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Development and Validation of a Risk Prediction Model for Frailty in Patients with Chronic Diseases

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Abstract

The occurrence rate of frailty is high among patients with chronic diseases. However, the assessment of frailty among these patients is still far from being a routine part of clinical practice. The aim of this study is to develop a validated predictive model for assessing frailty risk in patients with chronic illnesses. This study recruited 543 patients with chronic diseases, and 237 were included in the development and validation of the predictive model. A total of 57 frailty related indicators were analyzed, encompassing sociodemographic variables, health status, physical measurements, nutritional assessment, physical activity levels, and blood biomarkers. There were 100 cases (42.2%) presenting frailty symptoms. Multivariate logistic regression analysis revealed that gender, age, chronic diseases, Mini Nutritional Assessment score, and Clinical Frailty Scale score were predictive factors for frailty in chronic disease patients. Utilizing these factors, a nomogram model demonstrated good consistency and accuracy. The AUC values for the predictive model and validation set were 0.946 and 0.945, respectively. Calibration curves, ROC, and DCA indicated the nomogram had favorable predictive performance. Altogether, the comprehensive nomogram developed here is a promising and convenient tool for assessing frailty risk in patients with chronic diseases, aiding clinical practitioners in screening high-risk populations.

Keywords

frailty, chronic diseases, risk factors, prediction model, nomogram

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Background

In current society, with the exacerbation of the aging population trend, the proportion of patients with chronic diseases continues to increase (Prince et al., 2015). The ongoing development of chronic illnesses poses significant challenges to the health and medical resources of patients (Vos et al., 2015). Chronic disease patients often experience a decline in physiological functions and physical frailty (Zazzara et al., 2019), which not only impacts their quality of life but also increases the risk of other adverse health events. Frailty is an adverse health condition that occurs with aging. However, with appropriate intervention and preventive measures, the process of frailty can be halted or even reversed (Hoogendijk et al., 2019).

In clinical practice, early identification and prediction of frailty among patients with chronic diseases are of significant importance (Veronese et al., 2021). However, current research on predicting frailty among patients with chronic diseases remains insufficient (Buta et al., 2016). Previous studies have confirmed that sociodemographic factors (such as age [Dent et al., 2019], gender [Mielke et al., 2022], marital status [Kojima et al., 2020], income [Wennberg et al., 2023], education [Welstead et al., 2022], and place of residence [Liu et al., 2022]); behavioral factors (such as smoking [Lv et al., 2023], drinking [Kojima et al., 2018], exercise

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[Puts et al., 2017], and diet [Ghosh et al., 2020]); and biomarkers (such as Interleukin-6 [IL-6] [Picca et al., 2022], Creatine Kinase [CK] [Landino et al., 2021], Albumin [Picca et al., 2022], and Testosterone [Ketchem et al., 2023]) are all associated with frailty. Some existing research has focused on specific groups of patients with particular chronic conditions (Huang et al., 2022; J. Li et al., 2023; Luo et al., 2022) or has only concentrated on specific physiological indicators (Liu et al., 2021), lacking a comprehensive and reliable predictive model.

This study aims to construct and validate a comprehensive frailty prediction model specifically designed for patients with chronic diseases, covering multiple dimensions of indicators and factors. By integrating various data from sociodemographic characteristics, lifestyle factors, clinical indicators, and other aspects, we endeavor to establish a comprehensive model aimed at effectively predicting the risk of frailty among patients with chronic diseases. The construction and validation of this model will not only aid in identifying potential frail patient populations but also provide crucial support for medical management and personalized treatments.

Methods

Study Design

This study collected information from chronic disease patients in a tertiary hospital in China using a cross-sectional research design. Data from July 2022 to February 2023 were selected for analysis. Our study adhered to the standards of the Helsinki Declaration.

Participants

All patients who met the following inclusion criteria were consecutively enrolled in this study: (1) aged 60 years or over; (2) Hospitalized older patients and tumor patients with medical diseases such as heart system, respiratory system, kidney system and nervous system; (3) Vital signs are stable; (4) Conscious, communication barrier-free; (5) Completely bed-ridden, assisted walking and free walking; and (6) Voluntary participation in this study, with the written and informed consent of the patients or their primary caregivers (usually a member of their family). Patients would, however, be excluded if they (1) had fractures caused by recent trauma; (2) unable to walk due to joint disease or trauma; and (3) intend to undergo surgery. The information of 543 patients was collected, and after excluding patients in the pre-frail stage and those with missing data, a total of 237 cases were finally included for analysis.

Sample Size

Using the PASS 15.0 software, the sample size was estimated. Previous studies have reported an approximate frailty incidence rate of 40% among chronic disease patients (Bu et al., 2023; Daly et al., 2022). By reviewing relevant literature, it was found that the sensitivity of frailty risk prediction models in older adults is 77%, with a specificity of 83% (S. Li et al., 2022). To achieve 90% sensitivity and specificity for the new model, and assuming a significance level (α) of 0.05 and a power ($1-\beta$) of 80%, a total sample size (N) of 162 cases is needed, with 65 individuals affected by the condition. This study included a total of 237 patients, with 162 cases used for modeling, including 71 cases of frailty.

Data Collection

Frailty. The FRAIL scale was utilized to assess frailty among those participants. There were five areas: fatigue, resistance, ambulation, illness, and weight loss (Abellan van Kan et al., 2008). Each of these five impairments would receive a score of 1 from the participants, and the FRAIL scale's overall score varied from 0 to 5 (Daly et al., 2022). Higher scores indicate greater frailty. Participants were divided into three categories: normal (0), pre-frail (1–2), and frail (3–5), based on the previous study (Morley et al., 2012). So, if a patient scored ≥ 3, which is the primary outcome defined in this study, they would be regarded as frail.

Socio-Demographic Factors

The socio-demographic factors included age, gender, education level, marital status, residential address, and occupation. Gender is defined as male or female. Education level is categorized as "elementary school or below," "junior high school," "senior high school," or "University or above." Marital status is defined as married if the participant is currently married. If the participant is currently divorced, widowed, or never married, marital status is defined as unmarried. Residential address is defined as urban or rural. Occupation is classified as "professional/technical personnel," "workers," "farmers," or "retired or other."

