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Host Response in Critically Ill Patients Aged 65 Years or Older: A Prospective Study

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Background: The host response plays a critical role in the progression of all critical illnesses, especially in the aging population. With aging becoming a global phenomenon, understanding changes in the host response among elderly patients can provide valuable insights for diagnosis and treatment in the ICU.

Methods: This study included all patients aged 65 and older admitted to our geriatric intensive care unit (GICU). Demographic, clinical, and medication data were extracted from electronic medical records. The primary outcome was in-hospital mortality, while secondary outcomes included hospital length of stay (LOS) and ICU stay duration. We employed the generalized additive mixed model for analysis and utilized nomogram analysis to build a predictive mortality model.

Results: A total of 1204 patients, with a median age of 75 years and a maximum age of 110 years, were admitted to the GICU. Host response biomarkers were notably lower in patients over 85 years. White blood cell (WBC) count, lactate dehydrogenase (LDH), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α) were positively associated with mortality, while a higher platelet-to-lymphocyte ratio (PLR) was inversely related to mortality. Lymphocyte count was identified as a significant risk factor for mortality (RR = 1.2181). Elevated host response biomarkers were inversely associated with both hospital and ICU LOS. The predictive model integrating these biomarkers exhibited strong predictive performance for mortality.

Conclusion: Our findings underscore the significant impact of aging on host response in critically ill patients. Older patients, particularly those over 85, exhibited lower biomarker levels and higher mortality rates. The predictive model developed from inflammatory, immune, and coagulation markers demonstrated robust prognostic utility, aiding in the evaluation of critically ill elderly patients.

Keywords: host response, critically ill, old patients, immune response, inflammatory response, procoagulant response

Introduction

The host response in critically ill patients encompasses the body's comprehensive reaction to severe physiological stress, such as infections, trauma, or other life-threatening conditions, involving complex and dynamic interactions among the immune, inflammatory, and procoagulant systems. This multifaceted response aims to maintain homeostasis but may become dysregulated in severe cases, leading to worsening outcomes. The host response was first defined in the context of sepsis as the body's maladaptive response to infection, highlighting its role as a common pathway across critical illnesses.[1] Given this broad perspective, critical care experts advocate focusing on host response mechanisms in treating critical illnesses rather than only addressing syndromic outcomes.[2] In 2021, Professor Singer elaborated on this by categorizing host response components into immune, neural, hormonal, metabolic, and energetic responses.[3] Building on this, our team theorized a framework of host responses specific to critical illness, categorizing them into three core

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components: immune, inflammatory, and procoagulant responses; neural and hormonal responses; and metabolic and energetic responses.[4] Understanding these mechanisms in critically ill elderly patients is essential, as aging uniquely modifies each component, particularly the immune and procoagulant responses, potentially altering the prognosis and therapeutic approaches.

However, as a fundamental pathway across critical illnesses, the host response to external stimuli undergoes significant changes with aging, manifesting in altered immune, inflammatory, and procoagulant responses. With the global trend of aging, the demand for intensive care among elderly patients continues to rise, necessitating an understanding of age-specific host response biomarkers and their implications for care.[5] Recent studies have highlighted that aging is associated with immune senescence, chronic low-grade inflammation, and diminished adaptive immune responses, all of which impact critically ill older adults differently than younger populations.[6,7] Although studies have broadly explored host response biomarkers in ICU patients, there remains a paucity of research specifically examining these responses in older ICU patients, particularly in those over 85 years old, who represent a distinct group due to their unique physiological and immune profiles.[8,9] Furthermore, existing literature suggests that common ICU interventions such as immune-modulating therapies and metabolic support, may be less effective in elderly patients, especially the very old, potentially due to these age-specific changes in host response mechanisms.[10]

Studies such as those by[10,11] have examined biomarkers in elderly ICU patients with sepsis, emphasizing the importance of age-tailored treatment approaches to improve outcomes in this vulnerable group.[10,11] However, there remains a critical gap in research on predictive models that integrate inflammatory, immune, and coagulation biomarkers specifically for elderly ICU patients, providing clinicians with tools to better anticipate outcomes and customize treatments.

The aim of this study was to comprehensively evaluate the influence of age on host response biomarkers in critically ill patients aged 65 years and older who are admitted to a geriatric intensive care unit (GICU). Given the global trend of an aging population, understanding how age-related changes impact host response biomarkers in critically ill elderly patients may provide valuable insights for diagnosis and treatment in intensive care settings. Specifically, this study seeks to determine the associations between certain host response biomarkers including white blood cell count (WBC), lactate dehydrogenase (LDH), interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), platelet-to-lymphocyte ratio (PLR), and lymphocyte count and clinical outcomes, such as in-hospital mortality, length of in-hospital stay, and length of ICU stay.

Furthermore, this study aims to construct a predictive model that incorporates these biomarkers to estimate mortality risk in critically ill older patients. By integrating markers of inflammation, immunity, and coagulation, the model intends to offer a comprehensive assessment of prognosis, particularly for patients over the age of 85 years, who often exhibit distinct biomarker levels and higher mortality rates. This model may serve as a practical tool for clinicians to improve prognostic accuracy and inform treatment strategies tailored to the specific needs of elderly patients in intensive care.

Methods and Materials

Study Design and Research Population

This study was designed as a prospective observational study conducted at Peking Union Medical College Hospital, a top tertiary hospital that has ranked first on the Chinese hospital ranking board for 14 consecutive years. All patients aged ≥ 65 years who were admitted to the geriatric ICU (GICU) between January 2017 and December 2022 were included. The participants were either discharged or had passed away prior to data acquisition. The majority of patients were admitted to the ICU following high-risk, complex surgeries or with a diagnosis of sepsis or septic shock.

For host response evaluation, a range of routine blood, coagulation, and immune response biomarkers were assessed. However, certain clinical variables, such as detailed sepsis classification by type and source, have not been analyzed in depth. This decision was based on the primary focus of our study, which was to examine the broad impact of age on host response markers and their association with in-hospital mortality and ICU/hospital stay duration. Variability in source-specific sepsis responses has been investigated in other studies, which provides valuable insights into such correlations.[10,11] Our aim was to first establish baseline age-related host response patterns within the critically ill older population. Incorporating source-specific host responses in future studies may offer further insights into pathogen-specific responses in elderly sepsis patients.

Patients were excluded if they met any of the following criteria: age below 65 years or missing essential medical information, such as infection details or discharge date. According to the international expert consensus, sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, while septic shock was defined as sepsis requiring vasopressors to maintain a mean arterial pressure of 65 mmHg or greater and a serum lactate level exceeding 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.[1]

Data Collection

The electronic medical record system collected a wide range of data, including demographic data, clinical and medication details, medical information, testing and inspection results, pharmacy information, and patient outcomes. Demographic information included age and gender. Medical information included medical history, surgical details, use of antibiotics and vasopressors, length of in-hospital stay (LOS), and length of ICU stay. All inflammation-related indicators were recorded, including white blood cell (WBC) count, neutrophil (N) count, lymphocyte (L) count, platelet (PLT) count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), from routine blood examinations. Coagulation function tests were used to determine the fibrinogen (Fbg) and D-dimer levels. Additionally, interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), and lactate dehydrogenase (LDH) levels upon ICU admission were included along with other assessments, such as hepatorenal function, myocardial enzyme levels, and electrolyte levels, all extracted from the electronic system. The host response parameters were tested as clinically indicated.

