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Clinical drivers of hospitalisation in patients with mitochondrial diseases

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ABSTRACT

Background Mitochondrial diseases in adults are generally chronic conditions with a wide spectrum of severity contributing to disease burden and healthcare resource utilisation. Data on healthcare resource utilisation in mitochondrial diseases are limited.

Objectives We performed a retrospective longitudinal study to investigate the clinical drivers of hospitalisation in adult patients with mitochondrial diseases to better understand healthcare resource utilisation.

Methods We recruited participants from our specialised Mitochondrial Disease Clinic in Sydney, Australia between September 2018 and December 2021. We performed a retrospective chart review for the period 2013–2022 considering emergency department (ED) and/or hospital admission notes, as well as discharge summaries. We used multiple linear regression models to examine the association between the type of presenting symptom(s) and duration of hospital stay and frequency of admissions, while adjusting for relevant covariates.

Results Of the 99 patients considered, the duration of hospitalisation ranged from 0 to 116 days per participant and the number of admissions ranged from 0 to 21 per participant. Participants with one or more mitochondrial disease-associated admissions constituted 52% of the study cohort. 13% of the participants presented to the ED without requiring an admission and 35% never attended the ED or required a hospital admission during this period. Neurological ($p<0.0001$), gastroenterological ($p=0.01$) and symptoms categorised as 'other' ($p<0.0001$) were the main presentations driving the total number of days admitted to hospital. A statistically significant association was evident for the number of admissions and all types of presenting symptoms ($p<0.0001$).

Conclusion There are variable reasons for hospitalisation in adults with mitochondrial diseases, with neurological and gastroenterological presentations being associated with prolonged and complex hospitalisation. A better understanding of clinical drivers such as these allows for better informed and well-coordinated management aimed at optimising healthcare resource utilisation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mitochondrial diseases are a heterogeneous group of genetic disorders with a broad spectrum of phenotypical presentations and disease severity, and adult patients are generally expected to progress to a chronic multisystem disease pattern, even if patients were oligosymptomatic at the time of diagnosis. Being a chronic condition attributes a considerable disease burden to acute care models within public health systems, as mitochondrial diseases are collectively more prevalent than some other neurogenetic disorders.

WHAT THIS STUDY ADDS

⇒ This study evaluates the clinical drivers of hospitalisation in adult patients with clinically or genetically confirmed mitochondrial diseases, with a focus on duration of hospitalisation and frequency of admissions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a foundation for clinicians and healthcare providers to better understand the clinical drivers of hospitalisation for mitochondrial diseases. It is essential to examine health systems and services as they are rapidly becoming more unsustainable, predominantly due to the increasing burden of protracted and increasingly complex chronic conditions, particularly those associated with multiple comorbidities, such as mitochondrial diseases.

INTRODUCTION

Mitochondrial diseases are a group of multisystemic genetic disorders caused by pathogenic variants in the mitochondrial DNA (mtDNA) or nuclear DNA (nDNA).[1] Clinical heterogeneity is a hallmark of these conditions and severe clinical manifestations may occur in both adult and paediatric populations. Mitochondrial diseases in adults may also be considered chronic conditions (CCs), displaying a wide spectrum of severity. Severe or life-threatening multiorgan involvement has been described in all ages. Even patients with relatively mild forms at diagnosis may progress to severe chronic multisystemic disease during their life span.[2 3]

CCs are long-lasting conditions with duration of 12 months or greater accompanied by persistent effects including functional limitations and need for ongoing medical care.[4] CCs are 'the leading cause of illness,

disability and death in Australia'[5] and are an escalating challenge to population healthcare models worldwide. Due to the persistence of acute care models within public health systems, CCs cause increasing healthcare costs without the desired improvements in population health.[6] According to the Australian Burden of Disease Study 2022, CCs were among the five disease groups that contributed the most disease burden (62%) largely due to the long-term complex care, ongoing need for multiple services and frequent loss of independence.[7] This underscores the importance of studying healthcare resource utilisation in mitochondrial diseases as an example of CCs. Collectively, mitochondrial diseases are not as rare as some other neurogenetic disorders and prevalence of pathogenic mtDNA variants has been reported at 1 in 250 adults.[8]

Comprehensive multidisciplinary inpatient and outpatient care models incorporating medical specialties, allied health and other healthcare services are required to optimise quality of life (QoL) for both patients with CC and their carers, with mitochondrial diseases being no exception. While CCs impact global population health models, disability rates, premature mortality and escalating health costs, they also contribute to rising hospitalisation. Over the last 10 years to 2021–2022, the number of hospital admissions has increased from 9.4 million to 11.6 million in Australia.[9] Of these, 20.1% of people with CCs visit the emergency department (ED) compared with 8.9% of people with no long-term health issues. Consistently, 17.9% of hospital admissions are people with CCs compared with 7.1% without.[10]

Health outcome improvements for CCs, including mitochondrial disorders, and the application of cost-effective approaches are dependent on a better understanding of healthcare resource utilisation and related costs. However, these data are limited for mitochondrial disorders. A 2017 study investigated the impact of hospitalisation for mitochondrial diseases in the USA, focusing on rates of hospitalisation and clinical factors associated with in-hospital mortality.[11] Another population-based cohort study in Ontario, Canada estimated the prevalence of mitochondrial diseases and compared healthcare costs before and after hospitalisation.[12] Both of these studies provided insight into the impact of mitochondrial diseases on the USA and Canadian healthcare systems at an aggregate level, but data on clinical drivers of healthcare resource utilisation in hospitalised patients are lacking.

