

Outcome of COVID-19 in patients with autoimmune bullous diseases

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Abstract

Background: Data on outcomes of Coronavirus disease 2019 (COVID-19) infection in autoimmune bullous diseases (AIBDs) patients is scarce.

Materials and methods: This single-centre survey-based-observational study included patients registered in the AIBD clinic of the Postgraduate Institute of Medical Education and Research, Chandigarh, India. All registered patients were contacted over telephone between June and October 2021. A survey was conducted after obtaining informed consent.

Results: Among 1389 registered patients, 409 completed the survey. Two hundred and twenty-two (55.3%) patients were females and 187 (45.7%) were males. The mean age was 48.52 ± 14.98 years. Active disease was reported by 34% patients. The frequency of COVID-19 infection in responders was 12.2% (50/409), with a case-fatality ratio of 18% (9/50). Rituximab infusion after the onset of pandemic significantly increased the risk of COVID-19 infection. Active AIBD and concomitant comorbidities were significantly associated with COVID-19 related death.

Limitations: Relative risk of COVID-19 infection and complications among AIBD patients could not be estimated due to lack of control group. The incidence of COVID-19 in AIBD could not be determined due to lack of denominator (source population) data. Other limitations include telephonic nature of the survey and lack of COVID-19 strain identification.

Conclusion: Use of rituximab is associated with higher probability of COVID-19 infection, while advanced age, active disease and presence of comorbidities may increase the risk of COVID-19 mortality in AIBD patients.

Key words: Autoimmune bullous disease, COVID-19, pemphigus, bullous diseases, rituximab

Plain Language Summary

It is unknown whether COVID-19 infection outcomes differ in AIBD patients compared to the general population. In this survey-based study, we enquired about the outcomes of COVID-19 infections from patients registered in our AIBD clinic at a tertiary care centre in Northern India. All registered patients were contacted between June and October 2021. Out of 1389 registered patients, 409 completed the survey. Patients who received rituximab after the onset of pandemic were at higher risk of acquiring COVID-19 infection. Patients with advanced age, active disease and concomitant comorbidities were at higher risk COVID-19 related mortality.

Introduction

As severe COVID-19 indicates a hyper-inflammatory state, there is concern that the presence of pre-existing autoimmune disease or the use of immunosuppressants may increase

the risk of severe COVID-19 infection.¹ AIBD, especially pemphigus vulgaris and bullous pemphigoid, are potentially life-threatening. The management of AIBD is exigent and often needs the administration of high-dose systemic

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corticosteroids and other immunosuppressants.² Optimisation of AIBD treatment during the COVID-19 pandemic requires clinicians to identify factors associated with poorer disease outcomes in COVID-19-positive AIBD patients and to understand whether these treatment modalities impact the overall prognosis of COVID-19 infection.

This telephonic survey was aimed to determine the impact of AIBDs on the susceptibility and outcome of COVID-19 infection.

Materials and Methods

Setting

This single-centre survey-based observational study was conducted on patients already registered in the AIBD clinic of the Department of Dermatology, Venereology & Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh. The study was initiated after obtaining approval from the Institutional Ethics Committee (intramural).

Methodology

All patients registered with our AIBD clinic were telephonically interviewed between June and October 2021. After obtaining informed consent (verbal initially, followed by filling out an e-consent form using Google-forms application), the patients were asked survey questions. Clinico-demographic parameters such as age, sex, diagnosis, duration of illness, comorbidities and habits of smoking or alcohol consumption were obtained from their clinical records. Other parameters, such as course and status of AIBD at the time of survey and current treatment regimens, as well as history pertaining to COVID-19 infection, were sought over a telephone conversation. We considered the number of patients with AIBD acquiring COVID-19 infection, frequency of complicated COVID-19 infections in AIBD patients, and frequency of flare/relapse episodes of AIBD during active COVID-19 infection as our outcome measures. Clinical details of patients who died due to COVID-19 infection were collected by reviewing their medical records and through history obtained from family members.

