



Autoantibodies in severe COVID-19-related acute respiratory distress syndrome: Just innocent bystanders?

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1 | INTRODUCTION

Ever since coronavirus disease 2019 (COVID-19) was declared a global public health emergency, more than 60 million confirmed cases and more than one million confirmed deaths have been recorded globally. Although most patients have minimal flu-like symptoms, some of them develop a severe pneumonia, which may lead to multi-organ failure and death.¹ Systemic hyperinflammation and a procoagulant state play a major pathophysiological role in these severe forms.² Autoimmune diseases are also characterized by inflammation and often by a procoagulant state, and viruses may be involved in their development,³ so a link between COVID-19 and autoimmunity has recently been postulated. A report found that up to 35% of hospitalized patients with less severe COVID-19 have antinuclear antibodies, suggesting a possible role of autoimmune mechanisms, which may potentially imply specific treatments.⁴ At the time of data collection, no reports had been published that focused on the most severe patients, ie those undergoing mechanical ventilation. During the revision process, however, two papers were published on autoimmune aspects of severe COVID-19 patients.^{5,6} The present study aimed to assess the prevalence and clinical outcomes associated with the presence of autoantibodies in critically ill, mechanically ventilated patients admitted to the intensive care unit (ICU) for COVID-19-related respiratory failure.

2 | MATERIALS AND METHODS

Consecutive patients aged at least 18 years admitted to the ICU at Ospedale San Carlo Borromeo with confirmed severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were enrolled. Patients previously diagnosed with autoimmune diseases were excluded. The study was approved by the Hospital Ethics Committee; informed consent was obtained according to Italian regulations. At ICU admission, every patient was tested for the presence of anti-nuclear, anti-mitochondrial, anti-smooth muscle cell, and anti-neutrophil cytoplasmic antibodies. The primary outcome was hospital mortality. Secondary outcomes were the duration of mechanical ventilation, the ICU and hospital lengths of stay, the number of ventilator-free days in the first 28 days of ICU stay, and the proportion of patients who developed ventilator-associated pneumonia or bacteremia. Continuous variables are reported as mean \pm standard deviation or as median (1st; 3rd quartile), as appropriate; categorical variables as number and percentages. Analysis was performed with STATA 13.0 (Statacorp, College Station, TX, USA); $P < 0.05$ was considered statistically significant.

3 | RESULTS

Twenty-eight patients were enrolled in the present analysis; 15 (53.6%) of them had autoantibodies. Table S1 shows the demographic and clinical characteristics, comorbidities, treatment received before ICU admission, blood biochemistry, gas exchange and respiratory physiology at ICU admission. All patients were intubated and mechanically ventilated at ICU admission. No significant differences were found between the groups for any of the variables recorded, with the exception of a higher organ failure score at admission for patients who had autoantibodies. Of the patients with



autoantibodies, 3 (20%) had anti-nuclear antibodies, 1 (7%) had anti-mitochondrial antibodies, 12 (80%) had anti-smooth muscle cell antibodies, and 1 (7%) had anti-neutrophil cytoplasmic antibodies. Table S2 shows the lymphocyte subset counts and complement components. Both groups were lymphopenic; however, we were unable to find any difference in any lymphocyte subset or in complement components C3 or C4 between the two groups of patients.

Table 1 compares the clinical outcomes of patients with and without autoantibodies: no differences were found for hospital mortality, duration of mechanical ventilation, the ICU and hospital length of stay, the number of ventilator-free days in the first 28 days of ICU stay, and the proportion of patients who developed ventilator-associated pneumonia or bacteremia. Figure S1 shows the Kaplan-Meier curves for hospital mortality in patients with and without autoantibodies (Log-rank test $P = 0.2548$).

4 | DISCUSSION

In a small cohort of mechanically ventilated, adult COVID-19 patients, more than half of patients had autoantibodies, but we could not identify any specific risk factor associated with this finding. Patients with autoantibodies had a similar degree of disease severity as patients who did not have autoantibodies, and their clinical outcome was comparable. This is the first report on the finding of autoantibodies among COVID-19 patients receiving invasive ventilation. Autoimmunity develops as a result of a multifactorial interplay of genetic, hormonal, immunological, and environmental factors. Viral infections play a substantial role in triggering autoimmunity in predisposed patients.³ The viral disruption of self-tolerance can be caused by molecular mimicry, epitope spreading, bystander activation, stimulation of inflammasome platforms, or polyclonal immune activation. Of note, all these mechanisms have been found in the

setting of COVID-19.⁷ Moreover, it was hypothesized that COVID-19 pneumonia can be worsened by an autoimmune response, and that the presence of autoantibodies may be a surrogate marker of severity and poor prognosis.⁸ However, no such studies were performed in the most critically ill patients.

