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Original Article

Risk factors and development of a predictive model for frailty in patients with heart failure

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Abstract: Objectives: To identify factors influencing frailty in patients with heart failure (HF) and develop a predictive model for clinical use. Methods: A retrospective analysis was conducted on 350 HF patients at Shanghai Baoshan District Hospital of Integrated Traditional Chinese and Western Medicine between January 2020 and December 2023. Of these, 245 patients were allocated to the modeling group (n = 245) and 105 to the validation group (n = 105). In the modeling group, 135 patients were frail and 110 were non-frail. In the validation group, 47 patients were frail and 58 were non-frail. Logistic regression analysis was used to identify factors associated with frailty, and a nomogram was developed and validated to predict frailty risk. Results: Multivariate logistic regression analysis identified the following independent risk factors for frailty: fall history (OR: 0.101, 95% CI: 0.043-0.242, P < 0.001), advanced age (OR: 0.877, 95% CI: 0.828-0.928, P < 0.001), female sex (OR: 2.925, 95% CI: 1.294-6.613, P = 0.010), low hemoglobin levels (< 12 g/dL; OR: 2.547, 95% CI: 1.816-3.573, P < 0.001), and diabetes (OR: 3.202, 95% CI: 1.559-6.577, P = 0.002). Using these five variables, a nomogram was constructed to predict frailty risk, demonstrating an AUC of 0.822 (95% CI: 0.771-0.907). Conclusion: Fall history, advanced age, female sex, low hemoglobin levels, and diabetes are significant independent risk factors for frailty in HF patients. The nomogram prediction model demonstrated strong predictive performance, with high accuracy and clinical applicability.

Keywords: Heart failure, frailty, risk factors, predictive model, prognosis

Introduction

Heart failure (HF) is a prevalent and debilitating condition affecting over 64 million people worldwide [1]. Its prevalence increases significantly with age, impacting more than 10% of individuals over 70 years old [2]. Despite advances in medical management, HF remains a leading cause of hospitalization and mortality globally [3, 4]. The condition also incurs substantial healthcare costs, accounting for a significant portion of health budgets in developed countries [5]. The rising prevalence of HF is attributed to factors such as an aging population, improved survival rates from other cardiovascular diseases, and an increase in risk factors like hypertension, diabetes, and obesity [6]. Notably, the incidence and prevalence of HF vary across regions and populations, influenced by socioeconomic status, healthcare access, and the prevalence of comorbid conditions [7, 8].

Frailty, a syndrome characterized by unintentional weight loss, muscle weakness, exhaustion, slow walking speed, and low physical activity, increases vulnerability to adverse health outcomes like disability, hospitalization, and mortality [9]. It is particularly prevalent in HF patients, a chronic and progressive condition that imposes significant physiological stress on multiple organ systems [10]. The coexistence of frailty and HF not only worsens prognosis but also complicates treatment strategies, leading to higher rates of hospitalization, reduced quality of life, and increased mortality [11]. Despite its clinical significance, the mechanisms underlying frailty in HF remain poorly understood, and patients at risk are often identified only when frailty has reached advanced stages.

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Existing evidence suggests that frailty in HF is multifactorial, influenced by demographic, clinical, and biochemical factors [12]. Aging, comorbidities such as diabetes and chronic kidney disease, and systemic inflammation have been implicated in its pathogenesis [13-17]. However, the heterogeneity of HF patients, combined with the varied manifestations of frailty, makes it challenging for clinicians to identify high-risk individuals early in their clinical course. Moreover, while several frailty assessment tools have been proposed, their application in HF populations remains limited due to the lack of disease-specific predictive models [18].

To address this gap, the development of a robust predictive model for frailty in HF patients is critical. Such a model would enable early identification of at-risk individuals, facilitate targeted interventions, and ultimately improve patient outcomes. By integrating comprehensive clinical data with advanced statistical techniques, predictive models can offer valuable insights into the risk factors that contribute to frailty and provide personalized prognostic assessments.

