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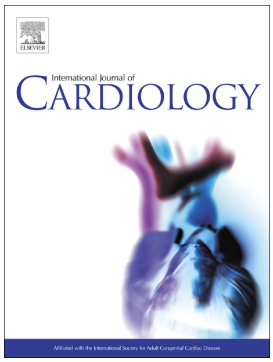

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Striking a Balance in Fabry Disease Research: Mitigating the Statistical Dilemma Arising from Small Sample Sizes and Modest Event Frequencies in Rare Disorders

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Abbreviations

CMR - Cardiac magnetic resonance imaging

FD – Fabry disease

LGE - late gadolinium enhancement

VT – ventricular tachycardia

Editorial

Cardiac involvement is a common and significant source of morbidity and mortality in Fabry disease (FD). The severity of cardiac involvement can vary widely among patients, making it difficult to predict outcomes and guide treatment decisions. Cardiac magnetic resonance imaging (CMR) is the non-invasive modality of choice in the detection of cardiomyopathy associated with FD due to its excellent spatial resolution and ability for soft tissue characterization. FD is an orphan disease and is still an underrecognized condition (1). Common findings such as increased maximal wall thickness of the left ventricle (LV) or myocardial scarring indicated by late gadolinium enhancement (LGE) are neither specific nor are they sensitive enough in early disease stages. Reduced native T1 times from parametric mapping may improve differentiation of subjects with FD from healthy controls and correlate to markers of disease severity such as LV wall thickness (2). However, an optimal cutoff does not exist since native T1 are dependent on the strength of the scanners magnetic field, vendor, and the applied sequences. Global longitudinal strain is a more reproducible method (3), and has been demonstrated to correlate well with reduced native T1 in FD (4). Although testing the activity of the enzyme alpha-galactosidase A can provide helpful information, it can also lead to false positive results in patients who are malnourished or who have chronic diseases such as those

undergoing dialysis (5). As a result, genotyping of alpha-galactosidase A has emerged as the current diagnostic gold standard. However, additional CMR parameters that could enable early diagnosis and risk stratification are still needed.

In this issue of the IJC, Hiestand and colleagues (6) present a retrospective imaging study on the prognostic implications of CMR findings in patients with FD confirmed by genetic testing. Included patients were followed for 4.9 years to assess event free survival and identify predictive imaging findings. Primary endpoint was a composite of cardiac death, new onset atrial fibrillation, heart failure, ventricular tachycardia and bradycardia requiring device insertion that occurred in 9 (16.3%) patients. One patient suffered from VT and died, while new onset atrial fibrillation and heart failure were more common. About half of the patients had cardiac involvement. The authors identified the presence and the extent of LGE and the maximal LV wall thickness as outcome predictors and concluded that both parameters might be useful in cardiac risk stratification of FD.

This study's strongest asset is also its most significant limitation. As mentioned, FD is quite a rare disease, and we sincerely congratulate the authors that they were able to enroll and consequently follow as many as 55 patients at only one center for this well-conducted study. Only a limited number of studies have been able to include a higher number of patients, and their results largely met the findings of the present one. However, the present study also illustrates the problems researchers are facing in the investigation of orphan diseases like cardiac involvement in FD.

At first, small sample size can introduce a number of statistical problems far beyond type II error that occurs when a false null hypothesis is not rejected due to insufficient statistical power. Increased skewness violating the assumptions of many statistical tests, unstable estimates

of population parameters, overfitting of models and limited representativeness of smaller cohorts are common issues that can arise with small sample sizes. The authors of the present study seemed to be aware of these aspects and acknowledged them in the limitation section. When sample size cannot easily be increased, composite endpoints can be especially valuable as they can help to maximize the information obtained from a limited sample and may be better able to detect a significant effect. However, they come at the price of diluting associations to so-called "hard endpoints" by implementing components of questionable clinical significance and there is a danger of outcome reporting bias and outcome switching. Repeat event analysis could be a way out but requires additional data acquisitions and analyses.

Secondly, a further challenge in investigating underdiagnosed orphan diseases like FD is that most studies only include highly selected patients, mostly those with previously diagnosed and often symptomatic disease. Without systematic screening in a cohort without known FD patients, symptomatic patients or members of families with mutations that are prone to develop cardiac events might be overrepresented, while asymptomatic mutation carriers or late onset FD patients might be naturally underrepresented in cohort studies. Although systematic screening could avoid selection bias, in a disease with a prevalence of <1%, it is less practical. Screening in high-risk populations, such as patients with chronic kidney disease or patients with LVH, can increase prevalence up to 1% (7,8), but there is still a relevant selection bias, which limits the generalizability of findings to the specific study setting.

Thirdly, inter-individual differences in FD disease manifestation and progression add another layer of complexity to interpreting findings. Slow disease progression over decades with low event rates in young patients increases the importance of confounders such as age. In the present study, age is an important predictor of outcomes, but this might not be a FD-specific

finding and could be attributable to higher age-associated morbidity and mortality in general. Adjustment for age is required to identify predictors that are of independent prognostic implication.

Finally, FD is a disease with a variety of cardiac manifestations, which further complicates the interpretation of findings. Although overlapping features exist, the underlying mechanisms of e.g. new onset atrial fibrillation and stroke on the one hand and ventricular arrhythmia and death on the other hand are not equal and it is not given that changes in the ventricle also correspond to high risk features in the atria. Merging of endpoints complicates to draw meaningful conclusions from studies and tailor therapy according to the patient's risk.

Despite the numerous limitations of smaller studies in cardiac FD, conducting research such as the present study is still crucial as it provides valuable insights into the underlying mechanisms and generates hypotheses even at small sample size. However, it is essential to acknowledge these limitations and interpret results with caution. Researchers must strive to address these issues and improve the rigor of their studies to enhance the validity and generalizability of their findings. In this context, we congratulate Hiestand and colleagues on their valuable contribution to the understanding of cardiac involvement in FD.

References

1. Germain DP, Fouilhoux A, Decramer S et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clin Genet 2019;96:107-117.
2. Ponsiglione A, Gambardella M, Green R et al. Cardiovascular magnetic resonance native T1 mapping in Anderson-Fabry disease: a systematic review and meta-analysis. J Cardiovasc Magn Reson 2022;24:31.
3. Fischer K, Linder OL, Erne SA et al. Reproducibility and its confounders of CMR feature tracking myocardial strain analysis in patients with suspected myocarditis. Eur Radiol 2022;32:3436-3446.

4. Vijapurapu R, Nordin S, Baig S et al. Global longitudinal strain, myocardial storage and hypertrophy in Fabry disease. Heart 2019;105:470-476.
5. Jahan S, Sarathchandran S, Akhter S et al. Prevalence of Fabry disease in dialysis patients: Western Australia Fabry disease screening study - the FoRWARD study. Orphanet J Rare Dis 2020;15:10.
6. Hiestand RS, Justyna M.; Chan, Raymond; Nowak, Albina; Ruschitzka, Frank; Manka, Robert; Gruner, Christiane. Clinical and CMR characteristics associated with cardiac events in patients with Fabry disease. International Journal of Cardiology 2023.
7. Doheny D, Srinivasan R, Pagant S, Chen B, Yasuda M, Desnick RJ. Fabry Disease: prevalence of affected males and heterozygotes with pathogenic GLA mutations identified by screening renal, cardiac and stroke clinics, 1995-2017. J Med Genet 2018;55:261-268.
8. Nagata A, Nasu M, Kaida Y et al. Screening of Fabry disease in patients with chronic kidney disease in Japan. Nephrology Dialysis Transplantation 2021;37:115-125.