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Early lymphopenia as a predictor of COVID-19 outcomes: A multicenter cohort study

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Abstract

Introduction: Lymphopenia is recognized as a biomarker for predicting outcomes in coronavirus disease (COVID-19). However, the optimal timing for its observation remains uncertain. We investigated the association between early lymphopenia and COVID-19 prognosis, as well as the relationship between lymphocyte count trends and disease outcomes.

Methods: We analyzed data from the J-RECOVER study, a multicenter retrospective cohort study in Japan, encompassing patients with COVID-19 between January and September 2020. The patients were categorized into lymphopenia (LP) (<800 cells/μL) and non-lymphopenia (NL) (≥800 cells/μL) groups based on the lymphocyte counts between days 1 and 4 post-onset. They were further divided into "persistent," "recovered," "exacerbated," and "stable" groups based on lymphocyte counts between days 7 and 10. The primary outcome was the in-hospital mortality. The Cox proportional hazard regression was used for the analysis.

Results: Of 995 enrolled patients, 212 patients (21.3%) were classified into the LP group. LP was significantly associated with in-hospital mortality (hazard ratio [HR] 2.32, [95% CI 1.39 to 3.87], *p*-value 0.001). In both the LP and NL groups, lower lymphocyte counts between 7 and 10 days—categorized as the "persistent" and "exacerbated" groups—was associated with in-hospital mortality (HR 4.65, [95% CI 2.07 to 10.47], *p*-value <0.001, and HR 5.59, [95% CI 2.24 to 13.97], *p*-value <0.001, respectively).

Conclusions: Early lymphopenia is predictive of poor prognosis in patients with COVID-19. A declining lymphocyte count trend post-onset further indicates disease deterioration.

KEYWORDS
biomarker, cytokine storm, J-RECOVER, lymphocyte, prognosis

INTRODUCTION

Since the declaration of a global pandemic in 2020, COVID-19 has imposed a significant burden on populations worldwide. Despite a gradual decline in the number of patients, severe cases of COVID-19 remain to be observed.[1] Given the significant mortality rate, efforts are still needed to manage severe cases. Early prognostic prediction could enable appropriate triage, efficient allocation of medical resources, and prompt intervention. Therefore, predicting severe outcomes is a key component of effective management in COVID-19.

The lymphocyte count has been a predictive biomarker of interest because of its simplicity and cost-effectiveness. Observational studies have shown that 85% of patients requiring intensive care unit (ICU) admission experience lymphopenia; notably, an inverse association has been found between the lymphocyte count at admission and the severity and prognosis of COVID-19.[2–4] Additionally, it has been noted that lymphopenia persists until death in non-survivors, whereas survivors tend to have higher lymphocyte counts during hospitalization.[5] However, it remains unclear whether severe cases exhibit lymphopenia at the onset of disease. Moreover, there is no consensus on whether changes in the lymphocyte count over time are correlated with disease progression. Identifying the lymphocyte count as a surrogate marker for COVID-19 progression from disease onset could aid clinicians in making treatment-related decisions based on the disease phase.

The objective of this study was to investigate the hypothesis that the lymphocyte count decreases immediately after the onset of COVID-19 in severe cases and to determine whether the temporal trend of lymphocyte count reflects disease progression in COVID-19.

METHODS

Study designs

We used patient data from the J-RECOVER study, a multicenter cohort study including consecutive COVID-19 patients admitted to 66 institutions across Japan between January and September 2020.[6] The diagnosis of COVID-19 was confirmed by the presence of the SARS-CoV-2 antigen or polymerase chain reaction results. Data on symptom onset, COVID-19 diagnosis, and laboratory test results were obtained from medical charts at each participating institution. We also gathered patient data from the Diagnosis Procedure Combination (DPC) database.[6] The DPC database, organized by the Ministry of Health, Labor, and Welfare in Japan, contains healthcare claims data, including patient demographics, dates of admission and discharge, treatments received during hospitalization, and outcomes at discharge.

