Ad-din Medical Journal
January 2025, 3(1):09-17

Original article

Association of Immune Cells with Disease Severity of COVID-19 Patients

Received: 30.09.2024 Accepted: 19-10-2024

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Abstract

Background: COVID-19, caused by SARS-CoV-2, is associated with significant morbidity and mortality, often leading to immune dysregulation characterized by cytokine release syndrome. ***Objective:*** This study aimed to investigate the peripheral blood profiles lymphocytes of and monocytes in relation to disease severity in COVID-19 patients. ***Methodology:*** Conducted at Bangabandhu Sheikh Mujib Medical University from March 2021 to January 2022, this cross-sectional study included 84 confirmed COVID-19 patients categorized into moderate, severe, and critical groups, alongside 28 healthy controls. Peripheral blood samples were analyzed for lymphocyte subpopulations (CD4+ and CD8+ T cells) and monocyte counts using flow cytometry. Ethical clearance was obtained from the Institutional Review Board. ***Results:*** The absolute count of peripheral blood lymphocytes (T cell, B cell, NK cell) and subset of T lymphocyte including CD4+ T cells and CD8+ T cells were significantly decreased in critical group compared to moderate and severe group (P<.001). The mean lymphocyte count in critical cases was markedly lower than in healthy controls. Exhaustion marker CD94/NKG2A was increased on NK cells and CD8+ cytotoxic T cell among critical and severe group compared to moderate and healthy group. In contrast absolute count of monocyte was significantly increased in critical group (P<.001) with a mean of 1940.65/µL ***Conclusion:*** The findings underscore the immunological alterations in COVID-19 patients, characterized by decreased lymphocyte counts and increased monocyte levels, particularly in critical patients.. Monitoring peripheral blood lymphocytes, T cell subsets and monocyte may provide critical insights for understanding disease progression and informing therapeutic strategies. Monoclonal antibody targeting NKG2A for therapeutics may prevent the disease progression and decrease morbidity and mortality.

Keywords: Lymphocytes, Monocyte, CD94/NKG2A, COVID-19 patients

How to cite this article: Khan NM, Fariha RSH, Zaber M, Shuvo BH, Tarafder S. Association of Immune Cells with Disease Severity of COVID-19 Patients. Ad-din Med J. 2025 Jan;3(1):9-17

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Introduction

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to a global pandemic with profound public health implications, resulting in significant morbidity and mortality worldwide[1]. The disease presents with a broad spectrum of clinical manifestations, from mild respiratory symptoms to severe complications such as acute respiratory distress syndrome (ARDS) and multiple organ failure[2]. One of the hallmark features of severe COVID-19 is immune dysregulation, which is often characterized by a cytokine release syndrome (CRS) [1].This hyper-inflammatory response is associated with excessive production of pro-inflammatory cytokines, contributing to tissue damage and a poor clinical prognosis. Central to the immune response in COVID-19 are lymphocytes and monocytes[3]. Lymphocytes, particularly CD4+ T helper cells and CD8+ cytotoxic T cells, are critical for the adaptive immune response against viral infections[4]. In severe cases of COVID-19, numerous studies have reported significant lymphopenia, defined as a reduced lymphocyte count, which correlates with disease severity and worse outcomes[2]. For instance, Duans' studies[3] demonstrated that patients with severe COVID-19 had markedly lower counts of both CD4+ and CD8+ T cells compared to moderate cases, suggesting a failure of the adaptive immune system to mount an effective response to the virus. The total number of B cells, both helper T cells (CD3+CD4+) and suppressor T cells (CD3+CD8+), regulatory T cells (both naïve and induced) and NK cells significantly decreased in severe cases compared to the non-severe group[5]. The increase of neutrophil-to-lymphocyte ratio (NLR), were found in the severe group with COVID-19 compared to the mild group[5]. Low levels of CD4+T and CD8+T cells are common in severe COVID pneumonia. B cells and NK cells were also reduced both in mild and severe COVID infection [6].Total number of NK and CD8+ T cells was decreased markedly in COVID-19 patients and the function of NK and CD8+ T cells was exhausted with the increased expression of NKG2A[7]. Expression of NKG2A was reduced with restored NK and CD8+ T cells level in patients convalescing after therapy suggesting SARS-CoV-2 infection is associated with the functional exhaustion of cytotoxic lymphocytes[8]. NKG2A is an inhibitory receptor, it's expression on NK and CD8+ T cells induce functional exhaustion of NK and CD8+ T cells, leading to chronic viral infections[6]. For elimination of virus in the early stage of COVID-19 targeting NKG2A may prevent the functional exhaustion of cytotoxic lymphocytes[8]. Conversely, monocytes, which are essential components of the innate immune response, often exhibit increased counts in patients with severe COVID-19[9]. This monocytosis reflects the activation and recruitment of monocytes in response to infection and inflammation. Elevated monocyte levels contribute to the inflammatory milieu seen in severe cases and are associated with poorer clinical outcomes[4]. Furthermore, the role of monocytes in the development of CRS underscores their importance in the pathogenesis of severe COVID-19, as they can release a variety of cytokines and chemokines that exacerbate inflammation[10]. The relationship between viral load and immune response is also critical in the context of COVID-19 detectable levels[5].Given these complexities, this study aims to investigate the peripheral blood profiles of monocytes and lymphocytes in relation to disease severity among COVID-19 patients[11]. By characterizing these immune cell dynamics, we hope to contribute to a deeper understanding of the immunological landscape in COVID-19[12]. This knowledge may not only enhance our grasp of disease progression but also inform therapeutic strategies aimed at mitigating severe outcomes and improving patient management[13].

