Autoimmune disease and COVID-19- a multicentre observational study in the United Kingdom

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Abstract

Objective: To establish the demographic characteristics, laboratory findings and clinical outcomes in patients with autoimmune disease (AD) in comparison to a propensity matched cohort of patients without AD admitted with COVID-19 to hospitals in the UK.

Methods: This is a multicentre observational study across 26 NHS Trusts. Data were collected both retrospectively and prospectively using a pre-designed standardised case record form. Adult patients (≥18 years) admitted between 1st of April 2020 and 31 July 2020 were included.

Results: Overall, 6288 patients were included to the study. Of these, 394 patients had AD prior to admission with COVID-19. Of 394 patients, 80 patients with systemic lupus erythematosus, rheumatoid arthritis or antiphospholipid syndrome were classified as severe rheumatologic AD. A higher proportion of those with AD had anaemia: 240(60.91%) vs 206(52.28%), p=0.015, raised LDH 150(38.08%) vs 43(10.92%), p<0.001 and raised creatinine 122(30.96%) vs 86(21.83%), p=0.01 respectively. A significantly higher proportion of patients with severe rheumatologic AD had raised CRP:77(96.25%) vs 70(87.5%), P=0.044 and LDH 20(25%) vs 6(7.5%), p=0.021. Patients with severe rheumatologic AD had significantly higher mortality [32/80(40%)] compared to propensity matched cohort of patients without AD [20/80(25%)], p=0.043. However, there was no difference in 180-day mortality between propensity matched cohorts of patients with or without AD in general, p=0.47.

Conclusions

Patients with severe rheumatologic AD had significantly higher mortality. Anaemia, renal impairment and raised LDH were more frequent in patients with any AD whilst raised CRP

and LDH were more frequent in patients with severe rheumatologic AD both of which have been shown to associate with increased mortality in patients with COVID-19.

Running title: Autoimmune disease and COVID-19

Key words: Autoimmune rheumatologic disease; COVID-19; mortality; thrombosis; bleeding; antiphospholipid syndrome; Systemic lupus erythematosus; Rheumatoid arthritis

Rheumatology key messages

Demographic characteristics, laboratory findings and clinical outcomes in autoimmune disease patients developed COVID-19 were established

Patients with severe rheumatologic autoimmune (AD) disease had significantly higher mortality following COVID-19

Anaemia, renal impairment and raised LDH were more frequent in patients with AD developed COVID-19

Introduction

Coronavirus disease-19 (COVID-19) is a global pandemic leading to an unprecedented health crisis. The World Health Organization (WHO) declared the novel coronavirus outbreak to be a pandemic in March 2020. Although the number of patients with severe infection is gradually falling in some countries due to mass vaccination, it remains a global threat.

COVID-19 is associated with increased risk for thrombosis in addition to causing respiratory failure with or without multi organ failure and death. Some studies found that patients with autoimmune and inflammatory conditions are at increased risk for COVID-19-associated hospitalizations and worse disease outcomes[1]. However, autoimmune diseases are a broad category of diseases with differing severity, from requiring no treatment to multiple immunosuppressive treatments. It is likely that the clinical course and the outcomes of COVID-19 varies in patients with AD depending on the severity of the autoimmune disease and the immunosuppressive treatment. There are more than 80 autoimmune conditions affecting over four million people in the UK. AD such as Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are generally considered to be severe rheumatologic autoimmune diseases associated with higher risk of developing thrombosis in addition to their other complications.[2] In a propensity score matched analysis from a nationwide multi-centric research network study assessing the short-term outcome of COVID-19 patients with SLE, the mortality was comparable to the general population but SLE patients had higher risks of hospitalisation, admission to intensive care unit, mechanical ventilation, stroke, venous thromboembolism (VTE) and sepsis[3]. Additionally, many studies have demonstrated frequent occurrence of autoantibodies including antiphospholipid antibodies (aPL) in patients with COVID-19 [4]. The prevalence of aPL was

even higher in patients with severe disease but there was no association between aPL positivity and disease outcomes including thrombosis, invasive ventilation, and mortality. As transiently positive aPL is a well-known phenomenon in patients with acute infection, the significance of these antibodies remains to be determined[5] although some studies demonstrated aPL from patients with COVID-19 caused thrombosis in a mouse model [6].

The aim of this study was to establish the demographic characteristics, laboratory findings and clinical outcomes in patients with autoimmune disease in comparison to a propensity matched cohort of patients with no autoimmune disease admitted with COVID-19 to hospitals in the UK.

Methods

This study is reported according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Study Design, population, and data collection

Study Design, population, and data collection

Coagulopathy associated with COVID-19 (CA-COVID-19) is a multicentre observational across 26 NHS Trusts (listed in Supplementary Appendix page 1–2, available at *Rheumatology* online) within the UK (https://clinicaltrials.gov/ct2/show/NCT04405232).

The study was approved by the human research authority (HRA) and health and care Research Wales (HCRW) and the local Caldicott Guardian at Scotland (reference number: 20/HRA/1785).

We included adult patients (≥18 years) admitted to hospital during the first wave of the COVID19 pandemic in the UK between 1st of April 2020 and 31 July 2020. This paper includes only the patients with autoimmune disease diagnosed prior to admission to hospitals with COVID-19 and an equal size propensity matched cohort of patients with no autoimmune disease with COVID-19 admitted to hospital during the first wave of the COVID-

19 pandemic (1st of March to 31st May 2020). All patients had SARS-CoV-2 confirmed by real time polymerase chain reaction (RT-PCR) on nasopharyngeal swabs or lower respiratory tract aspirates.

