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Research Article

SARS CoV-19 Infection and ABO Blood groups, correlation with Laboratory Blood Parameter analysis and Mortality, a Single Centre Study in UK

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Abstract

Background and Aim

There is controversial evidence available on the role of blood grouping in determining the susceptibility to SARS-CoV-19 infection. It is postulated that blood group anti-A antibodies offer some protection against SARS-CoV-19 infection and severity of illness due to anti- A antibodies blocking the binding of SARS-CoV-19 to respiratory epithelium. Hence people with blood group O may be protected against SARS-CoV-19 compared with blood group A and AB patients who may do worse. The aim of this study was to retrospectively analyse the ABO Rh blood group data on patients with SARS CoV-19 admitted in a single NHS center in UK hospital trust and further correlate the severity of infection and mortality with the type of blood group.

Material and Methods

We analysed data on 604 confirmed patients with SARS-CoV-19, who's blood groups were known, from a single NHS centre in UK, admitted between February 2020 and March 2021. We correlated ABO Rh blood groups with mortality and various clinical, haematological and biochemical parameters. Patients were classified into four groups according to their blood group (blood group A, 197 patients: blood group B, 117 patients; blood group AB, 34 patients and blood group O, 256 patients).

Results

The analysis showed a tendency towards higher mortality in patients with blood group-A. Certain biochemical and inflammatory markers were lower in patients with blood group AB with a tendency to less organ dysfunction and morbidity. Comparison between deceased patients in all groups revealed significantly higher white blood cells (WBCs) (p=0.0308), neutrophil count (p=0.0073) in the A and B blood groups compared to the AB and O groups. However no statistically significant differences were found between the four groups in regard to neutrophil to lymphocyte ratio (NLR), neutrophil to eosinophil ratio (NER) and the white blood cells* neutrophil to eosinophil ratio (WBCS*Neut/Eos) which are known prognostic factors for SARS-CoV-19. Blood group Rh positive patients tended to have higher CRP and platelet count irrespective of primary blood group but no significant impact on mortality.

Conclusion

The study shows a tendency towards more inflammatory reaction in patients with blood group A and B and Rh positive groups but with no difference in mortality between the blood groups. We acknowledge that the small sample size limits the ability to draw conclusions for a wider population but it adds valuable information and insight in to effects of blood groups on clinical outcomes and inflammatory response to SARS-CoV-19 infection. A larger multicentre retrospective data collection and analysis would be useful with inclusion of patients admitted in intensive care.

Keywords: ABO Rh groups; SARS CoV-19; Severity of infection

Introduction

SARS-CoV-19 has infected over 600 million people and killed over 6 million people worldwide since the first reported case in Wuhan China in December 2019. In the UK over 24 million people have been infected and 220,000 people died due to SARS-CoV-19 infection [8]. Clinical COVID-19 presentation ranges from being asymptomatic, to mild influenza-like symptoms to multiple organ failure and death [9] Various risk factors have been proposed to be correlated with mortality which includes age, male gender, ethnicity, comorbidities such as diabetes, obesity, cancer and immunocompromised state [7,10,11,12,13].

Hospitals worldwide have collected data prospectively as patients with COVID-19 present looking for patterns in clinical findings and patient specific demographics/markers that may predict risk of a poor health outcome in a variety of patient groups. Collected during an emerging pandemic, many of these have limitations, however, additional to learning from individual outcomes, publication allows the possibility of future data pooling and meta-analysis to increase the reliability of findings. Previously reported evidence suggests there may be increased risk of viral infections like hepatitis B and HIV in patients wih blood group A [14] and lower risk of hepatitis B in patients with blood group B [15]. It is postulated that blood group anti-A antibodies offer some protection against SARS-CoV-19 infection and severity of illness due to anti- A antibodies blocking the binding of SARS-CoV-19 to respiratory epithelium. Hence people with blood group O may be protected against SARS-CoV-19 compared with blood group A and AB patients who may do worse [1,2]. Many studies have therefore also looked at ABO blood groups as a risk factor for SARS-CoV-19 infection, severity of illness and death, with interesting but confounding findings. A review of studies published until January 2021 showed nine large studies on blood groups and SARS-CoV-19 related infection and severity. A significant correlation with ABO-Rh blood grouping and risk of infection and severity of illness and mortality with SARS-CoV-19 has been observed [16,17,18,19,20]. From these analysis blood group O and Rh negative appear to be protective against COVID-19 infection and severity of illness as compared to non-O and Rh positive individuals although all these studies are not uniform. There are however several other studies that although may have found higher risk of SARS-CoV-19 infection in blood group A, the severity of association is disputed [21,22].