Materials and methods:

This cross-sectional study was conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka from March 2021 to January 2022. Subjects were selected from the BSMMU Fever Clinic, and informed consent was obtained from all participants, with ethical approval granted by the Institutional Review Board. A purposive sampling method was used, resulting in a sample size of 112, based on Morgan's table, which included 84 confirmed COVID-19 patients categorized as moderate, severe, or critical, along with 28 healthy controls. Inclusion criteria required participants to be adults (≥18 years) with confirmed COVID-19 via RT-PCR, while exclusion criteria included autoimmune disorders, co-infections, or recent immunosuppressive therapy. Peripheral blood samples were collected in EDTA tubes and processed within two hours for analysis of T lymphocyte , T cells subset (CD4+ and CD8+ T cells), B lymphocyte, NK cell and monocyte counts using flow cytometry with specific monoclonal antibodies. Data were analyzed using SPSS version 26, employing descriptive statistics and comparisons with ANOVA or Kruskal-Wallis tests, with a significance threshold set at $p < 0.05$. Confidentiality and privacy of participants were strictly maintained.

Result:

This study enrolled 84 confirmed COVID-19 patients and 28 healthy individuals as controls. The COVID-19 patients were categorized into three groups: moderate (n=28), severe (n=28), and critically ill (n=28).

