



Managing ANCA-associated vasculitis during COVID-19 pandemic: a single-center cross-sectional study

Joydeep Samanta¹ · GRSNK Naidu¹ · Prateek Deo¹ · Sakshi Mittal¹ · Chandra Bhushan Prasad¹ · Diganta Das¹ · Varun Dhir¹ · Shefali Khanna Sharma¹ · Raja Ramachandran² · Manish Rathi² · Ritambhara Nada³ · Ranjana W. Minz⁴ · Sanjay Jain¹ · Aman Sharma¹

Received: 20 April 2022 / Accepted: 22 July 2022 / Published online: 2 August 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract

The objective of the study is to report the outcomes of COVID-19 in ANCA-associated vasculitis (AAV) patients. This was a registry-based observational study conducted at a tertiary care center in north India. AAV patients with at least one follow-up visit between March 2020 and September 2021 were included. Demographic features, clinical manifestations, disease activity, and treatment details of underlying AAV were noted in all patients. Details of COVID-19 infection including severity, treatment, and outcomes were noted. Predictors of COVID-19 severity were determined using univariate analysis. A total of 33 (18.3%) out of 180 AAV patients contracted COVID-19 infection. Moderate COVID-19 infection was seen in 33.3% and severe or critical infection was seen in 36.3% of patients. Seventeen patients (51.5%) required supplemental oxygen therapy. Nine patients had active disease at the time of COVID-19 infection and three of them died due to COVID-19 infection. The risk of COVID-19 infection and its severity did not differ between patients receiving different immunosuppressants including rituximab induction. Hypothyroidism ($p=0.046$) and ocular ($p=0.038$) involvement due to AAV predicted the development of moderate to severe/critical COVID-19. Three (9.1%) patients died from COVID-19 and the rate of AAV flare after COVID-19 was similar to that in non-COVID-19 patients (15.3/100 person-year vs. 15.6/100 person-year, $p=0.95$). Majority of the patients with AAV had moderate to severe or critical COVID-19 infection. The rate of death due to COVID-19 in AAV is higher than in general population. Use of standard remission induction regimens did not lead to increased risk of COVID-19 infection in our AAV cohort.

Keywords ANCA-associated vasculitis · Sars-cov-2 · Rituximab · Cyclophosphamide

Background

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-related Coronavirus disease 2019 (COVID-19) has posed challenges in the management of autoimmune rheumatic disease (AIRD) patients. Patients with AIRDs are at increased risk of various infections both due to the various immunosuppressive drugs used to control the disease manifestations and due to the immune dysregulation seen in these patients due to underlying AIRD [1]. Hence the ongoing COVID-19 pandemic has created a great dilemma for clinicians treating various AIRDs, especially life-threatening diseases like anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) which has been well recognized over past year [2]. Data from the OpenSAFELY database have shown that the mortality is definitely higher in patients with AIRDs compared to general population [3]. Besides

Joydeep Samanta and GRSNK Naidu have contributed equally as first author.

✉ Aman Sharma
amansharma74@yahoo.com

- 1 Clinical Immunology and Rheumatology Unit, Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India
- 2 Department of Nephrology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
- 3 Department of Histopathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India
- 4 Department of Immunopathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

most of the available data till now show that patients with AIRDs definitely have slightly higher risk of developing COVID-19 infection too [4–6].

AAV are a type of primary systemic small vessel vasculitis that are associated with very high morbidity and mortality if not treated appropriately. In patients with systemic manifestations of AAV, high-dose glucocorticoids along with cyclophosphamide or rituximab are commonly used for achieving disease remission [7]. Rituximab is also the preferred agent to maintain remission in these patients [7, 8]. However, some studies have shown that AIRD patients receiving rituximab had adverse outcomes in COVID-19 thus further complicating the situation [9–11]. Recently, data from COVID-19 Global Rheumatology Alliance Physician registry (C19 GRA) have been published describing outcomes of COVID-19 in primary systemic vasculitis patients [12]. However, it did not address the question of optimal management strategy for the patients who presents with life-threatening active vasculitis along with COVID-19 infection. A retrospective analysis of outcomes after remission induction of AAV during COVID-19 has been published recently [13]. But no study of treatment outcomes in a vasculitis cohort at different stages of therapy (induction/maintenance) has been published till date to the best of our knowledge. In the present study, we describe a cohort of AAV patients that developed COVID-19 and present their outcomes from a single tertiary care center in India.