Two physicians independently extracted the data using a standardized collection process and double-checked the data to ensure accuracy. In cases of inconsistent data, a third physician verified and confirmed any necessary changes. This study was approved by the ethics committee of the Peking Union Medical College Hospital (Approval No. S-617). Written informed consent was obtained from each patient or their legal representative, which included explicit permission for additional blood draws and biomarker profiling, ensuring that all participants or their representatives were fully informed about the study procedures and associated risks and benefits.

Blood Testing Assay

Routine Blood and Coagulation Tests

An appropriate amount of venous blood was collected, and red blood cell (RBC) and platelet (PLT) counts were measured using an automatic hemocytometer or microscope. The hemoglobin content (Hb) was determined using optical principles. The mean hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), and mean corpuscular volume (MCV) were measured using an automatic blood cell analyzer (Hangzhou Scion Biotechnology Co., LTD., Yuhang District, Zhejiang Province, China). Blood cell separation technology was employed to separate red blood cells from plasma, and the RBC-specific volume (HCT) was determined. A CS-1500 automatic coagulation instrument (Shanghai Tianju Biotechnology Co., Ltd., Biotechnology Industrial Park, Jing Bostan District, Shanghai, China) was used to assess the coagulation function. Plasma prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), D-dimer (DD), and fibrinogen (Fbg) levels were measured.

Cytokine Detection

A cytokine combination detection kit (immunofluorescence) from Jiangxi Saiji Biotechnology Co., LTD. (Nanchang High-tech Industrial Development Zone, China). Venous blood samples were collected according to standardized methods and allowed to coagulate naturally at room temperature. Approximately 0.5 mL of serum was isolated for detection, with analysis completed within 4 hours using the immunofluorescence method. A 12-coassay was used to detect IL-8 and a 6-coassay was used to detect IL-6, IL-10, and TNF-α. The kit included a capture microsphere mixture, fluorescence detection reagent, sample diluent, and microsphere buffer. Following the instructions, the process of preparation, quality control, reagent preparation, sample addition, fluorescence detection, and other steps were performed according to the sample requirements and testing procedures. Fluorescence detection was conducted using a FACS Calibur (BD, USA).

Other Biomarker Detection

ESR was measured using an Automatic Sedimentation Rate Analyzer (Shanghai Jumu Medical Equipment Co., LTD., Shanghai, China). LDH was measured with an Olympus AU2700 Analyzer (Olympus Corporation, Boston, MA, USA) using a lactate dehydrogenase kit (Wuhan CCY Corporation, Wuhan, China). High-sensitivity C-reactive protein (hsCRP) was measured using a P800 automatic biochemical analyzer (MODULARP model, RCHE, UK).

Endpoints

Except for the assessment of blood routine examination (WBC, N count, L count, PLT count, NLR and PLR); coagulation function test (Fbg and D-dimer); IL-6, IL-8, IL-10, TNF-α, hsCRP, ESR and LDH, the primary endpoint was in-hospital mortality, while the secondary endpoints included LOS, and length of ICU stay.

Statistical Analysis

The distributions of continuous variables were assessed for normality using the Kolmogorov–Smirnov test.[12] All continuous data in this study were represented by the minimum, 25th percentile, median, 75th percentile, and maximum values, following the confirmation of a skewed distribution. Categorical variables were presented as counts and percentages. The participants were divided into three age groups: 65–74, 75–84, and ≥85. Spearman correlation tests were applied to examine the associations between host response parameters due to the skewed distribution of the data.

The Generalized Additive Mixed Model was used for analysis, with results reported as risk ratios (RRs) or β values with 95% confidence intervals (CIs).[13] To minimize collinearity effects, we incorporated confounding factors into the model based on Spearman correlation results. Indicators with a correlation coefficient greater than 0.7 were excluded from appearing simultaneously in the model. Nomogram analysis was subsequently used to construct a prediction model for mortality.[14] The model was established based on results from Spearman correlation analysis to further address collinearity. The predictive accuracy of the model was evaluated by the area under the curve (AUC). A two-tailed P-value of <0.05 was considered statistically significant in all analyses.

Statistical analysis was performed using EmpowerStats, version 6.0 (http://www.empowerstats.com), R software, version 4.2.0 (http://www.R-project.org/), and Prism 10.0 software (GraphPad, San Diego, CA, USA).

Results

A total of 1204 patients were admitted to the GICU during the study period. The demographic characteristics, host response parameters, and outcomes of the study population are presented in Tables 1 and 2. The median age of the participants was 75 years, with the oldest patient being 110 years. Males comprised 65.1% of the study population. Of the patients, 55.9% were admitted to the ICU with an infection, and 58.1% underwent surgery. Based on clinical requirements, only a subset of participants had measurements taken for LDH, ESR, IL-6, IL-8, IL-10, and TNF-α.

The length of hospital stays (LOS) ranged from less than one day to 3144 days, with the longest ICU stay being 1518 days. These extended hospital and ICU stays reflect a small subset of patients whose complex, ongoing care needs, such as prolonged postoperative recovery, management of chronic comorbidities, or recurrent infections, necessitated sustained ICU support. In our study setting, patients aged ≥ 65 years often experienced extended recovery periods due to factors such as immune senescence, decreased physiological resilience, and heightened vulnerability to secondary infections. Although such long durations are exceptional, they underscore the challenges in managing critically ill elderly patients and highlight the need for strategies to reduce ICU dependency in this population.

Within different age groups, a notable characteristic among patients over 85 years old was a higher proportion of males (80.4%) and a significantly increased mortality rate (37.8%).

Figure 1 illustrates the host response biomarkers of critically ill patients stratified by age group. Host response biomarkers were relatively lower in patients over 85 years old (very old patients, or VOPs), including NLR, PLR, hsCRP, IL-10, WBC, D-dimer, and LDH. Conversely, lymphocyte count (L), platelet count (PLT), and fibrinogen (Fbg) levels were relatively higher in VOPs compared to other age groups.

