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ORIGINAL ARTICLE

Sex differences in the association between nutritional status and in-hospital mortality in HFpEF patients

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Abstract

Aims The study aimed to assess whether the effect of nutritional risk score (NRS-2002) on the odds of in-hospital mortality would be modulated by sex and body mass index (BMI) in patients with heart failure with preserved ejection fraction (HFpEF).
Methods and results A retrospective analysis was conducted on 234 patients admitted with acute heart failure, in whom HFpEF was identified as the underlying diagnosis, during the period 08.2018–08.2020. Nutritional status was assessed using BMI and NRS2002. NRS-2002 is a validated screening tool recommended by ESPEN that evaluates nutritional risk based on recent weight loss, reduced dietary intake, severity of illness and age. Logistic regression models were used to evaluate the associations between these nutritional indices and in-hospital mortality. The models were adjusted for sex, age and comorbidities. Interactions between NRS2002, BMI and sex were also explored to assess whether the effect of nutritional status on mortality was modulated by these factors. The analysis revealed that male patients with elevated NRS2002 scores had significantly higher odds of in-hospital mortality (odds = 47.512 at NRS2002 = 4 compared to odds = 0.031 at NRS2002 = 1; BMI = 28 in both cases). BMI negatively modulated the odds of death (OR = 0.843, P = 0.012) in the population sample. This effect was consistent across the sample regardless of NRS2002 score, as NRS2002 did not significantly influence the BMI–mortality relationship (P = 0.289). Importantly, this relationship was observed only in male patients, as no such association between NRS2002 and mortality was found in women.
Conclusions In male patients with HFpEF, elevated NRS2002 scores showed significantly higher odds of in-hospital mortality. Higher BMI was generally associated with lower odds of mortality, with this protective effect remaining consistent in the population sample, regardless of the NRS2002 score.

Keywords BMI; Heart failure; HFpEF; NRS2002; Nutritional status; Obesity

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Introduction

The incidence of heart failure (HF) is over 64.3 million people worldwide, and approximately 50% of patients with heart failure have preserved ejection fraction (HFpEF).[1] HFpEF represents a complex and increasingly prevalent clinical syndrome, particularly among the aging population. This condition contributes significantly to morbidity and mortality, yet remains challenging to treat due to its heterogeneous nature and the limited efficacy of existing therapeutic strategies.[2–4] Among the various factors influencing HFpEF outcomes, nutritional status has emerged as a critical determinant, with both malnutrition and obesity playing pivotal roles in patient prognosis.[5–7]

Malnutrition, defined as an imbalance between nutrient intake and the body's requirements, is frequently observed in HF patients and is associated with adverse clinical outcomes, including increased risk of in-hospital mortality, impaired immune function and decreased muscle strength.[6,8–12] On the other hand, obesity, often considered a risk factor for cardiovascular diseases, paradoxically appears to confer a survival benefit in chronic heart failure, a phenomenon referred to as the 'obesity paradox'.[13–15] However, the exact mechanisms by which these nutritional extremes affect HFpEF patients, particularly in relation to sex-specific outcomes, remain poorly understood.[16]

The assessment of nutritional status in HF patients typically involves various tools, including the Nutritional Risk Screening 2002 (NRS2002) and body mass index (BMI).[17–19] The NRS-2002 is a validated screening instrument recommended by ESPEN that assesses nutritional risk based on recent weight loss, reduced dietary intake, severity of illness and age. A score of $\geq$3 indicates a clinically relevant risk of malnutrition. This tool has demonstrated prognostic value across multiple inpatient populations, including those with cardiovascular disease.[20,21] These indices provide valuable insights into the patients' nutritional health and potential risks associated with undernutrition or overnutrition.[22,23] Previous studies have demonstrated the prognostic value of these assessments in chronic heart failure, but their specific impact on HFpEF, especially concerning in-hospital mortality, has not been fully elucidated.[5,24]

Sex differences in HFpEF are another critical aspect that requires further exploration. Men and women may exhibit distinct pathophysiological responses to both HF and its comorbidities, including nutritional status.[25,26] These differences can influence disease progression, response to treatment and overall prognosis.[27–29] Understanding how nutritional status interacts with sex and other risk factors such as age and comorbidities could lead to more personalized and effective management strategies for HFpEF patients.