The mechanism by which a blood group may be protective is not well understood. Blood groups have been known to be associated with malignancy, thromboembolic disorders as well as viral, bacterial and parasitic infections [23,24,25]. Blood group antigens act as receptors for pathogens and facilitate their intracellular uptake [26]. ABO polymorphism has been shown to associated with susceptibility to SARS CoV-19 and protective effect of anti-A antibodies against SARS-CoV 19 by interfering with adhesion of SARS-CoV-19 antigen to angiotensin receptor -2 expressing respiratory epithelial cells [2,27]. Other reports suggest anti-A immunoglobulin isotype, differences in serum Von Willebrand factor levels (VWF) in different ABO blood groups and anti-A iso-haemaglutinin titres [1,28,29,30,31].

We analysed data on patients with SARS-CoV-19 infection admitted to a single NHS trust in UK with varying ethnic mix. We performed a comparative analysis of ABO groups and other clinical and laboratory variables in order to see if ABO-Rh groups had a direct bearing on risk of infection with SARS-CoV-19 and its severity in this multi-ethnic population.

2. Materials and Methods

2.1. Study Design and Participants

This is a retrospective cohort study that included patients with confirmed COVID-19 infection, hospitalised for acute complications between February 2020 and March 2021, at a single UK National Health Trust (NHS).

Patients were identified as COVID-19 positive by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) from throat/nose swabs on a ROCHE COBAS analyser. Nasopharyngeal or oropharyngeal samples were collected from patients for the detection of SARS-CoV-19 RNA. The Xpert® Xpress SARS-CoV-real-time RT-PCR assay was performed to achieve qualitative detection of SARS-CoV-19 RNA. Ethical approvals were obtained through the Integrated Research Approval System (289571), sponsored by the research and development committee of the Trust site (20Haem60) and was designed and conducted in accordance with the tenets of the Declaration of Helsinki.

A total number of 604 patient with CoVID-19 confirmed cases were included in this study. Patients were classified into four groups according to their blood group (blood group A, 197 patients: blood group B, 117 patients; blood group AB, 34 patients and blood group O, 256 patients). Demographic information, clinical data and laboratory tests were collected from the patients' hospital electronic medical records (EMR). All patients received treatment strategies that were recommended by the UK National Health Service (NHS) COVID-19 management protocols [41].

2.2. General Assessments

Standard anthropometric measures of height and weight were recorded to determine body mass index (BMI = weight/height). Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured using an automatic Blood Pressure monitor (UA-767; A&D Instruments Ltd., Wokingham, UK) to determine mean arterial pressure (MAP = 2/3 DBP + 1/3 SBP). Eye opening and motor and verbal responses were assessed to all patients to objectively measure their level of consciousness using Glasgow Coma Score (GCS).[42]

2.3. Laboratory Procedures

Blood and plasma samples drawn from the antecubital fossa vein were assessed immediately for fasting glucose (GLUC), triglycerides (TG), total cholesterol (T-CHOL), high-density lipoprotein cholesterol (HDL-C), blood urea, bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), creatinine (CRE) using the Reflotron Analyzer). Low-density lipoprotein cholesterol (LDL-C) values were calculated using the Friedewald equation. Lactate dehydrogenase (LDH), C-reactive protein (CRP) and ferritin (FER) were examined using a clinical chemistry analyzer). Serum albumin levels (Alb) were measured using the ARCHI. TECT c Systemsinstrument using the 7D53 B albumin assay kit

