ORIGINAL ARTICLE

Adverse outcome and severity of COVID-19 in patients with autoimmune bullous diseases: A historical cohort study

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Abstract

The ongoing COVID-19 pandemic has raised concerns regarding the outcome of this infection in patients with autoimmune bullous dermatoses (AIBDs) due to effect of drugs used to treat these disorders. This investigation was performed from the onset of the pandemic to June 1, 2021. Patients with AIBDs who contracted COVID-19 were evaluated. A generalized linear model was employed to find the predictors of severe COVID-19 among patients with AIBDs. Ninety-three patients with AIBDs with a mean age of 50.3 years were evaluated. The most COVID-19 related symptoms were tiredness (76.3%) myalgia (69%), and cough (63.4%). During follow-up, the rate of hospitalization and death were 45.2% and 4.3%, respectively. Previous comorbidities ($\beta = 0.61$) and mean prednisolone dosage above 10 mg/day in the last 3 months ($\beta = 1.10$) significantly increased COVID-19 severity. Also, vaccination against SARS-CoV-2 ($\beta = -1.50$) and each passing month from the last rituximab dose decreased severity ($\beta = -0.02$). Notably, 19.3% of the patients developed AIBD flare-ups following COVID-19 infection. Higher prednisone dose and the shorter interval from the last rituximab infusion were determinants of severe COVID-19. Physicians should assess the risk versus the benefits when prescribing the medications. Moreover, vaccination could successfully attenuate COVID-19 severity.

KEYWORDS
autoimmune, autoimmune blistering disease, COVID-19, immunosuppression, SARS-CoV-2

1 | INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogen was announced a pandemic in March 2020.[1] The pandemic is still ongoing across the globe and causes a spectrum of manifestations from subclinical infection to death.[2]

Autoimmune bullous diseases (AIBDs) are a group of potentially life-threatening dermatoses characterized by blisters and erosions on the skin and/or mucosa.[3] This particularly middle-aged and older population are considered to be at increased risk of severe infections owing to epithelial barrier disruption, impairment of the immune system, and disease-related medications.[4,5] Therefore, since the public announcement of the COVID-19 pandemic, clinicians have faced many challenges in managing AIBDs.[6] Several papers have shown the increased risk of aggressive COVID-19 in patients with autoimmune diseases compared to the general population.[7,8] Contrarily, other studies did not find an association between COVID-19 outcomes and autoimmune diseases.[9–12]

Outcomes of COVID-19 in AIBD patients have been focused on only in a few studies so far and contradictory findings have been reported.[11,13–16] Herein, we sought to further characterize the impact of COVID-19 in these vulnerable patients and define the predictors of severe infection by evaluating the largest cohort of infected AIBD patients.

2 | MATERIALS AND METHODS

2.1 | Study design and enrollment

We performed a retrospective cohort study aiming at patients with a histopathologically confirmed diagnosis of AIBDs presented to the Razi dermatology university hospital. Ones who had a diagnosis of SARS-CoV-2 from the onset of the pandemic, March 1, 2020, to June 1, 2021. were selected to enroll. The patients or their next of kin were informed about the concept of the study, and those who wished to participate were included. The data were obtained from the medical records of the patients and follow-up phone calls. The study protocol was reviewed and approved by the Tehran University of Medical Sciences Ethics committee (IR.TUMS.VCR. REC.1399.189).

2.2 | COVID-19 identification

The SARS-CoV-2 diagnosis relied on a positive reverse transcriptase PCR (RT-PCR) test result or lung involvement on chest computed tomography (CT) scan compatible with SARS-CoV-2.[17] Patients who lacked confirmation of the diagnosis were excluded. Management of COVID-19 infection was done following Iran's Ministry of Health and Medical Education guidelines (Figure 1.).[18]

