ORIGINAL ARTICLE

Changes of hematological and immunological parameters in COVID-19 patients

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Abstract

The aim of this study was to identify the changes of hematologic and immunological parameters in COVID-19 patients. We collected and analyzed the data of 117 patients who were laboratory confirmed as SARS-CoV-2 infection. The cases were divided into regular group, severe group and critically ill group according to the sixth edition scheme for COVID-19 diagnosis and treatment of China. The laboratory tests included blood routine, cellular and humoral immunity indices, biochemical detections and inflammatory biomarker. Compared with regular patients, severe and critically ill patients had significantly lower lymphocyte count ($p < 0.01$), decreased red blood cell and hemoglobin ($p < 0.01$), low levels of immunoglobulin G ($p < 0.05$) and significantly higher in D-dimer ($p < 0.0001$), fibrinogen ($p < 0.01$), white blood cell count ($p < 0.01$), neutrophil count ($p < 0.0001$), interleukin-6 ($p < 0.05$), C-reactive protein ($p < 0.01$), procalcitonin ($p < 0.01$), erythrocyte sedimentation rate ($p < 0.05$), ferritin ($p < 0.01$) and lactate dehydrogenase ($p < 0.0001$). The specific immunoglobulin G antibodies to the SARS-CoV-2 in severe and critically ill patients were significantly lower than that in regular patients ($p < 0.05$). Our findings suggest that the lymphocyte counts, red blood cell counts and the immunoglobulin G antibodies of COVID-19 patients were impaired to varying degrees and the blood was in a state of hypercoagulation, which were more obvious in critically ill patients.

Keywords COVID-19 · SARS-CoV-2 · Hematological parameters · Immunological parameters

Introduction

Currently, novel coronavirus infection (COVID-19) has affected more than 200 countries and regions around the world. As the mid-May 2020, more than 4 million people have been infected and nearly 300,000 have died. Most patients infected with novel coronavirus present with novel coronavirus pneumonia. Acute respiratory tract infection is frequent in early symptoms, and some patients quickly progress to acute respiratory distress syndrome, acute respiratory

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failure, or other severe secondary complications [1]. On January 7, 2020, the Chinese Center for Disease Control and Prevention identified a novel coronavirus from a throat swab sample of one patient, first. On February 12, 2020, the World Health Organization (WHO) officially named novel coronavirus as severe acute respiratory syndrome-related coronavirus-2 (SARS-Cov-2), and the pneumonia caused by novel coronavirus was named COVID-19 [2].

SARS-CoV-2 belongs to the genus β coronavirus of the coronavirus family, which is a new independent branch of coronavirus related to severe acute respiratory syndrome (SARS-CoV) and Middle East Respiratory Syndrome-related coronavirus (MERS-CoV) and has a genetic homology of 79% to SARS-CoV and 51.8% to MERS-CoV [3, 4]. Respiratory droplets and contact transmission were the main transmission routes of SARS-CoV-2. As one of the medical teams supporting Wuhan to fight COVID-19, our medical team successively took over the treatment of COVID-19 patients in the critical illness ward of the *Tumor Department of Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology* and *Renmin Hospital of Wuhan University*. We have treated hundreds of COVID-19 patients and accumulated rich clinical experience. During the course of diagnosis and treatment, we found that there were characteristic changes in blood routine and immunological indicators of COVID-19 patients. The purpose of this paper is to further clarify the laboratory characteristics of the disease, and to guide the clinical medical staff to improve the level of diagnosis and treatment.
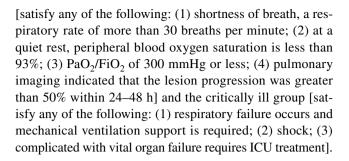
Materials and methods

Patients

This study was approved by the ethics committee of Fujian Medical University Union Hospital and approved to exempt patients from informed consent. Patients with COVID-19 were selected from two critical disease units of *Tumor Department of Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology* and *Renmin Hospital of Wuhan University* during the period from February 15 to March 30, 2020.

