Positive biopsy with interstitial involvement
Lung	30–90	Shortness of breath Dry cough Recurrent pleural effusions	Pleural effusions Interstitial pulmonary nodules	• Direct biopsy verification with symptoms, or • Radiographic pattern of interstitial infiltration
Peripheral nervous system	10–20	Dysaesthesia Paraesthesia Sensory loss	EMG Symmetric, axonal sensorimotor PN	• Clinical findings

Table 1. Most common presenting symptoms/signs, incidence, diagnostic findings and consensus criteria of AL amyloidosis depending on organ involvement.[13] (Cont'd)

Organ	Incidence (%)	Clinical manifestations	Investigations and diagnostic findings	Consensus criteria for involvement[14,15]
Autonomic nervous system	10–20	Orthostatic hypotension Early satiety Intestinal dysmotility (gastric-emptying disorder, pseudo-obstruction) Erectile dysfunction Voiding dysfunction	Delayed gastric emptying Positive tilt test	• Clinical findings
Soft tissue	10–20	Periorbital or upper body purpura Macroglossia Submandibular swelling Skeletal muscle pseudohypertrophy Arthropathy Myopathy Ecchymotic bullae Jaw or buttock claudication (vascular amyloid) Carpal tunnel		• Clinical findings

ECG: electrocardiogram; ECV: extracellular volume; EMG: electromyography; GLS: global longitudinal strain; LV: left ventricular; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; NT-proBNP: N-terminal pro-brain natriuretic peptide; PN: peripheral neuropathy; RHC: right heart catheterisation; TTE: transthoracic echocardiogram.
[a] Factor X deficiency can occur independently of liver involvement owing to the direct absorption of factor X by amyloid fibrils.

The biopsied tissue should demonstrate positive staining with Congo red by standard light microscopy and a characteristic apple-green birefringence by polarised light. The sensitivities of biopsy of the bone marrow, fat pad and rectal biopsies are 63%, 73%, and 69–97%, respectively, while biopsy of kidney, liver or cardiac tissue has a sensitivity of 87–98%.[17] Despite the higher sensitivity of biopsies from the liver, heart and kidneys, these have a higher bleeding risk. Therefore, sites such as bone marrow, fat pad and rectal biopsies are often preferred initial sites for biopsy. Careful attention to the patient's bleeding history or bleeding symptoms and signs, if any; and evaluation of platelet counts, a clotting screen with activated partial thromboplastin time (aPTT), prothrombin time (PT) and if indicated, additional factor levels (e.g. Factor X) are all essential before any biopsies are planned as several coagulation defects can be associated with AL amyloidosis. If there are bleeding symptoms or abnormal clotting results, patients need to be carefully managed with haemostatic and or blood products to reverse them before a biopsy can be performed safely. It cannot be overemphasised that all steps to avoid catastrophic peri-procedural bleeding needs to be taken (e.g. choice of least risky biopsy site, correction of coagulation of abnormalities, platelet transfusions, anticoagulation withdrawal, etc.) before the diagnostic procedure.

It is important to note that in the bone marrow biopsy, amyloid deposition within the stroma, as opposed to periosteal or vessel wall, is more suggestive of a diagnosis of systemic AL amyloidosis since AA or TTR-type amyloid could be seen in these latter locations. Hence, if Congo red-positive amyloid is noted only in the periosteal region or within the vessel wall in the marrow, it should warrant at least a concurrent fat pad biopsy to improve the specificity. Subcutaneous fat combined with bone marrow biopsy can diagnose approximately 90% of patients.[18] If the bone marrow and fat pad biopsy are negative, but the clinical suspicion remains high, a biopsy of end organs, especially the involved organ (e.g. kidney, peripheral nerve, liver, cardiac, etc.), is necessary for diagnosis.

The next step is to prove that the identified amyloid deposits are derived from monoclonal light chains. Mass spectrometry is the gold standard for characterising amyloid type with nearly 100% sensitivity and specificity.[19] Ideally, Congo red positivity should be subjected to mass spectrometric confirmation. However, since it is not available in Singapore and can be expensive to perform, we suggest that it is left to the discretion of treating individual physicians to pursue this based on the given clinical situation. Alternative typing methods that are available in Singapore include immunofluorescence and immunohistochemistry, which are particularly sensitive in kidney biopsies. The main limitation of these antigen-antibody-based assays is suboptimal sensitivity of 42–96%.[20] Electron microscopic studies can also differentiate light-chain amyloidosis from non-amyloid immunoglobulin deposition diseases.

It is paramount that tissue subtyping is accurate, as the presence of monoclonal protein or abnormal light chain ratio in a patient with amyloidosis does not prove that the amyloidosis is of the AL subtype. It is increasingly recognised that MGUS can co-exist with senile amyloidosis (ATTRw) in up to 23% of cases, as well as other forms of amyloidosis, including hereditary forms.[21]

Staging and prognostication of AL amyloidosis

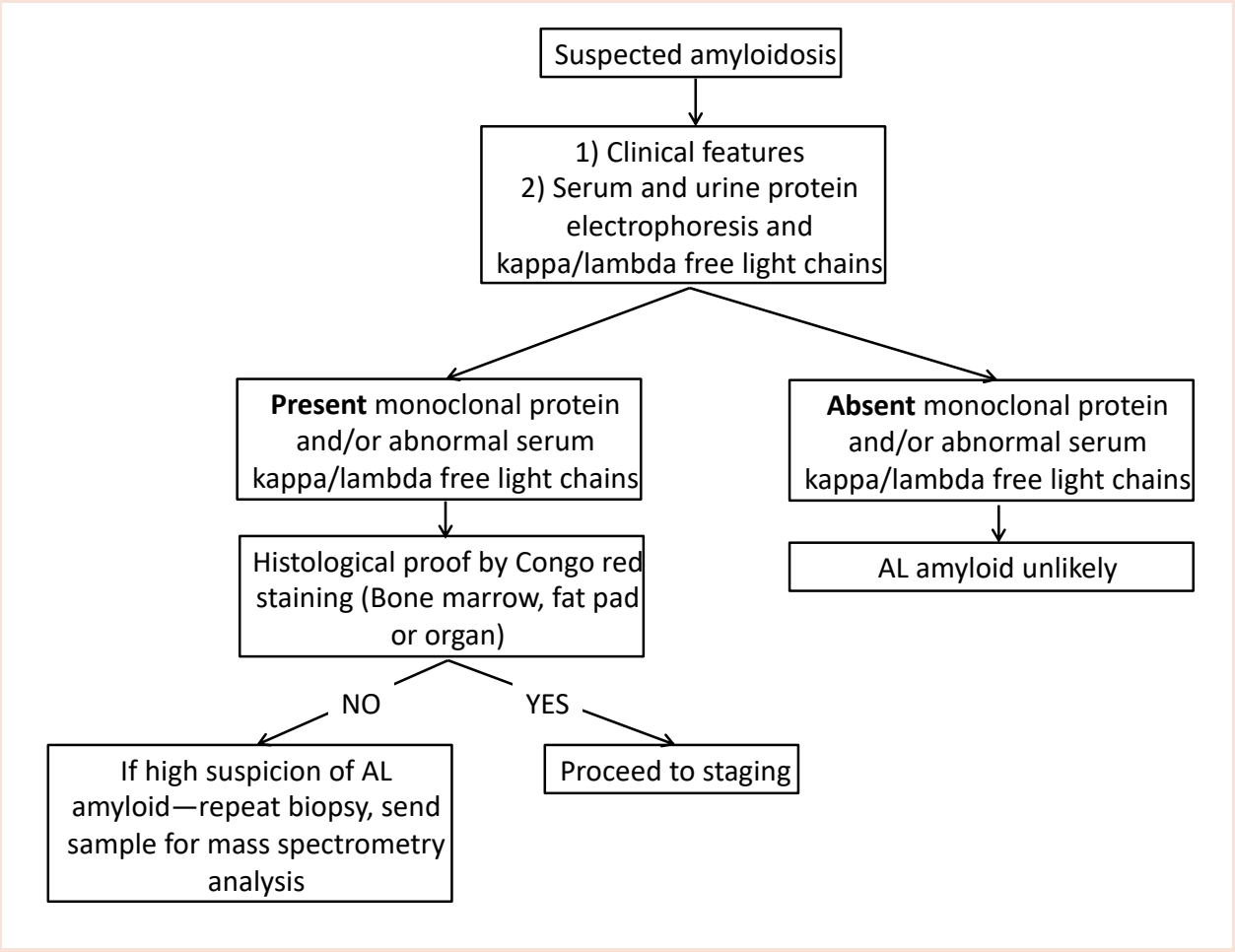
Once the diagnosis of AL amyloidosis has been established, further investigations are required to evaluate the underlying organ involvement, as outlined in Table 2.

The parameters used for staging and prognostication of AL amyloidosis include serum kappa lambda FLC and protein electrophoresis with immunofixation, and bone marrow plasma cells (BMPC) and FISH genetics.

With serum kappa lambda FLC and protein electrophoresis with immunofixation, a difference between the involved and uninvolved FLC (dFLC) of ≥50 mg/L at diagnosis has been defined as necessary for using changes in dFLC as a disease marker for monitoring treatment response[22] and prognostication as outlined in the next section. This includes about 85% of patients with newly diagnosed systemic AL amyloidosis. For 15% of patients with minimally abnormal FLC, monitoring the haematological response relies on a measurable monoclonal protein, defined as >5 g/L.[22] A minority of patients lack a good measurable marker of haematological response.

With BMPC and FISH genetics, a higher plasma cell burden has been correlated with a worse prognosis. A study by Muchtar et al. showed that survival was inversely associated with BMPC, with median overall survival being 81, 33 and 12 months for <5%, 5–19% and ≥20% BMPC, respectively, $P<0.001$, indepen-dent of cardiac risk category or stem cell transplant eligibility.[23] The presence of t(11;14) versus the absence of t(11;14) was associated with inferior haematologic median event-free survival (3.4 vs 8.8 months $P=0.002$), median overall survival (8.7

Fig. 1. Diagnostic algorithm for suspected amyloidosis.



vs 40.7 months) and remission rate (≥ very good partial response [VGPR] 23% vs 47% *P*=0.02) in a cohort of patients treated with bortezomib, cyclophosphamide and dexamethasone (VCD).[24,25]

Once the diagnosis of AL amyloidosis has been established, further investigations are required to evaluate the underlying organ involvement, as outlined in Table 2.

Cardiac staging and prognosis

The prognosis of AL amyloidosis is dependent on the underlying plasma cell clone and the extent of organ involvement. Survival has improved in the last few decades, but the proportion of patients dying within the first 6 to 12 months of diagnosis remains significant, at approximately 25%.[26]

The degree of cardiac involvement is the single most important predictor of short-term and long-term survival. This led to the development of prognostic models, with Mayo 2004 being the initial model developed to stratify patients into 3 prognostic groups based on troponin T and NT-proBNP values.[27] The subsequent European collaboration modification (Mayo 2004 with European modification) further risk-stratified the high-risk subgroups based on NT-proBNP levels. It was deemed the best in identifying patients with the highest risk of early death. Subsequently, the Mayo 2012 model incorporating dFLC at diagnosis was shown to have a better discriminating ability to identify patients with different outcomes from among the previous stage groups 3 years after diagnosis.[28] A later model by Boston University using troponin I and BNP allows centres without access to NT-proBNP to utilise the model[29] (Table 3).

Renal staging and prognosis

Renal staging models help predict the risk of dialysis dependence in patients. For example, the 3-stage model based on estimated glomerular filtration rate

Table 2. Investigations for patients with AL amyloidosis.

Group of patients	Investigations
All patients	Full blood count Renal (kidney) panel 24-hour urine protein or spot urine protein/creatinine ratio Serum calcium Liver panel Fasting blood sugar + HbA1C Haemetinics—iron panel/vitamin B12/folate (as required) Serum troponin T/high-sensitivity troponins Serum NT-proBNP ECG PT/aPTT (factor levels if indicated)
Cardiac involvement — signs and symptoms	Transthoracic echocardiogram Cardiac MRI
Neuropathy/autonomic symptoms	Nerve conduction study Autonomic function tests
Lung	Chest X-ray Lung function
Suspicion of myeloma	Bone investigation, e.g. PET-CT

aPTT: activated partial thromboplastin time; ECG: electrocardiogram; MRI: magnetic resonance imaging; PET-CT: positron emission tomography-computed tomography; PT: prothrombin time; HbA1C: haemoglobin A1C; NT-proBNP: N-terminal pro-brain natriuretic peptide

Table 3. A) Cardiac risk stratification models for AL amyloidosis, B) Median overall survival, based on respective risk stratification models.

A. Cardiac risk stratification models for AL amyloidosis

Source	hsTnT (pg/mL)/cTnI (ug/L)	NT-proBNP (ng/L)	dFLC (mg/L)	BNP (pg/mL)
Mayo 2004	>54/>0.1 (1 point)	>332 (1 point)		
Mayo 2004 with European modification	>54/>0.1 (1 point)	>332 (1 point) > 8500 (2 points)		
Mayo 2012	>54/>0.1 (1 point)	>1800 (1 point)	>180 (1 point)	
Boston University 2019	NA />0.1 (1 point)			>81 (1 point) >700 (2 points)

Thresholds for biomarkers are reported based on the proposed modification of the staging systems[29]

B. Stages with corresponding median overall survival (months)

Source	Stage 1 (0 points)	Stage 2 (1 point)	Stage 3a (2 points)	Stage 3b (or Stage 4 in Mayo 2012) (3 points)
Mayo 2004	130	54	10 (stage 3)	
Mayo 2004 with European modification	130	54	24	4
Mayo 2012	130	72	24	6
Boston University 2019	NR	9.4	4.3	1

BNP: brain natriuretic peptide; CTnI: cardiac troponin I; dFLC: difference between involved and uninvolved free light chain; hsTnT: high-sensitivity cardiac troponin; NR: not reached; NT-proBNP: N-terminal pro-brain natriuretic peptide
The median overall survivals are derived from application of the established staging systems to a more contemporary cohort[88]

(eGFR) and proteinuria was able to dichotomise patients into low vs high-risk of progression to dialysis as outlined in Table 4.[30]

Table 4. Renal risk stratification.

1 point each for: 1) eGFR <50 mL/min per 1.73m^2 2) urine protein >5 g/24h
3-year risk of dialysis dependence (%) Renal stage I (0 point): 4 Renal stage II (1 points): 30 Renal stage III (2 points): 85

TREATMENT

Goals of treatment

Summary

- The goal of treatment should be to achieve the best haematologic response possible for a given patient (involved free light chain [iFLC] <20 mg/L where feasible), as it offers the best chance of organ function improvement. However, this must be weighed against treatment-related toxicity and the limitations of the assays.
- Patients who do not achieve at least partial response (PR) within 2 cycles of treatment commencement or VGPR after 4 cycles or after autologous stem cell transplant (ASCT) should be considered for alternative therapy.
- Achievement of profound and prolonged clonal responses, which translates into better organ responses, should be the long-term goal of therapy.
- Early involvement of multidisciplinary subspecialists such as renal physicians, cardiologists, neurologists and gastroenterologists for optimal maintenance and support of involved organs is recommended.