Behavioral Factors

Behavioral factors include drinking history, smoking history, nightly sleep duration, and total daily time spent out of bed. Alcohol and smoking history are categorized as "yes" or "no." Nightly sleep duration data were obtained from the question "How many hours did you actually sleep at night on average in the past six months?" The total daily time spent out of bed was calculated as the 24-hour period minus the average nightly sleep duration and sedentary time over the past 6 months.

Health and Exercise Assessment

According to previous studies and discussions among our experts (Blackwood & Rybicki, 2021; Hageman &

Thomas, 2002; Strini et al., 2020; Young & Smithard, 2020), the factors selected as potential predictors of frailty include chronic disease history (hypertension, cancer, heart disease, chronic lung disease, stroke, liver disease, kidney disease, etc.), medication history (antihypertensives, lipid-lowering drugs, gastrointestinal drugs, hypnotics, etc.), surgical history, height, weight, body mass index (BMI), handgrip strength, 6-meter walk time, 5 Times Sit-to-Stand (5 × STS), Barthel Index (BI), Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score, and Clinical Frailty Scale (CFS)score.

Chronic disease and medication history were obtained from patient complaints, defined as "yes" or "no." Handgrip strength was measured three times using a dynamometer, and the average was taken. The 6-meter walk test recorded the time taken by the subject from the start point to the finish line using a timer (Hageman & Thomas, 2002). 5 × STS is a commonly used assessment for lower limb strength and functional capacity (Blackwood & Rybicki, 2021).

BI is used to assess the functional status and independence in activities of daily living (Strini et al., 2020). The assessment with the Barthel Index is often conducted on a scale of 10 or 100 points, where higher scores indicate greater independence in daily living activities, while lower scores indicate a greater need for assistance and support from others (Strini et al., 2020).

ECOG-PS (Oken et al., 1982) scale ranges from 0 to 5, with each level corresponding to different physical status and functional levels. A score of 0 indicates the patient is fully active and capable, while 5 indicates the patient has passed away.

CFS is a tool used to assess the degree of frailty and functional status in patients, particularly widely utilized in older adults (Church et al., 2020). It evaluates various aspects including activities of daily living, physical activity, cognitive abilities, disease burden, social support, and environment. The CFS consists of a series of descriptive stages (typically ranging from 1 to 9), representing different levels of frailty from "very fit, no frailty" to "severely frail and highly dependent" (Young & Smithard, 2020).

Nutrition Status Assessment

Measuring the bilateral calf circumference, upper arm circumference, waist circumference, and triceps skinfold thickness of patients to indirectly assess their nutritional status, while simultaneously conducting an overall nutritional assessment using the nutritional screening tools NRS (Nutritional risk screening)-2002 and Mini Nutritional Assessment (MNA). Bilateral calf circumference, upper arm circumference, and waist circumference are measured using a flexible tape measure, and triceps skinfold thickness is measured using a sliding caliper.

NRS-2002: NRS-2002 is a nutritional screening tool recommended by the European Society for Clinical Nutrition and Metabolism guidelines (Kondrup, Allison, et al., 2003). It consists of three components: nutritional score (BMI, weight loss, and dietary intake), severity of disease score, and age score (age $>$ 70 years) (Kondrup, Rasmussen, et al., 2003). When a patient's total score is $<$3, they are classified as low or no risk, and when the total score is $\geq$3, patients are categorized as moderate or high risk.

MNA is used to assess the nutritional status of elderly patients (Guigoz, 2006), comprising 18 questions that evaluate four different aspects: anthropometric assessment BMI, weight loss, and arm and calf circumferences); general assessment (lifestyle, medication, activity level, and signs of depression or dementia); brief dietary assessment (meal intake, food and liquid intake, and autonomy of eating); and subjective assessment (self-perception of health and nutrition). The MNA scores range up to 30 points. A score of 24 indicates a well-nourished status, 17 to 23.5 signifies a risk of malnutrition, and $<$17 points indicate malnutrition (Schrader et al., 2016).

Blood Biomarkers

Including white blood cell (WBC), red blood cell (RBC), haemoglobin concentration (Hb), Platelet number (Plt), neutrophil (N), hematocrit (Hct),mean corpuscular volume (Mcv), mean corpuscular hemoglobin (Mch), mean corpuscular hemoglobin concentration (Mchc), total lymphocyte count (Lym), Alaninetransaminase (Alt), Aspartate Transaminase (Ast), glutamyltransferase (Ggt), Alkaline phosphatase (Alp), Serum total protein (Tp), serum albumin (Alb), Serum globulin (Glb), prealbumin (Pa), albumin globulin ratio (A/G), total bilirubin (Tbil), direct bilirubin (Dbil), indirect bilirubin (Idbil), creatinine (Cre), uric acid (Ua), urea (Urea), Blood potassium (K), Natremia (Na), Blood chlorine (Cl), and fasting blood-glucose (Glu).

The above data was collected using a self-designed questionnaire, which was completed by the patients and the patients' primary caregivers within 48 hr after admission. Blood biomarkers were obtained from the medical record system through blood samples collected upon patient admission. All data collection was conducted in a quiet environment by research nurses who underwent multiple training and were qualified for the task.

Statistical Methods

The normality of continuous variables was tested using a Shapiro–Wilk test. Normality data were expressed as mean ± standard deviation (*SD*) and comparisons were made by *t*-tests. Non-normal data were expressed as the median and interquartile range (IQR) and were compared using the Mann–Whitney *U* test. Categorical variables were exhibited as numbers (percentages) and were compared using the Chi-square test. All tests were two-tailed and $p < .05$ was considered statistically significant.

The study population was randomly resampled at a rate of 70% to simulate the outsourced validation cohort (Wu et al., 2021). Univariate Logistic regression analysis was performed using the training set to screen for all characteristics ($p < .1$). For further dimension reduction, the Least Absolute Shrinkage and Selection Operator (LASSO) method was used. Selected predictors were included in multivariate Logistic regression analysis. To identify the most significant predictors for inclusion in the nomogram, a dual-direction stepwise procedure based on the Akaike information criterion statistic was used.

