Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2023;48(2):441-447
DOI: 10.17826/cumj.1229091

RESEARCH

COVID-19 and persistent inflammation, immunosuppression and catabolism syndrome

COVID-19 ve persistent inflamasyon, immünsüpresyon ve katabolizma sendromu

Derya Tatlısuluoğlu[1], Güldem Turan[1]

[1]Department of Intensive Care Unit, Basaksehir Cam and Sakura Education and Research City Hospital, Istanbul, Turkey

Abstract

Purpose: Multiple organ failure (MOF) is a disease group that necessitates intensive care monitoring and carries a significant mortality rate. If these individuals are not dead as a result of early MOF, they will either quickly restore immunological balance or their immunological dysfunction may persist, resulting in chronic critical illness (CCI). Some of these patients have CCI, which is characterized by chronic inflammation, immunosuppression, and the syndrome of catabolism (PICS). With this study, we aimed to evaluate PICS cases in our intensive care unit, their effects on mortality, and their biomarkers.

Materials and Methods: This is a retrospective, observational study involving 190 patients diagnosed with acute respiratory distress syndrome (ARDS) due to SARS-CoV-2 and followed up in the ICU. Patients' laboratory data and body mass index (BMI) were compared between the first and twenty-first days of ICU admission. In addition, the patients were evaluated according to PICS utilizing the number of days they spent in the ICU, CRP, albumin, prealbumin, lymphocytes, and BMI data.

Results: The laboratory values of the patients on the 21st day were as follows, and the results obtained were statistically significant when compared with the values on the 1st day. Albumin 2.56±0.57 g/L, prealbumin 9±15 g/L, d-dimer 4.41±4.70 (interquartile range (IQR): 2.53-4.76) µgFEU/mL, fibrinogen 497±189,35 mg/dl, hemoglobin 10.15±1.82 g/dL, leukocytes 13.94±8.12 (IQR: 12.34-7.69) 10^9/L, immature granulocyte 1.16±2.13 (IQR: 0.46-1)10^9/L and BMI of 26.92±3.27 (IQR: 26.7-4.8). Again in these patients, lymphocyte values were 0.92±0.80 (IQR: 0.71-0.74)10^9/L, CRP was 101.42±99,96 mg/L, and platelet values were 214.24±128.08 10^9/L.

Conclusion: PICS is a significant condition affecting mortality and morbidity in critical care patients. In this group of patients, immature granulocytes may also serve as a useful biomarker. Due to the lack of studies regarding

Öz

Amaç: Çoklu organ yetmezliği (MOF), yoğun bakım takibi gerektiren ve mortalitesi yüksek bir hastalık grubudur. MOF'lu hastalar MOF'un başlangıcında hemen kaybedilmez ise; ya hızla immünolojik homeostaz durumuna geri döner veya immünolojik disfonksiyon devam ederek kronik kritik hastalığa (KKH) dönüşebilirler. İşte bu grup hastaların bir kısmı, persistent inflamasyon, immünsüpresyon ve katabolizma sendromu (PICS) ile karakterize edilen KKH'den muzdariptir. Biz bu çalışma ile yoğun bakım ünitemizdeki PICS olgularını, mortalite üzerine etkilerini ve biyobelirteçlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışma SARS-CoV-2 nedeniyle akut solunum sıkıntısı sendromu (ARDS) tanısı alan ve yoğun bakım ünitesinde izlenen 190 hastayı içeren retrospektif, gözlemsel bir çalışmadır. Hastaların laboratuvar verileri ve vücut kitle indeksleri (BMI) yoğun bakıma kabulünün 1. günü ile 21. günü karşılaştırılmıştır. Ayrıca hastalar yoğun bakım ünitesinde kalış gün sayısı, CRP, albumin, prealbumin, lenfosit ve BMI verileri kullanılarak PICS açısından değerlendirildi.

