# Immune status in chronic critical illness: a systematic review

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***Abstract***

**INTRODUCTION:** Currently, there is an increase in the number of patients who are classified as chronically critically ill patients. **OBJECTIVE:** The review is aimed at studying the indicators of the immune status of chronically critically ill patients. **MATERIALS AND METHODS:** PubMed and Google Scholar were used to identify relevant articles. The following 3 searches were performed: "chronically critically ill patients AND immune", "chronic critical illness AND immune", "persistent inflammation, immunosuppression, and catabolism syndrome AND immune". The literature review was limited from 2012 to August 2022. The inclusion criteria were as follows: (1) patients with chronic critical illness (CCI) or persistent inflammation, immunosuppression and catabolism syndrome (PICS); (2) comparison groups are at least one of the specified — patients undergoing rapid recovery, healthy volunteers; (3) parameters of the immune status, inflammation and catabolism are the study endpoints; (4) original articles. To assess the validity of the results, a risk of bias assessment was performed for each study included in the analysis. The risk of bias in non-randomised studies of exposures (ROBINS-E) tool was used. The Delphi method was executed in two rounds by three researchers to assess bias. **RESULTS:** Chronically critically ill patients with the immunosuppressive status have reduced levels of HLA-DR and ALC and elevated sPD-L1 and IL-10 levels. The results of the studies were rated at 'high' and 'moderate' risk of reporting bias. Their findings should be considered as low-quality results. **CONCLUSIONS:** Chronic critical illness is a poorly understood condition that periodically occurs in patients in the ICU. The immune status of chronically critically ill patients is a debatable issue, as the current data are insufficient to draw a definitive con-

# Иммунный статус при хроническом критическом состоянии. Систематический обзор

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***Реферат***

**АКТУАЛЬНОСТЬ:** В настоящее время наблюдается увеличение количества пациентов, которые классифицируются как пациенты с хроническим критическим состоянием. Основной причиной данного явления представляется то, что в результате внедрения более современных подходов лечения пациентов снизилась госпитальная летальность, и часть выживших пациентов переходит в категорию пациентов с хроническим критическим состоянием. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Целью настоящего обзора является изучение показателей иммунного статуса пациентов с хроническим критическим состоянием. **МАТЕРИАЛЫ И МЕТОДЫ:** Для поиска статей использованы международные базы данных PubMed и Google Scholar. Использованы запросы: «chronically critically ill patients AND immune», «chronic critical illness AND immune», «persistent inflammation, immunosuppression, and catabolism syndrome AND immune». Поиск ограничен статьями, опубликованными в период с 2012 г. по август 2022 г. Критерии включения: (1) пациенты, которым диагностировано хроническое критическое состояние (ХКС) или синдром персистирующего воспаления, иммуносупрессии и катаболизма (ПИКС); (2) группами сравнения являются хотя бы одна из указанных — пациенты с быстрым восстановлением, здоровые добровольцы; (3) конечными точками исследования являются показатели иммунитета, воспаления и катаболизма; (4) оригинальные исследования. Для оценки достоверности результатов проведена оценка риска систематической ошибки для исследований, включенных в анализ. Инструмент оценки систематической ошибки: ROBINS-E (The Risk Of Bias In Non-randomized Studies — of Exposure). Оценка систематической ошиб-

clusion. Based on the systematic review, further prospective trials are required to study the immune status of chronically critically ill patients.

**KEYWORDS:** chronic critical illness; persistent inflammation, immunosuppression and catabolism; immune status

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*For citation*: Berikashvili L.B., Geize A.V., Kornelyuk R.A., Plotnikov G.P. Immune status in chronic critical illness: a systematic review. Annals of Critical Care. 2023;1:133–144. https://doi.org/10.21320/1818-474X-2023-1-133-144

*Received*: 10.09.2022
*Accepted*: 03.12.2022
*Published online*: 31.01.2023

ки проводилась по методу Delphi в 2 этапа тремя исследователями. **РЕЗУЛЬТАТЫ:** Пациенты с хроническим критическим состоянием имеют иммуносупрессивный статус, который отражается в сниженном уровне HLA-DR и ALC, на фоне более высоких значений sPD-L1 и IL-10. Результаты изучения иммунного статуса пациента в настоящее время имеют высокий и средний риск систематической ошибки, а потому должны рассматриваться как результаты низкого качества. **ВЫВОДЫ:** Хроническое критическое состояние в настоящее время является малоизученным явлением, с которым периодически сталкиваются врачи отделения реанимации и интенсивной терапии. Вопрос относительно иммунного статуса пациентов с ХКС остается открытым, так как современных данных недостаточно для формирования окончательных выводов. На основании обзора литературы можно утверждать, что требуется дальнейшее проведение проспективных исследований для изучения иммунного статуса пациентов с хроническим критическим состоянием.