2.3 | Outcome variables

Patient demographics, disease- and medication-related data, comorbidities, history of vaccination, characteristics of COVID-19 infection, and laboratory values were obtained. The variables of oxygen use, intubation, ward admission, ICU admission, hospitalization length, and death among those hospitalized were also noted.
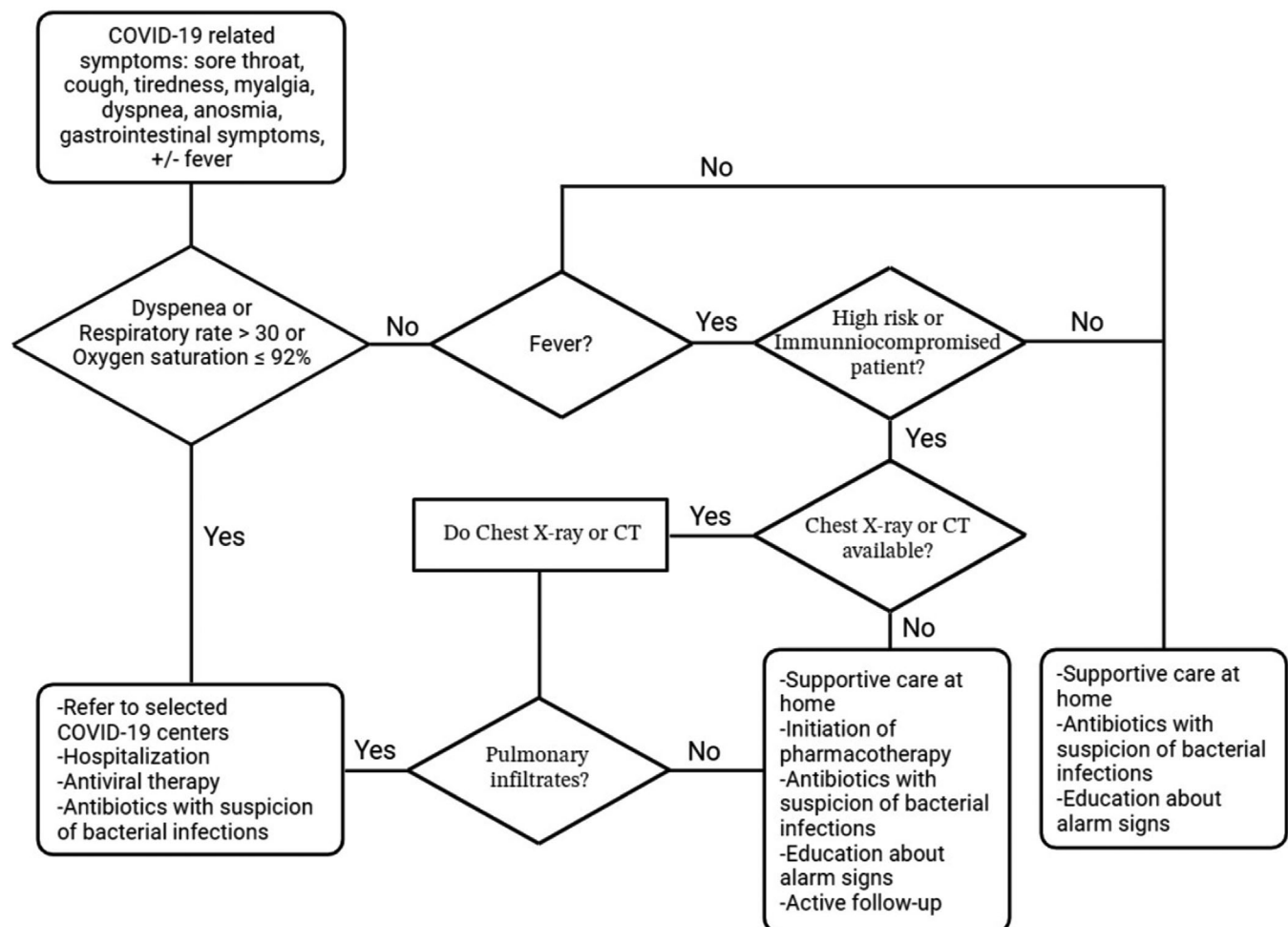

FIGURE 1 Flowchart of the COVID-19 management[18]

For assessing the severity of COVID-19, patients' clinical status at the most severe point of their COVID-19 course was noted based on a 7-point scale as follows. 1, Not hospitalized, no limitations on activities; 2, Not hospitalized, limitation on activities; 3, Hospitalized, not requiring supplemental oxygen; 4, Hospitalized, requiring supplemental oxygen; 5, Hospitalized, on noninvasive ventilation or high-flow oxygen devices; 6, Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 7, Death.