Table 1 Demographic Characteristics, Host Response Parameters and Outcomes of the Study Population

Items	N	Min	25th	Medium	75th	Max
Age: years	1204	65	69	75	86	110
ICU stay: days	1204	0.1	4	8	19	1518
LOS (Length of Stay): days	1204	0.24	15.78	25.04	47.94	3144
NLR (Neutrophil-to-Lymphocyte Ratio): ratio	1202	0	5.66	10.40	19.53	189.49
PLT (Platelet Count): $\times 10^9$/L	1203	6	109	156	214.5	653
PLR (Platelet-to-Lymphocyte Ratio): ratio	1202	1.74	107.80	179.84	312.35	5180
WBC (White Blood Cell Count): $\times 10^9$/L	1202	0.17	7.34	10.44	15	125
hsCRP (High-Sensitivity C-Reactive Protein): mg/L	1201	0.05	33.23	82.13	166.53	455.85
FBG (Fibrinogen): g/L	1203	0.3	2.27	3.13	2.39	9.81
D-dimer: mg/L FEU (Fibrinogen Equivalent Units)	1194	0.15	1.39	3.46	7.29	233.7
LDH (Lactate Dehydrogenase): U/L	497	7.7	164	227	387	14,407
ESR (Erythrocyte Sedimentation Rate): mm/h	435	1	20	40	73	140
IL-6 (Interleukin-6): pg/mL	472	2	30	96	308	1000
IL-8 (Interleukin-8): pg/mL	465	9	51	89	176	7500
IL-10 (Interleukin-10): pg/mL	460	5	5	7.8	15.65	1000
TNF-α (Tumor Necrosis Factor-alpha): pg/mL	437	4	10.5	15.1	23.4	195

Table 2 Distribution of Baseline Characteristics and Mortality Among Different Age Groups

Items	Total	65–74	75–84	≥85	P-Value
Gender					<0.01
Female	420(34.9%)	229 (39.2%)	125(44.0%)	66(19.6%)	
Male	784(65.1%)	355(60.8%)	159(56.0%)	270(80.4%)	
Mortality					<0.01
No	1035(84.0%)	561(96.1%)	265(93.3%)	209(62.2%)	
Yes	169(16.0%)	23(3.9%)	19(6.7%)	127(37.8%)	
Infection					0.92
No	531(44.1%)	280(47.9%)	102(35.9%)	149(44.3%)	
Yes	673(55.9%)	304(52.1%)	182(64.1%)	187(55.7%)	
Surgery					0.49
No	504(41.9%)	220(37.7%)	138(48.6%)	146(43.5%)	
Yes	700(58.1%)	364(62.3%)	146(51.4%)	190(56.5%)	

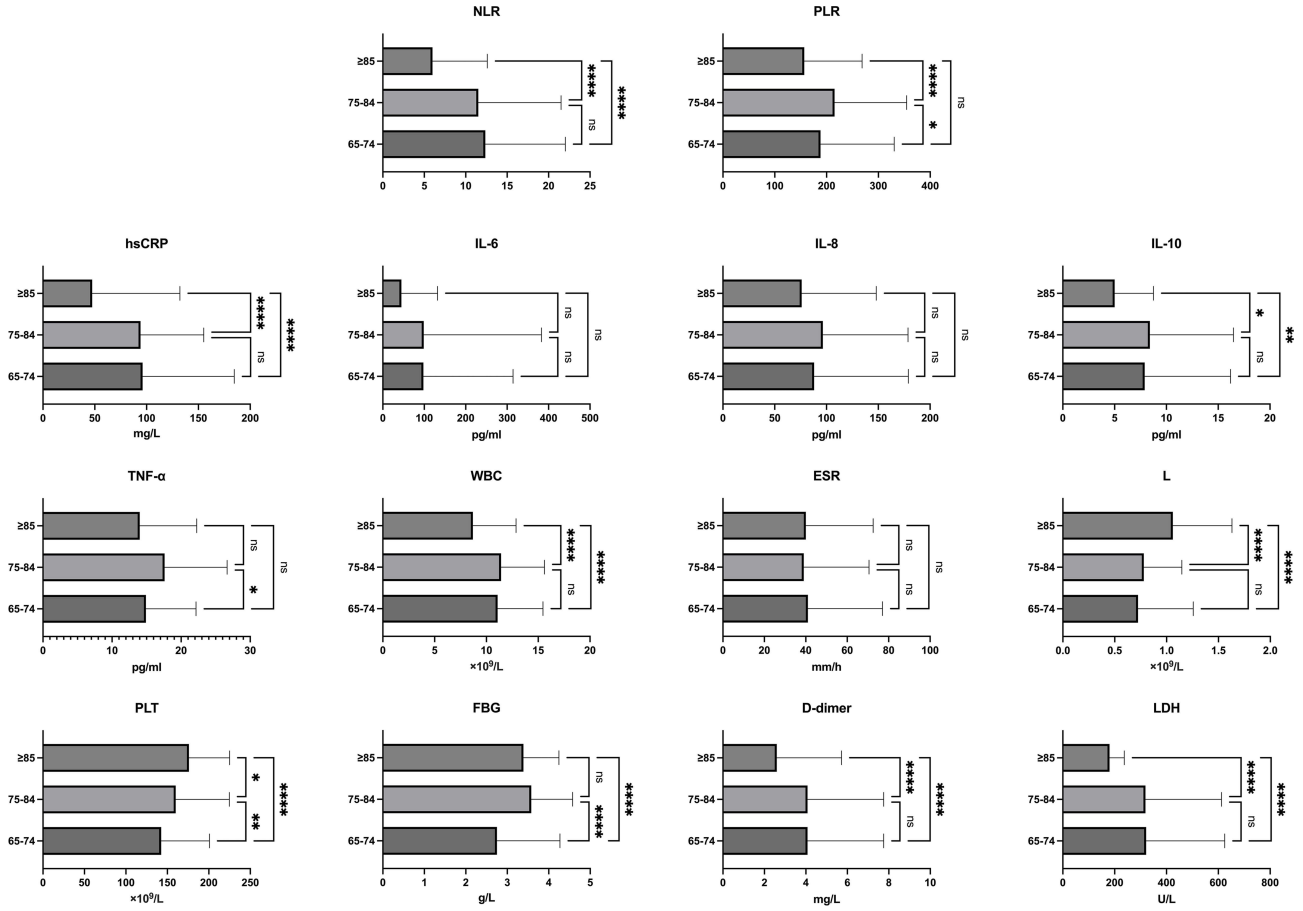

Figure 1 This figure presents the comparison of multiple inflammatory and hematological markers across three age groups: 65–74 years, 75–84 years, and ≥85 years. The markers include the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), high-sensitivity C-reactive Protein (hsCRP), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), Tumor Necrosis Factor-alpha (TNF-α), White Blood Cell count (WBC), Erythrocyte Sedimentation Rate (ESR), Lymphocyte count (**L**), Platelet count (PLT), Fibrinogen (FBG), D-dimer, and Lactate Dehydrogenase (LDH). Data are represented as bar graphs with significance levels indicated by ns (no significance), * ($p<0.05$), ** ($p<0.01$) and **** ($p<0.0001$).

The correlation coefficients among the various host response biomarkers are shown in Table 3. Strong correlations were observed between lymphocyte count (L) and both PLR and NLR, as PLR and NLR were calculated using lymphocyte count. Consequently, L and PLR/NLR were not simultaneously included in the regression and prediction models to avoid multicollinearity. Moderate correlations were found between PLR and NLR, PLT and PLR, IL-6 and hsCRP, IL-6 and IL-10, IL-8 and TNF-α, and FBG and ESR. The remaining biomarkers showed either weak or no correlation.

