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COVID-19: Lymphocyte Subpopulations Monitoring in Critically Ill Patients

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Abstract

Background: The alteration of lymphocyte subpopulations can help to predict the severity and the prognosis of severe Coronavirus disease 2019 (COVID-19). Our goal was to describe the kinetics of lymphocyte subsets, and their impact on the severity and mortality in critically ill COVID-19 patients. **Methods:** We collected demographic data, comorbidities, clinical signs on admission, laboratory findings on admission then a follow-up during hospitalization. Lymphocyte subsets including CD3+ T cells, CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells were counted by flow cytometer. **Results:** On admission, we observed lymphopenia in 57% of cases, decreased CD3+ T cells in 76% of cases, decreased CD4+ T cells in 81% of cases, decreased CD8+ T cells in 62% of cases, decreased B cells in 52% of cases, and decreased natural killer (NK) cells in 33% of cases. After treatment, decreased CD3+ T cells, decreased CD4+ T cells, decreased CD8+ T cells, and decreased natural killer cells were predictor factors of mortality, in the univariable analysis. **Conclusion:** CD3+ T cells, CD4+ T cells, CD8+ T cells, and natural killer cells were predictor factors of severity, ICU mortality, and also a useful tool for predicting disease progression.

Keywords

SARS-CoV-2, Coronavirus Disease 2019, Lymphocyte Subsets, Critical Care Outcomes

1. Introduction

In December 2019, a new disease due to SARS-CoV-2 infection appeared in China. A few weeks later, it spreads and becomes a pandemic; about 6,931,000 cases have been infected globally with 400,857 (5.8%) deaths, as of June 8, 2020 [1]. The pathophysiology of this infection remains not fully clarified. Although, it has been observed that SARS-Cov-2 is responsible for a reactive inflammatory storm as a result of an exaggerated host immune system response, with deleterious effects on multiple organs; firstly, in the most of the cases, it affects pulmonary tract, then, the others systems including cardiovascular, gastrointestinal, neurological, hematopoietic and immune system [2] [3] [4].

Even though T lymphocytes and natural killer cells are essential to control viral infections, lymphopenia is a frequent hematological disorder in serious COVID-19 patients [5] [6] [7]. This abnormality might be explained by firstly, the virus may directly affect lymphocytes [8], because of the expression of angiotensin-converting enzyme-2 on the surface of lymphocytes [9] [10]. Secondly, their inhibition by metabolic disorders (*i.e.* lactic acidosis) [11]. Thirdly, pro-inflammatory cytokines including tumor necrosis factor (TNF)α, and interleukin (IL)-6, could provoke lymphocyte deficit, and fourthly, the virus might engender lymphatic organs damage such as thymus and spleen [12]. Thus, the occurrence rate was between 44.5% [13], 67% [14], and 92.6%, (15) of critically ill COVID-19 cases, because of they adopted different definitions: lymphocytes < 500/mm^3 [13], lymphocytes < 1000 mm^3 [14], or lymphocytes < 1500 mm^3 [15]. Moreover, lymphocyte subpopulations decreased and predicted the severity and the prognosis of severe COVID-19 [16] [17]. Herein, our goal was to describe the kinetics of lymphocyte subsets, and their impact on the severity and mortality in critically ill COVID-19 patients.

2. Methods

For this prospective single-center study, we included all adult patients with confirmed COVID-19 infection by a positive reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a nasopharyngeal swab, admitted in the intensive care unit (ICU) of the Mohammed VIth University Centre of the Marrakech region, Morocco, from Mach 19, 2020, to May 15, 2020.

Critically ill patients were defined as admitted in the ICU because they required mechanical ventilation or more than eight liters per minute of oxygen to maintain pulse oxygen saturation (SpO_2) > 90% or had a respiratory rate of more than 40 breaths per minute.

We collected demographic data, clinical signs, laboratory findings on admission then a follow-up during hospitalization (lymphocytes, D-dimer, ferritin, lactate dehydrogenase (LDH), C-reactive protein, procalcitonin, PaO_2:FiO_2), chest CT scan if available, outcomes, time from onset of the first symptom to ICU admission, Charlson Comorbidity Index [18] and sequential organ failure assessment (SOFA) scores [19]. CD3+ T cells, CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells were counted by flow cytometer. All tests were performed at the discretion of the treating physician.

We expressed continuous variables as medians and interquartile (IQR) ranges or means (standard deviations (SD)), as appropriate. Categorical variables were described using percentages and compared using the χ^2 test, although Fisher exact test was used when the data were sparse. We performed a univariable analysis to evaluate the risk factors of mortality. The analysis was processed by SPSS 10.0 for Windows (SPSS, Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant.

Informed consent was waived due to the emergency of the disease, and researchers analyzed only anonymized data. All research was conducted following the national guidelines and regulations.

3. Results

Of 1618 COVID-19 patients hospitalized in our university center, 55 patients (3.4%) were admitted to the ICU. We list the basic, clinical characteristics, biological and radiological findings in **Table 1**. The mean age was 59 (16.5) years; 74.5% were men. Among all the patients, 84% had chronic medical conditions. The frequent symptoms were dyspnoea (85%), and cough (80%). The median length from the onset of symptoms to ICU admission was 7 (6 - 8) days. The median SOFA score on admission was 5 (4 - 17). On admission, lymphopenia was common (76%) with a median of 980/mm^3, the median LDH was 560 IU/L, the median D-dimer was 2975 mg/L, the median ferritin was 1135 ng/mL. The chest CT scan showed bilateral ground-glass opacification > 50% in 74% of cases.

