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Chronic Critical Illness: Definition, Epidemiology, Pathogenesis, and Clinical Manifestations (Brief Review)

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Summary

The combination of syndromes and organ failure manifestations that develop after an acute critical illness (ACI) and demand the continuation of intensive care does not currently have a single definition. Meanwhile, the steadily increasing number of patients with such manifestations poses a challenge to the entire healthcare system. The complex pathogenesis and the differences in subtypes of chronic critical illness (CCI) necessitate a personalized approach to management of these patients.

Objective. To clarify the available data on the terminology of CCI, its prevalence, development timelines, clinical manifestations, pathogenesis, subtypes, and outcomes.

Materials and Methods. A literature review wasconducted using the PubMed, Google Scholar, and eLibrary databases. The review included 60 papers covering approaches to CCI definition, associated terminology, the investigation on of pathogenesis, clinical aspects, and CCI subtypes.

Results. Several case definitions were identified for CCI, reflecting the attitude toward this condition — either as one of the phases of acute critical illness or as a new disease. Additionally, two main approaches to diagnosing CCI were established: the first based on the duration of patient's stay in post-anesthesia care and intensive therapy (PACU/ICU) due to the need for intensive care, and the second based on the emergence of newly identified specific clinical and laboratory manifestations. The development of CCI is an unfavorable outcome of acute critical illness, leading to increased patient disability and a rise in mortality.

Conclusion. Further research is needed for deeper insights into development of CCI, establishing unified approaches to its definition, assessing risk factors, identifying its subtypes and associated organ dysfunctions.

Keywords: chronic critical illness; chronic critical condition; epidemiology; pathogenesis; subtypes

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Early publications on patients with prolonged stays in the ICU addressed issues related to prolonged mechanical ventilation (PMV). For example, the article by Cox JM [1] discusses the indications for initiating MV, approaches and methods for its implementation, i. e. via tracheotomy or nasotracheal intubation for prolonged ventilation. The author describes his experience with MV in one child via a nasotracheal tube for 30 days, and in four children with a tracheostomy in place for 4.5 years, and addresses the criteria for extubation and weaning procedures.

Alternatively, other emerging studies [2, 3] were discussing how the extent of administered therapy depends on the condition of critically ill patients, what were the indications for limiting or discontinuing intensive care in order to avoid sustaining life in those «whose biological existence continues, but who no longer have a human identity» [3].

In 1982, F. J. Indihar, D. P. Forsberg [4] noted that «chronic, long-term, protracted illnesses are attracting increasing attention as a major medical and social problem of our time.» In the same article, the authors describe a three-level dependency of patients on intensive care in the setting of a prolonged respiratory support unit. Level 1 includes patients requiring oxygen therapy, nebulizer therapy, rehabilitation, and educational interventions. Level 2 includes patients with minimal activity during the day who require mechanical ventilation, tracheostomy care, and physical therapy. At level 3 are patients with no activity at all, fully dependent on nursing care and respiratory therapy.

The distribution of conditions leading to hospitalization in this unit is noteworthy: the majority

of patients suffered from chronic obstructive pulmonary disease (72 patients), the sequelae of closed head injury (5 patients), and neuromuscular disorders (11 patients).

Thus, by the time the term «chronic critical ill» was proposed in 1985 by K. Girard and T. A. Raffin [2], the problem of chronic ventilator dependence and other intensive care measures among patients who had survived the acute phase of a critical illness had already been highlighted in a number of publications [1, 4].

Recently, there has also been a growing interest in the development of chronic critical illness (CCI) in patients who have survived acute critical illness (ACI), as evidenced by relevant domestic and international publications [5, 6]. This can be explained by the increasing number of such patients, significant medical, social and ethical challenges, and the economic costs associated with their care.

Study objective: to clarify existing data on the terminology of CCI, its prevalence, time to onset, clinical manifestations, pathogenesis, subtypes, and clinical outcomes.

Materials and Methods

A search for articles on patients' prolonged stays in the ICU was conducted in the PubMed, Google Scholar, and eLibrary databases using the following keywords in English: «chronic critical ill», «chronic critical illness», «persistent critical illness», and keywords in Russian «chronic critical condition» ,and «chronic critical illness». Relevance to the review's topic (pathogenesis, terminology, and outcomes of CCI) and availability of full-text access were established as inclusion criteria. Exclusion criteria included publications with limited information and those published more than 10 years ago, with the exception of fundamental works of foundational importance for the development of terminology and concepts related to the issue under consideration.