Diagnostic criteria

According to the "novel coronavirus infected pneumonia treatment scheme-Sixth edition" issued by the National Health Commission of the People's Republic of China [5], the condition of the patients at the time of admission was classified as the regular group (fever, respiratory symptoms, and radiographic evidence of pneumonia), the severe group [satisfy any of the following: (1) shortness of breath, a respiratory rate of more than 30 breaths per minute; (2) at a quiet rest, peripheral blood oxygen saturation is less than 93%; (3) PaO_2/FiO_2 of 300 mmHg or less; (4) pulmonary imaging indicated that the lesion progression was greater than 50% within 24–48 h] and the critically ill group [satisfy any of the following: (1) respiratory failure occurs and mechanical ventilation support is required; (2) shock; (3) complicated with vital organ failure requires ICU treatment].

Data collection

COVID-19 has been included in the B class infectious diseases stipulated in the "Law of the People's Republic of China on Prevention and Control of Infectious Diseases", and the prevention and control measures of A class infectious diseases have been taken. In accordance with the law, all cases should be reported immediately (2 h) through the infectious disease information system. All case records contain personal identification numbers to avoid duplicate cases. In this study, the patient's age, gender, complications, clinical symptoms, laboratory blood routine, blood biochemistry, immunoglobulin assay, T cell subsets, cytokine assay, ferritin, blood sedimentation and inflammatory markers were obtained from the case information system. Specific antibodies against SARS-CoV-2 IgM and IgG were tested by colloidal gold method; detailed methods were described in [6], which has become a quantitative detection kit now.

Statistical methods

GraphPadPrism 6 software was used for data analysis. The measurement data were generally distributed in a non-normal distribution and uniformly represented by median (quartile spacing). The non-parametric test method Kruskal–Wallis was used. The counting data was represented by percentage, and $P < 0.05$ was considered statistically significant.

Results

Basic characteristics of the patients

Among the 117 patients, the median age was 66 years (interquartile range, 57–71; range, 29–92 years), and 56 (47.9%) were males. There were 61 cases in the regular goup, 46 cases in the severe group and 10 cases in the critically ill group. There was no significant difference in the median age and sex ratio of each group. The main clinical manifestations of the patients were cough, fever and fatigue in all patients, and shortness of breath was more common in severe and critically ill patients. In terms of coexisting disorders, except

for diabetes, hypertension, coronary heart disease, cerebrovascular disease, chronic renal disease and malignant tumor in the severe and critically ill groups are higher than that of the normal group. (Table 1).

Laboratory results

Due to the small number of cases of critically ill patients, to reduce the statistical deviation, the severe and critically ill groups were combined and compared with the regular group.

Blood routine and coagulation indicators

The first blood routine test was collected from all the patients after admission, except for one patient with chronic lymphocytic leukemia. The results showed that the white blood cell (WBC) count and neutrophil count (NEU) in COVID-19 patients were basically in the normal reference range; however, the median value in the severe and critically ill groups was significantly higher than that in the regular group ($p < 0.01$ and $P < 0.0001$, respectively). Most patients have reduced lymphocyte counts (LYM), and were much lower in severe and critically ill patients ($p < 0.01$). Many patients had different degrees of erythrocyte and hemoglobin decrease, and was more obvious in severe and critically ill patients ($p < 0.01$). The platelet count was generally normal in COVID-19 patients. Routine coagulation tests suggested that fibrinogen (FIB) and D-dimer (D-Di2) were increased in COVID-19 patients, and the increase was more pronounced

Table 1 Clinical characteristics of the 117 patients at baseline

Characteristic	Regular group (n=61)	Severe group (n=46)	Critically ill group (n=10)
Age—year—median (quartile)	66 (52, 69)	68 (61, 76)	67.5 (57, 85)
Male sex—no. (%)	30 (49.2)	21 (45.7)	5 (50.0)
Symptoms—no. (%)			
Fever	42 (68.9)	32 (69.6)	6 (60.0)
Cough	47 (77.1)	37 (80.4)	7 (70.0)
Sputum production	20 (32.8)	14 (30.4)	1 (10.0)
Shortness of breath	14 (23.0)	15 (32.6)	6 (60.0)
Anorexia	8 (13.1)	8 (17.4)	2 (20.0)
Diarrhea	6 (9.8)	5 (10.9)	0 (0.0)
Fatigue	31 (50.8)	26 (56.5)	6 (60.0)
Myalgia or arthralgia	12 (19.7)	10 (21.7)	2 (20.0)
Coexisting disorder—no (%)			
Hypertension	17 (27.8)	20 (43.5)	3 (30.0)
Diabetes	13 (21.3)	12 (26.1)	0 (0)
Coronary heart disease	4 (6.6)	5 (10.9)	2 (20.0)
Cerebrovascular disease	0 (0.0)	1 (2.2)	2 (20.0)
Chronic renal disease	2 (3.3)	3 (6.5)	1 (10.0)
Malignant tumor	5 (8.2)	2 (4.3)	3 (30.0)
≥ 2 Coexisting disorder	12 (19.7)	11 (23.9)	3 (30.0)

