DR. MATTHEW ALEXANDER RUTHERFORD (Orcid ID : 0000-0001-5626-2470)
DR. MARILINA ANTONELOU (Orcid ID : 0000-0001-6653-7511)
DR. SEERAPANI GOPALUNI (Orcid ID : 0000-0002-1584-6186)
DR. NEERAJ DHAUN (Orcid ID : 0000-0001-9128-6603)
DR. STEPHEN MCADOO (Orcid ID : 0000-0001-8260-8770)
DR. NEIL BASU (Orcid ID : 0000-0003-4246-3145)

Article type : Full Length

Risk factors for severe outcomes in patients with systemic vasculitis & COVID-19: a bi-national registry-based cohort study

Matthew A Rutherford, MBChB, MRCP,* Jennifer Scott, MRCPI,* Maira Karabayas, MBChB, MRCP, Marilina Antonelou, MBBS, PhD, Seerapani Gopaluni, MBBS, MRCP(Nephrology), David Gray, BSc, Joe Barrett, BA, Silke R Brix, MD, MRCP, Neeraj Dhaun, MD, PhD, Stephen P McAdoo, MBBS, PhD, Rona M Smith, MD, MRCP, Colin Geddes, FRCP(Glas), David Jayne, MD, FMedSci, Raashid Luqmani, DM, FRCP, FRCPE, Alan D Salama, PhD, FRCP, Mark Little, PhD, Neil Basu, MD, PhD

On behalf of UKIVAS

* These authors contributed equally

[1]Institute of Infection, Immunity and Inflammation, University of Glasgow, UK.
[2]Glasgow Renal and Transplant Unit, Queen Elizabeth University Hospital, Glasgow, UK.
[3]Trinity Health Kidney Centre, Trinity Translational Medicine Institute, Trinity College Dublin, Ireland.
[4]Aberdeen Centre for Arthritis & Musculoskeletal Health, University of Aberdeen, UK.
[5]Department of Rheumatology, Aberdeen Royal Infirmary, Aberdeen, UK.
[6]Department of Nephrology and Transplantation, Royal Free London NHS Foundation Trust, London, UK.
[7]Department of Renal Medicine, Royal Free Campus, UCL, London, UK.

[8]Department of Medicine, University of Cambridge, Cambridge, UK.
[9]Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK.
[10]Nuffield Department of Orthopedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK.
[11]Division of Cardiovascular Science, University of Manchester, UK.
[12]Renal, Transplantation and Urology Unit, Manchester Royal Infirmary, Manchester University Hospitals National Health Service Foundation Trust, Manchester, UK.
[13]Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, UK.
[14]Department of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK.
[15]Renal and Vascular Inflammation Section, Department of Medicine, Imperial College London, UK.
[16]Vasculitis Clinic, Imperial College Healthcare NHS Trust, London, UK.
[17]Department of Rheumatology, Glasgow Royal Infirmary, Glasgow, UK.

Financial statement

Matthew Rutherford is a clinical research fellow at the University of Glasgow, this position was funded by Vifor Pharma. No representatives from Vifor Pharma were involved in this study. There are no other relevant financial statements for this work.

Acknowledgements

The authors wish to thank the following individuals who contributed data for this project: Jocelyn Berdeprado, Nina Brown, Chee Kay Cheung, Denise De Lord, Oliver Flossman, Venkat Gangaram, Sian Griffin, Alex Hamilton, Philip Ind, Vikki Jubb, Maria King, Sarah Logan, Alice Lorenzi, Ann Morgan, Dan Pugh, Ravindra Rajakariar, Saira Risdale, Michael Robson, Bhrigu Sood, Katie Vinen, Zoe Wellbelove.

Abstract

Objective

COVID-19 is a novel infectious disease with a broad spectrum of clinical severity. Patients with systemic vasculitis have an increased risk of serious infections and so may be at risk of severe outcomes following COVID-19. It is important to establish the risk factors for severe COVID-19 outcomes in these patients, including the impact of immunosuppressive therapies.

Methods

A multi-centre cohort was developed through the participation of centres affiliated with national UK and Ireland vasculitis registries. Clinical characteristics and outcomes were described. Logistic regression was used to evaluate associations between potential risk factors and severe COVID-19 outcome, defined as a requirement for advanced oxygen therapy, invasive ventilation, or death.

