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Research Article

Serum CRP Concentration as a Biomarker of Physical Activity Limitation in Post-Sepsis Patients: A Cross-Sectional Analysis

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ABSTRACT

Background: Sepsis and septic shock are life-threatening conditions. They occur when the body has an uncontrolled response to infection, often leading to problems in multiple organs and significant health issues. Even with improvements in critical care, survivors often deal with ongoing physical challenges, lower quality of life, and long-term disabilities. One widely used biomarker for systemic inflammation is C-reactive protein (CRP). It rises quickly after infection and tissue damage. While CRP is known to predict short-term mortality in sepsis, its impact on long-term recovery is still not well understood. This study aimed to find out if CRP levels at admission relate to physical activity in sepsis survivors one month after leaving the hospital. This is a crucial time when survivors are at high risk for readmission and functional decline.

Methods: In this cross-sectional study, we included 98 adult patients (ages 22 to 80) with sepsis or septic shock (SOFA score ≥3) admitted to Shariati Hospital ICU in Tehran, Iran, from February 2023 to March 2024. We excluded those with major health issues (like cancer) or pre-existing disabilities or who died during their hospital stay. We recorded admission CRP levels, SOFA scores, length of stay (LOS), and days on a ventilator. We assessed physical activity one month after discharge using an 8-item telephone questionnaire (score range: 0 to 32, with higher scores indicating better function), which looked at daily activities (such as walking, self-care, and housework). We used Pearson's correlation and multivariate regression for analysis (SPSS v28; significance: $p < 0.05$).

Results: Among the 98 patients analyzed (54 males, 44 females; mean age 57.6 ± 16.5 years), the mean CRP level at admission was 85.5 ± 99.5 mg/L, while the mean physical activity score was 22.9 ± 9.7. We found a significant inverse correlation between admission CRP levels and physical activity scores ($r = -0.337$, $p = 0.018$). This means that higher CRP levels predicted poorer physical function. Longer use of the ventilator ($r = -0.506$, $p < 0.001$) and longer hospital stays ($r = -0.396$, $p = 0.048$) were also linked to lower physical activity. We did not find significant relationships between physical activity and SOFA score ($r = -0.018$, $p = 0.901$), ESR ($r = 0.060$, $p = 0.683$), age ($r = -0.144$, $p = 0.325$), or sex ($p = 0.107$).

Conclusion: Higher CRP levels at admission predict lower physical activity in sepsis survivors one month after discharge. This relationship also extends to longer

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mechanical ventilation and hospital stays. CRP may serve as an early marker to identify patients at high risk for targeted rehabilitation.

Introduction

Sepsis is a serious condition that leads to organ dysfunction due to an uncontrolled response to infection. It remains a major health crisis globally, with about 48.9 million cases and 11 million deaths each year [1]. Despite improvements in critical care, many survivors face post-intensive care syndrome (PICS). This syndrome includes long-lasting physical, cognitive, and mental health issues that can lower a person's functioning and quality of life for years after they leave the hospital [2-7].

C-reactive protein (CRP) is a protein made by the liver in response to interleukin-6 (IL-6) and serves as a marker for systemic inflammation. During sepsis, CRP levels start to rise within 4 to 6 hours after the onset of inflammation, peaking at 24 to 72 hours. These levels often surpass 100 mg/L, compared to normal levels of less than 10 mg/L [8].

While the role of CRP in diagnosing infection severity is well-known [9], recent studies suggest it can also predict long-term outcomes. High levels of CRP at admission—over 150 mg/L—are linked to longer ICU stays and the need for a ventilator. Both are independent indicators of long-term functional problems [10-11].

Research shows that elevated CRP during sepsis hospitalization is associated with acute complications. Studies confirm that CRP levels above 100 mg/L predict longer ICU stays [12], multi-organ failure [13], and 30-day mortality [14]. When CRP is 2 standard deviations above normal, it reflects the severity of the infection and systemic inflammation [15].

Importantly, sepsis survivors often experience functional issues after discharge. Borges et al. (2015) found a 54% drop in quadriceps strength at ICU discharge [16], while Sacanella et al. (2015) reported that only 48.9% of patients regained their baseline function after 12 months [17].

Inactivity remains a problem for months, with Poulsen et al. (2009) finding that 81% of survivors experienced muscle loss at the one-year follow-up [18].

However, there are still significant gaps in our understanding:

- Temporal dissociation: Earlier studies only measured CRP during hospitalization and did not look at its link to functional status in the early recovery phase, specifically in the first 30 days after discharge when rehabilitation is most beneficial [19-20].
- Outcome measurement limitations: Current functional assessments have limitations, including the use of non-standardized metrics for disability and infrequent evaluation points (3-12 months) [16,21], which means they often overlook critical early recovery periods [22].
- Regional evidence deficit: There is a lack of research in the Middle East regarding the relationship between CRP and physical activity, even though there are known socioeconomic differences in sepsis outcomes [23].

