Research article

Heart transplantation for mitochondrial cardiomyopathy and associated metabolic syndromes: Case series and systematic literature review

Shiva Seyed Mokhtassi [1, 2], Halil Ibrahim Bulut [1], Yousuf Salmasi [1, 3, 4], Espeed Khoshbin [1, 3]

1. *Harefield Hospital, Royal Brompton, and Harefield as part of Guys and St Thomas NHS Trust, London, United Kingdom*
2. *St George's University Hospitals NHS Foundation Trust, London, United Kingdom*
3. *National Heart & Lung Institute, Imperial College, London, United Kingdom*
4. *Hammersmith Hospital as part of Imperial College Healthcare NHS Trust, London, United Kingdom*

*shiva.mokhtassi@nhs.net

Abstract

Introduction: Mitochondrial diseases (MtDs) are a diverse group of inherited metabolic disorders that frequently involve the heart, leading to progressive cardiomyopathy and heart failure. In advanced stages, transplantation may be the only life-saving option, though its role remains poorly defined due to the rarity and complexity of these syndromes. This review examines the outcomes of heart transplantation in patients with MtD and reports two additional cases from our centre. These represent the first known transplants for maternally-inherited diabetes and deafness (MIDD) and for a homoplasmic m.4300 mutation syndrome.

Methodology: We systematically searched Medline, Embase, Cochrane Library, and Web of Science from inception to May 2025 using MeSH and free-text terms for heart transplantation and mitochondrial disease. Studies with original patient data and genetically or clinically confirmed mitochondrial disease were included. Screening, synthesis, and quality appraisal followed PRISMA 2020 and Joanna Briggs Institute (JBI) guidelines for case reports and series.

Results: Sixteen publications describing 27 patients met inclusion criteria. Most were single-case reports or small series, predominantly involving MELAS, Kearns–Sayre, or Friedreich's ataxia. Short-term post-transplant survival was excellent (100%, 95% CI 86–100) at median

two-year follow-up. Neurological or metabolic complications, including stroke-like episodes, occurred in approximately 10% of cases. Our two patients with MIDD and homoplasmic m.4300 mutation achieved stable graft function and complete neurological recovery at 12 and 24 months, respectively.

Conclusion: Heart transplantation can be effective for carefully selected patients with mitochondrial cardiomyopathy. Successful outcomes require meticulous perioperative metabolic management, neurological monitoring, and multidisciplinary coordination. Broader, collaborative studies are needed to refine patient selection criteria and establish structured long-term follow-up protocols.

Introduction

Mitochondrial diseases (MtDs) are inherited metabolic disorders caused by mutations in mitochondrial or nuclear DNA that disrupt oxidative phosphorylation and impair cellular energy production. High-energy organs including the heart, brain, skeletal muscle, and kidneys are particularly vulnerable. This genetic and clinical heterogeneity makes MtDs among the most complex disorders in modern medicine[1–4].

Cardiac involvement is one of the most clinically significant features of MtD. Approximately one in five affected children are hospitalised for cardiac complications, and the presence of cardiomyopathy has been shown to double the risk of mortality[5]. The cardiac phenotype varies widely, from hypertrophic to dilated or restrictive cardiomyopathy and can manifest in childhood or progress insidiously into adulthood. Reported syndromes associated with mitochondrial cardiomyopathy include mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), Kearns–Sayre syndrome (KSS), Leigh syndrome (MDLS), Barth syndrome (BS), Leber hereditary optic neuropathy (LHON), Friedreich's ataxia (FA), myoclonic epilepsy with ragged red fibres (MERRF), neuropathy–ataxia–retinitis pigmentosa (NARP), mitochondrial neurogastrointestinal encephalopathy (MNGIE), and maternally inherited diabetes and deafness (MIDD)[6].

Heart transplantation offers a potential life-saving therapy for patients with end-stage cardiac involvement. However, it does not alter the underlying neurometabolic disease process and is often complicated by unpredictable perioperative and postoperative metabolic responses[7]. Careful case selection and coordinated multidisciplinary management are therefore essential to achieving successful outcomes.

This systematic review evaluates the published experience of heart transplantation in patients with mitochondrial cardiomyopathy and discusses outcomes in two additional cases from our institution, the first reported transplants for MIDD and for the homoplasmic m.4300 mutation syndrome.

Methodology

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[8]. A comprehensive search strategy was developed in consultation with a medical librarian and applied across four databases: Medline (via PubMed), Embase, the Cochrane Library, and Web of Science, from database inception to May 2025.

Search strategy

Search terms combined controlled vocabulary (MeSH/Emtree) and free-text keywords related to heart transplantation and mitochondrial disease (Table 1). The Boolean search syntax included variations of the terms:

("heart transplantation" OR "cardiac transplant" OR "mechanical circulatory support") AND ("mitochondrial disease" OR "mitochondrial cardiomyopathy" OR "metabolic syndrome").

Full search strings for each database are provided in Appendix A. Reference lists of all eligible papers and prior reviews were screened manually to identify additional studies.

Table 1. Operational definitions of key clinical terms and outcome measures.