We have previously investigated the healthcare resource utilisation of patients with clinically or genetically confirmed mitochondrial diseases in the outpatient setting.[13] To gain better insight into how patients with mitochondrial disease use healthcare resources in an inpatient setting, we performed a retrospective longitudinal study focusing on length of stay and frequency of admissions to determine the clinical drivers of hospitalisation. Although prognostically challenging, a better understanding of these clinical drivers will enable well-informed and coordinated management planning for patients with mitochondrial disease in order to minimise metabolic crises, slow progression, improve QoL, reduce the overall burden of disease and minimise health system impact.

METHODS

Data source

Participants were enrolled from the Mitochondrial Disease Clinic at Royal North Shore Hospital (RNSH) in Sydney, Australia in the period September 2018–December 2021. This clinic provides medical care for adult patients with mitochondrial diseases (aged 16 years and above).

Data collection

Consecutive patients aged 16 years and above were offered enrolment in the study if they had a confirmed genetic diagnosis of mitochondrial disease. Patients were still eligible if they did not have a molecular diagnosis but fulfilled the possible, probable or definite (scores: 2–4, 5–7 and 8–12, respectively) Nijmegen clinical diagnostic criteria[14] and had muscle biopsy findings indicative of mitochondrial disease. The Nijmegen clinical criteria were originally developed for children with mitochondrial diseases, but in the absence of alternative validated criteria, a modified version is used for adults to reflect the wider phenotypical variability seen in older patients.[1 3] The muscle biopsy findings considered indicative included ragged red/blue fibres, reduced or negative COX staining in fibres and/or ultrastructural changes on electron microscopy, as determined by the reporting anatomical pathologist.[14 15]

We performed a retrospective chart review of hospital medical records and discharge summaries for ED presentations and hospital admissions for the period 1 January 2013–31 December 2022. The chart review commenced 6 months after the last participant was recruited in December 2021. If the patient had presented to a hospital other than or in addition to RNSH, the patient's signed consent was used as authorisation to access medical records from other hospitals. We collected data on the demographic profile, symptoms at the time of presentation to the ED and/or during hospital admission and final diagnoses as provided on discharge paperwork.

Analyses

We report descriptive statistics, including frequency counts and percentages. Variables considered included age at the time of diagnosis, gender, type of pathogenic variant, number of organs or bodily systems involved and the symptoms/complaints at the time of presentation to the ED and/or during admission to the hospital. We performed univariate and multivariate regression analyses to determine associations between variables, the total number of hospital admissions and total days admitted over the 10-year period (2013–2022) inclusive. We conducted all statistical analyses using R and RStudio (R V.4.2.1).

Table 1 Demographic characteristics of participants (n=99)

Participant characteristics	
Mean age at the time of diagnosis in years	44.7 (SD 15.3)
Gender	n
Male	35
Female	64
Type of pathogenic variant(s)	n
mtDNA SNVs or deletions	52
nDNA variants	18
Nil pathogenic variant identified on WGS (positive clinical diagnostic criteria and muscle biopsy changes)	29
Carer status/support level	n
Have a carer	24
Do not have a carer	75

.mtDNA, mitochondrial DNA; nDNA, nuclear DNA; SNVs, single-nucleotide variants; WGS, whole-genome sequencing.

RESULTS

We engaged 132 consecutive patients for enrolment. 25 patients declined to participate and 6 patients dropped out of the study after completion of the consent process. On further review, two participants were excluded as they did not meet the inclusion criteria. A total of 99 participants were enrolled in this study.

Table 1 displays the demographic characteristics of the participants in our study. The mean age of participants at the time of diagnosis was 44.7 years (SD 15.3). Only four participants in the cohort were diagnosed before 16 years of age. Females represented 64.6% and males constituted 35.4% of this cohort. Of the 99 participants in the study, 24 had a designated carer (relatives on carer pension or paid carers other than relatives).

52 participants had mtDNA single-nucleotide variants (SNVs) or deletions, 18 had nDNA variants and 29 participants did not have a genetic diagnosis on whole-genome sequencing (WGS) but fulfilled the diagnostic clinical criteria[14] with supportive findings on muscle biopsy. Of the pathogenic mtDNA variants, 49 were SNVs and 3 were deletions. Of the 18 patients with nDNA variants, 11 had autosomal dominant (AD) disease and 7 had autosomal recessive (AR) disease. For the AD patients, eight had pathogenic *OPA1* variants and three had *C10orf2* variants. For the AR patients, two had compound heterozygous variants in *YARS2* and five had compound heterozygous variants in *POLG*. The predominant phenotype for participants with nDNA variants was optic atrophy and/or chronic progressive external ophthalmoplegia.