Among the 55 patients, we analyzed the lymphocyte subsets from 21 patients. On admission, we observed lymphopenia in 57% of cases, decreased CD3+ T cells in 76% of cases, decreased CD4+ T cells in 81% of cases, decreased CD8+ T cells in 62% of cases, decreased B cells in 52% of cases, and decreased natural killer (NK) cells in 33% of cases. In these 21 patients, 71.4% (15/21) received chloroquine/hydroxychloroquine plus azithromycin, and 4.8% (1/21) treated with lopinavir/ritonavir. The monitoring of the lymphocyte subpopulation counts was reported in **Figure 1**. Effectively, after treatment, only 2/9 non-survivor patients improved their CD3+ T cells versus 10/12 survivor patients. Besides, regarding the CD4+ T cells, 11/12 survivor patients presented a normal count versus 1/9 non-survivor patients. The mortality rate was 43.6% of cases (24 patients). On admission, none of the decreased lymphocyte subsets was associated with mortality. However, after treatment, decreased CD3+ T cells (78% vs 17%; $p = 0.009$), decreased CD4+ T cells (90% vs 8%; $p < 0.001$), decreased CD8+ T cells (90% vs 8%; $p < 0.001$), and decreased natural killer cells (67% vs 0%; $p = 0.002$) were predictor factors of mortality, in the univariable analysis (**Table 2**).

Table 1. Basic and clinical characteristics, laboratory data and chest CT scan findings of all patients.

Characteristics	All patients (N = 55)
Mean age (SD) (year)	59 (16.5)
Sex (%)	
Male	74.5
Female	25.5
Comorbidities (%)	84
Hypertension	42
Diabetes	34
Coronary heart disease	11
Chronic kidney disease	9
Chronic obstructive pulmonary disease	4
Cerebrovascular disease	4
Cancer	4
Asthma	2
Cirrhosis	2
Connective tissue disease	2
Smoking	16
Alcoholism	4
Others	11
Charlson Comorbidity Index score, median (IQR)	3 (2 - 5)
Length from the onset of symptoms to ICU admission, median (IQR) (day)	7 (6 - 8)
Symptoms (%)	
Dyspnea	85
Cough	80
Respiratory struggle	54
Fever	26
Digestive signs	26
Agitation	22
SOFA score	
On admission, median (IQR)	5 (4 - 17)
Highest score during the first three days, median (IQR)	10 (5 - 16.5)
On day 7, median (IQR)	11 (4 - 16.75)

Continued

Laboratory data	
On admission	
Lymphocytes count, median (IQR) (per mm^3)	980 (565 - 1455)
D-dimer, median (IQR) (mg/L)	2975 (1490 - 7112)
Ferritin, median (IQR) (ng/mL)	1135 (547 - 2023)
LDH, median (IQR) (IU/L)	560 (381 - 766)
C-reactive protein, median (IQR) (mg/L)	173 (99 - 243)
Procalcitonin, median (IQR) (ng/mL)	0.31 (0.13 - 0.71)
PaO_2:FiO_2 ratio, median (IQR)	86 (70 - 130)
During the first 3 days	
Lowest lymphocytes count, median (IQR) (per mm^3)	810 (655 - 1035)
Highest D-dimer level, median (IQR) (mg/L)	3225 (289 - 9992)
Highest ferritin level, median (IQR) (ng/mL)	1416 (688 - 1940)
Highest LDH level, median (IQR) (IU/L)	560 (381 - 766)
Highest C-reactive protein level, median (IQR) (mg/L)	175 (111 - 253)
Highest procalcitonin level, median (IQR) (ng/mL)	2 (0.38 - 3.85)
Lowest PaO_2:FiO_2 ratio, median (IQR)	86 (70 - 130)
On day 7	
Lymphocytes count, median (IQR) (per mm^3)	763 (570 - 1540)
D-dimer level, median (IQR) (mg/L)	4045 (2752 - 9877)
Ferritin level, median (IQR) (ng/mL)	1325 (734 - 1940)
LDH, median (IQR) (IU/L)	402 (271 - 507)
C-reactive protein level, median (IQR) (mg/L)	98 (52 - 170)
Procalcitonin level, median (IQR) (ng/mL)	0,59 (0.18 - 4.25)
PaO_2:FiO_2 ratio, median (IQR)	98 (78 - 148)
Chest CT scan (%)	
Ground glass opacification <25%	10
Ground glass opacification 25% - 49%	16
Ground glass opacification 50% - 74%	37
Ground glass opacification 75% - 100%	37
Pleural effusion	0

IQR, interquartile range. SOFA, sequential organ failure assessment. LDH, lactate dehydrogenase. PaO_2:FiO_2, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.

Table 2. Predictor factors of mortality in univariable analysis.