Treatment of localised AL amyloidosis (e.g. tracheobronchial, lung, breast) is guided by the severity of the patient's symptoms and usually consists of local resection or, in select cases, local radiotherapy.[31] The overall recurrence rate of localised amyloidosis is approximately 20%, up to 50% for urothelial,[32] laryngeal[33] and tracheobronchial amyloidosis.[34] Chemotherapy is inappropriate in these forms as the deposits come from polyclonal plasma cells and are to be avoided.

Virtually all patients with systemic amyloidosis require treatment, except for localised amyloidosis and patients with MGUS or SMM with incidental amyloid deposits in the bone marrow without any evidence of organ involvement. Treatment of systemic AL amyloidosis is targeted at eliminating the plasma cell clone. In the past, therapy has primarily been directed at reducing precursor FLC production, limiting further organ damage, and allowing time for endogenous resorption of tissue amyloid deposits. However, with the advent of effective novel agent therapy resulting in reduced early mortality and improved patient selection, the focus has shifted to achieving more profound and sustained clonal responses, which appear to result in better organ function recovery. Accordingly, we recommend that the overall aim of treatment should be to achieve at least VGPR or better, with iFLC <20 mg/L as the optimal response. Early and profound reductions in FLC concentrations are associated with the greatest chance of organ recovery (Table 5) and downstream prolongation of progression-free survival (PFS) and overall survival (OS).

While attaining complete remission (CR) is the goal of therapy, recent studies have shown that iFLC <20 mg/L or the dFLC <10 mg/L is correlated with improved outcomes. A few studies have shown that patients who achieved a VGPR or better and with iFLC <20 mg/L had superior organ response (OR), PFS, and OS compared with levels >20 mg/L.[35-36] In a Mayo study, iFLC normalisation was not shown to predict organ response or survival, supporting the data that iFLC should be reduced as low as possible for the best outcomes, preferably to <20 mg/L.[36]

However, in patients with renal impairment or ongoing infection or inflammation, it is often impossible to discern if the elevation of iFLC is monoclonal or polyclonal. In these cases, repeat testing is advised, and if still inconclusive, a bone marrow assessment may be required to determine if there are residual clonal plasma cells.[36]

In addition to deep haematologic response (HR), rapid attainment of HR has portended a more favourable outcome. Studies have shown that rapid HR within 1 month translated into a survival benefit at 12 months,[38] suggesting that ongoing light chain toxicity is a critical factor in end-organ damage and is potentially reversible with early HR. Therefore, the Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) consensus statement 2020 has recommended that patients who do not achieve at least partial response within 2 cycles or VGPR within 4 cycles of therapy or after ASCT should be considered for alternative therapy.[39]

Minimal residual disease (MRD) assessment in AL amyloidosis has also been prognostic for PFS and OS. A study by the Mayo group recently

showed that MRD negativity was more likely to be achieved among patients who received ASCT and were in CR. MRD negativity to a sensitivity of 10^{-5} in patients who achieved CR was associated with a higher likelihood of cardiac response and improved 12-month PFS.[40] However, both prognostic evaluation and treatment decisions based on MRD values are currently underway in clinical studies, and these results will inform future practice. Hence, in the global context, MRD in AL amyloidosis remains a research tool, and we recommend against the routine use of this tool in clinical practice to guide treatment decisions at this point.

Put together, the likelihood of OR is contingent on achieving deep and rapid HR, with OR lagging behind HR. The median time from first-line treatment in the pre-novel agent era to heart, kidney and liver response was 9, 6 and 6 months, respectively, with the median time to best organ responses at 24, 29 and 35 months, respectively.[41]

Treatment options

Accurate risk stratification, as outlined above, is crucial in deciding the treatment strategy. Approximately 20–30% of newly diagnosed patients are candidates for ASCT, and more may be eligible after effective upfront therapy with organ recovery.[42]

Due to the rarity of AL amyloidosis, there is a paucity of large-scale randomised control trials to inform therapy. As such, enrolment into clinical trials should be considered if available.

Frontline therapy

Summary

- Recommended first-line induction is with combination chemotherapy; bortezomib cyclophosphamide and dexamethasone with or without daratumumab (Fig. 2).
- If the initial therapy is with VCD, patients with a suboptimal response (<VGPR) after 2 cycles can be considered for the addition of daratumumab to deepen the response.
- The duration of induction therapy is 4 to 6 cycles in patients with no co-existing MM or high-risk FISH abnormalities.
- Treatment response parameters (i.e. hazard ratio [HR] and odds ratio [OR]) must be evaluated after every cycle of chemotherapy.

Bortezomib

In the absence of large-scale randomised clinical trials, bortezomib-based therapy has been the standard of care for treating newly diagnosed AL amyloidosis in the last decade, primarily based on single-centre prospective or large retrospective cohort studies. The addition of bortezomib has been shown to improve outcomes. It is likely due to the increased sensitivity of plasma cells in AL amyloidosis to proteasome inhibition due to toxic light-chain-induced cellular stress.[43] A randomised phase 3 trial comparing bortezomib melphalan dexamethasone (VMD) vs melphalan dexamethasone (MD) showed that the addition of bortezomib-induced higher HR and VGPR/CR rates (79% vs 52%, VGPR/CR 64% vs 39%) and prolonged PFS and OS as compared to the MD arm (median OS not reached vs 34 months). There was no significant difference in the cardiac and renal response at 9 months after treatment initiation in both arms (cardiac response 38% vs 28%, renal response 44% vs 43%). The overall quality of life was also not affected by the addition of bortezomib.[44]

One of the largest studies examining the use of bortezomib in the frontline setting is a prospective trial from a UK group,[45] which examined 915 patients. In this study, a majority of patients were treated with frontline VCD (94%) without the use of ASCT. Haematologic response rates were high, with objective response rate (ORR) of 65% and 49% achieving VGPR/CR. In patients with end-organ involvement, cardiac, kidney and liver response at 12 months were seen in 32.5%, 15.4% and 30%, respectively. Overall median survival in this cohort was 72 months. The median time to next treatment as not reached in patients who achieved dFLC responses of <10 mg/L, approaching outcomes reported with upfront ASCT. However, mortality in stage 3 patients was 40% within 6 months of diagnosis.[45] Therefore, findings support that bortezomib therapy improves long-term outcomes in AL but does not negate the risk of early mortality in AL amyloidosis, especially among patients in advanced stages. With a once-weekly dose, bortezomib has acceptable tolerability and safety profile, with the main side effect being peripheral neuropathy.[46] VCd is the preferred pre-ASCT regime, as melphalan is generally avoided before stem cell collection and ASCT.

Daratumumab

Daratumumab is a CD38-directed monoclonal antibody that has been demonstrated to have potent plasma cell-directed killing with deep remissions and prolonged PFS and OS in relapsed refractory and frontline treatment of multiple myeloma in combination with other anti-myeloma agents.

Table 5. A–D) Haematologic response and organ response criteria CIBMTR).*

(A) Haematologic response

	Serum and urine immunofixation	serum FLC ratio	dFLC
CR *requires all	Negative	Normal	
VGPR	-	-	<40 mg/L
PR *requires any			>50% reduction (if >10 mg/dL or >100 mg/L at baseline)
NR/SD	Does not meet criteria		
PD *requires any	• If progressing from CR, any detectable monoclonal protein or abnormal FLC ratio (light chain must double) • If progressive from PR/SD, ≥ 50% increase in the serum M protein to > 5 g/L, or ≥ 50% increase in urine M protein to > 200 mg/day • Serum FLC increase of ≥ 50% to > 100 mg/L		

(B) Cardiac response

	NT-proBNP**	NYHA	cardiac troponin	EF
Cardiac response *Requires any	> 30% and > 300 ng /L decrease (if baseline ≥ 650 ng/L)	≥ 2 class decrease (if baseline class 3/4)		
NR/SD	Does not meet criteria	Does not meet criteria	Does not meet criteria	Does not meet criteria
PD *Requires any	> 30% and > 300 ng/L increase		≥ 33% increase	≥ 10% decrease

* CIBMTR amyloidosis response criteria https://www.manula.com/manuals/cibmtr/fim/1/en/topic/amyloidosis-response-criteria
** Recipients with progressively worsening renal function cannot be score for NT-proBNP progression. Progressively worsening renal function is defined as a 50% increase (at least 1g/day) of 24-hour urine protein from baseline to > 1g/day or a 25% worsening of serum creatinine or creatinine clearance from baseline

(C) Hepatic response

	Liver size	ALP
Hepatic response *Requires all	≥ 2 cm decrease (If baseline (liver > 15 cm)	≥ 50% decrease
NR/SD	Does not meet criteria	Does not meet criteria
PD		≥ 50% increase

(D) Renal response

	24h urine protein	eGFR
Renal response *Requires all	≥ 50% decrease of at least 0.5 g/24h (baseline > 0.5 g/24h)	< 25% decrease
NR/SD	Does not meet criteria	Does not meet criteria
PD *Requires any	≥ 50% increase of at least 1 g/24h to > 1g/24h	≥ 25% decrease

ALP: alkaline phosphatase; CR: complete response; eGFR: estimated glomerular filtration rate; FLC: free light chain; dFLC: difference between involved and uninvolved free light chain; NR: no response; NYHA: New York Heart Association; PD: progressive disease; PR: partial response; SD: stable disease; VGPR: very good partial response

The ANDROMEDA study[47] is the largest Phase III randomised control trial for AL amyloidosis, where subcutaneous daratumumab given in combination with VCd was compared to VCd. Patients were allowed to have ASCT based on the country or local investigator's preference. VCd was given for 6 cycles in each arm, with patients in the daratumumab arm receiving daratumumab on a standard schedule (weekly for the first 2 cycles, every 2 weeks in cycles 3 to 6, and every 4 weeks thereafter) for up to a total of 24 cycles.

The primary endpoint was the overall rate of haematologic complete response (CR), defined as the normalisation of FLC levels, FLC ratio, and negative serum and urine immunofixation. The secondary endpoints were major organ deterioration-PFS, major organ deterioration-EFS (event-free survival), organ response rate, time to haematologic response, overall survival, and safety. Major organ deterioration-PFS (MOD-PFS) is a composite endpoint defined as end-stage cardiac disease (requiring cardiac transplantation, left ventricular assist device, or intra-aortic balloon pump), end-stage renal disease (requiring haemodialysis or renal transplantation), haematologic progression per consensus guidelines, or death (whichever came first).

The HR and CR rates were significantly higher in the daratumumab-VCd (dara-VCd) arm than in the VCd arm (HR 92% vs 77%, CR 53% vs 18%). There were also improved 6-month cardiac and renal response rates and MOD-PFS in the dara-VCd vs VCd arm (cardiac response 42% vs 22%, renal response 54% vs 27%, MOD-PFS hazard ratio 0.58 CI 0.3-0.93; P=0.02). At the last update presented at 2021 American Society of Clinical Oncology Annual Meeting, when the median follow-up for dara-VCd was 18.5 months and 5.3 months for VCd, the overall haematologic CR rate continued to be higher with dara-VCd than VCd (59% vs 19%; OR 5.9; 95% CI 3.7–9.4; *P*< 0.0001). More patients achieved a ≥VGPR with dara-VCd than VCd (79% vs 50%; OR 3.7; 95% CI 2.4–5.9; *P*< 0.0001). Cardiac response rates were higher with dara-VCd than VCd at 6 months (42% vs 22%) and 12 months (57% vs 28%); renal response rates were 54% vs 27% at 6 months and 57% vs 27% at 12 months.

Of note, patients with severe cardiac impairment (NT-proBNP >8500 ng/L or New York Heart Association [NYHA] class 3B and 4) were excluded from the ANDROMEDA study. However, in a recent European Myeloma Network phase 2 study where NYHA class 3B patients with NT-proBNP>8500 ng/L were enrolled and received daratumumab monotherapy, the overall safety profile was favourable with rapid and deep haematologic responses.[48] As such, daratumumab must be used cautiously as we await further emerging data.

In the ANDROMEDA study, treatment-related severe adverse events were comparable between the dara-VCd and VCd. However, the dara-VCd arm had higher rates of pneumonia (8% vs 4%) and overall incidence of grade 3 and 4 events (17 vs 10%). Though a minority of patients died in both arms, patients in the daratumumab arm had a numerically higher percentage of deaths attributed to adverse events. In contrast, disease progression accounted for more deaths in the VCd arm. The caveats in this study were the longer treatment duration in the dara-VCd arm compared to the VCd arm (18.5 months vs 5.3 months) and the exclusion of Mayo stage 3b patients. Despite the caveats, overall findings are promising, as the addition of daratumumab yielded significantly better outcomes, especially organ responses with manageable toxicities. Longer-term follow-up is needed to assess the impact on overall survival. Since a proportion of patients in the study in both arms went on to receive ASCT, comparing the outcomes in the transplanted group with and without added daratumumab will also inform future practice. Based on the ANDROMEDA results, the FDA approved the use of daratumumab in newly diagnosed AL amyloidosis, and recently, it received approval under the cancer drug listing in Singapore.

We suggest using VCd with or without daratumumab as possible options for induction treatment in newly diagnosed AL amyloidosis. However, the efficacy vs toxicity information, limitations of the ANDROMEDA trial, the cost involved, and patient preferences must be considered when deciding.

Immunomodulatory agents

Regimens using immunomodulatory agents (IMiDs) though effective, are generally avoided in AL amyloidosis, especially in frontline, as they are poorly tolerated and are also associated with a rise in cardiac biomarkers and worsening renal functions.[49] IMiDs such as thalidomide and lenalidomide have been studied in frontline therapy for AL amyloidosis and are effective, with one study demonstrating deep responses with upfront bortezomib, lenalidomide, dexamethasone (VRD) (HR 71%, VGPR/VR 44%). However, they are not the first-choice, upfront therapy due to the side effects, especially with increased rates of polyneuropathy with thalidomide,[50] fluid retention, rash, infections, high discontinuation rates and early mortality with lenalidomide, and risk of thromboembolic complications with both the agents.[51,61]

There are phase 1 and 2 trials that demonstrate the efficacy of pomalidomide and dexamethasone, with HR rates reaching 48–50%, but with significant toxicities including grades 3 to 4 myelosuppression in 15–25% of patients, and grades 3 to 5 infection in 9–18% of patients.[53,54]

IMiDs were generally reserved for use in relapsed refractory settings and even then, with abundant caution. However, patients with significant neuropathy who cannot have proteasome inhibitors can be considered for IMiD-based treatment options if other options, like daratumumab, are not applicable. Lenalidomide is administered at a reduced dose of 5–15 mg per day x 21 days and pomalidomide is administered at a starting dose of 2 mg, with patients closely monitored for worsening clinical status.