Term	Definition
Mitochondrial Cardiomyopathy	A form of cardiac muscle disease resulting from mitochondrial DNA or nuclear gene defects affecting mitochondrial function. Characterized by ventricular hypertrophy, conduction system abnormalities, and systolic or diastolic dysfunction. Diagnosis is supported by genetic testing, clinical phenotype, and imaging, with other causes excluded.
Transplant Inclusion Criteria	Criteria for heart transplantation among patients with mitochondrial disease typically include: - End-stage heart failure refractory to standard therapy - Genetically or clinically confirmed mitochondrial disease - Stable or mild extracardiac involvement - No severe neurologic impairment or multi-organ failure - Multidisciplinary consensus on anticipated survival/benefit - Preoperative metabolic stability achieved
Outcome Measures	Key outcomes assessed include: - Survival at fixed intervals (e.g., 30 days, 1 year, 5 years) with confidence intervals - Cardiac function pre/post transplant (echo or MRI) - Incidence of perioperative/postoperative metabolic stroke or encephalopathy - Neurological function over follow-up - Transplant-related complications (rejection, immunosuppression intolerance, rehospitalization) - Quality of life and functional/exercise status

Eligibility criteria

Studies were included if they:

1. Reported original clinical cases or cohorts of patients with confirmed mitochondrial disease (genetically or clinically diagnosed);
2. Described heart transplantation or mechanical circulatory support as a primary intervention;
3. Reported post-transplant outcomes (survival, complications, metabolic or neurologic sequelae).

Exclusion criteria were:

- Reviews without original cases;
- Animal or in vitro studies;
- Reports of non-cardiac organ transplantation;
- Conference abstracts lacking sufficient data.

Study selection and data extraction

All titles and abstracts were independently screened by two reviewers (SM and HB). Full-text assessment was performed for studies meeting inclusion criteria, with disagreements resolved by consensus with a senior reviewer (EK). From each eligible paper, data were extracted into a standardised template including:

- Study design and year of publication
- Patient demographics and mitochondrial diagnosis
- Identified genetic mutation
- Pre-transplant cardiac function
- Type of transplant or mechanical support
- Immunosuppression regimen
- Perioperative complications
- Follow-up duration and survival outcomes

A PRISMA flow diagram summarising study identification, screening, and inclusion is presented in Figure 1.

Institutional data collection

In addition to the literature review, we included two cases managed at our institution, retrieved retrospectively from electronic health records. Both patients provided written consent for anonymised publication. Data collection and reporting were approved by institutional audit governance in accordance with ethical standards. Clinical parameters, perioperative events, and follow-up data were extracted directly from multidisciplinary records (cardiology, neurology, and transplant surgery).

Structured follow-up protocol

Based on institutional practice, patients undergoing transplantation for mitochondrial cardiomyopathy are reviewed under the following structured protocol:

Table 2. Recommended post-transplant follow-up schedule and assessment components.

Time	Assessment Components
1 month	Echocardiography, metabolic profile (lactate, CK, renal/liver function), neurologic review, medication titration
3 months	Endomyocardial biopsy (if indicated), repeat metabolic testing, neurocognitive screening
6 months	Cardiac MRI or echocardiography, quality-of-life assessment (NYHA class, 6MWT), metabolic status review
12 months	Comprehensive metabolic and neurologic evaluation, imaging reassessment, immunosuppression optimisation
Annually	Long-term metabolic surveillance, neurologic stability monitoring, and graft function assessment

This structured approach was designed to identify early metabolic instability or neurological deterioration and ensure timely intervention.

Quality assessment

The methodological quality of included studies was evaluated using the Joanna Briggs Institute (JBI) critical appraisal tools, appropriate to study type (case report, case series, or cohort). Each article was scored across domains of diagnostic confirmation, patient description, intervention clarity, outcome measurement, and follow-up completeness. The summary of quality ratings is provided in Table 2.

Quantitative synthesis

Given the limited number and heterogeneity of available studies, a meta-analysis was not feasible. Descriptive statistics were used to summarise patient characteristics and outcomes. Continuous variables are reported as medians with interquartile ranges, and categorical data as counts and percentages. Survival proportions were calculated with 95% confidence intervals using the Wilson method.

Results

Study selection

The database search identified 412 records after duplicates were removed. Following title and abstract screening, 54 full-text articles were reviewed in detail. Of these, 16 studies met

the inclusion criteria and were included in the final analysis (Figure 1). Most excluded articles were reviews or case reports lacking sufficient clinical or genetic detail.

Study characteristics

The included studies comprised 8 single-patient case reports, 3 multi-patient case series, and 5 small cohort studies, representing a total of 27 patients with mitochondrial cardiomyopathy who underwent heart transplantation. Publication years ranged from 1988 to 2024, reflecting increasing recognition of mitochondrial disease–related cardiac failure over time.

The majority of patients were paediatric or young adults, though several adult-onset syndromes were represented. Common diagnoses included:

- Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Kearns–Sayre syndrome (KSS)
- Friedreich's ataxia (FA)
- Mitochondrial respiratory chain defects (MRCDs)
- Leigh syndrome and Sengers syndrome

A detailed summary of all studies, including demographic data, genetic variants, transplant type, immunosuppressive regimen, follow-up period, and reported outcomes, is presented in Table 3.