Statistical methods

Clinico-demographic characteristics and COVID-19 outcomes of the study population were summarized by descriptive statistics. Quantitative variables have been presented as mean, median (interquartile range, IQR), and count (percentage) as applicable. Logistic regression was used to estimate associations with adjustments for potential confounders. We considered $\alpha = 0.05$ as statistically significant.

Results

We attempted to contact all patients registered with our AIBD clinic telephonically ($n = 502$). Among them, 42 patients refused to answer our survey as they were in remission off therapy for a long duration; 19 patients refused informed consent, and 32 patients had died of various causes prior to

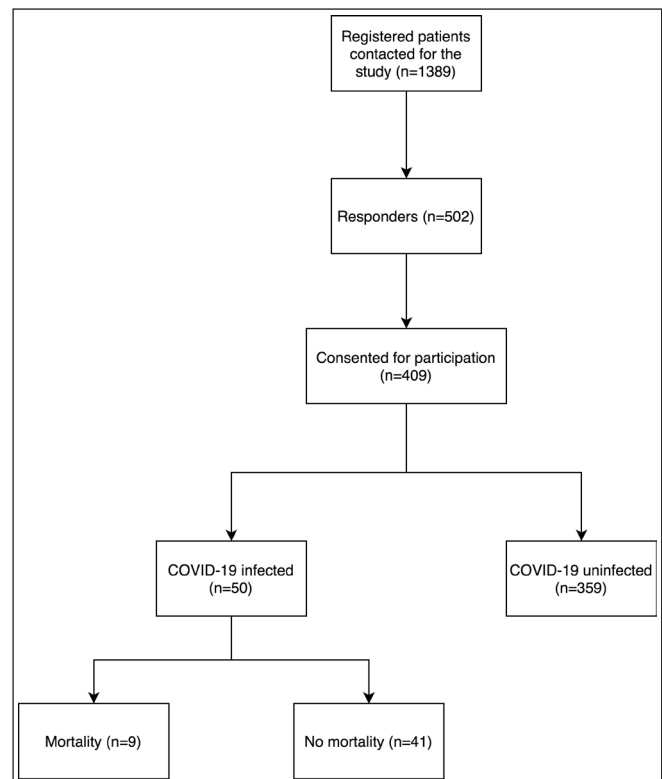


Figure 1: Number of patients at each step

the onset of pandemic. The remaining 409 patients or their attendants answered our survey [Figure 1]. We failed to contact the other patients due to incorrect phone numbers in their clinic files, or they failed to answer our calls (at least twice, on 2 different days).

Study participants

Among 409 responders, 222 (55.3%) patients were females and 187 (45.7%) were males. The mean age was 48.52 ± 14.98 years. The most frequent diagnoses were pemphigus vulgaris [281 (68.7%)], pemphigus foliaceus [19 (4.6%)], or bullous pemphigoid [33 (8.1%)]. Active disease at the time of answering the survey was reported by 34% patients. Eighty patients (19.5%) had received rituximab prior pandemic, while 220 (53.8%) patients received immunosuppression such as oral steroids/prednisolone or other steroid-sparing agents, including rituximab [30 (7.33%)] during the COVID-19 pandemic. Table 1 summarises the clinicodemographic profile of study participants.

COVID-19 and its outcomes in AIBD patients

Fifty patients (12.2%, $n = 409$) tested positive for COVID-19 before the survey. Of them, 17 (34%) patients were symptomatic, while the remaining 33 (66%) were incidentally detected. Only six (12%) patients reported a flare of AIBD lesions. Among 50 patients with confirmed COVID-19 infection, 31 patients (62%) were on some form of immunosuppression during the pandemic, including 10 (20%) patients who had received rituximab during the pandemic ($P < 0.05$). The average time period between rituximab infusion and

Table 1: Clinicodemographic profile of patients and summary of responses in AIBD teleconsultation survey (n = 409)