This study aims to explore the risk factors associated with frailty in HF patients and to develop a predictive model that accurately identifies frailty in this population. We hypothesize that by incorporating demographic, clinical, and laboratory data, we can create a reliable tool for predicting frailty, providing clinicians with a practical framework for early intervention. This work seeks to enhance our understanding of the interaction between HF and frailty and contribute to the growing body of research focused on improving outcomes for this high-risk population.

Materials and methods

Case selection

This retrospective study included 350 patients diagnosed with HF who were hospitalized at Shanghai Baoshan District Hospital of Integrated Traditional Chinese and Western Medicine between January 2020 and December 2023. The cohort was divided into a modeling group (n = 245) and a validation group (n = 105). In the modeling group, 135 patients (55.1%) were frail, and 110 patients (44.9%) were non-frail. In the validation group, 47 patients (44.8%) were frail, and 58 patients (55.2%) were non-frail. The overall prevalence of frailty was 52%. The study was approved by the Ethics Committee of Shanghai Baoshan District Hospital of Integrated Traditional Chinese and Western Medicine.

Inclusion criteria were: (1) age ≥ 18 years; (2) a diagnosis of HF, including HF with preserved ejection fraction, made according to the 2021 European Society of Cardiology guidelines [19]; and (3) availability of comprehensive medical records. Exclusion criteria included: (1) patients with acute decompensated HF requiring immediate intensive care upon admission; (2) terminal illnesses such as end-stage malignancies; and (3) incomplete clinical data or inability to assess frailty status.

Sample Size Estimation: For multivariate logistic regression, it is recommended that the sample size for the less frequent outcome category should be at least 10 times the number of predictor variables [20]. In this study, the dependent variable has two levels: frail and non-frail. Initially, we estimated 10 meaningful independent variables. Thus, the required sample size for the frail group would be approximately 10 × 10 = 100 cases. Given that the prevalence of frailty among HF patients is approximately 44.5%, the total sample size needed for modeling would be at least 100 ÷ 0.445 ≈ 225 cases. To ensure robustness, we included 245 cases in the modeling group. Following standard logistic regression practices, two-thirds of the total sample was allocated for model development, and one-third for validation. Based on the modeling sample size of 245, the total sample size required would be 245 ÷ (2/3) ≈ 368 cases. This study included 350 cases, with 245 cases used for model construction and 105 cases for model validation.

Frailty in HF patients was diagnosed using the Fried Frailty Criteria [21], a widely validated clinical tool. Patients were classified as frail if they met at least three of the following five conditions: (1) unintentional weight loss of more than 10 pounds in the past year; (2) weakness, measured by grip strength, adjusted for gender and body mass index (BMI); (3) slow walking speed, measured by the time to walk a set distance, adjusted for age and gender; (4) low physical activity, assessed by self-reported

weekly activity levels; (5) self-reported exhaustion, based on answers about energy levels and fatigue. Patients who met fewer than three criteria were categorized as non-frail. This objective classification allowed for a clear differentiation between frail and non-frail patients and was used to assess the relationship between frailty and other clinical risk factors in the HF population.

Data collection

Data were extracted from electronic medical records (EMRs) and included:

Demographic Information: age, sex, body mass index (BMI), smoking status.

Clinical Characteristics: comorbidities (e.g., diabetes, hypertension, chronic kidney disease), New York Heart Association (NYHA) functional classification, left ventricular ejection fraction (LVEF).

Laboratory Measurements: hemoglobin levels, N-terminal pro-B-type natriuretic peptide (NT-proBNP), serum creatinine, C-reactive protein (CRP), and albumin levels.

Frailty Assessment: frailty status was evaluated using the Fried Frailty Index [21], categorizing patients as frail or non-frail based on established criteria. The scale comprises 15 items covering three dimensions: social frailty, psychological frailty, and physical frailty. Scores range from 0 to 15, with a score of 5 or higher indicating frailty; higher scores correspond to greater frailty severity.