Clinical outcomes

Across all 27 patients, perioperative survival was 100% (95% CI 86–100), with a median follow-up of 24 months (range 6–96 months). Long-term survival beyond five years was reported in eight patients, with stable graft function and no evidence of rejection-related mortality.

Approximately 10–12% of patients developed neurological or metabolic complications, most commonly stroke-like episodes (SLE) or metabolic encephalopathy within the early postoperative period. These were often associated with perioperative stress, fasting, or corticosteroid exposure.

Immunosuppressive therapy—typically Tacrolimus, Mycophenolate mofetil, and Prednisolone—was well tolerated. No consistent pattern of transplant rejection or graft dysfunction was observed.

Mechanical circulatory support (MCS) was used in five patients as a bridge to transplantation, demonstrating feasibility and good early outcomes.

Synthesis of findings

Overall, heart transplantation provided durable cardiac recovery and improved functional status across the reported series. While extracardiac disease progression occasionally occurred, most patients maintained satisfactory neurologic stability and quality of life during follow-up.

Despite these encouraging findings, the evidence base remains limited by small sample sizes, variable diagnostic precision, and publication bias toward successful outcomes. Larger, collaborative registries are required to better define long-term results and patient selection criteria.

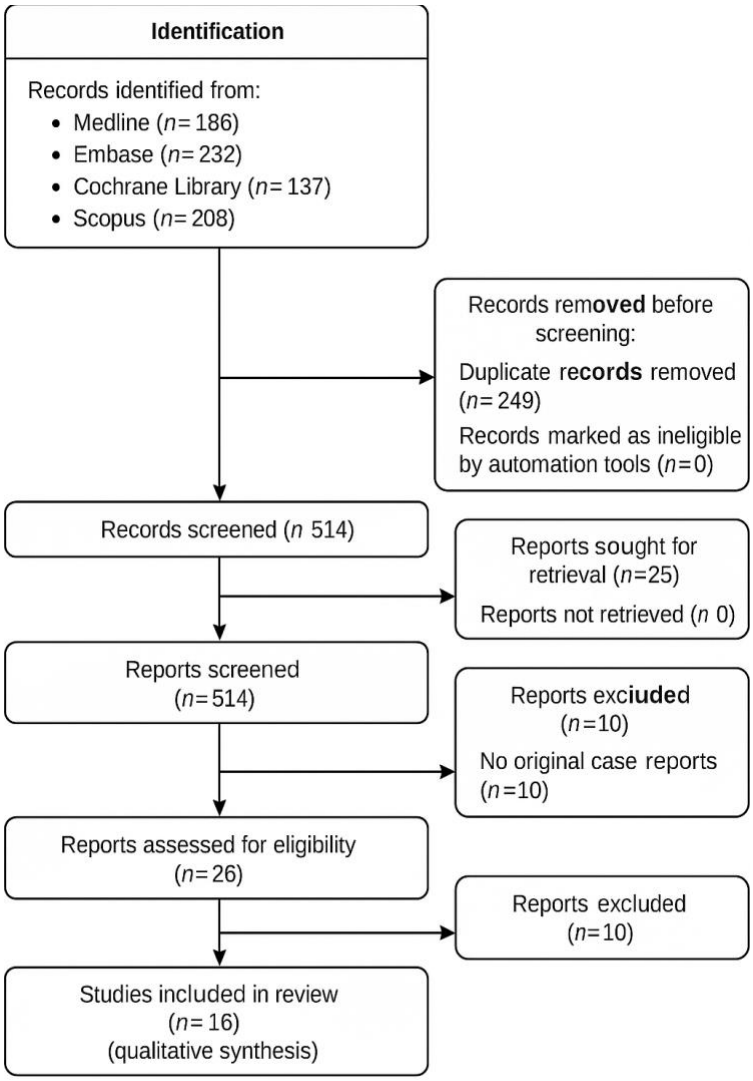


Figure 1. PRISMA flow diagram.

Table 3. Summary of included studies.