Study participants and definitions

This study enrolled adult patients diagnosed with COVID-19 who underwent lymphocyte count measurements 1–4 days after disease onset. For asymptomatic patients in the initial stages, the day of the first positive test result was deemed the onset day. Patients lacking lymphocyte count data between days 1 and 4 were excluded. The exclusion criteria also applied to children (aged 15 years or younger), pregnant women, and patients who had acquired the SARS-CoV-2 infection in hospitals.

Our initial evaluation focused on the impact of lymphopenia at disease onset. Patients were categorized into the lymphopenia (LP) and non-lymphopenia (NL) groups based on their lymphocyte counts measured between 1 and 4 days post-onset. Lymphopenia was defined as a lymphocyte count below 800 cells/μL during the observation period.

Subsequently, we examined dynamic changes in the lymphocyte counts. The patients in both the LP and NL groups were further divided into four categories based on the lymphocyte counts between 7 and 10 days post-onset. In the LP group, patients who continued to exhibit lymphopenia were classified as "persistent," while those whose lymphocyte counts increased to over 800 cells/μL were deemed "recovered." In the NL group, "exacerbated" described patients who developed lymphopenia, and "stable" referred to those who maintained a lymphocyte count of 800 cells/μL or greater. We investigated the associations between these classifications and patient outcomes.

Outcomes

The primary outcome was in-hospital mortality, which was censored at hospital discharge. The secondary outcomes included intubation rates and number of ICU-free, hospital-free, and ventilator-free days (VFDs) within the first 28 days. ICU-free and hospital-free days represent the number of days within a 28-day period during which the patient was not in the ICU and hospital, respectively. For patients who died in ICU and hospital within 28 days, these metrics were considered zero. VFDs were defined as the number of days within the first 28 days after treatment initiation during which a patient was alive and free from mechanical ventilation. If the patient died or remained on mechanical ventilation within 28 days, VFDs were recorded as zero.

Statistical analysis

A Cox proportional hazards regression model was conducted for the primary analysis, adjusting for confounding factors, such as age, intubation status, history of diabetes mellitus, and steroid use. Kaplan–Meier curves were generated to estimate mortality in each group, with differences evaluated using the log-rank test. Multivariate linear regression models

were applied for other outcomes represented by continuous variables.

Next, the same analysis was conducted to examine the association of clinical outcomes across the "recovered," "exacerbated," and "persistent" categories, using "stable" as the reference group. Patients who lacked lymphocyte count measurements between days 7 and 10 were excluded from this analysis because there was a large number of missing measurements of lymphocyte count during that period, ranging from 75% to 79% in each day.

To confirm the relationship between lymphocyte count dynamics and mortality, we employed a linear mixed-effects model for repeated measures, comparing the LP and NL groups. The model included fixed effects for mortality, time elapsed since onset, confounding factors, and the interaction between mortality and time. A patient-specific identifier was incorporated as a random effect to accommodate for individual variations.

We performed three sensitivity analyses to verify the robustness of the primary analysis. First, we adjusted the lymphopenia threshold to <1000 cells/μL. Next, we used the differential leukocyte counts, defining lymphopenia as a lymphocyte percentage below 10%. Finally, we utilized multiple imputation to address missing lymphocyte count data between days 1 and 10, as well as the missing information for other confounders. Multiple imputation was performed to generate 50 datasets using the predictive mean matching method. The results from multiple imputed datasets were pooled using Rubin's rules.

All statistical analyses were conducted using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria), with a two-sided p-value <0.05 considered as statistically significant.

RESULTS

Of 4700 patients registered in the J-RECOVER study, 995 met the inclusion criteria for this study. Of these, 212 patients (21.3%) exhibited lymphopenia between days 1 and 4 of disease onset (Figure 1). The patient characteristics are summarized in Table 1.

For the primary outcome, the Cox proportional hazards regression model demonstrated that LP was significantly associated with increased in-hospital mortality (hazard ratio (HR), 2.32, 95% confidence interval [CI] 1.39 to 3.87, $p=0.001$). The Kaplan–Meier curves illustrating these results are shown in Figure 2. Regarding the secondary outcomes, LP was associated with a higher intubation rate (HR 1.84, [95% CI 1.07 to 3.16], $p=0.03$) as presented in Table 2. Moreover, LP was linked to fewer ICU-free days (coefficient −0.82, 95% CI −1.41 to −0.23, $p=0.007$) and ventilator-free days (coefficient−0.43, 95% CI −0.82 to −0.05, $p=0.03$) at 28 days. There was no significant association between LP and the number of hospital-free days within 28 days (Table 2).

