Efficiency of nicotinamide-based supportive therapy in lymphopenia for patients with ordinary or severe COVID-19

A randomized controlled trial

Qiang Hu, MD a,b, Quan-Yu Zhang, MD, PhD a, Cheng-Fei Peng, MD, PhD a, Zhuang Ma, MD, PhD c, Ya-Ling Han, MD, PhD a,*

Abstract

Background: This study aimed to investigate the efficiency of nicotinamide-based supportive therapy for lymphopenia in patients with coronavirus disease-2019 (COVID-19).

Methods: Twenty-four patients diagnosed with COVID-19 were randomly divided into 2 groups (n = 12) during hospitalization in a ratio of 1:1. Based on conventional treatment, the treatment group was administered 100 mg nicotinamide 5 times a day for 2 days. The control group received routine treatment only. The primary endpoint was the change in the absolute lymphocyte count. The secondary endpoints included both inhospital death and the composite endpoint of aggravation, according to upgraded oxygen therapy, improved nursing level, and ward rounds of superior physicians for changes in conditions.

Results: Full blood counts before and after nicotinamide administration were comparable in each group (all P > .05). Before and after receiving nicotinamide, mean absolute lymphocyte counts were similar between the two groups ([0.94 ± 0.26] × 10^9/L vs [0.89 ± 0.19] × 10^9/L, P = .565; [1.15 ± 0.48] × 10^9/L vs [1.02 ± 0.28] × 10^9/L, P = .445, respectively). Therefore, there was no statistically significant difference in the lymphocyte improvement rate between the two groups (23.08 ± 46.10 vs 16.52 ± 24.10, P = .67). There was also no statistically significant difference in the secondary endpoints between the two groups.

Conclusion: Among patients with COVID-19, there was no statistically significant difference in the change of whole blood counts and absolute lymphocyte counts before and after intervention in both groups. Therefore, no new evidence has been found regarding the effect of niacinamide on lymphopenia in COVID-19 patients.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, ADPR = adenosine diphosphate ribose, ARB = angiotensin receptor blockers, cADPR = cyclic adenosine phosphate ribose, COPD = chronic obstructive pulmonary disease, COVID-19 = Coronavirus disease 2019, CRC = colorectal cancer, HIV = human immunodeficiency virus, IFN-γ = interferon-γ, IL-10 = interleukin-10, IL-1β = interleukin-1β, IL-6 = interleukin-6, MCP-1 = monocyte chemoattractant protein-1, NAADP = nicotinic acid adenine dinucleotide phosphate NF-kB = nuclear factor-kB, NLR = neutrophil to lymphocyte ratio, NR = nicotinamide riboside, PARPs = poly-ADP-ribose polymerases, PBL = peripheral blood lymphocytes, RdpR = RNA-dependent RNA polymerase, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2, TNF = tumor necrosis factor, ULN = upper limit of normal, WBC = white blood cell counts.

Keywords: COVID-19, cytokine storm, lymphopenia, niacinamide

QH and QYZ contributed equally to this work.

This research was supported by the National Natural Science Foundation of China (NSFC: 32071116), the Liangyangfan fund (BJUHFCSOARF201901-14), and the LIAONING S&T Project (2020JH110300002). The study funder had no role in the design of the study, the collection and analysis of the data, and the writing of the paper.

No individual person’s data was reported that would require consent to publish from the participant.

All participants provided written informed consent.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The data underlying this article will be shared upon reasonable request to the corresponding author.

Our study was approved by the National Health Commission of China, the institutional review board at Huo Shen Shan Hospital, and the institutional ethics committee of the General Hospital of Northern Theater Command of the Chinese People’s Liberation Army.

ClinicalTrials.gov, NCT04910230. Registered Jun 1 2021-retrospectively registered.