	Before treatment			After treatment		
	Non-survivors	Survivors	p	Non-survivors	Survivors	p
Decreased CD3+ T cells (%)	89	68	0.3	78	17	0.009
Decreased CD4+ T cells (%)	88	75	0.6	90	8	<0.001
Decreased CD8+ T cells (%)	88	42	0.06	90	8	<0.001
Decreased B cells (%)	56	50	0.9	11	0	0.4
Decreased natural killer cells (%)	34	33	0.9	67	0	0.002

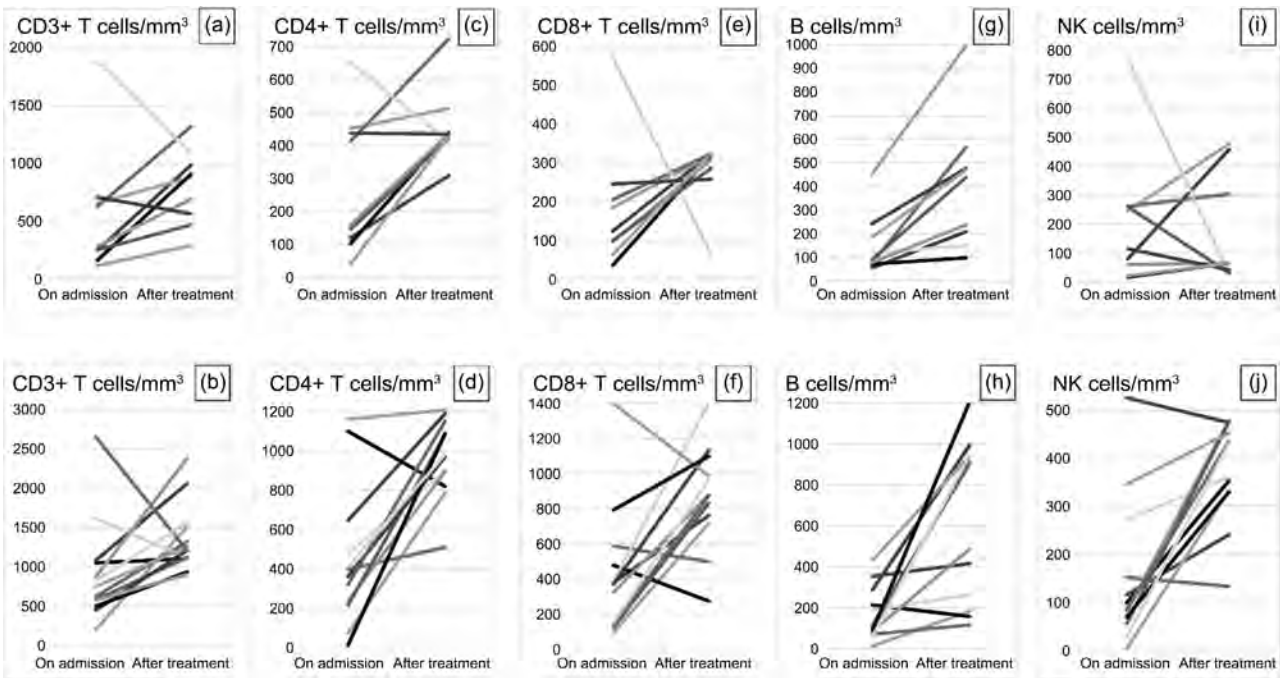

Figure 1. The kinetics of lymphocyte subpopulations (CD3+ T cells, CD4+ T cells, CD8+ T cells, B lymphocytes, and natural killer (NK)) between admission and after treatment in non-survivor patients ((a), (c), (e), (g), and (i)) and in survivor patients ((b), (d), (f), (h), and (j)).

4. Discussion

In our population, after treatment, decreased CD3+ T cells, decreased CD4+ T cells, decreased CD8+ T cells, and decreased natural killer cells were predictor factors of mortality; further, a large proportion of patients recovered lymphocyte subpopulations in survivor cases. At the best of our knowledge, this is the first report of the monitoring lymphocyte subsets in a Moroccan cohort of critically ill COVID-19 patients.

These findings were in line with the publishing data. Wang *et al.* [20] declared the count alteration of total lymphocytes, CD4+ T cells, CD8+ T cells, B cells, and natural killer cells in COVID-19 patients; as well, the CD8+ cells was an independent marker of severity and efficacy of treatment. And accordingly to Sun *et al.* [21] who observed that total T lymphocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, and NK cells decreased in un-discharged/died group at two weeks after treatment, compared with the discharged group. Additionally, CD4+ T cells and CD8+ T cells could help to evaluate the disease evolvement [22]. Besides, a recent meta-analysis concluded that lymphopenia was related to worsened outcomes [23].

This study has some limitations. The first concern was that our study was a single-centered study with only 55 severe patients, of whom only 21 patients who had lymphocytes subset counts. Secondly, we collected lymphocyte subset counts on admission in the intensive care unit, but some patients were initially hospitalized in a general ward for some days. Thirdly, the interpretation of our findings might be limited by the sample size. However, our ICU was the referral center in the region, thus we consider our study population is representative of cases diagnosed and treated in our region. Further studies through the country still needed.

5. Conclusion

CD3+ T cells, CD4+ T cells, CD8+ T cells, and natural killer cells were predictor factors of severity and ICU mortality. As well, they were a useful tool for predicting disease progression. Other larger sample studies are needed to validate risk factors and the lymphocyte threshold.

Ethical Considerations

Informed consent was waived due to the emergency of the disease, and researchers analyzed only anonymized data. All research was conducted following the national guidelines and regulations.

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Authors' Contributions

A.Z., A.H., H.R., B.A., and A.M.S. designed the study; A.Z. and A.H. wrote and edited the paper; R.H., I.B., B.A., and A.R.E. discussed results, and edited the paper; F.D., Y.Z., H.C., and S.Y. discussed results and edited the paper.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Uncertainty of Clinical Thinking and Patient Safety

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Abstract

Clinical thinking have the uncertainty, by which there are not a few mistakes caused. So it is necessary to discuss how to deal with the uncertainty of clinical thinking, which originates from the uncertainty of the objective world, social world and medicine knowledge, and can be seen all over clinical activities; Critical thinking which cautious about the interpretation and prediction of scientific theory is the best practice to explore the uncertainty. The essential purpose of medicine is rescuing people, So it is necessary and scientific to take "excluding life-threatening symptoms first" as the first principle of clinical thinking, which is also the primary method to deal with the uncertainty of clinical thinking; By the limited certainty of clinical thinking, procedural thinking is conducive to building a safer health system that is "easy to do right and difficult to do wrong".