2.4 | Statistical analysis

Absolute numbers and percentages were used for reporting qualitative variables. The quantitative variables were presented as mean with standard deviation (SD) for normal distributed variables and median with interquartile range (IQR) for non-normal ones. To predict probable factors contributing to the outcome of COVID-19 infection, generalized linear model with controlling confounding variables was used for COVID-19 severity and death. All p-values were two-sided with an α level of 0.05; all statistical analysis was performed using SPSS (version 24; IBM, New York, USA).

3 | RESULTS

In this study, 93 AIBD patients with a confirmed diagnosis of COVID-19 were evaluated. Of them, 69 were women (74.2%) and 24 were men (25.8%). The mean age was 50.3 years (SD = 11.1), with the youngest and oldest patients as 27 and 81 years old, respectively. Of the patients, five (5.4%) were fully vaccinated against SARS-CoV-2 before contracting COVID-19 infection. The vaccines' type and regime received by the patients were as follows: two doses of BBIBP-CorV (Sinopharm) vaccine 1 month apart in three, two doses of Gam-COVID-Vac (Sputnik) vaccine 1 month apart in one, and two doses of ChAdOx1 nCoV-19 (AstraZeneca) vaccine 3 months apart in one patient. The detailed demographic features of patients are presented in Table 1.

TABLE 1 Demographic features and disease characteristics of 93 AIBD patients at the time of COVID-19 infection

	Female	69 (74.2%)
Gender, n (%)	**Male**	**24 (25.8%)**
Age (years old), mean ± SD		50.3 ± 11.1
Comorbidities, n (%)	All comorbidities	57 (61.3%)
	Hypertension	28 (30.1%)
	Hyperlipidemia	27 (29.0%)
	Diabetes	22 (23.6%)
	Obesity	20 (21.5%)
	Hypothyroidism	9 (9.7%)
	Ischemic heart disease	7 (7.5%)
	Asthma	2 (2.2%)
	Others	13 (14.0%)
AIBD subtype, n (%)	Pemphigus vulgaris	77 (82.8%)
	Pemphigus foliaceous	7 (7.5%)
	Mucous membrane pemphigoid	5 (5.4%)
	Bullous pemphigoid	2 (2.2%)
	Epidermolysis bullosa acquisita	1 (1.1%)
	Paraneoplastic pemphigus	1 (1.1%)
AIBD duration (months), median (IQR)		48 (21–120)
AIBD medications, n (%)	Prednisolone	78 (83.9%)
	Mycophenolate mofetil	9 (9.7%)
	Rituximab	3 (3.2%)
	Dapsone	1 (1.1%)
Mean prednisolone dosage in the last three month of COVID-19 infection (mg/day), median (IQR)		7.5 (3.4–12.5)
History of rituximab administration, n (%)		72 (77.4%)
Duration from last rituximab, (months), median (IQR)		11.5 (3.9–24)

Abbreviations: AIBD, autoimmune bullous disease; IQR, interquartile range; SD, standard deviation.

Frequency of the reported COVID-19-related symptoms among these patients were tiredness 71 (76.3%), myalgia 65 (69%), cough 59 (63.4%), fever 57 (61.3%), dyspnea 49 (52.7%), loss of appetite 46 (49.5%), anosmia 23 (24.7%), diarrhea 22 (23.7%), headache 20 (21.5%), nausea 20 (21.5%), vomiting 9 (9.7%), and sore throat 9 (9.7%). At the first visit, 39 (41.9%) patients had O_2 saturation of ≤92%.

Based on the diagnostic and treatment criteria for COVID-19, 42 (45.2%) patients were admitted to the hospital. According to the laboratory findings at admission, 10 (23.8%) patients were found with lymphopenia and 21 (50.0%) with positive C-reactive protein. Of the

hospitalized patients, 34 (80.9%) underwent oxygen therapy, 11 (26.2%) required ICU care, and 9 (21.4%) were intubated for mechanical ventilation. Unfortunately, four deaths due to COVID-19 infection were also recorded. The frequency of COVID-19 severity among the patients is shown in Figure 2.

