Postprint: Development of a Nomogram Model for Frailty/Pre-frailty Risk Based on Routine Blood Test Inflammatory Markers

Authors: Shi Xiaotian, Wang Shan, Yang Huayu, Yang Yifan, Li Xu, Dou Guoze, Ma Qing, Ma Qing

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Abstract

Background Frailty is a common geriatric syndrome closely associated with adverse clinical outcomes. Current assessment relies primarily on various scales, lacking a unified gold standard. Chronic inflammation serves as one of the pathophysiological mechanisms of frailty, and routine blood inflammatory indicators are simple and easy to obtain; however, there are relatively few studies on the correlation between routine blood inflammatory indicators and frailty.

Objective To investigate the correlation between routine blood inflammatory indicators and frailty in elderly individuals undergoing health check-ups, analyze the influencing factors of frailty, and construct a predictive model for frailty risk.

Methods Elderly individuals who underwent health check-ups at the Healthcare Center of Beijing Friendship Hospital, Capital Medical University from August 2020 to September 2022 were selected. General information, physical examination, and laboratory test data of the study subjects were collected, and frailty was assessed using the FRAIL scale. Univariate and multivariate Logistic regression analyses were employed to explore the influencing factors of frailty and establish a nomogram prediction model, with Bootstrap used for internal validation of the model. Receiver operating characteristic (ROC) curve, Hosmer-Lemeshow calibration curve, and decision curve analysis (DCA) were used to evaluate the discrimination, calibration, and clinical effectiveness of the prediction model.

Results A total of 554 elderly individuals were included, among whom 213 (38.4%) had frailty/pre-frailty. Multivariate Logistic regression analysis revealed that the Age-Adjusted Charlson Comorbidity Index (ACCI) (OR=1.42, 95%CI=1.21~1.66), Mini Nutritional Assessment-Short Form (MNA-SF) (OR=0.71, 95%CI=0.61~0.83), Hemoglobin to Red Cell Distribution Width

Ratio (HRR) (OR=0.44, 95%CI=0.23~0.86), and polypharmacy (OR=0.54, 95%CI=0.36~0.81) were independent influencing factors for frailty/pre-frailty in the elderly (P<0.05). A frailty prediction model was constructed based on the influencing factors identified in the multivariate Logistic regression analysis. The area under the ROC curve (AUC) of this model for predicting frailty/pre-frailty in the elderly was 0.719 (95%CI=0.675~0.764). After internal validation using Bootstrap resampling, the nomogram model showed good fit; the Hosmer-Lemeshow calibration curve demonstrated good fit (P>0.05); DCA indicated that using the nomogram model to predict frailty risk was more beneficial when the patient' s threshold probability was 0.15~0.95.

Conclusion Age, comorbidities, polypharmacy, malnutrition, and HRR are influencing factors for frailty/pre-frailty in the elderly. The constructed prediction model exhibits good discrimination, consistency, and clinical utility, which can provide guidance for early screening of frailty/pre-frailty.

Full Text

Introduction

As the aging process continues to intensify, healthy aging has become a critical public health concern. Frailty, one of the most common geriatric syndromes, has garnered significant attention. It is characterized as a nonspecific state of decreased physiological reserve, diminished resistance to stressors, and impaired recovery following stress [**?**]. Research has demonstrated that frailty increases the risk of adverse clinical outcomes in older adults, including falls, hospitalization, functional decline, and even mortality, severely impacting their quality of life [**?**, **?**]. A meta-analysis incorporating 240 studies revealed that the prevalence of frailty among older adults is approximately 24%, with a marked increase in prevalence associated with advancing age [**?**]. Consequently, early identification of frailty is paramount. Although numerous frailty assessment scales currently exist, there is no unified gold standard. Exploring clinical biomarkers for frailty holds significant importance for facilitating multicenter research and evaluating interventional studies.

The pathophysiological mechanisms underlying frailty are highly complex, involving systemic metabolic dysfunction across multiple organs and systems [**?**]. Scholars now recognize chronic inflammation as a key mechanism in the development and progression of frailty. Many studies have focused on inflammatory cytokines such as interleukin (IL)-1 family members, IL-6, IL-8, IL-18, and tumor necrosis factor (TNF)-α. However, routine blood tests are simple, readily available, and warrant further investigation into the relationship between certain inflammatory markers in complete blood counts and frailty [**?**]. BODOLEA et al. [**?**] found that peripheral blood cells and platelets are closely associated with frailty in cardiovascular patients. The neutrophil-to-lymphocyte ratio (NLR) has attracted considerable research attention in recent years. HOU et al. [**?**] identified NLR as an independent risk factor for frailty in elderly patients with

