Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection 82 (2021) e33–e35

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

Predicting recurrence of respiratory failure in critically ill patients with COVID-19: A preliminary study

To the editor,

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses a serious global health threat. Clinical concerns include rapid deterioration of respiratory failure requiring mechanical ventilation, high mortality, and the possibility of reinfection after a successful recovery.[1] Recently, COVID-19 relapse after transient improvement has emerged as a clinically relevant issue[2–4]; reports suggest that COVID-19-related inflammation can remain even when patients have seemingly improved. Previous studies showed that the degree of lymphopenia and the levels of anti-SARS-CoV-2 antibodies were dependent on disease severity.[5] However, it remains unclear whether these factors are associated with disease recurrence in critically ill COVID-19 patients. Therefore, we evaluated the association between these factors and the recurrence of respiratory failure in COVID-19 patients who required mechanical ventilation.

We screened all consecutive COVID-19 patients who required invasive mechanical ventilation between March 2020 and October 2020 in the intensive care unit. SARS-CoV-2 positivity was confirmed by reverse transcription polymerase chain reaction (PCR) using nasopharyngeal and throat swabs. All patients were extubated after a successful spontaneous breathing trial.[6] Post-extubation respiratory failure was defined as the need for reintubation or death within 96 h. Laboratory data obtained within 24 h of extubation were collected. We did not use noninvasive ventilation or high-flow nasal cannula oxygen to avoid aerosolizing virus particles. Patients were excluded if they had coinfection such as bacterial, fungal, or viral infection or other differential diagnoses, including thrombosis, heart failure, or aspiration. Patients who never underwent extubation attempts were also excluded.

Data on serum SARS-CoV-2 PCR results and SARS-CoV-2 antibodies at extubation were analyzed. Levels of anti-SARS-CoV-2 IgG against nucleocapsid (N), spike S1, and spike receptor-binding domain (RBD) antigen, and the combination of N and S1 antigens were measured using the iFlash 3000 fully automatic CLIA analyzer (YHLO Biotech Co., Ltd., Shenzhen, China) with a cutoff value of 10 AU/mL. Antibody detection kits against N, S1, and RBD antigens were obtained from Shenzhen YHLO Biotech Co., Ltd. Cryopreserved sera obtained within 48 h from the time of extubation were included in this analysis. We evaluated factors involved in COVID-19 recurrence. Data are presented as median and interquartile range. The institutional review board approved this study and waived the requirement for informed consent.

Twenty-two patients with a confirmed COVID-19 diagnosis required invasive mechanical ventilation in the intensive care unit during the study period. Of 22 patients, 17 who underwent extubation attempts were finally enrolled. All patients were followed up for at least 2 weeks after extubation. Among 17 patients, 4 were women and 13 were men; they had a median age of 72 (61–74) years. Four patients were reintubated for refractory hypoxemia (relapse group) and 13 did not experience post-extubation failure (non-relapse group). The median age was higher in the relapse group than the non-relapse group (76.5 [73–80] years vs. 66 [58–73] years). The median times from symptom onset to intubation were 9.5 (8.75–10.25) days and 11 (9–13) days in the relapse and non-relapse groups, respectively. The median durations of mechanical ventilation were 8 (6.5–10.75) days and 7 (5–9) days in the relapse and non-relapse groups, respectively. Moreover, there were no significant differences between the groups with respect to sex, body mass index, smoking history, comorbidity, sequential organ failure assessment score at intubation, or treatments, including heparin, dexamethasone, and remdesivir. Although there were no differences between the groups with respect to laboratory data such as D-dimer, ferritin, and C-reactive protein levels, lymphocyte counts at extubation were significantly lower in the relapse group than in the non-relapse group (613/μL vs. 1046/μL; $P = 0.044$) (Fig 1).

Nine patients were evaluated for SARS-CoV-2 IgG at extubation. The median time from symptom onset to blood sample collection was 16 (14–17) days. All nine patients received corticosteroids based on the results of the RECOVERY trial.[7] Lymphocyte counts were increased in all patients except one who experienced post-extubation respiratory failure (Fig 2A). The relapse group tended to have lower lymphocyte counts and lower levels of SARS-CoV-2 IgG against S1 and RBD at extubation than the non-relapse group (Fig 2B). Among patients who developed post-extubation respiratory failure, one had no antibody response and another had heterogeneous IgG responses, including a sufficient response to the N antigen but an insufficient response to S1 and RBD antigens. Among nine patients, three had positive serum PCR SARS-CoV-2 test results at extubation, of whom one avoided post-extubation respiratory failure. This patient had sufficient IgG levels against S1 and RBD.