**КЛЮЧЕВЫЕ СЛОВА:** хроническое критическое состояние; синдром персистирующего воспаления, иммуносупрессии и катаболизма; иммунный статус

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*Для цитирования*: Берикашвили Л.Б., Гейзе А.В., Корнелюк Р.А., Плотников Г.П. Иммунный статус при хроническом критическом состоянии. Систематический обзор. Вестник интенсивной терапии им. А.И. Салтанова. 2023;1:133–144. https://doi.org/10.21320/1818-474X-2023-1-133-144

*Поступила*: 10.09.2022
*Принята к печати*: 03.12.2022
*Дата онлайн-публикации*: 31.01.2023

DOI: 10.21320/1818-474X-2023-1-133-144

## Introduction

The term chronic critical illness (CCI) was first proposed in 1985 [1]. Nevertheless, the definition of this state is still under discussion [2, 3]. The main reason for the absence of a standard definition of chronic critical illness is the lack of an obvious transition point between acute and chronic critical illness [2, 4]. Hence, there are so many approaches for defining CCI by the length of mechanical ventilation or hospitalization [5–17].

Currently, the number of patients with CCI in intensive care units has increased [18]. The principal cause of this phenomenon seems to be that recent advances in the medical care of patients with sepsis have decreased in-hospital mortality [19–21]. Consequently, some of the survivors enter a state of chronic critical illness [23, 24].