A Sysmex XN automated haematology analyser was used for complete blood count analysis including white blood cells (WBCs), haemoglobin (Hb), mean corpuscular volume (MCV), platelets (PLT), neutrophils (Neut), lymphocytes (Lymph), monocytes (Mono), eosinophils (Eos) and basophils (Baso) count. LAU ratio was calculated by dividing the LDH concentration by the albumin/urea concentration.

INR and D-Dimer values were measured using ACL TOP coagulation analyzer. For D-Dimer a Latex Reagent was used, which is a suspension of polystyrene latex particles of uniform size coated with the F(ab')2 fragment of a monoclonal antibody highly specific for the D-Dimer domain included in fibrin soluble derivatives to allow a more specific D-Dimer detection avoiding the interference of endogenous factors like the Rheumatoid Factor. When plasma, which contains D-Dimer, is mixed with the Latex Reagent and the Reaction Buffer included in the D-Dimer HS 500 kit, the coated latex particles agglutinate. The degree of agglutination is directly proportional to the concentration of D-Dimer in the sample and is determined by measuring the decrease of the transmitted light caused by the aggregates (turbidimetric immunoassay).

For prothrombin time (PT) the principle of Coagulometric (turbidimetric) clot detection is used in the system to measure and record the amount of time required for a plasma specimen to clot. This technique assesses coagulation endpoint by measuring change in optical density.

INR was calculated using the following equation, where ISI is the international sensitivity index. All laboratory tests were conducted within 3 days of COVID-19 diagnosis.

INR= (PT test/PT normal) ISI [44]

2.4. Sample Size and Statistical Analysis

As the study design was multifactorial in nature, it was calculated that a sample size of n = 604 is sufficient to provide 80% power at an alpha level of 0.05. All analyses were performed using SPSS® statistical software (version 25, IBM Corp., Armonk, NY, USA). Distributions of continuous variables were determined by the Shapiro–Wilk test. In cases where the normality of the data could not be confirmed, appropriate data transformations were made, or non-parametric statistical alternatives were used. Univariate associations were determined using Pearson's (normally distributed data) or Spearman's method (non-normally distributed data). Differences between groups were subsequently assessed using independent-samples t-test or ANCOVA, as appropriate. $p < 0.05$ was considered statistically significant.

3. Results

There were statistically significant differences between the four study groups with regard to mean age (p = 0.016) where patients with blood groups B & AB were younger than patients with blood groups A &O. No statistically significant differences were found between the four groups with regard to SBP (systolic blood pressure), DBP (diastolic blood pressure), HR (heart rate) and Glasgow Coma Scale (GCS) (Table 1).

	GP (A) (197)	GP (B) (117)	GP (AB) (34)	GP (O) (256)	P-value	Post-hoc
Age	67.05 (19.14)	61.51 (20.26)	60.68 (19.79)	67.33 (18.51)	0.016	B & AB< A &O
RR	19.67 (5.62)	20.54 (6.03)	8.51 (2.98)	19.38 (4.97)	0.170	-
DBP	70.55 (16.73)	70.87 (18.07)	74.24 (15.13)	71.35 (15.03)	0.711	-
HR	80.12 (20.15)	81.52 (21.60)	81.27 (16.67)	81.54 (21.03)	0.900	-
GCS	10.06 (6.62)	9.5 (6.85)	9.30 (7.16)	10.43 (6.51)	0.58	-

Table 1: Demographic and clinical observations findings of patients on admission

Abbreviations: RR; respiratory rate, DBP; diastolic blood pressure, HR; heart rate; GCS; Glasgow Coma Scale

Similarly, no statistically significant differences were found between the four groups in regard COVID-19 prognostic haematological ratios including the neutrophil to lymphocyte ratio (NLR), neutrophil to eosinophil ratio (NER) and the white blood cells* neutrophil to eosinophil ratio (WBCS*Neut/Eos) (Table 2).