*Correspondence: Ya-Ling Han, Department of Cardiology, General Hospital of Northern Theater Command, Shenyang 110016, China (e-mail: hanyaling@163.com).
1. Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has spread around the world rapidly, with high lethality.\(^{(1)}\) Several studies have shown that patients with coronavirus disease 2019 (COVID-19) in severe conditions may have many abnormal laboratory parameters, such as lactate dehydrogenase, D-dimer, C-reactive protein, and proinflammatory cytokines.\(^{(2-6)}\) Similarly, there is a decrease in lymphocyte counts at an early stage in patients with COVID-19, especially in severe cases.\(^{(4-7)}\) Previous studies reported that the percentage of peripheral blood lymphocyte count gradually decreased and remained low during the devastation of COVID-19.\(^{(8)}\) On the contrary, the improvement of lymphocyte counts from a low level indicates a relatively good prognosis. Therefore, early treatment to improve the lymphocyte counts of patients with COVID-19 can theoretically prevent further deterioration and decrease the mortality rate, finally improving their prognosis.

Lymphopenia is one of the most prominent characteristics of COVID-19, in contrast to other viral infections. Although the definite mechanism is unclear, recent studies suggested NAD+ consumption may be involved in this process.\(^{(9)}\) NAD+, known as the central catalyst of metabolism, has been shown connected to several stages of defense against SARS-CoV-2 infection and works like the fuel that supports immune defense. Upon activation of the innate immune response, poly-ADP-ribose polymerases (PARPs) hyperactivated due to virus entry leads to NAD+ depletion and cell death.\(^{(10)}\) During the adaptive immune response, the overexpression of CD38 activity in both CD4+ and CD8+ lymphocytes highly correlates with the lack of NAD+, which leads to increased proinflammatory cytokines.\(^{(11)}\) However, few studies have demonstrated the effectiveness of niacinamide on lymphopenia in COVID-19 patients. Based on the above research results, we intended to explore whether replenishing nicotinamide, a precursor of NAD+, can be used as supportive therapy for treating lymphopenia in patients with COVID-19.

2. Materials and Methods

2.1. Study design

This study was a single-center, randomized, open-label clinical trial designed to examine the effectiveness of nicotinamide-based supportive therapy in lymphopenia for patients with COVID-19. Patients diagnosed with COVID-19, who were admitted to Huo Shen Shan Hospital from March 1, 2020, to April 2, 2020, were eligible for participation, as shown in Figure 1. Our study was approved by the National Health Commission of China, the institutional review board at Huo Shen Shan Hospital, and the institutional ethics committee of the General Hospital of Northern Theater Command of the Chinese People’s Liberation Army, and the study was in accordance with Helsinki Declaration. The trial was registered with ClinicalTrials.gov, number NCT04910230. All participants provided written informed consent. An independent Data Safety Monitoring Board (DSMB) would review the unblinded data in each group regularly and make suggestions to the sponsors if our study warranted early termination. The authors declared our study adhered to the CONSORT guideline.

2.2. Patients

For inclusion criteria in the study, patients aged 18 to 85 who were diagnosed with COVID-19 coupled with lymphopenia were included in our study. The exclusion criteria included: mild or critically ill patients, participation in other clinical trials, pregnancy or lactation, ALT/AST > 5 times the upper limit of normal (ULN), neutrophils counts <0.5 × 10^9/L, platelets counts <50 × 10^9/L, patients diagnosed with rheumatoid immune-related diseases, long-term use of oral immunosuppressive drugs or immunomodulatory drugs, hypersensitive reaction to nicotinamide or any auxiliary materials, comorbidities including active tuberculosis or bacterial or fungal infections, undergone an organ transplant, mental disorders. The diagnosis and classification of COVID-19 were based on the “Guideline for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV)
Type was defined as patients with any of the following characteristics: respiratory distress (respiratory rate >30 times per minute), oxygen saturation SpO2 ≤ 93%, partial arterial oxygen pressure (PaO2)/fraction of inspired oxygen (FiO2) ≤ 300 mm Hg. Patients with critically ill were identified if they had one of the following features: respiratory failure requiring mechanical ventilation, shock, and organ dysfunction that needs ICU admission.