Keywords

Clinical Thinking, Uncertainty, Critical Thinking, Step-Down Thinking, Procedural Thinking

1. Introduction

Medicine is not only "science", but also like "art", with uncertainty and a certain degree of fuzziness. In the past, our understanding of the uncertainty of medicine was insufficient, and the uncertainty of clinical thinking was superficial. There are not a few mistakes caused by this. Research into medical practices at Harvard Medical School reported in 1991 that 3% - 4% of adverse events were related to hospitalization [1]. The book, *To Err Is Human*, published in 1999, showed that in that year more people died of medical errors than from traffic accidents in the United States, and the adverse events related to medical interventions were reported to be the third leading cause of death among citizens of the

United States [2]. The World Health Organization (WHO) reported on its website in September 2019 that the "occurrence of adverse events due to unsafe care is likely one of the 10 leading causes of death and disability in the world," and up to 80% of these injuries could be prevented [3]. These findings have sounded an alarm to physicians. In any field where we need to master complex and large amount of knowledge, it is difficult to avoid the "fault of incompetence" [4]. Only by deeply understanding the uncertainty of clinical thinking, can we deal with the uncertainty of clinical thinking with a more cautious attitude in clinical practice.

2. The Uncertainty of Clinical Thinking

We live in a world full of uncertainty, whether the objective world, the social world, or the knowledge formed in the process of exploring the world are full of uncertainty [5]. So is medicine. The uncertainty of medicine comes from the uncertainty of objective world, social world and knowledge, which determines the uncertainty of clinical thinking guiding our clinical practice, which is reflected in all aspects of clinical practice. The medical knowledge formed in the process of exploring the objective and social world of medicine is also full of uncertainty, which is not only caused by the limitation of human cognitive activities, but also the growth of medical knowledge in the future is unpredictable [6]. According to the records of classic medical books, there are as many as 40,000 kinds of diseases. Because there are variants in different populations, and different diseases have different stages and types and clinical manifestation, which makes medicine more complex [7]. Academician Daiming Fan mentioned in his article [7] "medicine and science" that Cochrane Collaboration Network is recognized as the most reliable evidence-based medical evidence website in the world. Of the 2435 systematic reviews of evidence-based medicine published by the website as of August 2005, only 30% of the evidence can give positive or negative answers, and the remaining 70% are ambiguous. In 2014, JAMA compared the published randomized clinical data with meta-analysis, and found that 35% of the meta-analysis conclusions were different from the original research, and the results directly affected the evaluation of clinical trials. 20 years ago, in order to prevent the occurrence of stress ulcer, the principle of treatment for large area burn was fasting water and only giving "intravenous high nutrition". With the developing of nutrition, people began to realize the importance of enteral nutrition. However, at that time, the "fasting water" treatment method, which seems to be wrong now, was the correct knowledge of certainty and the standard treatment to be strictly implemented. So a large number of uncertain medical knowledge leads to incomplete information, which also leads to the uncertainty of clinical thinking.

In clinical practice, there are uncertainties in the occurrence and development of diseases, the changes of patients' physical conditions and diseased organs. No matter how perfect the general law of medicine is, performance of disease will be different in each patient, and the general law cannot cover every individual. At present, with the rapid development of medicine and the innovation of various inspection technologies, the clinical diagnosis level is undoubtedly improved. However, how to evaluate the numerous examination results, clinicians need to make a comprehensive judgment. The "normal value" of various tests covers 95% of the population, and 5% of the normal value may be the "abnormal value" [8]. For the same disease, due to differences of the patient's temperament, ersonality, psychology, family environment and social environment, the patient's feelings are also different, and the diagnosis and treatment results will be different. The uncertainty of clinical thinking is reflected in all aspects of clinical activities, such as the uncertainty of patient data collection and disease judgment and prognosis; every doctor cannot give a full grasp of the correctness of the patient's diagnosis; the effect of treatment or operation according to the diagnosis is not necessarily satisfactory, or there is bad effect or even the opposite outcome, resulting in misdiagnosis or errors. Even if there is no misdiagnosis or mistreatment, there may be many new situations unexpected. Therefore, there is no absolute objective, universal and pure medical knowledge. Doctors can cure the disease and save people, most of them rely on the confirmed medical knowledge, but there is still uncertainty in the definite knowledge. The so-called deterministic knowledge only means the knowledge of "maximum probability event" within a certain space-time range and under certain conditions, and is the knowledge "not yet falsified" in the process of human cognition, which is also the "uncertainty of deterministic knowledge" [6].

3. How to Deal with the Uncertainty of Clinical Thinking

Physicians encounter decision-making in clinical practice every day and constantly use clinical thinking to provide patients with diagnostic and treatment decisions. Sometimes they need to make important decisions about life and death under insufficient information. For a long time, people have tried to find certainty in medical theory and practice, so as to improve diagnostic and therapeutic efficacy, but that uncertainty remains, and new uncertainties are sure to emerge as some certainties are hammered down.

As an emergency doctor, we feel deeply that our knowledge in clinical practice is overshadowed by what we don't yet know. For example, we don't know what illness the next patient will suffer from. We don't know if it will be a common disease or a rare one, if it will be life-threatening, or how the patient's condition will evolve. "I don't know" are perhaps the most important three words in medicine [9]. How to deal with the uncertainty of clinical thinking is more worthy of discussion.