Nomogram Development and Validation

A frailty prediction nomogram was developed using the independent predictors identified by multivariate Logistic regression analysis ($p < .05$). To quantify the discrimination performance of the nomogram, the area under the receiver operating characteristic curve (AUC) was calculated and plotted. A calibration curve analysis based on the bootstrap method was performed to assess the predictive accuracy of the nomogram by comparing the probability of frailty predicted by the nomogram with the observed actual probability of frailty. Discrimination and calibration were also checked in the validation set to test the generalizability of the model in patients. All analyses were carried out with an open-source software R (version 4.2.0, http://www.rproject.org).

Results

Participant Characteristics

Among the 543 chronic disease patients collected in this study, after excluding individuals in the pre-frail stage and those with missing data, a total of 237 cases were included in the analysis. Of these, 162 (70%) and 75 (30%) were randomly assigned to the training and validation sets, respectively. There were no significant differences between the two groups ($p > 0.05$). The frailty incidence rate in the training set was 43.8% (71/162) (Table 1), while in the validation set, it was 38.7% (29/75).

Univariate Logistic Regression Analysis

The univariate logistic regression analysis included a total of 57 variables. Among them, 32 variables (marital status, residence, education, nightly sleep duration, surgical history, BMI, waistline, Biceps circumference, triceps skinfold thickness, falls within the last 3 months, WBC, Plt, N, Mcv, Mch, Mchc, Lym, Alt, Ast, Ggt, Alp, Glb, Pa, A/G, Tbil, Dbil, Idbil, Urea, K, Na, Cl, and Glu) showed no significant association with frailty ($p > .1$). There were a total of 25 variables (grouping, gender, age, occupation, activities, chronic diseases history, medication history, height, weight, left calf circumference, hand grip strength, 6-meter walk time, $5 \times$ STS, NRS-2002, MNA score, BI, ECOG-PS score, CFS score, RBC, Hb, Hct, Tp, Alb, Cre, and Ua) significantly associated with frailty ($p < .1$) (Table 1).

LASSO and Multivariate Logistic Regression Analysis

In the LASSO regression model, this study selected non-1 coefficients as potential predictive factors for frailty (Figure 1a and b). The LASSO regression analysis chose 6 predictors for multivariate logistic regression analysis ($\lambda = 0.052$). Using the "rms" package in the "R" software, these potential factors associated with frailty were further included in a multivariate logistic regression model. The results revealed that 5 predictive factors were associated with the development of frailty in chronic disease patients: gender, age, chronic disease history, MNA score, and CFS score (Table 2). Female were 3.21 times more likely to develop frail than male (OR, 3.21; 95% CI [1.12, 9.17]; $p = .030$). The risk of frail increased with age, the older had 1.11 times frail risk compared with the younger (OR, 1.11; 95% CI [1.01, 1.21]; $p = .024$). With history of chronic diseases were 2.70 times more likely to develop frail than healthy adults (OR, 2.70; 95% CI [0.83, 8.77]; $p = .098$). Notably, the higher CFS greatly enhanced the risk of frail, with (OR, 8.02; 95% CI [3.48, 18.52]; $p < .001$). On the contrary, MAN score was an independent protective factor for frail (OR, 0.77; 95% CI [0.63, 0.93]; $p = .008$).

Predictive Model Development

Using LASSO regression analysis, the model's optimal predictive factors were selected based on a 10-fold cross-validation. A multifactorial logistic regression was employed to establish the predictive model. The predictive model comprised variables with a p-value less than .05 in the multivariate logistic regression. These variables included gender, age, chronic disease history, MNA score, and CFS score as predictive factors. A nomogram was constructed to visualize the predictive model, which could be used for quantitative prediction of frailty risk in patients with chronic diseases (Figure 2).

Predictive Model Validation

Discrimination. By examining the occurrence rate of frailty among patients with chronic diseases in the training and validation sets, we calculated the AUC value to assess the discriminative ability of the predictive model. As shown in Figure 3a and b, the predictive model generated an AUC value of 0.946 (95% CI [0.910, 0.982]), specificity of 0.846, and sensitivity of 0.958 in the training set. In the validation set, the AUC was 0.945 (95% CI [0.882, 1.000]), specificity was 0.957, and sensitivity

Table 1. Baseline Characteristics of the Training Cohort and Univariate Logistic Regression Analysis Between Characteristics and Frail.