2.3. Randomization and treatment
Eligible patients with ordinary or severe COVID-19 were recruited for participation when the first occurrence of the absolute lymphocyte level was under the 1.1 × 10^9/L (normal range: 1.1–3.2 × 10^9/L) during hospitalization. Enrolled participants were randomly assigned (1:1) into the intervention group receiving niacinamide treatment or the control group with only routine treatments. A random number table and opaque, sealed envelopes marked with the sequence number were used to conduct the randomization. The treatment group received 100 mg of niacinamide (Shanghai Xinyi Pharmaceutical Co. Ltd.) 5 times a day for 2 days. The routine treatment was performed in accordance with the Guidelines for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infection by The National Health Commission (trial version 6), which mainly included symptomatic supportive care, antiviral treatment, oxygen therapy, and respiratory support. The routine treatments in the intervention and control groups were prescribed at physicians’ discretion.

2.4. Data collection and clinical assessment
Baseline characteristics, including the demographic description, diagnosis, comorbidities, and medication, were collected via the electronic medical record system. Blood tests were done before and 48 hours after intervention in all participants. The whole blood counts in both groups were assessed before and 48 hours after treatment. As a result, we would have absolute lymphocyte counts before and after the intervention, both in the 2 groups. Meanwhile, we would compare the changes of absolute changes in lymphocyte counts and lymphocyte improvement rates between the 2 groups. Moreover, the secondary endpoints were recorded accordingly to compare the incidence of events in the 2 groups.

2.5. Endpoints
The primary endpoint was the change of absolute lymphocyte counts between the baseline and the 48-hour blood tests. The secondary endpoints included in-hospital death and the composite endpoint of upgraded oxygen therapy, improvement of nursing level, and ward rounds of superior physicians for changes in conditions. The upgraded oxygen therapy was defined as the upgrading of general high-volume oxygen intake from oxygen intake, ventilator use from high-volume oxygen intake, or transference to the intensive care unit from ventilator use. All adverse events would be documented and evaluated by an independent committee.

2.6. Sample size and statistical analysis
We defined the minimum improvement rate as the increase of lymphocytes by more than 40% per 24 hours. Assuming the mean change of lymphocyte counts in the treatment group and the control group was 0.7 and 0.5, respectively, then a total of 24 patients were needed with the power of 80%, with the 5% probability of type I error ($\alpha = 0.05$).

Continuous variables are expressed as mean ± SD and are compared using the independent $t$ test. Categorical variables are represented by numbers (percentages) and are compared using the chi-square test or Fisher exact test. A 2-sided $P$ value < 0.05 was considered significant. All statistical analyses were performed using SPSS version 22.0.

3. Results

3.1. Baseline characteristics
From March 1, 2020 to April 2, 2020, a total of 24 patients with the first occurrence of the absolute lymphocyte level <1.1 × 10^9/L during hospitalization were randomized to the intervention group, receiving the routine treatments plus niacinamide, and the control group, receiving routine treatments alone in a ratio of 1:1 (Fig. 1). The age of participants in our study ranged from 46 to 91 years old, with the mean age of 69.1 ± 11.8 years old. The mean age in the treatment and control groups was 69 ± 12 and 70 ± 12 years old, respectively ($P > .05$, Table 1). In our study, 11 participants (45.83%) were male, with 7 participants (58.3%) in the treatment group and 4 participants (33.3%) in the control group ($P = .219$, Table 1). Three patients (25%) in the treatment group and two patients (16.7%) in the control group were diagnosed as the ordinary type, with no statistical significance between the 2 groups ($P > .05$), as shown in Table 1.