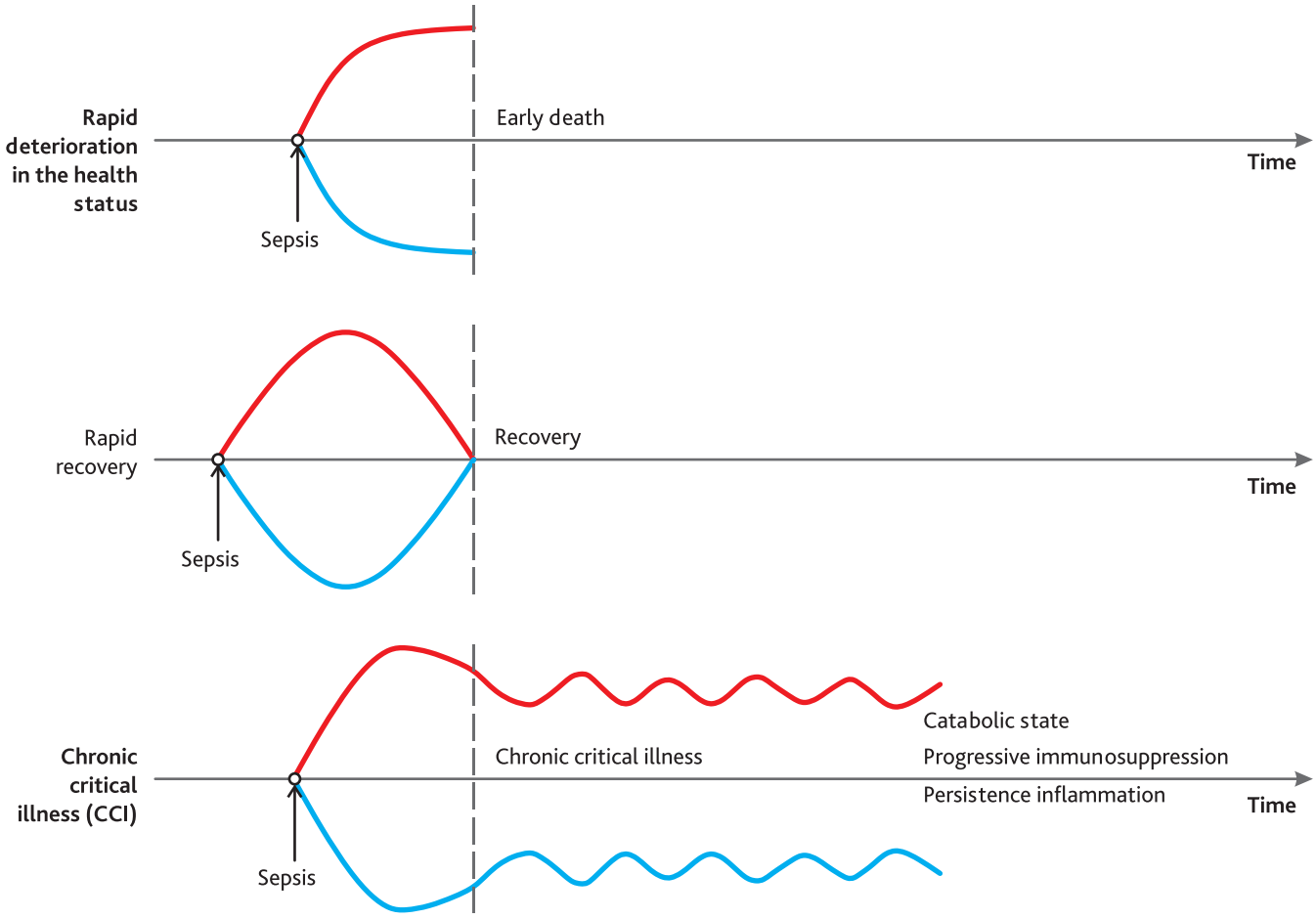


**Fig. 1.** Current concepts in the pathogenesis of PICS and CCI
Red line — the level of proinflammatory factors, blue line — the level of antiinflammatory factors.

Recently, evidence has emerged that patients with CCI have poor outcomes. For instance, CCI has been shown to be a risk factor of mortality within 1 year after diagnosis [24, 25]. Moreover, the pathophysiological studies describe the state of chronic critical illness as persistent inflammation, immunosuppression, and catabolism syndrome (PICS). The current concepts in the pathogenesis of PICS and CCI are presented in Fig. 1.

**Objective:** to evaluate the impact of chronic critical illness on the patients' immune status.

## Materials and methods

### Endpoints of the study

The primary endpoint of the study is the presence of statistically significant differences in the immune status of patients with chronic critical illness compared to patients with rapid recovery.

### Search strategy

Systematic literature search of studies was carried out in PubMed and Google Scholar on 10.08.2022. The search was limited to articles published between 2012 and August 2022. The following queries were used for the search: "Chronically critically ill patients AND immune", "Chronic critical illness AND immune", "persistent inflammation, immunosuppression, and catabolism syndrome AND immune". The filter "adults" was used. In addition, the backward snowballing method (analysis of references of included articles) for further studies was used.

### Eligibility criteria

Eligibility criteria were created according to the PICOS strategy (Table 1).

Therefore, the systematic review includes articles that meet the following inclusion criteria:

1) adult patients (age > 18) with CCI or PICS;
2) comparison group is patients with rapid recovery or healthy controls;

**Table 1.** Eligibility criteria according to PICOS

| Parameters | Inclusion criteria |
|---|---|
| Population | Adult patients (age > 18) with CCI or PICS |
| Intervention | Incident of critical state |
| Comparison | Patients with rapid recovery OR healthy controls |
| Outcome | Indicators of immune status, inflammation and catabolism |
| Study design | Original studies |

3) study endpoint are indicators of immune status, inflammation and catabolism
4) original studies.

### Study selection

The generated search queries were sent to three independent researchers, who screened the title/abstract of the articles. Studies that likely met the eligibility criteria were selected as articles for full text review. These articles were reviewed by two independent researchers. Articles that fully met the eligibility criteria were included in the systematic review. Any divergences were resolved by consensus with the involvement of an additional specialist.

### Risk of bias assessment

The risk of bias assessment was performed to assess the validity of the result of studies included in the systematic review. ROBINS-E (The Risk Of Bias In Non-randomized Studies — of Exposure) was chosen as a bias assessment tool [26].

Bias was assessed using the Delphi method in 2 rounds by three researchers.

**Delphi round 1.** In the first round, three researchers independently assessed articles for bias using ROBINS-E. The results were collected by the study director who identified divergences between the researchers' conclusions. The researchers were asked to anonymously provide a written rationale for each divergent domain of the ROBINS-E assessment results. These clarifications were sent to the study director.

**Delphi round 2.** Prior the second round, every researcher received from the study director the risk of bias assessment results and rationales written by other investigators. The anonymity was observed.

In the second round, the researchers were asked to assess the divergent domains again, taking into account the written rationales of two other researchers. Every researcher could anonymously agree or disagree with the colleagues' opinion. After reassessing the risk of bias using ROBINS-E, the results were sent to the study director for final decision.