3.1. Critical Thinking

Critical thinking is an effective way to solve the problem of uncertainty. It takes a cautious attitude towards the universal knowledge and objective laws found for a long time, and give a new interpretation and prediction for old scientific theories [10]. The core of critical thinking is "doubt", which doubts everything, so as to constantly verify the existing conclusions. In the view of medical uncertainty, we should keep a clear mind on the conclusion that clinical thinking is "universal, objective and inevitable"; whether clinical conclusion is truth does not depend on which doctor it comes from, but whether it can withstand falsification test. The most essential feature of critical thinking is to go to the bottom of the matter, to find by hard and thorough search, and to get reasonable and mature thinking for guiding the thinking process and laying the foundation for rigorous reasoning, and finally obtain the best effect [11].

The development of disease is a process, which is in dynamic evolution. The state of the patient changes with time, and the changes of any disease are the accumulation of quantity. The data collected in the early stage of the disease for diagnosis are not necessarily complete, or because the characteristics of the disease itself have not been fully demonstrated, the preliminary diagnosis may be imperfect or even wrong. Any preliminary diagnosis must be continuously observed, verified, supplemented in time in the process of medical practice, and differential diagnosis must be repeated and screened on the basis of new disease data, so that the correct diagnosis can be obtained [12], this cycle is the best practice of critical thinking.

Case 1: a woman, 32 years old, was injured in a traffic accident on her right foot with local swelling. Physical examination and CT showed no fracture. The patient worried about that and asked the doctor to confirm no fracture, the doctor replied: no fracture. The patient reconciled with the perpetrator on the same day and notarized and signed. Three days later, the local swelling of the patient's right foot did not subside, and the pain did not reduce when bearing weight. He came back to the hospital for further consultation. The doctor replied: if you hurt your muscles, it's OK to raise them slowly for more than 100 days. Ten days later, the patient's symptoms did not abate, and he went to another orthopedic hospital for consultation. Radiologic examination showed obvious foot bone fracture, which required a long time of plaster fixation, and lost work. However, it was difficult to continue to obtain compensation from the perpetrator, so he complained to the first hospital.

This case once again reveals the uncertainty of clinical thinking. The first doctor should not arbitrarily think that there is no fracture. Yes, there is no fracture at that time, but critical thinking and dynamic observation is needed all the time for patient's condition, Even after high-end imaging examinations. Dynamic observation is not so much experience as the concrete practice of clinical thinking uncertainty and critical thinking. American scholar Peter Facione said that "one of the reasons why American high education is favored by the world is that it has the potential to teach critical thinking". The Institute for International Medical Education (IIME) has listed critical thinking as one of the seven aspects of the "minimum basic requirements for global medical education" [10]. It can be seen that the cultivation of critical thinking is important for medical professional competence.

3.2. Excluding Life-Threatening Condition First

The ancient medicine developed through practice, its task is to resist fatal diseases and relieve the suffering of patients, which is the essential purpose of medicine [13] [14]. The famous Hippocratic Oath, with its "first do no harm" put to words the priority of patient safety more than 2000 years ago [15]. Even if one cannot cure the disease, the absolute need is to not harm the patient. Therefore, following the essential purpose of medicine, the first principle of clinical thinking is to ensure the life safety of patients.

Thinking has integrity and inertia, which is the guide of action. Thinking in an inherent way will always affect its behavior. Once the mode of thinking is formed, it will form inertia thinking. Respect for life is the origin of medicine, and clinical thinking of respecting for life is the safe thinking. Therefore, the first principle of clinical thinking is to rule out the possibility of life-threatening **condition** first during diagnosis, which is also the primary method to deal with the uncertainty of clinical thinking [8].

To practice clinical thinking by first ruling out the possibility of life-threatening **condition** during diagnosis is also a basic tenet of medical humanities, the core of which is to first respect life and to protect patients' safety [16]. To integrate medical humanities into clinical practice, it is first necessary to integrate medical humanities into clinical thinking. They complement each other, share the same root and serve the purpose of medicine. The biggest difference between medical humanities and general humanities is the practical characteristic. Whether in the field of education or research, medical humanities are reflected in the specific practice. Medical humanities should be integrated into clinical practice, first of all, clinical thinking should be integrated in it, and the clinical thinking guided by medical humanities should be advocated.

Ruling out the possibility of life-threatening conditions first during diagnosis requires to abandon the utilitarian. Utilitarianism often considers life-threatening **condition** rare, more than 80% **condition** are common diseases and frequently occurring diseases, and the focus of doctor's work should not be on diseases with 20% or even less probability, thus the principle of ruling out the possibility of life-threatening **condition** during diagnosis may lead to overtreatment. However, each life is unique and valuable. Life is of infinite value to everyone himself, and the value of life cannot be measured by utilitarianism [17].

Step-down Thinking was first put forward by the famous Chinese emergency Professor Wang Peiyan, in the emergency field. It has been more than ten years now. It refers to the exclusion of the patients' diseases in accordance with certain methods, from life-threatening diseases to general diseases, from rapid progress ones to the slow, from organic to functional diseases. Facing the uncertainty of clinical thinking, doctors' responsibility is to use scientific methods to reduce the impact of uncertainty on clinical practice and avoid damage to patients, and strive for better clinical effect.