The total number of hospital admission days from 2013 to 2022 per participant in our cohort ranged from 0 to 116 (mean: 10.9; SD: 22.5). The number of admissions per participant over the study period ranged from 0 to 21 (mean: 1.6; SD: 3.2). Figure 1 shows the distribution of the total number of hospital admission days and the total number of admissions over the analysis time frame per participant. With every additional admission, the average expected increase in the hospital bed days was 6.11 (95% CI: 5.19 to 7.04).

Figure 2 shows the distribution of ED presentations and hospital admissions in our cohort. Of the 99 participants, 52% (n=51) were admitted to hospital at least once due

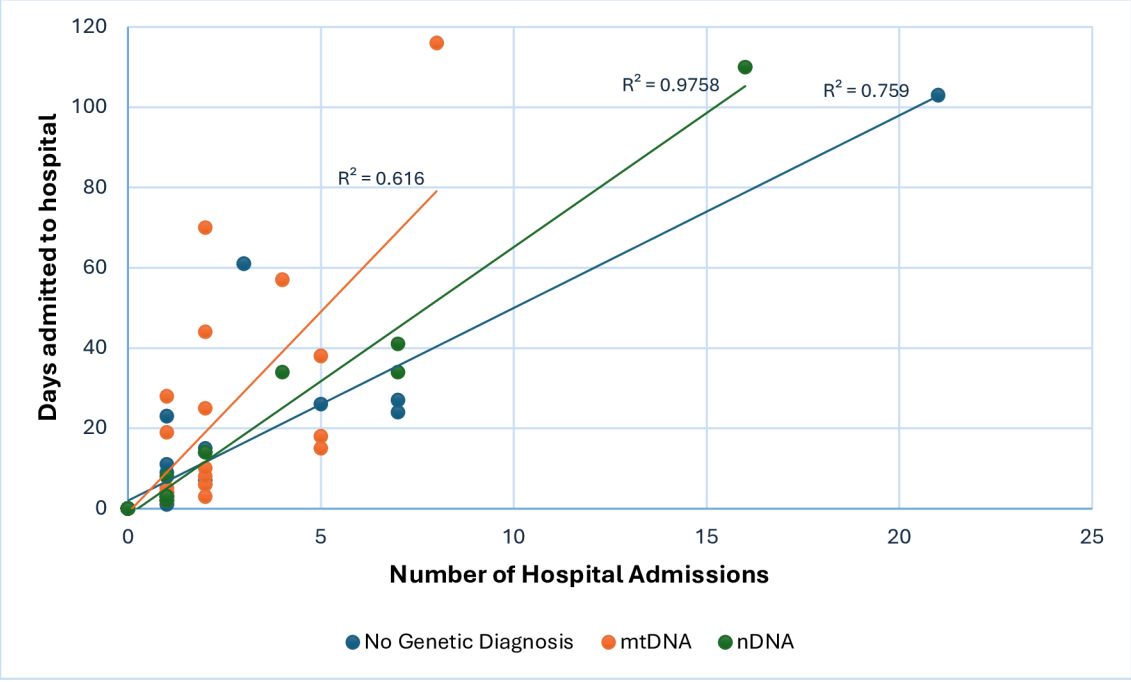

Figure 1 Total number of admissions versus total number of days admitted to hospital per participant (2013–2022). mtDNA, mitochondrial DNA; nDNA, nuclear DNA.