Results

Sixty-five cases of patients with systemic vasculitis who developed COVID-19 were reported (median age 70 years, 49% female) of whom 25 (38%) experienced a severe outcome. Most cases (55/65, 85%) had ANCA-associated vasculitis (AAV). Almost all patients required hospitalization (59/65, 91%), 7 patients (11%) were admitted to intensive care and 18 patients (28%) died. Background glucocorticoid therapy was associated with severe outcome (adjusted odds ratio [aOR] 3.7 (1.1-14.9, p=0.047)) as was comorbid respiratory disease (aOR 7.5 (1.9-38.2, p=0.006)). Vasculitis disease activity and non-glucocorticoid immunosuppression were not associated with severe outcome.

Conclusion

In patients with systemic vasculitis, glucocorticoid use at presentation and comorbid respiratory disease were associated with severe outcomes in COVID-19. These data can inform clinical decision making relating to risk of severe COVID-19 in this vulnerable patient group.

Introduction

Coronavirus disease 2019 (COVID-19) is a novel, multi-system infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 causes a broad spectrum of clinical severity (1), ranging from asymptomatic disease to severe respiratory failure and death. In March 2020 the World Health Organisation characterized COVID-19 as a global pandemic (2) prompting considerable concerns from health care systems globally about their resilience to manage this threat. Critical care service capacity was, and remains, a global priority.

Systemic vasculitis is a rare, multi-system autoimmune disorder. Compared to other rheumatic musculoskeletal diseases, it may result in major organ dysfunction and so is typically managed with more potent immunosuppression and higher doses of glucocorticoids in order to induce and maintain disease remission. While this therapeutic approach successfully manages vasculitis activity, glucocorticoid exposure contributes, in part, to the increased risk of infection in these patients (3,4). Thus, although risk factors associated wth poor outcomes from COVID-19 in this population are unknown, there is an assumption that these patients are at high risk.

The RECOVERY trial has demonstrated a benefit from moderate dose glucocorticoids in hospitalized general population patients with COVID-19 requiring supplemental oxygen or mechanical ventilation, but potential harm when used in milder disease (5). Given these paradoxical effects, it is unknown whether chronic background glucocorticoid exposure makes patients more susceptible to severe COVID-19 infection, or whether it might be protective.

We report the results of a coordinated bi-national effort to identify the predictors of severe outcome in the largest reported cohort of systemic vasculitis patients infected with COVID-19.

Methods

Study design

A registry-based multi-centre cohort was designed to facilitate rapid real-world data capture. Centres affiliated with the UK and Ireland Vasculitis Registry (UKIVAS; www.ukivas.org/) and the Irish Rare Kidney Disease Registry (RKD; www.tcd.ie/medicine/thkc/research/rare.php) were invited to contribute. UKIVAS covers 89 sites; RKD covers 8 sites across Ireland. Participating centres represent both secondary and tertiary centres across the UK and Ireland resulting in a broad population sampling frame. A vasculitis-focused COVID-19 case report form (CRF) was developed, underpinned by standardized BioPortal ontologies (e.g. SNOMED CT) (6) and interoperable with other emerging datasets such as the COVID-19 Global Rheumatology Alliance (GRA) (7), thereby facilitating future international data linkage as the COVID-19 pandemic progresses. This enables compatibility of these data with the principles of the global GO-FAIR initiative (8). Additional modules of the UKIVAS and RKD webapps were developed to support data capture.

Study population

Patients were eligible for case submission if they had a diagnosis of systemic vasculitis and COVID-19 (laboratory, radiological or clinical). The diagnosis of vasculitis was determined by the local specialist clinician, as per the International Chapel Hill Consensus Nomenclature of Vasculitides (9). Recruitment commenced on 28 March 2020 and is ongoing. For this analysis, the final case was submitted on 31 July 2020. The population sampling frame consisted of individuals under the clinical care of sites associated with the UKIVAS and RKD registries. At the end of July 2020 there were 795 patients in the RKD registry and approximately 7400 patients in the UKIVAS registry, with 4 patients being enrolled in both. In the UK, the Health Research Authority decision tool determined that ethics approval was not required and the local sponsor confirmed the project as a service evaluation (R&D reference GN20RH165). RKD registry ethics approval was originally granted by the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (ref 2019-08 List 29 (07)). All RKD participants provided informed consent. Additional approvals were not required.