Table 2 Comparisons of haematologic parameters between patients (median, quartile)

Parameters	Reference range	Regular (n=60)	Severe+critically ill (n=56)	P value
WBC (×10^9/L)	3.5–9.5	5.10 (4.30, 6.20)	6.44 (4.62, 8.02)	0.0076**
NEU (×10^9/L)	1.8–6.3	3.15 (2.40, 4.15)	4.38 (3.06, 6.26)	<0.0001****
LYM (×10^9/L)	1.1–3.2	1.36 (0.95, 1.61)	1.10 (0.65, 1.46)	0.0072**
MON (×10^9/L)	0.1–0.6	0.49 (0.38, 0.58)	0.46 (0.38, 0.66)	0.7771
RBC (×10^12/L)	3.8–5.1	3.84 (3.62, 4.11)	3.75 (3.35, 3.95)	0.0047**
HG (g/L)	125–165	123 (115, 130)	116 (106, 125)	0.0033**
PLT (×10^9/L)	125–350	230 (178, 291)	217 (143, 253)	0.3344
FIB (g/L)	2.0–4.0	3.68 (3.12, 5.00)	4.79 (3.86, 5.87)	0.0041**
D-Di2 (mg/mL)	<0.5	0.41 (0.20, 0.98)	1.17 (0.71, 2.87)	<0.0001****

** $P < 0.01$, **** $P < 0.0001$

in the severe and critically ill group than in the regular group ($p < 0.01$ and $P < 0.0001$, respectively) (Table 2).

T lymphocyte subgroup

The results showed that the proportion of total CD3 + T cells and CD4 + T cells in COVID-19 patients was within the normal reference range. However, the proportion of CD8 + T cells decreased compared with the normal reference value, and the decline degree was more obvious in the regular group, and there was a statistical difference between the two groups ($p < 0.05$). (Table 3).

Immunoglobulin and complement levels

Only 61 of the patients were tested for immunoglobulin (Ig) and complement (C) levels after admission. The results showed that IgG, IgM, IgA, C3 and C4 of COVID-19 patients were all in the normal reference range. However, the IgG level in severe and critically ill patients was much lower than that in the regular group, with a statistical difference ($p < 0.001$). In addition, specific antibodies against SARS-CoV-2 were quantitatively detected in 44 patients, the results indicated that the median of specific IgG antibodies to the SARS-CoV-2 in severe and critically ill patients was significantly lower than that in regular patients ($p < 0.05$). However, the median of specific IgM antibodies to the SARS-CoV-2 was higher in the severe and critically ill patients, but there was no statistical difference, which may be due to the small number of cases. See Table 4 for details.

Inflammatory cytokines and biomarkers

The plasma Il-6 level in most COVID-19 patients was slightly increased, while that of some severe and critically ill patients was progressively increased. The plasma IL-6 level in severe and critically ill patients was significantly higher than that in regular patients, with a statistically significant difference ($P < 0.05$). Except for IL-6, other cytokines such

Table 3 Comparisons of T cell subsets between patients (median, quartile)

T cell subsets	Reference range	Regular (n=50)	Severe + critically ill (n=48)	P value
CD3 (%)	58.17–84.22	76.46 (65.74, 81.69)	75.94 (65.40, 83.51)	0.4308
CD4 (%)	25.34–51.37	46.31 (38.92, 51.53)	43.68 (35.38, 55.33)	0.7632
CD8 (%)	26.35–51.37	20.53 (15.78, 25.37)	24.19 (18.40, 33.15)	0.0309*
CD4/CD8	0.41–2.72	1.95 (1.53, 3.25)	1.84 (1.26, 2.73)	0.1710