Characteristic	Overall ($N = 162$)	Normal ($n = 91$)	Frail ($n = 71$)	p^2	OR [95% CI]	p^2
Group (%)						
Free walking	139 (85.8)	89 (97.8)	50 (70.4)	<.001		
Assisted walking	19 (11.7)	1 (1.1)	18 (25.4)		32.04 [4.15, 247.20]	<.001
Bed-ridden	4 (2.5)	1 (1.1)	3 (4.2)		5.34 [0.54, 52.71]	.150
Gender (%)						
Male	106 (65.4)	66 (72.5)	40 (56.3)	.047	2.05 [1.06, 3.95]	.03
Female	56 (34.6)	25 (27.5)	31 (43.7)			<.001
Age[a]	69.00 [64.00, 73.75]	67.00 [63.00, 71.00]	71.00 [67.00, 78.00]	<.001	1.12 [1.06, 1.19]	<.001
Occupation (%)						
Professional/technical personnel	22 (13.6)	9 (9.9)	13 (18.3)	.224		
Worker	83 (51.2)	45 (49.5)	38 (53.5)		0.58 [0.23, 1.52]	.270
Farmer	4 (2.5)	2 (2.2)	2 (2.8)		0.69 [0.08, 5.86]	.740
Retirees and others	53 (32.7)	35 (38.5)	18 (25.4)		0.36 [0.13, 0.99]	.050
Marital status (%)						
Unmarried	10 (6.2)	5 (5.5)	5 (7.0)	.938		
Married	152 (93.8)	86 (94.5)	66 (93.0)		0.77 [0.21, 2.76]	.690
Residence (%)						
City	122 (75.3)	68 (74.7)	54 (76.1)	.991		
Village	40 (24.7)	23 (25.3)	17 (23.9)		0.93 [0.45, 1.92]	.850
Education (%)						
Primary school and below	52 (32.1)	27 (29.7)	25 (35.2)	.581		
Junior middle school	55 (34.0)	35 (38.5)	20 (28.2)		0.62 [0.28, 1.34]	.220
Senior high school	39 (24.1)	21 (23.1)	18 (25.4)		0.93 [0.40, 2.13]	.860
University degree or above	16 (9.9)	8 (8.8)	8 (11.3)		1.08 [0.35, 3.31]	.890
Activities[a]	6.00 [3.00, 8.00]	6.00 [3.75, 8.50]	5.00 [2.00, 7.18]	.038	0.93 [0.86, 1.00]	.060
Sleep[a]	6.56 [5.00, 8.00]	6.56 [6.00, 8.00]	6.00 [5.00, 7.00]	.112	0.88 [0.74, 1.05]	.160
Chronic disease history (%)						
No	49 (30.2)	38 (41.8)	11 (15.5)	.001		
Yes	113 (69.8)	53 (58.2)	60 (84.5)		3.91 [1.82, 8.41]	<.001
Medication history (%)						
No	52 (32.1)	37 (40.7)	15 (21.1)	.013		
Yes	110 (67.9)	54 (59.3)	56 (78.9)		2.56 [1.26, 5.19]	.010
Surgical (%)						
No	29 (17.9)	17 (18.7)	12 (16.9)	.931		
Yes	133 (82.1)	74 (81.3)	59 (83.1)		1.13 [0.50, 2.55]	.770
Height[b]	161.47 (9.12)	163.34 (8.71)	159.08 (9.14)	.003	0.95 [0.91, 0.98]	<.001
Weight[b]	61.23 (10.76)	63.33 (10.45)	58.54 (10.63)	.005	0.96 [0.93, 0.99]	.010
BMI[b]	23.43 (3.32)	23.62 (2.55)	23.20 (4.11)	.426	0.96 [0.88, 1.06]	.420
Left calf circumference[a]	33.60 [31.00, 36.00]	34.00 [32.00, 36.00]	33.00 [30.00, 35.50]	.019	0.87 [0.79, 0.96]	.010
Waistline[a]	86.00 [79.25, 93.00]	86.00 [81.00, 94.50]	87.00 [76.00, 91.50]	.476	0.99 [0.96, 1.01]	.420
Biceps circumference[a]	27.00 [25.00, 28.88]	27.00 [25.00, 28.00]	26.70 [24.00, 29.00]	.293	0.93 [0.85, 1.03]	.150
Triceps skinfold thickness[a]	18.00 [11.62, 23.38]	18.00 [10.15, 24.00]	18.00 [14.00, 22.00]	.741	0.99 [0.96, 1.03]	.660
Hand grip strength[b]	22.17 (9.05)	25.16 (8.36)	18.33 (8.47)	<.001	0.91 [0.87, 0.95]	<.001
6-meter walking time[a]	8.00 [6.00, 9.97]	6.70 [5.72, 8.20]	9.12 [7.45, 12.14]	<.001	1.31 [1.15, 1.50]	<.001
5 × STS[a]	12.03 [9.62, 14.79]	11.00 [8.95, 13.09]	13.96 [11.59, 18.88]	<.001	1.15 [1.06, 1.23]	<.001
NRS-2002[a]	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	2.00 [1.00, 3.00]	<.001	2.33 [1.64, 3.32]	<.001
MNA score[a]	23.50 [21.00, 25.00]	24.50 [23.00, 25.50]	21.50 [17.00, 23.50]	<.001	0.69 [0.60, 0.78]	<.001
BI[a]	100.00 [90.00, 100.00]	100.00 [100.00, 100.00]	90.00 [75.00, 100.00]	<.001	0.75 [0.67, 0.84]	<.001
Fall (%)						
No	155 (95.7)	88 (96.7)	67 (94.4)	.736		
Yes	7 (4.3)	3 (3.3)	4 (5.6)		1.75 [0.38, 8.09]	.470

(continued)

Table 1. (continued)