## Results

### Articles search result

During the initial search, 491 articles were found. After title/abstract analysis, 25 articles were selected for full-

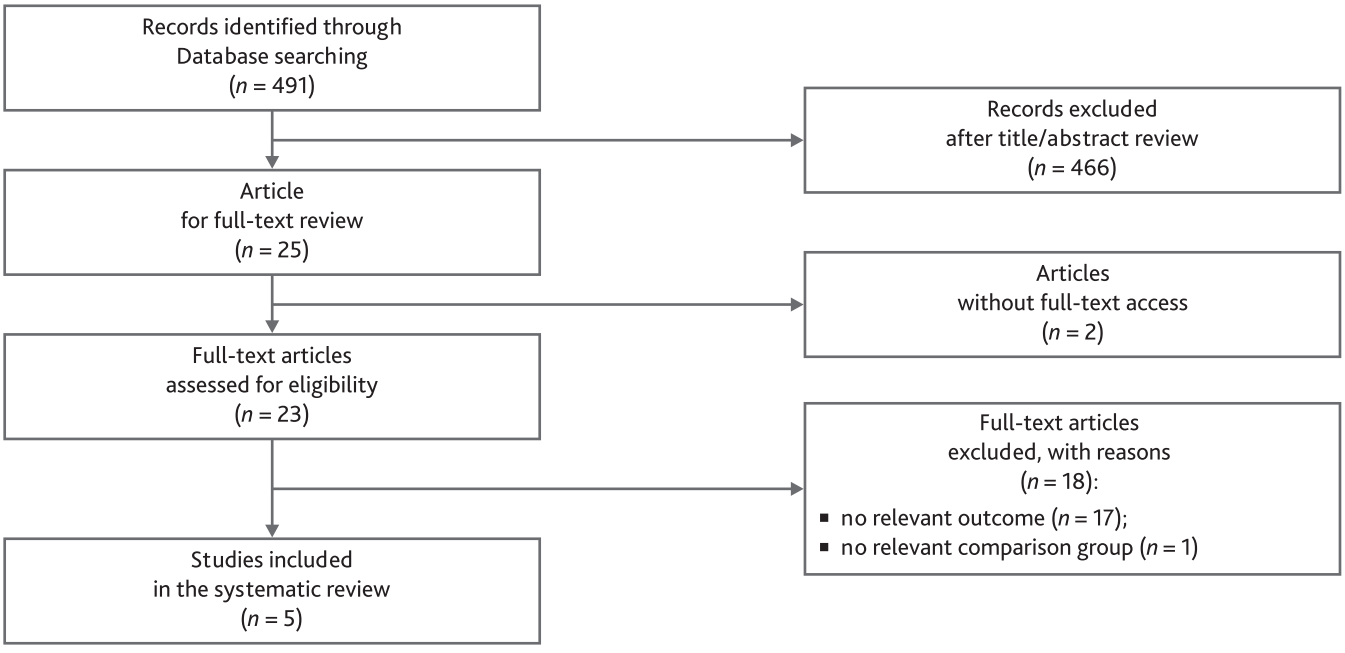


**Fig. 2.** Selection scheme for the articles reviewed in this study

text analysis. The full text of two of the 25 articles were not available. Consequently, only 23 articles were analyzed in full text. After the full-text review, only 5 of 23 articles met the eligibility criteria and were included in the systematic review (Fig. 2). Among the studies, 3 were prospective observational studies, 2 were post hoc analysis of prospective studies.

### Risk of bias assessment

Risk of bias assessed for all studies included in the systematic review (Table 2). According to the ROBINS-E, 2 of 5 studies have a moderate risk of bias, while 3 of 5 studies have a high risk of bias.

### Assessment of articles

Information about the articles included in the systematic review is presented in Table 3.

### Main results: Comparison of the immune status in patients with chronic critical illness and in patients with rapid recovery

**Immune status indicators: sPD-L1**. A number of studies have shown that patients with chronic critical illness had higher serum concentration of sPD-L1 compared to patients with rapid recovery ($p < 0.05$) [28, 30, 31]. J.A. Stortz, T.J. Murphy et al. [29] demonstrated that patients with rapid recovery were characterized by a gradual decrease in serum sPD-L1 concentration to normal range, while patients with chronic critical illness were characterized by a progressive increase in serum sPD-L1 concentration ($p < 0.05$).

**Immune status indicators: IL-10.** In two studies, patients with chronic critical illness had higher serum IL-10 concentration compared to patients with rapid recovery throughout the entire hospitalization period ($p < 0.05$) [30, 31].

**Immune status indicators: ALC.** J.A. Stortz, J.C. Mira et al. [30] showed that patients with chronic critical illness had a lower absolute lymphocyte count (ALC) compared to patients with rapid recovery on the 14th day after the diagnosis of sepsis. In another work, J.A. Stortz, T.J. Murphy et al. [29] demonstrated that patients with chronic critical illness and patients with rapid recovery had a lower absolute lymphocyte count (ALC) compared to normal range. Nevertheless, patients with rapid recovery were characterized by a rapid increase in ALC to normal range, while patients with chronic critical illness were characterized by a slow increase in ALC ($p = 0.036$).