Bulgular: Hastaların 21. gününde ki laboratuvar değerleri aşağıdaki gibi olup, 1. günde ki değerlerle karşılaştırıldığında istatiksel olarak anlamlı sonuçlar elde edildi. Albumin 2.56±0.57 g/L, prealbumin 9±15 g/L, d-dimer 4.41±4.70 (interquartile range (IQR): 2.53-4,76) µgFEU/mL, fibrinojen 497±189,35 mg/dl, hemoglobin 10.15±1.82 g/dL, lökosit 13.94±8.12 (IQR: 12.34-7.69) 10^9/L, immatür granülosit 1.16±2.13 (IQR: 0.46-1) 10^9/L ve BMI'leri 26.92±3.27 (IQR: 26.7-4,8) idi. Yine bu hastalarda lenfosit 0.92±0.80 (IQR: 0.71-0.74) 10^9/L, CRP 101.42±99,96 mg/L ve trombosit değerleri 214.24±128.08 10^9/L idi. 28 günlük periyotta 120 (63.8%), 90 günlük periyotta ise 132 (69.5%) hastanın vefat ettiği belirlendi.

Sonuç: PICS yoğun bakım hastalarında mortalite ve morbiditeyi etkileyen önemli bir sendromdur. İmmatür granülosit bu grup hastada kullanılabilecek bir diğer

Address for Correspondence: Derya Tatlısuluoğlu, Başakşehir Cam and Sakura Training and Research City Hospital, Department of Intesive Care Unit, Istanbul, Turkey E-mail: drdtatly@hotmail.com
Received: 04.01.2023 Accepted: 27.05.2023

PICS, we are in the premature phase of understanding the pathogenesis and management of PICS and therefore need more comprehensive research regarding the topic.

Keywords:. Persistent inflammation, immunosuppression, catabolism syndrome, PICS, COVID-19

biyobelirteç olabilir. PICS ile ilgili çalışmaların eksikliği nedeniyle, PICS'in patogenezini ve yönetimini anlamanın erken bir aşamasındayız ve bu nedenle konuyla ilgili daha kapsamlı araştırmalara ihtiyacımız bulunmaktadır.

Anahtar kelimeler: Persistent İnflamasyon, immünsüpresyon, katabolizma sendromu, PICS, COVİD-19

INTRODUCTION

Multi-organ failure (MOF) is a disease group that necessitates intensive care unit (ICU) monitoring and has a high mortality rate. If these patients are not lost due to early MOF, either the patient rapidly returns to immunological homeostasis or the immunological dysfunction persists, resulting in chronic critical illness (CCI), which requires an ICU stay of more than 14 days and is marked by persistent organ failure[1–3]. Long hospital lengths of stay, poor results, and significant long-term mortality rates are characteristics of those with CCI. A substantial proportion of these patients suffer from CCI that is characterized by "persistent inflammation, immunosuppression, and catabolizm[4]", and this condition is known as persistent inflammation, immunosuppression, and catabolism syndrome (PICS). PICS can be caused by a wide range of acute diseases, like sepsis, severe blunt trauma, burns, and serious complications like pancreatitis.

A significant element in the pathophysiology of PICS is hypercatabolism. Inflammation, hormonal alterations, mitochondrial dysfunction, and intestinal dysfunction have been proposed as underlying processes of hypercatabolism[5]. In PICS, hypercatabolism contributes to the development of chronic inflammation and immunosuppression[5].

Rosenthal et al. released a CCI patient study in 2020. In this investigation, CCI patients indicated that, despite obtaining appropriate macronutrients in the ICU's early phases, they did not respond in the same manner as patients with rapid recovery. Instead, they observed a sustained acute phase response (low albumin levels, high C-reactive protein, and negative acute phase reactants) and no anabolism[6].

Due to its poor prognosis and complicated management, PICS presents a difficult situation for intensive care doctors. Our hypothesis in this study is that PICS can also be seen in patients treated in intensive care due to COVID-19. Also, can COVID-19 patients have different PICS criteria? The answer to the question was also sought. Additionally, determining the mortality and morbidity of PICS cases associated with COVID-19 is another goal.

MATERIALS AND METHODS

Study design

This research was approved by the ethics committees of Başakşehir Çam and Sakura City Hospital. The number KAEK/2022.03.72 is the protocol number for this research. This study was conducted on patients with acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 in the 3rd-level ICU of Başakşehir Çam and Sakura City Hospital between September 2020 and March 2022.