The study was conducted in accordance with the international guidelines for writing systematic reviews and meta-analyses, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [7]. The source selection flowchart is presented in Figure.

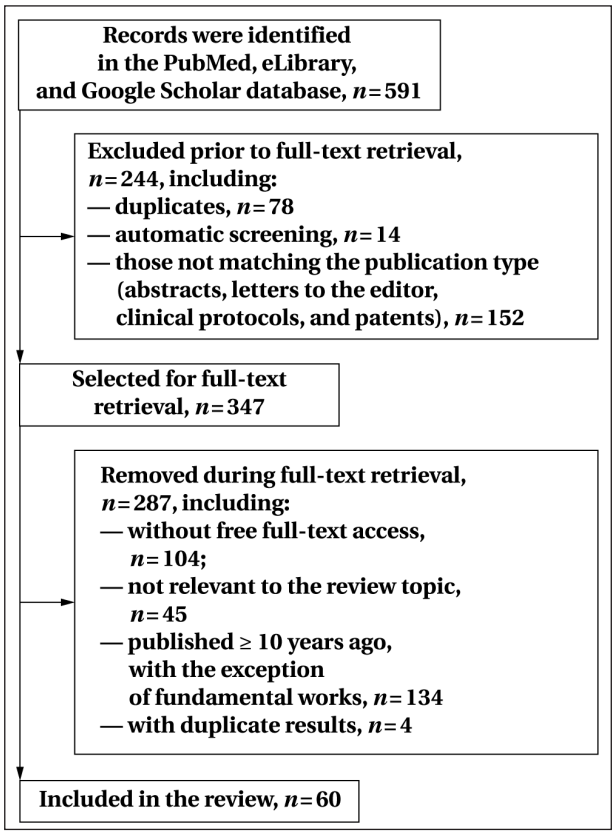

Figure. Source selection flowchart.

Results

Terminology of chronic critical illness. The term «chronic critical ill» was typically used in early studies, when forming cohorts of patients with prolonged stays in the ICU; however, since the late 2010s, the terms «chronic critical illness» and «persistent critical illness» have been used more frequently. All these terms have found widespread use in the English-language literature [2, 6, 8]. In French-language medical literature, it's «Patients Long Séjour» [9], which also refers to patients with prolonged stays in the ICU.

In Russian-language literature, both terms — «chronic critical illness» [5] and «chronic critical condition» (CCC) [10] are encountered.

At present, in addition to the lack of a single term to define this condition, there are also no uniform approaches regarding the circumstances under which a patient can be diagnosed with the development of CCI. The authors of the term CCI, K. Girard and T. A. Raffin, defined it as the patient's failure to survive despite extraordinary support over several weeks [2].

A number of authors consider the duration of stay in the ICU and the duration of mechanical ventilation to be the primary criteria for defining CCI.

In 1991, B. Daly et al. included the following factors as the criteria determining CCI: mechanical ventilation for at least 72 hours, provided that the patient survived and was discharged from the hospital [11].

In 1997, D. Scheinhorn et al. defined a patient with CCI as one with respiratory failure requiring PMV. Also in 1997, I. S. Douglas et al. categorize patients with CCI as those requiring PMV and intensive nursing care following intensive care for the primary illness, with a total ICU stay of at least 2 weeks.

In 2002, S. Carson et al. [12] defined a patient with CCI as one requiring prolonged therapy, including mechanical ventilation in an ICU setting,

and proposed a 21-day ICU stay as the simplest criterion.

In 2005, N. R. MacIntyre et al. [13] proposed the following criteria for CCI: a duration of continuous mechanical ventilation of 21 days or more, with for at least 6 hours per day. It's worth noting that mechanical ventilation lasting 21 days or more is considered PMV [10].

In 2008, M. D. Zilberberg et al. [14] published an article in which they attributed CCI development to the PMV for more than 96 hours after its initiation.

In 2019, G. Hermans et al. [15] proposed defining CCI as an ICU stay of 8 days or longer, based on their observations that once this time threshold was reached, patient mortality no longer depended on the initial severity of illness or the admission diagnosis.

All time-based criteria for establishing CCI in a patient have a drawback related to the fact that CCI is commonly associated with development of certain syndromes, which may be absent in a patient despite the predetermined duration of mechanical ventilation and ICU stay. It is believed that, depending on the characteristics of the underlying disease, CCI develops over varying timeframes — ranging from 7 to 22 days [16]. It has been proposed that CCI development begins at the point of time when the patient's ICU outcome is influenced not by the initial acute alteration of physiological parameters, but by their prior status [17]. It should be noted that in the study by T. Jeffcote et al., only 66% of patients with a confirmed diagnosis of CCI required mechanical ventilation by day 10 [18].