Based on the lymphocyte counts measured between days 7 and 10 post-onset, patients in the LP and NL categories were further divided into four groups: 72 in the "persistent" group, 64 in the "recovered" group, 48 in the "exacerbated" group, and 332 in the "stable" group (Figure 1). These subgroup characteristics are summarized in Table 3.

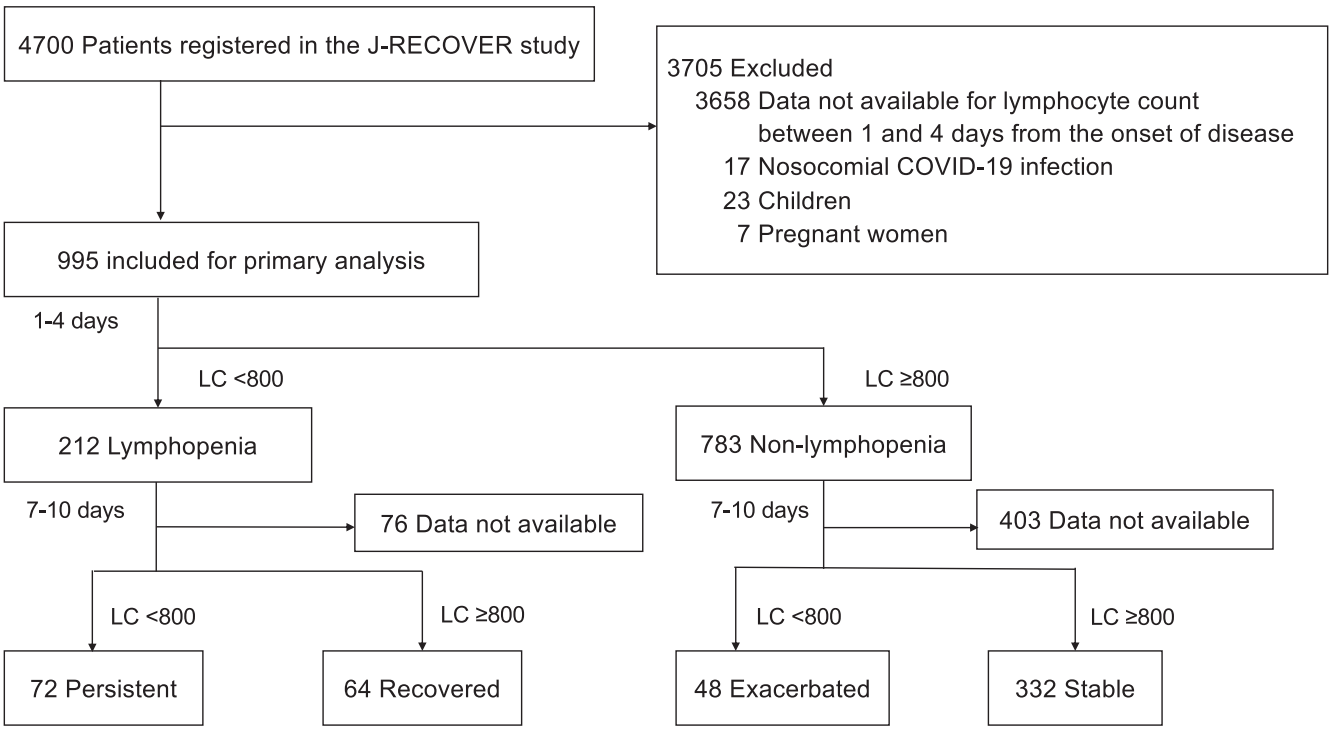

FIGURE 1 Study flow chart. LC, Lymphocyte count.

TABLE 1 Characteristics of patients who presented with lymphopenia and non-lymphopenia between 1 and 4 days from the onset of disease.