Parameter	Observed value
Age (mean ± SD), in years	48.52 ± 14.98 (5–89)
Gender	Males 187 (45.7%) Females 222 (55.3%)
History of regular alcohol intake	59 (14.4%)
History of smoking	24 (5.8%)
Comorbidities present	141 (34.5%)
Total number of comorbidities (n = 145)	Diabetes mellitus 58 Hypertension 79 Coronary artery disease 13 Thyroid disease 33 Chronic kidney disease 3 Active lung tuberculosis 1 Known lung disease except TB 3 Autoimmune disorder 3 Chronic liver disease 5
Diagnosis	Intraepidermal 302 (73.8%) Subepidermal 107 (26.1%)
AIBD disease status after onset of COVID-19 outbreak in India	Active and progressive 38 (9.3%) Active but non-progressive 66 (16.1%) In remission—on therapy 109 (26.7%) In remission—off therapy 161 (39.4%) Relapsing and remitting 35 (8.6%)
Active disease	Oral 101 (24.6%) Cutaneous 85 (19.5%) Mucocutaneous 45 (11%) Other mucosae 14 (3.4%)
Immunosuppressives/steroid sparing agents received prior to the pandemic (at any time during the course of disease, before March 2020)	Prednisolone 338 (82.6%) Azathioprine 115 (28.1%) Mycophenolate mofetil 11 (2.6%) Cyclophosphamide 41 (10%) Methotrexate 19 (4.6%) Rituximab 80 (19.5%) Omalizumab 3 (0.7%) Antibiotics 52 (12.7%)
Immunosuppressives/steroid sparing agents received during the pandemic (between March 2020 and the time of survey)	Prednisolone 208 (50.8%) Azathioprine 39 (9.5%) Mycophenolate mofetil 5 (1.2%) Cyclophosphamide 18 (4.4%) Methotrexate 9 (2.2%) Rituximab 30 (7.3%) IVIg 2 (0.48%) Antibiotics 24 (5.9%)
Immunosuppressives stopped during pandemic	Yes, by self without consultation 39 (17%) Yes, after consultation in at our clinic 24 (10.5%) Yes, after consultation elsewhere 17 (7.4%) No 149 (65.1%)
Tested positive for COVID-19	Yes 50 (12.2%)* No 359 (87.8%)

Parameter	Observed value
Mode of testing for COVID-19	Antigen testing 3 (6%) RT-PCR 44 (88%) CT-scan 2 (4%) Unaware of test used 4 (8%)
Suffered from symptoms of COVID-19	Yes 17 (34%) No 33 (66%)
Effect on AIBD	No lesions of AIBD 42 (84%) Flare of AIBD 6 (12%) Improvement of AIBD 2 (4%)
Medications for AIBD	Stopped 14 (28%) Continued, unaltered 20 (40%) Unsure 16 (32%)
Suffered from complications of COVID-19 requiring hospitalisation	17 (34%)
Reason for hospitalisation	Breathlessness 16 (32%) Thrombosis 1 (2%) Other organ dysfunction 1 (2%) Unsure 1 (2%)
Required ICU admission	13 (26%)
Required oxygen supplementation	17 (34%)
Required assisted ventilation (other than intubation)	9 (18%)
Required intubation	4 (8%)
Death due to COVID-19	9 (18%)

AIBD: autoimmune bullous disorder, SD: standard deviation, TB: tuberculosis, COVID-19: coronavirus disease 2019, RT-PCR: reverse transcriptase-polymerase chain reaction, CT scan: computed tomography scan, *data on viral variants (alpha, delta, omicron etc.) was not available

acquiring COVID-19 infection was 5.89 ± 6.01 weeks (1–20 weeks). On univariate analysis, AIBD patients receiving rituximab were 4.2 times more likely to acquire COVID-19 infection as compared to those not receiving any immunosuppression [OR: 4.263 (1.681–10.812), $P = 0.002$]. A total of 17 (34%) patients were hospitalised, all requiring oxygen supplementation, while nine (18%) required assisted ventilation (other than intubation) and 4 (8.5%) required intubation.