Further regression analyses were conducted to quantify the effects of different host response biomarkers on outcome variables across age groups. Single-factor models were employed to highlight the trends. As shown in Figure 2, WBC was positively associated with mortality, with a risk ratio (RR) of 1.02 (95% CI 1.00–1.02, P=0.01). LDH [RR 1.00 (95% CI 1.0001–1.0006, P=0.0038)], IL-10 [RR 1.00 (95% CI 1.0013–1.0056, P=0.0018)], and TNF-α [RR 1.01 (95% CI 1.00–1.02, P=0.0042)] were also positively associated with mortality. Conversely, PLR was negatively associated with mortality [RR 0.99 (95% CI 0.9975–0.9998, P=0.0178)].

In patients aged 65–74 years, higher levels of LDH, Fbg, and IL-10 were associated with increased mortality, with RRs of 1.00 (95% CI 1.0000–1.0007, P=0.03), 1.36 (95% CI 1.10–1.69, P=0.0038), and 1.00 (95% CI 1.0004–1.0056, P=0.0224), respectively. In this age group, slight variations were also observed, with LDH [RR 1.00 (95% CI 1.00–1.0009, P=0.0229)] and TNF-α [RR 1.01 (95% CI 1.00–1.03, P=0.01)] showing positive associations with mortality. In very old patients (VOPs), lymphocyte count was identified as a risk factor for mortality, with an RR of 1.21 (95% CI 1.00–1.48, P=0.0496).

Table 3 Spearman Coefficients Among Different Host Response Biomarkers

Items	NLR	PLR	CRP	IL6	IL8	IL10	TNF-α	WBC	ESR	L	PLT	FBG	D-Dimer	LDH
NLR: ratio	1.00													
PLR: ratio	0.60*	1.00												
hsCRP: mg/L	0.20*	0.09*	1.00											
IL-6: pg/mL	−0.20*	−0.11*	0.31*	1.00										
IL-8: pg/mL	−0.03*	0.03	0.09	0.24*	1.00									
IL-10: pg/mL	−0.09	−0.16*	0.03	0.46*	0.26*	1.00								
TNF-α: pg/mL	0.06	0.14*	0.23*	0.07	0.40*	0.26	1.00							
WBC: $\times 10^9$/L	0.48*	−0.07*	0.17*	−0.08*	−0.08	0.03*	−0.07	1.00						
ESR: mm/h	0.06	0.15*	0.25*	−0.15	−0.07	−0.11	0.02	0.09	1.00					
L (Lymphocyte Count): $\times 10^9$/L	−0.70*	−0.73*	−0.13*	0.08	−0.09	0.05	−0.18*	0.22*	−0.02	1.00				
PLT: $\times 10^9$/L	−0.04	0.45*	−0.05	−0.10*	−0.07	−0.20*	−0.03	0.19*	0.20*	0.21*	1.00			
FBG: g/L	0.14	0.30*	0.22*	−0.31*	−0.04	−0.25*	0.14*	0.09*	0.45*	−0.08*	0.36*	1.00		
D-dimer: mg/L FEU	0.22*	0.08*	0.12*	−0.24*	0.08	0.04	0.33*	0.09*	0.00	−0.19*	−0.12*	0.10*	1.00	
LDH: U/L	0.35*	0.03	0.29*	0.18*	0.19*	0.16	0.13	0.24*	0.03	−0.28*	−0.30*	−0.04	0.34*	1.00

Notes: *, P<0.05.

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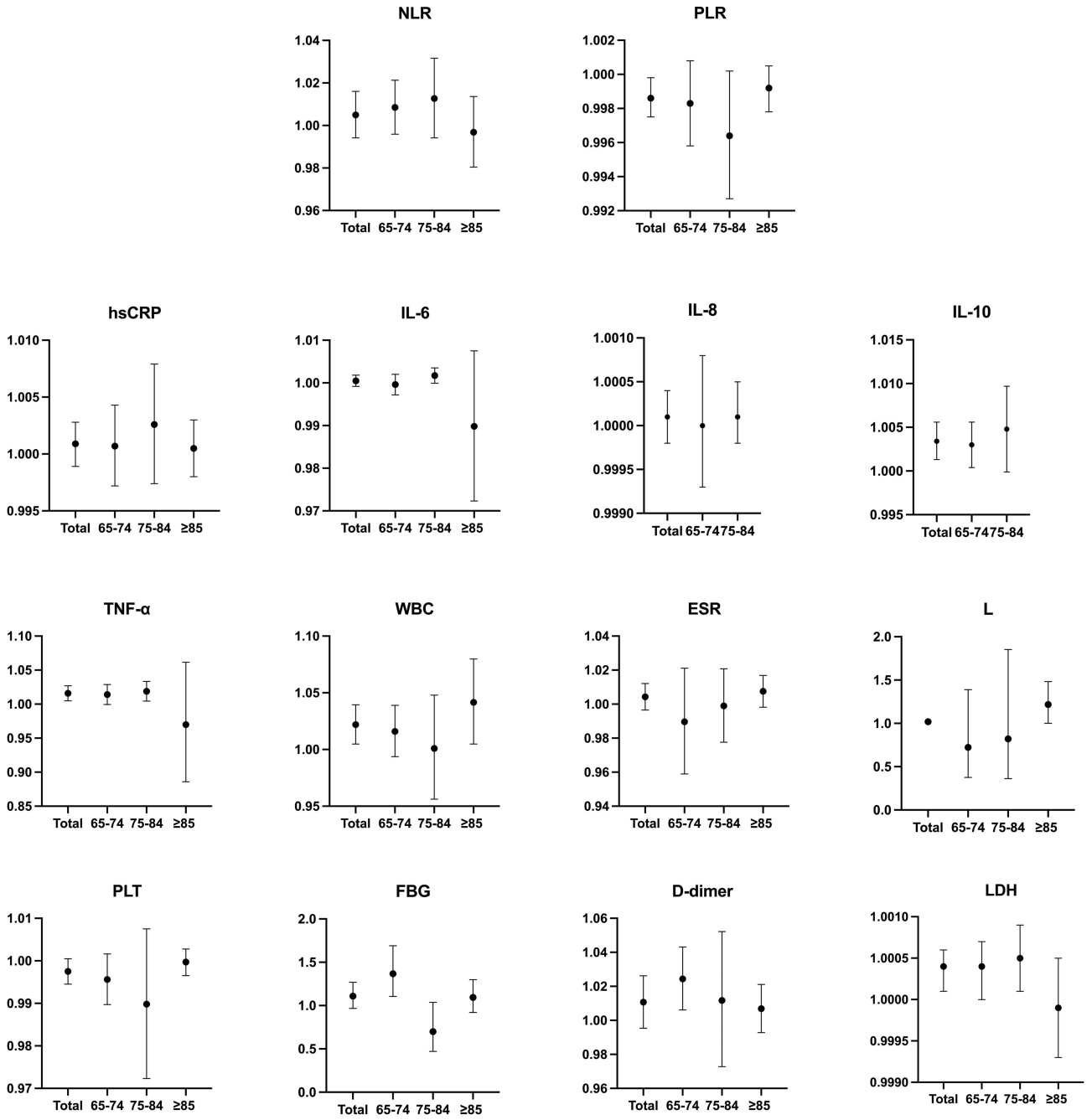

Figure 2 Risk ratio for mortality among different host response biomarkers in different age groups.

