Cardiovascular Outcomes in Patients With Mitochondrial Disease in the United States: A Propensity Score Analysis

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Mitochondrial disease comprises a wide range of genetic disorders caused by mitochondrial dysfunction. Its rarity, however, has limited the ability to assess its effects on clinical outcomes. To evaluate this relationship, we collected data from the 2016 National Inpatient Sample, which includes data from >7 million hospital stays. We identified 705 patients (mean age, 22 ± 20.7 yr; 54.2% female; 67.4% white) whose records included the ICD-10-CM code E88.4. We also identified a propensity-matched cohort of 705 patients without mitochondrial disease to examine the effect of mitochondrial disease on major adverse cardiovascular events, including all-cause in-hospital death, cardiac arrest, and acute congestive heart failure.

Patients with mitochondrial disease were at significantly greater risk of major adverse cardiovascular events (odds ratio [OR]=2.42; 95% CI, 1.29–4.57; P=0.005), systolic heart failure (OR=2.37; 95% CI, 1.08–5.22; P=0.027), and all-cause in-hospital death (OR=14.22; 95% CI, 1.87–108.45; P<0.001).

These findings suggest that mitochondrial disease significantly increases the risk of inpatient major adverse cardiovascular events. (Tex Heart Inst J 2021;48(3):e207243)
but confirming this in adults with MD has been limited by small sample sizes.\textsuperscript{2,12,13,17-21} To fill this gap, we evaluated the relationship between MD and CV outcomes in a large sample of hospitalized patients in the United States.

**Patients and Methods**

**Study Population**

For this cross-sectional study, we searched the 2016 National Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project, which includes data from >7 million hospital stays.\textsuperscript{22} The NIS is the largest all-payer inpatient care database in the U.S. Patients assigned to code E88.4 (mitochondrial metabolism disorders) in the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) were categorized as having MD (n=705). The remaining patients were categorized as not having MD (n=7132963). Demographics, comorbidities, and risk factors commonly associated with adverse CV outcomes were documented. These included hypertension, hyperlipidemia, obesity, history of stroke or percutaneous coronary intervention (PCI), chronic kidney disease, chronic HF, smoking, alcohol use, drug use, and hospitalization. Supplementary Table I presents the ICD-10-CM codes that we identified for each condition. No institutional review board approval was required for use of the NIS dataset.

**Clinical Outcome Measures**

The primary outcome was major adverse CV events (MACE), a composite endpoint including all-cause inhospital death, cardiac arrest, and acute congestive HF. Other CV outcomes included all HF, acute HF, systolic HF, diastolic HF, cardiomyopathy, cardiac shock, PCI, cardioversion, pacemaker placement, implantable cardioverter-defibrillator treatment, atrial fibrillation/flutter, and supraventricular tachycardia. Secondary outcomes included acute kidney injury (AKI), sepsis, and ventilation.

**Propensity Score Analysis**

Baseline patient characteristics were used to assemble a propensity-matched cohort to examine the effect of MD on the incidence of MACE. This matched cohort (N=1,410) comprised 705 patients with MD and 705 patients without MD. This analysis was designed to balance observed covariates between the 2 groups and mimic the populations used in randomized studies.\textsuperscript{23-25}

**Statistical Analysis**

The baseline demographic and clinical characteristics of patients with and without MD were compared by using \( \chi^2 \) and Student \( t \) tests. The matched cohort was used to estimate the odds ratios (OR) for MACE and other clinical outcomes. The statistical analyses were performed using SAS 9.4 (SAS Institute Inc.). \( P \) values <0.05 were considered statistically significant.

**Results**

**Baseline Characteristics**

In total, 705 patients (0.01%) in the 2016 NIS dataset had a diagnosis of MD (Table I), giving an estimated prevalence of 10 per 100,000 individuals. The mean age of patients with MD was 22.2 ± 20.7 years; the group comprised slightly more women (54%) than men, and was predominantly white (67%). Table I lists the baseline demographic and clinical characteristics of all patients with or without MD (the unmatched cohort), as well as those of the matched cohort. Of note, in the unmatched cohort, patients with MD were generally younger than those without it (22.2 vs. 49.0 yr; \( P <0.001 \)). Not surprisingly, given their older age, a larger proportion of patients without MD in the unmatched cohort had CV comorbidities, including type 2 diabetes, hypertension, hyperlipidemia, obesity, peripheral artery disease, chronic obstructive pulmonary disease, chronic kidney disease, and pulmonary hypertension. They were also less likely to have undergone PCI or coronary artery bypass grafting. Nevertheless, after matching, we found no statistically significant differences in the baseline characteristics between the 2 groups.