Duration of therapy

There are no randomised clinical trials to guide the optimal duration of induction treatment. However, as the median number of cycles achieved in clinical practice is 5, it has been suggested that induction therapy be continued for at least 6 cycles for patients with no coexisting MM or high-risk FISH abnormalities.[39] Patients with concomitant symptomatic myeloma or high-risk FISH abnormalities should be considered for 6–12 months of induction therapy and maintenance therapy after that.[39]

Autologous stem cell transplant

Summary

- Consider high-dose chemotherapy with autologous stem cell transplant (ASCT) in all eligible patients.
- The timing of ASCT is to be decided on a case-by-case basis.
- Patient selection and assessment in a centre with experience performing ASCT in amyloidosis are paramount. In patients who are eligible but unlikely to tolerate full-dose melphalan, a risk-adapted approach may be considered at the discretion of the transplant physician.

The next consideration would be whether the patient is a candidate for high-dose chemotherapy followed by an ASCT. While there are no randomised control trials to support ASCT as a superior therapy, several observational studies that support the use of ASCT have reported high response rates, durability of response and long-term survival. HR was achieved in 83–94% of patients, CR in 43–56%, and OR in 56–69%, with a median OS of 6.3–10.9 years.[45,55–57] A retrospective analysis of the CIBMTR database identified 1536 patients with AL amyloidosis who had ASCT between 1995 and 2012. Over this period, there was an evident decline in early mortality and improvement in OS. Among the 800 patients transplanted from 2007 to 2012, the treatment-related mortality up to 100 days was 5%; the estimated OS rate at 5 years was 77%. Outcomes were better at centres that regularly performed more transplants for AL amyloidosis.[38]

Optimal patient selection for ASCT is key to outcomes. Earlier studies had shown inferior outcomes with ASCT, mainly attributed to the higher early treatment-related mortality of approximately 24%.[58] However, with careful patient selection, medical advances in mobilisation, and peri-transplant supportive care, the transplant-related 100-day mortality has reached ≤ 5%.[59,58] The CIBMTR pooled analysis and multiple single-centre studies have come to similar conclusions, with a decline in transplant-related mortality over the years and very good long-term OS in patients who can proceed with ASCT and achieve good responses.[35,36,38,39,60] Patient selection is based on multiple factors, with the key determinants being patient-related clinical factors. One example from the European Hematology Association-International Society of Amyloidosis (EHA-ISA) working group is presented in Table 6 below.[61] Whilst these are guidelines, familiarity, volume and experience of the transplant physician and centre (referral to a centre with specific expertise in transplanting AL amyloidosis), needs and wishes of the patient and an individual risk-benefit assessment are all important factors to consider when deciding to proceed with ASCT.

In patients deemed frailer with cardiac involvement, renal impairment or older age, dose-attenuated melphalan has been employed as a strategy. The use of a risk-adapted ASCT approach has been recommended in the EHA-ISA working group guidelines, to reduce toxicity and early transplant-related mortality[62] (Table 7). This, however, needs to be weighed with the treatment efficacy as melphalan dose attenuation has been consistently shown to result in lower HR rates, inferior PFS and OS, and higher TRM rates and is an independent predictor for poor outcomes of ASCT.[57,63] Consideration should also be given to infusing the stem cell product over 2 days to reduce the risk of infusion-related toxicity related

Table 6. European Hematology Association-International Society of Amyloidosis eligibility criteria for autologous stem cell transplant.

- Age >18 and physiological age <70 years
- At least 1 vital organ involvement
- Left ventricular ejection fraction ≥40% and NYHA class <III
- Oxygen saturation ≥95% on room air and DLCO >50%
- Supine systolic blood pressure ≥90 mmHg
- ECOG performance score ≤2
- Direct bilirubin <2 mg/dL
- NT-proBNP <5000 pg/mL
- troponin I <0.1 ng/mL, troponin T <0.06 ng/mL, hs-troponin T <75 ng/mL

Exclusion
- Medically refractory pleural effusions
- Stage 3b cardiac involvement
- Acquired factor X deficiency with active bleeding
- GI involvement with GI bleeding

DLCO: diffusing capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; GI: gastrointestinal; hs: high-sensitivity; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association

to volume and dimethyl sulfoxide content.[64]

Bortezomib-based induction therapy is generally preferred in patients fit for ASCT prior to stem cell mobilisation and ASCT. While there is no consensus on induction therapy, in a Mayo Clinic study, induction therapy significantly improved post-ASCT response (CR from 18% without induction to 34% with induction) in patients with >10% plasmacytosis. However, there was no difference in HR or CR rates in those with ≤ 10% plasmacytosis.[66]

The optimal timing of ASCT, whether early or delayed, has yet to be discerned, as no clear difference in outcomes is seen between the 2 strategies. The role of ASCT in patients who have achieved CR after induction therapy remains unanswered; however, it has been found useful in patients with unsatisfactory responses to induction therapy. Experts have recommended stem cell collection, with the decision to proceed with ASCT made on an individual patient basis. Patients who may benefit and therefore be considered for an early ASCT include those with high-risk FISH abnormalities, concomitant active myeloma, sub-optimal response to bortezomib-based induction therapy, and those with concerns for ineligibility if ASCT is deferred. Ultimately, the decision must be made based on individual patient assessment/circumstances. Our preference for frontline ASCT in all eligible patients is based on currently available non-randomised data suggesting that it can result in long-term remissions with manageable toxicity profiles. However, with the expanding armamentarium in the treatment of amyloidosis and increasing CR rates, the role of ASCT will have to be continually revisited (see discussion under the use of daratumumab).

Stem cell mobilisation in patients with AL amyloidosis is associated with a higher morbidity-mortality risk than MM due to risks of hypoxia, hypotension, capillary leak syndrome, cardiac or cardio-pulmonary decompensation and arrhythmias. Both chemotherapy and granulocyte colony stimulating factor (G-CSF)-based mobilisations are associated with higher grade 3–4 severe adverse events than MM. Some evidence supports the use of G-CSF and plerixafor as it is more efficacious, with less incidence of mobilisation failure and an overall reduction in G-CSF dose and associated complications like weight gain and fluid retention. This is particularly relevant in patients with impaired renal function and older patients with higher rates of mobilisation-related adverse events and failure. We recommend GCSF with or without plerixafor for stem cell mobilisation for AL amyloidosis. If the patient has concurrent MM, chemotherapy mobilisation regimes are preferred. Overall, the higher cost of plerixafor and the potential benefit must be carefully weighed against the expected risk in an individual patient.[61,67]

Table 7. Risk-adapted melphalan dosing for ASCT conditioning (adapted from EHA-ISA, Boston University[65]).

	MEL200[a]	MEL200 vs non-SCT regimes[b]	MEL140
Age (years)	≤60		>61
Cardiac stage	I	II	
eGFR (mL/min/m^2)	>50	30-50	≤30

eGFR: estimated glomerular filtration rate; MEL140: melphalan at the dose of 140 mg/m^2; MEL200: melphalan at the dose of 200 mg/m^2; SCT: stem cell transplantation
[a] Requires all
[b] Multidisciplinary discussion recommended

Maintenance therapy in AL amyloidosis

Summary

- Maintenance therapy after ASCT can be considered for patients with high-risk FISH abnormalities or myeloma phenotype (>10% plasma cells at diagnosis).
- Patients who did not achieve CR after ASCT could be considered for further continued therapy while balancing the risk of treatment-related toxicity.
- Decisions on treatment based on MRD results are not recommended at present and should be considered only in the context of a clinical trial.

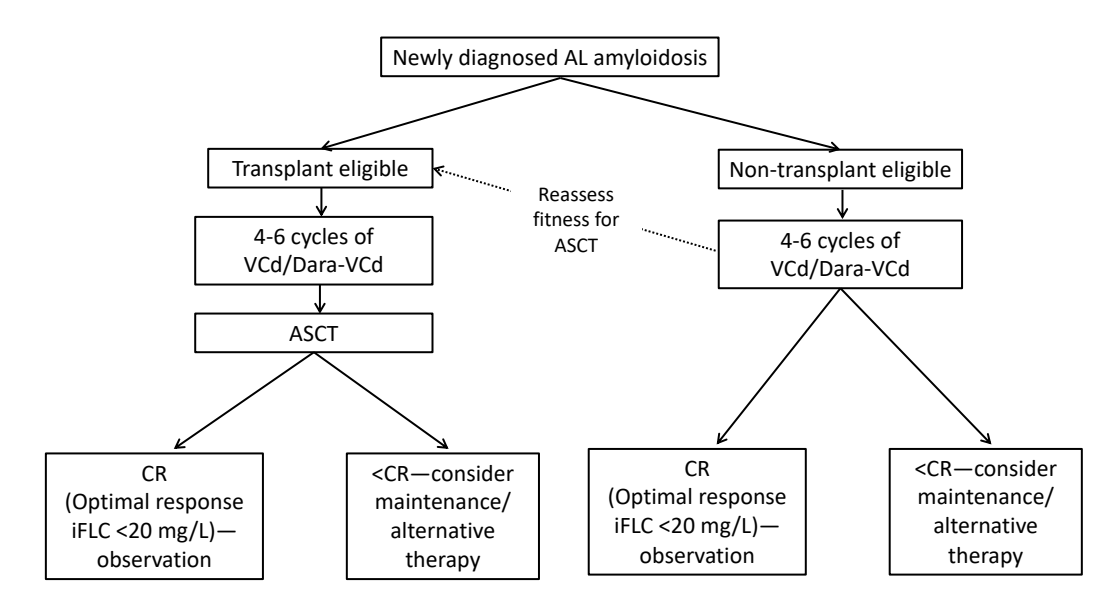
There is a paucity of data on maintenance therapy after an autologous transplant; as such, it is currently based on expert opinion and may not be required for most patients who have an excellent response to ASCT. The goal of maintenance therapy is to maintain responses while balancing toxicity.

A single-centre prospective study[9] with 19 patients who received 3 cycles of bortezomib/dexamethasone induction, or less if they have achieved a CR, followed by ASCT and 6 cycles of bortezomib/dexamethasone consolidation, showed that each phase of treatment deepened the response, with overall achievement of high HR (95%) and MRD negativity (37%) rates, and durable 12 and 24 months PFS and OS (PFS 84% and 68%; OS 84% and 84%). Toxicities were manageable, with the main side effect being peripheral sensory neuropathy (53% G2-3 toxicity). This was likely due to intravenous administration of bortezomib, and the incidence would probably have been lower with subcutaneous bortezomib.

It was noted that none of the patients who achieved MRD negative CR progressed, with improved PFS, compared with patients without MRD negativity, 1 year after initiation of treatment. This suggests that strategies that deepen response may translate into improved long-term outcomes, thereby fulfilling the overall goal of therapy, specifically in patients with initially sub-optimal responses. However, these results need further larger-scale validation, and as such, decisions of treatment based on MRD results are not recommended in routine practice and should be considered only in the context of a clinical trial.

Similarly, in a retrospective study from the Mayo Clinic, 72 patients who underwent ASCT and received post-transplant therapy with either a proteasome inhibitor (PI), IMiD, or PI-IMiD

Fig. 2. Treatment algorithm for newly diagnosed AL amyloidosis.



ASCT: autologous stem cell transplant; CR: complete response; Dara: daratumumab; iFLC: involved free light chain; VCd: bortezomib, cyclophosphamide and dexamethasone

combination showed improvement in CR/VGPR from 35% to 58% with further therapy.[68]

In the ANDROMEDA study, patients in the daratumumab arm received daratumumab maintenance for up to 24 months. Results from this study will further elucidate the role of maintenance therapy.[47]

As this is currently a standard of care in patients with MM, Mayo mSMART guidelines proposed that patients with AL amyloid with concomitant MM phenotype or with high-risk FISH—del(17p), t(4;14), t(14;16), t(14p20, gain 1q)—should be considered for maintenance with preferably a PI.[39]

Relapsed or refractory AL amyloidosis

Summary

- Daratumumab monotherapy with dexamethasone is the preferred salvage regime for patients not refractory to daratumumab.
- Bortezomib-dexamethasone is the preferred salvage regime for patients who are daratumumab-refractory, and bortezomib-sensitive. Ixazomib-dexamethasone is an alternative option.
- Lenalidomide-dexamethasone or pomalidomide-dexamethasone is the preferred salvage option for daratumumab and PI-refractory patients.

Starting second-line treatment for patients with AL amyloid is not a straightforward decision. Patients who do not achieve the optimal response of haematologic VGPR after first-line treatment should be considered for second-line therapy to further eliminate the plasma cell clone and achieve optimal OR. CIBMTR recommends that the assessment of HR requires 2 consecutive measurements made by the same method at any time before the institution of any new therapies.

No consensus exists on when treatment should be reinitiated at relapse. Most would agree that worsening organ function indicates the need for early initiation of therapy, as cardiac progression predicts shorter survival and renal progression predicts the early need for dialysis.[69] However, the decision to restart or change treatment due to rising iFLC before the development of organ progression, even if haematological progression is not met, is still a matter of debate (Fig. 3).

In a study by the Pavia group,[70] which looked at 259 non-transplant eligible patients, almost two-thirds of patients who started second-line therapy had "high-risk dFLC progression", defined as ≥ 50% increase in dFLC from nadir dFLC achieved after frontline treatment, an absolute value of dFLC >20 mg/L; and a dFLC level that is >20% of the baseline value. "High-risk dFLC progression" precedes cardiac progression by a median of 6 months in 85% of cases, thereby identifying patients at high risk for relapse and in whom second-line treatment should be considered.

In a Mayo study[66] of 235 patients who relapsed after ASCT, it was found that the better the post-ASCT response, the longer the time to initiate the next therapy. Patients who did not achieve VGPR post-ASCT were more likely to have absolute values of dFLC that were higher at baseline and post-ASCT, and required second-line treatment. Patients with subtle haematological progression (who did not meet haematologic criteria for progression) from VGPR had a median of 2 years before organ progression, in contrast to patients with less than a VGPR post-ASCT who had 3–6 months to organ progression. Therefore, these findings confirm that even low concentrations of serum amyloid light chains are sufficient to result in the deterioration of organ function and inferior survival. It has been postulated that patients with at least a VGPR post-ASCT may tolerate a gradual rise in dFLC, especially if they did not have a dFLC of >50 mg/L at diagnosis. However, organ progression in some patients could occur as late as 8.3 years after haematologic progression.

Therefore, the individual patient's performance status and potential treatment-related toxicity should be balanced with the desire to obtain the most profound responses when deciding to augment or restart therapy. Before starting salvage chemotherapy, re-evaluation of the patient's disease with a repeat of serum and urine immunofixation electrophoresis, end organs including repeat cardiac scans, urine analysis and repeat bone marrow studies to look for residual disease by next-generation flow or other sensitive methods is recommended.

The data that are currently available for potential regimens at relapse is highlighted in the paragraphs that follow. However, the data are generally of low quality, i.e. retrospective single institutional experience or equivalent and do not provide much evidence regarding choosing one regimen over another. Hence the choice will be dictated by prior therapy, refractoriness to specific agents, expected toxicity of a regimen vs residual toxicities in a patient, drug accessibility as well as physician or patient preferences.

Daratumumab-based therapy is the preferred salvage regime for patients who are not refractory to daratumumab, given its high efficacy and tolerability. In the relapsed/refractory (RR) setting, haematologic responses with daratumumab and dexamethasone occur rapidly, within 1–3 months of therapy and are lasting with VGPR/CR rates in 60–80% and CR in 10–40% of patients.[71] Currently available data have not shown added benefit in outcomes with the addition of other agents like bortezomib or IMiDs.