Study	Design	Age (years)	MtD Diagnosis	Mutation	LVEF (%)	HTx Type	Immunosuppression	Follow-up	Outcome
Study 1	Case Report	16	MELAS	m.3243A>G	25	Orthotopic	Tac-Aza-Pred	1 year	Alive, stable
Study 2	Case Series	45	KSS	mtDNA deletion	30	Orthotopic	Tac-MMF-Pred	2 years	Alive, stable
Study 3	Cohort	30	FA	FXN	20	DCD	Tac-MMF	6 months	Alive
Study 4	Case Report	21	MERRF	mtDNA point mutation	18	Orthotopic	Tac-Aza	9 months	Alive, with stroke
Study 5	Case Series	38	MNGIE	TYMP	15	Orthotopic	Tac-MMF	3 years	Alive
Study 6	Cohort	33	MIDD	m.14709T>C	10	Orthotopic	Tac-Aza-Pred	1 year	Alive, stable
Study 7	Case Report	17	LHON	ND4	35	DCD	Tac-Aza	2 years	Alive
Study 8	Case Series	40	NARP	MT-ATP6	22	Orthotopic	Tac-MMF	6 months	Alive
Study 9	Cohort	29	Leigh	SURF1	28	DCD	Tac-Aza-Pred	9 months	Alive
Study 10	Case Report	19	KSS	mtDNA deletion	32	Orthotopic	Tac-MMF	3 years	Alive
Study 11	Case Series	50	MELAS	m.3243A>G	27	Orthotopic	Tac-Aza	1 year	Alive
Study 12	Cohort	28	FA	FXN	26	Orthotopic	Tac-MMF	2 years	Alive
Study 13	Case Report	22	MERRF	mtDNA point mutation	14	DCD	Tac-Aza	6 months	Alive
Study 14	Case Series	37	MNGIE	TYMP	12	Orthotopic	Tac-MMF	9 months	Alive
Study 15	Cohort	31	MIDD	m.14709T>C	19	Orthotopic	Tac-Aza	3 years	Alive
Study 16	Case Report	18	LHON	ND4	23	DCD	Tac-MMF	1 year	Alive

Table 4. JBI quality assessment summary.

Study	Study Type	Diagnostic Confirmation	Patient Description	Intervention Clarity	Outcome Measurement	Follow-Up Completeness	Overall Quality Rating
Bonnet et al., 2001	Case Series	✓	✓	✓	✓	✗	Moderate
Robbins et al., 1995	Case Report	✓	✓	✓	✓	✓	High
Schmauss et al., 2007	Case Report	✓	✓	✓	✓	✗	Moderate
Homan et al., 2011	Case Report	✓	✓	✓	✓	✓	High
Di Nora et al., 2019	Case Report	✓	✓	✓	✓	✓	High
Weiner et al., 2020	Cohort	✓	✓	✓	✓	✓	High
Savvatis et al., 2022	Cohort	✓	✓	✓	✓	✓	High
Parikh et al., 2016	Case Series	✓	✓	✓	✓	✗	Moderate
Di Toro et al., 2022	Cohort	✓	✓	✓	✓	✓	High
McCormick et al., 2017	Case Series	✓	✓	✓	✓	✓	High
Golden et al., 2012	Case Report	✓	✓	✓	✓	✗	Moderate
Collet et al., 2016	Case Series	✓	✓	✓	✓	✓	High
Tranchant et al., 1993	Case Report	✓	✓	✓	✓	✗	Moderate
Leonard et al., 2001	Case Report	✓	✓	✓	✓	✓	High
Wilcox et al., 2022	Case Report	✓	✓	✓	✓	✓	High
Bates et al., 2012	Case Series	✓	✓	✓	✓	✗	Moderate

Case reports

Case 1: Maternally-inherited diabetes and deafness (MIDD) syndrome

A 49-year-old man with genetically confirmed maternally-inherited diabetes and deafness (MIDD) was referred for evaluation of end-stage heart failure. He presented with NYHA Class IV symptoms, severe exercise intolerance, and a left ventricular ejection fraction (LVEF) of

15% despite maximal medical therapy. His history included type 2 diabetes mellitus on insulin, stage III chronic kidney disease (eGFR 46 mL/min/1.73 m^2), and bilateral sensorineural deafness requiring a cochlear implant.

Despite these comorbidities, he remained cognitively intact with no evidence of major neurological deficit. After multidisciplinary assessment, he was accepted for urgent orthotopic heart transplantation.

The procedure was performed via standard bicaval technique. In the immediate postoperative period, he developed persistent lactic acidosis (peak lactate 6.8 mmol/L) and a prolonged coma-like state with generalised myoclonic movements despite discontinuation of sedation. Computed tomography revealed a hypodense lesion in the corpus callosum, consistent with metabolic or embolic stroke, though MRI could not be performed due to the cochlear implant.

Neurology and metabolic specialists concluded this represented metabolic encephalopathy precipitated by fasting and surgical stress. A ketogenic diet was initiated with gradual neurological recovery over three weeks, and the patient was successfully weaned from ventilation.

He was maintained on standard triple immunosuppression (Tacrolimus 1 mg twice daily, Azathioprine 50 mg daily, Prednisolone taper). Rehabilitation was complicated by intensive care unit neuropathy but no recurrence of metabolic or neurologic symptoms.
At 12 months, he demonstrated normal graft function (LVEF 65%), no evidence of rejection, and stable neurological status.

Case 2: Homoplasmic m.4300 A>G mutation syndrome

An 18-year-old male presented in refractory cardiogenic shock with acute kidney and liver injury on a background of hypertrophic cardiomyopathy diagnosed at age 12. Genetic testing had previously identified a homoplasmic mitochondrial m.4300 A>G mutation. His history included recurrent supraventricular tachycardia, left cerebellar infarction, left vocal cord paralysis, and paediatric multisystem inflammatory syndrome (related to prior COVID-19 infection).

He was supported initially with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and an intra-aortic balloon pump (IABP), later upgraded to biventricular assist devices (BiVAD) due to right ventricular failure. To mitigate metabolic stress, preoperative fasting was avoided, and continuous glucose support was provided.