The authors reviewed patient files and gathered the necessary data from the hospital database. All data collected during this study was kept confidential and not shared anywhere, both in terms of the reliability of the records and the privacy and confidentiality of the patients included in the study. This study was conducted in accordance with the Declaration of Helsinki.

Patient eligibility

In this investigation, 305 patients' data were examined. 115 patients' data were disregarded because they failed to satisfy the requirements for inclusion. The flowchart's overview is shown in Figure 1. The inclusion and exclusion criteria for the study are shown in Table 1.

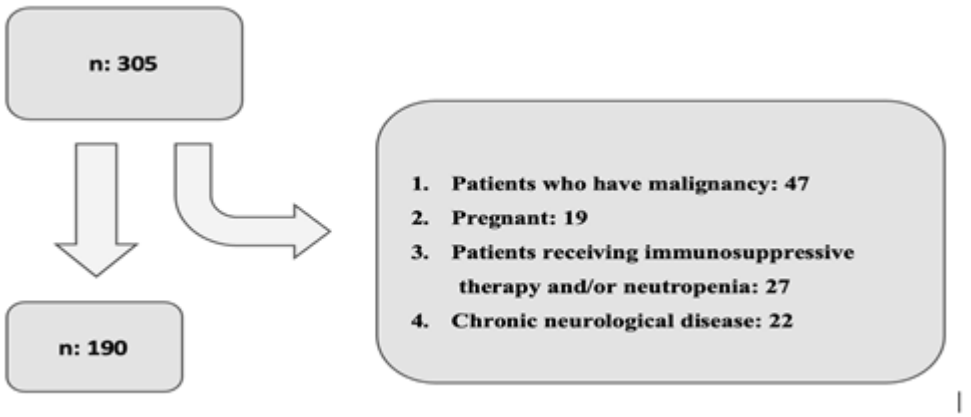

Figure 1. Patient selection flowchart

Table 1. Criteria for inclusion in the study

Inclusion criteria	Exclusion criteria
Be older than 18	Patients younger than 18
	Cancer patients
Number of days of stay in ICU >14 days	Pregnant women
	Those with a background of organ transplantation and/or immunosuppressive medication use
Patients with ARDS followed in the ICU	Patients with chronic neurological disease
	Those suffering from neuromuscular muscle disorders

Definition of ARDS and PICS

Patients diagnosed with ARDS according to the Berlin criteria were included in the study[7]. PICS criteria are as follows. Staying in the ICU for more than 14 days; CRP >50 μg/dL; total lymphocyte counts <0.80 x 109/L; serum albumin <3.0 g/dL; prealbumin <10 mg/dL; and weight loss >10% or BMI <18 during hospitalization[8].

Data collection

ICU admission demographic information was collected from a review of medical records, such as patients' age, gender, body weight, diagnosis at ICU admission, reasons for admission to ICU, chronic comorbidities, and BMI. In this study, laboratory data and body mass index (BMI) on the first and 21st days of admission to the ICU were compared. Examined laboratory data: complete blood count, kidney function tests (urea, creatinine), aspartate transaminase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), procalcitonin (PRC), fibrinogen, d-dimer, ferritin, albumin, and prealbumin. Acute Physiology and Chronic Health Assessment (APACHE) and Sequential Organ Failure Assessment (SOFA) scores were also examined. Laboratory data and APACHE and SOFA scores were obtained from patient files and the hospital database.

For the evaluation of the patients' outcomes, the number of ICU days, the number of hospitalization days, the 28-day mortality rates, and the patients' state on the 90th day were assessed.

Statistical analysis

Data were entered into the SPSS (Statistical Package for Social Sciences) for Windows 16.0 program and examined as part of the study. The one-sample Kolmogorov-Smirnov test was employed to determine if the continuous data adhered to the normal distribution. Numbers and percentages served as representations of categorical variables. The student's t-test was utilized for continuous data with a normal distribution, whereas the Mann-Whitney U test was utilized for those without. Also, the Chi-square test was utilized to compare the categorical data of the two groups.

Among the quantitative variables in our study, those with a normal distribution were the mean and standard deviation; those with a non-normal distribution were given as the median and interquartile range (IQR).