Data collection

Data were collected both retrospectively and prospectively using a pre-designed standardised case record form (CRF) to a central electronic database (Coagulopathy associated with COVID-19 [CA-COVDI-19]) (REDcap v10.0.10; Vanderbitt University, US) hosted by Imperial College London. At the time of writing the paper, all outcomes have been completed and no patient remained in hospital. As the data were collected by clinicians directly involved in patient care with no breach of privacy or anonymity by allocating a unique study number with no direct patient identifiable data and therefore consent was waived by the HRA. Baseline patient demographics, comorbidities, haematological and biochemical blood results on the day of admission and clinical outcomes until the day of discharge/death were collected. At the time of writing this paper, all patients had completed follow-up until day 180 post hospital admission or death.

Outcomes

The primary outcome was 180-day mortality. Secondary outcomes were thrombosis, major bleeding, the development of multiorgan failure (MOF) and ICU admission.

Definitions of clinical outcomes

Mortality

All-cause mortality was collected and classified as directly related to COVID-19, directly related to thrombosis, directly related to bleeding, or related to other causes.

Thrombosis and bleeding complications

Thrombotic and bleeding complications were identified on clinically indicated computed tomography scan (CT) or ultrasound (US) imaging. Thrombotic events were defined as image confirmed pulmonary embolism (PE), deep vein thrombosis (DVT) or arterial thrombosis. Bleeding events were defined as major or clinically relevant minor haemorrhages according to ISTH classification[7] (Supplementary Table S1, available at *Rheumatology* online).

Multiorgan failure

Defined as failure in two or more organ systems that required interventions to maintain homeostasis.

Admission to an intensive care unit

This was defined as patients who required continuous positive airway pressure ventilation (CPAP) or mechanical ventilation with or without extracorporeal membrane oxygenation (ECMO) or required other organ support.

Statistical analysis

Propensity score matching was performed using the nearest neighbours method, with a desired ratio of 1:1 between patients with and without autoimmune disease. Covariates (demographics and comorbidities) used for propensity score matching are summarised in Supplementary Figure S1, available at *Rheumatology* online. Laboratory results at presentation were not included in the propensity matching. Factors for propensity matching were chosen based on factors found to contribute to increased mortality in published studies of patients with COVID-19. Propensity matchings were performed for patients with any AD and for patients with severe rheumatologic AD separately. The characteristics of the treated and untreated patients were summarised and compared using descriptive statistics. The probability of survival between patients with and without AD were assessed using Kaplan-

Meier curves. Characteristics of patients who had AD were compared to patients who did not have AD using the Chi-squared or Chi-squared trend test. Propensity score matching and analysis were performed using R. Two-tailed $p<0.05$ were considered statistically significant.

Results

Overall, 6,288 patients with COVID-19 were admitted to 26 NHS Trusts in the UK between 1st of April and 31st of July 2020. Out of overall 6288 patients, we analysed 394 patients classified as having AD prior to admission with COVID-19 Patients with AD group include those with chronic inflammatory arthritis, including rheumatoid arthritis, psoriatic arthritis and spondylarthritis, connective disease (CTD), including SLE, Sjögren's syndrome, systemic sclerosis, polymyalgia rheumatica, vasculitides and APS (Supplementary Table S2, available at *Rheumatology* online). Out of 394 patients, 80 patients had SLE, rheumatoid arthritis or APS and were classified as having severe rheumatologic AD (Figure 1) which are more likely to require immunosuppressive medication and be associated with and increased risk of thrombosis which may cause severe complications when they develop COVID-19.

Of 80 patients classified as severe rheumatologic AD, 37 (46.2%) patients had RA, 34 (42.5%) had SLE and 9 (11.3%) had APS. Fifteen of 37 (40.5%) patients with RA were on methotrexate or other disease modifying drugs whilst 10 out 34 patients (29.4%) with SLE were on non-steroid immunosuppressive drugs (mycophenolate mofetil and cyclosporine). Patients with APS were not on any immunosuppressive drugs except 3/9 (33.5%) patients were on hydroxychloroquine (Supplementary Table S3, available at *Rheumatology* online).

All autoimmune diseases compared to non-autoimmune disease prior to propensity matching

There was no age difference between patients with and without AD; median age of patients with AD was 71(IQR 61-82) years compared to 74(IQR 59-83) years in patients without

autoimmune disease, p=0.78. As expected, the majority of AD patients were female (229/394: 58.12% vs 165/394: 41.88% p<0.001) although the majority of the patients admitted to hospitals with COVID-19 were male: (3279/5894 (55.6%) male vs 2615/5894 (44.4%) female (p<0.001). There were no differences in body mass index (BMI), ethnicity or comorbidities between patients with or without AD. The majority of patients with AD had below normal haemoglobin at the time of admission to hospitals: 240/394(60.91%) vs 2895/5894(49.12%), p<0.001. A higher proportion of patients with AD had raised creatinine levels whilst a lower proportion had raised prothrombin time (PT) compared those without AD respectively; creatinine above normal 122/394(30.96%) vs 1565/5894(26.56%), p=0.03, PT above normal: 4330/5894(73.46%) vs 263/394(66.75%), p=0.004. There were no differences in the other laboratory parameters notably lactate dehydrogenase, C-reactive protein, or D-dimer levels between patients with or without AD at the time of admission to hospitals with COVID-19. Patient characteristics, comorbidities, and laboratory parameters at admission are summarised in Table 1.

All autoimmune diseases compared to non-autoimmune disease after propensity matching

As expected, there were no differences in the demographics and comorbidities of the patients with and without AD after propensity matching (Table 1). However even after propensity matching, a higher proportion of patients with any AD had low haemoglobin compared to patients without AD: 240(60.91%) vs 206(52.28%), p=0.015. Furthermore, a higher proportion of patients with AD had raised LDH and creatine levels; raised LDH in 150(38.08%) vs 43(10.92%), p<0.001 and raised creatinine in 122(30.96%) vs 86(21.83%), p=0.01. There were no differences in the other laboratory parameters between the two groups (Table 1).