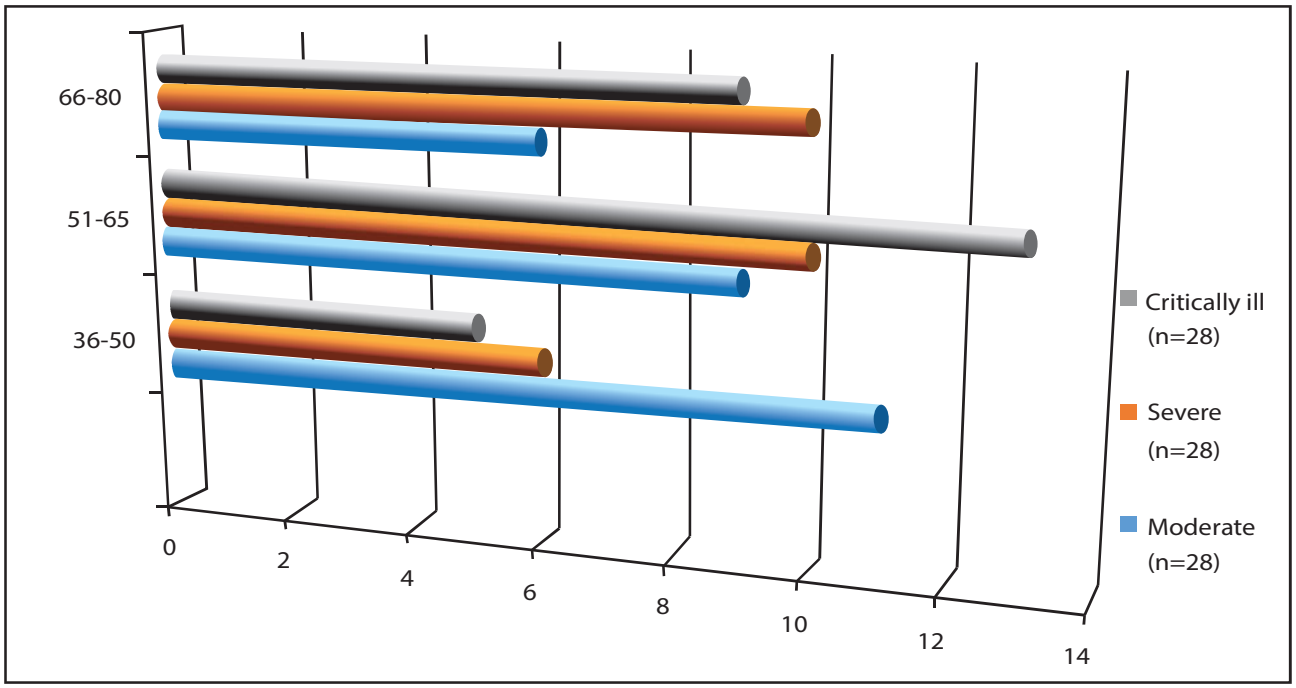

Figure 1:Frequency of age of the study cases (Fisher Exact test showed no significant statistical difference among the groups regarding age).

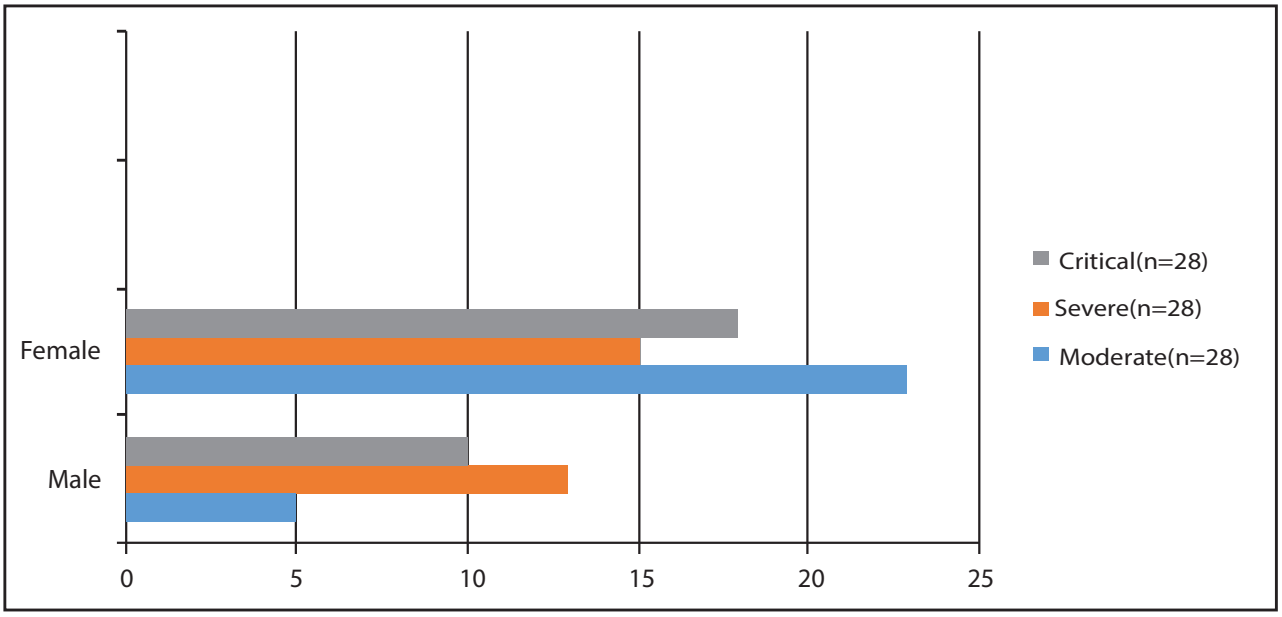

Figure 2: Gender distribution of the study cases (Chi-square test showed no significant statistical difference among the groups regarding gender).

Table 1: Summarizing the p-values for the comparison of absolute counts and percentages of peripheral blood lymphocytes among the different groups:

Comparison	Absolute Count P-value	Percentage P-value
Healthy vs Critical	P < .001	P < .001
Moderate vs Critical	P < .001	P < .001
Severe vs Critical	P < .001	P = .004
Healthy vs Severe	P < .001	P < .001
Moderate vs Severe	P < .001	P = .007
Healthy vs Moderate	P = 1.00	P = 1.00

Note: P < .05 indicates statistical significance. P-values were calculated using One-way ANOVA with post-hoc Bonferroni test.