Methodology

This was an Indian Vasculitis Registry (INVAR)-based observational study conducted at a tertiary care center in north India conducted between March 2020 and September 2021. INVAR is a prospective registry for systemic vasculitis that was established in 2018 and had been cleared by the Institute Ethics Committee (IEC).

Patients

Patients were diagnosed to have granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) or eosinophilic granulomatosis with polyangiitis (EGPA) according to the American College of Rheumatology (ACR) criteria or, Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides 2012 (CHCC2012) definitions or, European Medical Agency (EMA) algorithm. Patients with at least one follow-up visit, either physically or telephonically, during the study period were included in this study. The details of organ manifestations, treatment used, and disease activity as measured by BVASv3 at each visit were noted from the INVAR registry for all the patients. The regimen for remission induction and maintenance at

initial presentation and during follow-up was at the treating physicians' discretion and patients' preference and included use of glucocorticoids (GC) and GC sparing immunosuppressants-like rituximab, cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil. The patients were followed-up every 2–4 weeks during induction phase and every 3–6 months during maintenance phase. Since the onset of COVID-19 pandemic, patients were followed-up through teleconsultation services and called for physical consultation if required, as per the prevailing institute policy.

AAV patients who tested positive for SARS-CoV2 reverse transcriptase polymerase chain reaction (RT-PCR) or rapid antigen test for SARS-CoV2 antigen were included under COVID-19-AAV group and rest of the patients were included under non-COVID-19 group.

Patient assessment

COVID-19-AAV group

Details of AAV treatment and disease activity as measured by BVASv3 at the time of acquiring COVID-19 infection and the modification of immunosuppression during COVID-19 infection were noted in all patients. Details of COVID-19 severity, treatment received, outcomes of COVID-19 infection, and SARS-CoV2 vaccination were noted in all the patients. Severity of COVID-19 infection was classified as mild (without pneumonia/hypoxia), moderate (pneumonia with $SpO_2 \geq 90\%$ at room air), severe (pneumonia with $SpO_2 < 90\%$ at room air or respiratory rate > 30 breaths/min or severe respiratory distress), and critical (acute respiratory distress syndrome/ARDS) as per World Health Organization (WHO) definitions [14]. Details of AAV disease activity post-COVID-19 infection recovery were noted during follow-up.

Non-COVID-19 group

Details of AAV disease activity, treatment regimens, outcomes and disease flares were noted in all patients.

Definition of AAV flare

Flare was defined as BVASv3 score of ≥ 1 any time after achieving remission (BVASv3 score of 0).

Statistical analysis

Continuous variables were presented as median with range. Categorical variables were presented as proportions and percentages. Non-parametric tests were used to compare variables like Fisher's exact test or chi-squared test for

categorical variables and Mann–Whitney *U* test for continuous variables. Univariate analysis was performed to predict the factors associated with severity of COVID-19. For this, covariates were chosen a priori based on the available data like various organ involvement of AAV, use of various immunosuppressant and other known predictors of severe COVID-19 infections like gender and various comorbidities. Statistical analysis was done using SPSS software version 25 (IBM Corp, New York, USA). *p* value < 0.05 was considered significant.

Results

Out of 280 AAV patients registered in INVAR, 100 patients were excluded from the study. The reasons for exclusion were death before March 2020 (19 patients), no follow-up during study period (80 patients) and new onset GPA after recovery from COVID-19 infection (one patient). A total of 180 patients were included in the study out of which 33 (18.3%) patients were included in COVID-19-AAV group and 147 (81.7%) patients were included in non-COVID-19 group.