coronary heart disease, and additional research has demonstrated a significant positive correlation between frailty and NLR in older cancer patients [**?**]. Meanwhile, the Singapore Longitudinal Aging Study found that hemoglobin is an independent influencing factor for frailty [**?**]. Red cell distribution width (RDW), an important parameter of red blood cells used to measure erythrocyte heterogeneity, has also been shown to be closely related to the body' s inflammatory state [**?**]. Current research findings on the correlation between various complete blood count indices and frailty remain inconsistent. This study aims to explore the relationship between inflammatory markers in routine blood tests and frailty, providing clinicians with simple and convenient indicators for early identification of frailty risk to improve quality of life and promote successful aging in older adults.

Methods

Study Participants

This cross-sectional study enrolled older adults who underwent health examinations at the Healthcare Center of Beijing Friendship Hospital, Capital Medical University, between August 2020 and September 2022. Inclusion criteria were: (1) age $\geq$ 60 years; (2) ability to cooperate with comprehensive geriatric assessment; and (3) provision of signed informed consent. Exclusion criteria included: (1) acute illness or acute-on-chronic conditions, advanced malignant tumors, or other severe wasting diseases; (2) severe hepatic or renal insufficiency, psychiatric disorders; and (3) incomplete medical examination reports. This study was approved by the Institutional Review Board of Beijing Friendship Hospital, Capital Medical University (2020-P2-227-03).

Data Collection

General Information Demographic and baseline data were collected, including sex, age, education level, body mass index (BMI), smoking status (currently smoking), alcohol consumption (currently drinking), and polypharmacy. Comorbidities were assessed using the age-adjusted Charlson Comorbidity Index (ACCI), which evaluates disease type, number, and severity with age adjustment (scoring: 2 points for ages 60–69, 3 points for 70–79, and 4 points for $ $80).

Laboratory Examinations Data from routine laboratory tests were collected, including complete blood count parameters (white blood cell count, absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, hemoglobin, RDW, platelet count, platelet distribution width) and biochemical indices (albumin, total protein, uric acid, creatinine, blood urea nitrogen, triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein, fasting glucose, glycated hemoglobin). Inflammatory markers were calculated as follows: neutrophil-lymphocyte ratio (NLR) = absolute neutrophil count / absolute lymphocyte count; derived neutrophil-to-lymphocyte ratio (dNLR) =

(white blood cell count - absolute lymphocyte count) / absolute lymphocyte count; monocyte-to-lymphocyte ratio (MLR) = absolute monocyte count / absolute lymphocyte count; platelet-to-lymphocyte ratio (PLR) = platelet count / absolute lymphocyte count; hemoglobin-to-red cell distribution width ratio (HRR) = hemoglobin / RDW; and red blood cell distribution width to platelet ratio (RPR) = RDW / platelet count.

Comprehensive Geriatric Assessment Assessments were conducted on the day of the health examination by geriatricians who had undergone standardized professional training. Frailty was evaluated using the FRAIL scale, which comprises five components: fatigue, resistance/energy loss, limitation in activities of daily living, illness, and weight loss, with each component scoring 1 point (0 points = non-frail group; 1–5 points = frail/pre-frail group) [**?**]. Nutritional status was assessed using the Mini-Nutritional Assessment Short-Form (MNA-SF), which includes appetite decline or eating difficulties, weight loss in the past three months, acute disease or stress, neuropsychological problems, and BMI, with a total score of 14 points [**?**].

Quality Control

All laboratory tests were performed at the Department of Clinical Laboratory of Beijing Friendship Hospital Healthcare Center, which maintains a standardized quality system and certification. Data entry for enrolled participants was conducted using a double-entry verification method.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 and R version 4.3.0. Normally distributed continuous variables are presented as mean ± standard deviation and were compared between groups using independent samples t-tests. Non-normally distributed continuous variables are expressed as median (P25, P75) and were compared using non-parametric tests. Categorical variables are presented as frequencies and percentages, with inter-group comparisons performed using chi-square tests. Using frailty as the outcome variable, multicollinearity among included variables was assessed using the variance inflation factor (VIF) method. If severe multicollinearity was detected, ridge regression would be employed for variable selection. Multivariate logistic regression analysis was conducted to construct a nomogram model for predicting frailty risk, with internal validation performed using Bootstrap resampling. Model performance was evaluated using receiver operating characteristic (ROC) curves, the Hosmer-Lemeshow goodness-of-fit test with calibration curves, and decision curve analysis (DCA) to assess discrimination, calibration, and clinical utility. Statistical significance was set at $P < 0.05$.