**Clinical Outcomes**

In the matched cohort, the risk of MACE was higher in patients with MD (OR=2.42; 95% CI, 1.29–4.57; \( P =0.005 \)), as was the risk of all-cause in-hospital death (OR=14.22; 95% CI, 1.87–108.45; \( P <0.001 \)) (Table II and Fig. 1). Patients with MD were also at greater risk of cardiac arrest or acute congestive HF, although neither increase was statistically significant. Moreover, patients with MD were significantly more likely to have HF (OR=1.75; 95% CI, 1.01–3.03; \( P =0.043 \)), systolic HF (OR=2.37; 95% CI, 1.08–5.22; \( P =0.027 \)), and cardiomyopathy (OR=4.10; 95% CI, 2.10–8.01; \( P <0.001 \)). However, there were no significant differences between groups in the rates of diastolic HF, cardiac shock, PCI, cardioversion, pacemaker placement, implantable cardioverter-defibrillator treatment, atrial fibrillation, atrial flutter, or supraventricular tachycardia.

In the analysis of secondary outcomes, patients with MD were at increased risk of AKI (OR=2.04; 95% CI, 1.27–3.28; \( P =0.003 \)), sepsis (OR=8.33; 95% CI, 2.93–23.69; \( P <0.001 \)), and undergoing mechanical ventilation (OR=6.40; 95% CI, 3.92–10.43; \( P <0.001 \)) (Table II).

**Discussion**

To our knowledge, this is the first study to characterize the impact of MD on CV outcomes in a large sample of
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inpatients. Our propensity analysis revealed a significant 2.4-fold higher risk \( (P=0.005) \) of MACE in patients with MD, suggesting that MD increases the risk of CV disease. Our results also revealed an increase in the risk of cardiac arrest and acute HF in patients with MD, although neither increase was significant. Our findings are consistent with increased in-hospital mortality rates observed by McCormack and colleagues\(^1\) among approximately 2,000 hospitalized adult patients with MD, in a study using 2012 NIS data.

We noted an increased diagnostic prevalence of all HF, systolic HF, and cardiomyopathy among patients with MD when compared with the matched control group, consistent with findings in previous studies with smaller sample sizes.\(^4,17,19,20\) Several molecular mechanisms have been evaluated as potential links between mitochondrial dysfunction and cardiomyopathy. As mentioned earlier, one proposed mechanism is dysregulation in apoptosis and eventual myocyte cell death.\(^10,11\) Manifestations of mitochondrial cardiomyopathy vary

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**TABLE I. Baseline Demographic and Clinical Characteristics of Patients in the Cohorts**