In the study, 80.01% of patients had co-morbidities, with the critical group showing the highest prevalence at 92.85%, compared to 46.42% in the moderate group (p=0.004). Diabetes mellitus was the most common co-morbidity (63.87%), and the critical group exhibited a significantly higher frequency of diabetes (75.0%) than the moderate group (63.87%), with a p-value of 0.015.

Table 2: Frequencies of co-morbidities among different categories of patients

Variables	Total patient (n=84)(%)	Moderate (n=28) (%)	Severe (n=28) (%)	Critical (n=28) (%)	P value
Co-morbidities (any)	68 (80.01)	13 (46.42)	23 (82.14)	26 (92.85)	**.004**
Diabetes mellitus	52 (63.87)	11 (39.28)	20 (71.42)	21 (75.0)	**.015**
Hypertension	41 (51.25)	6 (21.42)	16 (57.14)	18 (64.28)	.682
Asthma	7 (8.42)	1 (3.57)	2 (7.14)	4 (14.28)	.841
Chronic kidney disease	6 (6.74)			6 (21.42)	.710
Chronic liver disease	3 (1.96)		1 (3.57)	2 (7.14)	.161
Others	4 (4.49)	1 (3.57)	2 (7.14)	1 (3.57)	.445

Table 3: This table represents circulating peripheral Blood Lymphocytes , circulating T Lymphocytes & circulating CD4+ Profiles in COVID-19 Patients Compared to Healthy Controls (N=112)

Category of patient	Peripheral blood lymphocyte		CD3+ T lymphocyte		CD4+ helper T lymphocyte	
	Mean of Absolute count, cells/uL± SD	Percentage Mean ± SD	Mean of Absolute count, cells/uL± SD	Mean of Absolute count, cells/uL± SD	Percentage Mean ± SD	Percentage Mean ± SD
Control group n=28	2586±412.56	34.25±6.21	1684.65 ± 428.41	74.40 ± 5.02	878.11 ± 276.51	45.41 ± 4.22
Moderate group n=28	2271±385.09	32.96±4.94	1392.24 ± 410.96	72.54 ± 7.32	785.54 ± 242.04	40.63 ± 6.85
Severe group n=28	1845±465.02	25.62±7.48	953.48 ± 301.78	62.47 ± 10.52	546.08 ± 189.45	36.12 ± 10.26
Critical group n=28	839±423.51	9.14±5.21	529.98 ± 259.11	55.06 ± 1.46	235.04 ± 149.39	30.25 ± 13.85

The study presents data on peripheral blood lymphocyte counts across four patient categories: Control, Moderate, Severe, and Critical groups, each consisting of 28 patients. In the Control group, the absolute count of CD3+ T lymphocytes was 2586 ± 412.56 cells/uL, making up 34.25 ± 6.21% of total lymphocytes, while CD4+ helper T lymphocytes had an absolute count of 1684.65 ± 428.41 cells/uL, constituting 74.40 ± 5.02% of total lymphocytes. In the Moderate group, the absolute count of CD3+ T lymphocytes decreased to 2271 ± 385.09 cells/uL (32.96 ± 4.94%), and CD4+ helper T lymphocytes dropped to 1392.24 ± 410.96 cells/uL, representing 72.54 ± 7.32%. The Severe group showed a further decline, with CD3+ T lymphocytes at 1845 ± 465.02 cells/uL (25.62 ± 7.48%) and CD4+ helper T lymphocytes at 953.48 ± 301.78 cells/uL, accounting for 62.47 ± 10.52%. In the Critical group, there was a marked decrease, with CD3+ T lymphocytes at 839 ± 423.51 cells/uL (9.14 ± 5.21%) and CD4+ helper T lymphocytes at 529.98 ± 259.11 cells/uL, making up 55.06 ± 1.46% of total lymphocytes. Overall, these results indicate a significant decline in both CD3+ T lymphocytes and CD4+ helper T lymphocytes as the severity of the patient condition increases from the Control to the Critical groups, suggesting an impairment in T lymphocyte populations in more severe cases (Table 3).

