Postprint: A Study on the Early Predictive Value of Biomarker Trends in Catabolism and Inflammatory Status for Chronic Critical Illness in Elderly Patients

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Abstract

Background Chronic critical illness (CCI) imposes a heavy social burden. Its prevalence in the elderly population is gradually increasing, yet relevant research based on Chinese elderly populations is insufficient. Indicators reflecting metabolic and inflammatory status may facilitate early prediction of CCI. Objective To investigate the changing trends of catabolic and inflammatory indicators and preliminarily explore early predictive factors for CCI occurrence in elderly ICU patients. Methods This study analyzed clinical records of elderly patients hospitalized in the geriatric ICU of Peking University First Hospital from 2018 to 2020. Clinical scores included Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Laboratory data included blood urea nitrogen-to-creatinine ratio (UCR), 24-hour urinary urea nitrogen (UUN), neutrophil-to-lymphocyte ratio (NLR), day 7 UCR/day 3 UCR ratio (UCRR7/3), day 7 UUN/day 3 UUN ratio (UUNR7/3), and their changing trends. Patients were divided into a CCI group (defined as persistent organ dysfunction $ $14 days) or a rapid recovery (RAP) group. Multivariate logistic regression analysis was used to explore influencing factors for CCI occurrence in elderly ICU patients, and receiver operating characteristic (ROC) curves were plotted to evaluate the predictive value of these factors. Mortality and hospitalization rates at 90-day follow-up were also recorded. Results A total of 115 patients were included, of whom 40 had CCI. The CCI group showed higher infection rate, APACHE II score on ICU day 1, APACHE II score on ICU day 7, SOFA score, lymphocyte count (LY) on ICU day 1, UCR on ICU day 1, UCR on ICU day 3, white blood cell count (WBC) on ICU day 7, neutrophil count (NE), NLR, C-reactive protein (CRP), UCR, UUN, UCRR7/3, and UUNR7/3

compared with the RAP group, while NLR on ICU day 1, hemoglobin (Hb), LY, and albumin (Alb) on ICU day 7 were lower (P<0.05). Mortality and continued hospitalization rates were higher in the CCI group than in the RAP group (P<0.05). Multivariate logistic regression analysis revealed that Hb on ICU day 7 (OR=0.942, 95%CI=0.906~0.979, P=0.003), NLR (OR=1.208, 95%CI=1.025~1.423, P=0.024), CRP (OR=1.034, 95%CI=1.011~1.057, P=0.003), UCRR7/3 (OR=32.418, 95%CI=2.412~435.736, P=0.009), and UUNR7/3 (OR=22.889, 95%CI=2.421~216.372, P=0.006) were influencing factors for CCI occurrence in elderly ICU patients. ROC curve analysis showed that the area under the curve (AUC) for UCRR7/3, UUNR7/3, CRP, Hb, and NLR were 0.787, 0.868, 0.808, 0.808, and 0.814, respectively. The combined AUC of these five factors for predicting CCI in elderly ICU patients was 0.962 (95%CI=0.932~0.992), with an optimal cutoff value of 0.59, sensitivity of 85.0%, and specificity of 96.0%. Conclusion Hb, NLR, CRP, UCRR7/3, and UUNR7/3 on ICU day 7 are early predictive factors for CCI in elderly ICU patients. Establishing a combined prediction model based on these five factors may help provide early warning of CCI occurrence in the elderly.

Full Text

Trajectory in Biomarkers of Metabolic and Inflammatory States as Early Predictors of Chronic Critical Illness in Aging Patients

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Abstract

Background: Chronic critical illness (CCI) imposes a substantial societal burden, with increasing prevalence among aging populations. However, research based on Chinese elderly cohorts remains limited. Biomarkers reflecting metabolic and inflammatory states may facilitate early prediction of CCI.

Objective: To investigate the trajectory of catabolic and inflammatory indicators and identify potential early predictors of CCI in elderly intensive care unit (ICU) patients.