Results

Baseline Characteristics

A total of 554 participants were included in the study, comprising 413 males (74.5%) and 141 females (25.4%), with ages ranging from 60 to 98 years and a mean age of 74.4 ± 9.5 years. The non-frail group included 341 individuals (61.6%), while the frail/pre-frail group consisted of 213 participants (38.4%), including 24 with frailty ($ $3 points) and 189 with pre-frailty (1–2 points). Comparisons between the non-frail and frail/pre-frail groups revealed no significant differences in sex, BMI, education level, living alone, smoking, alcohol consumption, glycated hemoglobin, white blood cell count, absolute neutrophil count, absolute monocyte count, platelet count, platelet distribution width, high-density lipoprotein, MLR, or PLR ($P > 0.05$). However, significant differences were observed in age, polypharmacy, MNA-SF score, ACCI, albumin, absolute lymphocyte count, red blood cell count, hemoglobin, RDW, total cholesterol, triglycerides, low-density lipoprotein, NLR, dNLR, HRR, and RPR ($P < 0.05$) .

Univariate and Multivariate Logistic Regression Analysis of Frailty/Pre-frailty Influencing Factors

Multicollinearity was assessed using the VIF method, with categorical variables converted to dummy variables. All VIF values were <5, indicating negligible collinearity among variables. Univariate logistic regression analysis was performed with frailty/pre-frailty as the dependent variable (yes = 1, no = 2) and the following independent variables: sex (male = 1, female = 2), polypharmacy (yes = 0, no = 1), smoking (yes = 0, no = 1), alcohol consumption (yes = 0, no = 1), ACCI, MNA-SF, glycated hemoglobin, white blood cell count, absolute neutrophil count, platelet count, absolute lymphocyte count, red blood cell count, hemoglobin, RDW, creatinine, NLR, dNLR, HRR, RPR, creatinine, blood urea nitrogen, total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein (remaining variables as continuous). The results showed that MNA-SF score (OR = 0.68, 95%CI = 0.59–0.78), ACCI (OR = 1.62, 95%CI = 1.40–1.86), absolute lymphocyte count (OR = 0.73, 95%CI = 0.56–0.93), red blood cell count (OR = 0.39, 95%CI = 0.26–0.60), hemoglobin (OR = 0.97, 95%CI = 0.95–0.98), creatinine (OR = 1.01, 95%CI = 1.01–1.02), NLR (OR = 1.39, 95%CI = 1.13–1.71), dNLR (OR = 1.40, 95%CI = 1.15–1.70), HRR (OR = 0.30, 95%CI = 0.19–0.47), and polypharmacy (OR = 0.35, 95%CI = 0.25–0.51) were influencing factors for frailty/pre-frailty ($P < 0.05$). Multivariate logistic regression analysis incorporating significant factors from the univariate analysis revealed that ACCI (OR = 1.42, 95%CI = 1.21–1.66), MNA-SF (OR = 0.71, 95%CI = 0.61–0.83), HRR (OR = 0.44, 95%CI = 0.23–0.86), and polypharmacy (OR = 0.54, 95%CI = 0.36–0.81) were independent influencing factors for frailty/pre-frailty in older adults .

Nomogram Prediction Model

A nomogram prediction model was constructed using R software based on the influencing factors identified in the multivariate logistic regression analysis. Each factor (ACCI, MNA-SF, polypharmacy, and HRR) was assigned a score, and the total score was calculated by summing individual item scores. The corresponding risk of developing frailty/pre-frailty for each total score represents the predicted probability of frailty occurrence [Figure 1: see original paper].

Model Validation

Internal validation was performed using Bootstrap resampling with 1,000 repetitions. The Hosmer-Lemeshow calibration curve demonstrated good model fit (^{2} = 9.9137, P > 0.05), and the calibration plot showed strong agreement between observed and predicted probabilities [Figure 2: see original paper]. Discrimination was assessed using ROC curve analysis, which yielded an area under the curve (AUC) of 0.719 (95%CI = 0.675–0.764) [Figure 3: see original paper]. DCA demonstrated that the model provided good clinical utility when the threshold probability ranged from 0.15 to 0.95 [Figure 4: see original paper].

Discussion

Frailty represents a major public health challenge in aging societies, and identifying intervention targets through frailty assessment can promote healthy aging. Current frailty evaluation relies heavily on various scales focusing primarily on physical function, with no standardized screening methods. Identifying biomarkers or combining physical function with biomarkers to facilitate early recognition of frailty and implement appropriate interventions can reduce disability, decrease long-term care needs, and lower healthcare costs. This study examined multiple complete blood count indices and found that only HRR was an independent influencing factor for frailty. Multivariate logistic regression analysis confirmed that ACCI, polypharmacy, MNA-SF, and HRR were independent influencing factors for frailty.