Patients with severe rheumatologic autoimmune disease

Comparison was made between the eighty patients classified as severe rheumatologic AD with 1:1 propensity matched cohort of patients without AD. As expected, no differences were seen in patient demographics and comorbidities between the two groups following the propensity matching. In patients with severe rheumatologic AD the female preponderance was higher than in the 'all AD' group: 55/80 (68.75%) female vs 25/80(31.25%) male (Table 2). Furthermore, a significantly higher proportion of patients with severe rheumatologic AD had raised CRP levels and LDH levels compared to patients without AD: raised CRP in 77 (96.25%) vs 70 (87.5%), p=0.044 and raised LDH in 20 (25%) vs 6 (7.5%), p=0.021. There were no differences in the other laboratory parameters between the two groups (Table 2).

Outcomes in patients with any autoimmune disease compared to non-autoimmune disease after propensity matching

Primary outcome: There was no difference in the 180-day mortality between propensity matched cohort of all patients with and without AD: overall mortality in patients with any AD was 121/304(30.71%) compared to 111/394(28.17%) in patients with no AD, p=0.435 (Figure 2A).

Secondary outcomes: No differences were observed in rate of thrombosis, major bleeding, the development of MOF or admission to ICU in patients with any AD compared to those with no AD. There was a trend towards more patients with AD supported with continuous positive airway pressure (CPAP) support [29/393 (7.36%) vs 17/394 (4.31%), p=0.068] (Table 3).

Outcomes in patients with severe rheumatologic autoimmune disease compared to non-autoimmune disease after propensity matching

Primary outcome: In contrast to patients with any AD, those with severe rheumatologic AD had significantly higher mortality [32/80(40%)] (all-cause mortality) compared to propensity matched cohort of patients with no AD [20/80(25%)], p=0.043 (Figure 2B). There was a trend towards higher mortality in patients with classified as severe rheumatologic AD (40%, 32/80) compared to patients with other AD (28.3%, 89/314), P=0. 056. Secondary outcomes: Similar to patients with any AD, no differences were observed in rate of thrombosis, major bleeding, the development of MOF or admission to ICU in patients with severe rheumatologic AD compared to those with no AD (Table 4)

Clinical interventions

There were no differences in the clinical interventions during the hospital admission in the patients with or without AD as a whole group or with severe rheumatologic AD except significantly higher proportion of patients with any AD or severe rheumatologic AD received steroids compared to patients with no AD [82/394 (20.81%) vs 40/394 (10.15%), p <0.001 and 18/80 (22.5%) 5/80 (6.25%), p=0.003 respectively] (Table 3 for any AD and Table 4 for severe rheumatologic AD).

Discussion

In this large multicentre observational study across UK assessing the clinical characteristics and outcomes of the patients with any AD and those with severe rheumatologic AD, we found that presence of any AD did not increase the risk of mortality or other outcomes (thrombosis, major bleeding, MOF, or admission to ICU) compared to propensity matched cohort of patients with no AD. However, patients classified as severe rheumatologic AD (SLE, RA or APS) had significantly higher mortality compared to patients with no AD. No differences were seen in the secondary outcomes between the two groups. Following propensity matching for demographics and comorbidities, a higher proportion of patients

with AD had low haemoglobin, raised LDH and creatine levels compared to patients with no AD. In those with severe rheumatologic AD, raised CRP and LDH were more common compared to patients without AD. Generally, AD are more common in women, occurring at a ratio of 2 to 1[8] whereas COVID-19 disease severity and admission rate is higher in men [9]. These differences were preserved in this study.

Autoimmune diseases are heterogeneous group of conditions typified by dysregulation of the immune system. Most of the patients with AD received or were receiving immunosuppressive medications which make them more susceptible to infections and complications. Observational studies assessing the risk of acquiring COVID-19 and outcomes in patients with AD reported conflicting results. A cross-sectional study in northeast Italy reported that patients with AD had a similar rate of COVID-19 compared with the general population [10]. Another Italian study also found that presence of autoimmune disease did not increase the risk of COVID-19[11]. Furthermore, they suggested that outcome of patients with AD did not differ from patients with no AD[11]. However, this study did not perform propensity matching for the study groups which as shown in this study are significantly different in important respects. In contrast, the results of a multicentre retrospective study from China showed that patients with AD might be more susceptible to COVID-19 compared those without[12]. Additionally, a Spanish study which assessed the association between the outcome and the potential prognostic variables, adjusted by COVID-19 treatment in patients with AD to a matched (for sex and age, and blinded to outcome or other variables but not propensity matching for all comorbidities) cohort of patients with no AD reported that hospitalized patients with AD have a more severe course[13]. In the current propensity matched study, we did not observe a difference in the mortality or secondary outcomes between patients with any AD compared to patients with no AD (Table 3). This could be due a higher proportion of patients with any AD being given steroids which has been shown to improve the mortality in patients with COVID-19[14]. However, the mortality

rate was still significantly higher in patients with severe rheumatologic AD despite a higher proportion receiving steroids. Additionally, there was a trend towards higher mortality in patients classified as severe rheumatologic AD compared to patients with other AD (P=0.056). The higher mortality in patients with severe rheumatologic AD could indicate that these patients suffer more severe rheumatologic COVID-19 although no differences were seen in the secondary outcomes such as rate of thrombosis, major bleeding, development of MOF or admission to ITU. Therefore, cause for increased mortality in patients with severe rheumatologic AD was not clear. It is possible prior non-steroid immunosuppressive drugs contributed to the increase mortality in these patients (Supplementary Table S3, available at *Rheumatology* online).