In 29 unselected critically ill, COVID-19 patients, several systemic autoimmune reactivities were found in 70% of the patients, suggesting a post-SARS-CoV-2 or para-SARS-CoV-2 infectious autoimmune activation.⁶ In a cohort of COVID-19 patients hospitalized both in the ICU and in the medical ward, antibodies against nuclear, vasculitis-associated, and phospholipid antigens were detected in 30% of the patients. Notably, similar levels of inflammatory markers and total immunoglobulin levels in autoantibody-positive versus autoantibody-negative patients were found, as well as a similar outcome.⁵

In SARS, immune-mediated mechanisms were described, and both autoimmune responses and a cross-reaction between viral antigens and autoantibodies were found.⁹ Some of the extensive cellular damage associated with COVID-19 may be the result of viral antigenic mimicry with human tissue, as the immune responses against SARS-CoV-2 showed cross-reaction with various tissue antigens.¹⁰ Indeed, a causal link between SARS-CoV-2 and the appearance of autoinflammatory diseases has not yet been firmly established; however, the temporal association with the current pandemic highly suggests this possibility. Of note, the pathogenicity of these autoantibodies is unknown, as well as the chance to induce autoimmune disorders in the long term. It is well-known that autoantibody seropositivity may also be found in healthy individuals;¹¹ however, the prevalence we found is higher than reported in other western countries.¹² Nevertheless, despite a higher Sequential Organ Failure Assessment score and hence a more severe clinical presentation of patients with autoantibodies, the similar outcome of patients with and without autoantibodies, and the lack of a clear risk factor for

TABLE 1 Clinical outcomes in patients with and without autoantibodies^a

	No autoantibodies (N = 13)	Autoantibodies (N = 15)	P
ICU mortality	7 (53.9)	6 (40)	.464
Duration of mechanical ventilation (days)	13 (4; 26)	10 (8; 17)	.7119
Duration of pressure support ventilation (days)	2 (1; 5)	3 (1; 6)	.9815
ICU length of stay (days)	17 (5; 26)	11 (8; 23)	.6280
Hospital length of stay (days)	27 (23; 37)	26 (21; 35)	.7967
Ventilator-free days (days)	0 (0; 24)	11 (0; 20)	.7891
Patients who developed VAP	7 (53.9)	8 (53.3)	.978
Number of VAP per patient	2 (1; 4)	2 (1; 2)	.4579
Patients who developed bacteremia (%)	6 (46.2)	7 (46.7)	.978
Number of bacteremias per patient	1 (1; 2)	1 (1; 2)	.8053

Abbreviations: ICU, intensive care unit; VAP, ventilator-associated pneumonia.

^aValues are given as number (percentage) or as median (1st; 3rd quartile).



their development, seem to suggest that autoimmunity is not yet to be considered the hallmark of COVID-19. Many of the other reported immune-mediated disorders in SARS-CoV-2 may just represent transitory epiphenomena accompanying a viral infection.

Immunosuppressive therapies at least short term, such as dexamethasone and tocilizumab, showed benefit in COVID-19 patients in the ICU. Whether this depends on an effect on autoimmunity is not clear. It would be interesting to note whether the rates of autoantibodies in these RCTs were any different between the placebo and control arms. Whether the use of immunosuppressive therapies may prove of benefit in such cases is a fascinating perspective, but definite evidence in support is still lacking.

The limitations of this study relate to its small-size and single-centre, retrospective, observational nature. Autoantibodies were only tested at ICU admission, and we cannot exclude a possible late appearance in some cases, nor did we assess any long-term consequence of our findings. In conclusion, we found that autoantibodies were present in more than half of critically ill patients undergoing mechanical ventilation for COVID-19. Their presence was not associated with a worse clinical outcome; however, we cannot exclude that, because of the small sample size, our study might be underpowered to detect such a difference. Further studies are needed to elucidate whether the presence of autoantibodies only represents a transitory epiphenomenon accompanying a viral infection or if it is associated with any different clinical outcome.

CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section. **How to cite this article:** Umbrello M, Nespoli S, Pisano E, Bonino C, Muttini S. Autoantibodies in severe COVID-19-related acute respiratory distress syndrome: Just innocent bystanders?. *Int J Rheum Dis*. 2021;24:462-464. <https://doi.org/10.1111/1756-185X.14077>