The study aimed to check whether the effect of nutritional risk score (NRS-2002) on the odds of death would be different modulated by sex and BMI in patients with HFpEF.

Methods

Participants

This study retrospectively analysed medical records of patients admitted to the cardiology unit (Institute of Heart Diseases) at the University Clinical Hospital in Wroclaw, Poland, due to acute decompensated heart failure (AHF). The data were collected from August 2018 to August 2020, following the STROBE guidelines to ensure accurate and transparent reporting of observational studies.

Study population and data

We analysed the records of all patients who met the inclusion criteria of being aged 18 years or older, diagnosed with HFpEF, and having documented data on BMI or NRS2002, which were required for the study objectives. The diagnosis of HFpEF was based on the 2016 European Society of Cardiology (ESC) Guidelines.[30] All patients were admitted with acute heart failure, and HFpEF was subsequently identified as the underlying cause based on clinical evaluation and documented in their discharge records. Patients were excluded if they had any form of heart failure other than HFpEF, were younger than 18 years, or had missing data regarding BMI or NRS2002 scores. The final analysis comprised data from 234 patients, including 129 females and 105 males. The study employed a convenience sampling approach, including all eligible patients admitted during the specified time frame. Key demographic and clinical data collected included patient age, sex, body mass index (BMI) and length of hospital stay. Laboratory results such as total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), high-sensitivity C-reactive protein (hsCRP) and albumin were also recorded. Additionally, we collected data on the New York Heart Association (NYHA) classification and the presence of comorbidities such as chronic kidney disease (CKD), arterial hypertension (HT), diabetes mellitus (DM), cerebral stroke (CS) and myocardial infarction (MI). Blood samples for laboratory assessments were obtained by a nurse at the time of admission. The nutritional status of each patient was evaluated using the NRS-2002 questionnaire, where a score of 3 or higher indicated a risk of malnutrition, while NRS2002 $<$ 3 indicated low risk. According to the World Health Organization (WHO) criteria, patients were classified into BMI categories: underweight (BMI $<$ 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), pre-obese (BMI 25–29.9 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2).[31] All data were meticulously documented in the patients' medical records at the time of admission.

Statistical analysis

Statistica 13.3 (on licence of Wroclaw Medical University) and Python 3.12.2 were utilized in the analytical phase of the study. The former was used for preprocessing, statistical analysis and visualization, whereas the latter was employed for visualization only. As the distribution of values of some of the analysed variables did not meet the normality assumption (checked with Q-Q plots and the Shapiro–Wilk test), Mann–Whitney *U* test was used as the mean of performing the pairwise comparisons in case of continuous variables. The chi-square test was utilized in case of categorical variables. Logistic regression was employed so as to check the possible multi-way modulation of the odds of death by BMI, NRS2002 and other variables. First and foremost, all

Table 1 Characteristics of the population sample based on selected parameters

HFpEF (N = 234)									
	Female (N = 129)				Male (N = 105)				
Variable (quant.)	n	Median	25%	75%	n	Median	25%	75%	P
Age	129	79	72	85	105	70	67	79	**<0.001**
NT-proBNP (pg/mL)	41	1982.2	1133.3	4175.7	28	3624.9	1427.4	5511.3	0.356
BNP (pg/mL)	87	412.1	164.4	821.7	79	341.8	154.8	712.6	0.398
TG (mg/dL)	126	106	76	133	101	99	77	142	0.905
LDL (mg/dL)	127	79	63	100	100	81	61.5	100	0.810
HDL (mg/dL)	127	46	38	55	100	38	30	45	**<0.001**
TC (mg/dL)	127	150	132	172	101	143	117	162	**0.029**
hsCRP (mg/l)	126	4.825	1.87	10.71	102	8.1	2.48	24.17	**0.017**
Albumin (g/dL)	38	3.25	2.8	3.8	36	3.25	3	3.55	0.875
Hospital stay (days)	129	6	4	12	105	6	4	10	0.738
Variable: category (qual.)		Observed n		Frequency (%)		Observed n		Frequency (%)	P
Mortality: Death		10		7.75		6		5.71	0.539
NYHA: 1		5		4.17		10		9.71	0.392
NYHA: 2		47		39.17		35		33.98	
NYHA: 3		36		30.00		32		31.07	
NYHA: 4		32		26.67		26		25.24	
BMI < 18.5		8		6.20		1		0.95	**0.030**
BMI 18.5–24.9		31		24.03		20		19.05	
BMI 25–29.9		41		31.78		27		25.71	
BMI ≥ 30		49		37.98		57		54.29	
CKD: Yes		55		42.64		38		36.19	0.316
HT: Yes		112		86.82		85		80.95	0.221
DM: Yes		58		44.96		51		48.57	0.582
CS: Yes		18		13.95		17		16.19	0.633
MI: Yes		26		20.16		15		14.29	0.240
NRS2002: <3		120		93.02		99		94.29	0.695
NRS2002: ≥3		9		6.98		6		5.71	

