Asia-Pacific Journal of Oncology Nursing 10 (2023) 100307

Contents lists available at ScienceDirect

Asia-Pacific Journal of Oncology Nursing

journal homepage: www.apjon.org

Original Article

Nomogram model for predicting frailty of patients with hematologic malignancies - A cross-sectional survey

Shuangli Luo [a], Huihan Zhao [a], Xiao Gan [a], Yu He [b], Caijiao Wu [a], Yanping Ying [a,*]

[a] Department of Nursing, The First Affiliated Hospital of Guangxi Medical University, Nanning, China
[b] Department of Clinical Laboratory, The First Affiliated Hospital of Guangxi Medical University, Key Laboratory of Clinical Laboratory Medicine of Guangxi Department of Education, Nanning, China

ARTICLE INFO

Keywords:
Hematologic malignancy
Frailty
Nomogram
Prediction
Risk-stratification

ABSTRACT

Objective: This study aimed to develop and validate an assessment tool for predicting and mitigating the risk of frailty in patients diagnosed with hematologic malignancies.
Methods: A total of 342 patients with hematologic malignancies participated in this study, providing data on various demographics, disease-related information, daily activities, nutritional status, psychological well-being, frailty assessments, and laboratory indicators. The participants were randomly divided into training and validation groups at a 7:3 ratio. We employed Lasso regression analysis and cross-validation techniques to identify predictive factors. Subsequently, a nomogram prediction model was developed using multivariable logistic regression analysis. Discrimination ability, accuracy, and clinical utility were assessed through receiver operating characteristic (ROC) curves, C-index, calibration curves, and decision curve analysis (DCA).
Results: Seven predictors, namely disease duration of 6–12 months, disease duration exceeding 12 months, Charlson Comorbidity Index (CCI), prealbumin levels, hemoglobin levels, Generalized Anxiety Disorder-7 (GAD-7) scores, and Patient Health Questionnaire-9 (PHQ-9) scores, were identified as influential factors for frailty through Lasso regression analysis. The area under the ROC curve was 0.893 for the training set and 0.891 for the validation set. The Hosmer-Lemeshow goodness-of-fit test confirmed a good model fit. The C-index values for the training and validation sets were 0.889 and 0.811, respectively. The DCA curve illustrated a higher net benefit when using the nomogram prediction model within patients threshold probabilities ranging from 10% to 98%.
Conclusions: This study has successfully developed and validated an effective nomogram model for predicting frailty in patients diagnosed with hematologic malignancies. The model incorporates disease duration (6–12 months and>12 months), CCI, prealbumin and hemoglobin levels, GAD-7, and PHQ-9 scores as predictive variables.

Introduction

Hematologic malignancies are a heterogeneous group of malignancies that affect the hematopoietic system, bone marrow, and lymph nodes. This group includes leukemia, multiple myeloma, lymphoma, and other related malignancies.[1] With an aging population, the incidence of hematologic malignancies is increasing; with 13,438,500 cases in 2019, such malignancies are a significant burden on the health care system.[2,3]

Frailty is a non-specific symptom of multisystem impairment, with sarcopenia being a fundamental feature. Frailty is characterized by reduced physiological function, a diminished capacity to respond to stress, and decreased ability to return to normal after experiencing stress.[4] In the general elderly community, approximately 12% of individuals are frail.[5] However, this percentage is notably higher in patients with cancer, with a median incidence of 42%.[6] For example, newly diagnosed multiple myeloma patients had a frailty incidence of 54%,[7] while those with chronic myeloid leukemia and diffuse large B cell lymphoma had rates of 49.6% and 49%.[8,9]

Patients with hematologic malignancies are predisposed to frailty due to the combined effects of reduced immune function and adverse reactions associated with treatment. Increased frailty can result in a higher incidence of treatment-related toxicities[10], longer hospitalization periods[11], and increased mortality.[10] Additionally, frailty significantly affects the overall quality of life.[12] Frailty is reversible through early

* *Corresponding author*.
E-mail address: yanpingying0116@126.com (Y. Ying).

https://doi.org/10.1016/j.apjon.2023.100307
Received 8 July 2023; Accepted 9 September 2023

identification and intervention.[13] Screening for risk factors for frailty in patients with hematologic malignancies and developing predictive models for early detection can help identify patients at high risk for frailty, thereby promoting better outcomes and resource utilization.

Currently, frailty assessments commonly employ the Fried frailty phenotype[4] and simple frailty questionnaire (FRAIL) scale[14] to classify patients into three categories: non-frail, pre-frail, and frail. Another approach uses the frailty index[15] to distinguish between frail and non-frail groups. Although these methods evaluate overall frailty levels and aid in identifying high-risk patients, they may not fully account for individual variations and specific dimensions of frailty. The Tilburg Frailty Indicator (TFI)[16] is valuable for precise health care interventions because it considers individual differences in frailty across physical, psychological, and social domains.

We employed Gobbens' holistic[16] conceptual model of frailty to guide the selection of predictor variables. Based on this model and insights from previous studies, the selected variables included demographic and social factors (eg, gender, age, literacy),[17,18] clinical factors (eg, comorbidities, disease duration),[19,20] ability to perform activities of daily living,[21] nutritional status,[22] psychological status (anxiety, depression),[23] and laboratory indicators (eg, levels of hemoglobin and albumin).[24,25] Although some of these factors have been explored in previous studies, a comprehensive predictive model that integrates risk factors for frailty in patients with hematological malignancies is lacking.

Therefore, this study aimed to examine the prevalence of frailty, investigate the factors contributing to its development, and develop a risk prediction model for more precise risk stratification of patients with hematologic malignancies. The ultimate goal was to reduce adverse clinical outcomes and improve patients' survival and quality of life.

Methods

Study setting

This study was conducted at the Department of Hematology of a tertiary hospital in Nanning, Guangxi, China, between October 2022 and March 2023.

Study design and population

This study used a cross-sectional design. Patients with a diagnosis of hematologic malignancies were selected using convenience sampling. The inclusion criteria were as follows: (1) patients with a diagnosis of hematologic malignancies; and (2) patients between the ages of 18–90 years. The exclusion criteria were: (1) patients who couldn't communicate due to hearing impairment, language issues, unconsciousness, or mental illness; (2) patients who refused to participate in the investigation; (3) patients with significant bone marrow infiltration in the acute stages of the disease; (4) patients who had a combination of other cancers or metastatic cancers; and (5) patients whose clinical data was missing. Fig. 1 shows the flowchart of the study design.

Data collection tool and procedure

Demographic data

The following information was obtained from a demographic questionnaire: gender, age, education level, marital status, residence, insurance, body mass index (BMI), etc.

Disease-related data

Disease-related information included smoking habits, alcohol use, disease duration, treatment, and the Charlson Comorbidity Index (CCI). The CCI was used to evaluate comorbidities. It comprises 19 items, each assigned a score from 1 to 6, indicating the severity of the underlying diseases.[26]

Daily activities

The Barthel index[27] measured functional abilities, with scores ranging from 0 to 100. Higher scores indicated better self-care, whereas lower scores indicated different levels of dependence.

Nutritional status

Nutritional status was evaluated using the Nutritional Risk Screening 2002 scale.[28] This scale comprises three components and provides a score between 0 and 7. Scores of < 3 and ≥ 3 indicate no nutritional risk and nutritional risk, respectively.

Psychological status

The patients' psychological status was evaluated using the Patient Health Questionnaire-9 (PHQ-9)[29] and Generalized Anxiety Disorder-7 (GAD-7) scales.[30] The PHQ-9 is used to assess depressive symptoms and is scored as follows: 0–4 = no depression, 5–9 = mild, 10–14 = moderate, 15–19 = moderately severe, and 20–27 = extremely severe depression. Similarly, the GAD-7 is used to evaluate anxiety symptoms and is scored as follows: 0–4 = no anxiety, 5–9 = mild, 10–14 = moderate, and 15–21 = severe anxiety.