Since albumin, prealbumin, fibrinogen, CRP, hemoglobin, platelets, and neutrophils showed normal distributions, the student's t test was applied for these variables. Since other variables did not show a normal distribution, they were evaluated with the Mann-Whitney U test.

For this study, using the G-Power 3.1 program with an effect size of 0.51 for the difference between two independent means (two groups) and an alpha error of 0.05, the minimum number of patients required to be included in order to reach 80% working power was 122[9].

RESULTS

This study consisted of 190 participants. 102 of these patients (53.68%) were male, and their average age was 61.24±17.4 years. The demographic information and clinical traits of the patients are listed in Table 2. By comparing the first day of hospital admission to the 21st day, BMI, albumin, prealbumin, fibrinogen, d-dimer, and hemoglobin levels were decreased on day 21 ($p < 0.001$), whereas white blood cell (WBC) and immature granulocyte (IG) values were up ($p < 0.001$). On the 21st day, lymphocyte levels ($p = 0.007$), CRP ($p = 0.002$), and thrombocyte ($p = 0.038$) readings were also observed to be lower (Table 3). The complications reported during ICU follow-up are summarized in Table 4, along with the number of ICU days, hospitalization days, days of mechanical ventilation, and APACHE and SOFA scores. The ICU and post-ICU circumstances of the patients, as well as their 28-day and 90-day mortality rates, are also detailed in this table. 120 (63.8%) of the patients died within 28 days, and 132 (69.5%) within 90 days. In addition, 57% of the patients had intestinal dysfunction (delayed stomach emptying, eating intolerance, decreased intestinal absorption, severe diarrhea, etc.).

Table 2. Demographic data and clinical characteristics of patients

Variable	n (%)
Gender (Male)	102 (53.68%)
Age	61.24±17.39
Hypertension	74 (38.9%)
Coronary artery disease	53 (27.89%)
Diabetes mellitus	62 (32.6%)
Hyperlipidemia	68 (35.78%)
Heart failure	12(6.3)
Chronic kidney disease	4 (2.1%)
Chronic obstructive pulmonary disease	20 (10.5%)

Tablo 3. Laboratory values of the patients

	1.th day (mean±SD) (median-IQR*)	21.th day (mean±SD) (median-IQR*)	P
Albumin (g/L)	3.17±0.40	2.56±0.57	0.000
Prealbumin(g/L)	27±6	9±15	0.000
Fibrinogen (mg/dl)	625.26±149.87	497±189.35	0.000
LDH (U/L)	462.17±160.87 439-199*	477.98±273.18 437-261.50*	0.26
D-dimer (µgFEU/mL)	3.32±4.74 1.29-2.82*	4.41±4.70 2.53-4,76*	0.000
Ferritin (ng/mL)	780.55±7.51 531-520*	895.83±916.16 633-770*	0.19
CRP (mg/L)	128.67±90.55	101.42±99.96	0.002
PCT (ng/mL)	2.79±12.67 0.2-0.54*	3.88±13.87 0.18-0.99	0.27
WBC (10^9/L)	11.28±7.04 9.6-6.36	13.94±8.12 12.34-7.69	0.00
HB g/dL	11.99±1.70	10.15±1.82	0.000
Platelet (10^9/L)	255.08±103.60	214.24±128.08	0.038
Lymphocyte (10^9/L)	1.17±1.32 0.83-0.71*	0.92±0.80 0.71-0.74*	0.007

Neutrophil (10^9/L)	15.37±20.46	20.06±25.34	0.077
Monocyte(10^9/L)	1.62±2.48 0.48-1.13*	1.10±0.59 0.59-0.81*	0.43
Immature granulocyte (10^9/L)	0.45±0.62 0.22-0.63*	1.16±2.13 0.46-1*	0.000
BMI	28.04±4.15 27.95-3,5*	26.92±3.27 26.7-4,8*	0.000
BUN (mg/dL)	62.74±45.03 50.50-39.30*	69.98±45.33 56-56.20*	0.11
Creatinine (mg/dL)	1.00±0.58 0.87-0.46*	0.94±0.53 0.80-0.46*	0.25