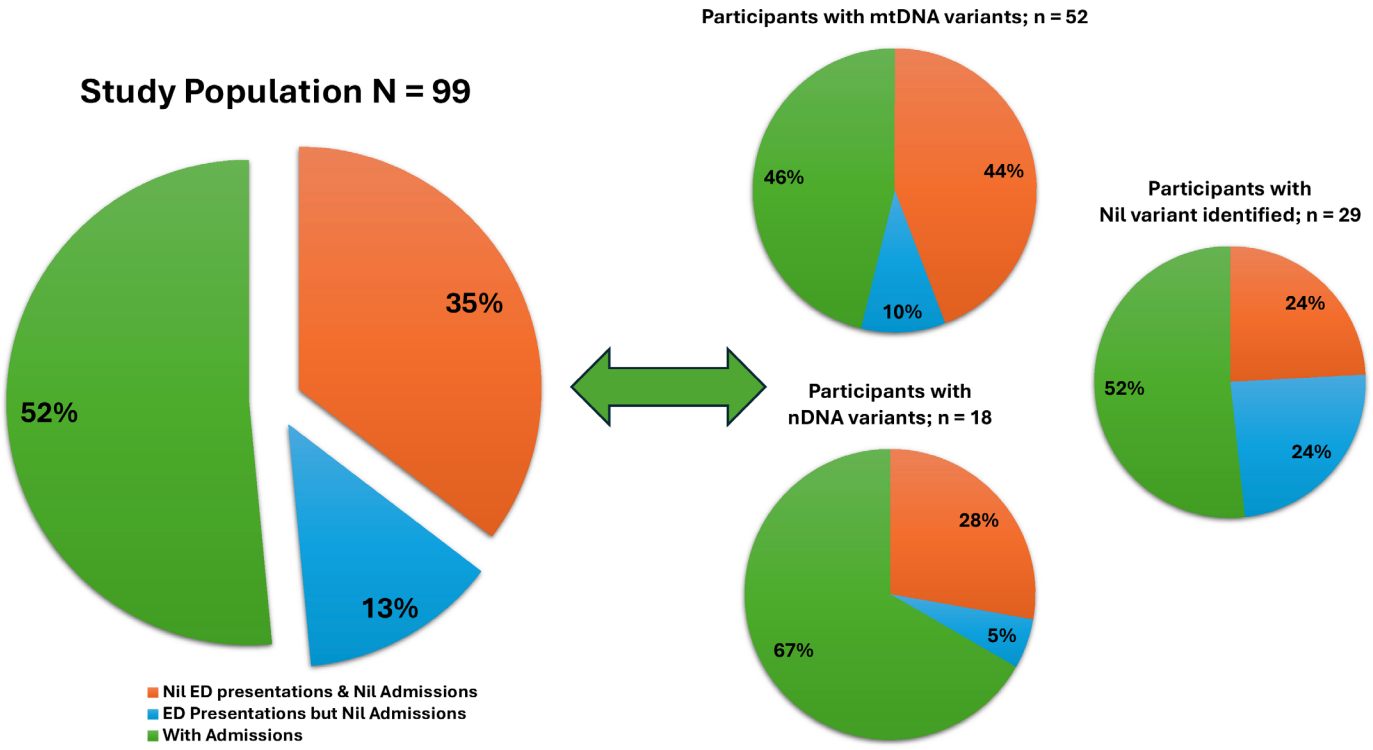

Figure 2 Distribution of emergency department (ED) presentations and hospital admissions. mtDNA, mitochondrial DNA; nDNA, nuclear DNA.

to mitochondrial disease-related issues during the analysis period. 13% (n=13) of participants presented to the ED but did not require a hospital admission, and 35% (n=35) never presented to the ED nor had an admission to hospital.

The percentage distribution of the number of admissions by the type of presenting symptoms is displayed in figure 3. Of the 144 total admissions in our study population, 31% had neurological complaints, 15% were cardiac, 14% were gastroenterological, and 7% were for endocrine