Other researchers, in turn, consider the emergence of new functional deficits and new syndromes in a patient to be indicative of CCI, which allows for a deviation from subjective criteria for establishing a CCI diagnosis — the duration of ICU stay and mechanical ventilation.

D. M. Nierman [19] in his paper published in 2002 categorizes patients with CCI as those who survived after ACI but developed severe functional impairments and remained dependent on intensive nursing care.

In 2010, J. E. Nelson et al. [20] defined CCI as a syndrome of significantly impaired metabolic, neuroendocrine, neuropsychiatric and immune functions in the presence of a tracheostomy and dependency on MV with persistent weaning failure. Emergence of such a robust criterion allows for objective recording the precise time of transition from acute to chronic critical illness.

In 2014, the Research Triangle Institute [21] developed and implemented a definition of CCI to standardize payment processes and patient location, incorporating the following criteria: the presence of a tracheostomy; sepsis or severe infections; severe injuries; multiple organ failure, ischemic stroke, intracerebral hemorrhage, or traumatic brain injury, combined with mechanical ventilation for at least 96 continuous hours and a stay in the ICU of at least 8 days. Including tracheostomy in CCI criteria has drawbacks as there are no universal standards regarding tracheostomy timing, which can vary significantly between different ICUs. (the decision is typically individualized rather than strictly protocol-driven).

Not all patients undergoing PMV can be classified as having CCI. For example, patients with irreversible neuromuscular diseases that necessitate PMV are not classified as having CCI due to the absence of systemic inflammation and multiple organ failure. The cohort of patients who are also not considered to have CCI includes those with end-stage cirrhosis and bronchopulmonary pathology, i. e., in cases where the disease itself has made it impossible to maintain the patient's homeostasis without intensive care [8].

The Methodological Recommendations «Rehabilitation in the Resuscitation and Intensive Care Unit (RehabIT)» [22] propose the following definition: «CCI is prolonged multi-organ failure with a shifting predominant syndrome of vital organ failure».

In 2024, H. Ohbe et al. proposed the following definition of chronic critical illness: CCI is a condition in which patients have survived a critical illness but require further prolonged stay in the ICU (typically 10 days or more); of these, the majority require prolonged mechanical ventilation (approximately 90%), approximately 50% of patients may require tracheostomy; these patients are characterized by prolonged reduced functional activity and the development of psychosocial problems [6]. The authors of this definition note that further research is needed to establish the characteristics of CCI and to standardize the definition itself.

An alternative perspective was presented by a group of Russian authors in a 2024 article [23]. When discussing the management of patients who have survived a critical condition, the authors move away from the definition of CCI, referring instead to the post-intensive care syndrome (PICS) and noting that the acute phase of this condition lasts from the 3rd to the 14th day of stay in the ICU.

In turn, the article by G. Voiriot et al. [24] defines CCI as the subacute stage of the disease requiring intensive care over an extended period, characterized by prolonged hospital stay, significant patient suffering, high mortality, and costly medical care. While PICS refers to associated with the ICU stay «residual health problems» to deal with after patient's discharge from the hospital.

CCI epidemiology, risk factors and outcomes. Data on the incidence of CCI vary depending on the country, year of assessment, level of the healthcare facility, organization of medical care, and criteria for CCI diagnosing [25].

An increase in the number of ICU patients who develop CCI has been reported in recent years, which is associated with improvements in intensive care and a reduction in early mortality. Based on data published in 2019, 88,000 patients were diagnosed with CCI in 1997, 380,000 patients — in 2009, and in 2020 the number of patients with CCI was expected to increase to 605,000 [15].

In a study by E. M. Viglianti et al., based on an analysis of 153,512 hospitalizations between 2015 and 2017 in the ICUs of 100 U.S. hospitals, it was shown that CCI developed in 4.9% of patients. In this study, patient's ICU stay exceeding 10 days was used by the authors as the CCI criterion [26]. A slightly earlier article by G. Van den Berghe [27] reported a significantly higher incidence of CCI in patients following ACI — 25%. The mortality rate for these patients in the ICU was 15–20%.