	Lymphopenia	*n* = 212	Non-lymphopenia	*n* = 783	*p*-value
Age, years	65	47–77	47	30–65	<0.001
Male, sex	115	54.2	467	59.6	0.18
Body Mass Index, kg/m^2	22.3	19.7–25.4	23.9	21.1–27.5	<0.001
Vital signs on admission					
Glasgow Coma Scale	15	15	15	15	0.73
Systolic blood pressure, mmHg	127	113–141	126	115–139	0.77
Heart rate, /min	87	84–100	84	75–96	0.23
Respiratory rate, /min	18	18–22	18	16–20	0.001
SpO2, %	97	97–98	97	96–98	<0.001
Lactate, mmol/L	1.3	0.9–1.7	1	0.9–1.7	0.57
Comorbidities					
Diabetes mellitus	32	15.1	85	10.9	0.11
Chronic heart failure	5	2.4	11	1.4	0.50
COPD	1	0.5	7	0.9	0.86
Chronic kidney disease	9	4.2	8	1.0	0.004
Laboratory data in the early phase					
White blood cell count, /μL	4700	3345–6600	4800	3800–6370	0.35
Neutrocyte count, /μL	3761	2492–5774	2932	2052–4313	<0.001
Lymphocyte count, /μL	576	456–693	1238	986–1560	<0.001
CRP, mg/dL	4.3	0.8–10.1	0.7	0.2–3.3	<0.001
LDH, U/L	247	199–372	199	168–247	<0.001
D-dimer, μg/mL	1	0.6–2.8	0	0.4–1.1	<0.001
Treatment					
Steroid	62	29.2	120	15.3	<0.001
Remdesivir	21	9.9	58	7.4	0.29
Intubation	25	11.8	30	3.8	<0.001
Prone positioning	14	6.6	13	1.7	<0.001
ECMO	7	3.3	7	0.9	0.02
Hospital course					
Duration from onset to hospital admission, days	3	1–4	3	1–4	0.89
Duration from onset to ICU admission, days	3	2–4	3	1–6	0.76
Mortality	35	16.5	28	3.6	<0.001
ICU admission	52	24.5	63	8.0	<0.001
Length of stay in ICU, days	0	0–0	0	0–0	<0.001
Length of stay in hospital, days	12	10–20	10	8–15	<0.001
Mechanical ventilation days, days	0	0–0	0	0–0	<0.001

Note: Data are shown in number (%) or median (IQR).

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LDH, lactate dehydrogenase.

The Cox proportional hazard regression model revealed that the in-hospital mortality was significantly higher in both the "persistent" (HR 5.59, [95% CI 2.24 to 13.97], $p < 0.001$) and "exacerbated" (HR 4.65, [95%CI 2.07 to 10.47], $p < 0.001$) groups (Table 4). The survival curves for these groups are shown in Figure 2B.

Figure 3 illustrates the changes in lymphocyte counts over time between survivors and non-survivors. The linear mixed-effects model indicated that elapsed time had a positive effect on lymphocyte counts in both LP (coefficient 47.13, $p < 0.001$) and NL (coefficient 25.94, $p < 0.001$) groups. However, the interaction between time and mortality negatively affected lymphocyte counts in both the LP (coefficient − 49.51, $p < 0.001$) and NL (coefficient − 51.25, $p = 0.001$) groups. This suggests that a declining trend in the lymphocyte counts over time was significantly associated with mortality.