	GP (A) (197)	GP (B) (117)	GP (AB) (34)	GP (O) (256)	P-value
NLR	8.7(10.26)	6.91(7.08)	6.71(10.05)	7.72(8.59)	0.254
NER	202.98(1562.21)	59.43(68.95)	62.43(64.27)	52.39(90.28)	0.572
WBCS*Neut/Eos	5346.94 (1783)	3150.03(5662.29)	2728.62(5961.84)	2479.74 (5441.70)	0.34

Table 2: Haematological Ratios Among Study Population

Abbreviations: NLR; neutrophil to lymphocyte ratio, NER; neutrophil to eosinophil ratio, WBCS*Neut/Eos; white blood cells* neutrophil to eosinophil ratio

Analysis of haematological findings of the study population showed statistically significant differences between the study groups with regard Glycated haemoglobin (HB-A1C) where group AB patients had higher HB-A1C levels compared to group A, B and O (p=0.002, 0.012, 0.032 respectively). On the other hand, mean corpuscular volume (MCV) was statistically lower in the AB group compared to group A, B and O (p=0.01, 0.004 and 0.023 respectively). No other statistically significant differences were identified between the 4 four groups regarding the rest of the assessed haematological parameters (p>0.05 in all) (Table 3).

	GP (A) (197)	GP (B) (117)	GP (AB) (34)	GP (O) (256)	P-value	Post-hoc

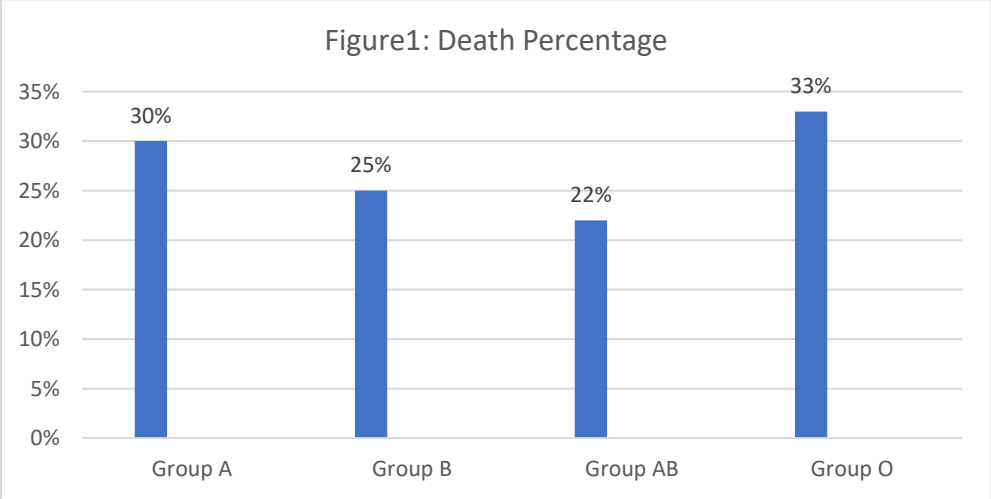
HB-A1C	47.61 (12.02)	49.86 (12.71)	63.11 (16.83)	52.95 (17.85)	0.004*	AB>A, B &O
T-CHOL	4.38 (0.97)	4.10 (1.00)	4.43 (1.33)	4.44 (1.062)	0.635	-
WBCs	10.15 (19.66)	8.33 (4.16)	7.78 (3.94)	7.98 (4.46)	0.265	-
HB	122.58 (24.52)	120.43 (26.43)	113.06 (26.25)	123.22 (21.81)	0.154	-
MCV	87.86 (8.68)	86.09 (10.1)	84.06 (12.82)	88.12 (8.60)	0.047*	AB< A, B &O
PLT	240.52 (114.16)	244.24 (112.4)	230.89 (105.33)	244.80 (107.68)	0.916	-
Neut	6.90 (8.20)	6.37 (3.73)	5.62 (3.63)	6.11 (3.98)	0.452	-
Lymph	1.95 (1.30)	1.31 (0.85)	1.58 (1.72)	1.18 (1.30)	0.664	-
Mono	0.89 (0.40)	0.55 (0.41)	0.49 (0.37)	0.58 (0.35)	0.498	-
Eos	0.057 (0.17)	0.054 (0.14)	0.044 (0.68)	0.0713 (0.33)	0.881	-
Baso	0.025 (0.028)	0.028 (0.42)	0.024 (0.24)	0.025 (0.029)	0.810	-