Nine patients (18%, n = 50) who tested positive for COVID-19 died of its complications. Four of these patients were on immunosuppressive therapy at the time of infection, including two patients who had received rituximab (lag period of 29 days and 14 days after infusion). Seven patients had other comorbidities (including hypertension, diabetes, thyroid disorder, coronary artery disease and carcinoma cervix). Active disease status during the pandemic, older age and concomitant comorbidities significantly increased the risk of death due to COVID-19 [Table 2]. Table 3 summarises the clinical data of patients who died due to COVID-19-related complications.

Discussion

Data on COVID-19 outcomes among patients with AIBD is not robust. Such patients may be at an added risk of acquiring infection due to chronic disease courses, requirement of

Table 2: Comparison between autoimmune bullous disease patients with fatal and non-fatal COVID-19 outcomes

Parameter (no. of patients)	Mortality (n = 9)	No mortality (n = 41)	P-value (Fisher's exact test)	Odds ratio (95% confidence interval)
Age (mean ± SD), in years	67.44 ± 11.99	47.61 ± 13.77	<0.001*	-
Continued follow up during lockdown (n = 23)	2 (22.2%)	21 (51.2%)	0.152	0.272 (0.50–1.470)
Presence of comorbidity (n = 21)	7 (77.7%)	14 (34.1%)	0.025	6.750 (1.235–36.908)
Disease status during pandemic				
Active and progressive (n = 5)	3 (33.3%)	2 (4.8%)	0.042 [#]	-
Active but non-progressive (n = 10)	0 (0%)	10 (24.3%)		
In remission- on therapy (n = 11)	1 (11.1%)	10 (24.3%)		
In remission- off therapy (n = 21)	5 (55.5%)	16 (39.0%)		
Relapsing and remitting (n = 3)	0 (0%)	3 (7.3%)		
Continued immunosuppression during the pandemic (n = 30)	4 (44.4%)	26 (63.4%)	0.454	0.462 (0.107–1.988)
Received rituximab during the pandemic (n = 9)	2 (22.2%)	7 (17.07%)	0.657	0.721 (0.123–4.229)

*Mann-Whitney U test, [#]post-hoc analysis revealed a significant association of mortality with the active and progressive disease only (adjusted Z-score >1.6)

Table 3: Clinical details of autoimmune bullous disorder patients who died due to COVID-19-related complications

Sr. No.	Age in years/sex	State	Diagnosis	Comorbidities	Alcohol/ smoking	Immunosuppressives in the past	Immunosuppressives during pandemic	Disease status during the pandemic	The month of getting COVID
1	80/M	Chandigarh	Pemphigus vulgaris	Diabetes mellitus, hypertension	No	Prednisolone, cyclophosphamide	None	Remission off therapy	December 2020
2	60/F	Haryana	Pemphigus vulgaris	Carcinoma cervix	No	Prednisolone, rituximab	None	Remission off therapy	October 2020
3	67/M	Chandigarh	Dermatitis herpetiformis	Coronary artery disease	No	Dapsone	None	Remission off therapy	April 2021
4	75/F	Punjab	Bullous pemphigoid	Diabetes mellitus, hypertension	No	None	None	Remission off therapy	March 2021
5	85/F	Chandigarh	Bullous pemphigoid	Hypothyroid, chronic kidney disease	No	Tetracycline	None	Remission off therapy	May 2021
6	65/F	Haryana	Bullous pemphigoid	Diabetes mellitus, hypertension	No	Prednisolone	Prednisolone	Active and progressive	December 2020
7	60/M	Haryana	Pemphigus vulgaris	Hypothyroidism	No	Prednisolone	Prednisolone	Remission on therapy	July 2020
8	45/M	Uttar Pradesh	Pemphigus vulgaris	None	Smoking	None	Prednisolone, cyclophosphamide, methotrexate and rituximab	Active and progressive	April 2021
9	70/M	Uttar Pradesh	Pemphigus vulgaris	None	Alcohol	None	Prednisolone, rituximab	Active and progressive	April 2021

frequent travel to healthcare facilities, and immunosuppression for the management of their primary disease.