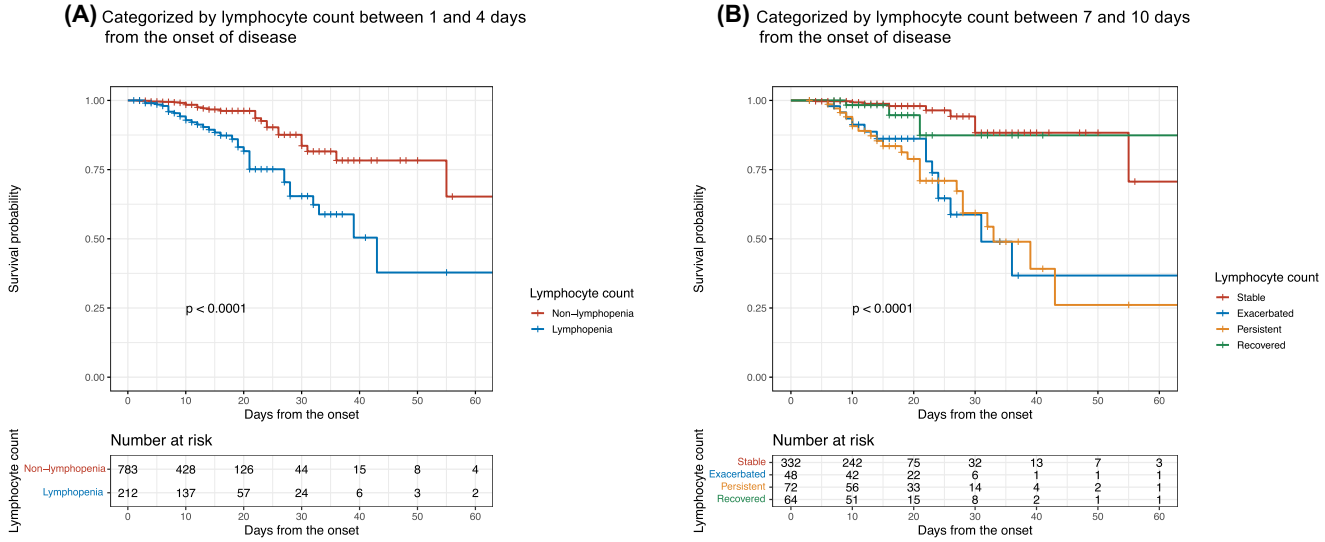

FIGURE 2 Kaplan–Meier curves for in-hospital mortality. (A) Survival curves comparing the lymphopenia group (<800/μL) and non-lymphopenia group (≥800/μL), based on lymphocyte count between 1 and 4 days after disease onset. Patients in the lymphopenia group demonstrated a significantly lower survival probability compared to those in the non-lymphopenia ($p < 0.0001$). (B) Survival curves stratified into four groups based on the temporal trends in lymphocyte count. Patients in the "persistent" and "exacerbated" lymphopenia group exhibited significantly low survival probabilities compared to the other groups ($p < 0.0001$).

TABLE 2 The association between the outcomes and lymphopenia between 1 and 4 days from the onset of disease.

Outcomes	Effect size	(95%CI)	*p*-value
In-hospital mortality	2.32	(1.39 to 3.87)	0.001
Intubation rate	1.84	(1.07 to 3.16)	0.03
ICU-free days	−0.82	(−1.41 to −0.23)	0.007
Hospital-free days	−0.17	(−1.17 to 0.82)	0.74
Ventilator-free days	−0.43	(−0.82 to −0.05)	0.03

Note: Effect size was shown as hazard ratio or regression coefficient. All models were adjusted for age, invasive mechanical ventilation, steroid use and history of diabetes mellitus.

Abbreviations: CI, confidence interval; ICU, Intensive care unit.

Sensitivity analyses, including redefinition of lymphopenia and the use of multiple imputation, confirmed the consistency of the main findings. These included varying the definition of lymphopenia and handling missing data with multiple imputations. The details were provided in Table S1–S6.

DISCUSSION

This study demonstrated a significant association between lymphopenia observed immediately after onset and in-hospital mortality. Additionally, we found that trends in lymphocyte counts were also associated with outcomes. These findings suggest that the lymphocyte count may serve as a marker of immunological status from the early stages of COVID-19, offering clinicians crucial insights into prognosis and informing therapeutic decisions. To our knowledge, this is the first to demonstrate the impact of lymphopenia from the onset of disease and subsequent trend on outcomes using multicenter data.