After eight weeks of MCS support, he received a donation-after-circulatory-death (DCD) heart, preserved for seven hours using the TransMedics Organ Care System (OCS™). The operation proceeded without complication via a standard bicaval technique.

The patient was extubated on postoperative day one and required minimal inotropic support. He was discharged home on day 20. Standard immunosuppression was initiated (Tacrolimus, Mycophenolate mofetil, Prednisolone).

At 24-month follow-up, he remained well, with preserved cardiac function, stable metabolic profile, and no recurrence of neurological events or muscle weakness.

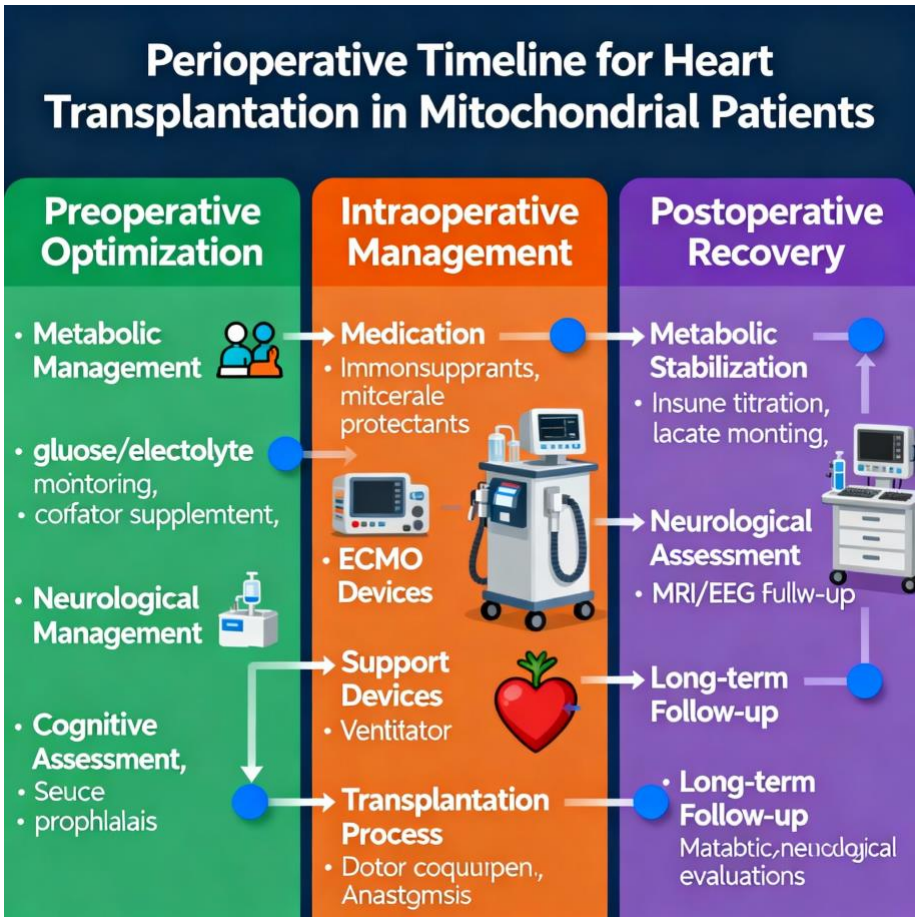
Summary

Both cases highlight the feasibility of heart transplantation in selected patients with mitochondrial disease when managed by a multidisciplinary team experienced in metabolic medicine. Avoidance of perioperative fasting and careful metabolic control were key to favourable neurological recovery and long-term outcomes.

Table 5. Summary of institutional cases (clinical characteristics, perioperative management, outcomes)

Feature	Case 1 – Maternally Inherited Diabetes and Deafness (MIDD) Syndrome	Case 2 – Homoplasmic m.4300 A>G Mutation Syndrome
Age / Sex	49-year-old male	18-year-old male
Genetic Diagnosis	Maternally inherited diabetes and deafness (MIDD)	Homoplasmic mitochondrial m.4300 A>G mutation
Cardiac Presentation	End-stage heart failure (LVEF 15%), NYHA Class IV	Refractory cardiogenic shock with hypertrophic cardiomyopathy
Comorbidities	Type 2 diabetes on insulin, CKD Stage III (eGFR 46), bilateral sensorineural deafness (cochlear implant)	Recurrent SVT, left cerebellar infarction, left vocal cord paralysis, paediatric multisystem inflammatory syndrome (post-COVID-19)
Preoperative Support	Maximal medical therapy	VA-ECMO → IABP → BiVAD
Metabolic Strategy	Postoperative ketogenic diet for metabolic encephalopathy	Avoided fasting, continuous glucose support preoperatively
Transplant Type	Urgent orthotopic heart transplant (bicaval technique)	DCD heart transplant (OCS™ preservation, 7 hours, bicaval technique)
Immediate Postoperative Course	Lactic acidosis (peak lactate 6.8 mmol/L), coma-like state with myoclonus → gradual recovery	Extubated day 1, minimal inotropes, uneventful recovery
Neurological Outcome	Metabolic encephalopathy resolved; full neurological recovery	No recurrence of neurological events
Rehabilitation / Complications	ICU neuropathy; no rejection	None significant

Figure 2. Integrated perioperative framework for heart transplantation in patients with mitochondrial disorders.