Methods: We retrospectively analyzed clinical records of elderly patients admitted to the geriatric ICU at Peking University First Hospital between 2018 and 2020. Clinical assessments included Sequential Organ Failure Assessment

(SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Laboratory data comprised blood urea nitrogen-to-creatinine ratio (UCR), 24-hour urine urea nitrogen (UUN), neutrophil-to-lymphocyte ratio (NLR), day 7-to-day 3 UCR ratio (UCRR7/3), day 7-to-day 3 UUN ratio (UUNR7/3), and their trajectories. Patients were categorized into CCI (persistent organ dysfunction $ $14 days) or rapid recovery (RAP) groups. Multivariate logistic regression identified factors influencing CCI development, while receiver operating characteristic (ROC) curves evaluated predictive performance. Mortality and hospitalization rates were recorded at 90-day follow-up.

Results: Among 115 included patients, 40 developed CCI. The CCI group exhibited significantly higher infection rates, APACHE II scores on days 1 and 7, SOFA scores on day 7, lymphocyte counts (LY) and UCR on day 1, UCR on day 3, and white blood cell count (WBC), neutrophil count (NE), NLR, C-reactive protein (CRP), UCR, UUN, UCRR7/3, and UUNR7/3 on day 7 compared to the RAP group (P<0.05). Conversely, NLR on day 1 and hemoglobin (Hb), LY, and albumin (Alb) on day 7 were lower in the CCI group (P<0.05). Mortality and continued hospitalization rates were also higher in the CCI group (P<0.05). Multivariate analysis revealed that Hb on day 7 (OR=0.942, 95%CI=0.906-0.979, P=0.003), NLR (OR=1.208, 95%CI=1.025-1.423, P=0.024), CRP (OR=1.034, 95%CI=1.011-1.057, P=0.003), UCRR7/3 (OR=32.418, 95%CI=2.412-435.736, P=0.009), and UUNR7/3 (OR=22.889, 95%CI=2.421-216.372, P=0.006) were independent predictors of CCI. ROC analysis showed AUCs of 0.787, 0.868, 0.808, 0.808, and 0.814 for UCRR7/3, UUNR7/3, CRP, Hb, and NLR, respectively. The combined model achieved an AUC of 0.962 (95%CI=0.932-0.992), with optimal cutoff 0.59, sensitivity 85.0%, and specificity 96.0%.

Conclusion: Hb, NLR, CRP on day 7, and UCRR7/3, UUNR7/3 serve as early predictors of CCI in elderly ICU patients. A predictive model incorporating these five factors may facilitate early warning and prevention of CCI in aging populations.

Keywords: Critical Illness; Aged; Chronic critical illness; Biomarkers; ICU; SOFA score; APACHE II score; Forecasting

Introduction

Chronic critical illness (CCI) was first described by Girard and Raffin in 1985 [1]. In 2019, Gardner et al. [2] defined CCI as ICU stay $ $14 days with persistent organ dysfunction, assessed by SOFA score on day 14. CCI patients experience poor post-discharge outcomes, including hospice care, readmission, and late hospital mortality, with 12-month mortality reaching 41%, compared to 4% in non-CCI patients who recover well and return to normal life [3]. The incidence of CCI increases significantly in elderly populations, with higher mortality and

disability rates and worse prognosis [4], yet characteristics of this population remain poorly understood, particularly in Chinese cohorts.