3.2. Comparison in laboratory tests
The median time for patients from hospitalization to enrollment into our study was 1 (1–3.75) days. Before treatment, the overall lymphocyte counts in our study were (0.91 ± 0.22) × 10^9/L with (0.94 ± 0.26) × 10^9/L in the treatment group and (0.89 ± 0.19) × 10^9/L in the control group. There was no statistical significance between the two groups ($P = .253$, Table 2). Other laboratory parameters, such as leukocyte counts, absolute monocyte counts, absolute lymphocyte counts, and absolute eosinophilic cell counts before and after receiving the intervention, were all comparable in the two groups ($P > .05$), as shown in Table 3.

3.3. Study endpoint
Based on routine treatments, patients in the intervention group additionally received niacinamide. For the primary endpoint, the lymphocyte counts after intervention in the treatment or control group were (1.15 ± 0.48) × 10^9/L and (1.02 ± 0.28) × 10^9/L, respectively. The difference was not statistically significant between the 2 groups ($P = .445$, Table 2). Moreover, although the lymphocyte improvement rate in the treatment group was higher than the control group (mean ± SD for the treatment group: 23.08 ± 46.10%; control group: 16.52 ± 24.10%, $P = .445$), there was no statistically significant difference between the 2 groups ($P > .05$), as is shown in Table 2. For the secondary endpoints, no patient died in the hospital within 48 hours after treatment, and there was no statistically significant difference in the composite endpoint of aggravation between the two groups ($P > .05$).

4. Discussion
In the present study, the efficiency of niacinamide on peripheral blood lymphocyte decline in COVID-19 patients was analyzed.

P = .565, Table 2).
Among patients with COVID-19, although the lymphocyte improvement rate was higher in the nicotinamide group, there was no significant difference in either the absolute change of lymphocyte counts or the elevation rate of lymphocytes between the intervention group with nicotinamide and the control group with only routine treatments. Besides, other laboratory parameters before and after receiving the intervention were also comparable in the two groups. As a result, we found no evidence that niacinamide may impose an effect on lymphopenia in patients with COVID-19.

Patients with severe or critically severe COVID-19 often have significantly increased white blood cell (WBC) counts, neutrophil to lymphocyte ratio (NLR), D-dimer, and fibrinogen levels but have decreased lymphocyte and platelet. [3–6] As a result, these biomarkers are recommended as indicators of the severity of COVID-19. [5] Among these biomarkers, the decrease in lymphocyte counts is highly related to the progression of COVID-19. [13] Fu et al. [6] showed that the lymphocyte counts were higher in the mild group compared with the severe group (1.42 ± 0.66 vs 0.97 ± 0.33, \( P = .009 \)), showing
the association between the illness severity and the lymphocyte counts. Moreover, the peripheral lymphocyte subset alteration also showed the characteristics of progression of the severe disease. The CD4⁺ T cells, CD8⁺ T cells, B cells, and NK cells all showed a significant reduction in the patients with severe COVID-19 compared to patients with ordinary or mild type.[11,14] and all these cells were gradually decreased as the disease progressed gradually. Some studies, therefore, showed the CD4⁺ T cells, CD8⁺ T cells, and the CD4⁺/CD8⁺ ratios were the independent predictors for the severity of COVID-19.[11,14] Besides, the percentage of interferon-γ (IFN-γ) producing CD8⁺ T cells and IFN-γ producing CD4⁺ T cells both increased in severe COVID-19 patients, which indicated the severity of the disease was associated with the hyperfunction of CD4⁺ T cells and CD8⁺ T cells, and the cytokines played a pivotal role in the progression of the disease.[15]