In a retrospective study conducted in Scotland [25] and including patients admitted to the ICU between 2005 and 2014, the reported CCI incidence was 33.8%. The authors diagnosed CCI in patients who had been in the ICU for more than 5 days and manifested signs of critical illness. It was noted that the total length of stay of these patients in the ICU accounted for 72.3% of the total number of bed-days. The 90-day survival rate in patients with CCI was the same as in patients without CCI, if CCI patients with CCI died within the first 30 days of their ICU stay were excluded from estimation.

Among the 2,500 patients admitted annually to ICU in Geneva, those with CCI accounted for 12% to 18%, with an average ICU stay of 13.8 days (the average stay for all ICU patients was 3.8 days). Approximately 52% of all ICU resources were spent on their treatment [9]. The authors note that the mean age of patients with CCI did not exceed that of the ICU patient population and was 60 ± 19 years. Mortality among patients with CCI was higher than among patients without this condition, reaching 15% compared to a mortality rate of 8–12% in the overall ICU patient population.

In the United Kingdom, the number of patients with PMV (21 days or more) was 4.4 per 100 ICU admissions; 6.3 per 100 patients who received mechanical ventilation upon admission to the ICU, and the total bed-days spent by these patients in the ICU accounted for one-third of all bed-days [28].

In a multicenter observational study by S. M. Bagshaw et al. [17], conducted between 2012 and 2014 in 12 ICUs in Alberta, Canada, with a total of 17,783 patients enrolled, CCI developed in 2,856 (16.1%) patients. In-hospital mortality in the group of patients with CCI was 23.9% compared to 15.5% in patients without CCI.

In the study by H. Ohbe [29], which included 2,395,016 ICU patients, 216,434 (9.0%) were diagnosed with CCI based on PMV following the development of sepsis, stroke, or tracheostomy. Mortality among patients with CCI was 28.6%. The authors note that in 2011, 47,729 cases of CCI were reported among ICU patients in Japan, and 46,494 cases — in 2017. During this period, while the mortality rate decreased from 30.6% to 28.2%, there was an increase in the number of patients who were completely dependent on care, and the proportion of patients discharged with impaired consciousness rose from 18.7% to 19.6%.

According to K. R. Chadda et al., 10% of ICU patients develop CCI, with a higher incidence among patients admitted with ACI, including sepsis (28%) and trauma (24%). The risk of developing CCI is higher in elderly patients with more severe course of the disease, and those with comorbidities [30]. Jeffcote et al. [18], in a study of CCI causes among 100 patients, found that patients admitted to the ICU due to respiratory failure, sepsis, or neurosurgical conditions are more likely to develop CCI.

In a study by Turkish authors, the incidence of CCI among patients treated in the ICU was 22%. A diagnosis of CCI was established when the patient's stay in the ICU lasted 21 days or more.

In a study by E. M. Viglianti et al. [31], which included patients from 6 ICUs at various university hospitals in the state of Michigan between 2014 and 2016, it was found that among 3,777 patients admitted to the ICU, 50 patients (13.2%) developed CCI (a ICU stay of more than 14 days was used as the criterion for CCI). In-hospital mortality of patients with CCI was 30%, while in patients without CCI, it was 8.2%. The researchers also found that the development of CCI is less likely in younger patients.

Baseline asthenia in a patient, which implies poor functional status, the presence of sarcopenia, muscle weakness, reduced physiological reserves, poor nutritional status, and decreased cognitive abilities, significantly increase the likelihood of adverse outcome [32], including higher mortality and longer ICU stay. It should be noted that asthenia occurs not only in elderly patients [33]. The CFS (Clinical Frailty Status) index, which characterizes age-related asthenia, was higher in patients with CCI. Thus, with a CFS score of 7–8, the risk of developing CCI reaches 4.8%, whereas with a CFS score of 1–2, the risk of developing CCI is only 2.8% [32]. The authors also noted that more severe asthenia, as assessed by the CFS scale, is associated with older age and a more severe condition as assessed by the APACHE III scale, was more common in women, and these patients were more likely to have sepsis at admission.

In published analysis of the medical records of 59,319 mechanically ventilated patients S. Okahara et al. [34] identified 8,331 (14%) patients with asthenia. The probability of weaning these patients

from MV was statistically significantly lower than in patients without asthenia. The authors also noted that the effect of asthenia on the failure to wean from MV was more evident in younger patients.

In a number of publications [35, 36], the authors indicate that neither the APACHE score nor other scales assessing the probability of death in patients with ACI demonstrated their predictive value in patients with CCI.