Frailty assessment

The TFI was used to assess frailty. It comprises 15 items covering the physical, psychological, and social dimensions. Scores range from 0 to 15, with a score of ≥ 5 indicating frailty. Critical scores for physical, psychological, and social frailty were 3, 2, and 2, respectively.[16]

Clinical laboratory indicators

This study collected the following clinical laboratory indicators from patients: levels of albumin (ALB), prealbumin (PA), hemoglobin (HGB), total protein, creatinine, total cholesterol, and triglycerides, as well as white blood cell count, platelet count, and lymphocyte count.

Two investigators collected the data, introduced the purpose of the study, uniformly instructed patients face-to-face to fill out the questionnaire, and checked for missing items on the spot. Patient disease- and treatment-related information and biochemical indicators were obtained from the electronic medical record system. In the case of multiple monitoring sessions during hospitalization, the tracking results closest to the survey date were selected. Patients hospitalized numerous times during the data collection period were not repeatedly surveyed.

Sample size

There is no gold standard method for estimating sample size requirements for risk prediction models. A commonly used rule of thumb in predictive modeling is to have a minimum of 10 events for each predictor variable parameter (β term) included in the regression equation.[31] For this study, which included ten variables, the sample size corresponded to at least 100 positive events. Fortunately, the original dataset met this requirement.

Data analysis

R software (version 4.3.0) was used for statistical analysis. The normality of continuous variables was assessed with the Kolmogorov–Smirnov test. Normally distributed variables were presented as mean ± standard deviation and compared between frail and non-frail groups using a *t*-test. Non-normally distributed variables were summarized using medians and interquartile ranges (P_{25}, P_{75}) and compared with non-parametric tests. The chi-square test was used to compare rates or component ratios, and statistical significance was defined as $P < 0.05$.

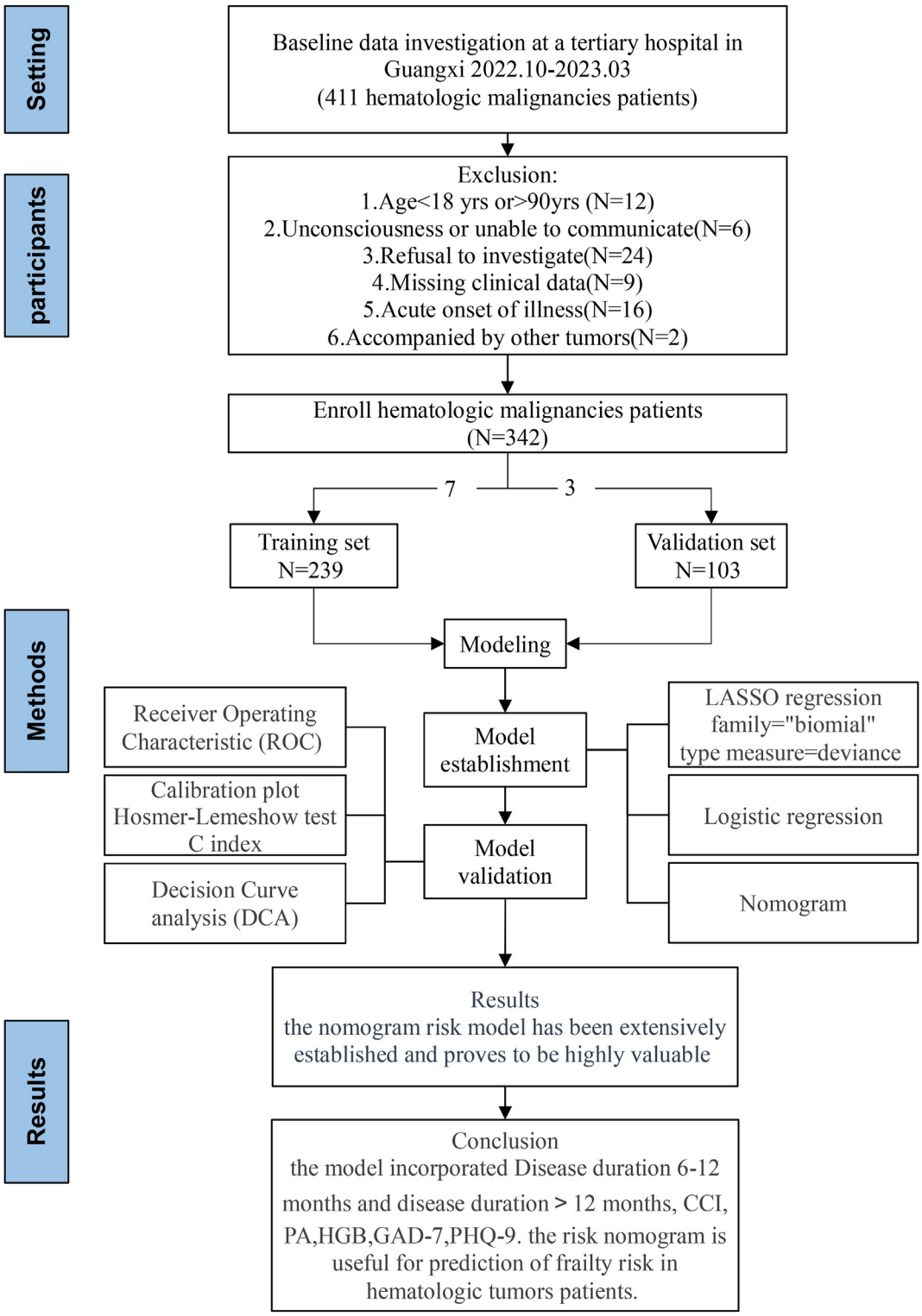

Fig. 1. Study design flow chart.

Constructing a predictive model

The original dataset was divided into training ($n = 239$) and validation ($n = 103$) sets in a 7:3 ratio using the "caret" package in R. We applied least absolute shrinkage and selection operator (Lasso) regression with the "glmnet" package to filter the variables, effectively reducing data dimensionality by compressing irrelevant variable coefficients to zero through a penalty term. This approach ensures model simplicity and stability.[32] A "binomial" family was used to model frailty (0/1). The penalty term, lambda values, were selected using 20-fold cross-validation, with lambda. lse showing superior performance when using the fewest independent variables. Next, we employed the "rms" package to conduct logistic regression, using the selected features from the Lasso regression model to build the prediction model. The model included odds ratios (OR), 95% confidence intervals (CI), and p-values. Statistically significant predictors from both groups were used to establish the frailty risk prediction model, and a nomogram prediction model was developed using the "rms" package.

Internal validation of the nomogram prediction model

To assess the predictive performance of the constructed model, we generated the receiver operating characteristic (ROC) curve using the "pROC" package and evaluated the area under the curve to measure the nomogram's ability to differentiate between true positive and false positive cases. Calibration was evaluated using calibration curves and the Hosmer–Lemeshow (HL) test with the "rms" package. The "survival" package was used for C-index analysis. Clinical utility was assessed through decision curve analysis (DCA) using the "rmda" package, helping determine the practical applicability of the nomogram.

Results

Clinical characteristics

The average age of the 342 patients with hematologic malignancies (181 males and 161 females) was 50.02 ± 15.07 years. Among them, 170 had leukemia, 108 had lymphoma, and 64 had multiple myeloma. 213 (62.3%) patients were classified as frail, and 129 (37.7%) were classified as non-frail. The total TFI score with a mean score of 5.66 ± 2.90. The physical, psychological, and social frailty scores were 2.77 ± 1.80, 1.99 ± 1.20, and 0.90 ± 0.51, respectively.