INR	1.26 (0.80)	1.24 (0.62)	1.13 (0.25)	1.18 (0.42)	0.542	-
D-dimer	4.84 (0.18)	1.12 (0.12)	1.81 (2.65)	5.20 (1.41)	0.705	-
Mg	0.85 (0.14)	0.84 (0.14)	0.79 (0.098)	0.83 (0.13)	0.316	-
Urea	9.05 (7.15)	7.52 (5.16)	7.90 (6.30)	8.40 (6.01)	0.210	-
Na	136.63 (4.95)	135.81 (5.32)	134.89 (4.70)	135.97 (5.01)	0.222	-
K	4.09 (0.55)	4.08 (0.54)	4.05 (0.51)	4.1 (0.63)	0.955	-
Albumin	34.76 (5.24)	35.40 (6.0)	37.0 (4.03)	35.26 (4.47)	0.161	-
Bilirubin	11.69 (9.3)	12.4 (15.1)	9.28 (5.17)	10.5 (7.36)	0.236	-
ALP	101.11 (74.11)	118.3 (135.8)	95.71 (42.39)	108.5 (68.35)	0.358	-
ALT	39.82 (78.24)	43.45 (46.75)	29.59 (25.20)	35.93 (37.11)	0.547	-
CRE	111.56 (77.04)	105.05 (56.72)	108.37 (66.41)	113.90 (95.24)	0.808	-
CRP	106.64 (92.38)	100.52 (84.34)	81.25 (99.53)	97.93 (91.44)	0.558	-
FER	908.10 (1357.2)	897.0 (1716.2)	592.41 (767.89)	983.18 (1428.9)	0.832	-
LDH	523.89 (410.47)	528.30 (351.01)	370.44 (138.55)	417.17 (258.33)	0.089	-
cTnI	314.03 (148.8)	62.92 (197.23)	16.69 (15.79)	139.96 (635.24)	0.349	-
25OHD	45.47 (30.8)	46.22 (27.97)	37.14 (23.58)	46.69 (30.32)	0.826	-

Table 3: Haematological Findings and Organ Function tests of the whole Study Population

Abbreviations: HB-A1c, haemoglobin A1C; T-CHOL, total cholesterol; WBCs, white blood cells; Hb, haemoglobin; MCV, mean corpuscular volume; PLT, platelets; Neut, neutrophils; Lymph, lymphocytes; Mono; monocytes; Eos, eosinophils; Baso, basophils; INR; INR, international normalized ratio; Mg; magnesium, Na; sodium, K; postassium, ALP, alkaline phosphatase; ALT, Alanine transaminase; CRE, creatinine; CRP, C-reactive protein; FER, ferritin, LDH, lactate dehydrogenase; cTnI, cardiac troponin-I; 25OHD, 25-hydroxycholecalciferol.

* Significant p-values are indicated where $p < 0.05$ was considered significant.

No statistically significant difference was found regarding the number of patients died in each group (A= 30%, B=25%, AB=22% and O= 33%) (Figure 1).