Study variables

Variables collected included potential predictors of severe outcome. The selection of predictive variables was informed by emerging risk factors for COVID-19 disease severity in other populations (10,11). These included age, sex, ethnicity, smoking status, comorbid conditions, immunosuppressive treatment for vasculitis and vasculitis disease activity. Within comorbid

conditions, respiratory disease refers to non-vasculitis related lower respiratory tract disease, though it is possible that some patients had coexistent vasculitis related respiratory disease. Intravenous immunosuppressive therapy was considered to be 'current' if the assessing clinician determined that the therapy was likely to be exerting a biological effect at the time of COVID-19 diagnosis, specific definitions were not provided. Vasculitis disease activity was determined according to global clinician assessment. Outcome data collected included complications, such as acute kidney injury (AKI), respiratory failure and vasopressor requirement, and death. To enable interoperability, the same standardized 1-8 graded outcome as the COVID-19 Global Rheumatology Alliance (GRA) was used (**Supplementary Table 1**) (10). A severe outcome was defined as a composite of requirement for advanced oxygen therapy (such as non-invasive ventilation or high-flow oxygen device), requirement for invasive ventilation or death. Dates of hospital and intensive care unit admission and discharge were collected in order to derive length of stay. Other variables were collected to characterize the clinical features of COVID-19 in patients with vasculitis. These included symptoms, laboratory tests and radiology results. Reporting clinicians were asked to indicate which of these variables contributed to diagnosis.

Statistical analysis

Continuous variables were described as median (IQR). Categorical variables were described as number and percentage (%). Association between various explanatory variables and the odds of severe outcome was determined. Unadjusted and age/sex adjusted logistic regression models were individually calculated for each explanatory variable and reported as odds ratios (OR), p-values and 95% confidence intervals (95% CIs). The adjusted odds ratios (aOR) for age and sex were derived from a single logistic regression model which included age and sex only. Where a potential interaction could account for a positive finding, logistic regression modeling incorporating the explanatory and interacting variables was used. Sensitivity analyses were performed where any effects may have been different in an important subgroup. Missing data were stated in the relevant tables. Statistical significance was set at 5%. R (version 4.0.2) was used for data analysis with packages including tidyverse and finalfit.

Results

In total, 65 patients with an established diagnosis of systemic vasculitis who developed COVID-19 were registered. Fifty-eight patients were submitted to UKIVAS and 7 were submitted to RKD, with no duplicate submissions.

Baseline Characteristics (Table 1)

Median age was 70 years (IQR 55-76) and 49% were female. The majority (55/65, 85%) had anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) (granulomatosis with polyangiitis (GPA): 24/55, 44%; microscopic polyangiitis (MPA): 25/55, 45% and eosinophilic granulomatosis with polyangiitis (EGPA): 6/55, 11%). The characteristics of AAV patients were broadly similar to the full cohort (data not shown). Thirty-two patients (49%) were assessed to have concurrent active disease. Fifteen patients (23%) were suspected to have contracted COVID-19 through a healthcare setting; of these, 9/15 (60%) had some degree of active vasculitis. In one case, COVID-19 was considered to have increased disease activity. For the remainder, COVID-19 was not perceived to have altered or induced disease activity.

Forty-seven patients (72%) were diagnosed by PCR testing, 3 (5%) did not have PCR confirmed disease but had radiological evidence, 3 (5%) were diagnosed by clinical presentation only. Data on diagnostic testing were unknown/missing for 12 patients (18%). The characteristics of those diagnosed by PCR testing were broadly similar to the full cohort (data not shown).

Most patients were receiving background glucocorticoids (45/65, 69%) at the time of COVID-19 diagnosis. Nineteen (29%) were receiving the equivalent of 5 mg prednisone or less, 26/65 (40%) were receiving more than 5 mg. For those on background glucocorticoid, the median dose was the equivalent of 7.5 mg prednisone daily (IQR 5-25 mg). Twenty-two (34%) and 10 (15%) were recently treated with rituximab and cyclophosphamide, respectively.

Symptom frequency (Figure 1)

The most common symptoms were dyspnoea (41/65, 63%), fever (38/65, 58%) and cough (37/65, 57%). Hemoptysis occurred in 3 individuals (5%) and epistaxis occurred in 3 individuals (5%) – of these, one patient had both epistaxis and haemoptysis. Of note, some of these patients had ongoing disease activity prior to COVID-19 diagnosis.

Complications frequency (Figure 2)

Respiratory failure was the most commonly reported complication (35/65, 54%), followed by AKI (12/65, 18%) and secondary infection (10/65, 15%).

Clinical outcomes **(Table 2)**

Almost all patients required hospitalization (59/65, 91%); 7/65 (11%) were admitted to an intensive care unit (ICU) and 18/65 (28%) died. Median length of hospital stay for discharged patients was 11 days (IQR 5-27). A severe outcome was experienced by 25/65 (38%).