C. A. R. Feijó et al. express the same opinion based on the analysis of 86 medical records, including 13 (15%) CCI cases. The authors concluded that higher score on the APACHE II and SOFA scales were not predicting development of CCI, whereas the presence of chronic conditions such as chronic kidney disease and diabetes mellitus were predisposing to CCI development [37]. In this study, the CCI diagnosis was established in patients on mechanical ventilation for at least 6 hours per day for a minimum of 21 days.

The study by Loss et al. identified the following predictors of CCI development: high BMI, use of mechanical ventilation, development of sepsis, reduced level of consciousness as assessed by the Glasgow Coma Scale, and inadequate nutritional support by the 7th day from the onset of the disease [35].

In a prospective observational cohort study, J. C. Mira et al. [38] identified the following risk factors for CCI in 135 adult patients with severe trauma and hemorrhagic shock who did not die within the first 48 hours following injury: patient age $\geqslant$55 years; severe shock on admission (systolic blood pressure $\leqslant$70 mm Hg); transfusion of 5 or more units of packed RBCs within the first 24 hours; severe organ failure by Denver Multiple Organ Failure Scale; and presence of infectious complications. In this study, CCI diagnosis was established in patients with organ failure and ICU stay for $\geqslant$14 days. CCI developed in 25 (19%) patients with 16% mortality rate within first 4 months (vs 1.6% mortality in patients without CCI); 56% of these patients required post-discharge care in medical rehabilitation facilities.

In 2008, S. S. Carson et al. [39] assessed factors increasing the likelihood of death within 3 months or one year of disease onset in patients after PMV. They identified the need for vasopressors, hemodialysis, a platelet count of less than 150×10^9/L, and age 50 years or older as predictors of death. The ProVent (Prolonged Mechanical Ventilation Prognostic) score, developed by the authors based on these parameters, has been widely used to assess the probability of death in patients undergoing MV. At the same time, the authors note that different approaches to patient management may lead to biased results when using these indicators for assessment.

Subsequently, the ProVent score demonstrated high sensitivity and specificity in predicting one-year mortality. Thus, in an observational study of 150 therapeutic and surgical patients experiencing PMV for more than 21 days from the time of tracheal intubation, S. Jaiswal et al. [36] confirmed the predictive value of the scale's parameters for identifying the probability of death both within the first 3 months and during the first year.

C. I. Udeh et al. found that PMV experience in patients aged over 65 years is the strongest predictor of death within the first year in surgical and therapeutic settings [40].

The modified ProVent scale assigns one score for each of the following on day 21 of PMV: for patient's age of 50 years or older, presence of thrombocytopenia (less than 150×10^9/L), need for therapeutic dialysis, and administration of vasopressors; and 2 scores — for patient's age 65 years or older. According to a study by C. Dibiasi [41], one-year mortality in patients with CCI reaches 49%.

While the ProVent scale assesses the risk of 1 year mortality in critically ill patients who have been on mechanical ventilation for $\geqslant$21 days, the ProVent14 scale developed by Hough et al. assesses the risk in CCI patients on day 14 of mechanical ventilation [42]. This scale includes 5 parameters: age 50–64 years — 1 score, age $\geqslant$65 years — 2 score, thrombocytopenia (less than $100{,}000 \times 10^9$/L) — 1 score, use of vasopressors – 1 score, hemodialysis – 1 score, and patient's admission to the ICU unrelated to trauma — 1 score. In patients with a ProVent score of 0–1, the one-year mortality rate was 30%, whereas in patients with a score of 4 or more, the one-year mortality rate was 90%.

The probability of death in patients with CCI was assessed using the ProVent and ProVent14 scales/ The tracheostomy-ProVent scale developed by Jang et al. was employed in patients with a tracheostomy. The authors included six parameters in this scale: platelet count $< 150 \times 10^9$/L; $PaO_2/FiO_2 < 200$ mmHg, BMI < 23.0 kg/m^2, albumin concentration $<$ 28 g/L, presence of chronic cardiovascular disease, and immunosuppression. The first 4 parameters were assessed on the 14th day of mechanical ventilation; the last two were evaluated at admission.

H. Ohbe et al. found that 25% of patients who develop CCI die in the hospital; more than 50% of survivors require prolonged hospitalization or admission to specialized inpatient facilities with access to highly skilled nursing care, where the subsequent one-year mortality rate reaches 45%, and approximately 25% of patients with CCI are discharged home [6].