PI-based salvage regimen is preferred in patients who are refractory to daratumumab and bortezomib-sensitive. Bortezomib used in the salvage setting achieved good HR and CR rates (HR 70–80%, CR 15–40%).[46] Bortezomib can be combined with alkylator drugs like melphalan or cyclophosphamide in this setting. Ixazomib-dexamethasone is a plausible option, especially given the lower incidence of neuropathy than bortezomib. The Tourmaline-AL1[72] phase 3 study comparing ixazomib-dexamethasone with physician's choice salvage regime (mainly comprising of melphalan-dexamethasone and lenalidomide-dexamethasone), however, did not meet its primary study endpoint of superior HR. However, patients treated with ixazomib-dexamethasone had better CR (26% vs 18%), organ response (36% vs 11%) and PFS (10m vs 5m) without OS advantage. Ixazomib may therefore be a potential option for PI-naive patients with polyneuropathy.

Carfilzomib was used in a phase 1 study for relapsed AL amyloid but was associated with significant cardiac, renal and pulmonary toxicities; hence, it is not recommended for patients with cardiac or renal impairment and requires close monitoring and careful dose adjustments.[73]

IMiDs are active in AL amyloidosis but are challenging to administer due to limitations by toxicities, as mentioned previously. Generally, lenalidomide and pomalidomide regimens are preferred over thalidomide regimens. They can be helpful in patients who are refractory to daratumumab and bortezomib or in patients with significant neuropathy, making bortezomib challenging. The doses used in AL amyloidosis are much lower than in MM—as lenalidomide doses greater than 15 mg/day was not tolerated. The most common adverse reactions include haematologic toxicities, rash, fatigue, infections and venous thromboembolism. In combination with an alkylator, lenalidomide yielded 40–60% HR, with 10% CR and infrequent ORs in most studies. A pomalidomide-dexamethasone study of 87 patients with RR AL amyloid showed an HR in 68%, VGPR/CR in 29%.[74]

Melphalan-based regimens (melphalan-dexamethasone or combined with bortezomib or lenalidomide) have also been used in relapsed settings and can produce responses.

Options for third-line salvage are limited—and these include any of the above regimens that patients are not refractory to, such as bendamustine, second ASCT in eligible patients and venetoclax in a subset of patients with t(11;14).

Venetoclax is effective in MM patients, especially those with t(11;14), as demonstrated in the phase 3 BELLINI study,[75] as approximately 50% of patients with AL amyloidosis harbour t(11;14), it is an appealing targeted treatment option.[76] The first retrospective study of 12 patients with RR AL amyloidosis in Mayo Clinic showed an ORR of 88% and CR of 44%, with manageable toxicities.[77] A second multicentre international, retrospective cohort study of 43 patients, reported 72% harbouring t(11;14). Patients with t(11;14), compared with patients who did not have the translocation had higher HR (81% vs 40%) and higher VGPR/CR rates (78% and 30%), with prolonged PFS (NR vs 6.7 months), with an increasing proportion of organ responses in patients with t (11;14). Grade 3 or high toxicity was 19%, with 7% being infection-related.[78] Overall findings demonstrate the efficacy of venetoclax in the RR setting for targeted treatment in patients with t(11;14) AL amyloidosis.

As T-cell engagers and chimeric antigen receptor-T cells are emerging as part of the armamentarium of myeloma treatment, further studies are necessary to elucidate their role in treating AL amyloidosis.

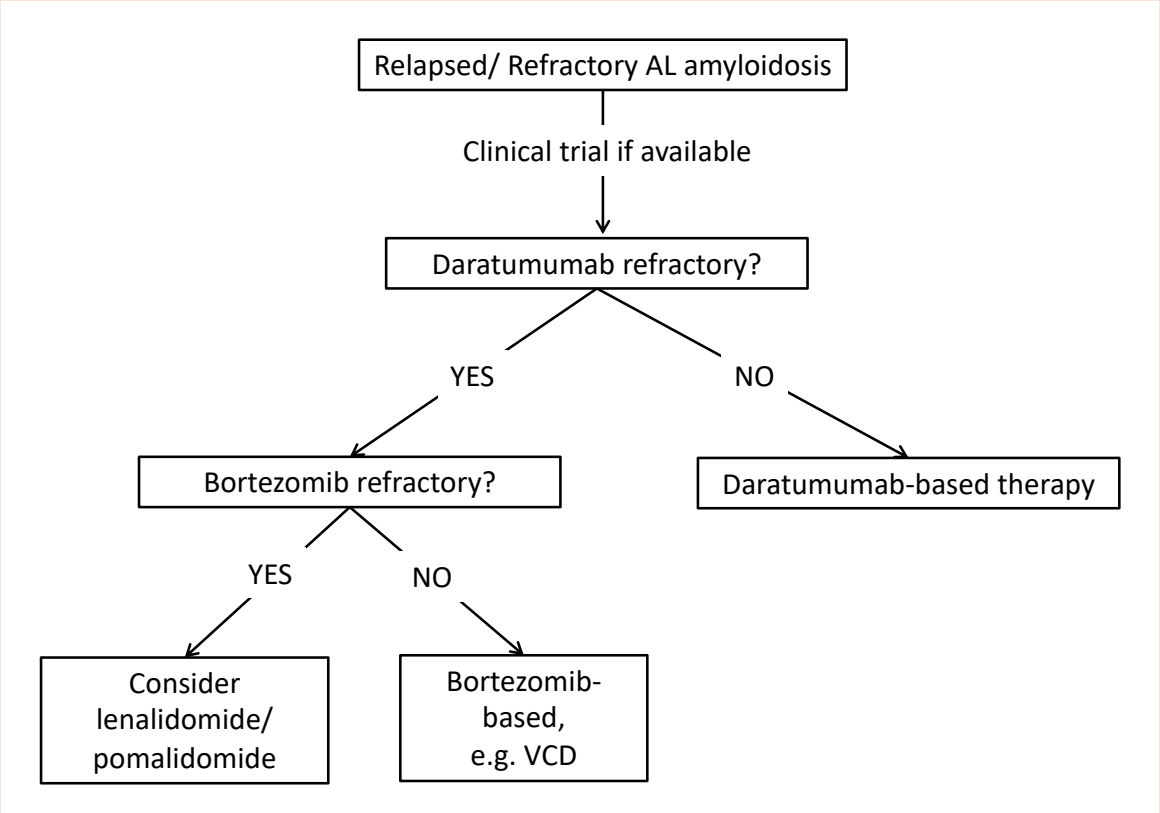
SUPPORTIVE THERAPY

As AL amyloidosis is often a multisystemic disease, it is imperative that a multidisciplinary approach be used for guiding management. This includes the involvement of cardiologists, nephrologists, neurologists, palliative care physicians and other specialists to help with symptom management. In addition, physical and occupational therapists and social workers also play a crucial role in providing appropriate support and advanced care planning.

Doxycycline

Pre-clinical studies have demonstrated that doxycycline has anti-fibril activity.[79] Additionally, 2 previous retrospective studies have also shown improved outcomes, and as such, is frequently recommended for patients with cardiac amyloidosis.

Fig. 3. Treatment algorithm for patients with relapsed refractory AL amyloidosis.



VCD: bortezomib, cyclophosphamide and dexamethasone

The first is a case-control study of patients with AL amyloidosis, including those with Mayo stage 3a disease treated with standard chemotherapy. The HR rate was significantly higher in the doxycycline group as compared with the control group (93% vs 59%), with higher CR rates (56% vs 35%), higher cardiac response rates (60% vs 18%) and improved 24-month survival (82% vs 53%).[80]

The second study from Mayo Clinic looked at patients who received doxycycline post-ASCT as part of the antibiotic prophylaxis given penicillin allergy.[81] In the initial 2012 analysis, a survival advantage was demonstrated in patients who achieved HR. However, a recent update after 12.7 years of follow-up of the same cohort showed a non-statistically significant trend towards improved survival with doxycycline among patients with VGPR or better or with OR.[82] In another recent multicentre randomised control trial in China where patients were randomised to doxycycline with VCD for 9 cycles vs VCD alone, the addition of doxycycline failed to show improved PFS or cardiac PFS.[83] Therefore, with evolving evidence, the role of doxycycline will need to be revisited.

Management of cardiac failure or complications

Summary

- A combination of loop and mineralocorticoid receptor antagonists should be used to treat fluid overload.
- Beta-blockers and ACEi/ARBs should be avoided or used cautiously due to risks of profound hypotension.
- Digoxin may be used cautiously for rate control of AF with frequent monitoring of digoxin levels/toxicity. Amiodarone and ablation are plausible options. Further discussion with a cardiologist is suggested.

The treatment of heart failure resulting from cardiac AL amyloidosis is a therapeutic challenge due to the complex nature of cardiac dysfunction, and concurrent renal and autonomic comorbidities. Diuretics are the primary treatment for managing fluid overload due to congestive heart failure, nephrotic syndrome or therapy. Combining

loop diuretics and mineralocorticoid receptor antagonists like spironolactone often yields the best results. However, doses are limited by the risk of symptomatic hypotension and worsening renal function. Therefore, careful titration with close monitoring of tolerance, renal function, and electrolytes should be performed upon initiation of therapy. Careful employment of oral vasopressors like midodrine could help minimise symptomatic hypotension and maintain blood pressure. Lifestyle measures such as fluid and salt restriction are also critical. Albumin infusions may be helpful if there is concomitant severe nephrotic syndrome.

In patients with cardiac amyloidosis, the underlying pathology is often severe diastolic dysfunction with preserved ejection fraction but reduced stroke volume due to restrictive filling[84]. Therefore, they depend on higher heart rates to maintain cardiac output. Standard medications often used to treat patients with heart failure with reduced ejection fraction, specifically beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), often worsen the patient's clinical condition. Beta blockade may result in profound hypotension, reduced cardiac output, or worsened renal functions in patients with cardiac AL amyloidosis. A multidisciplinary approach involving collaboration with cardiologists and renal physicians is valuable in managing these patients.

Patients with atrial fibrillation (AF) often cannot tolerate beta-blockade or calcium channel blockers traditionally used for rate control. Digoxin may be safely used in low doses, but caution should be taken to monitor electrolytes and kidney function closely.[85] Digoxin toxicity has been reported in AL amyloidosis, even at therapeutic doses, due to the drug binding and affinity to amyloid fibrils.[85] Amiodarone is the preferred alternative, albeit with insufficient evidence. Ablation of the atrioventricular node with permanent pacing may be advantageous for a subset of patients.[39] In some cases, no rate control agent is required if there is concomitant conduction system disease.

Sudden cardiac death in patients with amyloidosis has been reported in 15–23% and is commonly due to pulseless electrical activity often preceded by bradycardia.[86] The role of implantable cardioverter-defibrillators is controversial, and appropriateness needs to be decided by the cardiologists closely involved in the management of such patients.

Studies have shown a high prevalence of intracardiac thrombus in cardiac amyloidosis in up to 35% of patients with AL amyloidosis.[87] Most thrombi are found in the right or left atrial appendages (LAA). AF and echocardiography variables of left ventricular diastolic dysfunction and low LAA emptying are independent variables associated with intracardiac thrombus. In the setting of AF, anticoagulation should be considered independent of the CHA2DS2-VASc score to reduce thromboembolic risk. This, however, has to be weighed against the increased risk of bleeding, especially in patients with gastrointestinal (GI) involvement and coagulopathy.[87]

Management of renal failure or complications

The median time from diagnosis of patients with AL amyloidosis and nephrotic syndrome to dialysis is 14 months, with one-third requiring dialysis.[89] The mainstay of treatment of oedema is with diuretics. ACEI may reduce proteinuria in patients with proteinuria, but careful monitoring of electrolytes—given the risk of hyperkalemia—is necessary.[90] Dialysis in these patients can be challenging as many may have concomitant cardiac amyloid or orthostatic hypotension with recurrent intradialytic hypotensive episodes. Construction of an arteriovenous fistula may also have increased bleeding risk, especially in patients with coagulopathy or vascular and cutaneous amyloid.[91]

Management of GI complications

Some common symptoms of GI involvement in AL amyloidosis include alternating diarrhoea and constipation, weight loss, heartburn and nausea, and up to 50% may present with GI bleeding. In patients with dysmotility symptoms, nutritional supplementation and dietary modification—including frequent small-volume liquid or homogenised foods with low soluble fibre and fat, and prokinetic agents such as metoclopramide, erythromycin or domperidone—are advised. For patients with diarrhoea, anti-diarrhoeal such as loperamide can be initiated.

Organ transplant

Summary

- In exceptional cases, organ transplants (i.e. heart and kidney) can be considered.

Solid-organ transplantation is controversial in organ failure in AL amyloidosis, given concerns that the AL amyloid might recur in the transplanted organ. This is corroborated by multiple case series demonstrating recurrent AL amyloid in the transplanted heart and kidney.[86-92] Outcomes of cardiac transplant for AL amyloid are poorer than non-amyloid patients, with a 5-year survival of 43% vs 85%, respectively, with most deaths occurring from progressive amyloidosis.[93] However,

later studies have shown that with improved chemotherapy regimes and novel agents, cardiac transplant outcomes in AL amyloidosis improved.[94]

Mechanical circulatory support (MCS) is a feasible option in patients with acceptable outcomes as a bridge to transplantation.[95] With highly effective clone-directed therapies like daratumumab, salvaging patients presenting with more severe cardiac failure by temporarily employing left ventricular assist devices allowing for adequate organ function recovery has become a reality even in our local setting.[96,97] However, given the limited resources and morbidity related to MCS, it remains the exception rather than the norm.

In a large series of AL amyloid patients who have undergone kidney transplantation, potential good outcomes can be achieved with patients who have achieved CR or VGPR at the time of kidney transplantation.[98] Recent consensus guidance by the American Society of Transplantation suggested some criteria for proceeding with renal transplant[99] (Table 8).

Table 8. American Society of Transplantation organ transplant consensus for AL amyloidosis.

Criteria for organ transplantation in amyloidosis	Therapeutic response with dFLC of <40 mg/L
	Only 1 organ involved with amyloidosis
	Does not fulfil criteria for symptomatic myeloma
	Must be a candidate for stem cell transplantation following organ transplantation

dFLC: difference between involved and uninvolved free light chain

Neuropathy or autonomic dysfunction

Summary

- Neuralgesics can be used effectively in patients with neuropathy.
- Non-pharmacological methods (compression stocking, abdominal binders, exercise) and pharmacological methods (midodrine, pyridostigmine) can treat neurogenic orthostatic hypotension.

Peripheral neuropathy is a common presentation in 9.6–35% of patients. The pattern of involvement is symmetrical, length-dependent, lowed-limb neuropathy that is slowly progressing and painful.[100] Symptomatic treatment with neuralgesic agents including gabapentin, pregabalin, amitriptyline, nortriptyline or duloxetine should be considered for relief of discomfort. In patients with carpal tunnel syndrome, surgical carpal tunnel release or braces may benefit.[39]

Treatment of patients with orthostatic hypotension and secondary autonomic dysfunction may be challenging in patients with severe nephrotic syndrome or cardiomyopathy. Non-pharmacological therapy includes compression garments like compression stockings and abdominal binders, and regular exercise may benefit. Pharmacological treatment, including alpha-1 adrenergic receptor agonist midodrine or anticholinergic pyridostigmine may improve neurogenic orthostatic hypotension.[101] Fludrocortisone 0.1 mg twice a day or three times daily must be used cautiously as it may aggravate congestive heart failure. In patients with symptoms associated with gastroparesis, metoclopramide may be considered.