Anaemia is a frequent complication in patients with AD. It is generally classified as anaemia of chronic disease and usually multifactorial. Despite propensity matching for demographics and comorbidities, a higher proportion of patients with any autoimmune disease had anaemia on admission to hospital. However, a significantly higher proportion of patients with AD had raised LDH which could be due to ongoing tissue damage associated with AD and in some cases autoimmune haemolytic anaemia. Raised CRP, a marker of disease severity in many AD, was observed in a significantly higher proportion of patients with severe rheumatologic AD upon admission compared to patients without AD. Both raised CRP and LDH on admission are considered predictors of increased mortality in patients with COVID-19[15, 16] and indeed these patients had higher mortality rate compared to control group in this study. Finally, serum creatinine was elevated on admission in a higher proportion of patients with AD. Renal failure is a frequent complication in these individuals and may additionally contribute to anaemia.

The main limitation of this study is that some of the data were collected retrospectively, but relevant information and clinical outcomes were recorded directly using a predefined well-

structured electronic CRF. However, this did not include disease activity scores such as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) or Disease Activity Score (DAS28). The classification of RA; SLE and APS as severe rheumatologic AD compared to other ADs in the study can therefore be regarded as arbitrary. It is possible that disease severity of any given AD at the time of admission with COVID1-9 has an impact on primary or secondary outcomes beyond the primary AD diagnosis and immunosuppressive medications. As the disease severity scores were not included in the data collection, we were not able to assess the impact of the individual disease severity in the clinical outcomes in this study. Although the number of patients included into study is relatively small, it comprises patients admitted to 26 NHS Trusts across UK providing a representative view of AD in the UK.

In conclusion, we found no differences in the clinical outcomes in patients with any AD compared to patients with no AD admitted to hospitals with COVID-19 from the first wave of the pandemic. However, those with severe rheumatologic AD had significantly higher mortality. Anaemia, renal impairment and raised LDH were more frequent in patients with any AD whilst raised CRP and LDH were more frequent in patients with severe rheumatologic AD. Although vaccination has reduced the risk of mortality associated with COVID-19, patients with severe rheumatologic AD need additional attention if admitted to hospitals with COVID-19.

Author contributions

DJA conceptualised the study and acquired the funding acquisition and lead for the methodology, project administration, validation, visualisation, writing the original draft reviewing and editing the study as well as being involved in data curation. IR was involved with formal analysis, software and valuation of the study as well as supporting the review & editing of the paper. CP contributed to data interpretation, review and editing of the

manuscript. PN supported the project administration, data collection and review of the manuscript. MM supported Data curation, Project administration, resources, validation of the study and was involved in review and editing of the study. ML contributed to data interpretation, review and editing of the manuscript. All other authors reviewed and approved the final version of the study.

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Conflict interest

DJA received funding from Bayer plc to setup the multicentre database of the study as an investigator-initiated funding and received research grant from Leo Pharma. ML received consultation and speaker fees from Astra-Zeneca, Sobi, Leo-Pharma, Takeda and Pfizer. PN received research grants from Novartis, Principia and Rigel, unrestricted grants from Sanofi, Chugai and Octapharma and honoraria from Bayer. Others have no conflict of interest to declare.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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	Subgroup	No Autoimmune disease, N (%)	Auto immune disease, N (%)	P[1]	Propensity matched no autoimmune disease, N (%)	P[2]
Overall		5894	394		394	
Patient gender	Male	3279 (55.6%)	165 (41.88%)	**<0.001**	165 (41.88%)	1
	Female	2615 (44.4%)	229 (58.12%)		229 (58.12%)	
Patient age (years)	<=29	143 (2.42%)	10(2.53%)	0.87	6(1.52%)	0.94
	30-49	654(11.10%)	33(8.38%)		44(11.17%)	
	50-69	1639(27.81%)	122(30.96%)		120(30.46%)	
	70-89	2907(49.32%)	204(51.78%)		189(47.97%)	
	>= 89	551(9.35%)	25(6.35%)		35(8.88%)	
BMI	<=18.5	124(2.10%)	17(4.31%)	0.87	11(2.79%)	0.96
	18.6 – 24.9	1629(27.64%)	93(23.60%)		99(25.13%)	
	25-29.9	2095(35.54%)	147(37.31%)		137(34.77%)	
	30-39.9	1806(30.64%)	121(30.72%)		120(30.46%)	
	>=40	240(4.08%)	16(4.06%)		27(6.85%)	
Ethnicity	White	4312(73.16%)	313(79.44%)	0.08	277(70.30%)	0.09
	Mixed multiple ethnic	32(0.54%)	4(1.02%)		3(0.76%)	
	Asian / Asian British	333(5.65%)	16(4.06%)		26(6.60%)	
	Black African/Caribbean	181(3.07%)	12(3.05%)		9(2.28%)	
	Other ethnic group	187(3.17%)	7(1.78%)		11(2.79%)	
	Unknown	849(14.41%)	42(10.66%)		68(17.26%)	
Previous history of VTE	No	5554(94.23%)	363(92.13%)	0.13	375(95.18%)	0.08
	Yes	340(5.77%)	31(7.87%)		19(4.82%)	
Malignancy	No	5272 (89.45%)	353(89.53%)	0.99	359(91.11%)	0.55
	Yes	622 (10.55%)	41 (10.47%)		35 (8.89%)	
Hypertension	No	3129(53.08%)	205(52.03%)	0.72	202(51.27%)	0.89
	Yes	2765 (46.92%)	189 (47.97%)		192(48.73%)	
Hyper-cholesterolemia	No	4978(84.46%)	324(82.23%)	0.27	320(81.22%)	0.78
	Yes	916(15.54%)	70(17.77%)		74(18.78%)	
Heart.disease	No	4556(77.30%)	306(77.66%)	0.92	304(77.16%)	0.93
	Yes	1338(22.70%)	88(22.34%)		90(22.84%)	
Diabetes	No	4202(71.29%)	278(70.56%)	0.80	272(69.03%)	0.70
	Yes	1692(28.71%)	116(29.44%)		122(30.97%)	
History of smoking**	None	2285(39.11%)	143(36.39%)	0.87	143(36.39%)	0.95
	Current smoker	280(4.79%)	22 (5.60%)		22 (5.60%)	
	Ex-smoker	1240(21.22%)	105(26.71%)		105(26.71%)	
	Unknown	2038(34.88%)	124 (31.30)		124 (31.30)	
Liver disease	No	5687(96.49%)	370(93.91%)	0.09	376(95.43%)	0.43
	Yes	207(3.51%)	24(6.09%)		18(4.57%)	