Research has established that age is an independent risk factor for frailty, with prevalence increasing as age advances. Various age-related biological factors contribute to declining physiological function and frailty development [**?**]. A prospective cohort study in the United Kingdom found that frailty is strongly associated with comorbidities (OR = 27.1, 95%CI = 12.8–18.2), as multimorbidity leads to multi-system physiological imbalance, and interactions between conditions accelerate frailty onset and progression [**?**, **?**]. Frailty and polypharmacy share a complex relationship: frailty affects drug pharmacokinetics and treatment efficacy, while reduced metabolic capacity in older adults prolongs drug retention and increases adverse drug reactions, both of which accelerate frailty development [**?**]. KUME et al. [**?**] found in a community-based observational cohort study that frailty risk increased with the number of medications taken (RR = 1.4, 95%CI = 0.9–2.0). Our study also identified MNA-SF as

an influencing factor for frailty in older adults. A Singaporean observational study (n = 6,045) demonstrated that malnutrition was closely associated with frailty after adjusting for age, sex, and underlying diseases, with nutritional status significantly affecting frailty in community-dwelling older adults [**?**]. The relationship between frailty and malnutrition remains unclear. On one hand, malnutrition can cause weight loss and sarcopenia, leading to decreased muscle strength and fatigue. On the other hand, frailty affects dietary intake, thereby influencing nutritional status. Frailty and malnutrition are interrelated, and regardless of which condition appears first, a cyclic relationship may exist as both progress toward a combined frailty-malnutrition state [**?**].

HRR is a novel inflammatory marker. SUN et al. [**?**] first validated in esophageal squamous cell carcinoma patients that HRR is a more powerful prognostic indicator than hemoglobin or RDW alone, likely because HRR combines prognostic information from both parameters, providing more information than single variables. A study of 233 elderly patients with coronary heart disease showed that HRR was negatively correlated with frailty (K = -0.296, P $<$ 0.001), and low HRR was an independent risk factor for frailty in elderly hospitalized patients with coronary heart disease, consistent with our findings [**?**]. A Japanese study of outpatient older adults (aged 65–96) found that low HRR was significantly associated with frailty after adjusting for age and polypharmacy, suggesting that HRR could serve as a routine clinical indicator for identifying frailty [**?**]. Reduced HRR may result from decreased hemoglobin, increased RDW, or both. Anemia reduces oxygen-carrying capacity, leading to tissue hypoxia, while chronic diseases maintain the body in a state of low-grade chronic inflammation, which reduces hemoglobin levels. In older adults, malnutrition is also an important contributor to chronic anemia [**?**]. Elevated RDW can also decrease HRR, as studies have found that increased RDW is associated with inflammation—inflammatory cytokines reduce erythropoietin gene expression and receptor expression, leading to the release of immature red blood cells and increased erythrocyte volume heterogeneity [**?**]. Additionally, research has linked RDW to sarcopenia, a fundamental characteristic of frailty [**?**]. Therefore, low HRR in frail patients may be associated with inflammation, oxidative stress, malnutrition, aging, and sarcopenia. Although hemoglobin and RDW were not statistically significant in our multivariate analysis, HRR emerged as an influencing factor for frailty, suggesting that HRR has stronger predictive power than single parameters. As a simple, effective, and economical complete blood count parameter, HRR deserves greater clinical attention.

This study has several limitations. It is a single-center cross-sectional study, and future large-scale, multicenter studies are needed. Additionally, by including pre-frailty in the frailty group, we may have attenuated the association between some factors and frailty. Our research team plans to conduct follow-up studies to explore the relationship between changes in inflammatory markers and frailty progression.

In conclusion, age, comorbidities, polypharmacy, malnutrition, and HRR are

influencing factors for frailty/pre-frailty. The constructed predictive nomogram demonstrates good discrimination, consistency, and clinical utility, providing valuable guidance for early screening of frailty and pre-frailty.

Author Contributions: SHI Xiaotian conceptualized the study, designed the research, implemented the study, and wrote the manuscript. SHI Xiaotian, YANG Yifan, LI Xu, and DOU Guoze collected and organized data, performed statistical analysis, and prepared figures and tables. WANG Shan and YANG Huayu revised the manuscript. MA Qing was responsible for quality control, overall review, and supervision.

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ORCID IDs: - SHI Xiaotian: https://orcid.org/0000-0002-3330-6175 - MA Qing: https://orcid.org/0000-0002-5423-0325

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Note: Figure translations are in progress. See original paper for figures.