There are more and more kinds of clinical specialties with different characteristics, but the goal of resisting fatal diseases and relieve the suffering of patients is the same in medical practice .Objects and goals is the same and only the means are different for all medical workers. Therefore, "first of all, excluding life-threatening diseases" should be the thinking principle of all medical workers. diagnostic strategy of common diseases and frequently occurring are also based on "ensuring patient safety". John Murtagh, a famous Australian general practice Professor, has put this principle into his "safe diagnostic strategy" as a general practitioner's mode of thinking. Only by respecting life and reverence can we practice the essence and goal of Medicine [16], and strive to avoid the harm to patients' lives caused by the uncertainty of clinical thinking. Therefore, the principle of "descending step thinking" to exclude life-threatening condition is the general requirement to deal with the uncertainty of clinical thinking, and is the ultimate goal of medicine and the foundation of medical humanities [13].

3.3. Process Thinking

Process thinking has not been seen much emphasis or recognition valued and recognized in the past. Diagnostics has focused excessively on common diseases [12]. Admittedly, experienced physicians may arrive at correct diagnoses immediately. However, experience does not guarantee patient safety. Regardless of how experienced and skillful a physician becomes, he or she still cannot guarantee that they will always be at their best. In the other hand, accumulation of experience requires time, maybe it is a long time, and Patients will be hurt during this period.

The uncertainty of clinical thinking is more reflected in the uncertainty of clinical decision-making. Doctor's thinking is affected by many factors, such as doctor's state, mood, culture, knowledge and so on. So we can't always repeat a good way of clinical decision-making, and have the possibility of mistakes, even in common diseases. In the medical community, there is a story that the more familiar people are, the more likely mistakes they make (the more familiar, the more mistaken) .This is because people are familiar and omit the process that should be. An example: a 45 years old successful man suffered from thyroid nodules because of his busy work and no time to hospital, he turned to his classmate who was a surgeon. His classmate thought that the thyroid nodule could be cut off, so he underwent surgery on the same day. As a result, the patient appeared "hyperthyroidism crisis" and died in the evening. According to analysis of the case, the patient had not been given any necessary examination before the operation, even blood routine.

Process thinking tells us what to do first, what must be done and what is not necessary to do. We should sort out the key links, grasp the most critical elements, and carry out clinical decision orderly. More than 10 years ago, the American Institute of medicine submitted a report on the statistical analysis of medical errors. The title of the report is "To err is human: building a safer health system" [2]. It said the only way to deal with this problem is to establish a safety concept and workflow with "easy to do right and difficult to do wrong". This is the fundamental solution.

Process thinking is not only the workflow of operation, but also a kind of thoughts or ideas. It is because of the complexity of medicine and the diversity of clinical symptoms, not all workflow of medical links can be established. Therefore, Within the limited certainty of clinical thinking, process is a kind of thinking mode, doctors have a same thinking path, instead of different people having different opinions, and each of them will make diagnosis and decision according to their own experience. Process thinking carries out the basic principles of clinical thinking and critical thinking method, so as to ensure the safety of patients.

4. Summary

Doctors encounter medical uncertainty and deal with patients' vibrant lives, they should consciously use critical thinking, and respectfully question and revisit our clinical decisions and therapeutic regimens with the aim of putting patients' safety first. From the perspective of clinical thinking, practice the essence of medicine, face up to and awe the uncertainty of medicine and clinical thinking, put patient safety in the first place, and let uncertainty become the starting point and driving force for continuous pursuit of "ensuring patient safety".

Authors' Contributions

Jianguo Li had the idea for the article, Zhangshun Shen performed the literature search, Qian Zhao, Hui Guo wrote the article, and Jianguo Li is the guarantor.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Application and Nursing of Pulse Index Continuous Cardiac Output (PiCCO) Volume Monitoring in Early Fluid Resuscitation in Patients with Septic Shock

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Abstract

Background: Septic shock is a rapidly changing and fatal syndrome that can cause comprehensive deterioration of cardiopulmonary and renal function and multiple organ failure. At the same time, septic shock has the complex clinical manifestations and hemodynamics. PiCCO can accurately monitor blood flow, physical and volume indicators, and active and effective fluid resuscitation are important measures to reduce the fatality rate of septic shock and improve the prognosis of patients. **Objectives:** To explore the application and nursing of PiCCO in early fluid resuscitation in patients with septic shock. **Methods:** This was a retrospective observational study. The observation group and the control group each had 30 cases. The observation group used PiCCO to guide fluid resuscitation; the control group used conventional methods to guide fluid resuscitation. The changes in CVP, HR, MAP, and urine volume per hour were observed in the two groups. The changes of various indicators before and after fluid resuscitation, the length of stay in ICU and the mortality rate were compared between the two groups. All the outcomes were collected from the electronic medical case system after patients' discharge from the hospital. **Results:** APACHE II, CVP, HR, MAP were compared between the observation group and the control group, and the differences were statistically significant ($P < 0.05$). The blood volume of patients in the observation group was significantly improved after fluid supplementation ($P < 0.05$). Compared with the control group, the length of stay in ICU in the observation group was significantly shorter, and the mortality rate was also significantly reduced ($P < 0.05$). **Conclusion:** PiCCO can be better used in early fluid resuscitation of patients with septic shock.