DRUG TOXICITY AND DOSE ADJUSTMENTS

Recommendations

- Administer bortezomib once weekly subcutaneously.
- Close monitoring for toxic effects, including cardiac toxicity, hypotension, neuropathy.
- An initial lower dose of bortezomib and dexamethasone can be considered before dose escalation, if tolerated, to avoid excess toxicity in patients with advanced heart disease (Mayo stage 3b).

Bortezomib should be administered subcutaneously once weekly at an initial dose of 1.3 mg/m^2. A once-weekly bortezomib dosing was associated with a better toxicity profile than twice-weekly bortezomib, including fewer cardiac events, orthostatic hypotension, and dose modifications.[46] Risk-adapted dosing strategies may help abrogate the risk of early mortality. One such strategy—using bortezomib 1.3 mg/m^2 on days 1, 8 and 15 with dexamethasone 20–40 mg on the same days, compared to a standard dose of 1.3 mg/m^2 plus dexamethasone 40 mg on days 1, 4, 8 and 11 every 21 days for up to 8 cycles—significantly lowered 3-month death rates (4.5% in the dose-adjusted group vs 36%) in patients with Eastern Cooperative Oncology Group performance status ≥2, or cardiac dysfunction (Mayo stage 2 with proBNP > 1285 ng/L or Mayo stage 3), or age >70 years, or pre-existing peripheral neuropathy due to AL amyloidosis, or symptomatic orthostatic hypotension with systolic blood pressure at erect

Table 9. Dose adjustments suggested for patients with renal impairment.

Creatinine clearance	Dose adjustment for CrCl	Timing of administration if on dialysis
Bortezomib - Any CrCl	No	After dialysis
Cyclophosphamide - CrCl <10 or dialysis	75% dose	After dialysis
Oral melphalan (IMWG) - CrCl 15–59 - CrCl <15 or dialysis	- 75% dose - 50% dose	Before or after dialysis
Dexamethasone - Any CrCl	No	Before or after dialysis
Aciclovir - CrCl 10–25 - CrCl <10 or dialysis	- No adjustment or reduce to 200 mg q12h - 200 mg q12h	After dialysis
Co-trimoxazole - CrCl 15–30 - CrCl <15 or dialysis	- 50% of usual dose - Approx. 25–50% of usual dose. Use with caution.	After dialysis
Daratumumab	No	Before or after dialysis

ASCT: autologous stem cell transplant; CrCl: creatinine clearance; IMWG: International Myeloma Working Group

position <100 mmHg.[102] HR and CR rates were comparable in patients who received risk-adjusted vs standard doses of bortezomib/dexamethasone.

Dose adjustments in patients with renal impairment

Patients with renal impairment or on long-term dialysis will require adjustment of therapy (Table 9).

CONCLUSION

The current guidelines aim to provide a comprehensive review of the diagnosis and management of patients with AL amyloidosis in Singapore. As AL amyloid is a rare disease with a paucity of large-scale clinical trial data to inform therapy, referral to a centre with expertise in treating AL amyloidosis would be recommended from the point of clinical suspicion or diagnosis.

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Ann Acad Med Singap 2023;52:625-34
https://doi.org/10.47102/annals-acadmedsg.202323

REVIEW ARTICLE

Improving visual outcomes in patients with rare paediatric eye diseases

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ABSTRACT

Introduction: Rare paediatric eye diseases (RPEDs) threaten both vision and life. Recently, rare diseases were recognised as a global public health agenda, with children specified as a priority in the World Health Organization's VISION 2020 against avoidable visual loss.

Method: We conducted a review through a query of online databases (PubMed, Embase and Cochrane Library). Articles related to RPEDs were selected based on relevance by 2 authors, with any disagreements adjudicated by the third author.

Results: We synthesise the current state of knowledge regarding RPEDs, barriers to their care, and recommendations for the future. RPEDs often result in significant visual loss, profoundly impacting the way children comprehend and participate in the world. These diseases may also reduce life expectancy and even be life-threatening. Barriers to the care of RPEDs include an unclear definition of "rare diseases", missed or delayed diagnosis, inadequate knowledge and expertise in management, and challenging research environments.

Conclusion: Our findings provide an update on the diagnosis and management of RPEDs, which is of relevance to ophthalmologists, paediatricians, healthcare policymakers and social workers. We propose supportive policies and adequate resource allocation to these diseases, comprehensive and patient-centred care, alongside improved education and training, enhanced research capabilities and continued collaboration across institutions.

Ann Acad Med Singap 2023;52:625-34

Keywords: disease burden, eye disease, paediatric disability, preventable visual loss, rare disease

CLINICAL IMPACT

What is New

- We present, to our knowledge, the first review synthesising literature on rare paediatric eye diseases (RPEDs) and their burden, and a tabular list of these diseases and their characteristics.
- Barriers to care for RPEDs include lack of a consensus definition; insufficient knowledge, experience and expertise; and inadequate policy provision and resource allocation.

Clinical Implication

- Further understanding and awareness of RPEDs can encourage earlier recognition of these diseases and patient-centric care.

INTRODUCTION

Rare diseases are generally understood as those that affect less than 1 in 2000–2500 people in the general population.[1] They are defined to affect fewer than 200,000 people in the US, lesser than 1 in 2000 people in Europe and lesser than 1 in 2500 people in Japan.[2] Rare diseases are an important healthcare issue and a challenge to public health.[3] Although the individual incidence is low, rare diseases collectively affect 5–8% of the worldwide population or 1 in 15 persons,[4] reflecting individual, societal and global significance. The majority of rare diseases affect children, with 69.9% of these being exclusively paediatric in onset.[1]

Rare paediatric eye diseases (RPEDs) are serious and usually lifetime conditions resulting in visual impairment and blindness. In some instances, they can also be life-threatening. Recently, rare diseases were recognised as a global public health agenda,[6] and children were specified as a priority in the World Health Organization's VISION 2020 against avoidable visual loss.[5] There has also been increasing attention towards these diseases from international consortia and registries, disease-specific clinics, and divisions of academic children's hospitals.[6]

RPEDs significantly affect the quality of life and result in substantial loss of income and economic

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productivity,[7] especially in the context of a globally ageing population. Furthermore, paediatric patients are a vulnerable demographic as they are unable to care for themselves. Their well-being is susceptible to external factors and can be compromised by poor access to healthcare, socioeconomic deprivation and parental neglect.[8]

Given the emerging importance of RPEDs, we conducted a review of literature synthesising the current understanding of these diseases, their morbidity and mortality, along with barriers and gaps relating to their care. We cite examples of RPEDs, such as retinoblastoma (RB) and retinitis pigmentosa, contrasting them to more common childhood ocular conditions, such as myopia and amblyopia. We also included a list of the most common RPEDs, detailing their age of onset, course of the disease, area of primary involvement in the eye, treatment options, and whether they have any genetic basis (Table 1). Our findings that map the current landscape of RPEDs and recommendations for the treatment of these diseases will be of relevance to paediatric ophthalmologists, researchers and health policymakers.

METHOD

We conducted a search of 3 online databases (PubMed, Embase and Cochrane library) with the keywords "paediatric", "pediatric", "children", "child", "rare disease", "orphan disease", "neglected disease", "eye disease", "orbitopathy", "visual loss", "vision loss" and "blindness." Articles were included based on their relevance to the subject of RPEDs by 2 authors (FYCN and GS), with any conflicts resolved by the third author (PLT). The nature of the review article did not require an Institutional Review Board or ethical approval. The study adhered to the tenets of the Declaration of Helsinki.

RESULTS

Definition and prevalence

There is no universally accepted definition of "rare disease." A systematic review identified 296 definitions from 1109 organisations across 32 international jurisdictions,[2] and another review found a global average prevalence of 1 in 2500 people.[9] "Rare disease" may also be known as "orphan disease", a term emphasising the underappreciated and overlooked nature of these diseases by the medical community and drug companies.[10]

Similarly, there is no consensus on what constitutes a "rare paediatric eye disease", although these diseases are broadly understood to occur infrequently in the eyes of patients below the age of 18.[11] They comprise a heterogenous group of conditions encompassing over 900 eye disorders ranging from relatively prevalent conditions, such as retinitis pigmentosa, to extremely rare entities such as developmental eye anomalies.[12] Functionally, RPEDs can be divided into 2 categories: those that occur predominantly in children (e.g. inherited retinal disorders, RB, chloridaemia, coloboma), and those that more commonly occur in adults, but may occasionally present in children (e.g. uveitis, keratoconjunctivitis, optic nerve hypoplasia, optic nerve sheath meningioma). There are also other systemic rare diseases that involve the eye (e.g. Joubert syndrome, Revesz syndrome, Muckle-Well syndrome), but they are beyond the premise of this review.

Impact, morbidity and mortality

Although the total prevalence of rare diseases is low, their overall burden is socially and economically significant. Overall, there are up to 6000–8000 rare diseases affecting 400 million people worldwide;[22] 72% of these diseases are genetic and 70% of them originate in childhood.[12] RPEDs have severe consequences, posing a threat to both vision and life in children and young adults all around the world. Moreover, 35% of these result in deaths in the first year of life and reduced life expectancy in 36.8% of these diseases, with 25.7% of children born with rare diseases dying before 5 years old.[22]

Rare diseases are often complex and chronic. Their manifestation during childhood is associated with significant disability, impaired quality of life and premature death. The global burden of disease is conventionally measured using disability-adjusted life years (DALYs). However, the lack of national epidemiological studies on visual impairment and data on children requires the burden of childhood blindness to be inferred from the years lived with disability (YLD) component of DALYs instead.[23] YLD is substantially higher in children than in adults since disability occurs much earlier in the life course, by an average of 7 decades.[5] The impact of visual impairment and blindness on paediatric patients is lifelong and life-changing, given their young age and potential for development. In addition, most types of RPEDs are bilateral and progressive in nature, causing more severe vision loss and impediment to daily functioning as patients grow and mature. Visual loss can profoundly and irreversibly impact the way children interact with others, acquire information and interpret the world.[24] RPEDs such as retinitis pigmentosa and coloboma often result in permanent visual disability with the former being progressive, while more lethal conditions such as RB and Batten's disease might lead to early demise before children even have a chance to

Table 1. List of common rare paediatric eye diseases by age of onset, course of disease, area of primary involvement, treatment option and genetic basis.

Disease	Age of onset	Course of disease	Area of primary involvement	Treatment option	Genetic basis
Retinitis pigmentosa	Adolescence to adulthood	Bilateral progressive, eventual vision loss	Retina and RPE	No established therapeutic options	Present (AD)
Stargardt's disease (juvenile macular degeneration)	Adolescence to adulthood	Bilateral progressive, eventual vision loss	Macula	No established therapeutic options	Present (AR)
Anophthalmia/microphthalmia	At birth	Unilateral or bilateral stationary	Entire globe	No established therapeutic options	Present (combined genetic and environmental factors)
Coloboma	At birth	Unilateral or bilateral stationary	Eyelid/lens/macular/optic nerve/uveal/chorioretinal[13]	No established therapeutic options	Present (AD and AR)
Leber's hereditary optic neuropathy	Adolescence	Unilateral progressive with sequential involvement of other eye, painless loss of central vision	Optic nerve	No established therapeutic options	Present (inherited mitochondrial disorder)
Usher syndrome	10 years to early adolescence	Bilateral progressive, eventual vision loss	Retina and RPE (due to retinitis pigmentosa)	No established therapeutic options	Present (AR)
Congenital ectopia lentis	<10 years	Bilateral stationary	Lens	Refractive correction and co-management of systemic disease, possible lensectomy[14]	Present (AD and AR)
Retinoblastoma	<5 years	Unilateral progressive, vision loss and life-threatening if untreated	Entire globe	Intravenous chemotherapy, intra-arterial chemotherapy, intravitreal chemotherapy, intracameral chemotherapy, consolidation therapies (cryotherapy and transpupillary thermotherapy), radiation-based therapies (external beam radiotherapy and plaque radiotherapy), and enucleation[15]	Present (AD)
Best disease (vitelliform macular dystrophy)	Early childhood to second decade of life	Bilateral progressive, gradual vision loss	Retina and RPE	No established therapeutic options	Present (AD)
Batten disease (juvenile neuronal ceroid lipofuscinosis)	6–10 years old	Bilateral progressive, eventual vision loss	Retina and RPE	No established therapeutic options	Present (AR)
Leber congenital amaurosis	At birth to infancy	Bilateral progressive, eventual vision loss	Retina and RPE	No established therapeutic options	Present (AR)

Table 1. List of common rare paediatric eye diseases by age of onset, course of disease, area of primary involvement, treatment option and genetic basis. (Cont'd)

Disease	Age of onset	Course of disease	Area of primary involvement	Treatment option	Genetic basis
Autosomal dominant optic atrophy	Childhood to adolescence	Bilateral progressive, eventual vision loss	Retina	No established therapeutic options	Present (AD)
Optic nerve hypoplasia	At birth to infancy	Unilateral or bilateral stationary	Optic nerve	No established therapeutic options	Present (AR)
Bietti's crystalline dystrophy	Adolescence to third decade of life	Bilateral progressive, eventual vision loss	Cornea, retina and RPE	No established therapeutic options	Present (AR)
Primary congenital glaucoma	<3 years	Bilateral progressive, eventual vision loss	Trabecular meshwork and anterior chamber angle	Angle surgery to lower IOP	Present (AR)
Cystinosis	Infancy to childhood	Bilateral progressive, eventual vision loss	Cornea, retina and RPE	Oral and topical cysteamine[16]	Present (AR)
Axenfeld-Rieger syndrome	Infancy to childhood	Bilateral progressive, eventual vision loss	Anterior chamber	No established therapeutic options, prevention of 2' glaucoma[17]	Present (AD)
Choroideraemia	Childhood to adolescence	Bilateral progressive, eventual peripheral vision loss	Choroid, retina and RPE	No established therapeutic options	Present (X-linked)
Paediatric Graves' disease	<16 years, peaks from 11 to 15 years[18]	Bilateral progressive, pain, blurring of vision, and photophobia	Extraocular muscles, fatty and connective tissue	Anti-thyroid medication, surgical subtotal thyroidectomy, radioactive iodine[19]	Present (combined genetic, environmental and immune factors)[20]
Paediatric Behcet's disease	Childhood to adolescence	Bilateral progressive, pain, blurring of vision and photophobia	Uveal tract, retina and optic nerve[21]	Systemic corticosteroids and immunomodulatory therapy	Absent

AD: autosomal dominant; AR: autosomal recessive; IOP: intraocular pressure; RPE: retinal pigment epithelium
Superscript numbers: refer to REFERENCES

reach adulthood. Furthermore, most types of RPEDs do not have any known or established therapeutic options.

