Is etiology the dominant modifier of prognosis in all heart failure phenotypes?

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INTRODUCTION

In general the most common phenotype of heart failure is heart failure with reduced ejection fraction (HFrEF) followed by either heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF) (depending on population studied) [1–4]. In literature, the influence of ischemic etiology (IE) on the prognosis of HF regardless of the phenotype is a critical area of study, as ischemic heart disease is a prevalent cause of HF. Across all heart failure phenotypes, IE is a major determinant of prognosis, often leading to worse outcomes compared to non-ischemic etiology (non-IE) [5, 6]. However, the impact of IE on prognosis is influenced by various factors, including comorbidities and age, which can exacerbate the risk of adverse outcomes [7]. Therefore the aim of our study was to evaluate the survival of patients with HF according to the ischemic etiology in different HF phenotypes.

METHODS

It was a retrospective study using data from an electronic database of patients with hospitalization coded as HF billing codes, at the National Institute of Cardiology in Warsaw. We analyzed all patients hospitalized between January 2014 and May 2019 coded as HF hospitalization. For individuals with multiple hospitalizations, we used the first event for further analysis. We excluded patients who underwent heart transplantation/implantation of left ventricular assist devices or were misdiagnosed and individuals with missing data on EF. Patients who underwent left ventricular assist device implantation or heart transplantation during hospitalization were censored as alive. All patients were phenotyped based on the EF assessed during an echocardiography examination. Individuals with EF below 40% were labeled as HFrEF, those with EF between 40% and 49%, as HFmrEF, and those with EF equal or greater than 50%, as HFpEF, following the recommendations in force at the time. Medical history, such as comorbidities or invasive procedures performed, was based on medical records provided by the attending physicians and supplemented with data from the National Health Fund database. Data on their survival status were obtained from the Central Informatics Center, with the censoring date set at May 25, 2023 [1]. The study protocol was approved by the Biomedical Ethics Committee of the National Institute of Cardiology (No. IK-NPIA-0021/1799/2019; 11.06.2019).

Statistical analysis

The distribution of quantitative data was verified by the Shapiro–Wilk test in all subgroups. It did not follow a normal distribution and is therefore presented as median with interquartile range. The distribution of qualitative variables is presented as numbers and percentages. Patient characteristics were compared in subsamples by HF phenotype and etiology using the Mann–Whitney test for quantitative data and the χ^2 test for qualitative data. Survival probability was assessed and graphically presented using Kaplan–Meier survival curves with the log-rank test for comparison. Using, Cox proportional hazards methods, hazards ratios were calculated with 95% confidence intervals, first comparing by etiology in the whole group and then adjust-

ing for age, sex, and number of comorbidities. All data analyses were performed with STATA (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX, US: StataCorp LLC). The significance level was set at a *P*-value of less than 0.05.

RESULTS AND DISCUSSION

Between January 2014 and May 2019, 2597 patients were hospitalized with a hospitalization coded as HF. Among them, 1040 patients had an IE including 798 with HFrEF (49.8% within subgroup), 114 HFmrEF (34.4% within subgroup), and 128 with HFpEF (19.3% within subgroup). Patient characteristics by HF phenotype and IE vs. non-IE are presented in Supplementary material, *Table S1*. The median age in the overall HF group was significantly higher in the IE group compared to the non-IE group and male sex was more prevalent. Similar trends were observed across all HF phenotypes. These results for HF resemble those from other studies [3, 6]. Chronic HF was more frequent in IE, with comparable patterns observed in HFrEF and HFpEF.

Among the recorded comorbidities, hypertension was more prevalent in IE, and this trend persisted across all HF phenotypes. Diabetes was also more frequent in IE, with nearly 70% higher percentage of patients in all HF subtypes within the IE group. Renal dysfunction and stroke were also more common in IE, with similar patterns seen in all HF phenotypes. In contrast, atrial fibrillation was less frequent in IE, with this pattern observed only in the HFrEF group [1]. In general, our findings regarding comorbidities, resemble the observation from previous studies [3, 6]. The median number of comorbidities was higher in IE than in non-IE with nearly identical distribution across all HF phenotypes [7].

There was no significant difference between IE and non-IE in terms of asthma/chronic obstructive pulmonary disease or cancer, across all HF phenotypes. However, the highest prevalence of cancer was noted in HFpEF can be partially explained by an older age in this phenotype [1].

Pharmacology trends showed that angiotensin converting enzyme inhibitors, beta blockers and loops diuretics were used more often in IE compared to non-IE. However, angiotensin converting enzyme inhibitors and loops diuretics recommendations were only more prevalent in HFpEF, whereas beta blockers only in HFmrEF. On the contrary the use of mineralocorticoid receptor antagonists did not differ between IE and non-IE, but were less likely in HFrEF, with similar distribution in other phenotypes (Supplementary material, *Table S1*)

During a median (interquartile range) follow-up of 4.26 (1.56–5.47) years the mortality rate was significantly higher in the IE group compared to the non-IE group, similar to previous reports [3, 6, 8], with survival rates of 43.03% vs. 57.15% (P <0.001) at 5 years post hospitalization, respectively. Survival in the IE group was consistently worse than in the non-IE group across all HF phenotypes. As previously demonstrated, survival was worse for HFrEF compared to HFpEF and HFmrEF, which had similar outcomes [9].