Predictors of severe outcome **(Table 3)**

Patients with comorbid respiratory disease were more likely to suffer a severe outcome than those without (aOR 7.5, 95% CI 1.9-38.2, p=0.006) as were those prescribed glucocorticoids (aOR 3.7, 95% CI 1.1-14.9, p=0.047). Glucocorticoid exposure remained a poor prognostic indicator even after adjusting for vasculitis disease activity (data not shown). A sensitivity analysis including only those with confirmed PCR diagnosis (n = 47) was performed which demonstrated effect sizes consistent with these findings, this was statistically significant for comorbid respiratory disease but not for glucocorticoid exposure (data not shown). A sensitivity analysis was also performed for individuals with AAV (n = 55) with a similar result. There was insufficient power to assess the association between glucocorticoid dose and poor outcome. Similarly there was insufficient power to assess for differences between common non-glucocorticoid immunosuppressive agents. Associations were not demonstrated for any demographics, other comorbid conditions, vasculitis diagnosis, vasculitis disease activity or non-glucocorticoid immunosuppressant medication.

Discussion

This multi-centre study reports the largest cohort of patients with systemic vasculitis developing COVID-19 to date. It identifies comorbid respiratory disease and background glucocorticoid therapy as significant predictors of a severe outcome, as defined by need for advanced oxygen therapy or invasive ventilation, or death. Routinely used non-glucocorticoid immunosuppressants, such as rituximab and cyclophosphamide were not associated with a severe outcome and neither was vasculitis disease activity.

Glucocorticoids have pleotropic immunological effects and are generally considered risk factors for infections (12). Glucocorticoids at high dose have been associated with prolonged viral shedding, with a similar effect being observed in other coronaviruses (13,14). That glucocorticoids associate with worse COVID-19 disease is consistent with findings from across the rheumatic autoimmune spectrum, as reported by COVID-19 GRA (10). Our point estimate for the association of any glucocorticoid dose with severe outcome (OR 3.66; 95% CI 1.09-14.9) was comparable to the COVID-19 GRA study's evaluation of steroids at or above the equivalent of 10 mg prednisolone per day (OR 2.05; 1.06 to 3.96). The confidence interval for this finding is relatively wide and therefore it remains to be determined if there is a dose threshold at which risk commenses. This association between glucocorticoids and severe outcome may appear to conflict with findings from the RECOVERY trial. This trial found that low-dose dexamethasone had a substantial survival benefit in individuals hospitalised with COVID-19. However, the groups that benefited in RECOVERY were those requiring supplemental oxygen with the greatest benefit being derived in those requiring mechanical ventilation. In fact, the point estimate for those not requiring oxygen suggested that glucorticoids could be associated with increased mortality, though this was not a statistically significant finding (5). Therefore, prior to requiring oxygen, it may be that glucorticoids are deleterious, as observed in this and other studies of autoimmune disease (15). Our finding that co-morbid respiratory disease (most commonly chronic obstructive pulmonary disease, asthma and interstitial lung disease) was associated with severe disease outcomes was consistent with a recent general population meta-analysis (16). Enhanced respiratory tract ACE2 expression, the principal binding site for COVID-19 cell entry, among some patients with chronic lung disease is a possible explanation for this association (10). Consistent with the COVID-19 GRA report, we did not find an association with adverse disease outcomes for other immunosuppressive agents (17). This is reassuring since current guidance emphasises the importance of maintaining immunosuppression therapy among uninfected patients due to concerns of destabilising disease control (18).

This cohort represents a severely affected group, as reflected by the very high proportion of hospitalisation (91%). The mortality rate of 28% is similar to that reported in the largest UK study of hospitalised patients carried out by the ISARIC WHO Clinical Characterisation Protocol UK group in which 26% died (18). Age, sex and symptom distribution were also broadly similar to the ISARIC WHO report. The most common symptoms, in that cohort and ours, were those which have been most prominent in the case definition: breathlessness, fever and cough. Both active pulmonary vasculitis and COVID-19 are recognised causes of haemoptysis (18,19). In the ISARIC WHO UK group 3.5% had this symptom, 3 (4.8%) patients experienced this symptom in our cohort. None were thought to have diffuse alveolar haemorrhage, as judged by the responding clinician. Differentiating COVID-19 from active pulmonary vasculitis remains a challenge and indeed these presentations may coexist. Ensuring these diagnoses are considered where a patient with vasculitis presents with haemoptysis remains of high importance.