A recent systematic review including a pooled total of 732 AIBD patients documented COVID-19 symptoms in 70 patients (9.5%), while the diagnosis of COVID-19 was confirmed in 16 (2.1%) patients.³ Six (0.8%) patients developed severe symptoms requiring hospital admission and three patients (0.4%) died of COVID-19, all being elderly with/without comorbidities.³ In our study, the frequency of confirmed COVID-19 infection (12.2%) and mortality (2.2%) were over five times higher. This may be attributed to the timing of our survey in October 2021, after the spread of the delta variant of COVID-19, which had higher transmissibility and mortality compared to the initial Alpha variant.^{4,5}

The rate of infection with coronavirus in AIBD patients in our study was 12.2%, with a case-fatality ratio of 18%, compared

to the incidence rate of 2.7% and case fatality ratio of 1.87% in the general population of our region (states of Punjab, Haryana, Himachal Pradesh and union territory of Chandigarh) during a similar time period (calculated as the total number of cases observed in these four states from March 2020 to 31st October 2021, divided by the total population of these states as per the last population census).⁶ Our data projects an unfavourable prognosis of COVID-19 in AIBD patients compared to normal population. Attributable risk could not be calculated due to the observational nature of the current study.

Advanced age, active disease during the lockdown, and presence of comorbidities were significantly associated with death due to COVID-19 infection. Association of mortality with disease activity may be explained by a higher risk of exposure to infection due to frequent hospital visits and a higher likelihood of receiving immunosuppressants. Comorbidities such as cardiovascular disease, diabetes, obesity, reduced

kidney function, and chronic liver disease are well-established risk-factors for death due to COVID-19.^{7,8} Seven of nine patients who died in the present study had at least one comorbidity; while the remaining two patients received rituximab for the active disease.

Administration of rituximab after the onset of pandemic in India was significantly associated with COVID-19 infection in our study. Similar observations were made by Joly *et al.* who noted a more than five-fold higher incidence of COVID-19 infection in AIBD patients who received rituximab compared to those not receiving rituximab.⁹ Observational outcome statistics have been encouraging for several immunosuppressants, however, data pertaining to rituximab is not as reassuring.¹⁰ Worsened primary disease and mortality after COVID-19 infection in patients receiving rituximab have been documented in rheumatological diseases.^{11,12} The most plausible mechanism by which rituximab impacts COVID-19 outcomes is blunting of humoral immunity. A study by Anderson *et al.* observed that after adjusting for comorbidities and various other confounding factors, the use of most immunosuppressant drugs was not associated with increased mortality.¹³ Rituximab, whether used for autoimmune conditions or cancer, however, increased the risk of COVID-19 mortality.¹³ The association between rituximab treatment and adverse COVID-19 outcomes did not reach statistical significance in our study, likely due to the limited number of patients receiving rituximab and very low number of observed mortality. Two out of nine patients who died due to COVID-19-related complications had received rituximab for AIBD.

Rituximab has been advocated as the first-line treatment for pemphigus by several international guidelines and a recent surge in the availability of affordable biosimilars immensely increased its use.^{2,14} A safe approach to rituximab therapy for AIBD during the pandemic must be formulated.

Our study has some limitations. The relative risk of COVID-19 infection and complications among AIBD patients could not be estimated due to lack of a control group. The incidence of COVID-19 in AIBD could not be determined due to lack of denominator (source population) data.

Despite the ongoing pandemic for last two years, the formulation of evidence-based guidelines for the management of AIBD during the pandemic has been difficult due to the scarcity of data on COVID-19 outcomes in this population. This study has a clear relevance in this context as it is among the largest studies of COVID-19 in AIBD patients and is the only such study from the Indian subcontinent.

Conclusion

Use of rituximab increases the odds of acquiring COVID-19 infection, while advanced age, active disease status for AIBD, and presence of comorbidities may increase the risk of mortality due to COVID-19.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest

There are no conflicts of interest.

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