Compared to the non-frail group, the frail group included a higher proportion of individuals who lived in rural areas, were older, and had longer illness durations, more comorbidities, and poorer self-care abilities. Additionally, the frail group had lower BMI, ALB, PA, and HGB values and higher GAD-7 and PHQ-9 scores. Furthermore, the frail group scored higher on the physical, psychological, and social frailty subscales. These differences were all statistically significant ($P < 0.05$). In the training and test groups, the baseline characteristics were similar, with no statistically significant differences observed between the two groups except for the CCI and social frailty scores (Table 1).

Screening for predictors of frailty

Using frailty as the dependent variable and other factors as independent variables, the optimal penalty term lambda was determined using 20-fold cross-validation of the Lasso regression. The model performance was optimal when the lambda was set at 0.043. Nine potential influencing factors were identified at this lambda value: age, disease duration, CCI, Barthel index (BI), ALB, PA, HGB, GAD-7, and PHQ-9 scores (Fig. 2). The selected variables were then included in a multivariate regression analysis using the training set. The results indicated that disease durations of 6–12 months and > 12 months and CCI, PA, HGB, GAD-7, and PHQ-9 scores were influential factors for frailty in patients with hematologic malignancies (Table 2).

Constructing predictive models

The variables identified using multifactor logistic regression analysis with frailty as the outcome indicator were incorporated into the nomogram prediction model (Fig. 3a). The scale at the top of the nomogram represents the individual scores for each risk factor. The total score obtained by adding all risk factor scores corresponds to the patient's frailty rate. A higher total score indicates a greater likelihood of frailty. For instance, using information from a nomogram of a patient with a PHQ-9 score of 11, a GAD-7 score of 5, an HGB level of 97.2 g/L, a PA of 219.5 g/L, a CCI of 6, and a disease duration exceeding 12 months (Fig. 3b), we determined that the corresponding probability of frailty for this patient was 0.982.

Evaluation of the predictive model

The nomogram's predictive performance was robust, with an area under the curve (AUC) of 0.893 (95% CI: 0.852–0.933) for training and 0.891 (95% CI: 0.830–0.952) for validation (Fig. 4). The predicted results align with the observed effects on the calibration curve (Fig. 5). The HL goodness-of-fit test indicated good agreement between the model and the observed data for the training ($P = 0.084$) and validation sets ($P = 0.803$). The C-index for the training and validation sets was 0.889 (95% CI: 0.848–0.930) and 0.811 (95% CI: 0.751–0.871), respectively, demonstrating high discriminatory ability. The DCA curves demonstrated that using the nomogram for predicting the risk of frailty in patients with hematologic malignancies resulted in a higher net benefit when the threshold probabilities were 10%–98%. The consistent finding of higher net use in the validation group further supports the validity of the model for predicting frailty risk (Fig. 6).

Discussion

The incidence of frailty in patients with hematologic malignancies

The TFI, the self-assessment tool used in this study, showed that the incidence of frailty in patients with hematologic malignancies was 62.3%, which was significantly higher than the 45% incidence in lung cancer patients (from a multiple frailty assessment tool meta-analysis)[33] and notably higher than the 40.5% incidence observed in gastrointestinal tumor patients (using the comprehensive geriatric assessment tool).[34] This may be attributable to the use of different measurement tools. Conversely, the lower incidence of frailty compared to spinal metastasis patients (69%) can be explained by differences in the study population.[35] Patients with metastatic tumors generally have a higher incidence of frailty owing to the severity and duration of their illness.

Hematologic malignancies weaken the immune and blood cell systems, leading to fatigue that contributes to frailty. Chemotherapy and radiotherapy can also disrupt normal cell functions, compromising the immune and metabolic systems and increasing frailty risk.[36] Although the study did not find statistically significant differences in the incidence of frailty among patients with leukemia, lymphoma, and multiple myeloma ($P > 0.05$), it did reveal that the incidence of frailty was highest among patients with leukemia (53.1%), followed by lymphoma (29.6%) and multiple myeloma (17.4%). Leukemia is characterized by rapid progression and pronounced symptoms, which lead to more potent immunosuppressive treatments, and an increased risk of infection and frailty.[37] In contrast, lymphoma and multiple myeloma progress more slowly, allowing patients more time to adapt and reducing frailty risk.[38]

Therefore, it is crucial to screen for factors that contribute to frailty. Timely and effective interventions should be implemented for patients at high risk of frailty.

The impact of disease duration on frailty in hematologic malignancies

The findings of this study revealed a notable correlation between illness duration and an increased risk of frailty among patients with hematologic malignancies.

Similarly, a Chinese study on the factors influencing frailty in patients with lung cancer indicated that the longer the disease duration, the more severe the degree of frailty.[39] A study on patients undergoing chemotherapy for lung cancer also found that as the disease duration increased, the number of treatments also increased, resulting in a higher degree of frailty.[40] As a class of malignant tumors with rapid proliferation and spreading ability, hematologic malignancies spread further and invade other tissues or organs over time, leading to increased bone marrow destruction and decreased hematopoietic capacity. Additionally, prolonged medication treatment exerts a cumulative impact on the patient's physical condition, contributing to an increased degree of frailty. Health care professionals are advised to prioritize the screening and assessment of frailty in patients with longer disease durations. The implementation

Table 1
Characteristics of the 342 patients with hematologic malignancies enrolled in the study according to presence/absence of frailty and randomization to training set and validation set ($N = 342$).