	GP (A) (71) 30%	GP (B) (30) 25%	GP (AB) (8) 22%	GP (O) (85) 33%	P-value	Post-hoc
Age	74.92 (14.88)	71.20 (14.03)	72.00 (16.90)	77.32 (12.25)	0.172	-
HB-A1C	46.25 (6.95)	48.55 (10.12)	58.50 (14.84)	56.60 (21.34)	0.151	-
T-CHOL	4.09 (0.92)	4.90 (0.98)	4.13 (0.76)	4.39 (0.91)	0.228	-
WBCs	11.30 (20.09)	9.19 (5.53)	6.24 (3.06)	7.60 (3.81)	0.0308*	A=B > AB &O
HB	118.45(26.54)	115.00 (28.89)	113.62 (33.99)	121.53 (20.51)	0.575	-
MCV	89.81 (7.59)	90.77 (11.40)	90.88 (9.35)	89.91 (8.03)	0.949	-
PLT	225.74(97.28)	194.10 (93.28)	218.37 (152.25)	228.41 (93.74)	0.437	-
Neut	7.27 (4.65)	7.45 (4.63)	4.62 (2.59)	5.90 (3.59)	0.0073*	A=B > AB &O
Lymph	3.28 (1.74)	1.06 (1.12)	1.20 (0.81)	1.042 (0.74)	0.649	
Mono	0.67 (0.68)	0.59 (0.37)	**0.38 (0.20)**	0.57 (0.34)	0.0332*	AB<A, B & O
Eos	0.037 (0.95)	0.029 (0.06)	0.016 (0.04)	0.116 (0.57)	0.556	-
Baso	0.255 (0.343)	0.0381 (0.072)	0.024 (0.035)	0.022 (0.017)	0.253	-
INR	1.36 (1.114)	1.48 (0.91)	1.11 (0.199)	1.29 (0.68)	0.764	-
D-Dimer	6.79 (18.86)	6.59 (12.64)	2.07 (3.08)	5.25 (8.61)	0.00903*	AB<A, B & O
Mg	0.88 (0.16)	0.86 (0.15)	0.79 (0.042)	0.81 (0.14)	0.078	
Urea	12.30 (9.23)	11.09 (6.53)	7.56 (2.61)	10.25 (6.55)	0.0208*	AB<A, B &O
Na	136.34 (5.34)	136.27 (5.49)	134.62 (4.95)	136.06 (6.28)	0.882	-
K	4.21 (0.63)	4.19 (0.59)	4.18 (0.74)	4.09 (0.62)	0.736	-
Albumin	33.34 (5.23)	31.31 (5.86)	35.75 (5.55)	33.75 (4.30)	0.070	-
Bilirubin	12.69 (11.13)	15.93 (10.83)	8.62 (4.10)	11.52 (7.44)	0.0113*	AB<A, B &O
ALK2	104.37 (70.73)	157.79 (245.53)	77.12 (25.85)	123.13 (83.87)	0.172	-
ALT	50.68 (123.81)	47.27 (57.84)	21.25 (17.89)	30.87 (22.25)	0.435	-
CRE	134.13 (84.76)	128.87 (58.37)	122.62 (55.91)	130.01 (80.08)	0.971	-
CRP	132.59 (117.72)	141.70 (79.05)	74.62 (66.00)	106.96 (99.64)	0.0178*	AB<A, B &O
FER	992.34 (1571.01)	2009.06 (3058.71)	151.5 (89.61)	1179.24 (1451.01)	0.160	-
LDH	504.38 (522.6)	660.69 (384.81)	277.67 (62.42)	430.38 (194.01)	0.305	-
cTn (I)	649.11 (2164.76)	162.56 (348.42)	23.50 (21.35)	113.65 (211.07)	0.259	-
25-OHD	89.68 (113.36)	47.28 (33.73)	43.37 (12.82)	43.72 (30.42)	0.032*	A>AB, B &O

Comparison between deceased patients in all groups revealed significantly higher white blood cells (WBCs) (p=0.0308), neutrophil count (p=0.0073) in the A and B blood groups compared to the AB and O groups. Monocytes (p= 0.0332), D-dimer (p=0.00903), urea (p=0.0208), bilirubin (p=0.0113) and C-reactive protein (p= 0.0178) concentrations were lower in AB group compared to A, B and O groups, while 25-hydroxycholecalciferol was higher in A group compared to the B, AB, and O groups (Table 4).