The length of hospital stay (LOS), and ICU stay were also influenced by host response biomarkers. As shown in Table 4, IL-6 levels and lymphocyte counts were negatively associated with ICU stay in the 65–74 age group. In the 75–84 age group, PLR and IL-10 showed a similar negative association with ICU stay, whereas D-dimer had an opposing effect in both age groups.

Table 5 shows the β values of the biomarkers in relation to LOS. High-sensitivity C-reactive protein (hsCRP) was negatively associated with LOS in both the total study population and very old patients (VOPs). In the 65–74 years age group, lymphocyte counts were negatively associated with LOS, while in the 75–84 years age group, PLR and platelet counts (PLT) showed the same negative effect. Among VOPs, LDH levels were negatively associated with LOS.

Table 4 β Values for Length of ICU Stay Among Different Host Response Biomarkers in Different Age Groups

Items	Total			65–74			75–84			≥85		
	β Value	**95% CI**	**P Value**	**β Value**	**95% CI**	**P Value**	**β Value**	**95% CI**	**P Value**	**β Value**	**95% CI**	**P Value**
NLR: ratio	0.15	−0.07–0.36	0.14	0.05	−0.01–0.11	0.12	−0.01	−0.10–0.08	0.78	0.72	−0.58–2.02	0.28
PLR: ratio	0.00	0.00–0.01	0.39	0.00	0.00–0.01	0.18	**0.00**	**−0.01–0.00**	**0.05**	0.02	−0.03–0.08	0.45
hsCRP: mg/L	−0.02	−0.06–0.02	0.18	0.01	0.00–0.02	0.13	−0.01	−0.03–0.01	0.20	−0.09	−0.23–0.05	0.22
IL-6: pg/mL	0.00	−0.01–0.00	0.49	**−0.01**	**−0.01–0.00**	**0.02**	0.00	−0.01–0.01	0.86	−0.01	−0.02–0.01	0.55
IL-8: pg/mL	0.00	0.00–0.00	0.12	0.00	0.00–0.00	0.81	0.00	0.00–0.00	0.48	−0.02	−0.05–0.01	0.23
IL-10: pg/mL	−0.01	−0.01–0.00	0.30	0.00	−0.01–0.00	0.30	**−0.01**	**−0.03–0.00**	**0.01**			
TNF-α: pg/mL	0.06	−0.02–0.13	0.42	0.08	0.00–0.17	0.06	0.04	−0.09–0.17	0.52	−0.22	−0.90–0.46	0.53
WBC: $\times 10^9$/L	0.48	−0.12–1.09	0.31	0.05	−0.07–0.17	0.40	0.22	0.00–0.45	0.05	2.57	−1.13–6.26	0.17
ESR: mm/h	0.13	−0.04–0.30	0.07	0.04	−0.04–0.12	0.37	−0.06	−0.16–0.05	0.28	0.33	−0.11–0.77	0.15
L (Lymphocyte Count): $\times 10^9$/L	−0.24	−0.78–0.30	0.14	**−0.14**	**−0.25–−0.03**	**0.01**	3.32	−1.00–7.64	0.13	−3.22	−11.19–4.75	0.43
PLT: $\times 10^9$/L	0.01	−0.02–0.03	0.07	0.00	−0.02–0.03	0.72	−0.01	−0.03–0.01	0.47	0.04	−0.07–0.16	0.46
FBG: g/L	1.76	−0.17–3.68	0.74	1.97	1.05–2.89	0.00	0.59	−0.85–2.03	0.42	2.37	−6.46–11.19	0.60
D-dimer: mg/L FEU	0.80	−0.75–2.35	0.06	**0.10**	**0.01–0.18**	**0.02**	**0.20**	**0.02–0.38**	**0.03**	1.29	−1.40–3.98	0.35
LDH: U/L	0.00	0.00–0.00	0.14	0.00	0.00–0.00	0.45	0.00	0.00–0.00	0.96	−0.01	−0.03–0.01	0.31

Notes: Bold values represent statistically significant associations between host response biomarkers and ICU length of stay (ICU-LOS), with p-values less than <0.05.

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Table 5 β Values for Length of in-Hospital Stay (LOS) Among Different Host Response Biomarkers in Different Age Groups

Items	Total			65–74			75–84			≥85		
	β Value	**95% CI**	**P Value**	**β Value**	**95% CI**	**P Value**	**β Value**	**95% CI**	**P Value**	**β Value**	**95% CI**	**P Value**
NLR: ratio	−0.36	−0.84–0.11	0.14	0.10	−0.13–0.32	0.40	−0.12	−0.31–0.08	0.24	−2.25	−4.73–0.23	0.08
PLR: ratio	−0.02	−0.05–0.02	0.35	0.01	−0.01–0.04	0.28	**−0.01**	**−0.02–0.00**	**0.03**	−0.15	−0.42–0.12	0.28
hsCRP: mg/L	**−0.13**	**−0.26–0.00**	**0.05**	0.02	−0.01–0.05	0.21	−0.03	−0.08–0.03	0.33	**−0.54**	**−1.04–-0.03**	**0.04**
IL-6: pg/mL	0.00	−0.02–0.01	0.58	0.00	−0.01–0.01	1.00	0.00	−0.02–0.03	0.69	−0.07	−0.15–0.02	0.12
IL-8: pg/mL	0.00	−0.01–0.01	0.80	0.00	−0.01–0.00	0.06	0.00	−0.01–0.01	0.48	−0.04	−0.09–0.00	0.07
IL-10: pg/mL	0.00	−0.03–0.03	1.00	−0.01	−0.03–0.02	0.68	0.02	−0.08–0.12	0.69			
TNF-α: pg/mL	0.12	−0.12–0.37	0.33	0.07	−0.09–0.24	0.40	0.02	−0.14–0.17	0.82	2.48	−4.84–9.81	0.51
WBC: $\times 10^9$/L	0.75	−0.50–2.01	0.24	0.06	−0.31–0.44	0.75	0.30	−0。41–1.01	0.41	4.16	−3.61–11.93	0.29
ESR: mm/h	0.70	−0.19–1.60	0.12	0.20	−0.28–0.68	0.41	−0.17	−0.49–0.15	0.31	1.71	−0.58–4.00	0.14
L (Lymphocyte Count): $\times 10^9$/L	3.57	−4.84–11.97	0.41	**−0.39**	**−0.64–-0.15**	**0.00**	3.11	−2.95–9.16	0.31	32.25	−23.48–87.98	0.26
PLT: $\times 10^9$/L	0.11	−0.05–0.27	0.17	0.04	−0.05–0.13	0.33	**−0.07**	**−0.12–-0.02**	**0.01**	0.54	−0.18–1.27	0.14
FBG: g/L	4.47	−2.61–11.56	0.22	2.05	−0.22–4.32	0.08	−1.44	−4.06–1.17	0.28	17.41	−16.38–51.20	0.31
D-dimer: mg/L FEU	0.07	−1.72–1.86	0.94	0.04	−0.10–0.19	0.57	0.21	−0.22–0.64	0.34	0.06	−3.03–3.16	0.97
LDH: U/L	−0.01	−0.02–0.00	0.06	0.00	0.00–0.00	0.82	0.00	0.00–0.00	0.12	**−0.11**	**−0.21–-0.02**	**0.02**

Notes: Bold values indicate statistically significant associations between host response biomarkers and length of in-hospital stay (LOS), with p-values less than <0.05.