Variables	Total ($N = 342$)	Non-frail ($n = 129$)	Frail ($n = 213$)	Statistic value	Significant	Train ($n = 239$)	Test ($n = 103$)	Statistic value	Significant
[a] Gender									
Male	181 (52.9)	70 (54.3)	111 (52.1)	$\chi^2 = 0.149$	0.699	119 (49.8)	62 (60.2)	$\chi^2 = 3.127$	0.077
Female	161 (47.1)	59 (45.7)	102 (47.9)			120 (50.2)	41 (39.8)		
[b] Age (years)	53 (39, 61)	50 (36, 57)	55 (41, 63)	$Z = -3.762$	< 0.001**	52 (38, 60)	53 (40, 62)	$Z = -0.919$	0.358
[a] Education									
Primary or below	58 (17.0)	17 (13.2)	41 (19.2)	$\chi^2 = 7.524$	0.057	38 (15.9)	20 (19.4)	$\chi^2 = 1.312$	0.726
Secondary	106 (31.0)	41 (31.8)	65 (30.5)			72 (30.1)	34 (33.0)		
Senior	89 (26.0)	28 (21.7)	61 (28.6)			65 (27.2)	24 (23.3)		
College	89 (26.0)	43 (33.3)	46 (21.6)			64 (26.8)	25 (24.3)		
[a] Marital status									
Unmarried/Single	57 (16.7)	20 (15.5)	37 (17.4)	$\chi^2 = 0.364$	0.833	42 (17.6)	15 (14.6)	$\chi^2 = 0.515$	0.773
Married	270 (78.9)	104 (80.6)	166 (77.9)			187 (78.2)	83 (80.6)		
Divorced/Widowed	15 (4.4)	5 (3.9)	10 (4.7)			10 (4.2)	5 (4.9)		
[a] Residence									
Rural	199 (58.2)	65 (50.4)	134 (62.9)	$\chi^2 = 5.179$	0.023*	136 (56.9)	63 (61.2)	$\chi^2 = 0.537$	0.464
Urban	143 (41.8)	64 (49.6)	79 (37.1)			103 (43.1)	40 (38.8)		
[a] Insurance									
Medical insurance	313 (91.5)	119 (92.2)	194 (91.1)	$\chi^2 = 0.141$	0.707	222 (92.9)	91 (88.3)	$\chi^2 = 1.910$	0.167
Self-pay	29 (8.5)	10 (7.8)	19 (8.9)			17 (7.1)	12 (11.7)		
[a] Smoking									
No	280 (81.9)	100 (77.5)	180 (84.5)	$\chi^2 = 2.643$	0.104	197 (82.4)	83 (80.6)	$\chi^2 = 0.165$	0.685
Yes	62 (18.1)	29 (22.5)	33 (15.5)			42 (17.6)	20 (19.4)		
[a] Drinking									
No	263 (76.9)	93 (72.1)	170 (79.8)	$\chi^2 = 2.695$	0.101	181 (75.7)	82 (79.6)	$\chi^2 = 0.610$	0.435
Yes	79 (23.1)	36 (27.9)	43 (20.2)			58 (24.3)	21 (20.4)		
[a] Disease									
Leukemia	170 (49.7)	57 (44.2)	113 (53.1)	$\chi^2 = 2.531$	0.282	128 (53.6)	42 (40.8)	$\chi^2 = 5.043$	0.080
Lymphoma	108 (31.6)	45 (34.9)	63 (29.6)			68 (28.5)	40 (38.8)		
Multiple myeloma	64 (18.7)	27 (20.9)	37 (17.4)			43 (18.0)	21 (20.4)		
[a] Disease duration									
< 6 months	139 (40.6)	86 (66.7)	53 (24.9)	$\chi^2 = 61.415$	< 0.001**	97 (40.6)	42 (40.8)	$\chi^2 = 0.611$	0.737
6–12 months	98 (28.7)	27 (20.9)	71 (33.3)			66 (27.6)	32 (31.1)		
> 12 months	105 (30.7)	16 (12.4)	89 (41.8)			76 (31.8)	29 (28.2)		
[a] Treatment									
Chemotherapy	253 (74.0)	95 (73.6)	158 (74.2)	$\chi^2 = 2.457$	0.293	171 (71.5)	82 (79.6)	$\chi^2 = 5.606$	0.061
Transplantation	43 (12.6)	20 (15.5)	23 (10.8)			29 (12.1)	14 (13.6)		
Other	46 (13.5)	14 (10.9)	32 (15.0)			39 (16.3)	7 (6.8)		
[b] Charlson comorbidity index	3 (2, 4)	3 (2, 3)	3 (3, 4)	$Z = -4.887$	< 0.001**	3 (2, 4)	3 (2, 4)	$Z = -2.078$	0.038*
[b] Barthel index	95 (90, 100)	95 (90, 100)	95 (90, 95)	$Z = -4.265$	< 0.001**	95 (90, 95)	95 (90, 100)	$Z = -1.193$	0.233
[c] BMI (kg/m^2)	22.29 ± 3.37	22.81 ± 3.36	21.97 ± 3.35	$t = 2.249$	0.025*	22.29 ± 3.30	22.28 ± 3.55	$t = 0.043$	0.966
[a] Nutrition risk									
No	207 (60.5)	85 (65.9)	122 (57.3)	$\chi^2 = 2.495$	0.114	151 (63.2)	56 (54.4)	$\chi^2 = 2.339$	0.126
Yes	135 (39.5)	44 (34.1)	91 (42.7)			88 (36.8)	47 (45.6)		
[b] Albumin (g/L)	39.80 (35.70, 42.83)	41.50 (39.35, 43.65)	37.90 (34.75, 41.60)	$Z = -5.609$	< 0.001**	39.60 (35.70, 42.90)	40.10 (35.90, 42.20)	$Z = -0.164$	0.870
[b] Prealbumin (g/L)	225.65 (181.23, 267.70)	246.80 (200.95, 293.95)	218.80 (170.85, 245.20)	$Z = -4.564$	< 0.001**	228.90 (181.90, 268.00)	221.90 (177.40, 261.20)	$Z = -0.213$	0.831
[b] Hemoglobin (g/L)	103.00 (85.48, 115.53)	109.50 (89.90, 122.60)	100.10 (83.90, 110.20)	$Z = -4.414$	< 0.001**	102.90 (84.20, 114.70)	105.80 (88.30, 116.20)	$Z = -1.263$	0.207
[b] Total protein (g/L)	69.30 (64.10, 75.03)	69.10 (63.75, 73.50)	69.70 (64.10, 75.95)	$Z = -1.884$	0.060	69.60 (64.10, 75.30)	69.10 (64.10, 74.80)	$Z = -0.451$	0.652
[b] Creatinine (μmol/L)	63.00 (50.00, 80.00)	62.00 (50.00, 73.00)	64.00 (50.50, 84.50)	$Z = -1.467$	0.142	63.00 (49.00, 80.00)	63.00 (52.00, 82.00)	$Z = -0.184$	0.854
[b]Total cholesterol (mmol/L)	4.43 (3.56, 5.30)	4.42 (3.77, 5.27)	4.44 (3.49, 5.31)	$Z = -0.980$	0.327	4.30 (3.52, 5.19)	4.69 (3.81, 5.40)	$Z = -1.465$	0.143
[b] Triglycerides (mmol/L)	1.69 (1.13, 2.57)	1.68 (1.06, 2.48)	1.70 (1.17, 2.84)	$Z = -1.284$	0.199	1.65 (1.13, 2.68)	1.76 (1.17, 2.50)	$Z = -0.339$	0.734
[b] White blood cell count (10^9/L)	4.86 (3.18, 7.40)	5.14 (3.46, 8.71)	4.74 (3.08, 6.74)	$Z = -1.644$	0.100	4.87 (3.10, 7.39)	4.79 (3.30, 8.03)	$Z = -0.306$	0.760
[b] Platelet count (10^9/L)	200.15 (103.33, 278.90)	210.90 (95.20, 278.35)	190.70 (115.25, 279.30)	$Z = -0.083$	0.934	190.60 (88.70, 280.50)	208.90 (135.00, 275.50)	$Z = -1.414$	0.157
[b] Lymphocyte count (%)	1.09 (0.72, 1.69)	1.04 (0.66, 1.39)	1.16 (0.75, 1.97)	$Z = -1.621$	0.105	1.09 (0.75, 1.69)	1.08 (0.67, 1.70)	$Z = -0.417$	0.676

(*continued on next page*)

Table 1 (*continued*)

Variables	Total (N = 342)	Non-frail (n = 129)	Frail (n = 213)	Statistic value	Significant	Train (n = 239)	Test (n = 103)	Statistic value	Significant
[b]GAD-7 score	3 (2, 6)	2 (1, 3)	5 (3, 7.5)	$Z = -9.956$	< 0.001**	4 (2, 6)	3 (1, 6)	$Z = -0.977$	0.329
[b]PHQ-9 score	5 (2, 9)	2 (1, 4)	7 (3, 11)	$Z = -9.725$	< 0.001**	5 (2, 9)	3 (1, 9)	$Z = -1.950$	0.051
[b] Physical frailty score	2.5 (1, 4)	1 (1, 2)	3 (3, 5)	$Z = -13.470$	< 0.001**	3 (1, 4)	2 (1, 4)	$Z = -0.639$	0.523
[b] Psychological frailty score	2 (1, 3)	1 (0, 2)	3 (2, 3)	$Z = -12.843$	< 0.001**	2 (1, 3)	2 (1, 3)	$Z = -0.555$	0.579
[b] Social frailty score	1 (1, 1)	1 (0, 1)	1 (1, 1)	$Z = -8.740$	< 0.001**	1 (1, 1)	1 (1, 1)	$Z = -2.823$	0.005**

*$P \leq 0.05$, **$P < 0.01$. BMI, body mass index; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9.

[a] Representation of this variable is described in the form of ***n*** **(%)**, and the analysis of variance uses the chi-square test.