The median age of the patients was 45 (range:14–85) years and females constituted 61.7%. GPA was the most common type of AAV, diagnosed in 85.6% patients. Ear, nose and throat (66.7%), lung (63.9%), and eye (47.2%) were the common organs involved due to AAV. ENT, ocular involvement was significantly more in GPA compared to MPA or, EGPA. Pulmonary involvement was commonest in GPA followed by MPA and EGPA. Renal involvement was commonest in MPA followed by GPA and EGPA. Among the nervous system manifestation, central nervous system manifestation was seen in both GPA and EGPA while it was absent in MPA and peripheral nervous system manifestations was more common in EGPA. During the study period, 45 patients received remission induction therapy for either newly diagnosed AAV or relapse of AAV and 100 patients received at least one dose of rituximab therapy as a part of remission induction or, maintenance therapy. There was no significant difference in number of patients who received remission induction therapy or, at least a single dose of rituximab in the study period between all three types of AAV namely GPA, MPA, and EGPA.

Table 1 shows the baseline clinical features of the study cohort. Baseline features of different subtypes of AAV have been shown in supplementary table S1.

COVID-19 infection

A total of 33 (18.3%) patients contracted COVID-19 infection between March 2020 and September 2021. All of them had a diagnosis of GPA except one patient with EGPA. The

median age of the patients was 50 years (range 22–72) and females constituted 60.6%. Nine (27.3%) patients had active vasculitis at the time of developing COVID-19 infection and the rest were in remission. Two patients were partially vaccinated with SARS-CoV2 vaccines before developing COVID-19 infection and the rest were unvaccinated. Twelve (36.4%) patients were managed with home isolation and the rest were admitted at the nearest COVID-19 care center including our center. Ten patients (30.3%) had mild/asymptomatic COVID-19 disease while 11 patients (33.3%) had moderate COVID-19 infection. Severe or critical infection was seen in 12 patients (36.3%). Median age of the patients with severe/critical COVID-19 was 51 years (range 27–72) and 75% of them were female. Seventeen patients (51.5%) required supplemental oxygen therapy. Twenty-one (66.6%) patients had one or more comorbid illnesses other than AAV. Majority (81.8%) of the patients received glucocorticoids for COVID-19 management.

All patients, except one, were receiving immunosuppression including glucocorticoids for underlying AAV when they contracted COVID-19. Twenty-three patients were receiving glucocorticoids at the time of acquiring COVID-19 and the median dose was 5 mg/day of prednisolone or its equivalent. In all these 23 patients during COVID-19 infection, glucocorticoid was continued either at the same dose or, dose was hiked depending on COVID-19 severity. Six patients were receiving methotrexate, two patients were receiving azathioprine and 19 patients received one or more doses of rituximab in the preceding 1 year. Methotrexate and azathioprine were withheld at the time of COVID-19 infection and was restarted after recovery from COVID-19 illness. Among the 19 patients who received rituximab, six patients received rituximab as part of remission induction in the 6 months preceding the development of COVID-19 infection. Among the 19 patients who received rituximab in the last 1 year, 10 (52.6%) had mild to moderate COVID-19 infection while nine (47.4%) patients had severe to critical COVID-19 infection. Among the 14 patients who did not receive rituximab, 11 (78.6%) had mild to moderate COVID-19 infection and 3 (21.4%) had severe COVID-19 infection. Demographic and clinical details of COVID-19-AAV group are given in Table 2. Nine patients had active vasculitis when they developed COVID-19 infection. One patient expired before initiating therapy for AAV and one patient developed COVID-19 within 1 week of receiving rituximab for remission induction and succumbed to COVID-19 infection. In the other seven patients, glucocorticoids were started for vasculitis control and remission induction therapy was initiated after recovery from COVID-19. In one patient with severe glomerulonephritis and diffuse alveolar hemorrhage, intravenous immunoglobulins (IVIg) and plasma exchange (PLEX) were initiated for control of vasculitis and after recovery from COVID-19, rituximab was used for remission