Outcome measurements

The primary outcome was the presence of frailty among HF patients, which served as both a grouping criterion and an outcome of interest in this study. Secondary outcomes included identifying independent risk factors associated with frailty and developing a predictive nomogram to assess frailty risk in HF patients.

Statistical methods

All statistical analyses were conducted using SPSS v26.0 (SPSS Inc.) and R software v4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were expressed as percentages, while continuous variables were expressed as mean ± standard deviation. For comparisons of categorical data between groups, chi-square or Fisher's exact tests were used as appropriate. For continuous data, if normally distributed, t-tests or analysis of variance (ANOVA) were applied; for non-normally distributed data, the Kruskal-Wallis test was used. A multivariate logistic regression model was used to analyze factors associated with frailty and identify risk factors. A nomogram was constructed based on the results of the multivariate logistic regression analysis to calculate the predicted probability of frailty for each patient. The prognostic performance of the nomogram was evaluated using the concordance index (c-index), calibration curve, decision curve analysis (DCA), and AUC. $P < 0.05$ was considered statistically significant.

Results

Comparison of clinical characteristics between the two groups

The frailty group had a significantly higher proportion of individuals aged ≥ 75 years (68.0% vs. 28.3%, $P < 0.001$) and a lower proportion aged < 75 years (32.0% vs. 71.7%, $P < 0.001$). Gender distribution showed no statistical significance ($P = 0.088$), but the frailty group had a higher proportion of females (59.1% vs. 50.5%). Marital status and living situation were significantly associated with frailty, with a lower proportion of married individuals in the frailty group (79.5% vs. 90.9%, $P = 0.022$) and a higher proportion living alone (8.2% vs. 17.2%, $P = 0.006$). Fall history and heart function class showed the most significant differences; the frailty group had a markedly higher proportion of individuals with a history of falls (50.8% vs. 18.2%, $P < 0.001$) and Class IV heart function (66.4% vs. 30.3%, $P < 0.001$). Although not statistically significant, the frailty group tended to have lower education levels (54.9% with primary education or less, $P = 0.071$), lower physical activity (16.4% vs. 26.3%, $P = 0.050$), and slightly higher smoking and alcohol cessation rates. No significant differences were observed in sleep duration ($P = 0.189$) (**Table 1**).

Comparison of biochemical indexes between the two groups

Serum albumin levels were significantly lower in the frailty group compared to the non-frailty

Table 1. Comparison of clinical characteristics between the two groups

	Frailty group (n = 135)	Non-Frailty group (n = 110)	P
Age			< 0.001
< 75	43 (31.85%)	78 (70.91%)	
≥ 75	92 (68.15%)	32 (29.09%)	
Gender			
Male	54 (40.0%)	56 (50.91%)	0.088
Female	81 (60.0%)	54 (49.09%)	
Education Level			0.071
Primary or less	74 (54.81%)	43 (39.09%)	
Middle	29 (21.48%)	33 (30.0%)	
High	20 (14.81%)	20 (18.18%)	
College	10 (7.40%)	14 (12.73%)	
Marital Status			0.022
Married	107 (79.26%)	99 (90.0%)	
Others	28 (20.74%)	11 (10.0%)	
Living Situation			0.006
With family	124 (91.85%)	90 (81.82%),	
Alone	9 (8.25%)	20 (18.18%)	
Sleep Duration			0.189
< 6 hrs	24 (17.78%)	28 (25.45%)	
6-7 hrs	63 (46.67%)	40 (36.37%)	
≥ 8 hrs	48 (35.55%)	42 (38.18%)	
Smoking History			0.144
Never	97 (71.85%)	74 (67.27%)	
Quit	22 (16.30%)	13 (11.82%)	
Current	16 (11.85%)	23 (20.91%)	
Drinking History			0.169
Never	96 (71.11%)	83 (75.45%)	
Quit	32 (23.70%)	17 (15.45%)	
Current	7 (5.19%)	10 (9.09%)	
Fall History			< 0.001
Yes	68 (50.37%)	20 (18.18%)	
No	67 (49.63%)	90 (81.82%)	
Heart Function Class			< 0.001
Class III	45 (33.33%)	77 (70.0%)	
Class IV	90 (66.67%)	33 (30.0%)	
Physical Activity			0.050
Yes	22 (16.30%)	29 (26.36%)	
No	114 (83.70%)	81 (73.64%)	
Diabetes			
Yes	66 (48.89%)	30 (27.3%)	0.001
No	69 (51.11%)	80 (72.7%)	