A large proportion (49%) of patients had concurrent active vasculitis. Of these a considerable proportion was suspected to have acquired COVID-19 from a healthcare setting. Notably, the onset of vasculitis disease activity preceded COVID-19 infection in almost all cases. However, it is unknown if COVID-19 may trigger vasculitis activity in the longer term. The emergence of paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS), a condition bearing strong similarities to Kawasaki disease, is a potential example of SARS-CoV-2 triggering autoimmune vasculitis, though the pathogenesis is currently not understood (20). Our study did not find evidence of vasculitis being triggered in the short-term. Longitudinal studies will seek to address this question. The prevalence of active disease in this cohort is higher than expected – previous cross-sectional UK studies have reported disease activity prevalence at approximately 20% (21). Although disease activity was not associated with worse outcome, it may be that patients with unstable disease are more vulnerable to contracting COVID-19. Physician or patient-led reduction in immunosuppressive treatment, in a bid to limit the impact of COVID-19, is another potential reason accounting for a high proportion of disease activity. Due to study design, our data are limited in the extent to which they can inform this question.

Ascertainment bias is likely to have affected this study. Given that most patients were hospitalized, it is likely that patients with milder disease were not identified. The number of PCR diagnosed patients in our study as a proportion of the combined UKIVAS and RKD populations was similar to the proportion of UK cases relative to the UK population for a comparable time period (22). However due to study design, it is not possible to derive incidence rates and patients

with vasculitis may have been more likely to have contracted COVID-19 due to risk factors such as immunosuppressive therapy and need to attend healthcare facilities, therefore ascertainment bias remains possible. There was a high preponderance of small vessel vasculitis (SVV) in this study compared to giant cell arteritis (GCA). Although more common, individuals with GCA are typically older and may have adopted stricter self-isolation restrictions (as per national guidance). In addition, SVV may have predominated due to a disproportionate number of renal units compared to rheumatology centres represented in UKIVAS. Due to a large majority of patient in this study having SVV, the extent to which the findings of this study can be generalised to other vasculitides is limited. Other limitations of this study include relative lack of power. As a result, our analyses may not detect some clinically significant effects and conversely the risk of spurious findings are higher. Similarly, due to the limited number of events, our ability to control for multiple potential confounding factors was limited. Due to the heterogeneous immunobiology, phenotypes and management approaches of systemic vasculitis it is possible that individual disorders may incur different risks, due to insufficient power we were limited in the extent to which this could be examined.

This study is the first to describe a cohort of vasculitis patients with COVID-19. The clinical presentation of COVID-19 was similar to descriptions in large series of patients without autoimmune disease. Glucocorticoids were associated with increased risk of severe outcome, but other immunosuppressants were not. Individuals with autoimmune disease have been considered vulnerable during the COVID-19 pandemic and many governments have instructed that they adhere to exceptional social isolation restrictions. While patients with systemic vasculitis remain at higher risk, these data indicate that some patients may not need to face similar restrictions in the future, if other known risk factors are absent. Conversely, patients who are receiving background corticosteroids or have co-morbid respiratory disease, should be closely monitored when presenting with COVID-19 since their risk of progression to a severe state appears higher (11). This study largely describes a cohort of hospitalised patients and so more likely reflects severe COVID-19 disease. Future work should seek to establish risk factors for severe disease in a wider population. Comparisons with controls who did not contract COVID-19 would allow assessment of incidence and risk factors for contracting COVID-19.

Together with reports of other cohorts exposed to immunosuppressant medication, these data could inform future public health guidance for individuals with autoimmune disease. These data were designed to be interoperable with other national datasets. Future work should seek to

combine international efforts to allow for greater power to assess the factors which impact upon this potentially vulnerable group.

Table 1: Baseline characteristics (n = 65)

Age; median (IQR)	70 (55-76)
Female sex; n (%)	32 (49.2)
Ethnicity; n (%)	
Asian	7 (10.8)
Black	1 (1.5)
White	46 (70.8)
Not stated	6 (9.2)
(Missing)	5 (7.7)
Smoking status; n (%)	
Current	3 (4.6)
Former	15 (23.1)
Never	26 (40.0)
(Unknown / missing)	21 (32.3)
Comorbid conditions; n (%)	
Vasculitis diagnosis; n (%)	
GPA (or PR3 AAV)	24 (36.9)
MPA (or MPO AAV)	25 (38.5)
EGPA	6 (9.2)
LVV	2 (3.1)
Behçet disease	1 (1.5)
PAN	1 (1.5)
Other	5 (7.7)
(Missing)	1 (1.5)
Diabetes	13 (20.0)
Hypertension	25 (38.5)
CV disease	17 (26.2)
Respiratory disease**	13 (20.0)
Renal Disease	30 (46.2)
End stage kidney disease***	
Yes	17 (26.2)
No	46 (70.8)
(Missing)	2 (3.1)