As described earlier, the reduction of peripheral T cells and their subsets, as unique characteristics of COVID-19 patients, is closely related to the severity and prognosis of the disease, which has been repeatedly confirmed in clinical observation and autopsy pathological reports. Similar to SARS-CoV and SARS-CoV-2 infections, lymphopenia in acute COVID-19 patients may be associated with lymphocyte infiltration and sequestration in specific target organs, like lungs.[16,17] However, in the later stages of COVID-19 disease, lymphopenia is mainly mediated by hyper inflammation and cytokine release.[18] Therefore, we presumed that lymphopenia in COVID-19 patients might be principally related to the cytokine storm. Cytokine storm refers to an excessive immune response triggered by a sharp increase in proinflammatory cytokines, resulting in an abnormal immune response.[19,20] By analyzing the clinical characteristics of COVID-19 patients, we found that their serum proinflammatory cytokines significantly increased, which indicated the existence of a cytokine storm and predicted the severity of COVID-19.[16,17,21] A study including 138 hospitalized COVID-19 patients suggested that the death of COVID-19 patients might be related to the cytokine storm induced by the virus.[23] Liu et al.[21] also revealed that the severity of lymphocytopenia and proinflamatory cytokine storms were higher in patients with severe COVID-19 than in patients without severe COVID-19 and highly correlated with the severity of the disease. Furthermore, the biopsy samples analysis of 19 patients with COVID-19 undergoing autopsy showed abnormal host immune response and inflammatory cytokine storm as well as mononuclear inflammatory lymphocytes in the biopsy specimen. Fu et al.[24] thought that the pathogenic T cells and inflammatory monocytes could enter the pulmonary circulation in great quantities, resulting in cytokine storm in patients with severe or critically severe illnesses. The cytokine storm will gradually increase the alveolar exudate, hamper the alveolar gas exchange, and finally increase mortality in patients with severe disease. Previous studies also showed that the reduction of the inflammatory cytokine storm opposed lymphopenia.[21] RECOVERY study,[26] the largest RCT study which explored the therapeutic effect of tocilizumab (interleukin-6 inhibitors) on patients with COVID-19, demonstrated a significant benefit in 28-day mortality after the intervention. These results confirmed the promising application of modulating and stabilizing cytokine storms for COVID-19 treatment.

Previous studies have found that the increase of many cytokines, such as interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor (TNF)-2, IFN-γ was the leading cause of cytokine storm in vivo.[21,22,27,28] As a critical factor of inflammation triggering, IL-6 can be highly expressed in patients with COVID-19, which is associated with a decrease in the lymphocyte counts, inflammation caused by cytokine storm, and severity of disease.[21,22,28,29] So the target drug that inhibits IL-6 may theoretically block the cytokine storm.[25–31] NAD+, derived from niacinamide, modulate the cytokine action, regulate the intercellular adhesion molecules, block degranulation of mast cells and inhibit protease release from leukocytes.[32] Moreover, NAD+ is a substrate of PARP, which will act as an inflammatory mediator via the activation of nuclear factor-κB (NF-κB).[32] So the nicotinamide usefully blocks the cytokine storm by modulating inflammatory factors, including interleukin-1β (IL-1β), IL-6, interleukin-8 (IL-8), IL-10, monocyte chemoattractant protein (MCP-1), and TNF-α.[33] Recently, some hypotheses have been put forward that CD38 and CD38-mediated NAD+ metabolism plays a central role in altered immunometabolism resulting from COVID-19 infection. The CD38/NAD+ axis may become a promising therapeutic target that allows niacinamide therapy to have a brilliant future (Fig. 2). [14] Furthermore, recent

Figure 2. The immune response in patients with COVID-19. ADPR = adenosine diphosphate ribose, cADPR = cyclic adenosine phosphate ribose, COVID-19 = coronavirus disease 2019; NAADP = nicotinic acid adenine dinucleotide phosphate, NF-κB = nuclear factor-κB, PARPs = poly-ADP-ribose polymerases, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2.
studies have shown that nicotinamide riboside (NR), the precursor of nicotinamide, has close structural similarity to the proven RNA-dependent RNA polymerase (RdRp) inhibitors which inhibit the proliferation of the viruses. These studies further confirmed the therapeutic effect of nicotinamide in patients with COVID-19. Previous studies have demonstrated that nicotinamide reduced the apoptosis of peripheral blood lymphocytes (PBL) in patients with human immunodeficiency virus (HIV) by protecting mitochondria from the damage of TNF-alpha and reactive oxygen species, which are mainly induced by cytokine. Likewise, the replenishment of nicotinamide theoretically prevented the absolute counts of lymphocytes from decreasing in patients with COVID-19. However, whether the nicotinamide-based supportive therapy also increases the lymphocyte counts of patients with COVID-19 remains unclear.