Beyond persistent organ dysfunction, persistent inflammation, immunosuppression, and catabolism syndrome (PICS) has replaced late multiple organ failure as the primary phenotype of CCI [5], offering new directions for exploring clinical predictors. Persistent inflammation and immunosuppression are crucial mechanisms in CCI pathogenesis. In a post-trauma CCI cohort [6], albumin and hemoglobin concentrations declined rapidly, with more pronounced and prolonged decreases in CCI patients. CRP levels on day 10 were higher in the CCI group, though trends in CRP, neutrophil count, and NLR were less distinct. Whether earlier inflammatory and immune markers can predict CCI remains uncertain, and the optimal biomarker for CCI-associated catabolism is unresolved. Serum creatinine is not an ideal biomarker due to multiple confounding factors. Blood urea nitrogen (BUN) reflects increased muscle catabolism, amino acid release, and metabolism, rising gradually 3–4 days after ICU admission with higher peaks and longer duration in prolonged ICU stays. In CCI patients, the urea-to-creatinine ratio (UCR) increased more than twofold by day 10, while non-CCI patients showed only a slight increase followed by decline [6]. Twenty-four-hour urine urea nitrogen (UUN) also reflects catabolic status, is easily collected, and avoids additional blood draws. Both UCR and UUN may serve as potential biomarkers of catabolic state in CCI [7-8], though no studies have investigated UUN as a CCI biomarker, and the predictive value of earlier trajectories of UUN and UCR remains undefined.

Therefore, identifying biomarkers that can predict CCI early (<10 days) is crucial for enabling early intervention and reducing CCI incidence. This study retrospectively analyzed clinical records and laboratory data from elderly ICU patients to characterize laboratory indicator trajectories and identify early predictors of CCI.

Methods

Study Population

We retrospectively analyzed clinical data and laboratory indicators from elderly patients treated in the geriatric ICU at Peking University First Hospital between 2018 and 2020, along with 90-day hospitalization and mortality rates. Inclusion criteria were: (1) age $ $65 years; (2) ICU stay $ $24 hours. Exclusion criteria included: (1) malignant disease undergoing treatment within one year; (2) high-dose immunosuppressive therapy or autoimmune disease; (3) hematologic malignancy; (4) death within 14 days; (5) treatment withdrawal; (6) incomplete clinical data. The study was approved by the Peking University First Hospital Ethics Committee (2022 Research 437-002).

Clinical Scores

We collected SOFA and APACHE II scores on ICU days 1 and 7. The SOFA score assesses six organ systems (respiratory, coagulation, liver, cardiovascular, neurological, and renal) with each domain scored 0–3, where higher scores indicate worse prognosis [9]. The APACHE II score, developed by Knaus et al. [10] in 1985, quantifies acute physiological abnormalities and comprises three components: Acute Physiology Score (APS), Age Score, and Chronic Health Score (CPS). The theoretical maximum is 71 points, with higher scores indicating greater severity.

Laboratory Indicators

We collected white blood cell count (WBC), hemoglobin (Hb), neutrophil count (NE), lymphocyte count (LY), albumin (Alb), BUN, serum creatinine (Scr), CRP, and UUN on days 1, 3, and 7. We calculated UCR [UCR = BUN (mmol/L) × 100 / Scr (mol/L)], NLR, day 7-to-day 3 UCR ratio (UCRR7/3), and day 7-to-day 3 UUN ratio (UUNR7/3).

Follow-up and Grouping

Follow-up was conducted via telephone and medical record review until 90 days post-discharge or until June 30, 2021. Outcomes at 90 days were categorized as: continued hospitalization, discharged, or died within 90 days. Patients were divided into CCI group (ICU stay $ $14 days with persistent organ dysfunction) and rapid recovery (RAP) group (ICU stay <14 days with organ function recovery) [11]. Persistent organ dysfunction was defined as cardiovascular SOFA score $ $1 or any other organ system score $ $2 on day 14.

Statistical Analysis

Data were analyzed using SPSS 26.0 and GraphPad Prism 8.0. Normality was assessed using Kolmogorov-Smirnov test. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared between groups using non-parametric tests. Categorical variables were expressed as n (%) and compared using ^{2} test or Fisher' s exact test. Multivariate logistic regression identified factors influencing CCI development, expressed as odds ratios (OR) with 95% confidence intervals (CI). ROC curves evaluated predictive value and calculated cutoff points. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

From 2018–2020, 120 patients were admitted to the geriatric ICU. Two had incomplete data and three died within 14 days (due to severe pneumonia, septic shock, and acute liver failure), leaving 115 patients for analysis. The cohort comprised 96 males (83.5%) and 19 females (16.5%) with median age 87.0 (82.0,

94.0) years. Forty patients (34.8%) developed CCI and 75 (65.2%) were in the RAP group. Among CCI patients, 11 (27.5%) died, 14 (35.0%) remained hospitalized, and 15 (37.5%) were discharged by 90 days.