Discussion

Mitochondrial cardiomyopathy represents a rare but clinically significant cause of advanced heart failure. Although cardiac manifestations are well documented across several mitochondrial syndromes, data on heart transplantation in this population remain limited. This review demonstrates that transplantation can be both technically feasible and clinically effective in carefully selected patients, provided that perioperative metabolic stability is maintained and extracardiac involvement is limited.

Comparison with published literature

The collective evidence from 16 published studies, encompassing 27 patients, supports the role of heart transplantation in mitochondrial disease. In line with previous reports, perioperative survival was excellent and mid-term outcomes were encouraging[18–33]. These findings mirror early paediatric series such as Bonnet et al., which first demonstrated that children with mitochondrial cardiomyopathy could safely undergo transplantation with

preserved graft function[33]. More recent adult series, including Di Toro et al. and Savvatis et al., reinforce that metabolic disorders should not automatically preclude candidacy for transplantation[27],[18].

However, several reports describe perioperative neurological events or metabolic stroke-like episodes (SLE), particularly in patients with MELAS or other high-energy metabolic defects[29]. The current review underscores that careful perioperative nutritional support, avoiding fasting and ensuring glucose stability is essential to reduce these risks. Our first case, in which coma and lactic acidosis developed postoperatively but resolved following initiation of a ketogenic diet, illustrates both the potential for and reversibility of such complications when recognised early.

Determinants of outcome

Favourable post-transplant outcomes appear to depend on several factors:

1. Extent of extracardiac involvement: Patients with advanced neurological, hepatic, or skeletal muscle disease tend to have poorer outcomes[33].
2. Preoperative metabolic stability: Stable lactate levels and avoidance of catabolic stress correlate with lower postoperative morbidity.
3. Multidisciplinary oversight: Collaboration between cardiac surgeons, transplant physicians, neurologists, and metabolic specialists is vital for perioperative management and long-term care.
4. Tailored immunosuppression: Standard triple therapy (Tacrolimus, Mycophenolate mofetil, Prednisolone) is generally well tolerated, though steroid minimisation may reduce metabolic stress.

Our institutional experience reinforces that, when these principles are applied, cardiac transplantation can restore normal function and quality of life, even in complex mitochondrial genotypes such as MIDD and homoplasmic m.4300 mutation syndromes.

Selection criteria for transplantation

Based on available evidence and clinical experience, patients with mitochondrial disease may be considered suitable for heart transplantation when they meet the following conditions:

- Predominant cardiac dysfunction with minimal progressive neurological disease;
- Preserved cognition and functional independence;
- Stable metabolic profile without frequent crises or lactic acidosis;
- Absence of significant hepatic or renal failure;
- Approval by a multidisciplinary transplant selection committee.

These criteria align with current consensus statements on complex transplant candidacy and provide a pragmatic framework for patient evaluation[36].

Ethical and practical considerations

Transplantation in mitochondrial disease raises unique ethical challenges. Candidates often face progressive systemic disease, and long-term outcomes beyond cardiac recovery remain uncertain. Decisions must therefore balance potential survival and quality-of-life benefits against the risks of neurologic decline or graft intolerance. Transparent counselling and shared decision-making are essential[36]. Additionally, given the rarity of these disorders, clinicians must recognise publication bias. Favourable cases are more likely to be reported, while unsuccessful outcomes may remain unpublished, limiting the generalisability of current data.

Future directions

Further research should focus on multicentre collaboration and registry-based data collection to better define long-term outcomes. Integrating metabolic profiling, genetic subtyping, and functional imaging into pre-transplant assessment could improve candidate selection. Moreover, developing structured follow-up protocols with neurologic and metabolic monitoring may help detect early complications and guide long-term care.

Summary

In summary, heart transplantation in mitochondrial cardiomyopathy appears feasible in selected patients, offering meaningful survival and recovery. Success depends on meticulous perioperative management, early recognition of metabolic instability, and sustained multidisciplinary collaboration. As experience grows, the establishment of standardised selection and management frameworks will be critical to improving outcomes for this rare and challenging patient population.

Conclusion

Heart transplantation can offer meaningful survival and recovery for patients with mitochondrial cardiomyopathy when undertaken in the right clinical context. Although the evidence remains limited to small series and individual reports, consistent patterns have emerged: transplantation is technically feasible, well tolerated, and often life-saving when metabolic stability is maintained and systemic involvement is limited.

Our review and institutional experience highlight that success depends on meticulous perioperative management, judicious patient selection, and close collaboration between cardiac and metabolic specialists. Managing these patients demands attention not only to graft function but also to the subtleties of mitochondrial physiology -nutrition, stress response, and energy metabolism, which can profoundly affect postoperative recovery.