Characteristic	Overall ($N = 162$)	Normal ($n = 91$)	Frail ($n = 71$)	p^2	OR [95% CI]	p^2
ECOG-PS[a]	1.00 [1.00, 2.00]	1.00 [1.00, 1.00]	2.00 [1.00, 3.00]	<.001	6.66 [3.66, 12.13]	<.001
CFS score[a]	3.00 [3.00, 4.00]	3.00 [2.50, 3.00]	4.00 [4.00, 5.00]	<.001	11.52 [5.25, 25.27]	<.001
WBC[a]	5.96 [5.00, 7.28]	5.69 [4.98, 6.91]	6.30 [5.08, 8.00]	.129	1.06 [0.94, 1.19]	.320
RBC[b]	4.14 (0.70)	4.27 (0.54)	3.98 (0.83)	.009	0.54 [0.33, 0.87]	.010
Hb[a]	129.00 [113.00, 139.75]	132.00 [121.00, 141.50]	124.00 [103.00, 137.00]	.01	0.99 [0.98, 1.00]	.040
Plt[a]	195.50 [158.25, 238.75]	197.00 [155.00, 237.50]	189.00 [163.50, 239.50]	.91	1.00 [1.00, 1.00]	.830
N[a]	4.19 [3.14, 6.36]	3.90 [3.10, 5.64]	4.53 [3.34, 7.23]	.13	1.01 [0.99, 1.02]	.470
Hct[a]	39.20 [35.15, 42.48]	40.50 [36.55, 42.60]	36.90 [32.85, 42.25]	.014	0.93 [0.88, 0.98]	.010
Mcv [a]	92.90 [90.60, 96.30]	93.40 [91.15, 96.95]	92.50 [90.15, 94.55]	.052	0.98 [0.94, 1.02]	.330
Mch[a]	30.60 [29.22, 31.80]	30.80 [29.60, 32.10]	30.30 [29.00, 31.35]	.028	1.01 [0.97, 1.06]	.560
Mchc[a]	326.00 [319.00, 331.75]	327.00 [321.00, 332.00]	324.00 [318.00, 330.50]	.245	1.00 [0.99, 1.01]	.970
Lym[a]	1.38 [1.11, 1.81]	1.40 [1.14, 1.90]	1.37 [1.09, 1.71]	.399	0.96 [0.91, 1.02]	.200
Alt[a]	19.25 [13.35, 28.78]	19.90 [13.30, 28.78]	19.10 [13.40, 25.35]	.424	0.99 [0.98, 1.01]	.410
Ast[a]	23.95 [18.75, 26.98]	24.80 [19.80, 28.80]	23.10 [17.80, 26.73]	.231	0.99 [0.96, 1.01]	.300
Ggt[a]	31.25 [19.35, 41.35]	28.80 [19.85, 41.08]	34.80 [19.05, 42.40]	.511	1.00 [1.00, 1.01]	.600
Alp[a]	89.15 [72.55, 107.35]	89.70 [73.50, 102.50]	84.80 [70.30, 108.45]	.341	1.00 [0.99, 1.01]	.680
Tp[a]	66.65 [62.68, 71.97]	67.70 [65.15, 73.10]	65.30 [59.80, 70.45]	.004	0.95 [0.91, 0.99]	.020
Alb[b]	37.88 (5.33)	38.93 (5.21)	36.53 (5.21)	.004	0.91 [0.86, 0.97]	.010
Glb[a]	29.45 [25.90, 32.20]	29.55 [27.05, 32.30]	28.20 [25.70, 31.65]	.111	0.95 [0.89, 1.01]	.120
Pa[a]	220.30 [201.45, 252.40]	220.30 [220.30, 249.65]	220.30 [179.65, 261.60]	.301	1.00 [0.99, 1.00]	.260
A/G[a]	1.37 [1.15, 1.50]	1.41 [1.18, 1.50]	1.31 [1.11, 1.49]	.196	0.95 [0.73, 1.23]	.700
Tbil[a]	11.30 [8.83, 15.05]	11.30 [9.00, 13.85]	11.30 [8.60, 15.50]	.728	1.02 [0.98, 1.07]	.360
Dbil[a]	2.05 [1.52, 2.48]	2.00 [1.70, 2.48]	2.10 [1.40, 2.80]	.868	1.12 [0.89, 1.42]	.340
Idbil[a]	9.65 [7.50, 11.17]	10.16 [8.10, 10.50]	9.40 [7.20, 12.50]	.751	1.01 [0.93, 1.09]	.870
Cre[a]	68.30 [57.12, 89.00]	68.30 [56.20, 88.45]	68.30 [58.10, 91.00]	.362	1.00 [1.00, 1.01]	.060
Ua[a]	329.60 [273.50, 395.45]	326.90 [258.65, 380.25]	335.20 [298.20, 423.65]	.107	1.00 [1.00, 1.01]	.050
Urea[a]	6.35 [5.00, 8.47]	5.98 [4.86, 7.40]	6.66 [5.34, 9.51]	.069	1.05 [0.99, 1.10]	.120
K[a]	3.99 [3.70, 4.33]	4.00 [3.76, 4.31]	3.95 [3.63, 4.34]	.545	0.94 [0.48, 1.84]	.860
Na[a]	140.10 [138.10, 141.57]	140.20 [138.80, 141.65]	139.90 [137.35, 141.50]	.31	0.96 [0.90, 1.03]	.260
Cl[a]	105.25 [103.00, 107.60]	105.20 [103.40, 107.00]	105.40 [102.25, 108.40]	.881	1.02 [0.96, 1.10]	.490
Glu[a]	6.06 [5.18, 6.85]	6.18 [5.36, 6.85]	5.57 [4.78, 6.69]	.044	0.98 [0.84, 1.16]	.850

Note. p^1: Comparison of baseline characteristics between the frail and non-frail groups in the training set. $p > .05$ indicates no statistically significant differences, suggesting baseline comparability. p^2: Univariate analysis results of frail and non-frail groups in the training set. $p < .05$ indicates statistically significant differences, enabling further multivariate analysis. OR = odds ratio; CI = confidence interval; BMI = body mass index; STS = sit-to-stand; NRS = nutritional risk screening; MNA = mini nutritional assessment; BI = Barthel Index; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; CFS = Clinical Frailty Scale; WBC = white blood cell; RBC = red blood cell; Hb = haemoglobin concentration; Plt = platelet number; N = neutrophil; Hct = hematocrit; Mcv = mean corpuscular volume; Mch = mean corpuscular hemoglobin; Mchc = mean corpuscular hemoglobin concentration; Lym = total lymphocyte count; Alt = alaninetransaminase; Ast = aspartate transaminase; Ggt = glutamyltransferase; Alp = alkaline phosphatase; Tp = serum total protein; Alb = serum albumin; Glb = serum globulin; Pa = prealbumin; A/G = albumin globulin ratio; Tbil = total bilirubin; Dbil = direct bilirubin; Idbil = indirect bilirubin; Cre = creatinine; Ua = uric acid; K = blood potassium; Na = natremia; Cl = blood chlorine; Glu = fasting blood-glucose.
[a]Median [IQR].
[b]Mean (*SD*).

was 0.828. These data indicate that the nomogram possesses good discriminative ability and predictive value, accurately distinguishing between frail and non-frail patients.

Calibration of the Predictive Model

The assessment of the nomogram involved utilizing a calibration plot and conducting the Hosmer–Leme show goodness-of-fit test, where a *p*-value greater than .05

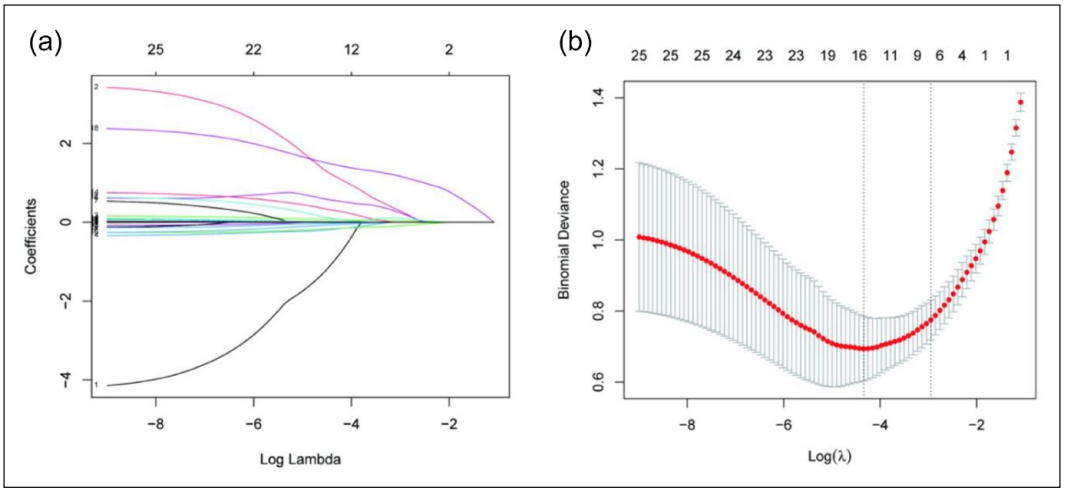

Figure 1. The LASSO regression analysis identified variables correlated with frail in patients with chronic diseases: (a) number of non-zero coefficients in the model and (b) number of variables corresponding to different λ values.