Table 1 Demographic details of entire AAV cohort

Category	Entire cohort	COVID-19- AAV group	Non- COVID-19 group	<i>p</i> value
Total number of AAV patients under active follow-up	180	33	147	
Age (years) (range)	45 (14–85)	50 (22–72)	44 (14–85)	0.119
Females (%)	61.7	60.6	61.9	1.0
GPA, <i>n</i> (%)	154 (85.6)	32 (96.9)	122 (82.9)	0.052
MPA, <i>n</i> (%)	17 (9.4)	0 (0.0)	17 (11.6)	0.045
EGPA, <i>n</i> (%)	9 (5.0)	1 (3.0)	8 (5.4)	1.0
Organ involvement, <i>n</i> (%)				
ENT	120 (66.7)	25 (75.8)	95 (64.6)	0.307
Ocular	85 (47.2)	12 (36.4)	73 (49.6)	0.182
Mucocutaneous	35 (19.4)	4 (12.1)	31 (21.1)	0.332
Musculoskeletal	48 (26.7)	16 (48.5)	32 (21.8)	0.004
Gastrointestinal	17 (9.4)	2 (6.1)	15 (10.2)	0.742
Cardiovascular	11 (6.1)	1 (3.0)	10 (6.8)	0.692
Central nervous system	18 (10.0)	2 (6.1)	16 (10.9)	0.534
Peripheral nervous system	21 (11.7)	3 (9.1)	18 (12.2)	0.77
Pulmonary	115 (63.9)	21 (63.6)	94 (63.9)	1.0
Renal	60 (33.3)	10 (30.3)	50 (34.0)	0.838
Patients received remission induction therapy during study period, <i>n</i> (%)	45 (25)	7 (21.2)	38 (25.9)	0.823
Remission induction regimen used				
Glucocorticoids	45	7 (21.2)	38 (25.9)	0.823
Cyclophosphamide	17	2 ^a (6.1)	15 (10.2)	0.077
Rituximab	23	5 (15.2)	18 (12.2)	0.773
Methotrexate	2	0 (0.0)	2 (1.4)	1.0
MMF	2	0 (0.0)	2 (1.4)	1.0
MMF + Tofacitinib	1	0 (0.0)	1 (0.7)	1.0
Received one or more doses of rituximab after March 2020, <i>n</i> (%)	100 (55.6)	19 (57.6)	81 (55.1)	0.848

^aTwo patients received cyclophosphamide after recovery from COVID-19 infection and have been excluded from Fisher's exact test

AAV ANCA-associated vasculitis, GPA granulomatosis with polyangiitis, EGPA eosinophilic granulomatosis with polyangiitis, MPA microscopic polyangiitis, ENT Ear-nose-throat, MMF mycophenolate mofetil

induction. Clinical details of these nine patients are provided in Table 3.

Outcomes

A total of three (9.1%) patients died after developing COVID-19 infection. Two patients died while being admitted with COVID-19 infection while one patient expired on follow-up after recovery from COVID-19 infection and the cause of death could not be ascertained. During the same period, six deaths (4.1%) were observed among 147 AAV patients who did not develop COVID-19 infection. Three (9.1%) patients had flare of AAV following recovery from COVID-19, giving a relapse rate of 15.3/100 person-year. A total of 33 relapses not attributable to COVID-19 were noted in the entire cohort, eight in COVID-19 positive

group before they tested positive for COVID-19 and 25 in the non-COVID-19 group. This gives a relapse rate of 15.6/100 person-years, which is similar to that noted post-COVID-19 ($p = 0.95$). Details of vasculitis relapse in COVID-19-AAV and non-COVID-19 groups are given in supplementary tables S2 and S3.