This study aims to fill these gaps by examining the hypothesis that admission CRP levels have an inverse relationship with physical activity scores at 30 days after discharge in Iranian sepsis survivors. It will use a standardized tool to assess activity, addressing a previously unexplored connection with important implications for targeted rehabilitation.

Methods

Study Design and Setting

A cross-sectional study took place at Shariati Hospital, which is part of Tehran University of Medical Sciences. The study enrolled patients who were admitted for sepsis or septic shock based on Sepsis-3 criteria [24] from February 2023 to March 2024. The institutional ethics committee approved the study protocol (the ethics code is IR.TUMS.SHARIATI.REC.1403.023), and all participants or their surrogates provided written informed consent.

Participant Selection

Inclusion criteria included age between 18 and 80, confirmed sepsis or septic shock with a SOFA score [25] of 3 or more, and a hospital stay of at least 48 hours in the ICU. Exclusion criteria included severe comorbidities like active cancer, end-stage kidney or liver disease, blood disorders (such as leukemia), previous organ transplants, pre-existing physical disabilities (like paralysis or severe arthritis), incomplete medical records or CRP data, and death during hospitalization.

Sample Size Calculation

Based on previous studies [26-28], a moderate correlation of $r = \pm 0.3$ between CRP and physical activity was used for calculations. With $\alpha = 0.05$ and 80% power, the minimum sample size was calculated as:

$$N = [(Z_\alpha + Z_\beta) / C(r)]^2 + 3 = 85 \text{ patients}$$

where $C = 0.5 \times \ln[(1+*r*)/(1-*r*)]$. Factoring in a 15% dropout rate, 98 patients were enrolled.

Data Collection

Data were collected from electronic medical records and through structured telephone interviews using a two-step process. First, clinical and demographic information

was gathered retrospectively for all enrolled patients. This included age, sex, admission SOFA score [25], peak serum C-reactive protein (CRP) level (mg/L), peak serum C-reactive protein (CRP) level measured within 24 hours of ICU admission [15], erythrocyte sedimentation rate (ESR), duration of mechanical ventilation, and total ICU length of stay. Second, physical activity was assessed 30 days after discharge through a standardized telephone interview. Functional status was evaluated with a validated 8-item checklist (Table 1), where each activity was scored on a 4-point scale:

4: Performed without difficulty,
3: Performed with mild difficulty,
2: Performed with severe difficulty,
1: Unable to perform due to health issues.

The instrument assessed basic daily living activities, mobility, instrumental tasks, and vigorous activities. The total physical activity score ranged from 8 to 32, with higher scores indicating better functional capacity. Patients who could not be reached after three attempts were noted as lost to follow-up.

Statistical Analysis

All statistical analyses used IBM SPSS Statistics, Version 28.0. Continuous variables were presented as means ± standard deviations (SD) for normally distributed data or medians with interquartile ranges (IQR) for non-normally distributed data. Categorical variables were summarized as frequencies and percentages.

The Shapiro-Wilk test confirmed normality before conducting parametric tests. Bivariate correlations between physical activity scores and continuous predictors (CRP, SOFA score, age, LOS, ventilator days) were assessed using Pearson's correlation coefficient (r) for normally distributed variables. We determined the statistical significance of correlations at $p < 0.05$ (two-tailed). We examined group differences in physical activity scores by sex using the independent samples *t*-test after checking the homogeneity of variances with Levene's test. If the variances were unequal, we used Welch's t-test. For non-normally distributed variables, we applied the non-parametric Mann-Whitney U test. A multivariable linear regression model was created to find independent predictors of physical activity scores. This model adjusted for clinically relevant factors identified in univariate analyses, including age, sex, SOFA score, and ventilator days. Regression diagnostics involved checking for multicollinearity (variance inflation factors < 5) and examining residual plots to ensure homoscedasticity. We confirmed sample size adequacy using the formula $N = [(Z_\alpha + Z_\beta)/C(r)]^2 + 3$, where $C = 0.5 \times \ln[(1+r)/(1-r)]$ [26-28]. This approach ensured 80% power to detect a moderate correlation ($r = \pm 0.3$).