Organ transplant	3 (4.6)
Vasculitis – active disease; n (%)	32 (49.2)
Vasculitis – disease duration (years); median (IQR)	2.2 (0.76 – 6.8)
Current immunosuppressive therapy, n (%)	
Any immunosuppressive therapy	56 (86.2)
Any immunosuppressive therapy and on glucocorticoids	43 (66.2)
Azathioprine	12 (18.5)
Glucocorticoid (any dose)	45 (69.2)
Prednisone 1.0-5.0 mg daily	19 (29.2)
Prednisone 5.1 mg daily or greater	26 (40.0)
(Glucocorticoid dose missing)	2 (3.1)
Cyclophosphamide	10 (15.4)
Hydroxychloroquine	4 (6.2)
IVIG	1 (1.5)
Mycophenolate	11 (16.9)
Rituximab	22 (33.8)
Tacrolimus	4 (6.2)
Other medications, n (%)	
ACEI	9 (13.8)
ARB	8 (12.3)
NSAID	2 (3.1)
(ACEI / ARB / NSAID: unknown / missing)	5 (7.7)
Laboratory tests (median, IQR)	
Creatinine (μmol/L)****	127 (69 – 204)
C-reactive protein (mg/L)	99 (44 – 149)
Lymphocytes (x10^9/L	0.7 (0.4 – 0.9)
COVID-19 diagnosis method	
PCR	47 (72.3)
Radiological	3 (4.6)
Symptoms only	3 (4.6)
(Method unknown / missing)	12 (18.5)

* Other vasculitis diagnoses included IgA vasculitis, leucocytoclastic vasculitis and unspecified vasculitis

** Respiratory disease refers to non-vasculitis related lower respiratory tract disease, though it is possible that some patients had coexistent vasculitis related respiratory disease.
*** includes 13 patients on haemodialysis, 3 kidney transplant recipients and 1 patient with sustained chronic kidney disease stage 5.
**** excludes patients on haemodialysis

Table 2: Outcomes (n = 65)

Hospitalized; n (%)	59 (90.8)
ICU; n (%)	
Yes	7 (10.8)
No	49 (75.4)
(Unknown / missing)	9 (13.8)
Graded outcome; n (%)	
1. Not hospitalized, no limitations on activities	2 (3.1)
2. Not hospitalized, limitation on activities	3 (4.6)
3. Hospitalized, not requiring supplemental oxygen	9 (13.8)
4. Hospitalized, requiring supplemental oxygen	25 (38.5)
5. Hospitalized, on non-invasive ventilation or high flow oxygen devices	4 (6.2)
6. Hospitalized, on invasive mechanical ventilation or ECMO	3 (4.6)
7. Death	18 (27.7)
(Missing)	1 (1.5)
Length of stay (days; median (IQR))	11 (5 - 27)
(Length of stay data missing)	40 (61.5)

Table 3: Unadjusted and adjusted odds ratios for various potential risk factors and association with severe outcome*

	No. severe / No. cases (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P **
Female	13 / 26 (50)	1.04 (0.51-2.10)	1.05 (0.52-2.13)	0.898
Age	-	1.01 (0.98-1.05)	1.01 (0.98 1.05)	0.456
Vasculitis diagnosis				
GPA (reference: not GPA)	12 / 24 (50)	1.71 (0.62-4.81)	2.19 (0.68-7.63)	0.198
MPA (reference: not MPA)	7 / 25 (28)	0.53 (0.17-1.52)	0.43 (0.13-1.36)	0.165
Comorbidities (reference: individual comorbidity not present)				
Hypertension	12 / 25 (48)	1.46 (0.71-3.04)	1.39 (0.64-3.04)	0.404
Cardiovascular disease	8 / 17 (47)	1.32 (0.59-2.93)	1.08 (0.52-2.23)	0.649
Respiratory disease***	10 / 13 (77)	7.50 (1.99-36.94)	7.53 (1.93-38.22)	0.00645
Diabetes	6 / 13 (46)	1.25 (0.51-2.99)	1.20 (0.48-2.92)	0.688
Renal disease	12 / 30 (40)	1.00 (0.49-2.03)	1.05 (0.52-2.14)	0.833
End-stage kidney disease	6 / 17 (35)	0.85 (0.25-2.65)	0.77 (0.22-2.48)	0.672
Smoking status				
Ever smoker (reference: never)	9 / 18 (50)	2.25 (0.65-8.05)	2.33 (0.62-9.28)	0.213
Immunosuppression				
Immunosuppression	24 / 55 (44)	3.10 (0.70-	3.66 (0.77-	0.138