[b] Indicates variables described in Median (P_{25}, P_{75}) form and non-parametric test for analysis of variance.

[c] Indicates variables described in Mean ± standard deviation form and independent samples t-test for analysis of variance.

of proactive preventive measures can delay the onset of frailty and enhance the overall quality of life of high-risk individuals.

The impact of comorbidities on frailty in hematologic malignancies

This study showed that the higher the CCI score, the higher the risk of frailty, and that the coexistence of multiple conditions was a risk factor for frailty. A frailty survey of cancer survivors showed that comorbidities were associated with frailty,[23] while a study exploring the factors affecting frailty in patients with lung cancer found that comorbid chronic diseases had an important influence on the occurrence of frailty,[39] which is consistent with the results of the present study. Disease and frailty share common pathological mechanisms including chronic inflammation, oxidative stress, and immune dysregulation.[41] Patients with hematologic malignancies experience a significant decline in body function and physiological reserves owing to chronic depletion over an extended period. When patients have multiple diseases, the shortage of body resources intensifies, and the interaction and influence between different conditions further weakens the patients' immunity, making them more prone to frailty. Frailty can exacerbate the progression and severity of an underlying physical disease, establishing a reciprocal cause-and-effect relationship in which illness and frailty mutually enhance each other, giving rise to a self-perpetuating cycle. In addition, patients with multimorbidity, who need to take multiple medications simultaneously, may experience drug interactions, side effects, and an increased burden on the body.[42] Given the diversity and complexity of hematologic malignancies, a multidisciplinary treatment model including medicine, nursing, and pharmacy, should be developed. Regularly checking patients' multiple medication status, closely monitoring their condition, actively treating and managing the presenting disease, emphasizing individualized medication use, and reducing unnecessary oral medications are essential for slowing frailty.

The impact of PA and HGB on frailty in hematologic malignancies

This study revealed a positive association between decreased PA and HGB levels and the risk of frailty in patients with hematologic malignancies. These findings are consistent with previous research indicating that HGB levels are significant in determining frailty risk in patients with hematologic malignancies.[43] Similar associations were observed in studies involving patients with gastric cancer[44] and colorectal cancer.[45]

PA is a widely used biochemical measure of the nutritional status of the body, and its decreased levels may indicate metabolic disorders or inadequate dietary intake.[46] Patients with hematologic malignancies frequently experience digestive problems such as loss of appetite, nausea, and vomiting, owing to the disease itself and the adverse effects of treatment, leading to inadequate nutritional intake.[47] These metabolic responses trigger muscle atrophy, weight loss, and increased susceptibility to infection. Prolonged inflammation in patients with hematologic malignancies affects the liver's ability to synthesize albumin, leading to accelerated albumin loss and a shortened half-life. Low albumin levels result in reduced immune function, elevated levels of inflammatory mediators, and an increased susceptibility to bacterial and opportunistic infections.[48] Collectively, these factors increase the risk of frailty in patients with hematologic malignancies.[49,50]

HGB plays a crucial role as an essential parameter in a complete blood count to assess the degree of anemia in patients. A longitudinal study on aging identified HGB levels as a risk factor for patient frailty.[51] Other investigations have also provided evidence of a significant association between anemia, hemoglobin concentration, and frailty.[52,53] From a medical perspective, hematologic malignancy patients often experience chronic inflammation and impaired blood cell production in the bone marrow. This process leads to lower hemoglobin levels and shorter red blood cell lifespans.[54,55] Low hemoglobin, responsible for carrying oxygen in the body, reduces oxygen supply to tissues and organs. This leads to weakened muscles, increased fatigue, and worsened frailty.

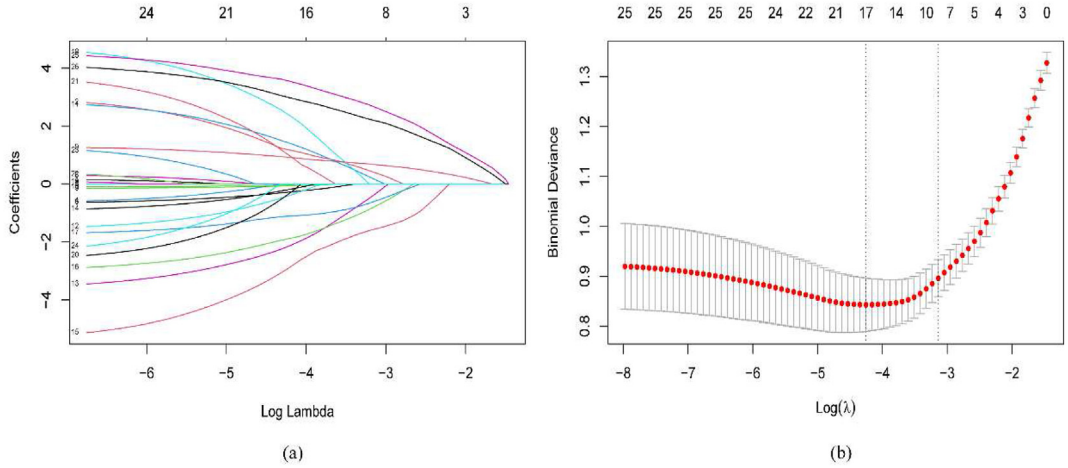

Fig. 2. Variable selection using the Lasso logistic regression model. (a) coefficient curves for 26 variable, (b) selection of the most appropriate variables by Lasso regression. Lasso, least absolute shrinkage and selection operator.

Table 2
Logistic regression analysis-frailty risk predictors in hematologic malignancies.

Variables	Estimate	SE	*Z* value	Significant	Odds ratio (95% CI)
Age	0.020	0.012	1.640	0.100	1.021 (0.996, 1.046)
Disease duration 6–12 months	1.604	0.464	3.460	0.001**	4.974 (2.003, 12.351)
Disease duration > 12 months	2.040	0.472	4.320	< 0.001**	7.691 (3.050, 19.395)
Charlson comorbidity index	0.399	0.165	2.420	0.015*	1.490 (1.079, 2.058)
Barthel index	−0.027	0.019	−1.390	0.166	0.974 (0.938, 1.011)
Albumin (g/L)	−0.054	0.042	−1.280	0.201	0.947 (0.872, 1.029)
Prealbumin (g/L)	−0.006	0.003	−2.440	0.015*	0.994 (0.989, 0.999)
Hemoglobin (g/L)	−0.022	0.011	−2.090	0.036*	0.987 (0.958, 0.999)
GAD-7 score	0.199	0.099	2.020	0.043*	1.221 (1.006, 1.481)
PHQ-9 score	0.188	0.066	2.860	0.004**	1.207 (1.061, 1.373)

*$P \leq 0.05$, **$P < 0.01$. GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9.