For the management of the COVID-19 infection, various medications were used, including hydroxychloroquine in 21 (22.6%), azithromycin in 19 (20.4%), dexamethasone in 15 (16.1%), remdesivir in 15 (16.1%), oseltamivir in 11 (11.8%), ritonavir in 7 (7.5%), favipiravir in 6 (6.5%), interferon beta-1a in 3 (3.3%), ribavirin in 2 (2.2%), and atazanavir in 1 (1.1%). The median time of hospital stay and complete
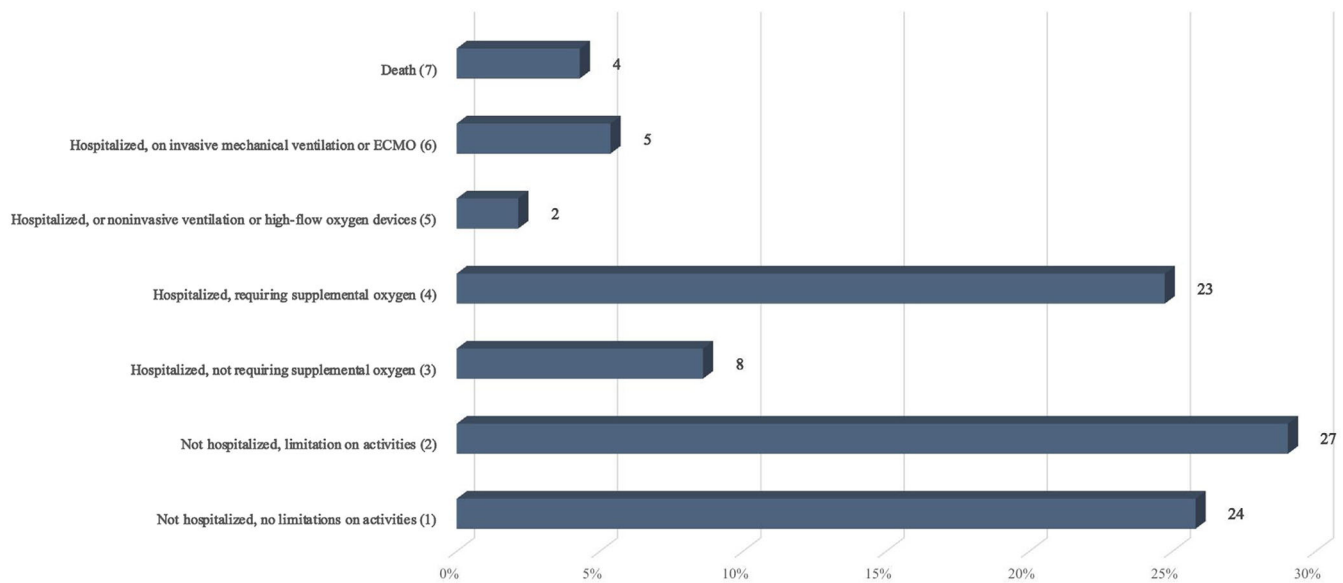

Abbreviations: ECMO, extracorporeal membrane oxygenation

FIGURE 2 Clinical condition rating of the severity scores of COVID-19 infection in patients with autoimmune bullous dermatoses

TABLE 2 The effect of probable factors on COVID-19 severity and death in patients with AIBDs

Variable	COVID-19 severity		Death due to COVID-19	
	Unstandardized beta coefficient	p-Value	Unstandardized beta coefficient	p-Value
Gender (male)	0.078	0.742	−0.044	0.970
Age (years)	−0.017	0.064	0.006	0.899
Comorbidities	0.608	0.004*	0.665	0.571
Vaccination	−1.498	0.001*	−19.522	1.000
Adjuvant therapy at the time of infection	0.182	0.556	−19.334	0.999
Mean prednisolone dosage above 10 mg/day in the last three months	1.1	<0.001*	1.546	0.215
Duration from last rituximab (months)	−0.017	0.001*	1.480	0.224
O_2 saturation ≤ 92 at first visit	2.265	<0.001*	20.081	0.999
Lymphopenia[a]	1.057	0.015*	21.389	0.999
Positive C-reactive protein[a]	0.434	0.572	20.014	1.000
Anti-viral therapy[a]	0.427	0.065	1.204	0.316

[a]The p-values for these variables were adjusted by controlling the effect of hospitalization.
*Significance level < 0.05.

resolution of COVID-19 symptoms were 7 (IQR, 7–13.25) and 14 (IQR, 14–30) days, respectively.