group (P < 0.001), highlighting the potential role of malnutrition and systemic inflammation in the development of frailty. Hemoglobin levels were also significantly lower in the frailty group (P < 0.001), suggesting that anemia may contribute to reduced physical resilience and increased vulnerability. Other biochemical markers, including calcium (Ca), creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), direct bilirubin (DBil), total bilirubin (Bil), globulin (Gib), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and B-type natriuretic peptide (BNP), showed no significant differences between the two groups (all P > 0.05). Although BNP levels were slightly elevated in the frailty group, the difference did not reach statistical significance (P = 0.141), and left ventricular ejection fraction (LVEF) showed no significant variation between the groups (P = 0.247) (**Table 2**).

Multivariate regression analysis of independent risk factors for frailty

Multivariate logistic regression analysis identified the following independent risk factors for frailty in HF patients: fall history (OR: 0.101, 95% CI: 0.043-0.242, P < 0.001), advanced age (OR: 0.877, 95% CI: 0.828-0.928, P < 0.001), female sex (OR: 2.925, 95% CI: 1.294-6.613, P = 0.010), lower hemoglobin levels (< 12 g/dL; OR: 2.547, 95% CI: 1.816-3.573, P < 0.001), and diabetes (OR: 3.202, 95% CI: 1.559-6.577, P = 0.002) (**Table 3**).

Development and validation of the nomogram

Based on the results of the multivariate logistic regression analysis, we constructed a nomogram incorporating the independent risk fac-

Table 2. Comparison of biochemical indexes between the two groups

	Frailty group (n = 135)	Non-Frailty group (n = 110)	t	p
Ca	1.61±0.06	1.60±0.06	1.049	0.295
Cr	55.28±3.85	54.47±3.51	1.690	0.092
BUN	3.96±0.57	3.86±0.59	1.415	0.158
UA	383.05±36.24	382.63±34.24	0.092	0.927
DBil	4.16±0.40	4.06±0.41	1.945	0.053
Bil	4.40±0.70	4.32±0.74	0.958	0.339
Alb	32.57±1.40	28.03±1.18	27.062	0.000
Glb	25.57±0.74	25.65±0.76	0.789	0.431
ALT	15.31±6.90	16.15±10.14	0.762	0.447
AST	23.93±6.63	24.98±6.67	1.226	0.222
BNP	2049.61±184.30	2080.06±124.66	1.479	0.141
LVEF	60.35±7.19	59.28±7.11	1.161	0.247
Hemoglobin	8.67±2.03	10.94±0.57	11.331	0.000
CHO	3.44±1.02	3.34±1.04	0.759	0.449
TG	1.21±0.57	1.18±0.58	0.370	0.712
HDL	1.34±0.32	1.27±0.33	1.697	0.091
LDL	2.10±0.42	2.13±0.44	0.641	0.522

Note: Ca: calcium, Cr: creatinine, BUN: Blood Urea Nitrogen, UA: Uric Acid, DBil: Direct Bilirubin, Bil: Bilirubin, Alb: Albumin, Glb: Globulin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, BNP: Brain Natriuretic Peptide, LVEF: Left Ventricular Ejection Fraction, CHO: cholesterol, TG: triglyceride, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