signifies an exemplary fit of the model. The test results indicated that the model exhibited excellent fit for both the training set ($\chi^2 = 12.935$, $df = 8$, $p = .1141$) and the validation set ($\chi^2 = 13.543$, $df = 8$, $p = .09449$). Calibration plots for the training and validation sets based on the multifactorial logistic regression model are shown in Figure 4a and b. The calibration curves of the nomogram demonstrated a high level of consistency between predicted frailty probability and actual probability in both the training set (Figure 4a) and the validation set (Figure 4b).

Table 2. Multivariate Logistic Regression Analysis Between the Clinical Variables and Frail.

Variables	OR [95% CI]	*p*
Gender	3.21 [1.12, 9.17]	.030
Age	1.11 [1.01, 1.21]	.024
Chronic disease history	2.70 [0.83, 8.77]	.098
MNA score	0.77 [0.63, 0.93]	.008
CFS score	8.02 [3.48, 18.52]	<.001

Evaluation of Clinical Validity

To evaluate the clinical validity of the nomogram, we conducted a DCA, calculating the net benefit at different frailty thresholds. Additionally, for comparison with the nomogram model, we plotted the decision curve of a model solely based on CFS, the results of which are shown in Figure 5a and b. From the DCA, it is evident that the predictive model exhibits significantly higher net benefit in the internal validation set compared to both extreme cases and CFS alone. This suggests that the nomogram model demonstrated superior advantages in net benefit and predictive accuracy.

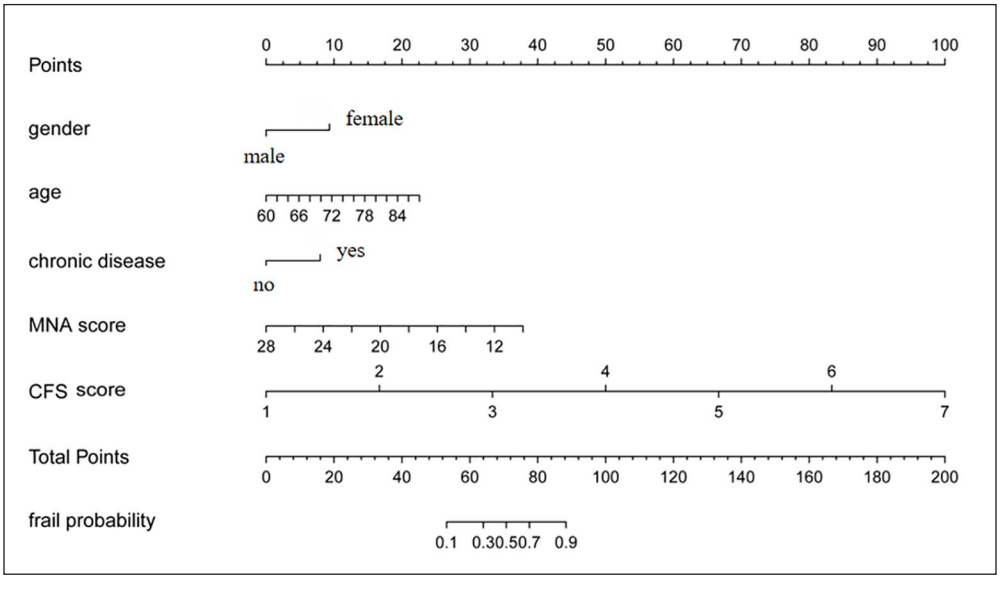

Figure 2. Nomogram for predicting frail in the elderly patients with chronic disease.
Note. The probability of frail was determined by calculating the corresponding score for each risk factor. MNA = the mini-nutritional assessment; CFS = the clinical frailty scale.

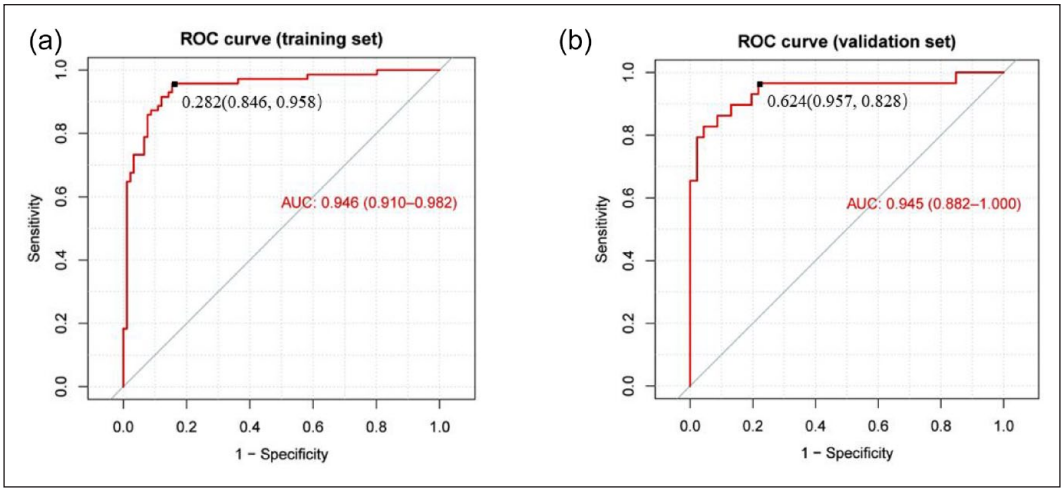

Figure 3. The ROC curves of the model in the training and validation sets: (a) training set and (b) validation set.
Note. The AUC of the model in the training set was 0.946 (95% CI [0.910, 0.982]), whereas it was 0.945 (95% CI [0.882, 1.000]) in the validation set. AUC = area under the receiver operating characteristic curve; CI = confidence interval; ROC = receiver operating characteristic.