Recent meta-analyses have established a correlation between lymphopenia and adverse outcomes in COVID-19.[4,7] However, previous analyses predominantly focused on lymphocyte counts on admission. Most patients were admitted to the hospital 5–11 days after disease onset,[2,3,5] a period typically associated with the development of respiratory failure due to COVID-19.[8] Although the precise mechanisms remain unclear, it has been hypothesized that an inflammatory cytokine storm plays a central role in the pathophysiology of lymphopenia in severe COVID-19.[9,10] The large amounts of pro-inflammatory cytokines suppress lymphopoiesis in the bone marrow. Additionally, a cytokine storm contributes to the development of acute respiratory distress syndrome, potentially leading to the sequestration of peripheral lymphocytes into the lungs and further reducing lymphocyte counts in the blood.[9] Based on the timing of observation, lymphopenia at admission was likely driven by a cytokine storm in previous studies. In this study, patients in the "exacerbated" or "persistent" groups, who presented with lymphopenia between 7 and 10 days post-onset, likely experienced a cytokine storm.

We also found that lymphopenia detected within 4 days of onset is associated with poor outcomes. This early-stage lymphopenia may result from an inherent response to the virus itself, distinct from cytokine storm-related effects.[11] A key feature of patients with severe COVID-19 who experience lymphopenia is a reduction in total T cell count.[12] Previous studies have detected SARS-CoV-2 RNA in T cells and B cells, although the clinical implications remain unclear.[13,14] One

TABLE 3 Characteristics of patients subdivided into four categories based on lymphocyte count between 7 and 10 days from the onset of disease.

	Lymphopenia				Non-lymphopenia				*p*-value
	Persistent	*n* = 72	Recovered	*n* = 64		Exacerbated	*n* = 48	Stable	*n* = 332
Age, years	74	62–83	60	47–74	71	56–78	55	37–70	<0.001
Male, sex	39	54.2	43	67.2	37	77.1	205	61.7	0.07
Body Mass Index, kg/m^2	22.5	19.8–26.0	23	21.4–25.3	23.3	20.8–26.5	24.6	21.8–28.3	0.00
Vital signs on admission									
Glasgow Coma Scale	15	15	15	15	15	15	15	15	0.01
Systolic blood pressure, mmHg	128	113–146	128	119–141	129	119–151	126	115–139	0.49
Heart rate, /min	86	70–100	92	80–102	92	77–101	84	74–98	0.13
Respiratory rate, /min	20	16–23	18	16–22	20	16–22	18	16–20	0.15
SpO2, %	96	94–97	96	94–97	96	95–98	97	95–98	0.00
Lactate, mmol/L	1.3	0.9–1.7	1.0	1.1–1.7	1.3	0.7–2.0	1.0	0.9–1.7	0.98
Comorbidities									
Diabetes mellitus	18	25.0	7	10.9	11	22.9	49	14.8	0.06
Chronic heart failure	4	5.6	0	0.0	4	8.3	5	1.5	0.01
COPD	0	0.0	1	1.6	1	2.1	6	1.8)	0.71
Chronic kidney disease	4	5.6	1	1.6	2	4.2	5	1.5	0.16
Laboratory data in the early phase									
White blood cell count, /μL	5040	3392–7050	5025	3625–7300	5950	4588–7350	4925	4100–6470	0.16
Neutrocyte count, /μL	4102	2600–5901	4388	2930–6242	4007	3189–6001	3339	2318–4683	0.01
Lymphocyte count, /μL	496	385–607	609	492–696	880	799–1053	1219	958–1486	<0.001
CRP, mg/dL	8.5	1.7–13.8	4.9	1.1–10.4	5.47	2.2–11.8	1.7	0.3–5.4	<0.001
LDH, U/L	302	227–482	255	198–356	263	212–364	215	179–281	<0.001
D-dimer, μg/mL	1.6	1.0–3.5	1.1	0.7–2.7	1.0	0.7–1.8	0.8	0.5–1.3	<0.001
Treatment									
Steroid	28	38.9	23	35.9	24	50.0	75	22.6	<0.001
Remdesivir	8	11.1	13	20.3	6	12.5	42	12.7	0.37
Intubation	19	26.4	5	7.8	10	20.8	17	5.1	<0.001
Prone positioning	6	8.3	6	9.4	6	12.5	6	1.8	<0.001
ECMO	2	2.8	4	6.2	1	2.1	6	1.8	0.22
Hospital course									
Duration from onset to hospital admission, days	3	1–4	3	1–4	3	2–4	3	1–4	0.51
Duration from onset to ICU admission, days	4	2–4	2	2–4	5	3–7	3	2–7	0.41
Outcomes									
Mortality	22	30.6	3	4.7	14	29.2	9	2.7	<0.001
ICU admission	24	33.3	14	21.9	17	35.4	31	9.3	<0.001
Length of stay in ICU, days	0	0–7.5	0	0–0	0	0–7	0	0–0	<0.001
Length of stay in hospital, days	18	10–27	13	10–18	19	12–24	13	9–19	<0.001
Mechanical ventilation days, days	0	0–1	0	0–0		0	0–0	0	(0–0)