| Characteristic                  | Unmatched \((N=7,133,668)\) | Matched \((N=1,410)\) |
|---------------------------------|-----------------------------|----------------------|
|                                | No MD \( (n=7,132,963) \)   | MD \( (n=705) \)     | P Value | No MD \( (n=705) \) | MD \( (n=705) \) | P Value |
| Age (yr)                        | 49.0 ± 27.4                 | 22.2 ± 20.7          | <0.001  | 22.2 ± 20.6          | 22.2 ± 20.7          | 0.993   |
| Female                          | 4,044,446 (56.7)            | 383 (53.9)           | 0.133   | 383 (54.3)           | 382 (54.2)           | 0.957   |
| Race/ethnicity                  |                             |                      |         |                      |                     |         |
| White                           | 4,425,353 (62.0)            | 479 (67.3)           | 0.004   | 475 (67.4)           | 475 (67.4)           | 0.999   |
| Black                           | 1,029,259 (14.4)            | 48 (6.7)             | <0.001  | 48 (6.8)             | 48 (6.8)             | 0.999   |
| Hispanic                        | 830,116 (11.6)              | 109 (15.3)           | 0.002   | 107 (15.2)           | 107 (15.2)           | 0.999   |
| Other                           | 482,591 (6.8)               | 24 (3.4)             | <0.001  | 24 (3.4)             | 24 (3.4)             | 0.999   |
| Behavioral                      |                             |                      |         |                      |                     |         |
| Smoking                         | 951,694 (13.3)              | 24 (3.4)             | <0.001  | 24 (3.4)             | 24 (3.4)             | 0.999   |
| Alcohol use                     | 363,755 (5.1)               | 3 (0.4)              | <0.001  | 3 (0.4)              | 3 (0.4)              | 0.999   |
| Drug use                        | 399,265 (5.6)               | 24 (3.4)             | 0.01    | 28 (4.0)             | 24 (3.4)             | 0.52    |
| Medical history                 |                             |                      |         |                      |                     |         |
| Type 2 diabetes                 | 1,478,142 (20.7)            | 63 (8.9)             | <0.001  | 62 (8.8)             | 63 (8.9)             | 0.925   |
| Hypertension                    | 2,322,373 (32.6)            | 93 (13.1)            | <0.001  | 93 (13.2)            | 93 (13.2)            | 0.999   |
| Hyperlipidemia                  | 1,873,092 (26.3)            | 63 (8.8)             | <0.001  | 63 (8.9)             | 63 (8.9)             | 0.999   |
| Obesity                         | 897,361 (12.6)              | 54 (7.6)             | <0.001  | 57 (8.1)             | 54 (7.7)             | 0.767   |
| Cerebral infarction             | 127,658 (1.8)               | 10 (1.4)             | 0.439   | 6 (0.9)              | 10 (1.4)             | 0.315   |
| Peripheral artery disease       | 218,694 (3.1)               | 6 (0.8)              | <0.001  | 3 (0.4)              | 6 (0.9)              | 0.316   |
| COPD                            | 920,870 (12.9)              | 22 (3.1)             | <0.001  | 28 (4.0)             | 22 (3.1)             | 0.388   |
| CKD                             | 955,924 (13.4)              | 41 (5.8)             | <0.001  | 28 (4.0)             | 41 (5.8)             | 0.109   |
| PAH                             | 211,686 (3.0)               | 6 (0.8)              | <0.001  | 10 (1.4)             | 6 (0.9)              | 0.315   |
| CABG                            | 275,740 (3.9)               | 5 (0.7)              | <0.001  | 8 (1.1)              | 5 (0.7)              | 0.403   |
| PCI                             | 89,045 (3.9)                | 1 (0.8)              | <0.001  | 8 (1.1)              | 6 (0.9)              | 0.591   |
| Chronic heart failure           | 270,528 (3.8)               | 11 (1.5)             | 0.002   | 6 (0.9)              | 11 (1.6)             | 0.222   |
| Depression                      | 833,170 (11.7)              | 60 (8.4)             | 0.007   | 61 (8.7)             | 60 (8.5)             | 0.924   |
| Anxiety                         | 803,851 (11.3)              | 78 (11.1)            | 0.792   | 60 (8.5)             | 78 (11.1)            | 0.107   |
| Hospital region                 |                             |                      |         |                      |                     |         |
| Northeast                       | 1,319,691 (18.5)            | 180 (25.3)           | <0.001  | 527 (74.8)           | 527 (74.8)           | 0.999   |
| Midwest                         | 1,586,631 (22.2)            | 166 (23.6)           | 0.384   | 169 (24.0)           | 168 (23.8)           | 0.950   |
| South                           | 2,803,599 (39.3)            | 216 (30.3)           | <0.001  | 214 (30.4)           | 214 (30.4)           | 0.999   |
| West                            | 1,424,457 (20.0)            | 148 (20.8)           | 0.584   | 144 (20.4)           | 145 (20.6)           | 0.947   |

CABG = coronary artery bypass grafting; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; MD = mitochondrial disease; PAH = pulmonary artery hypertension; PCI = percutaneous coronary intervention

Data are presented as mean ± SD or as number and percentage. \( P <0.05 \) was considered statistically significant.
widely, from hypertrophic and dilated cardiomyopathy to LV noncompaction.15,27-29 Hypertrophic remodeling is the most prominent pattern of cardiomyopathy in all forms of MD, the effects of which can mimic hypertrophic cardiomyopathy.17,18 Left ventricular noncompaction, also called LV hypertrabeculation, is another recognized cardiac manifestation of MD.30-32

Our study corroborates the established association between MD, HF, and cardiomyopathy. Of note, our data also showed a significantly increased risk of sepsis and the need for mechanical ventilation therapy among patients with MD, which may be related to mitochondrial crisis. Patients with MD are at higher risk of metabolic crisis, which is often precipitated by infection or surgery.

Our study has several strengths. First, its large sample size enabled us to characterize MD, a relatively rare and likely underdiagnosed condition, and to provide a robust prevalence estimate (10 per 100,000 individuals). Our estimate, based on an inpatient database, was higher than previous estimates of 3 to 6.5 per 100,000 individuals from epidemiologic studies.33-35 However, our study did not face certain challenges encountered in epidemiologic studies, such as the expanding number of genotypes and phenotypes and the ethical dilemma of performing invasive diagnostic tests (for example, muscle biopsy) on asymptomatic patients. Second, given that MD diagnosis can be missed, our findings can remind cardiologists about the broad, yet occasionally