Table 3. Multivariate regression analysis of independent risk factors for frailty

Risk factor	β	SE	P	OR	95% CI
Fall history	2.289	0.443	0.000	0.101	0.043-0.242
Age	0.132	0.029	0.000	0.877	0.828-0.928
Female sex	1.073	0.416	0.010	2.925	1.294-6.613
Hemoglobin (< 12 g/dL)	0.935	0.173	0.000	2.547	1.816-3.573
Diabetes	1.164	0.367	0.002	3.202	1.559-6.577
Constant	0.834	2.453	0.734	0.434	

tors (**Figure 1**). The regression equation based on these factors is:

logit(P) = -3.147 + 0.532 × fall history + 0.267 × age + 0.039 × sex + 0.042 × hemoglobin + 0.064 × diabetes.

To use this nomogram, the corresponding position on each variable axis is identified based on the patient's characteristics. Then, a vertical line is drawn to the points axis to obtain the respective points. Finally, the points from all variables are summed, and a line is drawn from the total points axis to the predicted probability axis to estimate the likelihood of frailty.

The calibration curve (**Figure 2**) for the training set showed that the predicted and actual risks of frailty are closely aligned, indicating the model's high prediction accuracy. The area under the ROC curve (AUC) was 82.2%, which was statistically significant ($P < 0.001$) (**Figure 3**), demonstrating good discrimination of the risk prediction model. The Hosmer-Lemeshow chi-square test showed $\chi^2 = 2.332$, $P = 0.116$. In the validation group, the AUC for the frailty risk prediction model was 0.802 (95% CI: 0.701-0.897) (**Figure 4**). The Hosmer-Lemeshow goodness-of-fit test showed no statistically significant difference between the predicted and actual frailty incidence ($\chi^2 = 2.096$, $P = 0.852$). The DCA curve (**Figure 5**) showed that the nomogram provided high clinical utility.

Discussion

This study identified key independent risk factors for frailty in HF patients and developed a nomogram to predict frailty risk with high accuracy and clinical utility. Multivariate logistic regression analysis revealed that fall history, advanced age, female sex, lower hemoglobin levels, and diabetes were significant predictors of frailty, highlighting the multifactorial nature of frailty in this population. These findings emphasize the interplay between physical, metabolic, and demographic factors in frailty pathogenesis. Notably, while cardiac function classification and prior hospitalizations demonstrated a trend toward increased frailty risk, their associations did not reach statistical significance, suggesting that frailty is influenced by broader systemic and patient-specific factors rather than solely by cardiac function.

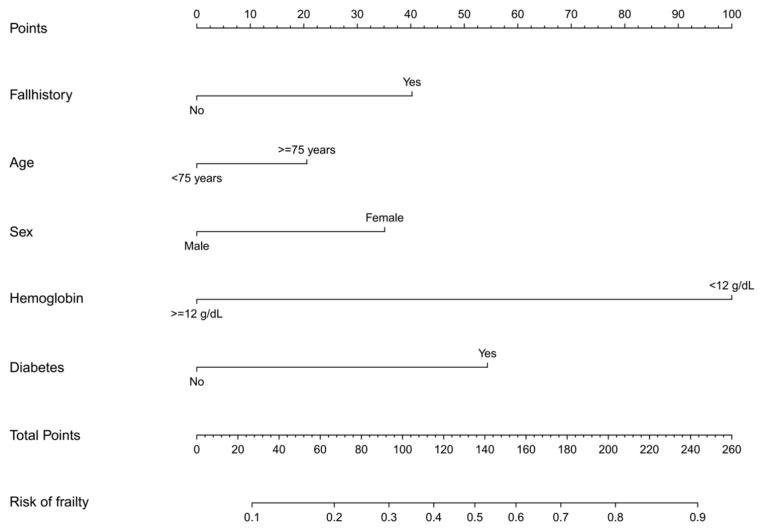

Figure 1. The nomogram for predicting the risk of frailty. To use this nomogram, the corresponding position on each variable axis were located first. Then, a line was drawn vertically to the points axis above to obtain the respective points. Finally, the points from all six variables were added up, and a line was drawn from the corresponding position on the total points axis to the predicted value axis to determine the probability of frailty.