Our findings suggest that the concomitant presence of lymphopenia and low levels of anti-spike S1 and RBD IgG at extubation is a potential risk of COVID-19 recurrence after extubation. Patients with sufficient S1- or RBD-specific IgG were unlikely to develop post-extubation respiratory failure, even if they had lymphopenia. Notably, these antibodies, rather than N-specific antibodies, were essential for disease stabilization. The RBD is located within the S1 portion of the spike protein, and RBD-specific antibodies can neutralize SARS-CoV-2 and play an essential role in the recovery of COVID-19 patients.[8,9] Sufficient S1- and RBD-specific IgG levels may have contributed to preventing post-extubation respiratory failure, even in patients who were positive for serum

https://doi.org/10.1016/j.jinf.2021.01.016

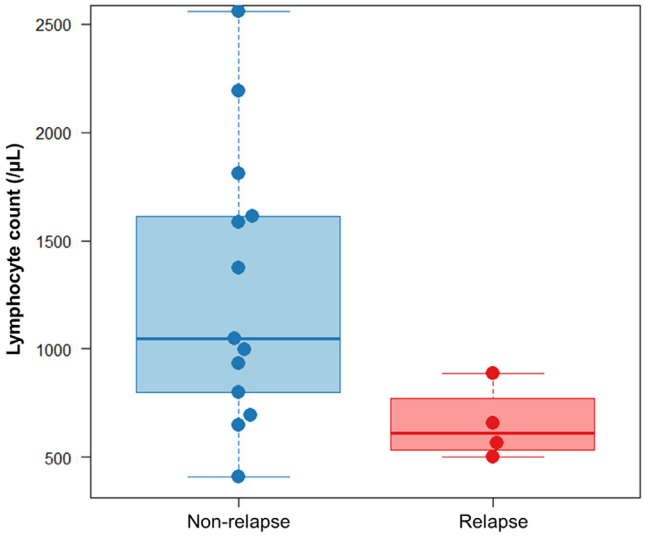

Fig. 1. Box plots showing lymphocyte counts at extubation in patients who did (relapse group) and did not (non-relapse group) experience post-extubation respiratory failure. Lymphocyte counts at extubation were significantly lower in the relapse group than in the non-relapse group ($P = 0.044$).

SARS-CoV-2 PCR at extubation, indicating persistent robust inflammation.[10] A previous report showed that low antibody levels increase the risk of re-detectable viral RNA.[9] Similarly, our results indicate that low S1- and RBD-specific IgG levels at extubation may increase the risk of post-extubation respiratory failure. Therefore, the combination of lymphocyte counts and S1 and RBD antibody levels may serve as surrogate markers of remnant COVID-19-related inflammation.

This study had some limitations. First, our study was a preliminary retrospective study with a small sample, precluding definite conclusions. Second, SARS-CoV-2 antibodies were not measured in all patients, which could lead to selection bias. Third, factors besides COVID-19 could not be excluded as the cause of post-extubation respiratory failure. Finally, we did not analyze the neutralizing activity of non-humoral mechanisms, including T-cell responses to SARS-CoV-2. Therefore, our findings should be regarded as hypothesis generating for future studies.

Declaration of Competing Interest

The authors declare no conflict of interest.

Funding

This study was supported in part by research grants from Cloud founding of peace winds Japan, and Japan Agency for Medical Research and Development (AMED) (grant number 200705710 and JP20fk0108265 (to A. K.). The research was designed, conducted, analyzed, and interpreted by the authors entirely independently of the funding sources.

Author's contributions

YA and TS designed the study and drafted the manuscript. YA, HH, SA, TN, YN, RH, TE, and AU contributed to data acquisition. YY, TM, TM, and YK analyzed the data. AK supported the study design setup and interpretation of the data. All authors contributed to the review and approval of the final copy of the manuscript.

References

1. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Center for disease control and prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html (accessed December 8, 2020)
2. Gousseff M, Penot P, Gallay L, et al. Clinical recurrences of COVID-19 symptoms after recovery: viral relapse, reinfection or inflammatory rebound? *J Infect* 2020;**81**(5):816–46.
3. Zhang J, He X, Hu J, Li T. Failure of early extubation among cases of coronavirus disease-19 respiratory failure: case report and clinical experience. *Medicine (Baltimore)* 2020;**99**(27):e20843.
4. Esnault P, Cardinale M, Hraiech S, et al. High respiratory drive and excessive