Predictors of COVID-19 infection and its severity

The incidence of COVID-19 infection was similar between patients receiving rituximab and not receiving rituximab (19 vs 17.5%; $p = 0.796$). Among the patients who received induction therapy, the risk of COVID-19 infection was similar between the patients receiving rituximab and the patients receiving other immunosuppressants ($p = 0.242$). Rituximab therapy was associated with higher odds of developing

Table 2 Details of COVID-19 illness in AAV cohort

AAV patients contracting COVID-19 infection, <i>n</i>	33
Age in years, median, (range)	50 (22–72)
Female, <i>n</i> (%)	20 (60.6)
COVID severity as per WHO definition, <i>n</i> (%)	
Mild/asymptomatic	10 (30.3)
Moderate	11 (33.3)
Severe	8 (24.2)
Critical	4 (12.1)
Comorbidities, <i>n</i> (%)	
Diabetes mellitus	7 (21.2)
Hypertension	10 (30.3)
Chronic kidney disease	7 (21.2)
Hypothyroidism	5 (15.2)
Obstructive airway disease	2 (6.1)
Coronary artery disease	1 (3.0)
Details of COVID symptoms, <i>n</i> (%)	
Asymptomatic	2 (6.0)
Fever	29 (87.9)
Cough	18 (54.5)
Shortness of breath	12 (36.4)
Sore throat	10 (30.3)
Headache/body ache/myalgia	7 (21.2)
Details of treatment for COVID-19	
Glucocorticoids	27 (81.8)
Remdesivir	4 (12.1)
Tocilizumab	1 (3.0)
Monoclonal antibody	1 (3.0)
Requiring supplemental oxygen therapy, <i>n</i> (%)	17 (51.5)
Active AAV at the time of COVID-19 infection, <i>n</i> (%)	9 (27.3)
Death, <i>n</i> (%)	3 (9.1)
Median dose of prednisolone at the time of COVID-19 infection (mg) (range)	5 (0–50)

AAV ANCA-associated vasculitis, WHO World Health Organization

severe or critical COVID-19 disease, but this increased risk was not statistically significant (odds ratio = 3.3; 95% CI 0.692, 15.74; $p = 0.16$). A univariate analysis was performed using various factors to predict the severity of COVID-19 infection. The presence of hypothyroidism ($p = 0.046$) and ocular involvement due to AAV ($p = 0.038$) predicted the development of moderate to severe or critical COVID-19 infection. Table 4 shows the various factors included in the univariate analysis. Among the 45 patients who received induction therapy during the study period, seven (15.5%) patients developed COVID-19 infection and there was no difference in the rate of COVID-19 infection with respect to the induction regimen used ($p = 0.411$).

Significantly higher number of patients with musculoskeletal manifestations due to AAV developed COVID-19 infection (32.7 vs 13%; $p = 0.004$). No significant difference

was noted with renal ($p = 0.838$), pulmonary ($p = 1.0$), ENT ($p = 0.227$), ocular ($p = 0.337$), neurological ($p = 0.481$) involvements, gender ($p = 1.0$), use of induction therapy ($p = 0.662$) or rituximab ($p = 0.848$) after onset of pandemic.

Discussion

In this INVAR registry-based observational study, we describe the clinical features, treatment regimens used, and the outcomes of COVID-19 infection among patients with AAV. The prevalence of COVID-19 among the 180 AAV patients included in our study up to September 2021 was 18.3%. Only one-third of the patients had mild/asymptomatic COVID-19 infection while 51.5% patients needed oxygen therapy and 9.1% patients died after developing COVID-19.

At the onset of COVID-19 pandemic, it was believed that patients with comorbidities and on immunosuppression are at higher risk of acquiring COVID-19 and developing severe COVID-19 infection. This created dilemma in the minds of physicians treating chronic life-threatening inflammatory diseases like AAV and systemic lupus erythematosus, whether to treat active disease with high-dose immunosuppression or to treat them with modified regimens that decrease the risk of infections. Findings of the COVID-19 Global Rheumatology Alliance physician registry, which included 353 patients with AAV, showed that patients receiving glucocorticoids at a dose ≥ 10 mg/day of prednisolone or its equivalent, moderate to high disease activity and more comorbidities had adverse COVID-19 outcomes [12].

