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Letter to the Editor

COX regression to predict heart failure and arrhythmias in mitochondrial disorders should include neglected determinants

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We read with interest the article by Savvatis *et al*. about the incidence and predictors of heart failure (HF) and arrhythmic major adverse cardiac events (MACE) using Cox regression in 600 adult patients with a mitochondrial disorder (MID) from a multicenter registry [1]. The study is appealing, but raises concerns that warrant further discussion.

A limitation of the study is that heteroplasmy rates of mtDNA point mutations and single deletions, which were present in 524 of the included patients, were not included in the analysis. Heteroplasmy rates can strongly influence the phenotype and thus cardiac disease, including heart failure and arrhythmic MACE. Another factor that determines the phenotype and not included in the evaluation is the mtDNA copy number.

Another limitation of the study is that the status of coronary arteries was not included in the analysis. Patients with a MID often manifest with arterial hypertension, diabetes, or hyperlipidemia, which is why MID patients can develop coronary heart disease and myocardial infarction [2]. Additionally, MID patients can develop arteriopathy whether or not classical cardiovascular risk factors are present. Arteriopathy in MIDs can manifest as dissection, ectasia, aneurysm formation, spontaneous rupture, or spasms [3]. Therefore, we should know how many developed myocardial infarction during the follow-up period.

Another limitation of the study is that the number of patients with large or small fiber neuropathy was not reported. Neuropathy in MIDs may not only be due to diabetes or renal failure, but may represent an inherent phenotypic feature of a MID (mitochondrial neuropathy). Particularly small fiber neuropathy can involve autonomous A-delta or C-fibers, thereby impairing the autonomic innervation of the heart.

There is no information how many had restrictive and histiocytoid cardiomyopathy respectively Takotsubo syndrome. All three have been identified as phenotypic manifestations of a MID.

Overall, the study has obvious limitations that require reassessment and discussion. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Predictive models for heart failure and arrhythmic MACE can be highly dependent on heteroplasmy rates, mtDNA copy number, and other determinants, which were not assessed.

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