Age, age of the patient; Albumin, albumin concentration (g/dL); BMI, body mass index; BNP, B-type natriuretic peptide concentration (pg/mL); CKD, chronic kidney disease; CS, cerebral stroke; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol concentration (mg/dL); HFpEF, heart failure with preserved ejection fraction; hsCRP, high-sensitivity C-reactive protein concentration (mg/L); HT, arterial hypertension; LDL-Chol, low-density lipoprotein cholesterol concentration (mg/dL); MI, myocardial infarction; Mortality, death; n, number of participants; NRS2002, Nutritional Risk Screening 2020; NT-proBNP, N-terminal pro b-type natriuretic peptide concentration (pg/mL); NYHA, New York Heart Association classification; TC, total cholesterol concentration (mg/dL); TG, triglyceride concentration (mg/dL).

continuous variables were centred around their median values in the population sample, and checked for linearity vs. log (odds) based on visualization and the Box–Tidwell test. Subsequently, all the possible interactions between BMI, NRS2002 and other analysed variables were screened for in terms of their potential significance based on the likelihood ratio type 1 test (LR1). Two interactions: NRS2002*Sex (P = 0.007) and BMI*NRS2002 (P = 0.028) were, then, employed altogether in the multivariate model containing both interactions and the three factors taking part in them (sex, NRS2002 and BMI). Wald test was used so as to check the significance of the effects/interactions in the model. Before drawing conclusions from the model, its diagnostics was performed in order to identify the possible influence of some observations on its estimation. Influential points were sought with use of the leverage and Cook's distance plot, whereas outliers were analysed based on Studentized residuals. As there was one observation of extreme influence on the model, and one observation showing extreme deviation, the original model and models that were not based on these observations were compared to each other in terms of their fit to the data [based on corrected Akaike information criterion (AICc), Bayesian information criterion (BIC) and Nagelkerke's pseudo-R^2]. ROC analysis was used so as to check the quality of the models and to identify the most optimal cut-off point with its estimated sensitivity and specificity metrics.

Results

Characteristics of the population sample

The analysed HFpEF population sample showed heterogeneity based on the sex of the participants. The median values of age, HDL and TC were higher among men ($P < 0.001$, $P < 0.001$ and P = 0.029, respectively), whereas women showed over 1.5-fold higher median value of hsCRP (P = 0.017) compared with men. Moreover, both sexes were discrepant in the distribution of BMI (P = 0.030)—values lower than 18.5 were more abundant among men, while

Table 2 Association between the odds of death among HFpEF individuals and: sex, NRS2002 and BMI—insights from the final model (best fit to the empirical data)

Effect/interaction	Description	*P*	Estimate
[A] Intercept (β_0)	The odds of a female individual with NRS2002 = 0 and BMI = 28	<**0.001**	0.084
[B] Sex	The fold change in [A] if the individual was male	**0.022**	0.032
[C] NRS2002	The fold change in [A] with each 1 unit increase in NRS2002	0.317	0.671
BMI	The fold change in [A] with each 1 unit increase in BMI	**0.012**	0.843
[D] Sex*NRS2002	The fold change in [C] if the individual was male	**0.001**	11.565

More thorough information on this model and its derivation is given in the supporting information (the model is shown *Table S1D*).
BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; NRS2002, Nutritional Risk Screening 2002; *P*, *P*-value.

women showed obesity (BMI > 30) more frequently. Notably, indicators of malnutrition such as NRS2002 and albumin did not differ significantly between the sexes (P = 0.695 and P = 0.875, respectively), indicating comparable nutritional status across both groups. More thorough characteristics are given in *Table 1*.