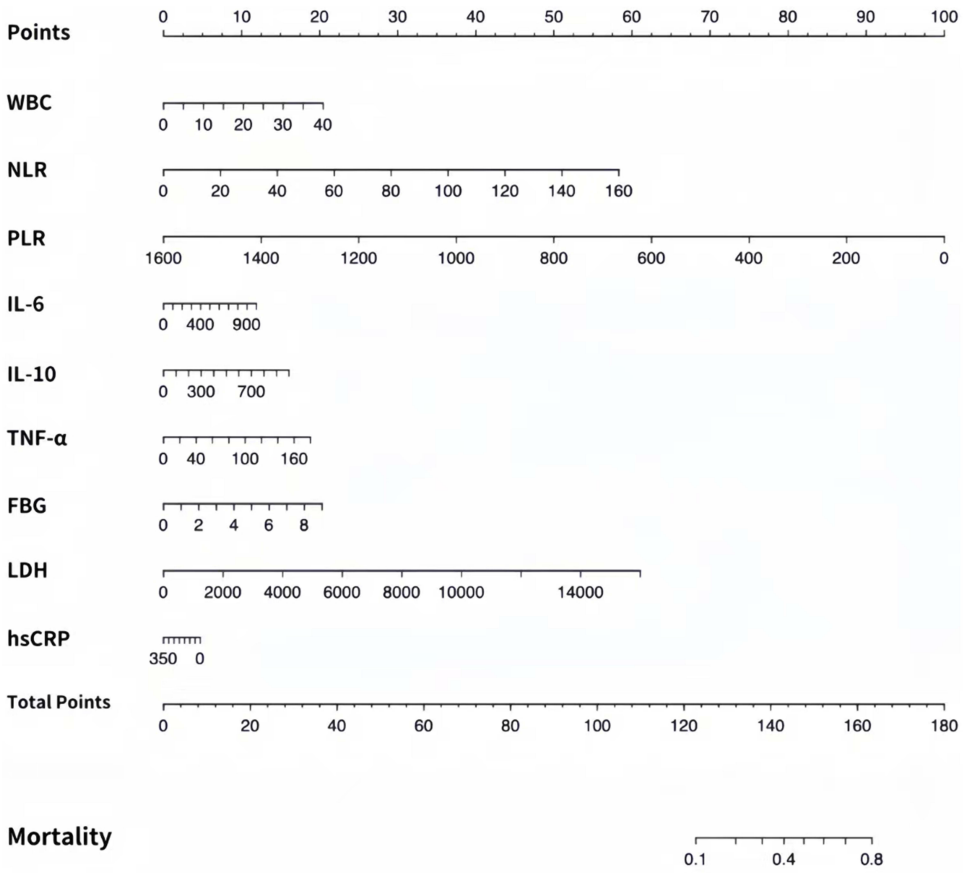

Figure 3 Nomogram model predicting mortality in the study population.

We developed a predictive mortality model based on host response biomarkers for the study population. As shown in Figure 3, biomarkers including WBC, NLR, PLR, IL-6, IL-10, TNF-α, Fbg, LDH, and hsCRP were included in the model to ensure predictive efficiency. The final predictive model equation is logit (MORTALITY) = −3.78666 +0.04508*WBC +0.03215*NLR −0.00551*PLR +0.00105*IL-6 +0.00142*IL-10 +0.00922*TNF-α +0.19901*FBG +0.00034*LDH −0.00119*CRP. The AUC for the prediction model was 0.802. The area under the curve (AUC) for the predictive model was 0.802 (Figure 4).

Discussion

Aging is a natural process that leads to various physiological changes. With advancements in living standards and healthcare, aging has increasingly become a societal concern. According to the World Health Organization, the global population of individuals aged 60 years and older is projected to reach 2.1 billion by 2050, with those aged 80 years and older expected to reach 426 million (https://www.who.int/news-room/fact-sheets/detail/ageing-and-health. A comprehensive data analysis from Brazil showed that from 2009 to 2015, the elderly population increased by 27%, ICU admission rates rose by 20%, and hospital mortality increased from 9.8% to 11.2%.[15] Similar trends have been observed in other studies.[5,16] Age has been identified as a unique risk factor for sepsis, independent of disease severity.[17]

In our study, we found that the in-hospital mortality rate for patients aged ≥ 85 years sharply increased from 3.9% to 37.8% compared to that for patients aged 65–74 years, aligning with general aging trends. Notably, when stratified by gender, males made up the majority of patients, especially among very old patients (VOPs). The likelihood of ICU admission for elderly patients in China is influenced by factors such as a patient's underlying health status, willingness to undergo invasive treatment, family financial circumstances, and other considerations. When making major decisions