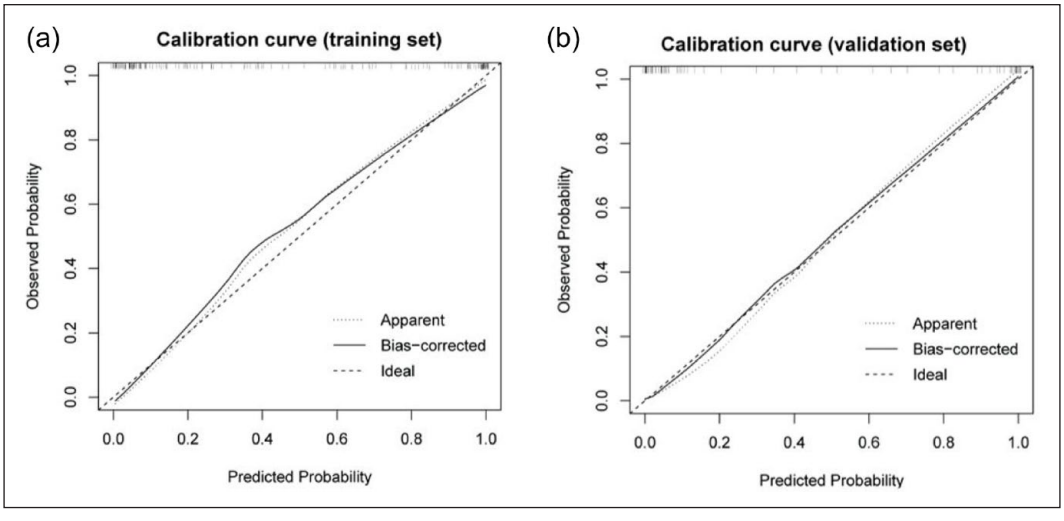

Figure 4. The calibration curves of the prediction model for frail in elderly patients with chronic disease: (a) training set and (b) validation set.
Note. The calibration curves of training set and validation set both are close to a straight line with a slope of 1.

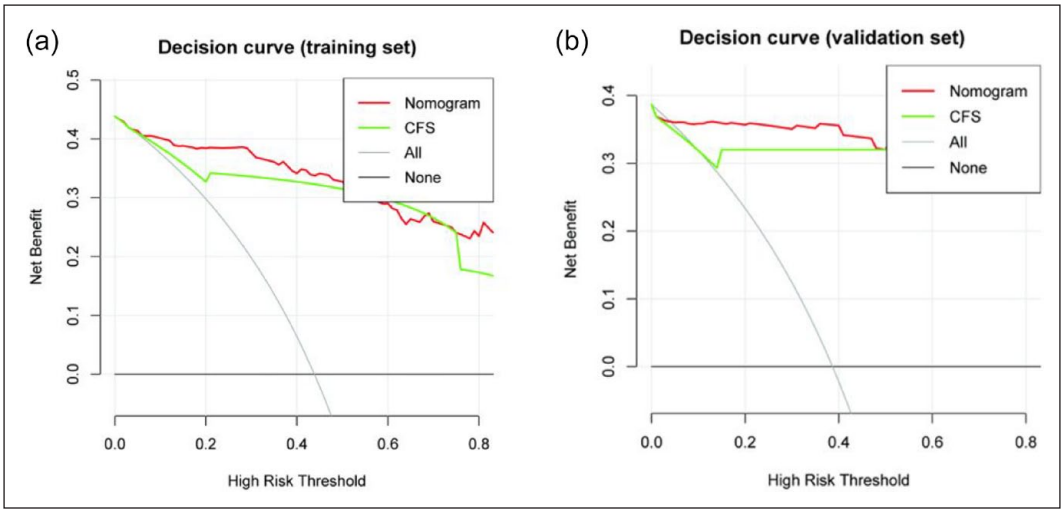

Figure 5. The DCA of the prediction model for frail in elderly patients with chronic disease: (a) training set and (b) validation set.
Note. Comparison of the newly developed model's prediction performance with that of previously published method CFS. DCA = decision curve.

Discussion

This study thoroughly considered the potential factors affecting frailty in chronic disease patients as suggested by previous research and developed a predictive model aimed at predicting the risk of frailty in elderly patients with chronic illnesses. Various validation methods indicated that this model has sufficient statistical power.

This study demonstrates that gender and age serve as predictive indicators for frailty in chronic disease patients. The results indicate that female chronic disease patients are more susceptible to developing frailty compared to male patients with chronic disease, consistent with previous research findings (Anand et al., 2020; Zhao et al., 2023). Gender differences may be related to hormonal fluctuations and biological characteristics of the immune system. Indeed, females seems to have higher inflammation evaluated by C-reactive protein (CRP) and fibrinogen than males at baseline (Gale et al., 2013). More importantly, CRP levels contribute to be frail by impacting sarcopenia and cognitive impairment, two core indicators of frailty, in females but not in males (Canon & Crimmins, 2011). In females, there is a significant association between frailty and elevated expression of inflammatory markers in muscles, whereas in males, frailty is associated with reduced PRKN expression and the size of type 2 (fast-twitch) muscle fibers (de Jong et al., 2023). What is more, with advancing age, females experience declines in estrogen levels leading to muscle weakness, fatigue and diminished functionality. For instance, estrogen can maintain skeletal muscle morphology by promoting satellite cell proliferation, as estrogen receptors are highly expressed in the muscle fibers (Geraci et al., 2021). In addition, estrogen can also protect skeletal muscle from inflammatory stress. Therefore, decreased estrogen levels in older females impair muscle homeostasis, thus leading to sarcopenia. It should be noted that decreased serum free testosterone levels and declining luteinizing hormone in elderly males can also contribute to frailty (Anand et al., 2020). Taken together, our data suggest that elderly female chronic disease patients deserve greater attention from healthcare professionals to mitigate their risk of developing frailty and to help maintain their quality of life.