Psychologically, socially and economically, the impact of rare diseases is often unseen but deeply felt by families grappling with these diseases. Families supporting children with such rare diseases reported substantial stress and frustration from delays in diagnosis, misdiagnosis, need for constant medical care, inadequate services and treatment options, and high costs, among others. Despite their increased need for support, few families can receive the psychological help they need. This contrasts with the abundant resources and support parents have for more common childhood eye diseases such as myopia and amblyopia, where there is abundant information online for parents to educate themselves, and readily available access to expert care and treatment options both in the developing and developed world. Many of these common childhood eye diseases also have straightforward treatment options (corrective lenses and surgeries) and relatively benign courses, hence not requiring as many visits to the clinic.

Children living with RPEDs are at increased risk of social isolation and psychological distress. Their illnesses have a major impact on their schooling and other social experiences, resulting in reduced health-related quality of life and emotional difficulties.[25] For example, children with RPEDs such as microphthalmia or severe colobomas, especially when bilateral, often miss out on school events and physical education (sports) as they have to attend medical appointments or are unable to participate for health reasons. Many RPEDs are associated with other physical deficiencies, such as hearing loss in Usher syndrome and neurological disturbances in Best disease. They are also at a greater risk of bullying and physical aggression due to their frequent absenteeism and physical deficiencies, with their peers finding it difficult to accept their differences or understand their struggles and experiences.[26] RPEDs such as anophthalmia/microphthalmia and RB present with obvious cosmetic and visual defects on inspection, and children may grow self-conscious or ashamed of their appearances, especially when poorly rehabilitated. Academically, with poor vision, these children are unable to capture information as easily and learn alongside their peers in the classroom. This contrasts with more common childhood diseases such as myopia and amblyopia, which are easily correctable, do not result in visual or cosmetic defects and are shared by many children in a similar age group—thus without social stigma or handicap. In addition, as paediatric patients with rare diseases progress through adolescence, transitional care to adult services becomes critical but is often lacking.[27] As a result, many teenagers with rare diseases feel abandoned by the healthcare systems and have trouble navigating the changes in service providers when they need the most support. This is common across all paediatric disorders, but especially acute in rare diseases, as access to qualified care providers with both knowledge of the diseases and aptitude to deal with the complex emotional and mental turmoil of adolescents with rare diseases is exceedingly rare.

Economically, rare diseases take a toll on healthcare resources, families and societies at large.[28] The complexity of rare disorders requires multidisciplinary care and an interplay of services from various healthcare providers and specialists from different disciplines.[29] Hospital admissions and the use of emergency services are common in rare diseases, driving up healthcare costs. For example, between 2003 and 2014, total health expenditures for the treatment of rare diseases in Taiwan increased from US$18.65 million to US$137.44 million, with a 20.43-fold difference in average health expenditures and a 69.46-fold difference in average drug expenditures between patients with rare diseases and the overall population.[30] In the US, the total economic burden of rare diseases in 2019 was $997 billion, including a direct medical cost of $449 billion (45%), $437 billion (44%) in indirect costs and $73 billion in non-medical costs (7%).[31] The top drivers for excess medical costs associated with rare diseases are hospital inpatient care and prescription medication; the top indirect cost categories are labour market productivity losses due to absenteeism, presenteeism and early retirement. Nevertheless, more research is required to ascertain the true economic impact of rare diseases, as a recent scoping review found a paucity of cost-of-illness studies in rare diseases.[32]

Barriers

Lack of consensus on the definition of RPEDs

The absence of a definition for RPEDs results in difficulty qualifying and quantifying their burden, hampering efforts to diagnose and treat these diseases. This is further exacerbated by the lack of an internationally or nationally unified systemic approach for diagnosis and surveillance, as well as the lack of a classified medical nomenclature for documentation in health information systems. The International Classification of Diseases 11th version (ICD-11), which most countries use to identify diseases, does not include individual codes for RPEDs,[33] and the Systematised Nomenclature of Medicine only lists around 40% of rare diseases.[34]

Disease-specific patient registries are an alternate means to identify patients with RPEDs.[3] However, the quality, scope and capacity of many registries are limited. They may not be updated to reflect the most current records of patients and may not have a classification system in place for RPEDs. This contrasts with the robust patient records for more prevalent childhood eye diseases like myopia and amblyopia, allowing high-quality and large-scale epidemiological studies to be carried out.[35]

Insufficient knowledge, experience and expertise

There is often a paucity of experience and expertise in the diagnosis and treatment of RPEDs. Due to the limited number of patients affected, especially in smaller, even in medically advanced countries like Singapore, there are only a handful of eye specialists who have direct experience with any given RPEDs, with most physicians having little to no exposure to these diseases. For example, in 2022, an 11-year-old girl was the first patient with orbital rhabdomyosarcoma in Singapore and Southeast Asia to receive interstitial brachytherapy treatment.[36] Many RPEDs also exhibit great genetic and phenotypic heterogeneity in their presentation, confounding the diagnostic conundrum. For example, in diffuse anterior retinoblastoma, a rare variant of RB, the retinal fundus examination may have atypical findings suggesting inflammation, leading to misdiagnosis and even mismanagement.[37] In addition, despite the impetus for a more in-depth understanding of RPEDs, there is a paucity of knowledge describing the field. The lack of widespread information and precedents of case studies to infer from hampers advancements in the care of RPEDs.

Furthermore, delayed diagnosis, misdiagnosis, or even failure of diagnosis are common in RPEDs. Studies show that half of those suspected to have a rare disease are undiagnosed, whereas those who receive a diagnosis have an average lag time of 5–6 years, with diagnostic delays as long as several decades.[38] For example, retinitis pigmentosa is a condition with a vast array of differential diagnoses, and the combination of multiple causative genes and the broad spectrum of clinical severity make both diagnosis and prognosis challenging, with genotypic multiplicity and phenotypic variability confounding the picture.[39] In a systematic review, time to diagnosis was prolonged by 3–5 months in RB with dire consequences, such as extraocular disease and higher mortality rates.[40] In another review, 42% of patients initially diagnosed with RB were found to be suffering from "pseudo-RB causes" such as Coats disease, persistent fetal vasculature—previously termed persistent hyperplastic primary vitreous and familial exudative vitreo-retinopathy[41].

In comparison, the diagnosis of common childhood eye diseases like myopia is often made early and with great accuracy, owing to early childhood eye screening in nationwide health programmes and developed eye screening protocols. Singapore, for example, formed the National Myopia Prevention Programme to address the high incidence of childhood myopia through public education and vision screening, for which the prevalence of myopia among students decreased from 37.7% to 31.6% between 2004 and 2015.[42] Similarly, prevalent childhood eye conditions like amblyopia or strabismus are often picked up during routine developmental health screenings for children, even when they are unable to complain of poor vision or other ocular symptoms.[39]

Even upon diagnosis, patients with RPEDs are commonly faced with inappropriate or inadequate treatment due to a lack of access to novel drugs, therapeutic modalities or professional expertise. Formalised diagnostic standards and clinical guidelines are not available for many rare diseases, leading to extreme variability and efficacy of treatment.[43] Due to the complexity of RPEDs, treatment options are involved, controversial and multidisciplinary. RB, for example, requires advanced treatment technology, techniques and expertise, for which there are discrepancies in protocols and a wide range of clinical outcomes.[44] Similarly, inherited retinal diseases require advanced treatment techniques, such as RNA editing and bionic vision.[45] This is opposed to the treatment of well-understood childhood eye diseases like myopia, which are uncomplicated and easily correctable with a pair of prescription glasses at a low cost even by allied health specialists such as optometrists.

Lack of consolidated and conclusive research

Randomised controlled trials (RCTs), the gold standard for clinical research, are difficult to carry out in RPEDs. The initial investment in capital is extensive, with unmet needs for staff and expertise limiting the number of centres able to conduct these trials.[46] In addition, it is challenging to enter sufficient patients into trials due to a small patient base. Problems in diagnosis, lack of standardised reporting and loss of patients to follow-up further compound the difficulty of identifying relevant patients. The majority of research on RPEDs is retrospective, non-randomised and underpowered by low participant numbers, consisting of mostly case reports or series. Research conclusions

derived are thus inadequate and subject to further validation, preventing the innovation of disease-specific therapies.[47]

Furthermore, the developmental trajectory of children with rare diseases is altered and unpredictable, making it difficult to establish common outcome measures at various developmental stages and prognosticate outcomes.[48] Studies are also complicated by the measurement and selection biases at play in rare paediatric diseases due to their complex disease states and the lack of understanding of these diseases.[48] Finally, the challenge of assessing clinical outcomes in very young children may prevent their inclusion in research and contribute to representation bias.[49]

Inadequate policy provision and resource allocation

From a public health point of view, rare diseases generally receive little policy support and resource allocation. They are not considered a national health priority, unlike prevalent childhood eye diseases like myopia that have nationwide health screening programmes.[50] Instead, RPEDs are diverse and heterogenous in nature, with any specific disease affecting only a few individuals at a time. Any advancements in their management only benefit a small segment of the population, skewing the cost–benefit analysis to disfavour the uptake of RPEDs by the public healthcare system.

From an industry point of view, the large amount of initial investment required for the development of novel therapies in RPEDs presents a substantial barrier to entry.[51] Research on these diseases will seldom produce tangible financial benefits, such as returns on investment or patents for intellectual property rights due to the small consumer base. Consequently, these diseases receive less attention and research grants from both government and pharmaceutical companies, requiring patient advocacy groups and private organisations to step in to bridge the gap.[52]

Recommendations

Supportive policies and adequate resource allocation

To enable children with RPEDs to receive timely treatment, a concerted effort is needed across key stakeholders, including paediatric ophthalmologists, healthcare policymakers, academic healthcare organisations, administrators and industry leaders.

Funding for research on RPEDs, together with financial support to enable patients to acquire these treatment therapies, is central to the management of these diseases, as few patients can afford the otherwise costly treatment. Society as a whole may stand to benefit from this, through reduced rates of preventable blindness, mortality, disability, years of life lost, rate of admission or readmission to hospital settings and cost of illness. In particular, more attention could be dedicated to the research of gene therapy options, as most RPEDs have an underlying genetic basis,[53] as shown in Table 1.

With the right screening programmes and systemic infrastructure, diagnosis and treatment for RPEDs can be made effective from an economic standpoint, even in developing countries. In India, a rapid screening strategy prioritising the order of exons to be analysed was developed for RB and identified mutations in 76% of patients in half the time and one-third the cost, facilitating better risk prediction in affected families and genetic counselling.[54] Another study on RB found a 3.5-fold cost saving for genetic screening as compared to conventional screening by clinical examination, demonstrating the potential of medical technology in the management of RPEDs. Moving forward, new models of risk and incentive sharing can be explored between the public and private sectors, spurring the development of novel technologies and therapies for RPEDs.

Enhanced research capabilities and continued collaboration

There is a need for wide-ranging and organised collaboration between tertiary care centres and research laboratories involved in the treatment of RPEDs on an international level. Multicentric, multinational collaboration is essential to the research and advancement of treatment options, and effective recruitment of patients can be achieved through partnership with patient organisations, rare disease registries and centres of expertise. Given how RPEDs are a group of heterogenous disorders with significant variability between diseases, individual research laboratories targeting specific diseases would need to run in parallel with each other, while sharing strategies and best practices that can be applied across rare diseases.

Researchers can collaborate with local healthcare professionals to administer these trials in local healthcare settings to overcome the barrier of patients having to travel to be a part of clinical trials. Technology can be leveraged to monitor responses to interventions remotely and facilitate the collection of real-time data, allowing synchronous delivery of these trials across different geographical settings. This will create greater convenience and feasibility of enrolment in trials, encouraging greater participation.

To overcome the challenge of a relatively small number of patients with RPEDs available to participate in research studies and difficulties in recruiting paediatric patients for clinical trials, various strategies can be employed. For example, statistical methods for small samples can be utilised, including continual reassessment methods for phase 1 trials,[55] along with dose-response modelling and adaptive designs for phase 2 and 3 trials.[56] Furthermore, international natural history studies can take into account the genetic heterogeneity of RPEDs in paediatric patients to predict the ages when rapid changes in disease progression occur, identifying key periods for therapeutic intervention and proof of efficacy.[46] Patient registries and databases, such as the Genetic and Rare Diseases (GARD) Information Centre, as well as eyeGENE, the US National Eye Institute's National Ophthalmic Disease Genotyping and Phenotyping Network, have also been established to recruit more patients and advance research in the genetic causes and mechanisms of RPEDs.[57]

Comprehensive and patient-centred care

Communication between physicians and patients is crucial in the management of RPEDs. Patients and their families often feel alone and isolated due to the rarity of their conditions and the lack of available information to understand them.[58] Physicians need to give adequate guidance to patients, providing regular progress updates and explaining possible treatment plans, involving them in the decision-making process and taking into account their fears, desires and unique circumstances. Physicians should also be forthcoming in admitting the gaps in their knowledge and expertise when unsure, explaining the rarity of these diseases and the lack of available information, and adopting a consultative and collaborative approach with patients.

Educational materials on RPEDs can be curated by healthcare professionals in collaboration with patient advocacy groups, to address the lack of authoritative and reliable information sources on these conditions. These can be given as pamphlets to patients and be used by doctors to explain information during consultations. By empowering patients and their families with knowledge, they are better equipped to understand and manage their conditions. Organisations such as EURODIS and Orphanet are already working towards this aim, by building an online database for rare diseases.[59]

Finally, as more clinical trials on RPEDs allow patients access to highly experimental interventions, it is important to discuss and define realistic expectations. Adequate information and advice should be provided about involvement in trials, as well as the personal use of nonregulated, experimental therapies. Paediatric patients are a special demographic who do not yet possess full personal autonomy due to their young age, relying instead on their parents to make medical decisions on their behalf in their best interests.[60] Nevertheless, the wishes, values and priorities of paediatric patients should still be considered when making decisions relating to their health and well-being. This can be facilitated through open dialogue and active discussion involving healthcare providers, patients and their families.[61] In the event where efficacy of treatment has yet to be proven or evidence is lacking for novel, experimental treatment options, a careful risk-to-benefit analysis should be undertaken with patients and their families.

Improved education and training, cross-sector collaboration

All healthcare professionals involved in the care of paediatric patients should be educated on RPEDs. Medical education can endeavour to spur the interests of young doctors and scientists in RPEDs, encouraging them to contribute further to the field. To this end, undergraduate, postgraduate and continuing educational curricula can include a segment covering the basics of RPEDs. Of note, general practitioners, who are usually the first point of contact for patients in the community, should be trained to pick up anomalies on routine eye examination suggesting a more severe disease, and be informed of the workflow of subsequent referrals.

Furthermore, cross-sector collaboration is required between healthcare professionals and industry researchers. More physicians should be involved in the design and administration of clinical trials for RPEDs, lending their clinical experience and expertise to the development of therapeutic options. Physicians serve as advocates for their patients when interacting with drug developers and regulatory bodies, ensuring research targets fulfil patients' needs and are aligned with patients' best interests. More emphasis can also be placed on providing better care for patients using a multidisciplinary approach, involving paediatricians, ophthalmologists, and other allied healthcare workers such as psychologists and medical social workers.