	Subgroup	No Autoimmune disease, N (%)	Auto immune disease, N (%)	P[1]	Propensity matched no autoimmune disease, N (%)	P[2]
Lung disease	No	4457(75.62%)	286(72.59%)	0.2	286(72.59%)	1
	Yes	1437(24.38%)	108(27.41%)		108(27.41%)	
Existing renal failure	No	4839(82.10%)	314(79.70%)	0.26	318(80.71%)	0.79
	Yes	1055(17.90%)	80(20.30%)		76(19.29%)	
Antiplatelet therapy prior to admission	No	4794(81.34%)	314(79.70%)	0.46	320(81.22%)	0.65
	Yes	1100(18.66%)	80(20.30%)		74(18.78%)	
Ferritin (ug/L)	Below normal (<20)	19(0.30%)	0	0.40	1(0.25%)	0.87
	Normal (20-186)	191(3.24%)	19(4.8%)		16(4.06%)	
	Above normal (>186)	5684(96.36%)	375(95.20%)		377(95.69%)	
Lactate (mmol/L)	Normal (<2.1)	5220(88.56%)	353(89.59%)	0.519	354(89.85%)	0.907
	Above normal (>2.1)	674(11.44%)	41(10.41%)		40(10.15%)	
Haemoglobin* (g/L)	Below normal <130 (<115)	2895(49.12%)	240(60.91%)	**<0.001**	206(52.28%)	**0.015**
	Normal 130-160 (115-150)	2670(45.3%)	138(35.02%)		166(42.13%)	
	Above normal >160 (>150l	329(5.58%%)	16(4.07%)		22(5.59%)	
Troponin (ng/L)	Normal (<19.8)	1764(29.93%)	126(31.98%)	0.399	120(30.46%)	0.645
	Above normal (>19.7)	4130(70.07%)	268(68.02%)		274(69.54%)	
LDH (IU/L)	Below normal (<266)	165(2.80%)	12(3.04%)	0.99	19(4.82%)	**<0.001**
	Normal (266-500)	3446(58.47%)	232(58.88%)		332(84.26%)	
	Above normal (>500)	2283(38.73%)	150(38.08%)		43(10.92%)	
Prothrombin Time (secs)	Below normal (<10.2)	76(1.29%)	9(2.28%)	**0.004**	6(1.52%)	0.092
	Normal (10.2-13.2)	1488(25.25%)	122(30.96%)		104(26.40%)	
	Above normal (>13.2)	4330(73.46%)	263(66.75%)		284(72.08%)	
APTT (sec)	Below normal (<26.0)	585(9.92%)	50(12.69%)	0.15	30(7.61%)	0.23
	Normal (26-36)	4568(77.50%)	299(75.88%)		318(80.71%)	
	Above normal (>36.0)	741(12.58%)	45(11.42%)		46(11.68%)	
Platelets (10^9/L)	Below normal (<150)	1001(16.98%)	61(15.48%)	0.319	71(18.02%)	0.567
	Normal (150-400)	4459(75.65%)	300(76.14%)		288(73.10%)	
	Above normal (>400)	434(7.36%)	33(8.38%)		35(8.89%)	
WBC (10^9/L)	Below normal (<4.1)	542(9.20%)	36(9.14%)	0.92	43(10.91%)	0.368
	Normal (4.1-11.1)	4019(68.19%)	268(68.02%)		268(68.02%)	
	Above normal (>11.1)	1333(22.61%)	90(22.84%)		83(21.07%)	
Neutrophils (10^9/L)	Below normal (<2.1)	249(4.22%)	17(4.31%)	0.654	16(4.06%)	0.185
	Normal (2.1-6.7)	3126(53.04%)	203(51.52%)		226(57.36%)	
	Above normal (>6.7)	2519(42.74%)	174(44.16%)		152(38.58%)	
Lymphocytes (μL)	Below normal (<1.3)	4484(76.08%)	299(75.89%)	0.938	286(72.59%)	0.29
	Normal (1.3-3.7)	1409(23.91%)	95(24.11%)		108(27.41%)	

	Above normal (>3.7)	1(0.01%)	0		0	
Fibrinogen (g/L)	Below normal (<1.5)	128(2.17%)	10(25.38%)	0.929	8(2.03%)	0.353
	Normal (1.5-4.5)	593(10.06%)	36(9.14%)		51(12.94%)	
	Above normal (>4.5)	5173(87.77%)	348(88.32%)		335(85.02%)	
ALT (IU/L)	Below normal (<8)	120(2.04%)	13(3.30%)	0.1	10(2.54%)	0.2
	Normal (8-40)	3988(67.66%)	267(67.76%)		264(67.0%)	
	Above normal (>40)	1786(30.30%)	114(28.93%)		120(30.46%)	
Bilirubin (μmol/L)	Normal (0-20)	5293(89.80%)	356(90.36%)	0.720	353(89.59%)	0.724
	Above normal (>20)	601(10.20%)	38(9.64%)		41(10.41%)	
Creatinine (μmol/L)	Below normal (<60)	833(14.13%)	67(17.01%)	**0.03**	56(14.21%)	**0.01**
	Normal (60-120)	3496(59.31%)	205(52.03%)		252(63.96%)	
	Above normal (>120)	1565(26.56%)	122(30.96%)		86(21.83%)	
CRP (mg/L)	Normal (0-10)	571(9.68%)	30(7.61%)	0.137	44(11.17%)	0.088
	Above normal (>10)	5323(90.31%)	364(92.39%)		350(88.83%)	
D-Dimer (ng/ml)	Normal (0-500)	445(7.55%)	35(8.88%)	0.367	33(8.38%)	0.8
	Above normal (>500)	5449(92.45%)	359(9.11%)		361(91.62%)	