Analysis of the odds of death in context of the selected interactions

The final model (*Table 2*, *Table S1D*), although of higher simplicity compared to the initial model, was characterized by a markedly better fit (AICc 94.61 vs. 107.72, BIC 111.58 vs. 128.08, pseudo-R^2 0.286 vs. 0.222). Based on its estimations, the baseline odds of a NRS2002 0, BMI 28 woman was 0.084 ($P < 0.001$), while a man of these characteristics would show approximately 0.003 odds of death (P = 0.022). BMI decreased the odds of death, regardless of sex, by 18.62% per 1 unit increase of BMI over 28 (P = 0.012). Although higher malnutrition risk would not alter the odds among women (P = 0.317), its influence on the odds would be significant among men (P = 0.001). A man of BMI 28 and a typical NRS2002 value in the population sample (NRS2002 = 1) would be characterized by odds 0.031, whereas in a man of BMI 28 and higher risk of malnutrition (NRS2002 = 4), these odds would be 47.51. The influence of the effect/interactions featured in this model are shown in *Figure 1*.

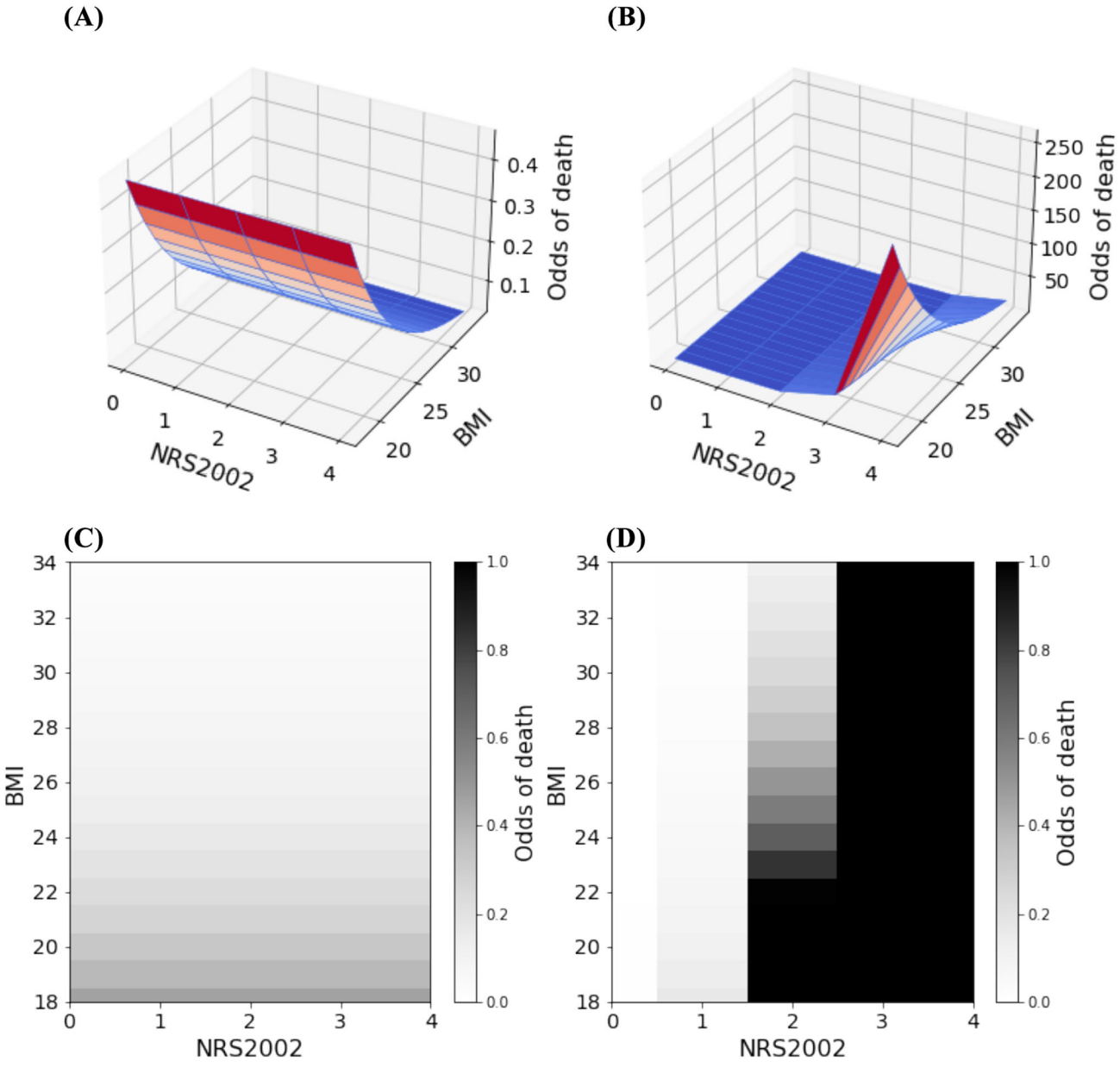
Discussion

We found that nutritional status influenced prognosis in men with HFpEF but not in women. Higher BMI was associated with a lower risk of in-hospital mortality in patients with HFpEF. Understanding the factors influencing the prognosis (including in-hospital mortality) of patients with HFpEF is very important from a clinical point of view. In our study, we assessed the effect of nutritional status (assessed using the NRS2002 and BMI) on the risk of in-hospital mortality in patients with HFpEF. We showed that with increasing NRS2002 values, mortality in men with HFpEF increased. We did not find such a relationship in women. It was shown that nutritional risk as defined by NRS2002 in hospitalized patients with HF was significantly associated with long-term mortality.[32]

In our previous studies involving the entire HF patient population, malnutrition status was shown to correlate with an increased risk of in-hospital mortality.[33] However, after stratification by sex (regardless of ejection fraction), both underweight and the risk of malnutrition were found to be direct predictors of in-hospital mortality in men, but not in women.[26] These findings align with current research, which emphasizes that not only sex, but also EF, must be considered when studying HF populations. Clinical profiles and outcomes differ significantly e.g. between HFpEF and HFrEF, making such distinctions crucial for accurate prognostic assessment and tailored therapeutic strategies.[34–36]