J. N. Darvall et al. found that the most common causes of death in patients with CCI were sepsis and multiple organ failure, which led to death of 16.7% of patients. In this study, CCI was diagnosed in patients who stayed in the ICU for more than

10 days, provided that the initial illness no longer determined the reason for their continued stay in the unit. Of notion, in one-third of these patients, MV had already been discontinued by the 10th day of their stay [43].

Patients who have survived CCI are characterized by a high rate of readmissions. According to M. Unroe et al., 67% of patients diagnosed with CCI were readmitted to hospitals within the first year after discharge [44].

In a study conducted at the respiratory center of the ICU at the University Hospital in Modena (Italy), A. Marchioni et al. found that ACI progressed to CCI in 33% of patients with acute respiratory failure [45]. Of these, 50% died within six months of discharge from the ICU, and only 10% were able to care for themselves at home. The researchers found that risk factors for development of CCI in patients with respiratory failure include a high APACHE II score — 17 scores or higher, the presence of septic shock on admission, the detection of multidrug-resistant flora, diaphragmatic dysfunction (as determined by ultrasonography), the development of a secondary infection during ICU stay, and an increase in C-reactive protein within 7 days of hospitalization. The diagnostic criteria for CCI in this study were: an ICU stay of more than 8 days, the presence of a tracheostomy, or mechanical ventilation for more than 21 days with a daily duration of at least 6 hours.

Publications by Russian researchers primarily address the issues of PMV in patients with acute cerebrovascular accidents. Thus, V. I. Ershov et al. [46], based on the study «Respiratory Therapy Registry in Patients with Acute Cerebrovascular Disease (RETAS)», conclude that development of ventilator-associated pneumonia determines mortality in patients with acute cerebrovascular disease after the acute phase of the stroke is over. In another article, the same authors note that the severity of neurological deficit in patients with acute ischemic stroke and a NIHSS score of >14 (moderate to severe stroke), combined with manifestations of malnutrition is an additional risk factor for an adverse outcome following PMV experience [47].

CCI pathogenesis. Disorders of the nervous, endocrine, and immune systems play a major role in CCI development. During the acute phase of illness, there is an increase in pituitary hormone levels, accompanied by fluctuations in «peripheral» hormones — concentrations of anabolic hormones and triiodothyronine decrease, while the concentration of the catabolic hormone cortisol increases. During transition to CCI, the entire hypothalamic-pituitary-adrenal (HPA) axis becomes hypo-reactive, yielding lower cortisol levels and increasing dopamine production. Meanwhile, impaired cortisol degradation and decreased rate of its systemic clearance results in gradual elevation of cortisol and suppression of ACTH secretion, disrupting normal feedback mechanisms. Dysregulated pulsatility in synchronized secretion of ACTH and cortisol results in breakdown of the normal dynamic correlation between the two hormones — so called ACTH-cortisol dissociation, leading eventually to the development of adrenal cortex atrophy [48]. Because of suppression of the gonadotropin-releasing hormone — follicle-stimulating/luteinizing hormones — gonads axis, there's a decrease of testosterone levels in men and progesterone levels in women with simultaneous paradoxical increase in estrogen concentrations, leading to increased aromatase enzyme activity. The circadian rhythm in critically ill is also disrupted, which is accompanied by impaired pulsatile function of the hypothalamic-pituitary system, pulsatile secretion of cortisol and thyroid-stimulating hormone, and fluctuations in melatonin levels. These changes lead to sleep disturbances in ICU patients, which negatively affect cognitive functions and adaptive immune response, leading to development of delirium. In addition to inflammation, artificial light, noise, and enteral nutrition also contribute in the development of circadian rhythm disturbances. Maladaptive processes buildup as CCI progresses, but unlike the adaptive processes observed during the acute phase, these processes promote excessive catabolism and suppress anabolic processes [49].

Disorders of the autonomic nervous system are associated with dysfunction of both the sympathetic and parasympathetic systems [50]. The hormones of the sympathetic nervous system — adrenaline and noradrenaline — activate leukocytes, increase cytokine synthesis, and stimulate the synthesis of acute-phase proteins in the liver. Acetylcholine, a hormone of the parasympathetic system, has an anti-inflammatory effect; when it interacts with acetylcholine receptors on leukocytes and lymphoid tissue, the synthesis of pro-inflammatory cytokines decreases. ACI is characterized by activation of the sympathetic nervous system and suppression of the parasympathetic nervous system. Transition to CCI in a bed-confined patient with inadequate protein-energy intake additionally augments parasympathetic system suppression.