Based on the current data, the risk of death was 52% higher in the IE group compared to the non-IE group (P <0.001) (Figure 1A). When stratified by HF phenotypes in the IE group, survival was worse in HFrEF and HFpEF compared to HFmrEF, with no significant difference between the former two phenotypes (Figure 1B). In the non-IE group, survival was worse in HFrEF compared to both HFmrEF and HFpEF, with latter having similar outcomes (Figure 1C). A comparison of survival by etiology within each HF phenotype revealed that survival was worse in IE compared to non-IE for all phenotypes (Figure 1D).

These findings suggest that IE was the strongest modifier of survival, regardless of HF phenotype, what confirms previous findings [3]. However, in a paper from the Italian network IE was not an independent factor in all phenotypes after adjustment for other variables [10]. Therefore, to further explore this issue, we constructed multivariable models for each phenotype, incorporating sex, age, number of comorbidities, and etiology (Supplementary material, *Table S2*). In these models, ischemic etiology was no longer a significant predictor of prognosis for any HF phenotype. However, age remained a significant risk factor for death across all phenotypes. Similarly the number of comorbidities was associated with increased mortality in all phenotypes. On the other hand, female gender was associated only with HFrEF, showing a better prognosis. Therefore, our data indicate that providing information on prognosis solely based on etiology might be misleading, as this association is often biased by significant differences in the characteristics of the analyzed groups [10]. To our knowledge, this is the first study to provide such information for the Polish HF population across diverse HF phenotypes and etiologies. In conclusion, the observed differences in survival, with worse outcomes for IE across all phenotypes, were largely influenced by patient characteristics, like age, number of comorbidities in the IE subgroups, rather than ischemic etiology alone.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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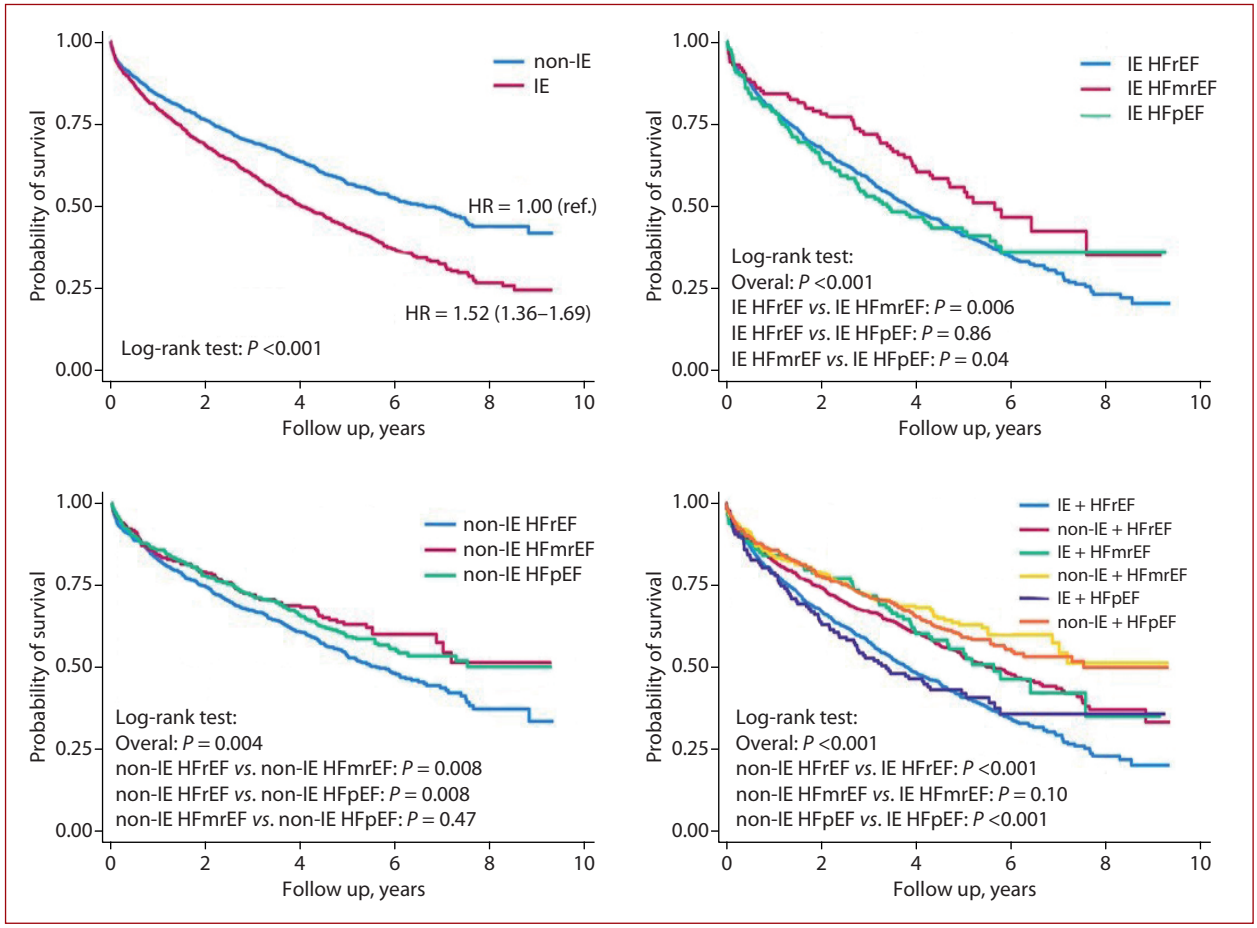

Figure 1. Kaplan–Meier survival estimates by phenotypes and etiology from univariable modeling

Abbreviations: HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction HR, hazard ratio; IE, ischemic etiology; non-IE, non-ischemic etiolog

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