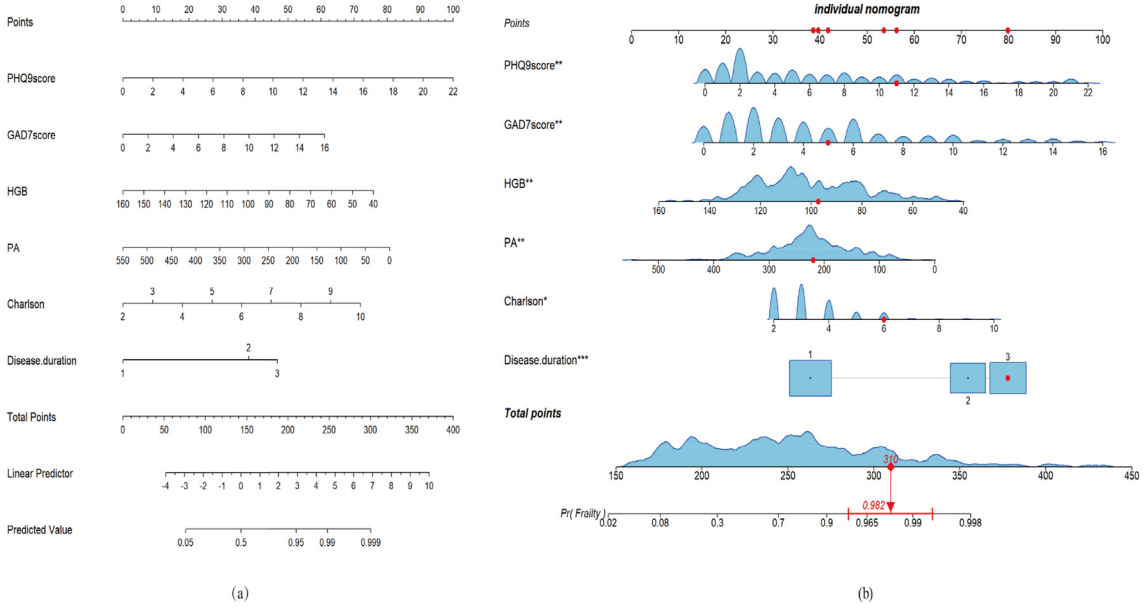

Fig. 3. (a) Nomogram predicting frailty in patients with hematological tumors. (b) individual dynamic nomogram as an example. In (a), the values of the variable "Disease duration" are coded as follows: 1 represents disease duration < 6 months, 2 represents disease duration 6–12 months, and 3 represents disease duration > 12 months. Charlson, Charlson Comorbidity Index; PA, prealbumin; HGB, hemoglobin; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9. The significance of the asterisks next to each variable in section b represents the importance of all risk factor.

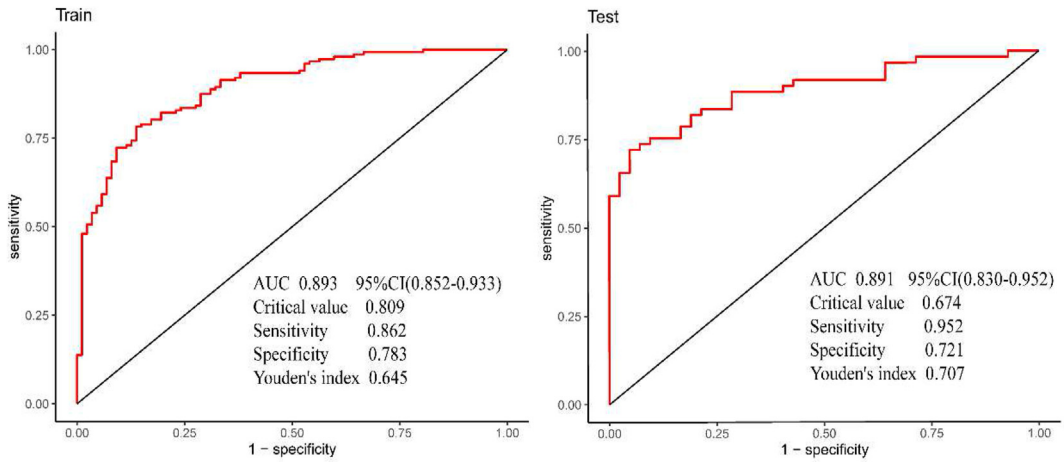

Fig. 4. Receiver operating characteristic curve (ROC) of the predictive nomogram for the risk of frailty in hematological tumor patients. (a) training set ROC curve. (b) validation set ROC curve. AUC, area under the curve.

Frailty is reversible, and many studies have highlighted the effectiveness of nutritional interventions in slowing the progression of frailty and reducing adverse outcomes in older adults.[56–58] Dynamic monitoring of relevant index levels in a clinical setting enables the early detection of changes in the patient's physiological function, making it a sensitive tool for identifying signs of frailty. Health care professionals should closely monitor their nutrition-related biochemical indicators and develop suitable dietary plans to improve their overall nutritional status. However, this group lacks standardized dietary guidelines owing to the different underlying conditions and nutritional statuses of patients with frailty and

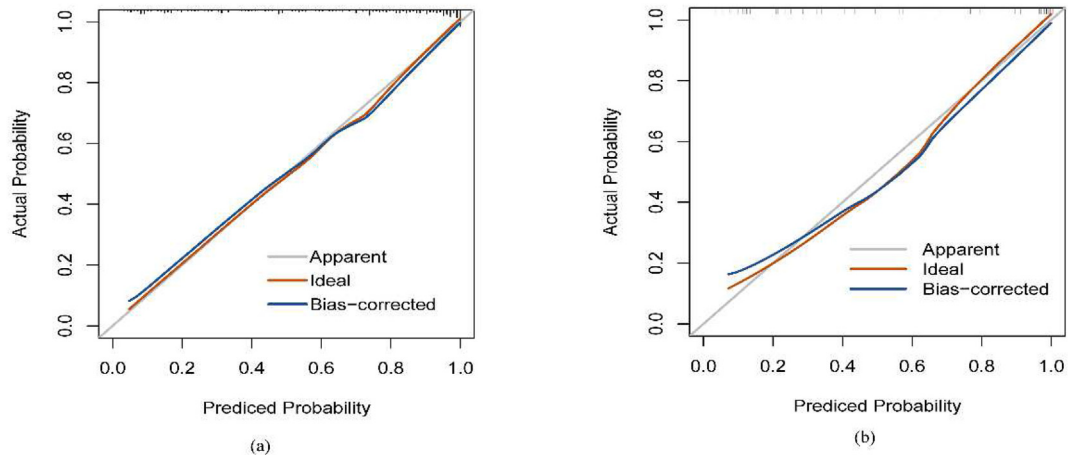

Fig. 5. Calibration curve for predicting the risk of frailty in hematological tumor patients by the predictive nomogram. (a) training set, (b) validation set.

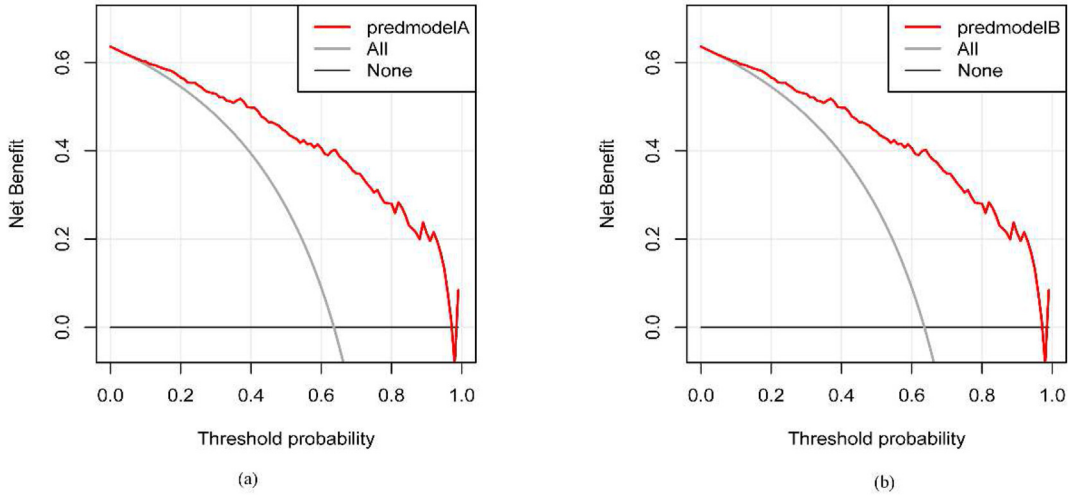

Fig. 6. Decision curve analysis for predicting the risk of frailty in hematological tumor patients by the predictive nomogram. (a) training set, (b) validation set.

hematologic malignancies. Therefore, there is an urgent need to develop evidence-based, patient-specific dietary guidelines.