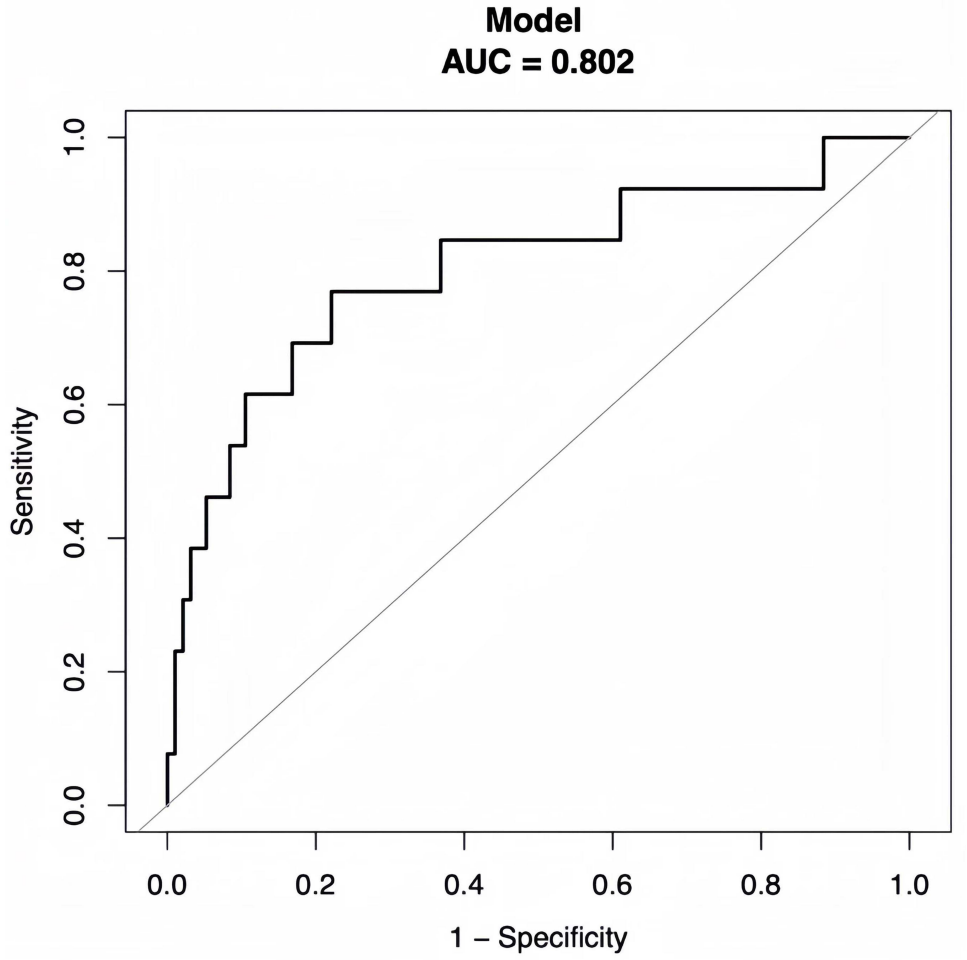

Figure 4 AUC curve for nomogram model.

regarding ICU admission for very old patients, family meetings are typically convened to discuss subsequent treatment plans. Physicians generally respect the collective decisions of patients and their family members.

Our study offers valuable insights into host response among critically ill elderly patients. We observed that advancing age significantly affects the levels of host response biomarkers, with very old patients (VOPs) displaying lower levels of certain biomarkers and higher mortality rates. These findings suggest that aging diminishes the immune response, potentially influencing clinical outcomes.

The host response functions as a defense mechanism against physiological stress.[4] Compared to younger patients, the host response in older adults, particularly VOPs (those over 85 years), is distinct.[7] This supports our study's findings of significantly higher hospital mortality rates among VOPs. Previous studies on how aging affects the host response in critically ill patients remain incomplete, as they typically examine diverse age groups. Our study focused exclusively on older patients, including those with > 300 cases of VOPs in the ICU. We observed that NLR, PLR, hsCRP, IL-10, WBC, D-dimer, and LDH levels were lower in VOPs, whereas lymphocyte (L), platelet (PLT), and fibrinogen (Fbg) levels were relatively higher. These findings may differ from those of other studies.

For example, a study based on data from Henan, China, found that in ostensibly healthy populations, PLT decreased in individuals aged 65 years or older compared to those aged 18–64 years, while NLR and PLR increased with age.[18] After sepsis, CRP and lymphocyte levels were lower in older patients (aged ≥65 years) compared to a younger group, whereas other inflammatory biomarkers, including IL-6, IL-8, IL-10, monocyte chemoattractant protein-1, and neutrophils (N) were higher in the older group.[19] A nationwide study in the Netherlands focusing on host response biomarkers of critically ill sepsis patients found higher PLT levels in individuals aged 70 years or older, while levels of CRP, soluble

E-selectin, soluble intercellular adhesion molecule 1, and fractalkine were significantly lower than in those aged 50–59 years. Coagulation biomarker levels between the different age groups showed no significant differences.[7] Additionally, one study on VOPs found that sepsis patients had lower WBC levels and higher hsCRP levels.[20]

Despite differing trends in biomarker levels across studies, it is clear from previous research that the host response, particularly the immune response, weakens with aging, which is a distinct feature of VOPs. Younger individuals typically have sufficient physiological and functional reserves, while aging gradually depletes these reserves, making homeostasis more susceptible to disruption.[21] Immune senescence, partly due to chronic low-grade systemic inflammation, leaves the aging body more vulnerable to stressors.[22] Biomarkers activated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) further suppress adaptive immunity.[23] Consequently, older populations frequently experience higher rates of organ dysfunction, mortality, and prolonged hospital and ICU stays.

Our study population consisted exclusively of older adults; a group that may display different inflammatory responses compared to younger cohorts in another study. Differences in the study design, patient selection, and specific methodologies for measuring inflammatory mediators may also have contributed to the variations observed.

Our study demonstrated that PLR serves as a protective factor within the study population. Previous studies on the association between PLR and mortality have produced inconsistent findings. A retrospective study indicated that PLR >200 was significantly associated with mortality, with an odds ratio (OR) of 1.0002 (95% CI: 1.0001 to 1.0004).[24] Conversely, a study conducted in Italy reported a statistically insignificant association, with a hazard ratio of 1.006 (95% CI 1.000–1.013, P=0.058).[25] In patients with acute kidney injury, U-shaped relationships were found between PLR and both 30-day and 90-day mortality.[26,] In a cohort of neonatal patients, however, lower PLR was associated with higher hospital mortality (OR 0.85, 95% CI 0.75–0.95) and 90-day mortality (OR 0.85, 95% CI 0.76–0.96).[27]

PLR is calculated by dividing the platelet count by the lymphocyte count. Thrombocytopenia is common in critically ill patients and is often associated with poor outcomes.[28–30] Several underlying mechanisms contribute to this association. Hematopoietic function deteriorates with age, and during stress, the procoagulant response consumes a significant number of platelets.[31] Consequently, patients with higher platelet counts were uncommon in our study population. As a result, a higher platelet count showed a trend toward being a protective factor against mortality. It is essential to recognize that many of the studies we reference include a broader age range, while our study focused specifically on older adults. This age-specific approach likely contributes to the observed differences, particularly in biomarkers such as platelets, which may behave differently in older populations due to age-related physiological changes.

Our study revealed that WBC and lymphocyte (L) counts are risk factors for mortality in the study population, while neutrophils (N) act as protective factors in very old patients (VOPs), with this effect being more pronounced in VOPs. A Korean study of 1,000 participants aged ≥ 65 years showed a protective trend for lymphocytes, while higher neutrophil levels were associated with increased mortality.[32] Other studies have reached similar conclusions.[33,34] In contrast, a study in Leiden found that mortality was associated not with lymphocyte count but with lower levels of CD4+ T lymphocytes.[35] However, none of these studies reached the same conclusion as ours. A study on lymphocyte subsets found that CD4 +CD45RA- T cells, a type of regulatory T cell, increase with age.[36] In VOPs experiencing intense stress, these regulatory T cells may play a greater role in moderating the body's inflammatory response, indicating the severity of the host response. However, although the number of regulatory T cells may be higher, their functionality is often reduced. This results in the decoupling of the stress from the host response. Consequently, more lymphocytes may indicate a stronger host response, potentially leading to a poorer prognosis. Further research is required to confirm this hypothesis.