**Immune status indicators: HLA-DR.** J.A. Stortz, T.J. Murphy et al. [29] demonstrated that patients with chronic critical illness and patients with rapid recovery had lower serum HLA-DR concentration compared to the healthy controls. At the same time, the dynamic of changes in the serum HLA-DR concentration between patients with CCI

**Table 2.** Risk of bias assessment using ROBINS-E

| Study | | | Risk of bias domains | | | | | | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|---|
| First author | Year | Bias due to confounding | Bias arising from measurement of the exposure | Bias in selection of participants into the study | Bias due to post-exposure interventions | Bias due to missing data | Bias arising from measurement of outcomes | Bias in the selection of the reported result | Low/Moderate/ High/Very high |
| Brakenridge S.C. [27] | 2019 | High | Moderate | Low | Low | Low | Low | Moderate | High |
| Stortz J.A., Murphy T.J. [29] | 2018 | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Cox M.C. [28] | 2020 | High | Moderate | Low | Low | Low | Low | Moderate | High |
| Stortz J.A., Mira J.C. [30] | 2018 | High | Moderate | Low | Low | Low | Low | Moderate | High |
| Mankowski R.T. [31] | 2022 | Low | Moderate | Low | Low | Low | Low | Low | Moderate |

**Table 3.** Article Information

| Author | Design | Patients' cohort | Comparison groups | Definition | Main results |
|---|---|---|---|---|---|
| Brakenridge S.C. [27] | *Post hoc* analisys, *n* = 157 | Sepsis | Patients with chronic critical illness, patients with rapid recovery | Chronic critical illness: ICU length of stay ≥ 14 days with persistent evidence of organ dysfunction by SOFA score<br>Rapid recovery: ICU length of stay < 14 days | 1. An elevated GLP-1 serum level at 24 hours after the diagnosis of sepsis was a significant independent predictor for the development of chronic critical illness ($p$ = 0,027).<br>2. Both GLP-1 and IL-6 serum levels were significantly elevated within 28 days after the diagnosis of sepsis in patients with chronic critical illness compared to patients with rapid recovery.<br>3. Patients with chronic critical illness demonstrated the presence of persistent inflammation (IL-6) and catabolic state (GLP-1) |
| Stortz J.A., Murphy T.J. [29] | Prospective observational study, *n* = 88 (20 healthy volunteers in addition) | Sepsis | Patients with chronic critical illness, patients with rapid recovery, healthy controls | Chronic critical illness: ICU length of stay ≥ 14 days with persistent evidence of organ dysfunction by SOFA score<br>Rapid recovery: ICU length of stay < 14 days | 1. Patients with sepsis had lower absolute lymphocyte count (ALC) compared to healthy controls.<br>2. Patients with sepsis had higher sPD-L1 serum level compared to healthy controls.<br>3. The difference in the dynamic of changes in the serum ALC concentration between patients with CCI compared to patients with rapid recovery was statistically significant ($p$ = 0.036): patients with rapid recovery were characterized by a rapid increase in ALC to normal range, while patients with CCI were characterized by a slow increase in ALC. This fact indicates the presence of immunosuppression in the CCI group.<br>4. The difference in the dynamic of changes in the serum HLA-DR concentration between patients with CCI compared to patients with rapid recovery was statistically significant ($p$ < 0.05): patients with rapid recovery were characterized by a rapid increase in serum HLA-DR concentration to normal range, while patients with CCI were characterized by a slow increase in HLA-DR. This fact indicates the presence of immunosuppression in the CCI group.<br>5. The difference in the dynamic of changes in the serum sPD-L1 concentration between patients with CCI compared to patients with rapid recovery was statistically significant ($p$ < 0.05): patients with rapid recovery were characterized by a gradual decrease in serum sPD-L1 concentration to normal range, while patients with CCI were characterized by a progressive increase in sPD-L1. This fact indicates the presence of immunosuppression in the CCI group |
| Cox M.C. [28] | *Post hoc* analysis, *n* = 144 (27 healthy volunteers in addition) | Sepsis | Patients with chronic critical illness, patients with rapid recovery, healthy controls | Chronic critical illness: ICU length of stay ≥ 14 days with persistent evidence of organ dysfunction by SOFA score<br>Rapid recovery: ICU length of stay < 14 days | 1. Serum concentrations of IL-6, IL-8 (indicators of inflammation) and sPD-L1 (indicator of immunosuppression) in patients with sepsis were statistically significantly higher compared to healthy controls at each time point within 14 days after the diagnosis of sepsis ($p$ < 0.001).<br>2. Serum concentrations of IL-6 and IL-8 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p$ < 0.05). This fact indicates the presence of persistent inflammation in patients with chronic critical illness. |