Development of critical condition- associated polyneuromyopathy is an integral manifestation of CCI [51]. According to researchers, the development of polyneuromyopathy is associated with both microvascular insufficiency and impaired permeability of the blood-nerve barrier, as well as with processes of myosin molecule loss in the backdrop of lysosomal autophagy [52]. These processes are triggered by an inflammatory response, malnutrition, and muscle inactivity due to patient's immobility. Sedation, the use of muscle relaxants and corticosteroids, and

hyperglycemia are also risk factors for the development of critical condition polyneuromyopathy.

Involvement of cardiovascular system in CCI manifests as heart failure; disorders in the respiratory system are associated both with impaired ventilation (ventilator-induced weakness of the diaphragm and accessory respiratory muscles) and with development of infections — ventilator-associated and nosocomial pneumonia. Renal manifestations may include the development of acute kidney injury, oliguria, or anuria. In the endocrine system, CCI manifests as increased catabolism with loss of muscle mass, bone resorption due to immobility, vitamin D deficiency, development of adrenal insufficiency, and substitution of lean mass by adipose tissue. Involvement of hematopoietic and immune systems results in anemia, immunodeficiency and development of chronic inflammation. Infectious diseases manifest as recurrent infections caused by multidrug-resistant flora with poor wound healing. CCI — associated gastrointestinal tract disturbances manifest as malnutrition and malabsorption [20, 52, 53].

Two simple models of CCI development were discussed by C. E. Cox in his article published in 2012 [54]. According to the first model intensive care measures are still required after acute phase of critical illness is over. In this model, according to the author, it remains unclear which factors account for the continued need for such measures. The second model suggests the role of switchover to a prolonged inflammatory response and development of chronic post-shock syndrome with specific manifestations.

In their 2012 study, L. F. Gentile et al. [55] identified the following criteria characteristic of CCI: persistent inflammation, immunosuppression, and catabolic syndrome (PICS): chronicity of the condition (ICU stay of 10 days or more, or hospital stay exceeding 14 days); presence of inflammation (C-reactive protein concentration > 1.5 mg/L); immunosuppression (absolute lymphocyte count $< 0.80 \times 10^9$/L); manifestations of catabolism (albumin concentration < 30 g/L, creatinine-to-height ratio < 80%, weight loss > 10%, weight to height ratio < 18, retinol-binding protein concentration < 100 μg/L).

According to J. C. Mira et al., PICS occurs in 30–50% of patients with CCI [38]. The authors propose the following laboratory markers of PICS: CRP > 0.5 mg/L as a marker of persistent inflammation; an absolute lymphocyte count of $< 0{,}80 \times 10^9$/L—an indicator of persistent immunosuppression; and indicators of a catabolic state include: albumin concentration < 30 g/L, prealbumin < 100 mg/L, creatinine-height index < 80%, patient weight loss > 10% from baseline, or weight to height ratio < 18. The PICS concept, which implies the development of persistent inflammation, immunosuppression, and catabolic syndrome, was described based on observations of surgical ICU patients in whom the causes of primary severe inflammation were trauma or surgical sepsis and who experienced repeated damaging effects, primarily nosocomial infection. PICS represents a self-perpetuating cycle of organ failure, inflammation, and immunosuppression, leading to recurrent infections, metabolic disorders, and loss of muscle mass [56]. It should be noted that the presence of PICS is not a prerequisite for the development of CCI.

The study by Q. Zhou et al. [57] assessing potential concurrence of CCI and PICS among 168 patients with an ICU stay of 14 days or more, discovered discordant rates of the two conditions: 17 patients had isolated PICS without CCI; 70 patients developed CCI without manifestations of PICS; 50 patients were diagnosed with both CCI and PICS simultaneously; and 30 patients showed no signs of either CCI or PICS. These patients differed in terms of manifestations of organ failure, length of hospital stay, and mortality by the 28th day of hospital stay. In authors' opinion emergence of PICS in CCI worsens patient's prognosis. V. V. Likhvantsev et al. [58] make similar conclusions in their study: the presence of the triad of symptoms — inflammation, catabolism, and immunosuppression (the authors use the acronym ICIS in this context) — leads to a 2.5-fold mortality increase in patients with CCI.