The impact of anxiety and depression on frailty in hematologic malignancies

The study findings revealed that anxiety and depression independently influenced frailty in patients with hematologic malignancies. This aligns with Xue et al.'s[59] findings on patients with esophageal cancer, which indicate that patients with depression have a 2.762 times higher prevalence of frailty than non-depressed patients. However, the exact mechanisms that link frailty, anxiety, and depression remain unclear. Previous research suggests shared pathophysiological mechanisms including neuroendocrine dysregulation, inflammation, and oxidative stress.[60,61] Patients often experience negative emotions such as sadness and anxiety, owing to decreased physiological function, adverse treatment reactions, prolonged medical care, and financial burden. These emotions can reduce patients' motivation to engage in social activities and exercise, leading to smaller social networks and perpetuating social isolation.[62] Negative emotions can also affect appetite and food intake, leading to acute cardiovascular changes and autonomic dysfunction, which may contribute to the occurrence and progression of frailty.[63] Therefore, health care workers should accurately assess patients' psychological and social conditions and provide timely guidance and support.[64] Establishing a diversified social support system and connecting with community health personnel is crucial for extending psychological and social support beyond the hospital setting. Moreover, given that family is the primary source of emotional support,[65] health care professionals should guide spouses and children and emphasize the importance of increased communication with patients. Offering appropriate daily care, emotional comfort, and financial support is essential.

Clinical utility of the predictive model

In this study, the ROC, calibration, and DCA curves demonstrate the strong diagnostic performance of the model. The factors in the model can be easily obtained from patient medical records or self-reports, making it easy to use in clinical settings. Caregivers can assess frailty risk in patients with hematologic malignancies based on predictive factors and tailor care measures accordingly. This approach offers essential guidance for clinical decision-making, optimal resource allocation, and potential improvements in patient prognosis and quality of life.

Limitations

However, the data analysis lacked inflammation indicators (eg, C-reactive protein [CRP]), potentially limiting the model's ability to understand the influence of inflammation on frailty. Additionally, the single-center nature of the study may restrict the generalizability of the findings to patients with hematologic malignancies. Although the TFI has good reliability and validity, additional validation is required for its use in patients of all ages with hematologic malignancies.

Conclusions

The seven indicators verified by nomogram in this analysis, including disease duration of 6–12 months and > 12 months, CCI, prealbumin, hemoglobin, GAD-7, and PHQ-9 as predictive variables, are significant in terms of identifying risk for frailty in hematologic malignancy patients. Future studies should focus on validating this model in diverse populations and exploring its integration into routine clinical practice.

CRediT author statement

Shuangli Luo: Design this study, collect and analyze data, and make graphs. Writing the manuscript. **Huihan Zhao, Xiao Gan** and **Yu He:** participated in writing and revising the manuscript. **Caijiao Wu:** quality control of data, statistical analysis. **Yanping Ying:** revised and finalized the manuscript. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

All authors have none to declare.

Funding

This study was supported by Guangxi Zhuang Autonomous Region Health and Health Commission self-financing research projects (Grant Nos. Z-A20220418, Z-A20220414 and Z-A20210779). The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Ethics statement

This study was approved by the First Affiliated Hospital Ethics Committee of Guangxi Medical University (IRB No.2023-E286-01). All participants provided written informed consent.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, LS. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools/services were used during the preparation of this work.

References

1. Lim EA, Ruffle JK, Gnanadurai R, et al. Differentiating central nervous system infection from disease infiltration in hematological malignancy. *Sci Rep*. 2022;12(1):15805.
2. Zhang N, Wu J, Wang Q, et al. Global burden of hematologic malignancies and evolution patterns over the past 30 years. *Blood Cancer J*. 2023;13(1):82.
3. Keykhaei M, Masinaei M, Mohammadi E, et al. A global, regional, and national survey on burden and Quality of Care Index (QCI) of hematologic malignancies; global burden of disease systematic analysis 1990-2017. *Exp Hematol Oncol*. 2021;10(1):11.
4. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–M156.
5. Dong L, Liu N, Tian X, et al. Reliability and validity of the Tilburg Frailty Indicator (TFI) among Chinese community-dwelling older people. *Arch Gerontol Geriatr*. 2017;73:21–28.
6. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol*. 2015;26(6):1091–1101.
7. Brioli A, Manz K, Pfirrmann M, et al. Frailty impairs the feasibility of induction therapy but not of maintenance therapy in elderly myeloma patients: final results of the German Maintenance Study (GERMAIN). *J Cancer Res Clin Oncol*. 2020;146(3):749–759.
8. Huan-Tze L, Yun-Ru L, Kuan-Der L, Huey-En T. Frailty in chronic myeloid leukemia: evidence from 2016-2018 Nationwide Inpatient Sample of the US. *BMC Geriatr*. 2023;23(1):334.
9. Vijenthira A, Mozessohn L, Nagamuthu C, et al. Frailty in patients with newly diagnosed diffuse large B-cell lymphoma receiving curative-intent therapy: a population-based study. *J Natl Compr Cancer Netw*. 2022;20(6):635–642.e9.
10. Chan H, Chong YH, Seow MY, et al. Electronic FRAIL score may predict treatment outcomes in older adults with myeloma. *J Geriatr Oncol*. 2021;12(4):515–520.
11. Rubens M, Cristian A, Ramamoorthy V, et al. Impact of frailty on hospital outcomes among patients with lymphoid malignancies receiving autologous hematopoietic stem cell transplantation in the United States. *Clin Lymphoma, Myeloma & Leukemia*. 2022;22(7):e427–e434.
12. Engelhardt M, Dold SM, Ihorst G, et al. Geriatric assessment in multiple myeloma patients: validation of the International Myeloma Working Group (IMWG) score and