*Continuation of the Table 3*

| Author | Design | Patients' cohort | Comparison groups | Definition | Main results |
|---|---|---|---|---|---|
| | | | | | 3. Serum concentration of sPD-L1 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of persistent immunosuppression in patients with chronic critical illness.<br>4. Serum concentration of GLP-1 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of a catabolic state in patients with chronic critical illness |
| Stortz J.A., Mira J.C. [30] | Prospective observational study, $n = 145$ | Sepsis | Patients with chronic critical illness, patients with rapid recovery | Chronic critical illness: ICU length of stay ≥ 14 days with persistent evidence of organ dysfunction by SOFA score<br>Rapid recovery: ICU length of stay < 14 days | 1. Serum concentrations of IL-6 and IL-8 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 28 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of persistent inflammation in patients with chronic critical illness.<br>2. Serum concentration of sPD-L1 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 28 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of persistent immunosuppression in patients with chronic critical illness.<br>3. Serum concentration of IL-10 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 21 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of persistent immunosuppression in patients with chronic critical illness.<br>4. Absolute lymphocyte count (ALC) in patients with chronic critical illness were statistically significantly lower compared to patients with rapid recovery on the 14$^{th}$ day after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of persistent immunosuppression in patients with chronic critical illness.<br>5. Serum concentration of IGFBP3 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of a catabolic state in patients with chronic critical illness.<br>6. Urinary excretion of 3-methylhistidine (3MHIS) in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery on the 7$^{th}$ and 14$^{th}$ day after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of a catabolic state in patients with chronic critical illness |

*End of the Table 3*

| Author | Design | Patients' cohort | Comparison groups | Definition | Main results |
|---|---|---|---|---|---|
| Mankowski R.T. [31] | Prospective observational study *n* = 363 (37 healthy volunteers in addition) | Sepsis | Patients with chronic critical illness, patients with rapid recovery, healthy controls | Chronic critical illness: ICU length of stay ≥ 14 days with persistent evidence of organ dysfunction by SOFA score<br>Rapid recovery: ICU length of stay < 14 days | 1. Serum concentrations of IL-6, IL-8, MCP-1 and CRP in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of persistent inflammation in patients with chronic critical illness.<br>2. Absolute neutrophil count (ANC) in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of persistent inflammation in patients with chronic critical illness.<br>3. Serum concentration of sPD-L1 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of persistent immunosuppression in patients with chronic critical illness.<br>4. Serum concentration of IL-10 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of persistent immunosuppression in patients with chronic critical illness.<br>5. Serum concentration of GLP-1 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of a catabolic state in patients with chronic critical illness.<br>6. Serum concentration of IGF1 and IGFBP3 in patients with chronic critical illness were statistically significantly higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$). This fact indicates the presence of a catabolic state in patients with chronic critical illness |

3MHIS — 3-methylhistidine; ALC — absolute lymphocyte count; ANC — absolute neutrophil count; CRP — C-reactive protein; GLP-1 — glucagon-like peptide-1; HLA-DR — human leukocyte antigen-DR; IGF1 — insulin-like growth factor 1; IGFBP3 — insulin-like growth factor-binding protein 3; IL-10 — interleukin-10; IL-6 — interleukin-6; IL-8 — interleukin-8; MCP-1 — monocyte chemoattractant protein 1; sPD-L1 — soluble programmed death-ligand 1.

compared to patients with rapid recovery was similar to the dynamic of changes in the serum ALC concentration: patients with rapid recovery were characterized by a rapid increase in serum HLA-DR concentration to normal range, while patients with chronic critical illness were characterized by a slow increase in serum HLA-DR concentration to normal range ($p < 0.05$).

**Indicators of persistent inflammation: IL-6 and IL-8.** According to the researches, serum concentrations of IL-6 [27, 28, 30, 31] and IL-8 [28, 30, 31] in patients with chronic critical illness were higher compared to patients with rapid recovery at each time point within the entire hospitalization period ($p < 0.05$).

**Indicators of persistent inflammation: MCP-1, CRP, ANC.** R.T. Mankowski et al. demonstrated that serum concentrations of MCP-1, CRP and ANC in patients with chronic critical illness were higher compared to patients with rapid recovery at each time point within 14 days after the diagnosis of sepsis ($p < 0.05$) [31].