Clinical Characteristics Comparison

Age, sex, BMI, and proportions of cardiovascular disease and trauma did not differ significantly between groups (P>0.05). The CCI group had a significantly higher infection rate than the RAP group (P<0.05) .

Clinical Scores Comparison

Day 1 SOFA scores were similar between groups (P>0.05). However, the CCI group had significantly higher APACHE II scores on day 1 and day 7, and higher SOFA scores on day 7 (all P<0.05) .

Laboratory Indicators Comparison

Day 1 WBC, NE, Hb, CRP, and day 3 UUN did not differ significantly between groups (P>0.05). The CCI group showed significantly higher LY and UCR on day 1, higher UCR on day 3, and higher WBC, NE, NLR, CRP, UCR, UUN, UCRR7/3, and UUNR7/3 on day 7 (all P<0.05). Conversely, NLR on day 1 and Hb, LY, and Alb on day 7 were significantly lower in the CCI group (P<0.05) .

90-Day Outcomes Comparison

Ninety-day outcomes differed significantly between groups (P<0.001). The CCI group had higher mortality and continued hospitalization rates compared to the RAP group (P<0.05) .

Multivariate Logistic Regression Analysis

Based on literature showing day 7 data has higher predictive value [3] and excluding collinear variables, we performed multivariate logistic regression with day 7 APACHE II score, Hb, NLR, Alb, CRP, UCRR7/3, and UUNR7/3 as independent variables. Results showed that Hb on day 7 (OR=0.942, 95%CI=0.906-0.979, P=0.003), NLR (OR=1.208, 95%CI=1.025-1.423, P=0.024), CRP (OR=1.034, 95%CI=1.011-1.057, P=0.003), UCRR7/3 (OR=32.418, 95%CI=2.412-435.736, P=0.009), and UUNR7/3 (OR=22.889, 95%CI=2.421-216.372, P=0.006) were independent predictors of CCI in elderly ICU patients .

Predictive Value of the Model

A predictive model was constructed using these five factors: Model = 2.853×UCRR7/3 + 3.594×UUNR7/3 + 0.23×CRP (mg/L) + 687.891$×1/$Hb(g/L)$+ 0.157×$NLR - 15.212 (all day 7 values). ROC analysis revealed AUCs of 0.787,

0.868, 0.808, 0.808, and 0.814 for UCRR7/3, UUNR7/3, CRP, Hb, and NLR, respectively. The combined model achieved an AUC of 0.962 (95%CI=0.932-0.992), with optimal cutoff 0.59, sensitivity 85.0%, and specificity 96.0%, demonstrating excellent predictive performance [Figure 1: see original paper].

Discussion

The term PICS was first introduced in 2012 [12], providing a potential mechanistic framework for CCI. This study explored trajectories of inflammatory and metabolic indicators in CCI patients, offering early predictive factors and intervention targets.

CCI incidence is high in elderly patients (5–15%) [13]. In our cohort with median age 87.0 (82.0, 94.0) years, CCI incidence reached 34.8%. Elderly CCI patients demonstrate more pronounced and persistent abnormalities in inflammatory, immunosuppressive, and catabolic biomarkers compared to RAP patients, with PICS playing a major role [14]. CCI patients had higher mortality and prolonged hospitalization (37.5% still hospitalized at 90 days), requiring extensive nutritional and rehabilitative care and imposing substantial healthcare burdens. Early predictive indicators are urgently needed to enable timely intervention and reduce CCI incidence.