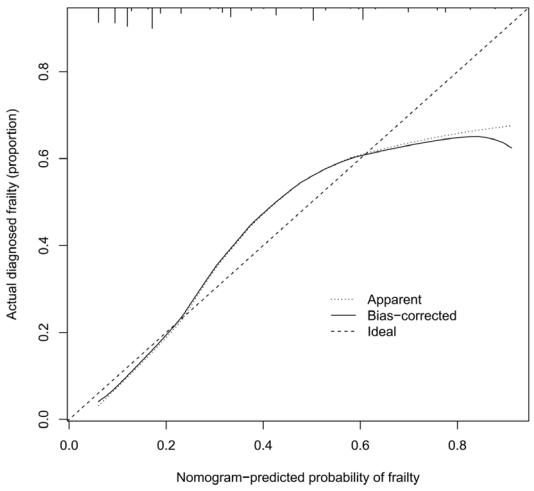

Figure 2. Calibration curve of the nomogram. The Ideal line represents a perfect model where predicted probabilities exactly match the actual probabilities. The Apparent line represents the performance of the nomogram model before applying the bootstrap re-sampling method, while the Bias-corrected line shows the model's performance after bootstrap correction.

Fall history emerged as an independent predictor of frailty, reflecting the critical role of physical instability and impaired functional capacity in frailty development [22]. Frequent falls in HF patients may indicate sarcopenia, reduced physical performance, or impaired balance, which are hallmark features of frailty [23]. Early assessment of fall risk and interventions, such as physical therapy or balance training, could help mitigate this risk and improve outcomes in frail patients. Advanced age was another strong risk factor for frailty, consistent with previous evidence that frailty is an age-related syndrome driven by physiological decline, reduced reserve, and increased vulnerability to stressors [24, 25].

Importantly, female sex was independently associated with frailty. This may reflect sex-specific differences in body composition, hormonal changes, and health behaviors [26, 27]. Women are more likely to experience reduced muscle mass and osteoporosis, which contribute to physical weakness and functional decline. Understanding these sex-specific vulnerabilities is essential for developing tailored preventive and therapeutic strategies. Lower hemoglobin levels and diabetes were also significant predictors of frailty, highlighting the role of metabolic and systemic factors in frailty development. Anemia, as indicated by reduced hemoglobin levels, is a well-established contributor to frailty, impairing oxygen delivery to tissues, reducing exercise capacity, and exacerbating fatigue [28-30]. Similarly, diabetes, through mechanisms such as chronic inflammation, microvascular complications, and insulin resistance, may accelerate frailty development [31, 32]. Addressing these metabolic factors through optimized medical management and lifestyle interventions could reduce frailty risk in HF patients.

While NYHA showed a trend toward increased frailty risk, its lack of statistical significance suggests that frailty in HF extends beyond the severity of cardiac dysfunction alone. This highlights the need to consider broader systemic and patient-specific factors when assessing frailty risk. Similarly, prior hospitalizations, often associated with functional decline and

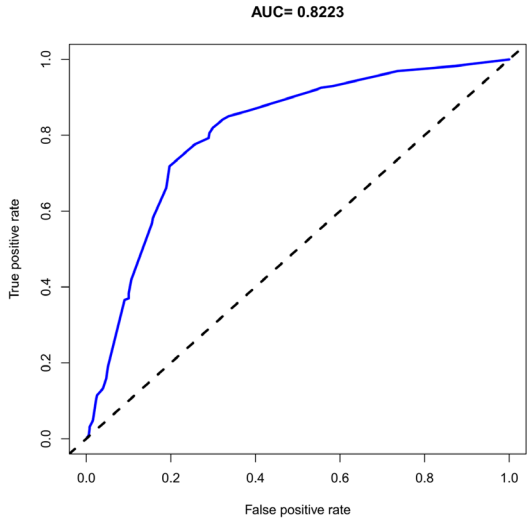

Figure 3. ROC curve analysis of the predictive performance of the nomogram in modeling group, with an AUC of 0.822 (95% CI: 0.771-0907).