BUN: Blood urea nitrogen, **AST**: Aspartate transaminase, **ALT**: Alanine aminotransferase, **LDH**: Lactate dehydrogenase, **WBC**: White blood cell, **HB**: hemoglobin, **PCT:** Procalcitonin**, CRP:** C-reactive protein, **SD**: Standard deviation **IQR**: Interquartile range

Table 4. Complications and other data seen during ICU follow-up

Complications and other data	n (%)
Mortality 28th day	120 (63.8%)
Acute renal failure	74 (9.5%)
Stroke	4 (2.1%)
Epilepsy	4 (2.1%)
Diabetic ketoacidosis	40 (10.5%)
Elevated Liver Enzymes	6 (3,2%)
Pulmonary embolism/ Deep vein thrombosis	18 (9.6%)
Bowel dysfunction	108 (56.84%)
Duration of MV/day	19.31±21.17
LOS in ICU / day	28.07±19.13
LOS in hospital /day	34.11±19,21
SOFA	4.52±2.22
APACHE	13.88±9.99
Intubation	158 (83.15%)
Tracheostomy	56 (29.5%)
90th day situation	Exitus 132 (69.47%)
	Palliative care 8 (4.2%)
	Extended hospitalization in the ICU 6 (3.1%)
	Inpatient service 22 (11.57%)
	Discharge 22 (11.57%)

LOS: Length of stay, **MV**: Mechanical ventilation, **SOFA**: Sequential Organ Failure Assessment Score, **APACHE**: The Acute Physiology and Chronic Health Evaluation,

DISCUSSION

In our study, the levels of prealbumin, albumin, lymphocytes, d-dimer, and CRP were observed to be lower on the 21st day of ICU admission compared to the first day. Nevertheless, WBC, neutrophil, and IG levels were found to be increased. According to studies, a substantial proportion of CCI patients progress to PICS with sustained acute phase reaction activity (e.g., increase in CRP and decrease in prealbumin), immunosuppression (lymphopenia), inflammation (neutrophilia), and protein catabolism[1,4,10]. We obtained comparable results with our patients, and we defined them as PICS. In a study that they conducted; Mira et al. reported the diagnostic criteria for PICS[8] (Table 5). These criteria are: admission to the ICU for more than 14 days; CRP >50 μg/dL; total lymphocyte counts <0.80 x 10^9/L; serum albumin <3.0 g/dL; prealbumin <10 mg/dL; creatinine height index <80%, and weight loss >10% or BMI <18 during hospitalization[8]. In our study, albumin on day 21 was 2.56±0.57 g/dL, prealbumin was 9±15 mg/dL, CRP was 101.42±99.96 mg/L, lymphocytes were 0.92±0.80 10^9/L, and neutrophils were 20.06±25.34 10^9/L. Unfortunately, no data on the creatinine height index could be obtained for this study. When the BMI values at ICU admission and week 3 were compared, there was a significant weight loss (p <0.000).

Table 5. PICS (8)

PICS criteria	Measurement
Critically ill patients	Admission to the ICU >14 days
Persistent inflammation	CRP >50 g/dL
Persistent immunosuppression	Total lymphocyte count <0.80X10^9/L
Catabolic State	Serum albumin <3 mg/dL
	Pre-albumin <10 mg/dL
	Creatinine height index <80%
	Weight loss> 10% or BMI <18 during hospitalization

PICS: Persistent inflammation, immunosuppression, and catabolism syndrome; **CRP**: C-reactive protein; **BMI**: Body mass index

Skeletal muscle loss in critically ill individuals has been demonstrated to be correlated with high levels of circulating inflammatory cytokines[11]. In clinical practise, CRP is commonly used as a marker of both acute and chronic phases of inflammation to assess a patient's inflammatory condition. High CRP levels have also been associated with decreased muscle mass, strength, and physical performance in chronic conditions like type 2 diabetes, cardiovascular disease, and sarcopenia[12]. Because CRP is so simple to obtain, it is frequently employed in this field of study to determine whether systemic inflammation is associated with low muscle mass or strength. We also discovered elevated CRP levels in our patients during the third week.