According to the generalized linear model with the assessment of all included variables, it was found that previous comorbidities and mean prednisolone dosage above 10 mg/day in the last 3 months significantly increased COVID-19 severity. In addition, vaccination against SARS-CoV-2 and each passing month from the last rituximab dose attenuated disease severity by approximately $\beta = 1.5$ and $\beta = 0.02$, respectively. O2 saturation ≤ 92% at the first visit and lymphopenia at admission were other factors with significant effect in this regard. None of those items were associated with death due to COVID-19 (Table 2).

In this study, 18 (19.3%) patients experienced a flare of AIBD course following COVID-19 infection. Reported flares were managed with an increase in prednisolone dosage in 14 patients, rituximab administration in 6, and initiation of mycophenolate mofetil in one. No factor significantly affected AIBD flares after COVID-19 infection.

4 | DISCUSSION

Since the outbreak of the COVID-19 pandemic, there have been concerns regarding the course of the COVID-19 in autoimmune disorders, namely AIBDs. These blistering disorders are not common, and data remain sparse concerning the outcome of COVID-19 in these patients. Herein, we specifically shared our clinical experience.

The present study assessed patients with AIBDs who contracted COVID-19 infections. In our population, which represents one of the largest studies of patients with AIBDs, the most observed COVID-19-related symptoms were tiredness (76.3%), followed by myalgia (69%). Of note, the rate of hospitalization and death due to COVID-19 was 45.2% and 4.3%, respectively. Our hospitalization rate was in accordance with 45%, 46%, and 49% of other studies evaluating autoimmune diseases.[7,19,20] Nevertheless, it was slightly higher than 35% of the Global Rheumatology Alliance registry.[21] In addition, our population's mortality rate of 4.3% was less than the studies above but somehow matched the mortality rate of 3.5% reported by the Global Rheumatology Alliance registry.[7,19–21]

There have been controversies regarding the course and severity of COVID-19 in patients with autoimmune disorders compared to those without autoimmunity. These patients, however, may be predisposed to getting COVID-19 infection for impairment of the immune system, immunosuppressive treatments, and, probably, epithelial barrier breakdown.[5,22] A cohort study reported similar hospitalization and mortality rates but a higher risk of respiratory failure in patients with autoimmune diseases compared to healthy individuals.[19] Similarly, another study reported no increased risk of ICU admission, intubation, or death among hospitalized individuals with autoimmune disease.[10] On the other hand, a matched control cohort stated that patients with rheumatoid arthritis are at higher risk of hospitalization or death from severe COVID-19 than those without RA.[23] In a national-based survey of primary care patients from the UK, patients diagnosed with RA, lupus, or psoriasis were found to have a 19%

higher risk of COVID-19-related death.[8] Another study demonstrated that rheumatic disease patients infected with COVID-19 were more likely to require ICU admission and ventilation, and died more frequently versus uninfected patients with autoimmune diseases. Moreover, those on chronic glucocorticoids were hospitalized more frequently.[7] In the field of AIBDs, Kridin et al. reported that patients with BP experienced increased COVID-19-associated mortality than the healthy controls while having the same rate of hospitalization. The authors also indicated that maintaining systemic corticosteroids and immunosuppressive adjuvant agents during the pandemic would not worsen the outcomes.[11] A recent study by Joly et al. with including the possible cases of COVID-19, showed the hospitalization rate of 50.8% in patients with AIBDs.[15] They reported a 5.9-fold higher risk of mortality among AIBD patients with COVID-19 than patients without COVID-19. Notably, they found rituximab as a major risk factor of COVID-19 infection in which AIBD patients treated with rituximab had >5-fold higher incidence of COVID-19.

We found that having comorbidity and mean prednisolone consumption above 10 mg/day in the last 3 months would lead to a more severe COVID-19 infection. Further, vaccination against SARS-CoV-2 and each passing month from the last rituximab administration accompanied by a 1.5 and 0.02 decrease in COVID-19 severity, respectively. Concerning COVID-19 infection, patients with O_2 saturation ≤ 92% at the first visit and lymphopenia at admission experienced more severe infection. Notwithstanding, none of these variables were associated with an increased risk of death due to COVID-19. Although age is a known risk factor for severe COVID-19 outcomes,[8] it did not reach a significant level to be an independent risk factor for developing a severe form of COVID-19 in this study. It can be attributed to the fact that most of the patients with AIBDs are middle-aged or old, which could mediate these associations.