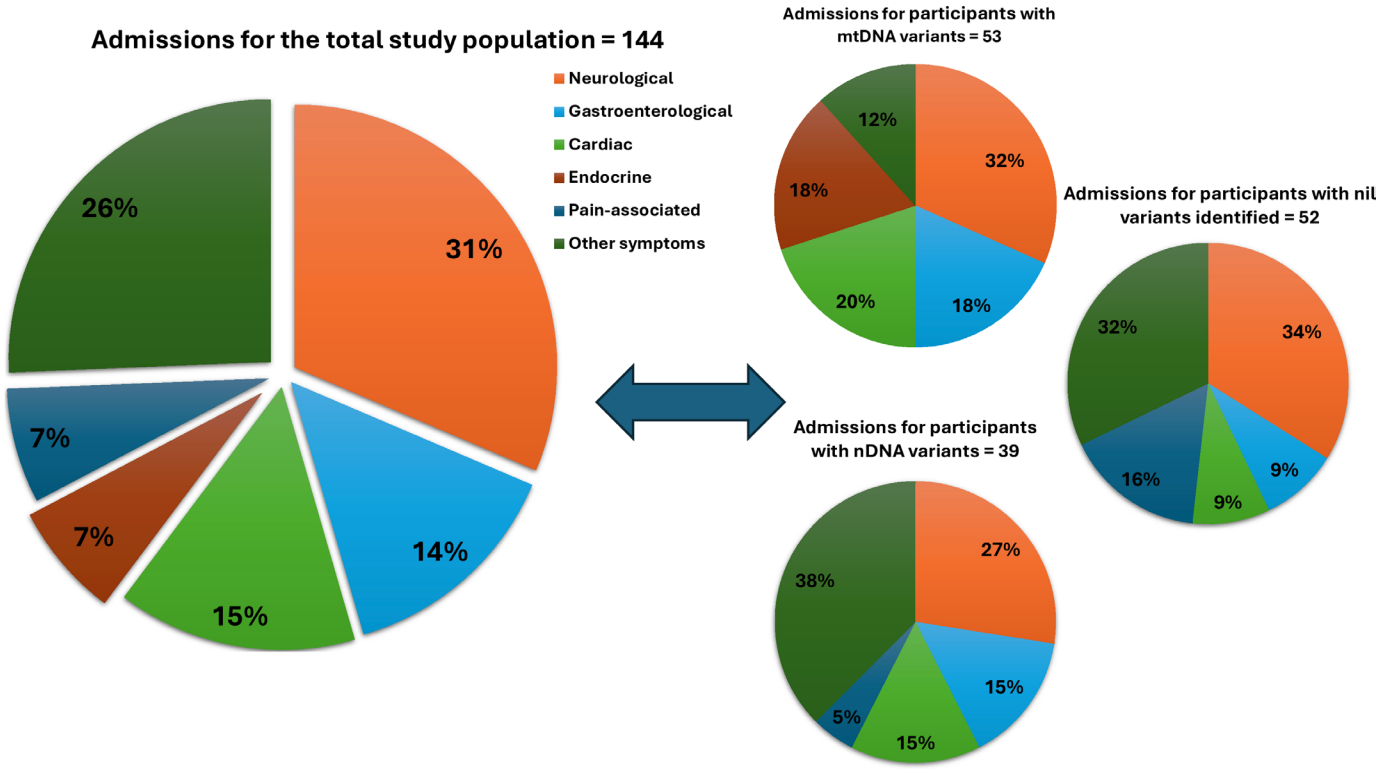

Figure 3 Number of admissions by the type of presenting symptom(s). mtDNA, mitochondrial DNA; nDNA, nuclear DNA.

Table 2 Symptoms/diagnoses during admissions

Category of symptoms/complaints during an admission	Symptoms and/or diagnoses	Number of presentations identified during admissions
Neurological n=50	Progressive and/or exacerbation of muscle weakness	16
	Stroke-like episodes	9
	Headaches/migraines	9
	Seizures	8
	Encephalopathy	5
	Ataxia and/or vertigo	3
Gastroenterological n=23	Pseudo-obstruction of bowel	4
	Constipation	4
	Subacute bowel obstruction	3
	Gastrointestinal dysmotility	3
	Gastroparesis	2
	Stoma-related symptoms and/or complications	1
	Diarrhoea or alternating diarrhoea and constipation	6
Cardiac n=28	Cardiac structural disease/cardiomyopathy/heart failure	10
	Cardiac conduction abnormalities	7
	Syncope	5
	Hypertension (non-essential)	5
	Postural hypotension	1
Endocrinological n=11	Hyperglycaemia	7
	Hypoglycaemia	2
	Diabetic ketoacidosis	2
Pain related n=9	Mitochondrial-related chest pain (non-cardiogenic)	6
	Pain crisis	3
Other n=47	Haematological	13*
	Renal issues	13*
	Fatigue	7
	Falls	6
	Mental health issues and/or psychosis	4
	Aspiration pneumonia	2
	Electrolyte abnormalities±generalised weakness	1
	Complication from recent admission	1

*12 out of 13 admissions for haematological presentations were for a single participant with pathogenic *YARS2* variants and 12 out of 13 admissions for renal presentations were for a single participant with no pathogenic variant identified on whole-genome sequencing.

issues and/or complications. Seven per cent of presentations were related to pain associated with mitochondrial disease and 26% of admissions were due to 'other' causes, including haematological and renal complications, as well as mental health issues and psychosis in the context of mitochondrial disease (table 2). For haematological presentations, 12 out of 13 admissions were recurrent presentations for a single patient. Similarly, 12 out of 13 admissions for renal complaints were recurrent admissions for a different individual. For 12 of the admissions, more than one systemic complaint was identified during initial assessment in the ED.

Symptoms and diagnoses related to mitochondrial diseases, as recorded during the admission of the patient, are summarised in table 2. These include additional symptoms developed over the course of admission after initial ED assessment or diagnoses, confirmed by medical teams (including neurology) once admitted. Neurological symptoms and complications were most reported; for 50 admissions, followed by cardiac and gastroenterological complaints at 28 and 23 admissions, respectively.

Four patients required monitoring in the intensive care unit (ICU) once or more during this time frame. The ICU admissions included (1) recurrent status epilepticus,