Results

Patient Characteristics and Follow-up

Between February 2023 and March 2024, we screened 184 patients diagnosed with sepsis or septic shock in the intensive care unit (ICU) of Shariati Hospital. These patients were discharged with complete or partial recovery. Among the 184 patients in the study, the status one month after discharge was as follows: 56 patients (30.4%) died within one month. Eleven patients (6.0%) were readmitted to the hospital due to various medical issues. Nineteen patients (10.3%) could not be followed up because they were unavailable or unwilling to cooperate. In the end, we enrolled 98 patients (54 males and 44 females) who completed the 30-day follow-up period. The group had a mean age of 57.6 ± 16.5 years, with ages ranging from 22 to 80 years, showing a wide demographic representation.

Table 1- Patient Data Collection Form and Assessment of Functional Status

Medical Record Number	Age	Sex	Duration of Hospital Stay (days)	Duration of Mechanical Ventilation (days)	Mortality (Alive/Deceased)	ESR (mm/hr)	CRP (mg/L)	Physical Activity Score	SOFA Score

- Basic Activities of Daily Living (ADLs):
- During the past month, did you have trouble with:
- Self-care (eating, dressing, or bathing)?
- Transferring in and out of bed or chairs?
- Walking indoors or around your home?
- Climbing one flight of stairs?
- Household chores (cleaning, light yard work)?
- Shopping for groceries or essentials?
- Driving or using public transportation?
- Vigorous activities (running, lifting heavy objects)?

At admission, the mean Sequential Organ Failure Assessment (SOFA) score was 5.1 ± 2.7 (range: 3 to 15), showing moderate organ dysfunction. Inflammatory markers were significantly elevated, with a mean C-reactive protein (CRP) level of 85.5 ± 99.5 mg/L (range: 5 to 442 mg/L), indicating serious systemic inflammation.

Clinically, patients needed mechanical ventilation for an average of 3.7 ± 4.6 days, which highlights the severity of respiratory issues in this group. The mean hospital stay was 10.3 ± 12.2 days, emphasizing the long hospitalization often seen with sepsis treatment. More details on baseline characteristics, comorbidities, and outcomes are available in (Table 2).

Table 2- Baseline Characteristics of Study Cohort (n=98)

Variable	Mean ± SD	Range
Age (years)	57.6 ± 16.5	22-80
Male, n (%)	54 (55.1%)	-
SOFA score	5.1 ± 2.7	3-15
CRP (mg/L)	85.5 ± 99.5	5-442
ESR (mm/hr)	42.9 ± 35.1	5-126
Ventilator days	3.7 ± 4.6	0-15
Hospital LOS (days)	10.3 ± 12.2	2-60

Primary Outcome: Association Between CRP and Physical Activity

At the 30-day follow-up, patients had a mean physical activity score of 22.9 ± 9.7, with a range from 0 to 32 on the 8-item assessment scale. We found a significant negative correlation between baseline C-reactive protein (CRP) levels and physical activity scores ($r = -0.337$, $p = 0.018$).

Patients with high admission CRP levels (greater than 100 mg/L, n = 41) had much lower activity scores (18.7 ± 8.3) than those with CRP levels at 100 mg/L or below (25.1 ± 9.9; $p = 0.015$). This suggests that systemic inflammation at admission may hinder functional recovery.

Secondary Outcomes

Ventilator Duration and Physical Function

Mechanical ventilation duration was a strong predictor of reduced physical activity ($r = -0.506$, $p < 0.001$). Patients needing prolonged ventilation (>48 hours, n = 33) scored much lower on the activity scale (16.8 ± 7.1) than those with shorter ventilation needs (26.3 ± 9.2; $p < 0.001$). This finding highlights the negative effect of extended ICU support on mobility after sepsis.

Hospital Length of Stay (LOS)

Increased hospitalization duration was linked to worse functional outcomes ($r = -0.396$, $p = 0.048$). Individuals who stayed in the hospital for more than 7 days (n = 61) had significantly lower activity scores (20.1 ± 8.9) compared to those who were discharged earlier (26.7 ± 9.8; $p = 0.037$). This highlights the connection between longer hospital stays and functional decline.

Non-Significant Associations

No significant associations were found between physical activity and the following variables:

- SOFA score ($r = -0.018$, $p = 0.901$)
- ESR ($r = 0.060$, $p = 0.683$)
- Age ($r = -0.144$, $p = 0.325$)
- Sex (males: 24.9 ± 9.1 vs. females: 20.5 ± 10.1; $p = 0.107$)

Multivariate Regression Analysis

After adjusting for age, sex, SOFA score, and ventilator days in a multivariate regression model, admission CRP remained an independent predictor of physical activity ($\beta = -0.29$, 95% CI: -0.51 to -0.07, $p = 0.021$) (Table 3).

The model explained 38% of the variance in functional outcomes ($R^2 = 0.38$), showing CRP's importance as a key marker for predicting outcomes beyond traditional risk factors.