Table 1. Clinical characteristics and admission laboratory parameters of patients with autoimmune or without autoimmune disease

P^1 refers to the comparison of the autoimmune disease vs no autoimmune disease groups, whilst P^2 refers to the comparison of the autoimmune disease group and the propensity matched autoimmune disease group. P values <0.05 are shown in bold. BMI= body mass index; VTE= venous thromboembolism; LDH= lactate dehydrogenase; APTT= activated partial thromboplastin time; ALT =alanine transferase; CRP= C-reactive protein

	Subgroup	Severe auto immune disease, N (%)	Propensity matched NO autoimmune disease, N (%)	P value
Overall		80	80	
Patient gender	Male	25(31.25%)	25(31.25%)	1
	Female	55(68.75%)	55(68.75 %)	
Patient age (years)	<=29	2(2.5%)	2(2.5%)	0.587
	30-49	0	0	
	50-69	25(31.25%)	20(25%)	
	70-89	48(60%)	46(57.5%)	
	>= 89	5(6.25%)	12(15%)	
BMI	<=18.5	4(5%)	2(2.5%)	0.587
	18.6 – 24.9	17(21.25%)	29(36.25%)	
	25-29.9	27(33.75%)	29(36.25%)	
	30-39.9	30(37.5%)	17(21.25%)	
	>=40	2(2.5%)	3(3.75%)	
Ethnicity	White	66(82.5%)	60(75%)	0.269
	Mixed multiple ethnic	0	1(1.25%)	
	Asian / Asian British	2(2.5%)	3(3.75%)	
	Black African/Caribbean	2(2.5%)	0	
	Other ethnic group	0	1(1.25%)	
	Unknown	6(12.5%)	15(18.75%)	
Previous history of VTE	No	79(98.75%)	77(96.25%)	0.734
	Yes	1(1.25%)	3(3.75%)	
Malignancy	No	68(85%)	71(88.75%)	0.486
	Yes	12(15%)	9(11.25%)	
Hypertension	No	45(56.25%)	46(57.5%)	0.874
	Yes	35(43.75%)	34(42.5%)	
Hyper-cholesterolemia	No	69(86.25%)	71(88.75%)	0.079
	Yes	11(13.75%)	9(11.25%)	
Heart.disease	No	62(77.5%)	64(80%)	0.701
	Yes	18(22.5%)	16(20%)	
Diabetes	No	59(73.75%)	61(76.25%)	0.717
	Yes	21(26.25%)	19(23.75%)	
History of smoking**	None	32(40%)	28(35.45%)	0.230
	Current smoker	3(3.75%)	4(5.06%)	
	Ex-smoker	26(32.5%)	15(19.99%)	
	Unknown	19(23.75%)	32(40.5%)	
Liver disease	No	79(98.75%)	78(97.5%)	0.563

	Subgroup	Severe auto immune disease, N (%)	Propensity matched NO autoimmune disease, N (%)	P value
	Yes	1(1.25%)	2(2.5%)	
Lung disease	No	53(66.25%)	54(67.5%)	0.868
	Yes	27(33.75%)	26(32.5%)	
Existing renal failure	No	68(85%)	65(81.25%)	0.530
	Yes	12(15%)	15(18.75%)	
Antiplatelet therapy prior to admission	No	61(76.25%)	62(77.5%)	0.852
	Yes	19(23.75%)	18(22.5%)	
Ferritin (ug/L)	Below normal (<20)	0	2(2.5%)	0.587
	Normal (20-186)	4(5%)	2(2.5%)	
	Above normal (>186)	76(95%)	86(95%)	
Lactate (mmol/L)	Normal (<2.1)	70(87.5%)	73(91.25%)	0.445
	Above normal (>2.1)	10(12.5%)	7(8.75%)	
Haemoglobin* (g/L)	Below normal <130 (<115)	24(30%)	17(21.25%)	0.269
	Normal 130-160 (115-150)	49(61.25%)	55(68.75%)	
	Above normal >160 (>150l	7(8.75%)	8(10%)	
Troponin (ng/L)	Normal (<19.8)	20(25%)	23(27.75%)	0.595
	Above normal (>19.7)	60(75%)	57(71.25%)	
LDH (IU/L)	Below normal (<266)	3(3.75%)	1(1.25%)	**0.021**
	Normal (266-500)	57(71.25%)	73(91.25%)	
	Above normal (>500)	20(25%)	6(7.5%)	
Prothrombin Time (secs)	Below normal (<10.2)	0	1(1.25%)	0.143
	Normal (10.2-13.2)	21(26.25%)	19(23.75%)	
	Above normal (>13.2)	59(73.75%)	60(75%)	
APTT (sec)	Below normal (<26.0)	8(10%)	8(10%)	0.508
	Normal (26-36)	60(75%)	64(80%)	
	Above normal (>36.0)	12(15%)	8(10%)	
Platelets (10^9/L)	Below normal (<150)	14(17.5%)	13(16.25%)	0.875
	Normal (150-400)	59(73.75%)	60(75%)	
	Above normal (>400)	7(8.75%)	7(8.75%)	
WBC (10^9/L)	Below normal (<4.1)	6(7.5%)	5(6.25%)	0.761
	Normal (4.1-11.1)	57(71.25%)	57(71.25%)	
	Above normal (>11.1)	17(21.25%)	18(22.5%)	
Neutrophils (10^9/L)	Below normal (<2.1)	3(3.75%)	2(2.5%)	0.667
	Normal (2.1-6.7)	42(5.25%)	47(58.75%)	