Note: Data are shown in number (%) or median (IQR).

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LDH, lactate dehydrogenase.

plausible explanation for early lymphopenia is the cytopathic effect of direct viral infection on T cells, leading to cell death. Alternatively, high-dose viral exposure, which may delay viral clearance and result in ineffective T and B cell responses, could be associated with lymphopenia.[9] Severe cases may undergo these immunopathological changes following the infection.

The mechanisms underlying lymphopenia could be more complicated. Following the cytokine storm,

pro-inflammatory cytokines could induce lymphocyte apoptosis[9,10] and suppress T cell proliferation,[15] exacerbating lymphopenia. Chronic inflammatory stimulation may also cause the exhaustion of CD8+ T cells and natural killer (NK) cells,[10] further aggravating lymphopenia. These mechanisms might contribute to persistent lymphopenia later in the disease course.

Given the multifactorial nature of lymphopenia in COVID-19, we hypothesize that the mechanisms transition throughout the disease course. Previous research has documented that critically ill COVID-19 patients who died often present with persistent lymphopenia at admission and thereafter, whereas patients surviving from critical illness tend to experience a gradual recuperation of lymphocyte counts.[16,17] It suggested that the lymphocyte count trend could reflect immunological alterations across different phases of COVID-19. In the present study, patients in the "recovered" group experienced an initial reduction in lymphocyte count, probably due to an initial viral attack, yet appeared to avoid the subsequent cytokine storm. In contrast, patients in the "exacerbated" group did not experience lymphocytopathic change early on but developed a cytokine storm at a later stage. The factors influencing the development of a cytokine storm are yet to be proven and could be affected by risk factors such as age, sex, and comorbidities. This topic warrants further investigation.

This study has several limitations. First, the onset of disease was determined by patient self-reporting. In cases where patients were asymptomatic or had impaired consciousness, the date of the first positive SARS-CoV-2 test result was deemed as the onset. This definition may introduce discrepancies in onset dates between symptomatic and asymptomatic patients. These discrepancies should be acknowledged when interpreting and comparing results. Second, data collection was limited to 2020, restricting us from evaluating the effects of the recent advancements in COVID-19 clinical practices, including vaccination, therapeutic agents, and emerging viral variants. However, our findings could provide a baseline for understanding early COVID-19 disease dynamics, reflecting the inherent characteristics. Third, the retrospective nature of the study resulted in a significant number of missing lymphocyte count measurements, particularly between 7 and 10 days after onset, with 75%–79% of the data unavailable. While primary analysis excluded patients without lymphocyte count data between days 7 and 10 to ensure consistency, this could introduce selection bias, as missing data may not be completely random. However, the sensitivity analysis involving imputed missing data yielded similar results, mitigating concerns about bias and affirming the robustness of our findings. These limitations highlight the need for prospective studies to validate the findings in broader and contemporary populations. Nonetheless,

TABLE 4 Results of Cox proportional hazards regression model for in-hospital mortality among patients subdivided into four categories based on lymphocyte count between 7 and 10 days from the onset of disease.

	Hazard ratio	(95%CI)	*p*-value
Stable	(Reference)		
Persistent	5.59	(2.24–13.97)	<0.001
Exacerbated	4.65	(2.07–10.47)	<0.001
Recovered	2.00	(0.53–7.59)	0.31

Note: Hazard ratio was adjusted for age, invasive mechanical ventilation, steroid use and history of diabetes mellitus.