Nimmo et al. reported the use of adapted regimens with oral azathioprine (two patients) or oral cyclophosphamide (one patient) along with glucocorticoids for remission induction in AAV patients during the COVID-19 pandemic [15]. They reported that two out of the eight patients receiving oral or intravenous cyclophosphamide developed COVID-19 infection and both these patients died of the virus. Thus, they concluded that adapted remission regimens might be beneficial in some patients with AAV in reducing the development of COVID-19 infection. However, data from larger cohort by Salas et al. have contradicted this hypothesis by showing that there was no difference in susceptibility to COVID-19 among patients receiving rituximab or cyclophosphamide for remission induction and concluded that standard regimens need to be continued for optimal management of AAV [10]. Out of 191 patients included in their study, 16 (8.4%) patients developed COVID-19 infection. Similar rate (11.6%) of COVID-19 infection was noted in our cohort among the patients receiving induction therapy. Also, in our cohort, there was no significant difference in the rate of COVID-19 infections with respect to the induction regimen, similar to that reported by Salas et al. Besides, barring the

Table 3 Details of AAV patients who had active vasculitis at the time of COVID-19 illness

Serial	Organ involvement	New or relapsing disease	BVASv3	Severity of COVID-19	Treatment for active disease
Patient 1	Constitutional, scleritis, arthralgia, vasculitic skin rash, sino-nasal disease, RPRF, DAH	New	29	Severe	Glucocorticoid, IVIG, plasma exchange followed by rituximab
Patient 2	Renal dysfunction, proteinuria	Relapsing	12	Moderate	Glucocorticoid followed by rituximab
Patient 3	Necrotizing scleritis	Relapsing	2	Moderate	Glucocorticoid
Patient 4	Pulmonary nodules, cavities, arthralgia	New	4	Mild	Glucocorticoid followed by cyclophosphamide
Patient 5	Sino-nasal disease, episcleritis, RPRF	New	12	Mild	Glucocorticoid followed by Cyclophosphamide
Patient 6	Constitutional, nasal crusting, sensorimotor neuropathy	Relapsing	12	Critical	Succumbed to COVID-19
Patient 7	Constitutional, pseudotumor of kidney	Relapsing	2	Critical	Succumbed to COVID-19
Patient 8	Pulmonary nodules	Relapsing	3	Moderate	Glucocorticoid followed by rituximab
Patient 9	RPRF	Relapsing	6	Severe	Glucocorticoid followed by rituximab

AAV ANCA-associated vasculitis, *BVASv3* Birmingham vasculitis activity score version 3, *DAH* Diffuse alveolar hemorrhage, *RPRF* rapidly progressive renal failure, *IVIG* Intravenous immunoglobulin

Table 4 Details of univariate analysis to predict the severity of COVID-19 infection in AAV patients

Parameter	<i>p</i> value
Active AAV	0.350
Glucocorticoids > 10 mg/day	0.480
Rituximab use	0.430
Methotrexate use	0.722
Any comorbid illness	0.193
Diabetes mellitus	0.761
Hypertension	0.419
Hypothyroidism	0.046 ^a
Chronic kidney disease	0.603
Gender	0.635
Renal involvement due to AAV	0.594
Lung involvement due to AAV	0.767
ENT involvement due to AAV	0.923
Musculoskeletal involvement due to AAV	0.050
Ocular involvement due to AAV	0.038 ^a
Neurological involvement due to AAV	0.883

AAV ANCA-associated vasculitis

^aPredictors of moderate to severe or critical COVID-19 infection

two patients who expired due to severe/critical COVID-19 illness, all patients with active vasculitis and concomitant COVID-19 infection were successfully managed by steroid (adjunct IVIG and PLEX in one patient) initially and addition of immunosuppression (rituximab/cyclophosphamide) after recovery from COVID-19 infection.