The malnutrition status correlates with an increased risk of death during hospitalization in HF patients.[33] Some studies have shown that higher body weight was associated with better prognosis and shorter hospitalization time (e.g., in patients hospitalized due to exacerbation of HF.[18] In our study, we also showed that higher BMI was associated with a lower risk of in-hospital mortality in HFpEF patients. This is the so-called 'obesity paradox', or rather, as more detailed analyses have shown - the 'BMI paradox'.[37] In our previous study, we showed that extending the analysis of the impact of BMI on the prognosis of patients with HFrEF to include a history of stroke eliminated the 'BMI paradox'.[18] BMI, although commonly used to diagnose obesity, is a parameter that poorly reflects the actual content of body fat. In a meta-analysis of 32 studies conducted by Sommer et al., it was found that the use of BMI for diagnosing obesity (defined as percentage of fat mass) was characterized by low sensitivity (detection of the disease in a priori patients) 51.4% (95% CI: 38.5–64.2) and good specificity (exclusion of the disease in a priori healthy individuals) 95.4% (95% CI: 90.7–97.8) in women and 49.6% (95% CI: 34.8–64.5) and 97.3% (95% CI: 92.1–99.1) in men, respectively.[38] Therefore, the exclusive use of BMI in diagnosing obesity may result in its under identification. BMI does not always have explanatory power in the assessment of body mass, because it does not take into account the percentage of fat distribution (it does not reflect the distribution of visceral fat tissue) lean body mass and swellings

Figure 1 Three-way modulation of the odds of death among HFpEF individuals by sex [female: (A), (C); male: (B), (D)], nutritional risk (NRS2002) and BMI, based on the model of the best fit, shown in *Table 2D*. The first row of plots shows the estimated odds, while the second row indicates the conditions in which death is more likely than survival (odds >1).