Keywords

Septic Shock, Pulse Index Continuous Cardiac Output (PiCCO), Nursing

1. Introduction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality and it has always been a problem that plagues the world's medical community [1] [2]. For such patients, a large amount of fluid resuscitation is very important in early treatment. However, excessive fluid resuscitation may lead to pulmonary edema or circulatory overload. Therefore, it is important to understand the patient's blood volume status. Through effective fluid resuscitation, the lack of blood volume in the blood vessels is corrected, and the tissue perfusion is ensured, thereby reducing the fatality rate of septic shock [3] [4]. PiCCO can monitor cardiac output (CO), cardiac index (CI) and volume indicators such as intrathoracic blood volume index (ITBVI), global end-diastolic volume index (GEDVI), stroke volume variation (SVV) and vascular resistance, etc. PiCCO is simple and easy to operate [5] [6]. This study explores the application and nursing of PiCCO volume monitoring in early fluid resuscitation in patients with septic shock, and the report is as follows.

2. Objects and Methods

2.1. Objects

Sixty patients with septic shock who were admitted to the surgical ICU from July 2014 to July 2020 were selected. Inclusion criteria: patients aged 18 - 60 years old, with diagnosis of septic shock, and with fluid resuscitation treatment. Exclusion criteria: patients during pregnancy, patients with previous arteriovenous fistulas, patients who give up active treatment, and patients with other types of shock such as cardiogenic shock or hemorrhagic shock. In this group of patients, there were 38 males and 22 females; they were 18 - 60 years old, with an average age of 34 years. Thirty patients with septic shock who used routine monitoring to guide fluid management were set as the control group, and 30 patients with septic shock who used PiCCO monitoring to guide fluid management were set as the observation group. The age and gender of the two groups were not statistically significant ($P > 0.05$), and they were comparable. This study was performed by referring to the medical records, and there was almost no risk to the objects. So the written informed consent was exempted. We have obtained permission from the hospital's ethics committee.

2.2. Methods

2.2.1. Control Group

Routine monitoring methods was used to guide fluid management: continuous electrocardiogram (ECG) monitoring, hourly monitoring of heart rate (HR), percutaneous oxygen saturation, arterial blood pressure, central venous pressure (CVP), hourly urine volume and intake, and dynamic mastering of hourly and total intake and output. The level of CVP was maintained at 8 - 12 mmHg to guide fluid rehydration, active fluid rehydration at < 8 mmHg, and fluid rehydration at > 12 mmHg. Resuscitation 6 hours target was achieved by using vasoactive drugs to maintain the mean arterial pressure ≥ 65 mmHg, CVP 8 - 12 mmHg, and urine volume ≥ 0.5 ml/kg·h.

2.2.2. Observation Group

PiCCO monitoring was used to guide fluid management based on guiding fluid replenishment according to conventional methods. PiCCO module was connected to the monitor for hemodynamic monitoring through the central venous catheter's main passage in the neck or clavicle and the femoral artery thermodilution catheter. Generally, 0.9% sodium chloride solution was injected every six-hour at 2˚C ~ 5˚C, 10 ml/time. The injection was completed at a uniform rate within four seconds, and the average value was taken for three consecutive measurements. When the patient has changed in circulatory kinetics, the measurement is carried out at any time. PiCCO Active fluids was given when EVLWI < 7 ml/kg and ITBVI < 850 ml/m^2; limit fluid replacement when EVLWI < 10 ml/kg and ≥ 7 ml/kg, ITBVI > 1000 ml/m^2; limit fluid rehydration and use diuretics when EVLWI≥ 10ml/kg; adjust vasoactive drugs according to the results of CI and systolic function; and adjust norepinephrine dosage according to system vascular resistance index. Resuscitation six-hour goal was: SVV ≤ 10%, CI > 3.0 L/min·m^2, EVLWI < 10 ml/kg, MAP ≥ 65 mmHg, and urine volume ≥ 0.5 ml/kg·h.

2.3. Observation Indicators

APACHE II score [7] was calculated before treatment and 72 hours after treatment. The HR, CVP, MAP, GEDVI, the length of ICU stay, and mortality of the two groups were collected at two time points, namely before treatment and 72 hours after treatment. All the above indicators were collected from the electronic medical case system after patients' discharge from the hospital.

2.4. Statistical Methods

Statistical analysis was performed using SPSS23.0. Express the measurement data as X ± S, and use the independent sample t test. Express the count data as a ratio (n%) and use the χ^2 test. The Chi-square test was used to test the differences between the observation group and the control group. $P < 0.05$, the difference was statistically significant.

3. Results

The comparison of APACHE II score, HR, CVP, MAP between the two groups of patients showed that the difference in APACHE II score, HR, CVP, MAP in the observation group was statistically significant ($P < 0.01$), and the HR and MAP of the control group were statistically significant ($P < 0.05$) (**Table 1**).

The comparison results of the changes of various indexes before and after fluid management of patients in the observation group showed that the differences in CO, CI, GEDVI, EVLWI indexes in the observation group were statistically significant ($P < 0.05$) (**Table 2**).

The comparison of the length of stay in ICU and the mortality of the two groups. The difference was statistically significant ($P < 0.05$) (**Table 3**).

4. Discussion

The reduction of useful circulating blood volume is one of the features of septic shock. Effective fluid resuscitation is the key to treatment. PiCCO assisting clinical acquisition of accurate, dynamic, and continuous hemodynamic monitoring data, to be earlier, provide treatment guidance more accurately [8]. Compared with the traditional CVP monitoring method, this continuous cardiac output monitoring method based on arterial waveform has its unique advantages [9] [10].

From **Table 1** that the observation group has significantly improved APACHE II score, HR, CVP, MAP compared with the control group, indicating that PiCCO monitoring can help patients with septic shock. The safe and effective implementation of early resuscitation programs.