More can also be done to facilitate open and free access to information between institutions and across borders for learning and development. Experts in the field of RPEDs can collaborate on projects and coordinate research efforts, promoting

scientific exchange and sharing of discoveries, outcomes and best practices. This can be facilitated by conferences and symposiums on RPEDs where physicians convene to learn from each other. Potential areas of interest in RPEDs include gene therapeutics, intrauterine screening, and early postnatal diagnosis of these diseases.

CONCLUSION

The future for RPEDs is promising. Although RPEDs remain an underserved need and a substantial burden to public health, it is receiving more attention from governments and public healthcare institutions. Rapid advancements in the discovery and application of novel technologies and therapeutics for these diseases have also been encouraging, providing patients with more treatment possibilities. Nevertheless, efforts towards better understanding of RPEDs, and to increase awareness among the public, general and family practitioners, and general and subspecialty ophthalmologists must continue to help patients preserve their vision and lead active, fulfilled lives.

Disclosure

The authors declare no conflicts of interest with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

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Ann Acad Med Singap 2023;52:635-8
https://doi.org/10.47102/annals-acadmedsg.2023188

COMMENTARY

Value the patient as a person: Answering the call for a person-centred model of care

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There has been a change in patients' attitudes towards healthcare professionals in recent decades, coupled with an increasingly evident shift in the care paradigm. In 2015, the World Health Organization released a framework of care that recommends healthcare professionals consciously consider the perspectives of individuals, carers, families and communities. Practitioners and policymakers are graduating from a more prescriptive culture towards a more consultative form of practice known as person-centred care (PCC),[1] where a person—more than a patient—is valued as an active participant in the health service and an expert of their perceptions and experiences.[2] PCC advocates for more equality in the doctor-patient relationship.

The need for a PCC model is clear, not least because of the growing presence of multimorbidity. In a recent systematic review, the global prevalence of multimorbidity among adults is estimated at 37.2%, rising to 51% in those above 60.[3] The consequences of such a landscape can be devastating, with multimorbidity reducing the quality of life, worsening mortality rates, and increasing healthcare utilisation and expenses.[3] While applying conventional disease-centric care models to multimorbidity will likely lead to fragmented care, integrated care models guided by the principles of PCC could streamline care.

The adoption of a PCC approach to care delivery is increasingly gathering interest. In countries like Australia, Sweden and the UK, regulatory bodies and advisory committees have been set up to ensure healthcare transformation aligns with the core values of PCC.[2,4,5] In 2007, the UK implemented personalised care and support planning through the Year of Care Partnerships (YOC).[6] This model enables patients with long-term medical conditions to identify their treatment goals through focused conversations with their physicians. Mirroring the YOC, a team from Singapore comprising endocrinologists and primary care physicians collaborated on the Patient Activation through Community Empowerment/Engagement for Diabetes Management (PACE-D) trial to evaluate the efficacy of personalised care and support planning in optimising glycaemic control.[7]

Patient engagement and activation are at the core of any PCC model. Engaging patients involves strengthening their roles as co-producers of health services and policies, thus enhancing mutual accountability and understanding between patients and healthcare professionals. Activating patients means supporting them to develop confidence and skills to engage in care, mainly focusing on achieving specific improvement goals for diseases.[8] While the vision of PCC may seem intuitive, health services need to be sufficiently organised to support it directly. A fundamental lack of understanding of its principles among patients and healthcare professionals, a paternalistic practice culture, and the absence of a facilitative infrastructure are current barriers to a successful PCC model in Singapore. The Donabedian model of examining health services, which focuses on the domains of structure, process and outcomes, may be adopted as a framework to guide the implementation of PCC (Fig. 1).[9]

A redesign of the healthcare structure is imperative in creating a conducive environment for PCC to flourish. First, infusing a culture of codesign is particularly helpful in better engaging patients. The development and maintenance of systems within our healthcare institutions traditionally involved only administrators and healthcare professionals—ironically, an area that needs more active input from patients who are the end users of our healthcare systems. Patient advisory councils and the involvement of patient advocates in designing care pathways are active ways to engage patients in shaping the care they would like to receive. Patients and healthcare professionals may codesign the development and implementation of programmes to better educate themselves on developing personalised care plans and self-management strategies. Second, a revamp of the healthcare infrastructure is necessary. Hospitals and clinics may be given a more person-centric touch through modifications that

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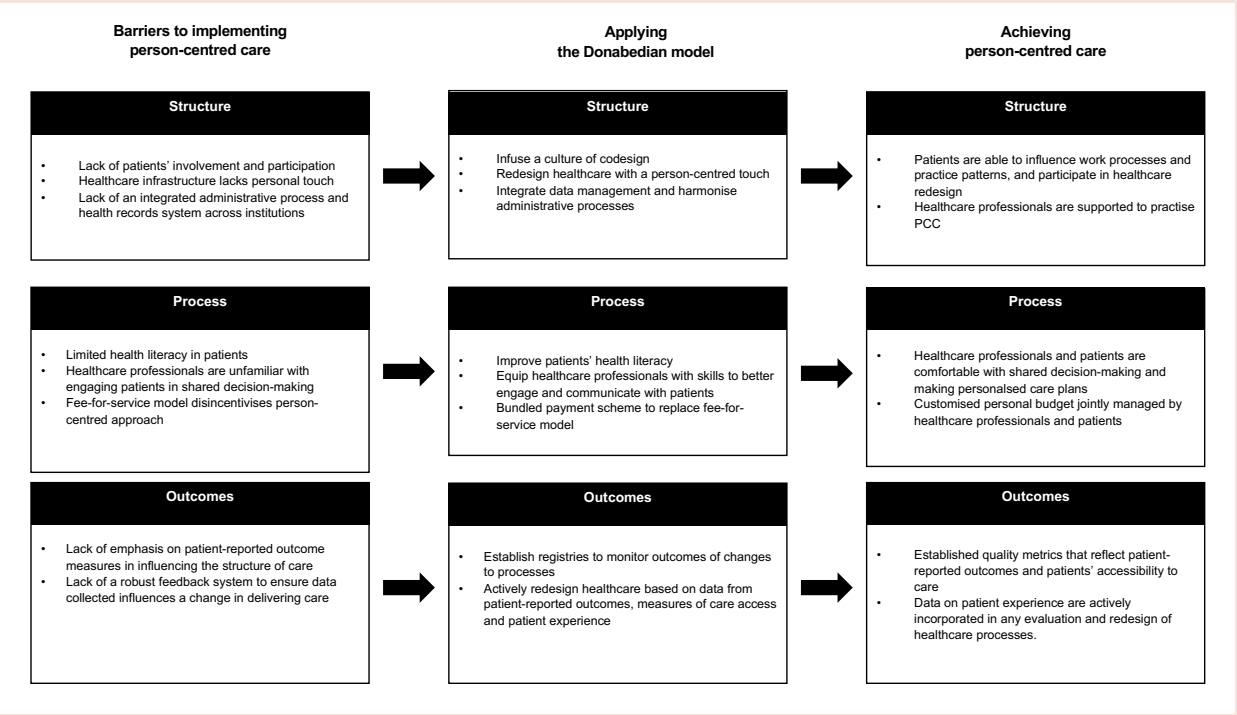
Fig. 1. Applying the Donabedian[9] model of examining health services to the implementation of a person-centred care model.



include allocating private rooms and spaces to facilitate conversations, extending the duration of consultations for sharing ideas between physicians and patients without time pressure, and prompt provision of interpretation and language services.[9] Third, harmonising administrative workflows across institutions and the availability of an integrated electronic platform that enables the seamless sharing of health records and medical information between care providers could improve the efficiency of care delivered to patients.

Evaluating the patient-healthcare-provider interaction is pivotal in effecting a person-centred change in the processes within healthcare. Healthcare providers must change the way that patients are engaged and strive to work towards developing personalised care plans—through shared decision-making, as opposed to being overtly prescriptive in their practice. To this end, healthcare professionals need to be more responsive and sensitive to patients' values and preferences through a deeper understanding of their psychosocial and cultural contexts. There is also an imperative need for healthcare professionals to cultivate communication through actively listening to their patients, including the sharing of medical information with patients. From the patients' point of view, knowing about their health is essential in empowering them with the confidence and desire to have an opinion about their care. However, health literacy often needs to be improved. A recent national survey of older adults found that over two-thirds of adults had difficulties reading, understanding, exchanging and using health information and resources.[10] Programmes to improve people's medical knowledge and understanding of their medical conditions are thus vital.

A restructuring of the healthcare financing framework is necessary to incentivise PCC adoption and an essential step in effecting a person-centred change in the care delivery process. As the principles of PCC mainly drive the adoption of qualitative changes in a health system, financial incentives positively associated with quantitative tasks may be ineffective in nudging an uptake of PCC. Bundled payment schemes, which assign costs based on an overall assessment of a person's utilisation of health services, might be a better alternative in encouraging physicians to adopt principal ownership of persons, compared to the conventional fee-for-service model.[11] In Singapore, patients may claim up to SGD500 to SGD700 yearly for outpatient payment of any chronic disease covered by MediSave, a national medical savings scheme apportions a part of a citizen's income for healthcare needs.[12] Such a payment scheme may be customised to serve as a personal budget jointly managed by patients and their principal physicians, promoting conscious care provision and resource utilisation based on a commonly agreed upon action plan.

In assessing the effectiveness of any new model of care to deliver PCC, the choice of tracked outcomes should be an accurate measure of PCC. We can consider building national quality registries to provide real-time feedback on care processes. In addition to tracking administrative data that reflect access to care (e.g. wait times for referrals to specialists), indicators that reflect patient-reported outcome measures and patient experiences—including the health-related quality of life, patients' psychosocial outcomes and their assessment of care—should also be included[9] because data will help inform the process of refining PCC delivery.

On top of the suggested tangible changes to the healthcare system, the medical fraternity must recognise that a fundamental change in the practice culture is essential, as the move towards PCC challenges the conventional organ-specific, disease-centric and specialty-based approach to medicine. Health systems must adapt to facilitate this change. First, to develop a less fragmented approach to patient management, specialists should adopt a more generalist approach, and generalists need to be supported to practise with a deeper understanding of specialised care.[13] Such a culture has been fostered in Alexandra Hospital in Singapore, which has successfully driven the inaugural implementation of an integrated general hospital model that exemplifies the principles of PCC.[14] Second, health systems should emphasise the holistic concept of a principal physician to reduce the fragmentation of care frequently encountered when patients have multiple concurrent providers. In Alexandra Hospital, from our internal quality data project in 2021, we note that at least 90% of patients had their care by different parties consolidated and thus saw only one physician. Third, our health system should break down silos, enabling collaboration and sharing of information about PCC indicators between healthcare institutions, academic centres, community partners and government.

The Healthier SG campaign, a nationwide initiative the Singapore government launched in July 2023, is an example of us gravitating towards a PCC model. In the spirit of a culture of codesign, the white paper on Healthier SG was shaped by consultations that the government had conducted with over 6000 residents and stakeholders, including primary care and community partners.[15] Singaporeans are encouraged to take ownership of their health, participate actively in preventive health measures like annual screenings, and develop long-lasting and trusting relationships with their family physicians—principal physicians who oversee their health. With the introduction of digital applications like HealthHub and Healthy 365, which are compatible with personal digital assistant devices, Singaporeans have greater and easier access to their medical information and data. Such initiatives that improve the transparency and the availability of medical information can better support patients and healthcare professionals in the shared decision-making process and in the development of personalised care plans.

Much is still needed to realise the dream of delivering PCC in Singapore. The culture of how we design and deliver care needs to change. It will take a strong mandate and commitment from Singapore's healthcare fraternity to carry this through and to make that all-important shift to value our patients more as persons. As Hippocrates prophetically said more than 2500 years ago, "It is more important to know what sort of person has a disease than to know what sort of disease a person has."

Declaration

The authors declare that there are no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed.

Keywords: *family medicine, internal medicine, nephrology, public health, quality of life*

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Ann Acad Med Singap 2023;52:639-42
https://doi.org/10.47102/annals-acadmedsg.2023111

LETTER TO THE EDITOR

The practice patterns and perceptions of surgeons in Singapore regarding breast-conserving surgery

Dear Editor,

Breast-conserving surgery (BCS) is often the preferred treatment in operable breast cancer.[1] While tumour biology and systemic therapy are major determinants of disease control, surgical effectiveness remains a key factor in ipsilateral breast tumour recurrence.[1] As heterogeneity in surgical approach has been observed, we sought to understand Singaporean surgeons' practice patterns and perceptions. Breast surgeons from Singapore's public and private healthcare institutions were invited to participate in a Dillman's Tailored Design Method online-based survey and their responses are summarised in Table 1. We discuss how surgeons' perception may influence overall management.

Breast surgery landscape in Singapore. Breast surgical practice in Singapore is predominantly sub-specialised, with breast cancer managed mostly by breast surgical specialists rather than general surgeons. A large proportion of specialists are fellowship-trained to develop skills that include oncoplastic and minimally invasive breast surgery (Table 1A).

Diagnostics. Core biopsy is usually the first-line action to obtain histological sampling for diagnosis. Reviews from other countries have reported higher rates of routine diagnostic excisional biopsies.[2,3]

Preoperative assessment and indications. BCS is defined as complete breast tumour removal with a concentric margin of surrounding healthy tissue, performed in a cosmetically acceptable manner and usually followed by radiation therapy.[1] Once recommended only for unifocal disease, consensus guidelines now describe the only absolute contraindication to be widespread disease, which cannot be incorporated by local excision of a single region or segment of breast tissue that achieves negative margins with satisfactory cosmetic result.[4] Interestingly, only half of our respondents have adopted this guideline, while 13.6% have conversely begun offering BCS for multicentric disease (Table 1B). The St. Gallen 2017 consensus endorsed technical and cosmetic feasibility of BCS in multiple ipsilateral breast cancer,[5] and practice is beginning to reflect this.

Intraoperative techniques. There was marked variation in intraoperative surgical technique,

Table 1. Singaporean breast surgeons' practice patterns and perceptions.