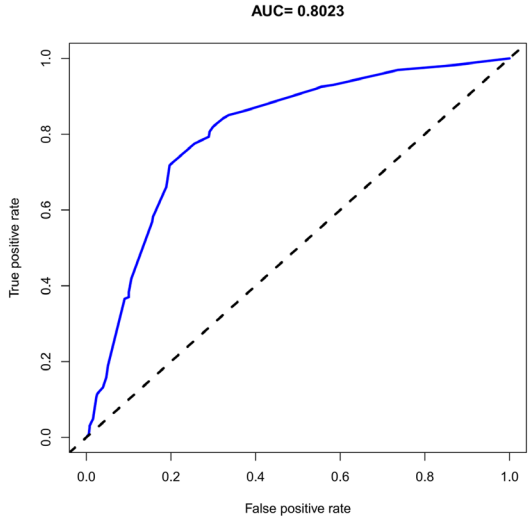

Figure 4. ROC curve analysis of the predictive performance of the nomogram in validation group, with an AUC of 0.802 (95% CI: 0.701-0897).

deconditioning, did not independently predict frailty in this study, possibly due to overlapping effects with other risk factors.

From a clinical perspective, this nomogram provides a practical tool for individualized risk assessment. By integrating readily available clinical variables - such as fall history, age, sex, hemoglobin levels, and diabetes status - the model allows clinicians to estimate a patient's likelihood of frailty with precision. DCA further

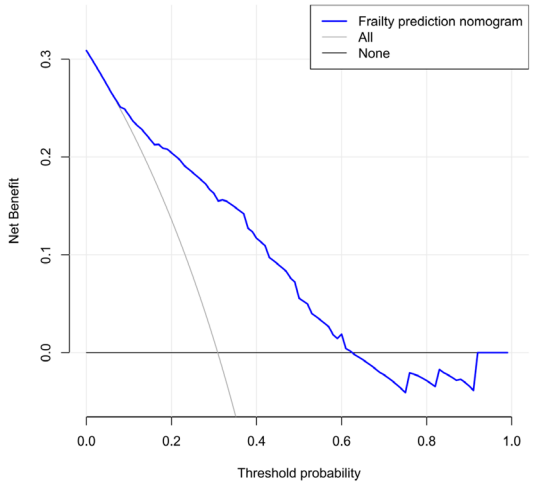

Figure 5. Decision curve analysis of the nomogram model. The decision curve indicates that when the threshold probability of frailty is between 30% and 70%, applying this nomogram would provide a net benefit.

supports the clinical utility of the model, showing a net benefit in risk prediction when the threshold probability of frailty is between 30% and 70%. This makes the model particularly valuable for early identification of high-risk patients who could benefit from targeted interventions.

While the model demonstrates strong predictive capabilities, certain limitations should be acknowledged. First, the study population was derived from a single center, which may limit the generalizability of the findings. Future research should validate the model in diverse and larger populations. Second, although the model incorporates key clinical variables, it does not account for psychosocial or environmental factors that may also contribute to frailty. Incorporating these dimensions in future studies could enhance the model's comprehensiveness.

In conclusion, the identified risk factors - including fall history, advanced age, female sex, lower hemoglobin levels, and diabetes - provide valuable insights for early risk stratification and management. The validated nomogram introduced here, with high discrimination and calibration, can guide clinicians in identifying high-risk patients and tailoring interventions to improve outcomes. Future efforts should focus on external validation and the integration of

additional risk factors to further refine this predictive tool.

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Disclosure of conflict of interest

None.

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