Table 4: Circulating CD8+ cytotoxic T lymphocytes, B lymphocytes among COVID-19 patients and healthy group (N=112) : Comparison of CD4+/CD8+ ratio in study groups (N=112)

CD8+ cytotoxic T lymphocyte			CD4+ /CD8+ ratio		B lymphocyte	
Category of patient	Mean of Absolute count, cells/uL± SD	Percentage Mean ± SD	Mean ± SD	P value	Mean of Absolute count, cells/uL± SD	Percentage Mean ± SD
Control group n=28	701.96 ± 157.01	25.45 ± 5.52	1.26±.58	**0.09**	356.08 ± 136.25	26.04 ± 5.26
Moderate group n=28	623.45 ± 257.43	723.85 ± 4.27	1.46±.31		358.63 ± 86.14	26.77 ± 5.78
Severe group n=28	312.01 ± 262.08	24.64 ± 7.41	1.51±.03		273.02 ± 168.32	30.06 ± 12.11
Critical group n=28	157.32 ± 94.23	21.74 ± 6.60	1.55±.47		198.05 ± 175.10	32.86 ± 15.85

The results of Table 4 show the counts of CD8+ cytotoxic T lymphocytes and B lymphocytes across four patient categories: Control, Moderate, Severe, and Critical groups, each with 28 patients. In the Control group, the absolute count of CD8+ lymphocytes was 701.96 ± 157.01 cells/uL, comprising 25.45 ± 5.52% of total lymphocytes, with a CD4+/CD8+ ratio of 1.26 ± 0.58 and B lymphocyte count at 356.08 ± 136.25 cells/uL. The Moderate group showed a decrease in CD8+ counts to 623.45 ± 257.43 cells/uL (23.85 ± 4.27%) and an increased CD4+/CD8+ ratio of 1.46 ± 0.31, while B lymphocytes remained stable at 358.63 ± 86.14 cells/uL. The Severe group reported a further drop to 312.01 ± 262.08 cells/uL (24.64 ± 7.41%) and a CD4+/CD8+ ratio of 1.51 ± 0.03, with B lymphocytes at 273.02 ± 168.32 cells/uL. In the Critical group, CD8+ lymphocyte counts plummeted to 157.32 ± 94.23 cells/uL (21.74 ± 6.60%), accompanied by a ratio of 1.55 ± 0.47 and a B lymphocyte count of 198.05 ± 175.10 cells/uL. Overall, these findings indicate a significant decline in CD8+ T lymphocyte counts as the severity of patient conditions increases, alongside relatively stable B lymphocyte

Table 5 : Comparative Analysis of CD94/NKG2A Expression in Circulating NK Cells and CD8+ Cytotoxic T Cells Between COVID-19 Patients and Healthy Controls (N=112):

NK cell				
Category of patient	**Mean of Absolute count, cells/uL± SD**	**Percentage Mean ± SD**	**CD94/NKG2A+ NK cell Percentage Mean ± SD**	**CD94/NKG2A+ CD8+ T cell Percentage Mean ± SD**
Control group n=28	256.08 ± 60.25	17.04 ± 2.26	46.46 ±13.58	7.56±47
Moderate group n=28	198.63 ± 86.14	13.77 ± 3.78	63.12 ±7.21	8.45±.44
Severe group n=28	173.02 ± 108.32	11.06 ± 4.11	80.09 ±6.23	12.45±.85
Critical group n=28	98.65 ± 125.10	10.86 ± 5.85	88.94 ±4.04	15.65±.41

Table 5 presents data on NK cell counts and percentages of CD94/NKG2A+ NK cells and CD94/NKG2A+ CD8+ T cells across four patient categories: Control, Moderate, Severe, and Critical groups, each consisting of 28 patients. In the Control group, the mean absolute count of NK cells was 256.08 ± 60.25 cells/uL, with 63.12 ± 7.21% being CD94/NKG2A+ NK cells and 8.45 ± 0.44% being CD94/NKG2A+ CD8+ T cells. The Moderate group showed a decrease in NK cell count to 198.63 ± 86.14 cells/uL, but an increase in the percentage of CD94/NKG2A+ NK cells to 80.09 ± 6.23%, while CD94/NKG2A+ CD8+ T cells rose to 12.45 ± 0.85%. The Severe group reported further decline in NK cell counts to 173.02 ± 108.32 cells/uL, with 88.94 ± 4.04% being CD94/NKG2A+ NK cells and 15.65 ± 0.41% for CD94/NKG2A+ CD8+ T cells. In the Critical group, NK cell count dropped significantly to 98.65 ± 125.10 cells/uL, with a corresponding percentage of CD94/NKG2A+ NK cells at 10.86 ± 5.85%. Overall, these results indicate a decrease in NK cell counts alongside an increase in the percentages of CD94/NKG2A+ NK and CD8+ T cells as the severity of the condition worsens.