(A) Respondent characteristics (n=22), no. (%)			
Duration of specialist experience		**Technical expertise**	
0–9 years	13 (59.1)	Level 1 oncoplastic volume displacement techniques	18 (81.8)
10–19 years	7 (31.9)	Level 2 oncoplastic volume displacement techniques	11 (50)
20–29 years	1 (4.5)	Oncoplastic volume replacement surgery	9 (40.9)
Over 30 years	1 (4.5)	Contralateral symmetrisation	5 (22.7)
Fellowship-trained	8 (36.4)	Minimally invasive breast conserving surgery (e.g. endoscopic)	3 (13.6)
(B) Indications for surgery (BCS and axillary surgery) (n=22), no. (%)			
Cancer focality and centricity			
BCS offered for appropriate unifocal lesion			22 (100)
BCS offered for appropriate multifocal lesion			11 (50)
BCS offered for appropriate multicentric lesions			3 (13.6)
Upfront surgery versus neoadjuvant therapy			
BCS is safe post-neoadjuvant systemic therapy			22 (100)
Axillary surgery			
Will omit axillary lymph node dissection in BCS if the ACOSOG Z0011 trial protocol criteria are fulfilled			16 (72.7)
Will omit axillary lymph node dissection for micrometastases			21 (95.5)

Table 1. Singaporean breast surgeons' practice patterns and perceptions. (Cont'd)

(C) Intraoperative technique, no (%)				
Methods of intraoperative margin assessment (n=22)	**Always**	**Frequently**	**Sometimes**	**Never**
Radiological: Ultrasound assessment	9 (40.9)	6 (27.3)	5 (22.7)	2 (9.1)
Radiological: Specimen X-ray	5 (22.7)	3 (13.6)	10 (45.5)	4 (18.2)
Pathological: Frozen section of radial margins	4 (18.2)	2 (9.1)	3 (13.6)	13 (59.1)
Pathological: Frozen section of skin margins	0	3 (13.6)	6 (27.3)	13 (59.1)
Technique for performing pathological assessment of radial margins (n=9)				
Obtaining separate breast tissue samples from the specimen		4 (44.5)		
Obtaining separate breast tissue samples from the cavity		2 (22.2)		
Performing shaved margin sampling		3 (33.3)		
Performing total cavity circumference excision		0		
Have never offered intraoperative conversion to mastectomy based on frozen section results (n=22)				17 (77.3)
(D) Margin status and thresholds in determining the need for reoperation (n=22), no. (%)				
Margin status by type of breast cancer	**Ink on tumour**	**<1 mm**	**<2 mm**	**<5 mm**
Invasive carcinoma	15 (68.2)	4 (18.2)	3 (13.6)	0
Invasive carcinoma with DCIS	8 (36.4)	3 (13.6)	11 (50)	0
Invasive carcinoma with EIC	6 (27.3)	1 (4.5)	13 (59.1)	2 (9.1)
DCIS with microinvasion (≤1 mm)	3 (13.6)	3 (13.6)	16 (72.8)	0
Pure DCIS	1 (4.5)	3 (13.6)	18 (81.8)	0
(E) Patient counselling (n=22), no. (%)				
Communicates that BCT has a higher locoregional recurrence rate but equivalent survival outcomes			4 (18.2)	
Communicates that BCT is oncologically equivalent to mastectomy			16 (72.8)	
Communicates that BCT may be oncologically superior to mastectomy			0	

ACOSOG: American College of Surgeons Oncology Group; BCS: breast-conserving surgery; BCT: breast-conserving therapy; DCIS: ductal carcinoma in situ; EIC: extensive intraductal component

especially concerning margin assessment (Table 1C). The most popular choice is a combination of clinical and radiological methods, and less often histology.[6] Various other techniques have not been universally adopted due to differing availability of resources, time constraints, accuracy and concerns about cost-effectiveness.

There remains different opinions in defining margin involvement and threshold for recommending reoperation (Table 1D), which have been observed internationally and in our Singapore review.[2,3] National Comprehensive Cancer Network Guidelines summarises best practice recommendations with clarity, suggesting "no ink on tumour" for invasive cancer, invasive cancer with DCIS and invasive cancer with EIC; and 2 mm margin for pure DCIS and DCIS with microinvasion.[4] The natural history, treatment and outcomes are largely similar within each of these 2 groups of disease entities.[4]

Beyond general consensus recommendations, granular details of surgical technique are infrequently discussed on wider platforms, making it impossible for consensus on the best technical approach to BCS. Arguably, achieving the international standard of acceptable rates of margin positivity reported to be between 10–20%[7] and good overall survival outcomes would meet the standard of care.

Perception influences patient counselling. Notably, while randomised controlled trials with patients recruited from the 1970s to the 1990s have previously established that BCT has comparable survival outcomes to mastectomy,[8] more recent observational and population-based registry studies have reported improved outcomes in terms of both locoregional recurrence and survival.[9] More study is required to analyse if Singapore surgeons ought to update their counselling practice in tandem with recent evidence (Table 1E).

Surgeons related that patients "sometimes" to "frequently" (77.3%) maintained preconceived notions that mastectomy is "more effective", "more thorough" or "safer", despite having gone through a risk-benefit discussion. There were 63.6% of surgeons who had patients who "sometimes" requested contralateral prophylactic (non-oncological) mastectomy, although only an estimated 18.2% patients eventually received it. Our authors previously determined that the rate of BCS among SingHealth (a group of healthcare institutions in Singapore) female early breast cancer patients was 56%, a proportion that is considered low-normal by Western standards, but higher than previous Singapore studies had suggested.[10] This qualitative data reveals that patients in Singapore hold preconceived notions about the effectiveness of mastectomy that are challenging to influence even after a thorough risk-benefit discussion. Despite this, rates of non-indicated bilateral mastectomy in Singapore remain low compared with those among Western populations.

Breast cancer is a physically and emotionally stressful experience. The myriad of treatment options that a patient can choose from is unique to breast surgery, compared with treatment of other anatomical regions where there is often a more "take-it" or "leave-it" approach. Patient autonomy is important when it comes to treatment decisions and appropriate emphasis is rightfully accorded to the individual's preferences. Many surgeons would have had their patients ask them: "what would you choose?". Our survey found that 50% of surgeons would choose BCT, 27.3% mastectomy and 18.2% did not know or declined to disclose. Among them, 54.5% of respondents were female, 22.7% male and 18.2% preferred not to disclose. When we looked at the opinions of only female surgeons, 50% preferred BCT, 41.6% mastectomy and 8.3% preferred not to disclose. This simple question forces breast specialists, as professionals, to also consider their personal convictions. It appears that even breast surgeons with their specialised knowledge, hold contrasting opinions. It is inevitable that individual beliefs and biases can influence the way professionals counsel their patients. These convictions may evolve over time as personal experiences grow, techniques are refined and new data emerge.

Given that an individual's practice is a cumulation of one's respective training, mentorship, institutional influence and interpretation of best evidence, variations are to be expected. Surgical principles and techniques across centres and surgeons in Singapore still remain reasonably similar. This is likely because the community is small and hospitals are in close geographical proximity, which allow trainees to be exposed to a rapid yet wide dissemination of evidence-based guidelines, multidisciplinary tumour board meetings and strong opinion leaders in the field. Overall results of this survey have been discussed and presented to the participants, in the interest of education and community development.

The breast surgeon's responsibility to provide appropriate surgical options while respecting the patient's wishes remains a cornerstone of breast cancer management. The profession can only do that if we keep abreast of evidence, continually update our skills and participate in ongoing dialogue to offer our patients the best medical practice tailored to their needs.

Acknowledgements

The authors thank all colleagues who participated in this review.

Keywords: *breast cancer, breast conserving surgery, oncoplastic breast conserving surgery, surgery*

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Ann Acad Med Singap 2023;52:643-4
https://doi.org/10.47102/annals-acadmedsg.2023254

LETTER TO THE EDITOR

Outcomes of a targeted congenital cytomegalovirus infection screening approach among infants born ≥35 weeks gestation

Dear Editor,

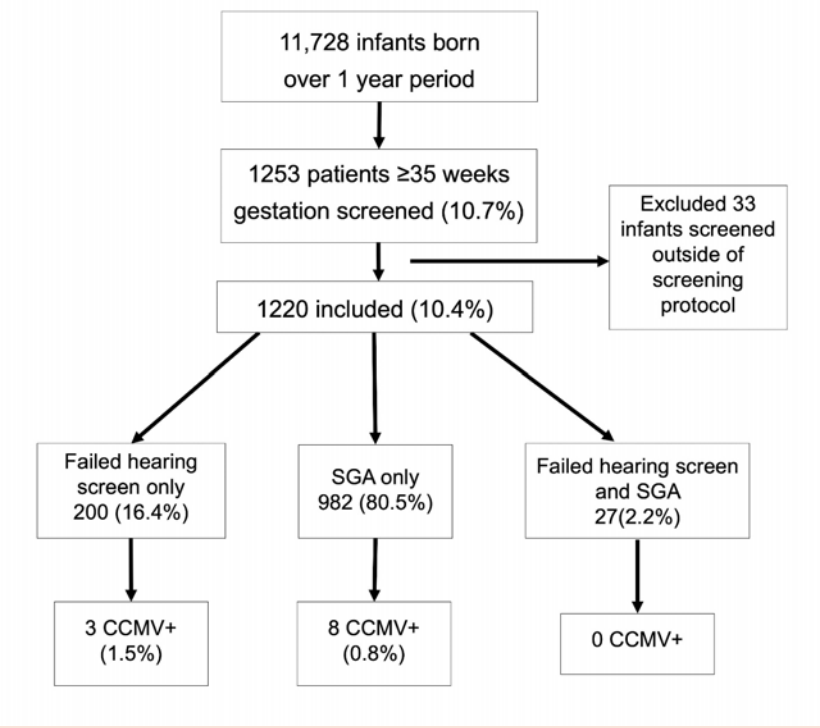
Cytomegalovirus (CMV) is a common cause of congenital viral infection. The estimated incidence of congenital CMV (CCMV) is about 1–6% worldwide, although reliable estimates from Singapore and surrounding countries are unavailable.[1,2] Previous local serologic studies among pregnant women reported high rates of CMV seropositivity (>80%),[3] highlighting the possible high burden of CCMV. With the establishment of oral valganciclovir as an effective treatment for infants with CCMV, prompt diagnosis and treatment of infants with symptomatic disease is important to reduce the risk of moderate to severe sensorineural hearing loss (SNHL) and neurodevelopmental impairment.[4] We report the findings of a targeted CCMV screening approach using failed newborn hearing screen (NHS) or small-for-gestational-age (SGA) status as triggers for screening among infants born ≥35 weeks gestation.

We performed a retrospective evaluation of targeted CCMV screening programme from 1 April 2022 to 31 March 2023 at KK Women's & Children's Hospital, a tertiary-level perinatal centre in Singapore with approximately 12,000 deliveries annually. Our screening strategy recommended CMV screening by urine polymerase chain reaction (PCR) for all infants born ≥35 weeks gestation who failed NHS prior to initial discharge and/or were born SGA (Supplementary Fig. S1). Hearing screen is routinely performed for all newborns using automated auditory brainstem response testing. SGA was defined as birthweight <10th percentile based on local growth charts.[5] Urine sample for CMV was collected <21 days of life.

Descriptive analysis was performed with proportions presented with percentages and median expressed with interquartile ranges (IQRs). Data were analysed using SPSS Statistics v23.0 (IBM Corp, US). This study protocol received an exemption from the SingHealth Centralised Institutional Review Board (Reference No: 2023/2345).

Over the 1-year period of our screening protocol, 1220/11,728 infants (10.4%) were screened (Fig. 1). A total of 200 (16.4%) infants were screened for failing NHS, 982 (80.5%) due to SGA, and 27 (2.2%) had both indications (Fig. 1). Eleven infants (0.9%) were diagnosed with CCMV—3/200 (1.5%) NHS failure and 8/982

Fig. 1. The proportion of infants screened and confirmed with congenital cytomegalovirus infection according to indications of the screening programme.



CCMV: congenital cytomegalovirus; SGA: small for gestational age

(0.8%) SGA. There were 2 additional CCMV cases that were detected outside the screening protocol—1 infant born to a mother with non-primary CMV infection during pregnancy and another was screened after her SGA twin was positive.

The mothers of affected infants had a median age of 30.5 years (IQR 29.5– 31.5), were predominantly multigravida (69.2%) and majority delivered via vaginal route (61.5%). The affected infants were predominantly female (9/13, 69.2%) with a median testing age of 2 days (Supplementary Table S1). Quantitative blood CMV PCR testing was performed on 11 patients—7/11 (63.6%) had detectable CMV copies when tested as part of the initial workup within <3 weeks of life (range from <500 copies/mL to 780,000 copies/mL) (Supplementary Table S2). All patients had normal initial ophthalmologic examination, and 3 had non-specific findings on cranial ultrasound (2 [15.4%] with thalamostriate vasculopathy, 1 [7.7%] with germinal matrix haemorrhage). Two of the 3 infants with initial failed NHS prior to discharge were started on valganciclovir treatment for CCMV at days 24 and 27 of life. They failed subsequent hearing tests at 2–3 months of life.

Based on our targeted screening strategy, we determined the incidence of CCMV among our group of high-risk infants to be 0.9%. This incidence is higher than the reported estimated pooled incidence of 0.67% (95% confidence interval [CI] 0.54–0.83%) from countries with universal screening of newborns.[2] Our rates were also about twice the estimated pooled prevalence of 0.48% (95% CI 0.40–0.59%) from 54 high-income countries.[2] The difference in the rates is very likely due to the targeted approach of our screening programme which sampled a high risk group and constitutes only 10% of the annual birth cohort.

While targeted screening using failed NHS provides a practical approach for the identification of infants with CCMV, this strategy may miss a large group of infected infants without hearing loss after birth. CCMV-associated hearing loss can occur later in childhood—up to 50% of infants with CCMV who passed their NHS can go on to develop SNHL by 3.5 years of age.[6] In a large prospective study involving 99,945 newborns, a hearing screen-based strategy detected 57% of all infants with CCMV-related SNHL but missed 43% of infected infants without hearing loss.[7] In this study, the proportion of CCMV among infants in the well-infant nursery with hearing loss prior to discharge was 2.8%. Screening infants with confirmed permanent neurological hearing loss through subsequent detailed audiological testing has been shown to increase the CMV detection rate—up to 5.9% of the infants tested.[8] However, this strategy leads to inability for timely testing for CCMV (by 21 days, a prerequisite for confirmation of CCMV) and a missed opportunity for treatment and counselling for this congenital infection.

The indication of screening infants who are SGA is based on the established link between intrauterine growth restriction and congenital infections, such as CMV. Older studies have reported significant association between CCMV and SGA status, although subsequent studies have shown conflicting data.[9] SGA status continues to be a trigger for considering CMV screening in our setting and hence, it was adopted as an indication to supplement the NHS in our screening strategy. While none of the SGA infants had evidence of hearing loss after birth, 4/8 had detectable CMV copies in their blood, which may highlight their continued risk for long-term sequelae.[10]

These data are limited by small sample size in a single institution, limited range of clinical indicators included and short follow-up period (1 year). All infants with CCMV are currently being followed-up by a multidisciplinary team to ensure the early detection of any long-term complications, and treatment is commenced in timely manner if it is required. These initial data from this screening programme provides important information on the burden of CCMV and the potential clinical benefit of targeted screening programme in Singapore. This information would also facilitate the assessment of cost-effectiveness of this targeted screening approach when compared to a universal screening strategy in order to provide valuable insights prior to deploying any such approaches.

Ethics approval

This study protocol was reviewed and granted an exemption from full review by the SingHealth Centralised Institutional Review Board (Reference No: 2023/2345).

Conflict of Interest

The authors declare no conflicts of interest.

Funding

This study is part of a CMV research project which received funding from Paediatric Academic Clinical Programme General Fund for CMV Research. The funders had no role in the study design and decision to publish this study.

Data availability statement

Data are available upon reasonable request from the corresponding author.

Keywords: *congenital, cytomegalovirus infection, hearing loss, infant, infectious disease, neonatology, small for gestational age*

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