Along with present results, our preliminary study assessing characteristics and outcomes of the COVID-19 course in 21 patients with AIBDs from the first emergence of COVID-19 to May 29, 2020, identified prednisolone consumption of doses above 10 mg/day as an independent risk factor for the severity of COVID-19 infection.[16] All those patients were included in this study as well. In that study, it has also been found that each passing month from the last dose of rituximab decreased the risks of hospitalization.[16] The lower oxygen saturation and lymphocytes counts seen in more severe COVID-19 infection were consistent with other studies as these both are indicators of disease severity.[24,25]

There have been great concerns about the therapeutic strategies of AIBDs in the era of COVID-19.[5,26] Experts suggested controlling the mild disease with topical or intralesional corticosteroids, dapsone, and doxycycline. Systemic steroid doses of ≤10 mg/day can be continued, while prednisolone >10 mg/day should be tapered to the lowest effective dose. In this regard, AIBD severity should be considered in reducing the steroid dose. Noteworthy is that significant dose reduction or treatment withdrawal can result in disease flare-up, and after that higher risk of morbidity and mortality would be encountered.[5,26]

Data regarding the use of biologic agents, specifically rituximab, are controversial.[27,28] It has been hypothesized that rituximab causes

depletion of CD20-expressing B cells, resulting in impaired immune response and ultimately preventing a rapid virus clearance. That would cause an exaggerated immune response leading to a more severe COVID-19 .[14–16,23,29] In contrast, some authors found no association between rituximab and increased disease severity in autoimmune diseases.[7,11,30,31] A recent study in pemphigus showed that low-dose rituximab could be as efficient as a standard dose.[32] Therefore, administering lower doses of rituximab seems more reasonable to reduce the risks of severe infection during the COVID-19 pandemics with controlling the disease.[33] Dermatologists should also consider IVIG in cases of severe AIBD when immunomodulation cannot be deferred. The drug has proven effective as an adjuvant treatment in both AIBDs and COVID-19.[13,34]

Regarding recommendations on biologics, American Academy of Dermatology (AAD) guidelines suggested that postponing rituximab treatment be considered on a case-by-case basis; when it comes to low-risk patients, but defer initiation of biologic therapy for high-risk patients.[26,29] All in all, the patient should not be left untreated because of the unreasonable fear of fatal outcomes.[35,36] Extra caution should be exercised when initiating rituximab or high-dose steroids, and most of these need decision-making of the physician on a case-to-case basis.

In the present study the number of vaccinated patients was small, as infections had occurred mostly before the start of the universal vaccination program of country. Despite the limited number of vaccinated patients, it was found that vaccine could lower COVID-19 severity. This finding suggests that although the underlying disease and immunosuppressive medications might reduce the immunogenicity of the vaccine, it can still prevent more severe cases.[37] All immunocompromised dermatology patients should be vaccinated against SARS-CoV-2, and clinicians should consider future vaccine schedule when prescribing immunotherapeutic agents.[38,39] It is preferred to vaccinate AIBD patients in remission phase of disease to boost its efficacy and lower the risk of disease flare post vaccine.[5,40]

This study also had limitations. First, many patients with COVID-19 are left undiagnosed, especially in mild cases, and therefore, the hospitalization rate may be overinflated. Second, there might be numerous unmeasured confounding factors due to the investigation's observational design that might affect COVID-19 outcome, including individual genetics, adherence to personal protection, and SARS-CoV-2 variant. Third, although diagnostic and therapeutic measures were performed according to the guidelines, it was to some extent dependent on the opinion of in charge physicians, which may cause potential misclassification of the COVID-19 severity scores. Despite these limitations, our findings build on the growing literature on risk factors and the course of COVID-19 in individuals with AIBDs. However, it may not be generalizable to other populations and countries, and caution should be exercised when interpreting our results. Further studies from different regions are advocated to better define the association between COVID-19 disease and AIBDs; precisely, the risk of rituximab should be weighed against its efficacy in AIBD patients. Moreover, serological studies following COVID-19 infection to determine the characteristics of the immune response to COVID-19 will be of great value.

5 | CONCLUSION

Findings in this study highlighted that AIBD patients receiving high-dose steroids and those with recent exposure to rituximab should be closely monitored. Moreover, vaccination could effectively prevent severe COVID-19 infection. Strict adherence to social distancing and following health principles while adhering to the therapeutic protocols recommended by experts would help patients overcome this pandemic healthy.

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