Neutrophils have been shown to be a risk factor for mortality in septic patients.[37] Yet, patients with neutrophil counts below the upper normal limit in the emergency room have been found to have an increased risk of death.[38] Our results were similar in VOPs, suggesting that higher neutrophil counts may help the aging body better manage physiological stress.

In contrast to mortality outcomes, higher levels of host response biomarkers were associated with shorter ICU and hospital stays. Multiple factors may have contributed to this finding. First, decisions regarding hospital or ICU stay are often made jointly by family members and patients, with emotional support playing an essential role in the therapeutic process. VOPs often require more family support than medical support, and after discussions with family members, many opt to spend time together outside the hospital or ICU rather than remain hospitalized. Second, increased levels of host

response biomarkers may indicate a higher mortality risk, thereby potentially reducing hospital and ICU stay duration. Further research is necessary to substantiate these hypotheses in VOPs.

We further developed a predictive model to evaluate the relationship between host response indicators and mortality. Assessing the host response status of elderly patients using a single indicator is challenging, as previous research on the host response in critically ill patients has primarily focused on plasma cytokines and other inflammatory markers.[39,40] The final model was selected from several models based on its superior predictive performance and includes both inflammatory and procoagulant indicators. This model combines the inflammatory, immune, and coagulation conditions of the host, providing a comprehensive evaluation of individual patients.

One aspect of the model that is challenging to interpret is the proportion and clinical significance of hsCRP. Previously, nomogram models were constructed using only factors with prognostic significance in regression analysis.[41] Although hsCRP level did not show significance in our single-factor analysis, it has shown statistical significance in previous studies.[42,43] Therefore, we included hsCRP in our model, which enhanced its predictive value. This model serves as a predictive tool for critically ill patients aged ≥ 65 years; however, additional studies are needed to validate its effectiveness. Fibrinogen levels should not be considered linearly associated with mortality, as both high and low levels present risk factors.[44–46]

Our study had some limitations. First, it was a single-center, six-year prospective study that was not registered in any clinical trial directory. A complete clinical analysis was conducted on a relatively small sample, with approximately one-third of the total participants due to source limitations. Although some correlations were observed, the results still require validation on a larger scale. As part of a national multicenter prospective study on the host response to intensive care, these results will be verified in a larger population across China, offering greater reliability.

Second, we collected host response biomarkers only upon ICU admission and based outcome predictions on a single measurement. Since biomarkers were tested as clinically indicated, only a subset of participants had their IL-6, IL-8, IL-10, and TNF-α levels measured at admission. However, biomarker levels change over time and may influence primary outcomes. Therefore, repeated measurements may improve predictive accuracy. Other factors, such as educational level and family economic conditions, may also affect the results. We are including all relevant data in our ongoing multicenter study and anticipate findings from a larger population. Third, some results, especially those concerning VOPs, remain unexplained. Further clinical and fundamental studies focusing on VOPs are necessary to provide additional insights.

Our study provides novel insights into host response biomarkers in critically ill elderly patients, specifically identifying the associations between immune and inflammatory markers and mortality. This finding is particularly valuable as it enhances the understanding of how aging modifies host responses to critical illnesses, offering new perspectives for targeted therapeutic approaches. By showing that specific biomarkers, such as IL-10, TNF-α, and PLR, are linked to mortality in older populations, our research emphasizes the need for age-specific strategies for managing critical illness. These results contribute to the broader literature on aging and critical care, underscoring the importance of integrating biomarkers that capture the unique physiological changes associated with advanced age.

Table 6 provides a comparative overview of various predictive mortality models developed for elderly ICU populations, highlighting the key biomarkers, model types, and predictive accuracy (AUC). Our study model, focused on

Table 6 Comparison of Predictive Mortality Models in Elderly ICU Patients

Model	Key Biomarkers/Parameters	Type of Model	Population	Predictive Efficacy (AUC)
Current Study	WBC, NLR, PLR, IL-6, IL-10, TNF-α, FBG, LDH, hsCRP	Nomogram model	Critically ill patients ≥65 years	0.802
Bruno et al (2021)	SOFA score, age, lactate, sepsis markers	Logistic regression model	Elderly sepsis patients	0.76
Peters-Sengers et al (2022)	Source-specific biomarkers, IL-6, IL-8, CRP	Cox proportional hazards	Elderly ICU sepsis patients	0.81
Chen et al (2024)	C-reactive protein (CRP), procalcitonin, serum creatinine (Scr)	Machine learning model	Patients ≥65 years (underwent non-cardiac, non-urological elective surgeries)	Scr × PCT 0.750 Scr × CRP 0.724

critically ill patients aged ≥ 65 years, integrates host response biomarkers including WBC, NLR, PLR, IL-6, IL-10, TNF-α, Fbg, LDH, and hsCRP within a nomogram framework. This model achieved an AUC of 0.802, reflecting a strong predictive performance for mortality in elderly ICU patients.

For comparison, the Bruno et al[10] model, designed for elderly sepsis patients, employs a logistic regression approach and incorporates clinical markers such as the SOFA score and lactate, achieving an AUC of 0.76. Similarly, Peters-Sengers et al[11] used a Cox proportional hazards model focusing on source-specific biomarkers, yielding an AUC of 0.81. Chen et al[47] applied a machine learning model for patients aged 65 and older, underwent non-cardiac, non-urological elective surgeries using procalcitonin, CRP, and serum creatinine as key predictive parameters, achieving an AUC of 0.79.

Conclusions

Age significantly affects host response in critically ill patients, with older patients generally having lower levels of host response biomarkers accompanied by higher mortality, especially in VOPs. Our study effectively complements the changes in host response in critically ill older patients, especially in VOPs, which may be conducive to further clinical exploration of the specific treatment of dysregulated host responses in such patients. Some host response biomarkers are positively associated with in-hospital mortality, and a predictive model was constructed to comprehensively evaluate the prognosis of critically ill older patients by including indicators of inflammation, immunity, and coagulation. The combination of these biomarkers has a good prediction of mortality, which might be a trend for evaluating the host response in the future.

Abbreviations

AUC, area under the curve; CIs, confidence intervals; ESR, erythrocyte sedimentation rate; Fbg, fibrinogen; GICU, geriatric ICU; hsCRP, high sensitive C reactive protein; ICU, intensive care unit; IL, interleukin; L, lymphocyte; LDH, lactic dehydrogenase; LOS, length of in-hospital stay; N, neutrophil; NLR, neutrophil lymphocyte ratio; ORs, odds ratios; PLR, platelet lymphocyte ratio; PLT, platelet; RRs, risk ratios; TNF-α, tumor necrosis factor-α; VOPs, very old patients; WBC, white blood cells.

Data Sharing Statement

All datasets used and analyzed during the current study are available from the corresponding author (Xiaoting Wang) on reasonable request.

Ethics Approval and Consent to Participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the ethics committee of Peking Union Medical College Hospital, Beijing, China (Approval No. S-617). Written informed consent was obtained from each patient.

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Disclosure

The authors declare that they have no competing interests.

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