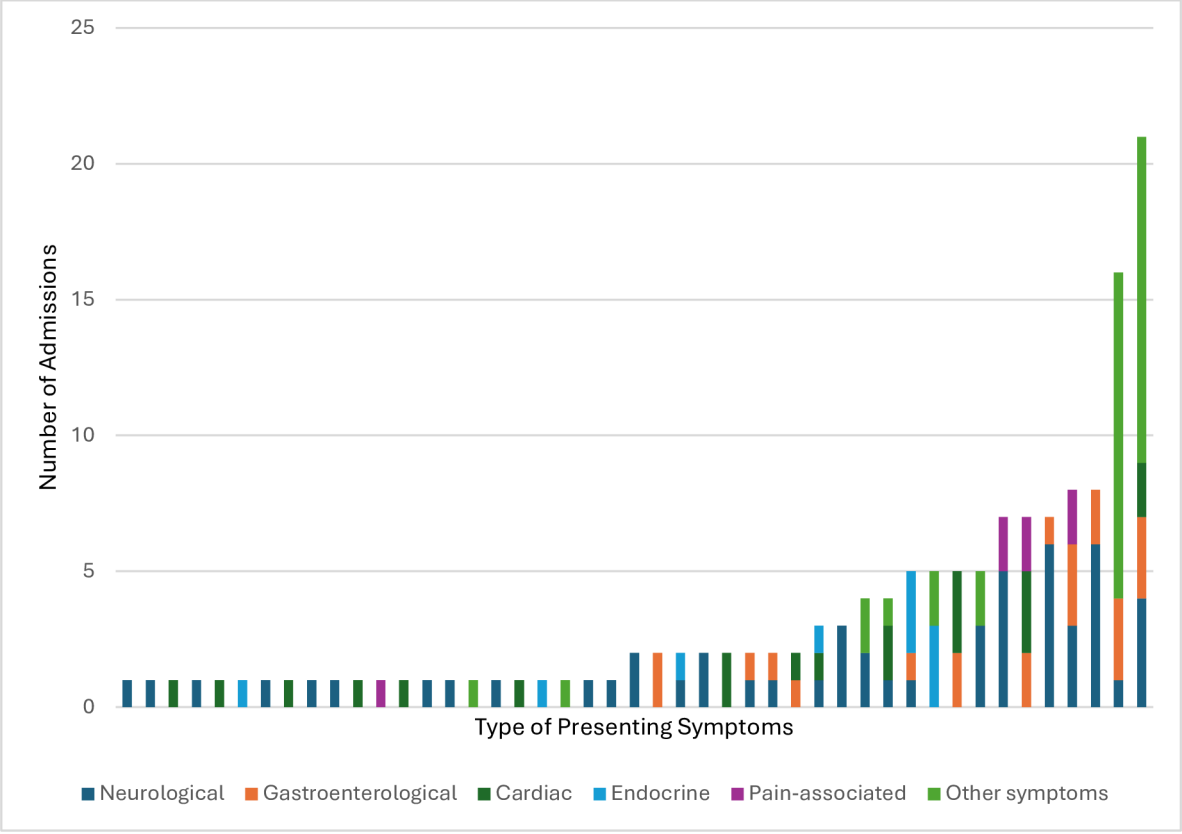

Figure 4 Number of admissions (1– 21) per participant by presenting symptoms.

stroke-like episodes and encephalopathy in two patients (three admissions for one patient; one admission for the other patient); (2) decompensated **m**itochondrial myopathy, **l**actic **a**cidosis and **s**ideroblastic **a**naemia (MLASA), transfusion-refractory anaemia and multiorgan failure in one patient (two admissions); and (3) intestinal pseudo-obstruction in one patient (one admission). Five patients passed away during the study period (following recruitment), including these four ICU patients.

For the participants with a history of hospitalisation due to mitochondrial diseases, the number of admissions by primary systemic complaint at the time of presentation is shown in figure 4. The maximum number of admissions by a participant was 21, who presented with variable symptoms associated with their mitochondrial disease. Consistently, most participants with multiple admissions showed at least some variability in the presenting complaints (figure 4).

At a univariate level, the age at diagnosis, gender, type of pathogenic variants (mtDNA SNVs or deletions vs nDNA variants vs no genetic diagnosis), the number of organs/bodily systems affected in the patient (at the time of first hospital admission) and carer status (ie, having a carer vs no carer) were not associated with the total duration of hospitalisation or the number of admissions.

On multivariate linear regression analysis, we identified that neurological, gastroenterological and symptoms categorised as 'other' were the main clinical presentations driving the total number of days admitted to the hospital. We concluded that there was very strong evidence that neurological presentations ($F_{1,82}$=67.22, p<0.0001) and presenting complaints categorised as 'other' ($F_{1,82}$=34.27, p<0.0001) were associated with the total number of hospital admission days after adjusting for age at the time of diagnosis and gender. There was also strong evidence of association of duration of hospitalisation with gastroenterological ($F_{1,82}$=7.96, p=0.01) presentations. For each additional neurological presentation, the number of admitted days increased on average by 9.61 (95% CI: 7.28 to 11.94). For each additional gastroenterological or 'other' presentation, the number of admitted days increased on average by 8.37 (95% CI: 2.47 to 14.28) and 4.89 (95% CI: 3.23 to 6.55), respectively.

For the number of admissions, a statistically significant association was evident for all types of presenting symptoms in patients with mitochondrial diseases. Our study showed very strong evidence of association of number of admissions with neurological ($F_{1,82}$=362.82, p<0.0001), gastroenterological ($F_{1,82}$=96.54, p<0.0001), cardiac ($F_{1,82}$=118.50, p<0.0001) and endocrinological presentations ($F_{1,82}$=85.85, p<0.0001), pain associated with mitochondrial disease ($F_{1,82}$=226.07, p<0.0001) and complaints categorised as 'other' ($F_{1,82}$=895.43, p<0.0001) after adjusting for age at the time of diagnosis and gender. On average, for each additional presenting symptom, the increase in number of admissions was 0.87 for neurological (95% CI: 0.78 to 0.96), 1.14 for gastroenterological (95% CI: 0.91 to 1.37), 0.87 for cardiac (95% CI: 0.71 to

1.03), 0.88 for endocrinological (95% CI: 0.69 to 1.07), 1.03 for presentation associated with pain (95% CI: 0.89 to 1.16) and 0.98 for presentation categorised as 'other' (95% CI: 0.91 to 1.04).

DISCUSSION

Our study examined the clinical drivers of hospitalisation in adult patients with mitochondrial diseases in Australia. We investigated the association between the type of presenting symptoms or complications of mitochondrial diseases with rate and length of hospitalisation, which contribute to an understanding of healthcare resource utilisation for mitochondrial diseases in an inpatient setting.