comparison with other common comorbidity scores. *Haematologica*. 2016;101(9):1110–1119.
13. Ribeiro AR, Howlett SE, Fernandes A. Frailty-A promising concept to evaluate disease vulnerability. *Mech Ageing Dev*. 2020;187:111217.
14. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. 2012;16(7):601–608.
15. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Sci World J*. 2001;1:323–336.
16. Gobbens RJ, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Towards an integral conceptual model of frailty. *J Nutr Health Aging*. 2010;14(3):175–181.
17. Chen FF, Pang YH, Mao NQ, Luo JN, Cai DL. Current status of frailty and depression and its correlation study in elderly patients with lung cancer. *Nurs Pract Res*. 2020;17(24):9–12.
18. Kehler DS, Ferguson T, Stammers AN, et al. Prevalence of frailty in Canadians 18-79 years old in the Canadian health measures survey. *BMC Geriatr*. 2017;17(1):28.
19. Vetrano DL, Palmer K, Marengoni A, et al. Frailty and multimorbidity: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2019;74(5):659–666.
20. Scheepers ERM, Vondeling AM, Thielen N, van der Griend R, Stauder R, Hamaker ME. Geriatric assessment in older patients with a hematologic malignancy: a systematic review. *Haematologica*. 2020;105(6):1484–1493.
21. Wu XY, Cao HJ. Construction and evaluation of a column chart prediction model for preoperative debilitation risk in elderly lung cancer patients. *Chin J Gerontol*. 2022;42(12):3098–3102.
22. Wu J, Wang CY, Wei ZX, Cui MZ. Research advances of nutritional intervention on frailty in elderly. *Int J Geriatr*. 2022;43(4):483–486.
23. Koll TT, Semin JN, Brodsky R, et al. Health-related and sociodemographic factors associated with physical frailty among older cancer survivors. *J Geriatr Oncol*. 2021;12(1):96–101.
24. Yanagita I, Fujihara Y, Iwaya C, et al. Low serum albumin, aspartate aminotransferase, and body mass are risk factors for frailty in elderly people with diabetes-a cross-sectional study. *BMC Geriatr*. 2020;20(1):200.
25. Kane AE, Sinclair DA. Frailty biomarkers in humans and rodents: current approaches and future advances. *Mech Ageing Dev*. 2019;180:117–128.
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis*. 1987;40(5):373–383.
27. Shiao CC, Hsu HC, Chen IL, et al. Lower Barthel index is associated with higher risk of hospitalization-requiring pneumonia in long-term care facilities. *Tohoku J Exp Med*. 2015;236(4):281–288.
28. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr*. 2003;22(4):415–421.
29. Manea L, Gilbody S, McMillan D. A diagnostic meta-analysis of the Patient Health Questionnaire-9 (PHQ-9) algorithm scoring method as a screen for depression. *Gen Hosp Psychiatr*. 2015;37(1):67–75.
30. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092–1097.
31. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ*. 2020;368:m441.
32. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Software*. 2010;33(1):1–22.
33. Komici K, Bencivenga L, Navani N, et al. Frailty in patients with lung cancer: a systematic review and meta-analysis. *Chest*. 2022;162(2):485–497.
34. Giannotti C, Sambuceti S, Signori A, et al. Frailty assessment in elective gastrointestinal oncogeriatric surgery: predictors of one-year mortality and functional status. *J Geriatr Oncol*. 2019;10(5):716–723.
35. Zhao LL, Pei JS, Wei RQ, et al. Analysis of influencing factors of frailty in patients with spinal metastases. *Chin Nurs Res*. 2022;36(4):618–623.
36. Arneth B. Tumor microenvironment. *Medicina*. 2019;56(1).
37. Panuciak K, Margas M, Makowska K, Lejman M. Insights into modern therapeutic approaches in pediatric acute leukemias. *Cells*. 2022;11(1).
38. Stephens M, McKenzie H, Jordens CF. The work of living with a rare cancer: multiple myeloma. *J Adv Nurs*. 2014;70(12):2800–2809.
39. Chen FF, Mao NQ, Luo JN, Cai DL, Pang YH. A study of the correlation between preoperative debilitating conditions and postoperative complications in elderly lung cancer patients. *Chin Nurs Res*. 2022;36(6):988–992.
40. Zhang GL, Li YH, Wen HW. Analysis of the frailty condition and influencing factors of elderly patients with lung cancer undergoing chemotherapy. *Mod Hosp*. 2018;18(12):1773–1775, 9.
41. Messaoudi I, Warner J, Nikolich-Zugich D, Fischer M, Nikolich-Zugich J. Molecular, cellular, and antigen requirements for development of age-associated T cell clonal expansions in vivo. *J Immunol*. 2006;176(1):301–308.
42. Kimura H, Kalantar-Zadeh K, Rhee CM, Streja E, Sy J. Polypharmacy and frailty among hemodialysis patients. *Nephron*. 2021;145(6):624–632.
43. Mailliez A, Guilbaud A, Puisieux F, Dauchet L, Boulanger É. Circulating biomarkers characterizing physical frailty: CRP, hemoglobin, albumin, 25OHD and free testosterone as best biomarkers. Results of a meta-analysis. *Exp Gerontol*. 2020;139:111014.
44. Chen Y, Yang YJ, Gao D, Yang L. Current status of preoperative frailty, related influencing factors and nursing measures in elderly patients with gastric cancer. *Int J Nurs*. 2022;41(16):2913–2918.
45. Tsai HF, Liu CY, Yang SH, Chiou AF. Factors related to frailty in older cancer patients undergoing colorectal surgery: a longitudinal study. *Cancer Nurs*. 2022;45(6):E865–E873.
46. Chen H, Zhang F, Luo D, et al. Advanced lung cancer inflammation index predicts the outcomes of patients with non-metastatic gastric cancer after radical surgical resection. *J Gastrointest Oncol*. 2023;14(1):85–96.
47. Muscaritoli M, Arends J, Bachmann P, et al. ESPEN practical guideline: clinical Nutrition in cancer. *Clin Nutr*. 2021;40(5):2898–2913.
48. Kim YI, Lee H, Nirmala FS, et al. Antioxidant activity of valeriana fauriei protects against dexamethasone-induced muscle atrophy. *Oxid Med Cell Longev*. 2022;2022:3645431.
49. Hammami S, Zarrouk A, Piron C, Almas I, Sakly N, Latteur V. Prevalence and factors associated with frailty in hospitalized older patients. *BMC Geriatr*. 2020;20(1):144.
50. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. *JPEN - J Parenter Enter Nutr*. 2019;43(2):181–193.
51. Cheong CY, Nyunt MSZ, Gao Q, et al. Risk factors of progression to frailty: findings from the Singapore longitudinal ageing study. *J Nutr Health Aging*. 2020;24(1):98–106.
52. Pires Corona L, Drumond Andrade FC, de Oliveira Duarte YA, Lebrao ML. The relationship between anemia, hemoglobin concentration and frailty in Brazilian older adults. *J Nutr Health Aging*. 2015;19(9):935–940.
53. Cecchi F, Pancani S, Vannetti F, et al. Hemoglobin concentration is associated with self-reported disability and reduced physical performance in a community dwelling population of nonagenarians: the Mugello Study. *Intern Emerg Med*. 2017;12(8):1167–1173.
54. Dinkla S, van Eijk LT, Fuchs B, et al. Inflammation-associated changes in lipid composition and the organization of the erythrocyte membrane. *BBA Clin*. 2016;5:186–192.
55. Palaka E, Grandy S, van Haalen H, McEwan P, Darlington O. The impact of CKD anaemia on patients: incidence, risk factors, and clinical outcomes-A systematic literature review. *Internet J Nephrol*. 2020;2020:7692376.
56. Kelaiditi E, Guyonnet S, Cesari M. Is nutrition important to postpone frailty? *Curr Opin Clin Nutr Metab Care*. 2015;18(1):37–42.
57. Lorenzo-López L, Maseda A, de Labra C, Regueiro-Folgueira L, Rodríguez-Villamil JL, Millán-Calenti JC. Nutritional determinants of frailty in older adults: a systematic review. *BMC Geriatr*. 2017;17(1):108.
58. Rashidi Pour Fard N, Amirabdollahian F, Haghighatdoost F. Dietary patterns and frailty: a systematic review and meta-analysis. *Nutr Rev*. 2019;77(7):498–513.
59. Xue Q, Zou SQ, Qiao Y, Tang WL, Bi C, Yang JL. Investigation on the preoperative debilitation status in elderly patients with esophageal cancer. *Hebei Medical Journal*. 2022;44(11):1732–1735.
60. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol*. 2018;15(9):505–522.
61. Bortolato B, Hyphantis TN, Valpione S, et al. Depression in cancer: the many biobehavioral pathways driving tumor progression. *Cancer Treat Rev*. 2017;52:58–70.
62. Taylor HO, Taylor RJ, Nguyen AW, Chatters L. Social isolation, depression, and psychological distress among older adults. *J Aging Health*. 2018;30(2):229–246.
63. Feigin VL, Norrving B, George MG, Foltz JL, Roth GA, Mensah GA. Prevention of stroke: a strategic global imperative. *Nat Rev Neurol*. 2016;12(9):501–512.
64. Niu XY, Ding LY, Lu JL, Zhu HF, Xu Q. Advances in the application of mHealth in the extended care of patients with gastrointestinal tumors. *Chin Nurs Res*. 2022;36(8):1431–1435.
65. Chen JY, Fang Y, Zeng YB. A study on the impact of diversified social involvement and family support on the mental health of elderly people in China. *Chin J Health Policy*. 2021;14(10):45–51.