The number of patients not requiring hospitalization (36.4%) and the number of patients requiring oxygen supplementation (51.5%) were similar to that reported by Sattui

et al. Nearly one-third of the patients in our cohort had severe or critical COVID-19 infection and Sattui et al. also reported that 30.3% of the patients needed mechanical ventilation or oxygen support. Despite these characteristics being similar, the mortality rate (9.1%) in our cohort was much lower than that reported from elsewhere. Salas et al. reported that 25% of the patients died of the virus in their cohort of 16 patients while Sattui et al. reported that 22.1% of the patients died of COVID-19 infection in the COVID-19 GRA registry. This difference could be due to the differences in the baseline characteristics of the patients included in the different studies along with a small sample size of our study. The study by Salas et al. included AAV patients that received induction therapy during the pandemic period indicating that all the patients having active disease and receiving high-dose immunosuppression, both of which are known to adversely affect the COVID-19 outcomes. In our study, majority of the patients were in remission and receiving low dose maintenance immunosuppression at the time of acquiring COVID-19 infection, which might have resulted in better COVID-19 outcomes. Also, the overall death rate from COVID-19 in India is much lower than the worldwide death rate, indicating that there might be some racial and genetic factors contributing to the COVID-19 outcomes in different parts of the world [16].

In our cohort, the presence of hypothyroidism and ocular involvement due to AAV associated with the severity of COVID-19 infection with majority of the patients with hypothyroidism and ocular involvement developing moderate to severe or critical COVID-19 infection. In two recent systematic review by Premana et al. and Damara et al. pre-existing thyroid disorder was found to be associated with adverse COVID-19 outcome [17, 18]. Our study also had similar findings. However, ocular involvement due to AAV was not found

to be associated with adverse COVID-19 outcome in the previous studies. This finding can be due multiple reasons. First, we had very small sample size. Besides, among the 33 patients of AAV who contracted COVID-19 infections, 12 patients had ocular involvement. Among these 12 patients, eight patients (66.6%) received at least one dose of rituximab during study period and four patients had glucocorticoid dose > 10 mg/day at the time of contracting COVID-19 infection. These background immunosuppression can also be postulated as a possible reason for the finding of ocular involvement being associated with adverse COVID-19 outcome. Sattui et al. have reported that older age, rituximab use, cyclophosphamide use, moderate to high disease activity and the presence of underlying chronic kidney disease were associated with worse COVID-19 outcomes. We could not perform such analysis in our cohort due to very small number of patients (three) died due to COVID-19. Similar to that reported by Salas et al. there was no major change in the induction regimen used in our patients with active vasculitis during the COVID-19 pandemic. Although rituximab use was associated with higher odds of severe or, critical COVID-19 disease, it did not reach statistical significance which might be due to small sample size of our study. Overall, there was no difference in the rate of COVID-19 infection with respect to the induction regimen used in our cohort.

The major limitation of our study would be the selection bias. Some patients who might have been managed at local COVID-19 care centers and had adverse COVID-19 related outcomes might have been missed from the analysis. Besides, small sample size was another concern which might be responsible for not finding association of COVID-19 severity with various comorbidities or, immunosuppressants-like rituximab unlike previous studies.

Conclusion

To conclude, this study showed that AAV patients had higher COVID-19 related mortality compared to general population. The presence of hypothyroidism and underlying ocular involvement due to AAV was associated with the development of severe COVID-19 infection in this cohort. The use of standard remission induction regimens was not associated with increased risk of COVID-19 infection in our cohort, hence adequate control of vasculitis needs to be prioritized. Use of glucocorticoids during active COVID-19 infection with the use of standard induction regimens after recovery from COVID-19 infection can be an effective strategy in AAV patients with severe vasculitis and concomitant COVID-19 infection.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00296-022-05177-2>.

Author contributions AS, GSRSNKN, and JS planned the study; AS, GSRSNKN critically reviewed the study proposal; JS, PD, SM, CBP, and DD Collected data; AS, GSRSNKN, VD, SKS, MR, RR, RN, RWM, SJ, JS, PD, SM, CBP, and DD provided and cared for the study patients; AS, GSRSNKN, VD, SKS, MR, RR, RN, RWM, and SJ served as scientific advisor.

Funding None of the authors has any financial disclosure or funding sources.

Declarations

Ethical approval Ethically cleared by Institutional Ethics Committee.