The total number of hospital bed days and the number of admissions per patient with mitochondrial disease between 2013 and 2022 showed a broad range (figure 1). This reflects the clinical heterogeneity and spectrum of disease severity in mitochondrial disorders.[2 3] Our study showed an increase in hospital bed days by an average of 6.11 for every additional admission, consistent with previous findings that people with CCs have a higher rate of admission than those without CCs.[10]

Of the study participants in our cohort, 52% required one or more admissions over the 10 years. As shown in figure 2, the highest proportion of admissions was observed within the group with nDNA variants (mtDNA SNVs=46%; nDNA variants=67%; nil pathogenic variant identified=52%). In our study, the participants with nDNA variants constituted the smallest group but the rate of hospital admissions was comparatively higher. Shepherd *et al* showed in their study that a decrease in ATP synthesis in fibroblasts from patients with nDNA-related mitochondrial disease was more marked than in fibroblasts from patients with mtDNA-related mitochondrial disease.[16] This underlies the notion that nDNA disorders can cause a more severe biochemical defect and may explain why patients within this subgroup of mitochondrial diseases typically present earlier and/or have a more rapid and severe disease course.

Neurological symptoms were the most common presenting feature in the 144 admissions recorded over the 10-year analysis period. The neurological presentations in our study population included exacerbation or progression of myopathy, stroke-like episodes, intractable migraines, seizures and encephalopathy (table 2). Consistently, in a study by Grier *et al*, the most frequent patient-reported symptoms were neurological, including weakness, fatigue, walking difficulty, ptosis and incoordination.[17] They also reported that in 55% of cases, a diagnosis of mitochondrial disease was made by neurologists. Our results, consistent with prior research, underscore the prominent role of neurological manifestations in the clinical profile of patients with mitochondrial diseases, including those undergoing hospital admission.

Here, the length of hospitalisation was strongly associated with neurological and gastroenterological presentations and symptoms categorised as 'other'. Using multivariate linear regression modelling, the highest average increase in the number of hospital bed days was demonstrated by neurological presentations, followed by gastroenterological and 'other' presentations (9.90, 7.94 and 5.11 days, respectively). Patients with certain neurological presentations, such as stroke-like episodes and status epilepticus, and gastroenterological presentations, like intestinal pseudo-obstruction (table 2), can be quite unwell with greater risk of acute deterioration leading to longer and more complex hospitalisation.

Stroke-like episodes are most commonly reported in association with the m.3243A>G variant, followed by recessive *POLG* variants.[18] Recovery from stroke-like episodes in **m**itochondrial **e**ncephalomyopathy, **l**actic **a**cidosis and **s**troke-like episodes (MELAS) is typically complete early in the disease course, but following the first episode, the neurological status continues to deteriorate, resulting in disability and premature death.[19] L-arginine infusion, along with aggressive seizure management and treatment of concomitant complications, is recommended, often requiring close monitoring in the ICU.[20] However, the semiology of epileptic seizures in mitochondrial diseases is variable, with drug-resistant epilepsy and a higher occurrence of status epilepticus apparent in MELAS.[21 22] In our cohort, two patients with the pathogenic m.3243A>G variant presented with recurrent seizures and status epilepticus requiring repeated ICU-based care.

Comparatively, cardiac and gastroenterological complaints led to approximately similar numbers of admissions, as shown in figure 3. 28 (15%) admissions were due to cardiac presentations, including 10 for cardiomyopathy and 7 for conduction abnormalities. Wahbi *et al* reported major adverse cardiac events in 10% of their study cohort with both mtDNA and nDNA variants.[23] These included sudden death, heart failure, third-degree atrioventricular block and sinus node dysfunction. The main cardiac complications reported in adult patients with mitochondrial diseases are hypertrophic cardiomyopathy complicated by congestive cardiac failure and cardiac conduction abnormalities, with the highest prevalence described in patients with m.3243A>G variants and large-scale mtDNA deletions, respectively.[23–25] Our study findings are consistent with the literature, with cardiac presentations contributing to hospitalisation being most frequent in patients with mtDNA SNVs and deletions (20%), compared with the other two groups (nDNA variants=15%, nil pathogenic variant identified=9%).

Refractory constipation and intestinal pseudo-obstruction were the most frequent gastroenterological causes for hospitalisation in our study population. Gastrointestinal dysmotility in mitochondrial diseases leads to symptoms such as abdominal pain and distension, dysphagia, constipation and intestinal pseudo-obstruction.[26 27] Ng *et al* demonstrated that stroke-like episodes, cardiomyopathy, low body mass index or high mtDNA heteroplasmy in patients with the m.3243A>G

variant are strong predictors for the development of severe intestinal pseudo-obstruction.[28]

Of the participants in this study with mtDNA variants, 18% had endocrinological presentations related to management or complications of mitochondrial diabetes. Mitochondrial diabetes is most commonly observed in patients with pathogenic m.3243A>G variants. The onset of diabetes in mitochondrial disease can be insidious and is usually diagnosed by the late 30s or early 40s.[29 30] Up to 8% of mitochondrial diabetes may present acutely with diabetic ketoacidosis, but the majority of patients do not require insulin at onset.[31 32] In our cohort, 2 of the 11 endocrinological presentations were due to diabetic ketoacidosis. Mitochondrial diabetes has been reported in patients with mtDNA deletions and pathogenic nDNA variants in genes such as *POLG*.[29 33] In our study population, two participants with nDNA variants and seven participants with no identified pathogenic variant on WGS had diabetes, but none of these participants were hospitalised with primary endocrinological presentations over the 10-year period, as shown in figure 3.