	Subgroup	Severe auto immune disease, N (%)	Propensity matched NO autoimmune disease, N (%)	P value
	Above normal (>6.7)	35(43.75%)	31(38.75%)	
Lymphocytes (μL)	Below normal (<1.3)	62(77.5%)	59(73.75%)	0.584
	Normal (1.3-3.7)	18(22.5%)	21(26.25%)	
	Above normal (>3.7)	0	0	
Fibrinogen (g/L)	Below normal (<1.5)	2(2.5%)	1(1.25%)	0.327
	Normal (1.5-4.5)	5(6.25%)	12(15%)	
	Above normal (>4.5)	73(91.25%)	67(83.75%)	
ALT (IU/L)	Below normal (<8)	2(2.5%)	2(2.5%)	0.863
	Normal (8-40)	61(76.25%)	60(75%)	
	Above normal (>40)	17(21.25%)	18(2.25%)	
Bilirubin (μmol/L)	Normal (0-20)	75(93.75%)	73(91.25%)	0.551
	Above normal (>20)	5(6.25%)	7(8.75%)	
Creatinine (μmol/L)	Below normal (<60)	22(27.5%)	16(20%)	0.308
	Normal (60-120)	47(58.75%)	51(63.75%)	
	Above normal (>120)	11(13.75%)	13(16.25%)	
CRP (mg/L)	Normal (0-10)	3(3.75%)	10(12.5%)	**0.044**
	Above normal (>10)	**77(96.25%)**	**70(87.5%)**	
D-Dimer (ng/ml)	Normal (0-500)	5(6.25%)	6(7.5%)	0.757
	Above normal (>500)	75(93.75%)	74(92.5%)	

Table 2. Clinical characteristics and admission laboratory parameters of patients with or without severe rheumatologic autoimmune disease

P values <0.05 are shown in bold. BMI= body mass index; VTE= venous thromboembolism; LDH= lactate dehydrogenase; APTT= activated partial thromboplastin time; ALT =alanine transferase; CRP= C-reactive protein

Interventions	**Autoimmune disease (394)**	**Propensity matched patients with no autoimmune disease (394)**	**P Value**
CPAP	29 (7.36%)	17 (4.31%)	**0.068**

Mechanical Ventilation	27(6.85%)	38 (9.64%)	0.155
Antiplatelet treatment	27(6.85%)	25(6.35%)	0.774
Thromboprophylaxis on admission	206(52.28%)	201(51.01%)	0.722
Thromboprophylaxis on discharge	25(6.35%)	22(5.58%)	0.652
Thrombolysis	2(0.5%)	0	0.158
IVIg	1(0.2%)	2(0.5%)	0.563
Tocilizumab	1(0.2%)	1(0.2%)	1
Steroids	**82(20.81%)**	**40(10.15%)**	**<0.001**
Haemostatic Support	6(1.52%)	7(1.78%)	0.780
Outcomes			
Renal Failure	10(2.54%)	13(3.30%)	0.526
HIT	1(0.2%)	1(0.2%)	1
Minor Bleeding	10(2.54%)	3(0.76%)	0.050
Major Bleeding	12(3.04%)	9(2.29%)	0.508
Venous Thrombosis	17(4.31%)	15(3.80%)	0.718
Arterial Thrombosis	7(1.78%)	6(1.52%)	0.780
Multi-organ Failure	10(2.54%)	11(2.79%)	0.825
Secondary Infection	65(16.49%)	64(16.24%)	0.923
Death	121(30.71%)	111(28.17%)	0.435

Hospital Associated thrombosis	2(0.5%)	1(0.2%)	0.564

Table 3: Medical interventions and clinical outcomes in patients with or without autoimmune disease

CPAP= continuous positive airway pressure; IVIg= Intravenous immunoglobulins; HIT= heparin induced thrombocytopenia

Interventions	**Severe rheumatologic Autoimmune disease (80)**	**No autoimmune disease (80)**	**P Value**
CPAP	8(10%)	6(7.5%)	0.579
Mechanical Ventilation	6(7.5%)	4(5%)	0.517
Antiplatelet agent	5(6.25%)	7(8.75%)	0.551
Thromboprophylaxis on admission	46(57.5%)	42(52.5%)	0.528
Thromboprophylaxis on discharge	5(6.25%)	3(3.75%)	0.471
Thrombolysis	0	1(1.25%)	0.320
IVIg	0	1(1.25%)	0.320
Tocilizumab	1(1.25%)	0	0.320
Steroids	**18(22.5%)**	**5(6.25%)**	**0.003**
Haemostatic Support	2(2.5%)	1(1.25%)	0.563
Outcomes			
Renal Failure	3(3.75%)	3(3.75%)	1
HIT	0	0	NA
Minor Bleeding	1(1.25%)	1(1.25%)	1
Major Bleeding	3(3.75%)	1(1.25%)	0.315
Venous Thrombosis	2(2.5%)	5(6.25%)	0.249

Arterial Thrombosis	0	0	NA
Multi-organ Failure	4(5%)	1(1.25%)	0.176
Secondary Infection	16(20%)	9(11.25%)	0.129
Death	**32(40%)**	**20(25%)**	**0.043**
Hospital Associated thrombosis	1(1.25%)	1(1.25%)	1