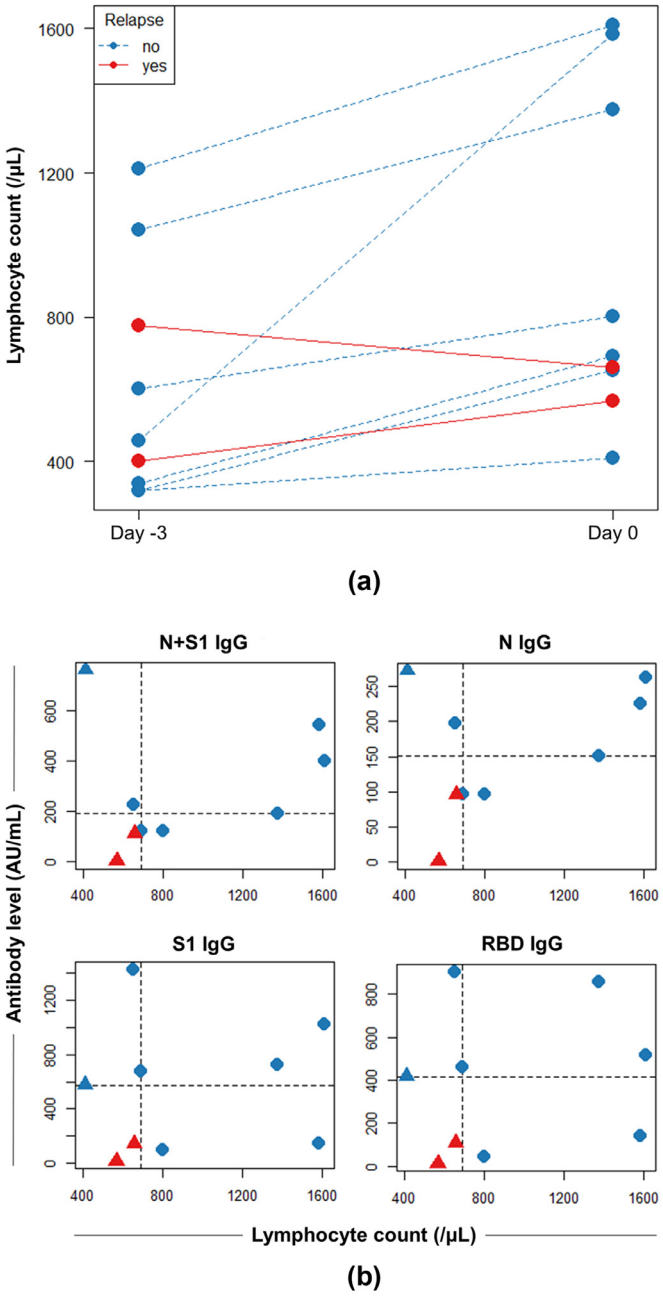

Fig. 2. Lymphocyte counts and IgG antibody levels of nine patients whose antibody levels were measured. (A) Comparison of lymphocyte counts at extubation (Day 0) and 3 days before extubation (Day −3). Data from 3 days before extubation were used for comparison to avoid the influence of the timing of steroid initiation. All patients received corticosteroids for at least 4 days before extubation. (B) Scatterplot of the lymphocyte counts and levels of SARS-CoV-2 IgG antibodies. Blue dots indicate patients who did not develop post-extubation respiratory failure, and red dots indicate patients who did. Triangles indicate patients with positive serum PCR test results at extubation. The dashed line indicates the median value. IgG = immunoglobulin G; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; PCR = polymerase chain reaction; *N* = nucleocapsid; RBD = receptor-binding domain.

respiratory efforts predict relapse of respiratory failure in critically ill patients with COVID-19. *Am J Respir Crit Care Med* 2020;**202**(8):1173–8.
5. Wang Y, Zhang L, Sang L, et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. *J Clin Invest* 2020;**130**(10):5235–44.
6. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;**43**(3):304–77.
7. Horby P, Lim WS, Emberson JR. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020. Published online Jul 17. doi:10.1056/NEJMoa2021436.
8. Iyer AS, Jones FK, Nodoushani A, et al. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. *Sci Immunol* 2020;**5**(52):1–13.
9. Li K, Huang B, Wu M, et al. Dynamic changes in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery from COVID-19. *Nat Commun* 2020;**11**(1):6044.
10. Li F, Chen X, Zhao B, et al. Clinical infectious diseases 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**(8):1937–79.

Yuichi Adachi, Takayuki Shiroyama*, Yuta Yamaguchi, Teruaki Murakami, Haruhiko Hirata, Saori Amiya, Takayuki Niitsu, Yoshimi Noda, Reina Hara, Takatoshi Enomoto, Takayoshi Morita
Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita City, Osaka 565-0871, Japan

Yasuhiro Kato
Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita City, Osaka 565-0871, Japan
Department of Advanced Clinical and Translational Immunology, Osaka University Graduate School of Medicine, Osaka, Japan

Akinori Uchiyama
Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Yoshito Takeda, Atsushi Kumanogoh
Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita City, Osaka 565-0871, Japan

*Corresponding author.