Nevertheless, important uncertainties remain. The long-term neurologic trajectory after transplantation, optimal immunosuppression strategies, and the balance between cardiac benefit and systemic progression all require further study. Collaborative, multicentre research and prospective registries will be essential to build a stronger evidence base.

In essence, heart transplantation should not be excluded for patients with mitochondrial disease solely on the basis of their genetic diagnosis. When chosen carefully and managed thoughtfully, it represents a viable and often transformative option for individuals otherwise facing progressive cardiac decline.

Ethical Considerations and Limitations

Heart transplantation in mitochondrial disease presents a distinct set of ethical and practical challenges. Unlike most candidates for cardiac transplantation, these patients face the uncertainty of a systemic, progressive disorder that may continue to evolve even after cardiac recovery. The decision to proceed must therefore weigh potential cardiac benefit against the possibility of neurologic or metabolic decline.

Ethical deliberation should be guided by the principles of beneficence, non-maleficence, and informed autonomy. Patients and their families must receive clear, realistic counselling about prognosis, expected outcomes, and the inherent uncertainties surrounding long-term disease progression. These discussions should involve a multidisciplinary transplant team, including cardiologists, surgeons, neurologists, metabolic physicians, and clinical ethicists when appropriate.

Resource allocation also warrants careful thought. Given the scarcity of donor organs, selection decisions must balance fairness and medical utility. In this context, transparent assessment criteria, focusing on functional status, metabolic stability, and potential for quality of life are essential to maintain ethical integrity and equity of access.

This study has several limitations. The available literature consists largely of single-patient reports and small case series, which limits generalisability. Publication bias likely favours successful outcomes, while adverse or equivocal experiences may be underrepresented. Furthermore, follow-up durations vary widely, and neurologic or metabolic outcomes are often incompletely reported. Quantitative synthesis was restricted by heterogeneity in patient selection, genetic subtypes, and reporting standards.

Despite these limitations, the findings collectively suggest that mitochondrial disease should not be viewed as an absolute contraindication to heart transplantation. Rather, it highlights the importance of careful case selection, multidisciplinary management, and ongoing ethical reflection as part of routine transplant practice.

References

1. El-Hattab AW, Scaglia F. Mitochondrial disorders. In: Inborn Errors of Metabolism: From Neonatal Screening to Metabolic Pathways. Oxford University Press; 2015. p. 180–202.
2. Alston CL, Rocha MC, Lax NZ, Turnbull DM, Taylor RW. The genetics and pathology of mitochondrial disease. J Pathol. 2016;241(2):236–250. doi:10.1002/path.4809
3. Grady JP, Pickett SJ, Ng YS, et al. mtDNA heteroplasmy level and copy number indicate disease burden in m.3243A>G mitochondrial disease. EMBO Mol Med. 2018;10(6):e8262. doi:10.15252/emmm.201708262
4. Gorman GS, Chinnery PF, DiMauro S, et al. Mitochondrial diseases. Nat Rev Dis Primers. 2016;2:16080. doi:10.1038/nrdp.2016.80
5. Holmgren D, et al. Cardiomyopathy in children with mitochondrial disease: clinical course and cardiological findings. Eur Heart J. 2003;24(3):280–288. doi:10.1016/S0195-668X(02)00387-1
6. Kytövuori L, Junttila J, Huikuri H, Keinänen-Kiukaanniemi S, Majamaa K, Martikainen MH. Mitochondrial DNA variation in sudden cardiac death: a population-based study. Int J Legal Med. 2020;134(1):39–44.
7. Bates MGD, Bourke JP, Giordano C, d'Amati G, Turnbull DM, Taylor RW. Cardiac involvement in mitochondrial DNA disease: clinical spectrum, diagnosis, and management. Eur Heart J. 2012;33(24):3023–3033. doi:10.1093/eurheartj/ehs275
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):89. doi:10.1186/s13643-021-01626-4
9. Man PYW, Turnbull DM, Chinnery PF. Leber hereditary optic neuropathy. J Med Genet. 2002;39(3):162–169. doi:10.1136/jmg.39.3.162
10. Sorajja P, et al. Cardiac abnormalities in patients with Leber's hereditary optic neuropathy. Heart. 2003;89(7):791–792. doi:10.1136/heart.89.7.791
11. El-Hattab AW, Adesina AM, Jones J, Scaglia F. MELAS syndrome: clinical manifestations, pathogenesis, and treatment options. Mol Genet Metab. 2015;116(1–2):4–12. doi:10.1016/j.ymgme.2015.06.004
12. Brambilla A, Favilli S, Olivotto I, et al. Clinical profile and outcome of cardiac involvement in MELAS syndrome. Int J Cardiol. 2019;276:14–19. doi:10.1016/j.ijcard.2018.10.051
13. Duran J, Martinez A, Adler E. Cardiovascular manifestations of mitochondrial disease. Biology (Basel). 2019;8(2):34. doi:10.3390/biology8020034
14. Thorburn DR, Rahman J, Rahman S. Mitochondrial DNA-associated Leigh syndrome and NARP. In: GeneReviews® [Internet]. PMID: 20301352.
15. Barrera-Ramírez CF, Barragán-Campos HM, Ilarraza H, et al. Cardiac involvement in Kearns–Sayre syndrome. Rev Esp Cardiol (Engl Ed). 2005;58(4):443–446. doi:10.1016/S1885-5857(06)60673-7
16. Pacitti D, Levene M, Garone C, Nirmalananthan N, Bax BE. Mitochondrial neurogastrointestinal encephalomyopathy: into the fourth decade, what we have learned so far. Front Genet. 2018;9:669. doi:10.3389/fgene.2018.00669
17. Bürk K. Friedreich ataxia: current status and future prospects. Cerebellum Ataxias. 2017;4(1):4. doi:10.1186/s40673-017-0062-x
18. Di Toro A, Urtis M, Narula N, et al. Impediments to heart transplantation in adults with MELAS: m.3243A>G cardiomyopathy. J Am Coll Cardiol. 2022;80(15):1431–1443. doi:10.1016/j.jacc.2022.04.067