Table 4: Haematological Findings and Organ Function tests of the Deceased Patients in Each Group

Abbreviations: HB-A1c, haemoglobin A1C; T-CHOL, total cholesterol; WBCs, white blood cells; Hb, haemoglobin; MCV, mean corpuscular volume; PLT, platelets; Neut, neutrophils; Lymph, lymphocytes; Mono; monocytes; Eos, eosinophils; Baso, basophils; INR; INR, international normalized ratio; Mg; magnesium, Na; sodium, K; postassium, ALP, alkaline phosphatase; ALT, Alanine transaminase; CRE, creatinine; CRP, C-reactive protein; FER, ferritin, LDH, lactate dehydrogenase; cTnI, cardiac troponin-I; 25OHD, 25-hydroxycholecalciferol.

* Significant p-values are indicated where $p < 0.05$ was considered significant.

Similar to whole population analysis no statistically significant differences were found between the four groups in regard COVID-19 prognostic haematological ratios including NLR, NER and the WBCS*Neut/Eos ratio (p>0.05 in all) (Table 5).

Comparison of the study population using Rh blood group system showed lower HB-A1C and 25-OH concentrations in the A+ compared to the A- group (p=0.028 and 0.045 respectively). Similarly, lower HB-A1C concentrations were found in the O+ compared to the O- group (p=0.001). On the other hand, platelets count was higher in the B+ compared to the B- group (p=0.001), while CRP was higher in the in the O+ compared to the O- group (p= 0.006)

	GP (A) (71)	GP (B) (30)	GP (AB) (8)	GP (O) (85)	P-value
NLR	10.70 (10.56)	10.44 (10.35)	4.35 (2.45)	8.99 (10.03)	0.150
WBCs*Neut/Eso	12128.86 (30314.55)	5975.08 (10262.76)	240.77 (282.8)	2368.85 (3422.68)	0.132

NER	463.68 (651.13)	388.51 (403.05)	43.87 (13.96)	355.92 (455.31)	0.158

Table 5: Haematological Ratios Among Deceased Patients in each Study Population

Abbreviations: NLR; neutrophil to lymphocyte ratio, NER; neutrophil to eosinophil ratio, WBCS*Neut/Eos; white blood cells* neutrophil to eosinophil ratio

Discussion

This is a retrospective review of patients with SARS-CoV-19 infection who were admitted at a single NHS trust in UK who's blood groups were known. The analysis on 604 patients showed that majority were with blood group O(256), followed by group A(197), group B (117) and group AB (34). The three groups had similar mean age, with blood groups O and A being older. There were no significant differences in clinical observations such as blood pressure, heart rate or Glasgow Coma Scale (GCS) suggesting no differences in the severity of illness among four groups. However, in our study clinical and laboratory responses in different ABO blood groups are interesting to note. We note group AB patients may have a lower risk of organ dysfunction or respiratory failure due to COVID-19. Although we found no significant statistical difference in mortality between different ABO groups, in fact blood group O had the highest mortality amongst all four groups but certain haematological indices and biochemical markers of inflammation were favourable in patients with blood group AB with a tendency to lower mortality. In this study we did note that neutrophil/Lymphocyte (N/L) ratio which is a known adverse factor for severity of SARS-CoV-19 infection was higher in patients with blood group A compared with other groups. This suggests more severe inflammatory response inpatients with blood group A[7]. Of interest this study also showed higher WBC/neut/eosinophil ratio in patients with blood group A. Our study is consistent with four other studies that have shown no significant correlation of ABO blood groups with mortality in patients with SARS-CoV-19. Battacharia et al in their pooled meta-analysis of eleven studies including 233006 patients did not show any correlation of ABO blood groups with adverse mortality [3]. The meta-analysis did not however include all studies published on severely ill patients in intensive care, hence interpretation of this analysis should be taken with caution. Unfortunately we don't have data on gender distribution in this data set as we know males often do poorly with SARS-CoV-19 infection. Our study also lacks data on patients admitted to intensive care which represents seriously ill patients. Adua et al did a detailed analysis of nine published studies on ABO blood grouping in patients with SARS-CoV-19 published till January 2021. These studies cover thousands of patients across different continents and ethnic groups. Five of these studies showed correlation of some blood groups with susceptibility to SARS-CoV 19 infection, but the type of blood group susceptible to infection varied in these studies. However only four of nine studies showed correlation with severity of infection and mortality [16]. Analysing these studies in more detail, Ray et all published one of the largest study from Canada on blood type in patients with COVID-19. They found blood group O and Rh negative individuals were less susceptible to COVID-19 and had less severe secondary outcomes [17]. Zhao et al also found similar findings in a Chinese study on COVI-19 and found that people with blood group O were infected less often and had lower mortality as compared to patients with blood group A. They also found blood group B and AB were not at increased risk of infection [18]. Zietz et al from a study in New York also found patients with blood group A more susceptible to COVID-19 infection but contrary to other studies mortality and rate of intubation was less in patients with blood group-A as compared to blood group B and AB [19], similar to our study. Another study by Hoiland et al also found blood group A and AB had a prolonged stay in intensive care and were more likely to require intubation [20].