L. Hesselink et al. [59] note in their study that there is no single definition for either CCI or PICS. The authors consider PICS to be present when ICU stay is 14 days or more, when patient experienced three or more infectious complications and manifests persistent catabolic state. Infectious complications were defined as presence of infection at hospital admission that required any intervention — administration of antibiotics and/or surgery. A catabolic state was defined as: weight loss of 10% or more, weight to height ratio < 18, or serum albumin concentration below 30 g/L. The authors considered this variant of PICS to be «clinical PICS» as opposed to «laboratory PICS,» in which a decrease in the absolute lymphocyte count $< 0{,}8 \times 10^9$/L for 2 or more days as a manifestation of immunosuppression, CRP > 50 mg/L for 2 or more days, and catabolic state meeting the criteria for «clinical PICS» during the first 30 days of hospital stay. Among 183 patients with polytrauma, 78 were diagnosed with CCI, of whom «clinical PICS» was diagnosed in 18 patients, «laboratory PICS» in 22 patients, and in 8 patients — a combination of both «clinical and laboratory PICS».

In the article discussing influence of persistent inflammation and immunosuppression on CCI development, R. B. Hawkins et al. [56] conclude that CCI has several phenotypes, including those associated not only with inflammation but also with the development of immunosuppression, or

a combination of inflammation and immunosuppression.

The differences identified by authors in a comparative study, including 29 patients with primary brain injuries (PBI) (traumatic brain injury (TBI), acute cerebrovascular accidents (ACVA)), and 121 patients without PBI allowed the authors to propose a neurometabolic type of CCI development characteristic of patients with brain injuries [60]. For this variant of CCI, on the first day of ICU admission patients with TBI/ACVA were characterized by higher levels of hemoglobin, hematocrit, lymphocyte count, total protein, and albumin, and lower levels of blood urea nitrogen, creatinine, and glucose compared to patients without PBI, while on the 20th day of hospital stay patients with brain injury had lower levels of blood calcium, creatinine, blood urea nitrogen, and glucose.

According to the study by E. M. Viglianti et al., patients with CCI are characterized by development of «new» organ failure in the long term [31]. The authors found that only 11 out of 50 patients with CCI did not develop new organ failure on days 4–14 of their stay in the ICU (ICU stay > 14 days was used as the criterion for CCI). A single organ system failure was documented in 15 (30%) patients with CCI, while in 24 (48%) patients organ failure involved more than one system. Cardiovascular failure was the most common — in 24 (61.5%) patients; respiratory failure — in 13 patients; renal failure — in 14 patients; liver failure — in 14 patients; and coagulopathy — in 5 patients. The causes of cardiovascular failure were sepsis in 19 of 27 cases, hypovolemia in 5 cases, cardiogenic causes in 2 cases, and tension pneumothorax in 1 case. 22 of the 50 patients were successfully extubated within 14 days of admission to the ICU (the median time to extubation was 5 days), and only 28 patients were on mechanical ventilation on the 15th day of their stay in the ICU. This allowed the authors to conclude that recurrent organ failure plays a greater role in CCI development than PMV, and focusing solely on the duration of ventilation may lead to an underestimation of CCI rate.

Similar findings were reported by T. Jeffcote et al. [18] — by the 10th day of ICU stay, more than 66% of patients with CCI were not on mechanical ventilation. At the same time, in patients with CCI, unlike in those without it, the authors observed treatment-resistant metabolic disorders significantly more often (in 12% and 3%, respectively), ventilator-associated pneumonia (in 21% and 1%, respectively), respiratory distress syndrome (in 10% vs 0%), liver failure (in 10% and 5%), systemic inflammatory response syndrome (in 57% and 14%), delirium (in 51% and 24%), and surgical complications (in 15% and 2%). Meanwhile, the incidence of critical illness myopathy was low in both groups — in patients with CCI (2 cases) and patients without CCI (1 case). The authors believe that CCI involves a cascade of interrelated pathophysiological processes affecting multiple systems and organs.

Conclusion

Improvements in intensive care practice have led to increasing the number of patients surviving ACI who develop a complex of new syndromes not related to CCI. Approaches to determining the time of CCI onset vary depending on the authors' views regarding the timing of the development of new functional deficits and the onset of new organ failure. Various subtypes of CCI may develop, characterized by a complex of indicators qualifying the states of protein and carbohydrate metabolism, immunosuppression, inflammation, and blood electrolyte composition, which influence the severity of its course.

Unified approaches are needed to define CCI, assess risk factors for its development, identify subtypes of progression, and detect characteristic organ dysfunction.

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