Similarly, our findings reveal that age is also a risk factor for frailty development in patients (Lee et al., 2014; Trevisan et al., 2017). As individuals age, there is an accumulation of molecular and cellular damage, including inflammation, genomic instability, epigenetic alterations, etc., all of which can contribute to the occurrence of frailty (Gordon & Hubbard, 2022; Zampino et al., 2020). Interestingly, genomic instability can be induced by different approaches like age, UV radiation and oxidative stress, but they all could lead to DNA damage (Niedernhofer et al., 2018). Kravvariti et al. (2023) reported that nonfrail older adults show higher DNA damage levels by checking γH2AX levels and alkaline comet assay olive tail moment, compared to young healthy controls, supporting that age increases genomic instability. Furthermore, increased DNA damage formation is much higher than nonfrail older adults, indicating that frailty is closely associated with genomic instability. Consistently, our study finds that the older show higher frail risk compared to the younger. Recently, the critical roles of epigenetics in human diseases have been widely demonstrated (Xu et al., 2023). During the aging process, several epigenetic alterations are found, including global DNA hypomethylation with CpG island hypermethylation and reduced global heterochromatin (Kane & Sinclair, 2019). Not surprisingly, the importance of epigenetic alterations in frailty has been implied. For instance, epigenetic frailty risk score, based on the methylation of 20 CpGs (cytosine-guanine islands) loci, has been proposed by X. Li et al. (2022) and epigenetic frailty risk score has been demonstrated to be highly associated with frailty in different cohorts, indicating the importance of epigenetics in frailty. Furthermore, X. Li et al. (2022) show that these CpGs corresponding genes like Glycolytic glyceraldehyde-3-phosphate dehydrogenase (GAPDH) have been found to be likely related to the pathogeneses of Huntington's disease, one of neurodegeneration diseases contributing to frailty. Therefore, future studies are warranted to check how age-related genomic instability, epigenetic alterations influence on the progression of frailty, which contribute to better understanding molecular mechanisms of frailty and identification of treatment targets for frailty.

Our predictive model indicates an association between low MNA scores and high CFS scores with frailty. Chronic disease patients with lower MNA scores are more prone to experiencing frailty. MNA scores reflect an individual's nutritional status, where good nutritional status contributes to reducing the risk of frailty (Amasene et al., 2022). Previous studies have also shown that nutritional interventions for frail patients can improve their functional status, reduce hospital stays, and lower readmission rates (Wang et al., 2023). Our research highlights high CFS scores as a risk factor for frailty, consistent with previous study findings (Dent et al., 2016). CFS scores reflect an individual's functional capacity and frailty status (Cords et al., 2023). Patients with high CFS scores often exhibit poor functional abilities, which may further impact their dietary habits and nutritional status. Additionally, declining physical function leads to reduced activity levels, making patients more susceptible to muscle wasting and osteoporosis, further contributing to frailty (Perna et al., 2017). Therefore, incorporating MNA and CFS scores into routine assessments of chronic disease patients can assist healthcare providers in assessing the risk of frailty and devising interventions that have a positive impact on reducing frailty and other adverse health outcomes.

Furthermore, this study discovered that a history of chronic diseases stands as an independent predictive factor for frailty. In this study, the incidence rate of

chronic diseases among the frail group was significantly higher than the non-frail group. This aligns with previous research findings, indicating an association between frailty and history of chronic diseases (Bansal et al., 2023; Metze et al., 2023; Pizzarelli et al., 2023; Zhu et al., 2020). For instance, chronic conditions such as diabetes within a chronic disease context may lead to weight loss, increasing the risk of malnutrition and muscle atrophy, consequently contributing to frailty (Bu et al., 2023). The relationship between chronic diseases and frailty can be explained through shared pathological mechanisms, such as chronic inflammation and oxidative stress (Fabrício et al., 2020). These shared mechanisms enable their interaction and mutual promotion. Therefore, there should be an emphasis on the management of chronic diseases in patients. Timely therapeutic interventions for chronic disease patients are crucial to slow down the decline in physical function, aiding in the prevention of frailty.

Our model selected gender, age, medical history of chronic diseases, MNA, and CFS scores as indicators for constructing the predictive model. The predictive model, based on these five factors, demonstrated good discriminative ability, calibration, and clinical validity. The model's AUC values on the training and validation sets were 0.946 and 0.945, respectively, with specificities of 0.846 and 0.957, and sensitivities of 0.958 and 0.828. These results indicate the high accuracy and reliability of our model in predicting whether patients have frailty. Furthermore, the results from the DCA curve further confirmed the clinical utility of the model. Under different frailty thresholds, the model showed higher net benefits for patients compared to both extreme cases and situations relying solely on CFS assessment, demonstrating the model's advantage in guiding clinical decisions. Additionally, incorporating CFS assessment into routine risk factors is more convincing than solely relying on individual clinical data for assessing frailty. Therefore, this study's findings are more easily applicable and implementable. The predictive model we constructed holds significant value in effectively identifying chronic disease patients at high risk for developing frailty.

Although the results of this study are promising, it is essential to note some limitations. Firstly, the study employed a single-center design, which might limit the representativeness of the sample. Secondly, there might be other potential factors not accounted for in the model that could influence the development of frailty, such as interleukin-6, which was excluded due to severe data loss. Finally, this study only underwent internal validation and was not externally validated. Therefore, our future research endeavors will focus on further validation and optimization across multiple centers to comprehensively explore predictive and intervention methods for frailty.

Conclusion

This study established and validated a nomogram model to predict frailty in chronic disease patients. Our nomogram model incorporated gender, age, chronic disease history, MNA, and CFS scores, proved to be a useful tool for risk assessment during internal validation. The developed predictive model is valuable for screening high-risk frailty in chronic disease patients.

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Author Contributions

Yuanchun Xu and Zongsheng He wrote the main manuscript text, and Wei Cao and Nuoyi Wu prepared figures. Mingyu Cai implemented Investigation. Li Yang, Shuying Liu, and Haiyan He implemented project administration. Wangping Jia and Yaling Wang obtained Fundings. All authors reviewed the manuscript. Data curation: Li Yang and Shuying Liu.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval and Consent to Participate

The research protocol was approved by the Ethics Committee of Daping Hospital (Chongqing, China) (Approval No. 2022-212) and registered on the Chinese Clinical Trial Registry website chictr.org.cn (Registration No. ChICTR2300068076). All participants provided informed consent prior to their involvement.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

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