From **Table 2**, the indicators of CO, CI, GEDVI, and ELVWI of the observation group were significantly stable after the implementation of PiCCO monitoring and guiding fluid management. The possible reason is that PiCCO monitoring enables medical staff to visually observe various hemodynamic indicators of the patient from the monitor. Through the analysis of monitoring indicators,

Table 1. Comparison of APACHE II score, HR, MAP, CVP before and after treatment between the two groups.

Group	Age	Observation time	APACHE II	HR	MAP	CVP
Control group	35.1 ± 8.6	Before treatment	24.4 ± 6.8	143.5 ± 32.2	64.4 ± 16.8	4.5 ± 2.8
		72 h after treatment	22.3 ± 5.4	134.1 ± 28.6	74.1 ± 14.2	6.5 ± 3.2
t			3.97	3.46	18.70	15.83
P			0.75	0.03*	0.04*	0.08
Observation Group	34.0 ± 8.7	Before treatment	23.8 ± 5.3	142.9 ± 31.5	63.4 ± 17.8	4.4 ± 3.2
		72 h after treatment	18.6 ± 5.0	122.3 ± 22.9	84.4 ± 15.9	8.5 ± 2.2
t	0.51		13.76	22.05	32.06	29.55
P	0.61		<0.01**	<0.01**	<0.01**	<0.01**

Note: **means $P < 0.01$; *means $P < 0.05$; APACHE II: Acute Physiology And Chronic Health Evaluation II; HR: Heart Rate; MAP: Mean Arterial Pressure; CVP: Central Venous Pressure.

medical staff can more accurately assess the cardiopulmonary function and volume status of patients with septic shock, thereby adjusting the type of fluid, input sequence and time at any time. The feasibility and accuracy of the total end-diastolic volume index and the thoracic volume index in measuring the blood volume of patients have been confirmed. EVLWI can directly reflect the severity of pulmonary edema, including lung water caused by high permeability and high hydrostatic pressure. Therefore, the blood flow in the thoracic cavity and extravascular lung water monitoring guidance can avoid excessive fluid load from the second blow to the heart and circulatory system, protect or even improve the heart function to the greatest extent, thereby accelerating the stabilization of hemodynamics [11] [12]. But oneprevious study showed that in the early phase of severe sepsis among patients receiving mechanical ventilation, there was no constant relationship between GEDI and fluid reserve responsiveness [13]. Further, another recent study showed that echocardiography measurements of CO and CI were comparable to PiCCO measurements, which was non-invasive compared with PiCCO. This result indicated the limitation of PiCCO, and thus echocardiography measurement could be used to guide fluid and vasoactive-inotropic management of critically ill pediatric patients [14].

From **Table 3**, it was found that the observation group patients effectively shortened the length of stay in the ICU and reduced the mortality rate. Fluid resuscitation management is considered to be the key to the treatment of patients with septic shock. In the past, conventional fluid management often failed to provide an accurate and intuitive basis for patient safety. If the fluid resuscitation period cannot be passed smoothly, it may aggravate the patient's condition, even life-threatening. PiCCO monitoring can better guide the cardiopulmonary management of critically ill patients, and early circulatory stability in critically ill patients has important clinical significance for the protection of tissue perfusion and organ function [15]. It can be seen the condition of septic shock patients who use PiCCO monitoring to guide fluid body management can be stabilized earlier than patients who use conventional monitoring methods to guide infusion, which provide an excellent platform for disease treatment, and enable patients to pass the critical period safely [16].

Table 2. Changes in various indicators of PiCCO volume monitoring before and after fluid management in the observation group (n = 30).

	CO (L/min)	CI (L/min/m^2)	GEDVI (mL/m^2)	ELVWI (ml/kg)
Before treatment	2.9 ± 0.3	2.6 ± 0.5	415.0 ± 95.4	10.7 ± 4.5
72 h after treatment	4.6 ± 0.5	4.5 ± 0.3	703.0 ± 112.4	9.2 ± 3.3
t	251.10	159.40	58.39	7.55
P	<0.01*	<0.01*	<0.01*	<0.01*

Note: *means $P < 0.05$. CO: cardiac output; CI: cardiac index; GEDVI: global end-diastolic volume index; EVLWI: extra vascular lung water index.

Table 3. Comparison of the length of stay in ICU and the number of deaths (rate) between the two groups.

Group	n	Length of stay in ICU	Number of deaths (rate)
Control group	30	25.3 ± 4.9	7 (23)
Observation Group	30	20.1 ± 3.5	1 (3)
Statistics		t = 18.25	$\chi^2 = 5.19$
P		0.04*	0.03*

Note: *means $P < 0.05$.

In summary, the application of the PiCCO volume index can accurately and reliably assess the patient's volume status, can accurately indicate the patient's cardiopulmonary function, provide the most direct basis for the patient's fluid management, and facilitate timely adjustment of the fluid management plan, so that can help patients who with septic shock through the dangerous period successfully. At the same time, the monitoring method is simple, safe, and accurate. It can meet the requirements of rapid fluid resuscitation. It has essential value for fluid resuscitation of patients with septic shock and is beneficial to the observation and the care of patients with septic shock.

5. Limitations

This study was limited in several ways. First, this study's observation period was limited to the period of patients staying in the ICU, which was relatively short. The treatment effect of patients after leaving the ICU needs to be tracked. Secondly, the study subjects were limited to a tertiary university hospital in China and therefore were more likely to have more severe diseases, which may hinder the generalization of the results among patients in the general hospital.

Authors' Contributions

All authors contributed in study conception, design and critically revised the article. Miss Li and Liang have equally contributed as first authors to the article and drafted the article and in acquisition of data.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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