TABLE II. Clinical Outcomes in the Matched Cohort Based on the Presence of Mitochondrial Disease

| Variable                          | No MD (n=705) | MD (n=705) | Odds Ratio (95% CI) | P Value |
|-----------------------------------|---------------|------------|---------------------|---------|
| MACE                              | 14 (2.0)      | 33 (4.7)   | 2.42 (1.29–4.57)    | 0.005   |
| All-cause in-hospital death        | 1 (0.1)       | 14 (2.0)   | 14.22 (1.87–108.45) | <0.001  |
| Cardiac arrest                     | 2 (0.3)       | 6 (0.9)    | 3.02 (0.61–15.00)   | 0.156   |
| Acute congestive heart failure     | 9 (1.3)       | 14 (2.0)   | 1.56 (0.67–3.64)    | 0.293   |
| Other cardiovascular outcomes      |               |            |                     |         |
| All heart failure                  | 21 (3.0)      | 36 (5.1)   | 1.75 (1.01–3.03)    | 0.043   |
| Acute heart failure                | 2 (0.3)       | 4 (0.6)    | 2.01 (0.36–10.99)   | 0.413   |
| Systolic heart failure             | 9 (1.3)       | 21 (3.0)   | 2.37 (1.08–5.22)    | 0.027   |
| Diastolic heart failure            | 11 (1.6)      | 10 (1.4)   | 0.90 (0.38–2.15)    | 0.826   |
| Cardiomyopathy                     | 11 (1.6)      | 43 (6.1)   | 4.10 (2.10–8.01)    | <0.001  |
| Cardiac shock                      | 1 (0.1)       | 5 (0.7)    | 5.03 (0.59–43.15)   | 0.102   |
| PCI                               | 1 (0.1)       | 1 (0.1)    | 1.00 (0.06–16.02)   | 0.999   |
| Cardioversion                      | 1 (0.1)       | 2 (0.3)    | 2.00 (0.18–22.14)   | 0.563   |
| Pacemaker placement               | 5 (0.7)       | 11 (1.6)   | 2.22 (0.77–6.42)    | 0.131   |
| ICD placement                     | 2 (0.3)       | 5 (0.7)    | 2.51 (0.49–12.98)   | 0.256   |
| Atrial fibrillation/flutter        | 16 (2.3)      | 18 (2.6)   | 1.13 (0.57–2.23)    | 0.728   |
| SVT                               | 7 (1.0)       | 5 (0.7)    | 0.71 (0.23–2.25)    | 0.562   |
| Secondary outcomes                |               |            |                     |         |
| Acute kidney injury                | 27 (3.8)      | 53 (7.5)   | 2.04 (1.27–3.28)    | 0.003   |
| Sepsis                            | 4 (0.6)       | 32 (4.5)   | 8.33 (2.93–23.69)   | <0.001  |
| Ventilation                       | 20 (2.8)      | 111 (15.7) | 6.4 (3.92–10.43)    | <0.001  |

ICD = implantable cardioverter-defibrillator; MACE = major adverse cardiovascular events; MD = mitochondrial disease; PCI = percutaneous coronary intervention; SVT = supraventricular tachycardia

Data are presented as number and percentage or as odds ratio and 95% CI. P <0.05 was considered statistically significant.

![Forest plot shows the odds ratios for key clinical cardiovascular outcomes in patients with mitochondrial disease. Note especially the increased odds of all-cause in-hospital death and major adverse cardiovascular events (MACE).](image-url)

HF = heart failure
nonspecific, spectrum of CV disease presentations in patients with MD. Third, by using propensity score matching, we were able to adjust for the differences in baseline characteristics, thus limiting the number of possible confounders.

Limitations. Our study also has limitations. First, NIS is an inpatient, administrative database that relies on provider-reported diagnoses and interpretation by the medical reviewers assigning ICD codes to them. Second, NIS cannot be used to investigate long-term health effects in patients with MD, so our analysis may underestimate the true rate of CV complications. Third, because of MD’s broad spectrum, we did not include some medical conditions that may be considered MDs, such as Kearns-Sayre syndrome (ICD-10-CM code H49.81), hereditary optic atrophy (H47.22), Leigh disease (G31.82), and mitochondrial myopathy (G71.3). Instead, to focus on the relationship between MD and MACE, we chose code E88.4 for MD. Fourth, this was a cross-sectional study, and despite the propensity score matching, we were able to adjust for the differences in baseline characteristics, thus limiting the number of possible variables not included in the final logistic regression model.

Conclusion

Our study substantiates the increased risk of CV morbidity and mortality in patients with MD. Further research to study the correlation between subclassifications of MD and MACE and to design more targeted medical treatments for this patient population is warranted. Meanwhile, as recognition of MD and its CV effects grows, cardiologists should be vigilant for CV manifestations and worsening prognosis on hospitalization among patients who have MD.

Supplementary Material

A supplemental table for this article is available at 10.14503_THIJ-20-7243.s1.pdf.

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