**Indicators of the catabolic state: GLP-1.** In three studies, serum GLP-1 concentration in patients with chronic critical illness were higher compared to patients with rapid recovery at each time point within 28 days after the diagnosis of sepsis ($p < 0.05$) [27, 28, 31].

**Indicators of the catabolic state: IGFBP3.** In two studies, serum IGFBP3concentration in patients with chronic critical illness were higher compared to patients with rapid recovery at each time point within 28 days after the diagnosis of sepsis ($p < 0.05$) [30, 31].

**Indicators of the catabolic state: IGF1.** R.T. Mankowski et al. demonstrated that patients with chronic critical illness had higher serum IGF1 concentration compared to patients with rapid recovery within 14 days after the diagnosis of sepsis ($p < 0.05$) [31].

**Indicators of the catabolic state: 3MHIS.** J.A. Stortz, J.C. Mira et al. showed that urinary excretion of 3-methylhistidine (3MHIS) in patients with chronic critical illness was higher compared to patients with rapid recovery on the 7th and 14th day after the diagnosis of sepsis ($p < 0.05$) [30].

### Additional results: mortality in chronic critical illness and rapid recovery groups

Mortality in patients with chronic critical illness and patients with rapid recovery has also been evaluate in several studies. For instance, M.C. Cox et al. [28] estimated 30-days and 1 year mortality in patients with CCI and rapid recovery. In patients with chronic critical illness, the 30-days mortality was 19 %, while in patients with rapid recovery it was 1 % ($p < 0.001$). The difference was more pronounced at 1 year (42 % in patients with CCI and 7 % in patients with rapid recovery, $p < 0.001$). J.A. Stortz, T.J. Murphy et al. [29] demonstrate that mortality within 30 days after the diagnosis of sepsis was statistically significantly higher in patients with CCI compared to patients with rapid recovery (11 % *vs* 0 %, $p = 0.015$). A similar result was observed for mortality within 6 months (26 % *vs* 4 %, $p = 0.002$). J.A. Stortz, J.C. Mira et al. [30] also showed a comparable result in 6 months mortality (37 % *vs* 2 %, $p < 0.001$).

## Discussion

This systematic review summarizes the results of various studies evaluating immune status in patients with chronic critical illness. The comparison groups consisted of patients with chronic critical illness and patients with rapid recovery after the diagnosis of sepsis. It is important to emphasize that all studies in this systematic review used the same criteria for chronic critical illness. Therefore, the low heterogeneity in diagnostic criteria improves the quality of evidence in the absence of a standard definition of chronic critical illness.

The differences between groups obtained in each study are unidirectional. All the studies provided evidence for persistent inflammation, immunosuppression and a catabolic state (Fig. 3). Moreover, the differences between patients with chronic critical illness and patients with rapid recovery after the diagnosis of sepsis were statistically significant.

In this systematic review was demonstrated that patients with chronic critical illness had lower absolute lymphocyte count (ALC) and serum HLA-DR concentration compared to patients with rapid recovery, but higher serum concentration of sPD-L1 and IL-10 (Fig. 3, *B*) [27–31]. All these parameters indicate the presence of persistent immunosuppression in patients with chronic critical illness. Particularly, a higher incidence of secondary infections in patients with chronic critical illness was found [28, 29, 31]. The authors associated these findings with an immunosuppressive status of their patients. Moreover, this adverse event may lead to an increase in the length of hospitalization.

At the same time, patients with critical chronic illness were characterized by persistent inflammation. According to the analyzed articles, patients with CCI had statistically significantly higher absolute neutrophil count (ANC) and serum concentration of IL-6, IL-8, MCP-1 and CRP (Fig. 3, *A*) [27–31]. These results indicate the presence of persistent inflammation in patients with chronic critical illness.

In addition, patients with critical chronic illness were characterized by the presence of a catabolic state. This state was caused by both a decrease in serum concentration of growth factors (IGF1 and IGFBP3) [30, 31] and a muscle destruction (increased urinary excretion of 3-methylhistidine) [30]. Also, patients with chronic critical illness were characterized by an increased serum GLP-1 concentration (Fig. 3, *C*) [27, 28, 31].