* $P < 0.05$

Table 4 Comparisons of immunoglobulin between patients (median, quartile)

Parameters	Reference range	Regular (n=32)	Severe + critically ill (n=29)	P value
IgG (g/L)	7.51–15.6	12.20 (10.49, 14.93)	9.46 (8.89, 10.26)	0.0001***
IgA (g/L)	0.82–4.53	2.56 (2.12, 3.01)	2.66 (2.25, 3.24)	0.5301
IgM (g/L)	0.46–3.04	0.88 (0.69, 1.23)	1.21 (0.66, 1.36)	0.2840
C3 (g/L)	0.79–1.52	0.89 (0.76, 1.10)	0.82 (0.77, 0.93)	0.2782
C4 (g/L)	0.16–0.38	0.24 (0.17, 0.28)	0.20 (0.14, 0.29)	0.2143
SARS-Cov2-IgM[a]		19.45 (8.40, 48.71)	45.12 (13.25, 68.08)	0.1006
SARS-Cov2-IgG[a]		184.9 (138.9, 531.7)	141.7 (100.6, 175.5)	0.0187*

* $P < 0.05$, *** $P < 0.001$

[a]Regular group n=20, Severe + critical n=22

Table 5 Comparisons of cytokines between patients (median, quartile)

Cytokines	Reference range	Regular (n=53)	Severe + critically ill (n=54)	P value
IL-6 (pg/ml)	0.1–2.9	7.75 (4.96, 17.48)	16.25 (7.19, 29.58)	0.0147*
IL-2 (pg/ml)	0.1–4.1	3.59 (2.45, 4.35)	3.52 (2.47, 4.11)	0.5956
IL-4 (pg/ml)	0.1–3.2	2.89 (2.08, 3.85)	3.00 (1.93, 3.81)	0.7562
IL-10 (pg/ml)	0.1–5.0	4.58 (3.14, 5.05)	4.72 (3.55, 6.12)	0.0812
TNF-α (pg/ml)	0.1–23	4.04 (3.10, 6.29)	4.27 (2.70, 9.24)	0.8644
INF-γ (pg/ml)	0.1–18	3.17 (1.88, 3.77)	3.08 (1.97, 3.57)	0.7727

* $P < 0.05$

as IL-2, IL-4, IL-10, TNF-α and INF-γ were not significantly abnormal (Table 5).

The levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and ferritin (FER) in most COVID-19 patients increased in different degrees. The increased degree of severe and critically ill patients was more significant than that of regular patients, with statistical differences ($P < 0.01$, $P < 0.01$ and $P < 0.05$, respectively). The median value of procalcitonin (PCT) in regular patients was < 0.1 ng/mL, but the PCT was increased by different degrees in severe and critically ill patients, with a median value of 0.2 ng/mL, which was statistically different from that of regular patients ($P < 0.01$). (Table 6).

Serum biochemical indexes

Serum biochemical test results suggested that the indicators of total bilirubin (TBil), transaminase (ALT and AST), creatinine (CRE) and blood urea nitrogen (BUN) in COVID-19 patients were basically within the reference range. Serum albumin (ALB) levels in severe and critically ill patients were significantly lower than those in regular patients ($P < 0.01$), while lactate dehydrogenase (LDH) levels were significantly higher than those in regular patients ($P < 0.001$). See Table 7 for details.

Discussion

Coronavirus infections are the second leading cause of the common cold, after rhinoviruses. The infection is seasonal, with high incidence in spring and winter. Mostly the incubation period is 2–5 days, the population is generally susceptible, and mainly through person-to-person contact transmission. SARS-CoV-2 also has all the characteristics of coronavirus, and studies have found that the ability of SARS-CoV-2 to bind the receptor ACE2 in vivo is 10–20 times that of SARS-CoV, which determines that it is more easily transmitted from person to person and causes a global pandemic [7]. It has been reported that the clinical characteristics of COVID-19 patients are mainly fever, dry cough and fatigue [1, 8]. We observed the clinical symptoms of 117 COVID-19 patients in the ward where we worked, and found that the clinical manifestations were similar to previous reports. Here, we mainly analyzed and summarized the laboratory examination of COVID-19 patients, especially hematological and immunological parameters.