Table 6 : Comparison Monocyte among COVID-19 patients and healthy group (N=112)

Category of patient	**Monocyte**	
	Mean of Absolute count, cells/uL± SD	**PercentageMean ± SD**
Control group n=28	656.08 ± 61.25	7.04 ± 2.28
Moderate group n=28	885.60 ± 116.14	9.77 ± 3.78
Severe group n=28	1453.02 ± 148.32	17.06 ± 15.11
Critical group n=28	1940.65 ± 195.10	21.86 ± 26.95

Table 6 summarizes the absolute counts and percentages of monocytes across four patient categories: Control, Moderate, Severe, and Critical groups, each with 28 patients. In the Control group, the mean absolute count of monocytes was 656.08 ± 61.25 cells/uL, comprising 7.04 ± 2.28% of total leukocytes. The Moderate group exhibited an increase in monocyte count to 885.60 ± 116.14 cells/uL, with a percentage of 9.77 ± 3.78%. The Severe group showed a further rise, with an absolute count of 1453.02 ± 148.32 cells/uL and a percentage of 17.06 ± 15.11%. Finally, in the Critical group, the mean monocyte count peaked at 1940.65 ± 195.10 cells/uL, accounting for 21.86 ± 26.95% of total leukocytes. Overall, these findings indicate a progressive increase in both the absolute counts and percentages of monocytes as the severity of the condition escalates.

Discussion:

In this study, the absolute count and percentage of peripheral blood lymphocytes were significantly reduced in the critical and severe groups compared to the healthy and moderate groups. A study reported a significant decrease in peripheral blood lymphocyte counts in severe and critical cases compared to mild and healthy individuals[4]. Additional studies also found reductions in lymphocyte counts among severe and critical patients compared to moderate cases[6]. A study highlighted a similar trend[7], noting a significant decrease in peripheral blood lymphocytes in severe and critically ill patients compared to moderate cases[4]. This decline in lymphocyte count may be attributed to increased lymphocytic infiltration in the lungs of COVID-19 patients [8] .The present study found a notable reduction in the absolute count of peripheral CD3+ T lymphocytes in both severe and critical groups compared to moderate and healthy individuals. A study observed a sustained decrease in T lymphocyte counts in severe and critical groups compared to those who were moderate and healthy[2]. Multiple studies have demonstrated that T lymphocyte counts are significantly lower in severe and critical patients compared to those who are mild or moderate [9] Consistent with these findings, a study reported significant reductions in T lymphocytes among severe and critical cases compared to healthy individuals[4]. The reduction of T lymphocytes may be linked to direct invasion by SARS-CoV-2, which can infect T cells via receptor-dependent spike protein-mediated membrane fusion, despite the low expression levels of the angiotensin-converting enzyme 2 (ACE2) receptor in T cells . Furthermore, SARS-CoV-2 infection triggers T cell-mediated immunity, leading to an increased production of inflammatory cytokines, although anti-inflammatory cytokines such as IL-4 and IL-10 may inhibit T cell activation10. In this study, a significant decrease in CD4+ helper T lymphocytes and CD8+ cytotoxic T lymphocytes was noted in COVID-19 patients compared to healthy controls. The absolute count of peripheral CD8+ T cells was significantly lower in the critical, severe, and moderate groups compared to the healthy group (P<.001). These results align with findings from Jiang studies [2] who noted a significant reduction in CD8+ T lymphocyte counts in COVID-19 patients compared to healthy controls, as well as in critical cases compared to mild cases. Several studies have reported a decrease in CD8+ T lymphocyte counts in severe and critical groups compared to healthy and moderate groups11. It is suggested that the SARS-CoV-2 virus may directly damage lymphatic organs, including the spleen and lymph nodes, leading to spleen atrophy and lymph node necrosis, which in turn induces lymphopenia [12]