(any; reference: not on immunosuppression)		21.79)	27.29)	
Glucocorticoid				
No prednisone	4 / 18 (22)	ref	ref	
Prednisone (any dose)	22 / 45 (49)	3.35 (1.02-13.2)	3.66 (1.09-14.9)	0.047
1.0 to 5.0 mg	10 / 19 (53)	3.89 (0.98-17.93)	3.76 (0.91-18.02)	0.0771
5.1 mg or greater	12 / 26 (46)	3.00 (0.82-12.86)	3.32 (0.86-15.35)	0.0964
Other immunosuppression				
Azathioprine (reference: not on azathioprine)	6 / 12 (50)	1.65 (0.46-5.97)	1.57 (0.42-5.85)	0.493
Cyclophosphamide (reference: not on cyclophosphamide)	5 / 10 (50)	1.62 (0.41-6.48)	1.83 (0.44-7.76)	0.4
Rituximab (reference: not on rituximab)	9 / 22 (41)	1.06 (0.36-3.01)	1.25 (0.40-3.90)	0.699

* A severe outcome was defined as a composite of requirement for advanced oxygen therapy (such as non-invasive ventilation or high-flow oxygen device), requirement for invasive ventilation or death.

** P values for adjusted models. A separate logistic regression model including sex and age as a continuous variable was calculated for each explanatory variable. The adjusted models for age and sex were derived from a single logistic regression model which included sex and age as a continuous variable.

*** Respiratory disease refers to non-vasculitis related lower respiratory tract disease, though it is possible that some patients had coexistent vasculitis related respiratory disease.

References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–1062.

2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed September 14, 2020.

3. Neumann I. Immunosuppressive and glucocorticoid therapy for the treatment of ANCA-asssociated vasculitis. *Rheumatology* 2020;59:iii60–iii67.

4. Walsh M, Merkel PA, Peh C-A, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. *N Engl J Med* 2020;382:622–631.

5. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N Engl J Med* 2020. Available at: http://dx.doi.org/10.1056/NEJMoa2021436.

6. Musen MA, Noy NF, Shah NH, Whetzel PL, Chute CG, Story M-A, et al. The National Center for Biomedical Ontology. *J Am Med Inform Assoc* 2012;19:190–195.

7. The COVID-19 Global Rheumatology Alliance. The COVID-19 Global Rheumatology Alliance. Available at: https://rheum-covid.org/. Accessed August 22, 2020.

8. Wilkinson MD, Dumontier M, Aalbersberg IJJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 2016;3:160018.

9. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65:1–11.

10. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020. Available at: http://dx.doi.org/10.1136/annrheumdis-2020-217871.

11. The OpenSAFELY Collaborative, Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. *Epidemiology* 2020. Available at: http://dx.doi.org/10.1101/2020.05.06.20092999.

12. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol* 2017;17:233–247.

13. Johnson RM, Vinetz JM. Dexamethasone in the management of covid -19. *BMJ* 2020;370:m2648.

14. Li S, Hu Z, Song X. High-dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19. *Clin Infect Dis* 2020. Available at: http://dx.doi.org/10.1093/cid/ciaa829.

15. Sanchez-Ramirez DC, Mackey D. Underlying respiratory diseases, specifically COPD, and smoking are associated with severe COVID-19 outcomes: A systematic review and meta-analysis. *Respir Med* 2020;171:106096.

16. Smith JC, Sausville EL, Girish V, Yuan ML, Vasudevan A, John KM, et al. Cigarette Smoke Exposure and Inflammatory Signaling Increase the Expression of the SARS-CoV-2 Receptor ACE2 in the Respiratory Tract. *Dev Cell* 2020;53:514-529.e3.

17. Landewé RB, Machado PM, Kroon F, Bijlsma HW, Burmester GR, Carmona L, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. *Ann Rheum Dis* 2020;79:851–858.

18. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020;369:m1985.

19. Kitching AR, Anders H-J, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis. *Nat Rev Dis Primers* 2020;6:71.

20. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis* 2020;79:999–1006.