Most viruses cause lymphocytosis when they infect humans because lymphocytes are virus-fighting effector cells [9]. The coronavirus family SARS-CoV, MERS-CoV and SARS-CoV-2 all caused lymphocytic depletion in infected patients [4, 10], and the mechanism may be caused by direct attack of coronavirus on lymphocytes or by immune-mediated apoptosis of lymphocytes [11–13]. Our study also found that the peripheral blood lymphocyte count of COVID-19 patients decreased to different degrees, at present, it is not

Table 6 Comparisons of inflammatory biomarker between patients (median, quartile)

Biomarker	Reference range	Regular (n=60)	Severe+critically ill (n=56)	P value
PCT (ng/mL)	< 0.5	0.08 (0.04, 0.14)	0.20 (0.14, 0.56)	0.0012**
CRP (mg/L)	< 8	6.58 (1.93, 18.55)	23.99 (4.12, 57.44)	0.0097**
ESR (mm/h)[a]	0–15	25 (15, 51)	54 (38, 75)	0.0023**
FER (μg/L)[b]	4.6–204	235.8 (110.8, 325.2)	365.3 (234.7, 601.9)	0.0156*

* $P < 0.05$, ** $P < 0.001$

[a]Regular group n=29, Severe+critical n=30

[b]Regular group n=20, Severe+critical n=24

Table 7 Comparisons of serum biochemical between patients (median, quartile)

Parameters	Reference range	Regular (n=61)	Severe+citically ill (n=56)	P value
TBil (μmol/L)	5.1–19.0	11.25 (9.50, 15.43)	12.00 (9.50, 16.70)	0.2681
ALT (U/L)	5–40	22.00(17.00, 47.00)	32.50 (21.00, 48.50)	0.1111
AST (U/L)	8–40	25.50 (21.00, 34.75)	30.00 (20.00, 40.00)	0.0750
ALB (g/L)	35–55	37.90 (34.80, 42.83)	34.20 (30.00, 37.90)	< 0.0001****
CRE (μmol/L)	44–133	68.00 (58.00, 81.00)	79.00 (64.00, 94.00)	0.0111*
BUN (mmol/L)	2.9–8.2	4.30 (3.40, 5.10)	4.60 (3.73, 6.71)	0.1083
UA (μmol/L)	208–428	263.0 (2230, 344.0)	280.5 (206.3, 352.5)	0.7796
LDH (U/L)	109–245	178.0 (154.0, 219.0)	245.0 (188.5, 345.5)	< 0.0001****

** $P < 0.05$, **** $P < 0.0001$

clear why SARS-CoV-2 causes lymphocytopenia in the patient. Limited autopsy and pathologic findings included necrosis of the spleen, lymph nodes and other lymphoid tissues in the infected patient, reduction of bone marrow hematopoiesis and lymphocytic infiltration in the alveolar septum [14]. The autopsy report of the deceased patient indicated that the number of CD4 + and CD8 + T cells in peripheral blood of the patient was significantly reduced, but they were in the state of over activation. The proportion of highly positive CCR6 + Th17 in CD4 + T cells increased, while CD8 + T cells carried high concentrations of cytotoxic particles [14]. This indicated that the overactivation of T cells in COVID-19 patients was mainly manifested by the increase of Th17 pro-inflammatory regulatory T cells and the high cytotoxicity of CD8 + T cells, which to a certain extent led to the over-immune response of patients to SARS-CoV-2 infection, causing serious immune damage. However, after analyzing the T lymphocyte subsets of patients in our clinical data, we did not find a decrease in the proportion of CD3 + and CD4 + T lymphocytes. Instead, the proportion of CD8 + T cells decreased compared with the normal reference value, and the ratio of regular patients was more obvious, this may due to the proportion of T lymphocyte subsets we examined, rather than the absolute values of each subset. However, our study suggested that the proportion of CD8 + cells in severe and critically ill patients with COVID-19 still increased in response to regular patients, suggested that the cellular immunity in severe and critically ill patients was still active.