Despite the significance of the results, 3 out of 5 studies have a high risk of bias due to incomparability of groups according to the initial parameters and absence of matching

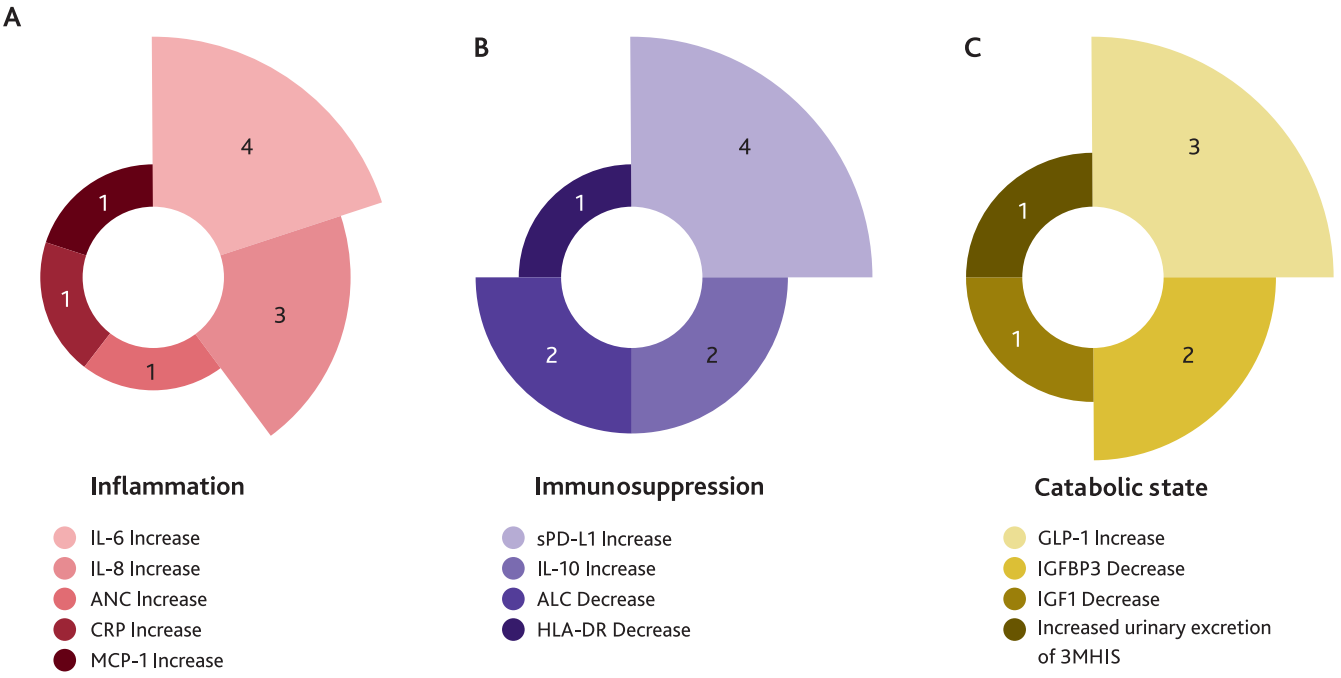


**Fig. 3.** Evaluation of biomarkers of chronic critical illness in the selected studies

Note: each slice corresponds to one biomarker, biomarker orientation is indicated below the pie chart; the size of each slice, as well as the numbers next to each slice, indicate the number of studies that found a statistically significant difference in the biomarker level between the CCI group and the rapid recovery group.

or multivariate analysis [27, 28, 30]. Only 2 out of 5 studies have a moderate risk of bias [29, 31]. Studies with a low risk of bias were not found. Therefore, the quality of evidence should be considered low and the further research is needed. Furthermore, all the studies have an additional risk of bias due to the absence of a standard definition of chronic critical illness. Probably, the obtained result can't be extrapolated to patients who will meet the standard criteria of chronic critical illness in the future.

In conclusion, there are few studies of immune status in patients with chronic critical illness. In this regard, the immune status in patients with CCI is still poorly understood. In particular, further studies of cellular and humoral immunity in patients with chronic critical illness are required in order to reduce mortality, length of mechanical ventilation and hospitalization.

### Limitations

The main limitation is the design of the study — a systematic review without statistical analysis. This study design was chosen because of the impossibility to compare studies results to each other.

## Conclusion

Patients with chronic critical illness have a persistent immunosuppression, which is reflected in lower absolute lymphocyte count (ALC) and serum HLA-DR concentration compared to patients with rapid recovery, but higher serum concentration of sPD-L1 and IL-10. Risk of bias in the included studies ranges from moderate to high. The quality of evidence should be considered low. The immune status in patients with chronic critical illness is still poorly understood, so the further prospective observational studies are required.

**Disclosure.** The authors declare that they have no competing interests.

**Author contribution.** All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

**Funding source.** This study was not supported by any external sources of funding.

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