Table 4. Medical interventions and clinical outcomes in patients with or without severe rheumatologic autoimmune disease

CPAP= continuous positive airway pressure; IVIg= Intravenous immunoglobulins; HIT= heparin induced thrombocytopenia

Figure 1

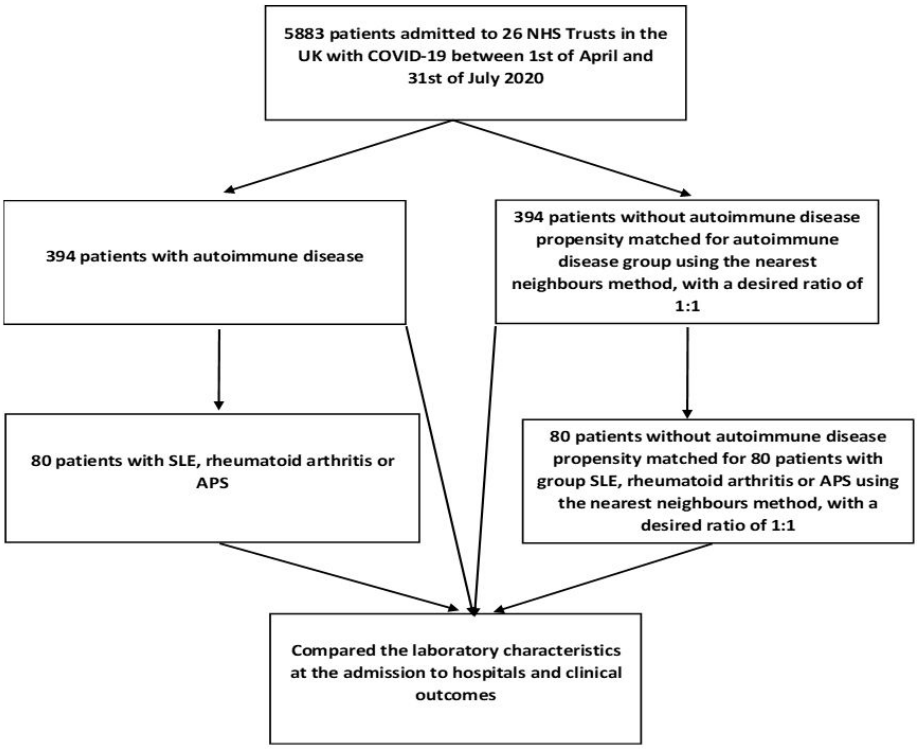

Figure 1: Inclusion of patients into the study and analysis plan

Figure 2A:

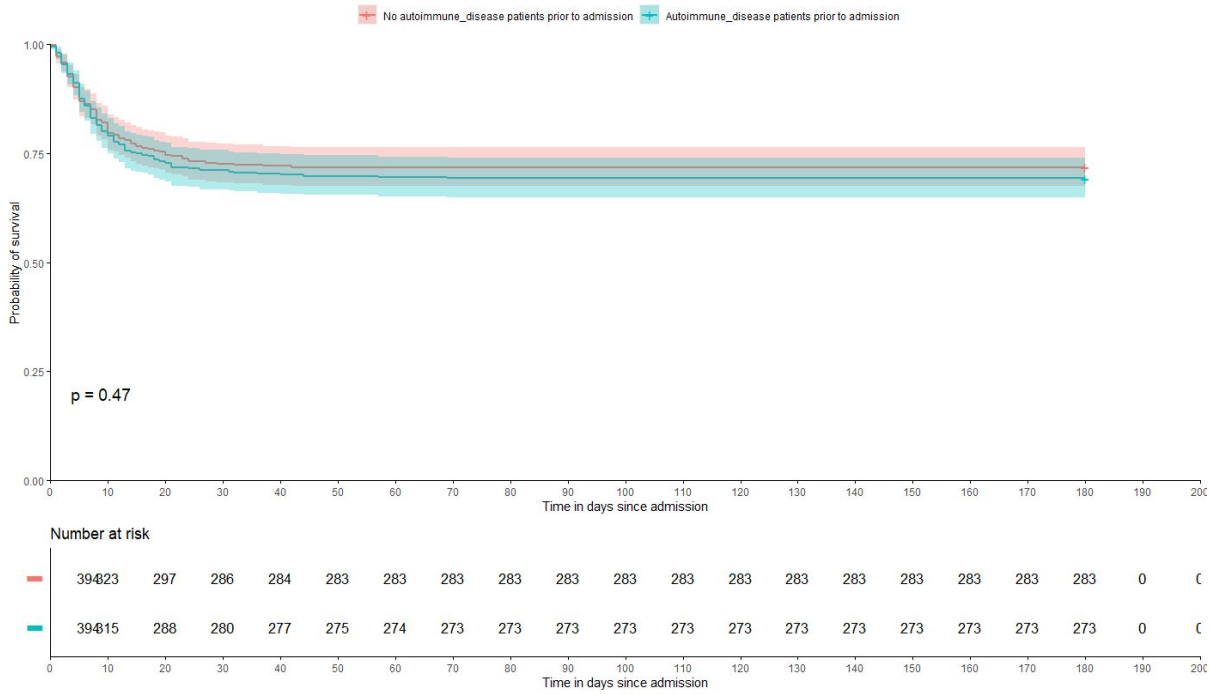

Figure 2: Probability of 180-day survival in patients with or without autoimmune disease

A: Probability of 180-day survival in patients with autoimmune disease vs no autoimmune disease admitted with COVID-19. B: Probability of 180-day survival in patients classified as severe autoimmune disease vs no autoimmune disease admitted with COVID-19

Figure 2B