in HF patients. Moreover, BMI does not assess skeletal muscle mass or strength. These parameters are extremely important in the context of assessing the prognosis of patients.[39,40] Moreover, the 'obesity paradox' is observed in more physically active individuals with better glycaemic control.[41–43] It is worth emphasizing that the 'BMI paradox' was reduced in patients with HFpEF and concomitant type 2 diabetes.[44] Analysis of the relationship between BMI and prognosis, extended to include treatment, region, age, gender, systolic blood pressure, heart rate, renal function, left ventricular ejection fraction, BMI, NYHA functional class, HF aetiology, HF duration, previous hospitalization due to HF, history of diabetes, atrial fibrillation and NT-proBNP eliminates the 'obesity paradox'. The use of the waist-to-hip ratio (WHR) correlates better with the prognosis of patients.[45] In our study, after taking into account nutritional risk (according to NRS2002), we found that it did not influence the protective effect of BMI on mortality in women with HFpEF, while the malnutrition risk did not cause the 'BMI paradox' in men with HFpEF. Such observations may be inter alia with a more detailed

conclusion regarding the nutritional status based on the NRS2002 in women (they may report a more rigorous justification). Moreover, men were more likely to be of nutritional risk than women. Obesity does not always coexist with metabolic disorders, which is why we distinguish between metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO). Moreover, we can also distinguish metabolically unhealthy normal body weight (MUNW). Both MUO and MUNW are characterized by higher cardiovascular risk and worse prognosis.[46] Based solely on BMI measurement, it is impossible to determine whether a patient has MHO or MUO, and even more so MUNW. It is worth emphasizing that BMI does not always correlate with the degree of nutrition. High BMI does not exclude the presence of malnutrition.[47]

Our results have important clinical implications, as they indicate that the prognosis of patients with HFpEF cannot be assessed solely on the basis of BMI (based on the erroneous assumption of the 'obesity paradox'). The assessment of the prognosis of a patient with HFpEF should be based on an individual and holistic assessment of their health status.

Study limitation

Despite the valuable insights gained from this study, there are some limitations that should be acknowledged. One notable constraint is the limited number of patients identified as being at risk of malnutrition, representing only 6.98% of the entire cohort. This small sample size may reduce the statistical power of the study and limit the generalizability of the findings. Additionally, some medical records lacked essential data, such as NRS scores and BMI results, which could have provided a more comprehensive understanding of the patients' nutritional status. Furthermore, the absence of detailed information on prior treatments, such as the use of lipid-lowering medications, and the lack of body composition assessments are other notable limitations. The reliance on BMI alone may not adequately capture the nuances of overweight and obesity, as measurements like the waist-to-hip ratio (WHR) and central obesity based on waist circumference were not reported. Moreover, as no alternative causes of in-hospital death were documented in the available medical records, all deaths were classified as heart failure-related, which may introduce a degree of classification bias. Finally, due to the anonymization of medical records, assessing the long-term survival of HFpEF patients was not possible.

Conclusions

Males with HFpEF and elevated NRS2002 scores have significantly higher odds of in-hospital mortality, with their odds of death increasing by approximately 11.565-fold for each unit increase in NRS2002 score. This relationship was not observed in females. Higher BMI is generally associated with lower odds of mortality, with this protective effect remaining consistent in the whole population sample. These findings underscore the need for personalized nutritional assessments and targeted interventions, particularly considering the distinct ways in which sex and nutritional status interact to influence the odds of mortality in HFpEF patients.

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Conflict of interest

The authors declare no conflicts of interest.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Association between the odds of death among HFpEF individuals and: sex, NRS2002 and BMI based on the compared logistic regression models with interactions. Abbreviations: Abbreviations: AICc, Akaike Information Criterion (corrected); BIC, Bayesian Information Criterion; BMI, body mass index; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; NRS2002, Nutritional Risk Screening 2002; p, *p*-value; Pseudo-R^2, Nagelkerke Pseudo-R-squared; SE, standard error; Wald, Wald test statistic.

Figure S1. Three-way modulation of the odds of death among HFpEF individuals by sex (female: A, C; male: B, D), nutritional risk (NRS2002) and BMI, based on the initial model, shown in Table S1A.

The first row of plots shows the estimated odds, while the second row indicates the conditions in which death is more likely than survival (odds >1).

Figure S2. Leverage vs. Cook's distance plot which revealed an observation (#34) of utmost influence on the conclusions driven by the initial model. Leaving this observation in the model posed the BMI*NRS2002 interaction as significant.

Figure S3. Studentized residuals of the observations used by the initial model, showing an extreme outlier (#143) yielding a residual over 8 SD higher than the expected value (thus – posing a high risk of increasing the estimated confidence intervals and leading to bias).

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