Failure to control an infection locally leads to systemic bacterial dispersion, resulting in increased neutrophil consumption. To counteract neutrophil depletion and meet the massive demand for neutrophils during an infection, steady-state granulopoiesis is switched to emergency granulopoiesis, which is characterized by significantly increased de novo generation of neutrophils, accelerated cellular turnover, and the release of immature and mature neutrophils from the bone marrow into the peripheral blood[13]. The level of IG was observed to be higher on day 21 compared to day 1 of the investigated parameters. We consider that IG may be an additional criterion that can be employed in the diagnosis and follow-up of PICS patients.

Bowel dysfunction is common among ICU patients and is linked to poor outcomes among the severely ill. An estimated greater than 50% of mechanically ventilated patients suffer from gastrointestinal dysfunction[14]. Intestinal dysfunction is distinguished by delayed stomach emptying, feeding discomfort, inadequate intestinal absorption, and severe diarrhea[15]. 57% of our patients exhibited identical nutritional issues. In addition, bowel hypoperfusion, which is common in patients with sepsis and CCI, decreases intestinal blood flow, resulting in decreased absorption in the small intestine[16]. Reduced absorption of nutrients then reduces anabolism. As a result, there is an increase in catabolism to meet the basic energy demand. In our study, besides the changes in inflammatory parameters, the BMI, albumin, and prealbumin values of the patients were found to be low. Low BMI, albumin, and prealbumin levels may be associated with nutritional intolerance, impaired intestinal absorption, and increased catabolism.

Estimates indicate that 30–50% of people with CCI display continuous low-grade inflammation, diminished immunity, and ongoing catabolism despite dietary treatments[8,17]. In addition, these patients have greater rates of comorbidities, a longer ICU stay (>14 days), chronic organ failure, and long-term death[19]. According to research by Darden et al., the annual mortality rate is 40%[18]. In our study, it was determined that 120 (63.8%) patients died in the 28-day mortality period, and 132 (69.5%) patients died in the 90-day mortality period. In addition, on the 90th day, 8 (4.2%) of these patients continued their treatment and care in the palliative service, 6 (3.3%) in the ICU, and 22 (1.6%) in the internal medicine service. Only 22 patients (11.6%) could be discharged home.

The optimal therapeutic options for reversing persistent catabolism and minimizing muscle loss in PICS are not yet known. Clinical regimens that involve early mobilization and exercise and also suitable and regular execution of protein and calorie requirements are necessary as part of a multimodal approach to treatment[19]. Deficiencies in substrate use are probably a major contributor to this catabolic condition. Hence, proper diet and/or physical rehabilitation are likely sufficient as therapies alone. Reductions in metabolic and catabolic load through the administration of medications like propranolol and oxandrolone have resulted in considerable healing properties for pediatric burn patients[20-22].

The limitations of this study are the unavailability of creatinine height index data, the rehabilitation processes of patients in the ICU, the failure to evaluate mobilization status, and the retrospective design.

As a result, PICS is an important cause of mortality and morbidity in patients treated in the ICU due to COVID-19. Its pathophysiology is still unclear. IG can be a biomarker that can help us understand the pathophysiology of PICS and can be used for diagnosis and follow-up. However, additional research is needed in this regard.