In addition, we also found that the red blood cell counts of COVID-19 patients were relatively lower compared with the normal reference value, most merger mild anemia, it was more obvious in severe and critically ill patients. This phenomenon has not been reported before; it is suggested that the infection of SARS-CoV-2 significantly inhibited hematopoiesis in the bone marrow of patients. Andrey Prilutskiy et al. report autopsy results on four patients who succumbed to COVID-19, they found three of the four cases had histologic evidence of hemophagocytosis within pulmonary hilar/mediastinal lymph nodes. One case showed hemophagocytosis in the spleen but none showed hemophagocytosis in liver or bone marrow, which suggests that anemia and the elevation of ferritin may due to hemophagocytosis [15], but the detailed anemia mechanism is still unclear due to the limitation of bone marrow biopsy.

As to humoral immunity, either the total antibody or the specific antibody against SARS-CoV-2, we found that the IgG level in severe and critically ill patients was much lower than that in regular patients, while the IgM level was reversed. IgM levels reflect humoral immunity in the early stages of infection, while IgG levels reflect sustained humoral immunity. However, the patients we treated were basically ill from late January to early February; therefore,

the difference between the two groups due to different disease duration could be basically excluded. Our results suggest that IgG transformation in severe and critically ill patients was slower than that in regular patients, and the production of specific IgG antibody against SARS-CoV-2 is insufficient.

Acute respiratory distress syndrome (ARDS) is the leading cause of death in COVID-19 patients. One of the major mechanisms of ARDS is cytokine storm (also known as cytokine release syndrome, CRS), a deadly, uncontrolled systemic inflammatory response caused by the release of large amounts of pro-inflammatory cytokines [16]. Among the excess cytokines produced by activated macrophages and reticuloendothelial cells, IL-6 is one of the key cytokines. Our study showed that the plasma IL-6 level of COVID-19 patients increased to different degrees, and the increase was more significant in severe and critically ill patients than in regular patients, confirming that IL-6 played an important role in the pathophysiological process of COVID-19. Elevated plasma IL-6 levels in COVID-19 patients have been reported in a number of studies and have been used in clinical trials as a therapeutic target for critically ill patients, for example, the use tocilizumab, and the level of IL-6 may be used as an indicator of disease severity [17, 18].

Our study found that the blood was hypercoagulable in COVID-19 patients, and the levels of D-dimer and fibrinogen in severe and critically ill patients were higher than that in regular patients. Another study also reported that 71.4% of non-survivors and 0.6% survivors met the criteria of disseminated intravascular coagulation during their hospital, and abnormal coagulation results, especially markedly elevated D-dimer and FDP are common in deaths with COVID-19 [19]. Marisa Dolhnikoff et al. also observed a variable number of small fibrinous thrombi in small pulmonary arterioles in areas of both damaged and more preserved lung parenchyma in 8 out of 10 cases using ultrasound-based minimally invasive autopsies [20]. Based on these findings, it was suggested that COVID-19 patients were in a state of high coagulation, and that plasma D-dimer and FDP levels might have the potential to guide treatment and evaluate prognosis.

In addition, we found the CRP, PCT, ESR, FER and LDH were all higher in severe and critically ill patients than in regular patients, suggesting that the inflammatory response was more prominent in severe and critically patients. Elevated neutrophils and PCT in severe and critically ill patients may also be due to secondary bacterial infections. The level of albumin in severe and critically ill patients was lower than that in regular patients, which may be due to relatively insufficient nutrition consumption by severe and critically patients.

However, our research also has many shortcomings. Limited to retrospective analysis, the dynamic data collection of the patients was not comprehensive, and the influence

of changes in hematological and immunological indicators on the prognosis of the patients could not be analyzed. In addition, our lymphocyte subpopulation analysis lacked B cell data to perfectly explain the functional status of B cells in COVID-19 patients; further research and reports are also expected.

In summary, we systematically analyzed the hematological and immunological parameters of COVID-19 patients, we found that the lymphocytes and erythrocytes in COVID-19 patients were decreased to different degrees, and the blood was in a state of hypercoagulation, which was more obvious in severe and critically ill patients. Insufficient IgG production in severe and critically ill patients suggests humoral immune impairment. The increased levels of Il-6, LDH, CRP, PCT, ESR and FER were positively correlated with disease severity in COVID-19 patients. Therefore, the above indicators should be paid close attention to in the clinical treatment of COVID-19 patients to realize the early identification and intervention of critically ill patients.

Compliance with ethical standards

Conflict of interest All authors declare no competing interests.

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