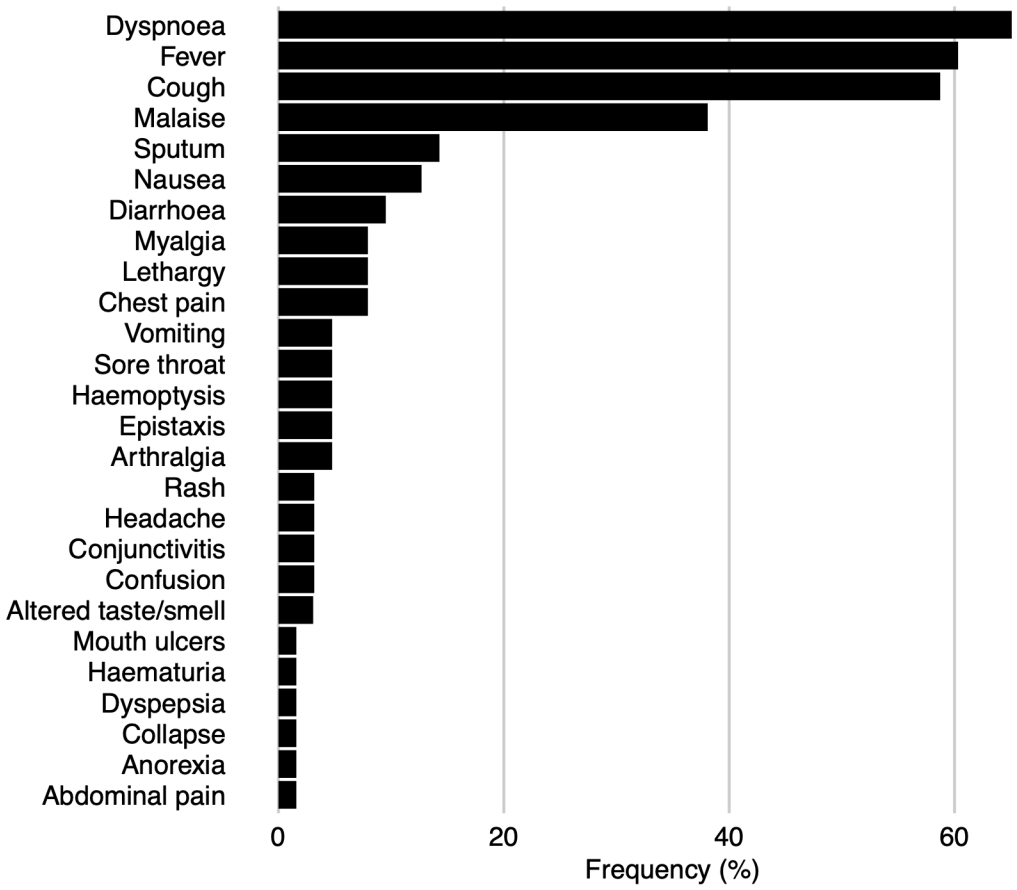
21. Basu N, McClean A, Harper L, Amft EN, Dhaun N, Luqmani RA, et al. The characterisation and determinants of quality of life in ANCA associated vasculitis. *Ann Rheum Dis* 2014;73:207–211.

22. Public Health England. Official UK Coronavirus Dashboard. Available at: https://coronavirus.data.gov.uk/details/cases. Accessed January 29, 2021.

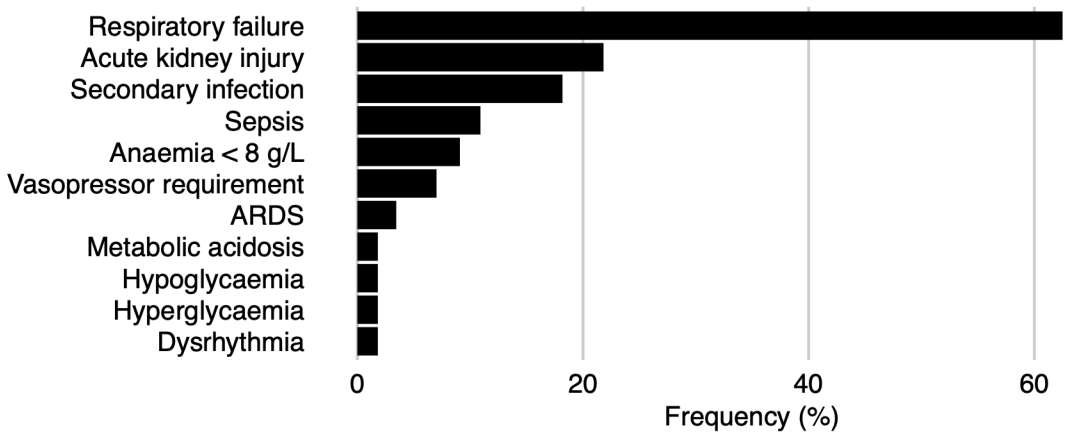
Figure legends

Figure 1 – Symptoms at initial presentation - frequency

Figure 2 – Complication frequency



art_41728_f1.tiff



art_41728_f2.tiff