Symptoms categorised as 'other' led to 38% and 32% of admissions, respectively, in participants with nDNA variants and those with no genetic diagnosis. Among the participants with nDNA variants, one patient with *YARS2* variants had a total of 16 admissions, 12 of which were due to haematological issues, explaining the higher admission frequency attributed to 'other' symptoms in this group. Pathological *YARS2* variants are associated with the MLASA syndrome. Patients develop early transfusion dependency, with progressive shortening of intervals between transfusions. Multisystem involvement is common and death in the adult cohort has been reported in late teens and 20s.[34 35] Our patient died during the study period at the age of 37 years.

In the 'other' category of symptoms, 13 hospital admissions were also due to renal presentations. 12 of these admissions were in a single participant with no pathogenic variant identified on WGS. As per the medical records, other non-mitochondrial causes of kidney dysfunction had been excluded in this patient. Nephropathies associated with mitochondrial diseases reported in the literature include tubulointerstitial nephropathies and glomerular diseases with focal segmental glomerulosclerosis.[36 37]

Of note, six presentations in the 'other' symptoms were due to recurrent falls. Skeletal myopathy, exercise intolerance, generalised polyneuropathy, cerebellar dysfunction, vestibulopathy and visual impairment, alone or in combination, can contribute to falls in adults with mitochondrial diseases.[38–40] The participants who presented with falls in our cohort were 70 years or older at the time of recruitment. The falls were attributed to progressively worsening mitochondrial disease in the medical records. However, age-related decline in mobility and function due to sarcopenia and other geriatric comorbidities may have contributed, even if not explicitly mentioned in the medical records. Nevertheless, falls risk is potentially greater in patients with mitochondrial disease, with associated risk of hospitalisation, reduced mobility, decline in QoL and increased need for carer support.

Our study shows that all types of presenting complaints were associated with an increase in the number of admissions on presentation to ED, irrespective of the age at diagnosis or gender. For participants with more than one admission, the reasons for hospitalisation were variable, as shown in figure 4, consistent with protean clinical manifestations and wide variation in disease spectrum.

LIMITATIONS

We recognise that evaluation of heteroplasmy levels and use of severity scales like the Newcastle Mitochondrial Disease Adult Scale (NMDAS)[41] could provide more objective information to determine association with disease severity. However, NMDAS or comparable severity scores were not uniformly documented for our study participants in the medical records and so were unable to be considered. Additionally, diagnostic genetic results for mtDNA variants were not always coupled with heteroplasmy levels, which differ with tissue tested. Hence, this information could not be included in the analyses for the purpose of this study.

The informed consent model used here prioritised ethical standards and privacy but does preclude data from patients unable to attend outpatient clinics for regular review or who had died prior to recruitment. Nevertheless, our study focused on clinical drivers of hospitalisation in patients presenting to clinic and able to consent, yielding valuable insights. Future research employing alternative study designs may better define factors contributing to mortality in hospitalised patients with mitochondrial disease.

CONCLUSION

Mitochondrial diseases in adults present with heterogeneous clinical manifestations and reasons for hospitalisation are variable. While the hospital journey ranged from short-stay to longer complex admissions, consistent patterns were evident among the presenting symptoms and disease courses of our cohort. Patients with mitochondrial disease with neurological or gastroenterological presentations ended up having prolonged hospital stays.

A higher number of admissions were attributed to neurological complaints, which demonstrates the vital role neurologists play in the hospital care of patients with mitochondrial diseases and heightens their importance in chronic care plans to pre-empt deterioration. Similarly, the non-neurological presentations of certain phenotypes in patients with nDNA variants allow for early recognition and opportunities to address and minimise these presentations in a timely fashion.

Contributors SH—major role in the acquisition of data; study concept and design; analysis and interpretation of data; drafting of the manuscript for content,

including medical writing for content. KC—major role in the acquisition of data; drafting of the manuscript for content, including medical writing for content. RD—interpretation of data; drafting of the manuscript for content, including medical writing for content. DS—study concept and design; analysis and interpretation of data. RS—study concept and design; analysis and interpretation of data. CMS—study concept and design; interpretation of data; drafting of the manuscript for content, including medical writing for content. SH as guarantor accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Northern Sydney Local Health District Human Research Ethics Committee (NSLHD-HREC reference number: LNR/17/HAWKE/268) in accordance with the National Health and Medical Research Council National Statement and NSW Health Policy Directive. Written informed consent was obtained from all participants or their guardians.

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