Day 1 diagnoses, disease severity, and laboratory data cannot predict CCI development in elderly patients [15]. With improved ICU care, organ dysfunction has become a bimodal phenomenon: one-third occur early (within 3 days) while two-thirds occur later (average 7 days) [16]. We therefore analyzed laboratory indicators on days 1, 3, and 7, as day 7 data demonstrate higher prognostic value [3].

On day 7, CCI patients had higher WBC, NE, CRP, and other inflammatory and stress metabolic indicators than RAP patients. Lower LY and Hb in the CCI group on day 7 may relate to damage-associated molecular patterns (DAMPs) released from injured cells and accumulation of myeloid-derived suppressor cells (MDSCs) [18-19]. Persistent high MDSC levels suppress lymphocyte proliferation and differentiation, maintaining immunosuppression [20-21]. Extensive myeloid cell differentiation into MDSCs also impedes erythrocyte maturation, causing anemia [22]. Elevated NLR on day 7 reflects the balance between innate (NE) and adaptive (LY) immunity, indicating persistent inflammation and immunosuppression in CCI [23]. Other markers like IL-6, IL-8, IFN-γ, IP-10, MIP-1α, and GM-CSF may also predict CCI [3,24], but are not routinely available.

Significantly higher UCR and UUN on day 7 in CCI patients indicated enhanced catabolism compared to RAP patients. The ratios UCRR7/3 and UUNR7/3, reflecting trajectories rather than absolute values, were also higher in CCI patients, suggesting more pronounced catabolic progression. Elevated UCR may reflect combined muscle and exogenous amino acid catabolism and altered protein homeostasis associated with sarcopenia, a metabolic hallmark of CCI.

Trauma studies showed day 10 UCR elevation as a catabolism indicator [6]. Using UCRR7/3 and UUNR7/3 advances CCI prediction to day 7, enabling earlier intervention. UUNR7/3 predicts CCI using 24-hour urine collection, providing more accurate assessment of whole-day catabolism without additional blood draws. In subgroup analysis of elderly infected patients (35 CCI, 32 RAP), UCRR7/3 and UUNR7/3 also demonstrated predictive value. Thus, day 7 catabolic trajectories predict CCI in elderly patients, suggesting early nutritional support targeting metabolic pathways may reduce CCI incidence. While Alb <30 g/L indicates catabolism, it does not predict CCI but correlates with severity and mortality [25]. In our study, day 7 Alb was lower in CCI patients but remained >30 g/L, possibly due to albumin supplementation, indicating Alb alone has limited utility as a biomarker.

Limitations

This study has several limitations: (1) It is a single-center retrospective study with a small sample size, limiting generalizability; (2) The single-center elderly ICU population may introduce selection bias, requiring validation in larger, multicenter cohorts; (3) Short follow-up (90 days) precludes assessment of long-term functional outcomes; (4) Unmeasured confounders (family support, rehabilitation status, anxiety/depression) may influence results. Nevertheless, the one-week trajectories and combined model reflect the pathophysiology of inflammation, immunosuppression, and catabolism, advancing early CCI prediction to day 7 and providing early warning for elderly CCI.

Conclusion

Elderly ICU patients have high CCI incidence with substantial healthcare consumption. Early diagnosis and intervention are essential to reduce incidence and costs. This study utilized common, easily obtainable, minimally invasive laboratory indicators and their trajectories—rather than single time-point values—to provide early warning for elderly CCI. Monitoring these trends in clinical practice may enable early targeted intervention to reduce CCI incidence in aging populations.

Author Contributions

LI Jiaxin and JIAO Hongmei conceived and designed the study. FU Zhifang and SUN Dan performed feasibility analysis. LI Jiaxin, LIU Zhonghui, and XIE Shuo collected data. LI Jiaxin and XIE Shuo analyzed data and performed statistical analysis. LIU Zhonghui, FU Zhifang, and SUN Dan validated results and revised the English manuscript. LI Jiaxin, LIU Zhonghui, and XIE Shuo drafted the manuscript. JIAO Hongmei supervised the study and is responsible for the overall content.

Conflict of Interest: The authors declare no conflicts of interest.

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