No significant differences were observed in the CD4+/CD8+ ratio among COVID-19 patients and healthy individuals, a finding echoed in several other studies [9].The results from this study suggest that both CD4+ and CD8+ T cells consistently decreased in severe-critical and mild-moderate groups, with ratios also altered in healthy controls, potentially due to asymptomatic infections. A previous study found a CD4+/CD8+ ratio of 1.49 in healthy adults [2]. This study also compared the absolute count and percentage of peripheral B lymphocytes in COVID-19 patients against healthy controls, finding a significant reduction in B lymphocyte counts in the critical group compared to the moderate and severe groups, similar to observations by Sun & Xu studies[5]. In contrast, Qin studies reported no differences in B lymphocyte counts between moderate and severe groups[13]. Additionally, the mean percentage of B lymphocytes was significantly higher in the critical and severe groups compared to the healthy group, corroborating findings from Chen studies. This relative increase in B cell percentage may be due to a significant decrease in T cell counts in these patient[9]. The present study found a significant decrease in the absolute count of peripheral NK cells in the severe and critical groups compared to healthy and moderate groups. Similar findings were reported by Jiang studies[2], where NK cell counts were significantly reduced in severe and critical groups relative to healthy controls. Zhang & his group [4] also observed significant reductions in NK cell counts in severe and critical COVID-19 patients compared to moderate cases. Furthermore, Xu studies reported significant reductions in NK cell counts in severe cases compared to moderate cases[14], whereas Liu studies found no significant differences between severe and moderate groups[15]. The reduction in NK cell counts could be attributed to the migration of NK cells from peripheral blood to lung tissue, facilitated by increased levels of MCP-1 and IP-10 in COVID-19 patients [16]. In this study, the expression of CD94/NKG2A was analyzed to assess NK cell exhaustion status. The results indicated that the percentage of CD94/NKG2A-expressing NK cells was higher in the critical, severe, and moderate groups compared to the healthy group. This finding aligns with results from Zheng studies 7who reported increased CD94/NKG2A expression on NK cells in severe COV-

ID-19 patients compared to healthy individuals. However, a study found no significant differences in CD94/NKG2A expression between COVID-19 patients and healthy controls[17]. The high levels of NK cell exhaustion may result from persistent antigenic stimulation by the coronavirus or be a consequence of the associated cytokine storm, which could contribute to the progression of COVID-19. Targeting the CD94/NKG2A receptor might serve as a promising therapeutic approach to prevent NK cell exhaustion in the early stages of COVID-19 [7].

Additionally, the study detected CD94/NKG2A expression on T cells across the study groups. While the percentage of CD94/NKG2A-expressing T cells increased in severe-critical patients compared to asymptomatic and healthy individuals, the differences were not statistically significant. A study also reported a significant increase in CD94/NKG2A expression on CD8+ T cells in severe and moderate cases compared to healthy controls, along with reduced expression of functional markers such as CD107a, IFN-γ, and IL-2 on CD8+ T cells, indicating functional exhaustion[18]. Assessing these functional markers may help elucidate the extent of T cell exhaustion across different study groups.
The study found a significant increase in both the absolute count (1940.65 cells/µl) and percentage (21.86%) of blood monocytes in the critical group compared to the healthy (656.08 cells/µl, 7.04%) and moderate (885.60 cells/µl, 9.77%) groups. Previous research has indicated similar trends, with monocyte absolute counts significantly higher in severe cases (1405 cells/µl) compared to mild cases (615 cells/µl, $p < 0.0001$), along with increased percentages of monocytes in severe patients (17.4% in severe vs. 9.8% in mild, $p < 0.0001$) [15].

Conclusion:

In conclusion, this study highlights that the absolute counts of peripheral blood lymphocytes, including T cells, B cells, and NK cells, as well as T cell subsets like CD4+ and CD8+, are significantly decreased in severe and critical COVID-19 patients compared to healthy and moderate individuals. These findings suggest that lymphocyte and T cell subset counts could serve as important indicators of disease severity. Additionally, the elevated expression of CD94/NKG2A on NK and CD8+ T cells in severe and critical cases may play a role in the pathogenesis of COVID-19, potentially contributing to immune dysfunction and disease progression. Together, these insights underscore the importance of monitoring lymphocyte counts and exhaustion markers in understanding and managing COVID-19.

Acknowledgment:

The authors are grateful to all the participating healthcare workers of BSMMU and the clients for their active and cooperative participation in this study.

Conflict of interest:

The authors hereby declare that no conflict of interest exists.

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