Author Contributions: Concept/Design : DT, GT; Data acquisition: DT, GT; Data analysis and interpretation: DT, GT; Drafting manuscript: DT, GT; Critical revision of manuscript: GT; Final approval and accountability: DT, GT; Technical or material support: DT, GT; Supervision: DT, GT; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Başakşehir Cam and Sakura City Hospital with the decision numbered 2022.03.72.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Stortz JA, Mira JC, Raymond SL, Loftus TJ, Ozrazgat-Baslanti T, Wang Z et al. Benchmarking clinical outcomes and the immunocatabolic phenotype of chronic critical illness after sepsis in surgical intensive care unit patients. J Trauma Acute Care Surg. 2018;84:342-49.
2. Loftus TJ, Mira JC, Ozrazgat-Baslanti T, Ghita GL, Wang Z, Stortz JA et al. Sepsis and critical illness research center investigators: protocols and standard operating procedures for a prospective cohort study of sepsis in critically ill surgical patients. BMJ Open. 2017;7:1-7.
3. Mira JC, Cuschieri J, Ozrazgat-Baslanti T, Wang Z, Ghita GL, Loftus TJ et al. The Epidemiology of chronic critical illness after severe traumatic injury at two level-one trauma centers. Crit Care Med. 2017;45:1989-1996.
4. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72:1491-501.
5. Zhang J, Luo W, Miao C, Zhong J. Hypercatabolism and anti-catabolic therapies in the persistent inflammation, immunosuppression, and catabolism syndrome. Front Nutr. 2022:13:941097.
6. Rosenthal MD, Bala T, Wang Z, Loftus T, Moore F. Chronic critical illness patients fail to respond to current evidence-based intensive care nutrition secondarily to persistent inflammation, immunosuppression, and catabolic syndrome. JPEN J Parenter Enter Nutr. 2020;44:1237–1249.
7. ARDS definition task force. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526–33.
8. Mira JC, Brakenridge SC, Moldawer LL, Moore FA: Persistent inflammation, immunosuppression and catabolism syndrome. Crit Care Clin. 2017;29:245-58.
9. Ding RY, Qiu JN, Liu BY, Li XX, Sun YN, Liang YJ et al. A retrospective clinical study of sixty-three cases with persistent inflammation immunosuppression and catabolism syndrome. 2016:1;55:941-4.
10. Stortz JA, Murphy TJ, Raymond SL, Mira JC, Ungaro R, Dirain ML et al. Evidence for persistent immune suppression in patients who develop chronic critical illness after sepsis. Shock. 2018;49:249-58.
11. Bano G, Trevisan C, Carraro S, Solmi M, Luchini C, Stubbs B et al. Inflammation and sarcopenia: A systematic review and meta-analysis. Maturitas. 2017;96:10-15.
12. Reintam Blaser A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J et al. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM working group on abdominal problems. Intensive Care Med. 2012;38:384-94.
13. Manz MG, Boettcher S. Emergency granulopoiesis. Nat Rev Immunol. 2014;14:302-14.
14. Kalaitzakis E. Gastrointestinal dysfunction in liver cirrhosis. World J Gastroenterol. 2014;28:14686-95.
15. Chapple LAS, Plummer MP, Chapman MJ: Gut dysfunction in the ICU: diagnosis and management. Curr Opin Crit Care. 2021;29:141-6.
16. Hawkins RB, Raymond SL, Stortz JA, Horiguchi H, Brakenridge SC, Gardner A et al. Chronic critical illness and the persistent inflammation, immunosuppression, and catabolism syndrome. Front Immunol. 2018;9:1511.
17. Hesselink L, Hoepelman RJ, Spijkerman R, de Groot MCH, van Wessem KJP, Koenderman L et al. Persistent inflammation, immunosuppression and catabolism syndrome (PICS) after polytrauma: A rare syndrome with major consequences. J Clin Med. 2020;9:191.
18. Darden DB, Brakenridge SC, Efron PA, Ghita GL, Fenner BP, Kelly LS et al. Biomarker evidence of the persistent inflammation, immunosuppression and catabolism syndrome (PICS) in chronic critical illness (CCI) after surgical sepsis. Ann Surg. 2021;274:664-73.
19. Rosenthal MD, Kamel AY, Rosenthal CM, Brakenridge S, Croft CA, Moore FA. Chronic critical illness: application of what we know. Nutr Clin Pract. 2018;33:39-45.
20. Chao T, Porter C, Herndon DN, Siopi A, Ideker H, Mlcak RP et al. Propranolol and oxandrolone therapy accelerated muscle recovery in burned children. Med Sci Sports Exerc. 2018;50:427-35.
21. Herndon DN, Voigt CD, Capek KD, Wurzer P, Guillory A, Kline A et al. Reversal of growth arrest with the combined administration of oxandrolone and propranolol in severely burned children. Ann Surg. 2016;264:421-8.
22. Herndon DN, Rodriguez NA, Diaz EC, Hegde S, Jennings K, Mlcak RP et al. Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. Ann Surg. 2012;256:402-11.