In our study, the absolute lymphocyte counts didn’t increase significantly at 48h after intervention in both the treatment and control groups. The reason may be that the cytokines leading to the reduction of lymphocytes could not be instantly blocked by niacinamide, and there are still other underlying mechanisms in the progression of the disease besides cytokine storm. Unfortunately, our study could not evaluate the long-term effect of nicotinamide on lymphopenia for the limited resource during the pandemic. We hope that the therapeutic effect of long-term, even after discharge, administration of niacinamide could be confirmed by more large-scale clinical studies in the future.

4.1. Study limitations

This study has several limitations. Firstly, our study enrolled 24 COVID-19 patients, covering a small portion of the population. Although the sample size was calculated in our study to meet our demand, there are still few patients who should be enrolled. Secondly, we only compared the outcomes between the two groups at 48h after intervention and did not evaluate the long-term effect of nicotinamide on lymphopenia for the resource shortage during the pandemic. Moreover, our study adopted the laboratory parameter as our primary endpoint rather than a hard endpoint such as death, primarily because of the inconvenience of eligible patients enrolled.

5. Conclusions

In our present study, changes in absolute lymphocyte counts between the niacinamide group and the control group were not significantly different. Therefore, there is currently no evidence in the present study supporting the effect of niacinamide on lymphopenia in patients with COVID-19.

Acknowledgments

We would like to thank the staff of the No. 7 Department of Infectious Diseases, Wuhan Huo Shan Hospital, Wuhan Hubei Province.

Author contributions

QH was responsible for the statistical analysis and wrote the draft; QYZ collected the data and revised this draft; CFP collected the data; ZM collected the data; YLH designed this study. All the authors read and approved the final manuscript.

Conceptualization: Ya-Ling Han.
Investigation: Cheng-Fei Peng, Zhong Ma.
Methodology: Qiang Hu.

