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LETTER TO THE EDITOR

Lymphopenia in critically ill COVID-19 patients: A predictor factor of severity and mortality

Dear editor,

We read with interest the recent article by Terpos et al.[1] They reviewed different hematologic findings and complications of COVID-19. Especially, we are interested in lymphopenia in severe COVID-19 patients, which is a predictor factor of severity and mortality. We aimed to report the occurrence of lymphopenia, lymphocyte subsets, and its impact on ICU mortality in critically ill patients with COVID-19.

In this single-center cohort, we included 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 hospital of the Marrakech region (Morocco), from March 19, 2020 to May 15, 2020. We collected demographic data, comorbidities, clinical signs at the ICU admission, laboratory findings, chest CT scan if available, outcomes, time from onset of the first symptom to ICU admission, and sequential organ failure assessment (SOFA) scores. We expressed continuous variables as medians and interquartile (IQR) ranges or means (standard deviations (SD)), as appropriate, and compared using independent group Student's *t* test or the Mann-Whitney *U* test. Categorical variables were described using percentages and compared using the χ^2-test, although Fisher's exact test was used when the data were sparse. We performed univariable 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 <.05 was considered statistically significant.

TABLE 1 lymphocytes subsets count on admission and outcomes in 24 patients and outcomes

Patients	CD3+	CD4+	CD8+	CD4+/CD8+	B cells	NK cells	Outcome
1	246	119	124	0.96	55	80	Deceased
2	656	452	185	2.44	453	246	Deceased
3	1084	647	376	1.72	353	114	Survivor
4	209	74	93	0.8	10	1	Survivor
5	626	413	205	2.01	76	262	Deceased
6	1051	400	584	0.68	70	151	Survivor
7	1620	1100	474	2.32	213	97	Survivor
8	875	479	390	1.22	188	271	Survivor
9	158	101	36	2.8	70	17	Deceased
10	1886	654	1270	0.51	116	774	Deceased
11	582	238	323	0.73	85	81	Survivor
12	452	219	122	1.8	113	53	Survivor
13	280	158	97	1.62	77	61	Deceased
14	751	365	367	0.99	288	527	Survivor
15	2644	1163	1396	0.83	434	346	Survivor
16	500	323	135	2.39	89	82	Survivor
17	824	314	791	0.4	91	68	Survivor
18	249	144	100	1.44	91	261	Deceased
19	576	412	151	2.72	59	26	Survivor
20	708	438	246	1.78	242	115	Deceased
21	114	39	63	0.62	185	21	Deceased
22	1134	547	732	0.74	249	115	Survivor
23	1056	987	429	2.3	540	223	Survivor
24	1589	675	562	1.2	378	178	Survivor

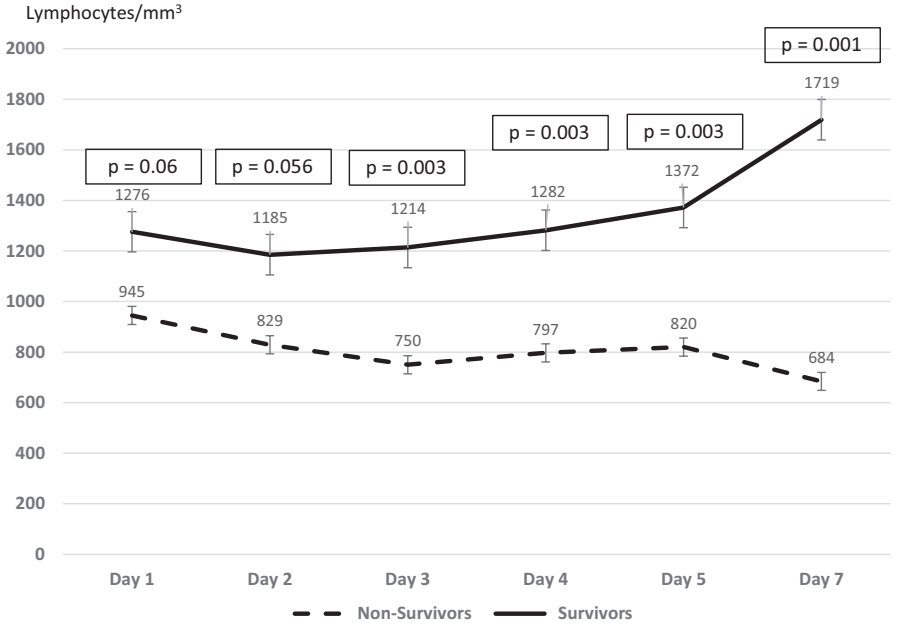

FIGURE 1 the impact of the lymphocyte counts on the ICU mortality in univariable analysis

Of 1618, COVID-19 patients hospitalized in our teaching center, 55 (3.4%) were admitted to the ICU. The mean age was 59 (16.5) years (Min-Max: 21-90); 74.5% were men. Among all the patients, 84% had chronic medical conditions. The common comorbidities were hypertension (42%) and diabetes (34%). 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 at admission was 5 (4-17). The length from the onset of symptoms to ICU admission was an independent risk factor of lymphopenia <1000/mm^3 (OR 1.5; 95% CI 1.006-2.2; $P = .04$).