References

- Atzeni F, Bendtzen K, Bobbio-Pallavicini F, Conti F, Cutolo M, Montecucco C et al (2008) Infections and treatment of patients with rheumatic diseases. *Clin Exp Rheumatol* 26(1 Suppl 48):S67–S73
- Kopp CR, Naidu G, Misra DP, Deo P, Jakulla RS, Mankan K et al (2021) Managing ANCA-associated vasculitis during the COVID-19 pandemic: results from an online survey. *Rheumatol Int* 41(11):1941–1947
- Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE et al (2020) Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 584(7821):430–436
- England BR, Roul P, Yang Y, Kalil AC, Michaud K, Thiele GM et al (2021) Risk of COVID-19 in rheumatoid arthritis: a national veterans affairs matched cohort study in at-risk individuals. *Arthritis Rheumatol* 73(12):2179–2188
- Grainger R, Kim AHJ, Conway R, Yazdany J, Robinson PC (2022) COVID-19 in people with rheumatic diseases: risks, outcomes, treatment considerations. *Nat Rev Rheumatol* 18(4):191–204
- Conway R, Grimshaw AA, Konig MF, Putman M, Duarte-García A, Tseng LY et al (2021) SARS-CoV-2 infection and COVID-19 outcomes in rheumatic diseases: a systematic literature review and meta-analysis. *Arthritis Rheumatol*. <https://doi.org/10.1002/art.42030>
- Chung SA, Langford CA, Maz M, Abril A, Gorelik M, Guyatt G et al (2021) 2021 American college of rheumatology/vasculitis foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol* 73(8):1366–1383
- Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P et al (2014) Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 371(19):1771–1780
- Zen M, Fuzzi E, Astorri D, Saccon F, Padoan R, Ienna L et al (2020) SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: a cross-sectional study on 916 patients. *J Autoimmun* 112:102502
- Daoussis D, Leonidou L, Kalogeropoulou C, Paliogianni F, Tzouvelekis A (2021) Protracted severe COVID-19 pneumonia following rituximab treatment: caution needed. *Rheumatol Int* 41(10):1839–1843
- Andersen KM, Bates BA, Rashidi ES, Olex AL, Mannon RB, Patel RC et al (2022) Long-term use of immunosuppressive medicines and in-hospital COVID-19 outcomes: a retrospective cohort study using data from the national COVID cohort collaborative. *Lancet Rheumatol* 4(1):e33–e41

12. Sattui SE, Conway R, Putman MS, Seet AM, Gianfrancesco MA, Beins K et al (2021) Outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica from the COVID-19 global rheumatology alliance physician registry: a retrospective cohort study. *Lancet Rheumatol*. [https://doi.org/10.1016/S2665-9913\(21\)00316-7](https://doi.org/10.1016/S2665-9913(21)00316-7)
13. Salas A, Kant S, Floyd L, Kratky V, Brix SR, Predecki M et al (2021) ANCA vasculitis induction management during the COVID-19 pandemic. *Kidney Int Rep* 6(11):2903–2907
14. Clinical management of COVID-19 : Living guidance. WHO/2019 nCoV/clinical/2021.1.
15. Nimmo A, Risdale S (2021) Adapted treatment of ANCA-associated vasculitis during the COVID-19 pandemic. *Rheumatol Adv Pract* 5(2):rkab041
16. <https://www.worldometers.info/coronavirus/#countries>. Accessed on 11–01–2022.
17. Damara FA, Muchamad GR, Ikhsani R, Hendro, Syafiyah AH, Bashari MH (2021) Thyroid disease and hypothyroidism are associated with poor COVID-19 outcomes: a systematic review, meta-analysis, and meta-regression. *Diabetes Metab Syndr* 15(6):102312
18. Permana H, Soeriadi EA, Damara FA, MulyaniSoetedjo NN (2022) The prognostic values of thyroid disorders in predicting COVID-19 composite poor outcomes: a systematic review and meta-analysis. *Diabetes Metab Syndr* 16(5):102464

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.