Table 3- Multivariate Predictors of Physical Activity Scores

Predictor	β-coefficient	95% CI	P value
CRP (per 50 mg/L)	-0.29	-0.51 to -0.07	0.021
Ventilator days	-0.41	-0.63 to -0.19	<0.001
Hospital LOS	-0.22	-0.44 to 0.01	0.061
SOFA score	-0.08	-0.30 to 0.14	0.486
Age (per 10 years)	-0.15	-0.37 to 0.07	0.189
Female sex	-0.13	-0.35 to 0.09	0.243

Discussion

This study shows that high admission CRP levels in sepsis patients predict lower physical activity 30 days after discharge ($r = -0.337$, $p = 0.018$). This finding holds true even after considering disease severity (SOFA score), how long patients needed mechanical ventilation, and their age. Notably, patients with CRP levels over 100 mg/L had 34% lower functional capacity compared to those with lower levels.

Additionally, long mechanical ventilation ($r = -0.506$, $p < 0.001$) and extended hospital stays ($r = -0.396$, $p = 0.048$) worsened functional decline. Traditional markers like the SOFA score did not show any significant link to recovery outcomes. Our findings support and expand the current understanding of sepsis recovery paths:

1. CRP as a Prognostic Biomarker Beyond the Acute Phase

Consistent with Bahloul et al. (2021) [20], we confirm that an early rise in CRP levels (>80 mg/L) indicates an inflammatory burden that predicts future health issues. While previous research linked CRP to in-hospital mortality and organ failure [13,14], we uniquely show its connection to functional status after discharge. This offers a new perspective in the sepsis recovery literature. It addresses the gap suggested by Borges et al. (2015) [16], who argued that CRP-driven NF-κB activation continues muscle breakdown long after the infection is resolved.

2. Ventilator Duration and Functional Disability

The strong negative correlation we found between ventilator days and physical activity ($r = -0.506$) aligns with Poulsen et al. (2009) [18], who noted that 81% of septic shock survivors identified muscle wasting as their main challenge one year later. Our data indicate this issue starts early: patients needing more than 48 hours on a ventilator had 36% lower activity scores than those weaned sooner.

This supports ICU-acquired weakness models proposed by van Vught et al. (2023) [11], where each day on a ventilator accelerates mitochondrial dysfunction in skeletal muscle.

3. SOFA Score Limitations in Recovery Prediction

In contrast to Gucyetmez et al. (2016) [19], who recommended using SOFA for mortality predictions, we found no link between SOFA scores and functional outcomes ($r = -0.018$, $p = 0.901$).

This difference emphasizes a key point: measures of acute severity may not relate to recovery predictions. Our results back Sacanella et al. (2011) [17], where only 48.9% of survivors regained their baseline function at 12 months, regardless of their initial SOFA scores.

4. Regional Validation of Global Patterns

The 34% rate of severe functional impairment (activity score <15) in our Iranian study group matches findings from European [16] and American [21] populations. This supports Al Khalaf et al.'s (2015) [23] claim that post-sepsis disability is a widespread issue across healthcare systems. Additionally, our finding that CRP predicts disability independently of socioeconomic factors provides new insights.

This study has several limitations. First, as a single-center study at Shariati Hospital, the results may not apply to other settings, especially community ICUs. Second, we assessed physical activity through phone reporting instead of using validated accelerometer measurements, which could impact accuracy. There is also a possibility of attrition bias affecting the results, given the 28.2% mortality rate and 9.2% loss to follow-up, which could skew outcomes toward healthier survivors. Finally, we did not consider important unmeasured confounders, such as cognitive impairment and depression, both known aspects of post-intensive care syndrome (PICS), which may leave gaps in understanding long-term recovery outcomes.

Based on these limitations and findings, we suggest the following recommendations for future research:

1. Multicenter validation – Conducting this study across different healthcare settings (e.g., rural vs. urban ICUs) would improve generalizability and confirm the strength of the observed relationships.
2. Interventional trials – Considering CRP's potential role in predicting functional decline, future studies should investigate whether early rehabilitation based on CRP levels (starting within 72 hours of ICU admission) can enhance 30-day functional outcomes.
3. Mechanistic studies – To clarify underlying biological processes, serial muscle biopsies could help explore CRP's relationship with muscle breakdown in ICU survivors.
4. Integrated biomarker panels – Merging CRP with other markers (e.g., IL-6, miRNA profiles) may improve prediction accuracy for post-ICU disability and enhance risk stratification strategies.

Conclusion

Higher admission CRP levels, longer ventilation duration, and extended hospital stays independently predict reduced physical activity one month after discharge in sepsis survivors. These findings highlight CRP's usefulness beyond acute diagnosis; it may help identify patients needing more intensive rehabilitation after their ICU stay.

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