Abbreviation: CI, confidence interval.

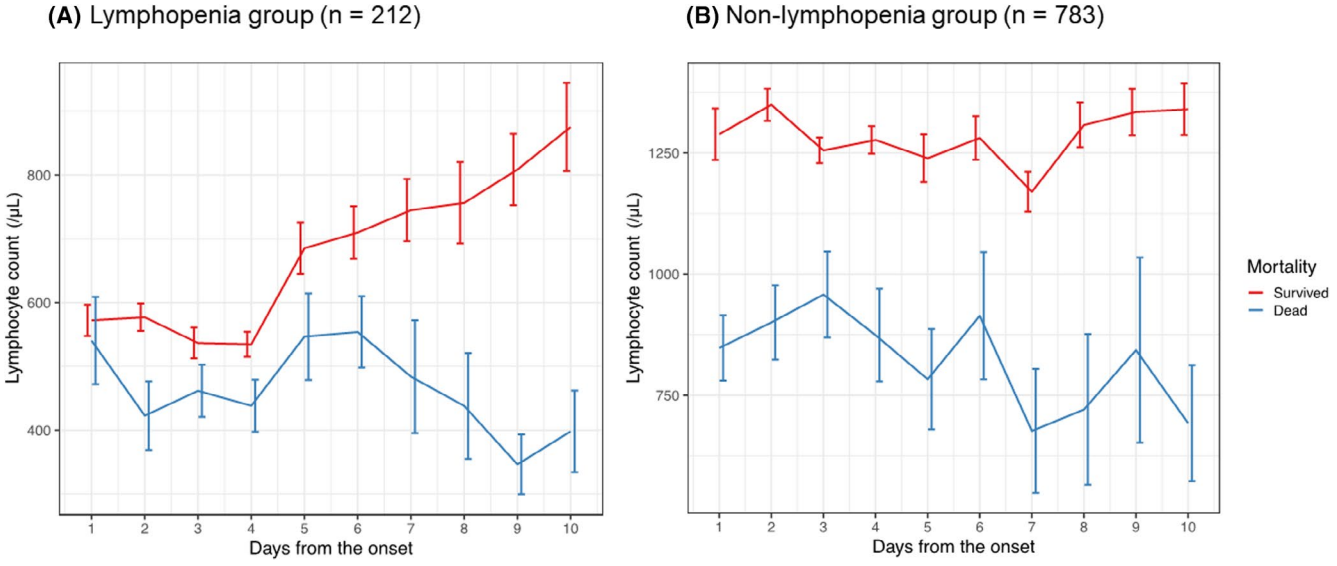

FIGURE 3 Temporal changes in lymphocyte count. (A) Patients with lymphopenia (<800/μL) between 1 and 4 days after the onset. In the lymphopenia group, patients who survived exhibited a gradual increase in lymphocyte count, whereas those who died showed persistently low lymphocyte counts. (B) Patients without lymphopenia (≥800/μL) between days 1 and 4 after onset. In the non-lymphopenia group, patients who survived maintained consistently high lymphocyte counts, while those who died experienced a progressive decline in lymphocyte counts over time.

the multicenter approach and consistency of results across sensitivity analyses provided robust preliminary insights into lymphopenia and COVID-19 outcomes.

In conclusion, a significant association was observed between lymphopenia immediately after the onset of COVID-19 and poor outcomes. Furthermore, a declining trend in lymphocyte count over time was associated with adverse outcomes. Monitoring lymphocyte counts can thus provide valuable information for assessing disease progression throughout the clinical course.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Approval of the research protocol: The study adhered to the Declaration of Helsinki. The Institutional Review Board of Nippon Medical School approved this study.

Informed consent: Informed consent was waived by the Nippon Medical School Ethics committee because of the retrospective nature of the study design.

Registry and the registration no. of the study/trial: The Institutional Review Board of Nippon Medical School approved this study (registration number M-2023-167).

Animal studies. N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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