References

[1] Huang W, Berube J, McNamara M, et al. Lymphocyte subset counts in COVID-19 patients: a meta-analysis. Cytometry A. 2020;97:772–6.
[2] Mustafa F, Giles R, Pepper MS. Rapid evolution of our understanding of the pathogenesis of COVID-19: implications for therapy. S Afr Med J. 2020;110:1180–5.
[3] Ponti G, Maccaferri M, Ruini C, et al. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57:389–99.
[4] Akbari H, Tabrizi R, Lankarani KB, et al. The role of cytokine profile and lymphocyte subsets in the severity of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Life Sci. 2020;258:118167.
[5] Henry BM, de Oliveira MHS, Benot S, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020;58:1021–8.
[6] Fu J, Kong J, Wang W, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: a retrospective study in Suzhou China. Thromb Res. 2020;192:3–8.
[7] Zhang W, Li L, Liu J, et al. The characteristics and predictive role of lymphocyte subsets in COVID-19 patients. Int J Infect Dis. 2020;99:92–9.
[8] Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Sig Transduct Target Ther. 2020;5:33.
[9] Bogan-Brown K, NkruMah-Elly E, Istaqy E, et al. Potential efficacy of nutrient supplements for treatment or prevention of COVID-19. J Diet Suppl. 2022;19:336–65.
[10] Rahimneshi I, Khoupayeh S, Azizi Y, et al. Conceptual framework for SARS-CoV-2 related lymphopenia. Adv Biomed Res. 2022;11:16.
[11] Mehmel M, Jovanovic N, Spitz U. Nicotinamide riboside-the current state of research and therapeutic uses. Nutrients. 2020;12:1616.
[12] China. NHCoPSPoR. Guidelines for the diagnosis and treatment of novel coronavirus (2019-nCoV) infection by The National Health Commission (trial version 6) [EB/OL]. Available at: http://www.nhc.gov.cn/yzygj/s7653p/202002/8334a83266d94d329df351d7a8aefc2.shtml. [Access date July 3, 2020].
[13] Klöppel R, Zöllner H, Wieniecki P, et al. [Multivariate discrimination analysis of enzyme patterns in tumor patients]. Radiobiol Radiother (Berl). 1982;23:127–33.
[14] Wang F, Nie J, Fang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis. 2020;221:1762–9.
[15] Wang F, Hou H, Luo Y, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI Insight. 2020;5:e137799.
[16] Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Resp Med. 2020;8:420–2.
[17] Li T, Qiu Z, Zhang L, et al. Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome. J Infect Dis. 2004;189:648–51.
[18] Scarpa R, Costa L, Del Puente A. Role of thymopoiesis and inflammation in COVID-19 phenotype. Ped Neonatol. 2020;61:364–5.
[19] Padmanabhan R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39:529–39.
[20] Faigenbaum DC, June CH. Cytokine storm. N Engl J Med. 2020;383:2255–73.
[21] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–5.
[22] Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763.
[23] Zhu Z, Cai T, Fan L, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis. 2020;95:533–9.
[24] Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med. 2020;18:164.
[25] Fathi N, Rezaei N. Lymphopenia in COVID-19: therapeutic opportunities. Cell Biol Int. 2020;44:1792–7.
[26] RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397:1637–45.
[27] Chen L, Liu HG, Liu W, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43:203–8.
[28] Wang J, Jiang M, Chen X, et al. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol. 2020;108:17–41.
[29] Chen X, Zhao B, Qu Y, et al. Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (RNAemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019. Clin Infect Dis. 2020;71:1937–42.
[30] Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016;8:959–70.
[31] Zhang S, Li L, Shen A, et al. Rational use of tocilizumab in the treatment of novel coronavirus pneumonia. Clin Drug Investig. 2020;40:511–8.
[32] Omran HM, Almaliki MS. Influence of NAD+ as an ageing-related immunomodulator on COVID-19 infection: a hypothesis. J Infect Public Health. 2020;13:1196–201.
[33] Monfrecola G, Gaudiello F, Cirillo T, et al. Nicotinamide downregulates gene expression of interleukin-6, interleukin-10, monocyte chemoattractant protein-1, and tumour necrosis factor-alpha gene expression in HaCaT keratinocytes after ultraviolet B irradiation. Clin Exp Dermatol. 2013;38:185–8.
[34] Zeidler JD, Kashyap S, Hogan KA, et al. Implications of the NADase CD38 in COVID pathophysiology. Physiol Rev. 2022;102:339–41.
[35] Esam Z, Akhavan M, Lotfi M, et al; structure BAJjom. Molecular docking and dynamics studies of Nicotinamide Riboside as a potential multi-target nutraceutical against SARS-CoV-2 entry, replication, and transcription: a new insight. J Mol Struct. 2022;1247:131394.
[36] Li R, Li Y, Liang X, et al. Network pharmacology and bioinformatics analyses identify intersection genes of niacin and COVID-19 as potential therapeutic targets. Brief Bioinform. 2021;22:1279–90.
[37] Cossarizza A, Mussini C, Mongiardo N, et al. Mitochondria alterations and dramatic tendency to undergo apoptosis in peripheral blood lymphocytes during acute HIV syndrome. AIDS. 1997;11:19–26.
[38] Savarino A, Martini C, Orofino GC, et al. Apoptotic DNA fragmentation, and its in vitro prevention by nicotinamide, in lymphocytes from HIV-1-seropositive patients and in HIV-1-infected MT-4 cells. Cell Biochem Func. 1997;15:171–9.