We noted that lymphopenia <1000/mm^3 was present in 53% of our patients. We performed lymphocyte subset counts in 43.6% (24/55) of cases on admission (Table 1). CD3 + T cells (normal range 1000-2200/mm^3) decreased in 66.6% (16/24) of patients. CD4 + T cells (normal range 530-1300/mm^3) decreased in 70.8% (17/24) of patients. CD8 + T cells (normal range 330-920/mm^3) decreased in 54.2% (13/24) of patients. B cells (normal range 110-570/mm^3) decreased in 45.8% (11/24) of patients, and natural killer cells (normal range 70-480/mm^3) decreased in 29.1% (7/24) of patients. Statistically, comparing survivors to nonsurvivors, the difference was not significant in CD3+ ($P = .1$), CD4+ ($P = .1$), CD8+ ($P = .3$) T cells, B cells ($P = .8$), NK cells ($P = .5$), and CD4+/CD8 + ratio ($P = .5$).

Liu Z et al[2] found that CD4 + T cells diminished in 56.4% of patients, CD8 + T cells diminished in 71.8% of patients, B cells diminished in 69.2% of patients, and NK cells diminished in 76.9% patients. In addition, the severe patients had lower lymphocyte count ($P = .0007$), CD4 + T cells ($P = .024$), CD8 + T cells ($P = .005$), and B cells ($P = .018$), but the difference was not significant in CD4+/CD8 + ratio ($P = .392$) and NK cells ($P = .177$), compared to cases with mild severity.[3]

Lymphopenia <1000/mm^3 on admission was more frequent in nonsurvivors (67% vs 30%; $P = .01$) compared with survivors. The lymphocyte counts on day 3, day 4, day 5, and day 7 of hospitalization were predictor factors of the ICU mortality in univariable analysis (Figure 1) and the lowest count of lymphocyte was on day 2 after hospitalization in survivors. Compared to patients with lymphopenia >1000/mm^3, those with lymphopenia <1000/mm^3 needed more inotrope use (43% vs 12%; $P = .01$), with an increased ICU mortality rate (79% vs 44%; $P = .01$).

A recent meta-analysis proposed that lymphopenia is an important hematological signal of severe COVID-19 and a lymphopenia <1500/mm^3 could be a practical parameter to predict severe outcomes.[4] Moreover, it was a risk factor of myocardial injury[5] and acute respiratory distress syndrome (ARDS).[6] Besides, it was a risk factor for death with a nadir of lymphocytes on day 7 in survivors.[7] This nadir was on day 2 in our study as a result of the delay in the hospitalization of our patients. Additionally, Tan et al[8] showed that the kinetic of the lymphocyte percentage between two time points (10-12 days and 17-19 days after symptom onset) was a credible marker of the severity in COVID-19 cases; indeed, in the death group, the lymphocyte% was more than 10% on the first time point and <5% on the second time point. As well, the neutrophil-to-lymphocyte ratio was an independent risk factor for the occurrence of critical events.[9]

In conclusion, lymphopenia is a frequent biological disorder in patients with COVID-19. It is a predictor factor of the severity, the myocardial injury, the occurrence of ARDS, and a risk factor of ICU mortality. Furthermore, it is a useful tool for predicting poor outcomes. Other larger sample studies are needed to validate risk factors and the lymphocyte threshold.

KEYWORDS

COVID-19, intensive care unit, lymphocyte, lymphocyte subset

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CONFLICT OF INTEREST

All authors declare no competing interests.

ETHICAL APPROVAL

Informed consent was waived because of the emergency of the disease. All research was conducted following the national guidelines and regulations. No patient identifiers were collected.

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REFERENCES

1. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020;95(7):834-847.
2. Liu Z, Long W, Tu M, et al. Lymphocyte subset (CD4+, CD8+) counts reflect the severity of infection and predict the clinical outcomes in patients with COVID-19. *J Infect*. 2020;81(2):318-356.
3. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis*. 2020;221:1762-1769.
4. Zhao Q, Meng M, Kumar R, et al. Lymphopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a systemic review and meta-analysis. *Int J Infect Dis*. 2020;96:131-135.
5. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802.
6. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934.
7. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
8. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther*. 2020;5:33.
9. Liu J, Liu Y, Xiang P, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. *J Transl Med*. 2020;18:206.