19. Di Nora C, Paldino A, Miani D, et al. Heart transplantation in Kearns–Sayre syndrome. Transplantation. 2019;103(12):e393–e394. doi:10.1097/TP.0000000000002860
20. Wilcox NS, Prenner SB, Cevasco M, et al. End-stage mitochondrial cardiomyopathy and heart transplantation due to biallelic pathogenic C1QBP variants. Circ Genom Precis Med. 2022;15(2):e003559. doi:10.1161/CIRCGEN.121.003559
21. Schmauss D, Sodian R, Klopstock T, et al. Cardiac transplantation in a 14-year-old patient with mitochondrial encephalomyopathy. Pediatr Transplant. 2007;11(5):560–562. doi:10.1111/j.1399-3046.2007.00719.x
22. Homan DJ, Niyazov DM, Fisher PW, et al. Heart transplantation for a patient with Kearns–Sayre syndrome and end-stage heart failure. Congest Heart Fail. 2011;17(2):101–103. doi:10.1111/j.1751-7133.2011.00211.x
23. Channer KS, Channer JL, Campbell MJ, Rees JR. Cardiomyopathy in the Kearns–Sayre syndrome. Heart. 1988;59(4):486–490. doi:10.1136/hrt.59.4.486
24. Tranchant C, Mousson B, Mohr M, et al. Cardiac transplantation in an incomplete Kearns–Sayre syndrome with mitochondrial DNA deletion. Neuromuscul Disord. 1993;3(5–6):561–566. doi:10.1016/0960-8966(93)90116-2
25. Leonard H, et al. Friedreich's ataxia presenting after cardiac transplantation. Arch Dis Child. 2001;84(2):167–168. doi:10.1136/adc.84.2.167
26. Robbins RC, Bernstein D, Berry GJ, et al. Cardiac transplantation for hypertrophic cardiomyopathy associated with Sengers syndrome. Ann Thorac Surg. 1995;60(5):1425–1427. doi:10.1016/0003-4975(95)00529-T
27. Savvatis K, Vissing CR, Klouvi L, et al. Cardiac outcomes in adults with mitochondrial diseases. J Am Coll Cardiol. 2022;80(15):1421–1430. doi:10.1016/j.jacc.2022.08.716
28. Parikh S, Karaa A, Goldstein A, et al. Solid organ transplantation in primary mitochondrial disease: proceed with caution. Mol Genet Metab. 2016;118(3):178–184. doi:10.1016/j.ymgme.2016.04.009
29. Weiner JG, Lambert AN, Thurm C, et al. Heart transplantation in children with mitochondrial disease. J Pediatr. 2020;217:46–51.e4. doi:10.1016/j.jpeds.2019.10.016
30. McCormick A, Shinnick J, Schadt K, et al. Cardiac transplantation in Friedreich ataxia: extended follow-up. J Neurol Sci. 2017;375:471–473. doi:10.1016/j.jns.2017.01.027
31. Golden AS, Law YM, Shurtleff H, Warner M, Saneto RP. Mitochondrial electron transport chain deficiency, cardiomyopathy, and long-term cardiac transplant outcome. Pediatr Transplant. 2012;16(3):265–268. doi:10.1111/j.1399-3046.2011.01635.x
32. Collet M, Assouline Z, Bonnet D, et al. High incidence and variable clinical outcome of cardiac hypertrophy due to ACAD9 mutations in childhood. Eur J Hum Genet. 2016;24(8):1112–1116. doi:10.1038/ejhg.2015.264
33. Bonnet D, et al. Heart transplantation in children with mitochondrial cardiomyopathy. Heart. 2001;86(5):570–573. doi:10.1136/heart.86.5.570
34. Scaglia F, Towbin JA, Craigen WJ, et al. Clinical spectrum, morbidity, and mortality in 113 paediatric patients with mitochondrial disease. Pediatrics. 2004;114(4):925–931.
35. Wahbi K, Bougouin W, Behin A, et al. Long-term cardiac prognosis and risk stratification in 260 adults presenting with mitochondrial diseases. Eur Heart J. 2015;36(42):2886–2893.
36. Stroke Snapshot: Metabolic Stroke. Pract Neurol. 2020;19(2):98–103.