Similarly a meta-analysis of Spanish and Italian cohort when adjusted for age and gender did show worst outcome with increased incidence of respiratory failure in patients with blood group A and AB [34]. Recent further meta-analyses of 30 studies on SARS CoV-19 infection and ABO blood groups, 14 studies showed increased susceptibility in patients with blood group A as compared with 15 studies which showed reduced risk of infection in patients with blood group O but without any effect on mortality [43].

We did not have enough data in this study on Rh groups, although there was a tendency for higher inflammatory markers and platelet count in patients who were Rh blood group positive irrespective of primary blood ABO blood group. Blood group Rh have been shown to correlate with risk of SARS-CoV-19 infection and severity of illness in at least five studies [19,32,33)]. Two further studies showed that Rh negative groups are associated with less risk of infection, severity of illness and mortality whereas studies by Adua and Leaf et all only showed reduced risk of infection without an impact on mortality [4,16,17,19,].

Summarising the findings from our study and published literature, there does appear to be an association between risk of SARS-CoV-19 infections with blood groups. There is more evidence particularly for blood group A and perhaps for blood group B and Rh positive groups and consistent protection in patients with blood group O. However there is inconsistency as regards blood groups and clinical outcomes, severity of the disease and mortality in patients with SARS-CoV-19. It does however make one wonder as to if there are any molecular mechanisms which may explain the differences to susceptibility. As noticeable from the previous studies that blood group O and B is less common among patients infected with SARS-CoV-19 suggesting there may be a beneficial role of anti-A antibodies [1,28,29]. Previously it has been shown that anti-A antibodies block the adhesion of SARS-CoV-1(sharing similar receptor binding domain as SARS-CoV-19) to ACE-2 receptor cell on respiratory epithelium and hence could reduce the severity of illness [2]. There is some evidence in favour of this observation. Ellinghaus et all have shown those with blood group A have higher risk of sever disease as compared blood group O while Holland et all have shown that patients with blood group A or AB had higher need for mechanical ventilation and prolonged stay in intensive care [20]. There may be other factors influencing the outcome in blood group A patients such as anti-A immunoglobulin isotype, anti-A isohaemaglutinin titres, ACE-2 polymorphism and levels of plasma VWF [4,5,6)]. Blood group O and B both have anti -A antibodies in their serum, yet it is mostly blood group O who are underrepresented with SARS-CoV-19. This may be perhaps due to anti-A IgG isotype in group O patients that may be more protective as compared to group B patients who possess anti-A IgM isotype. Elevated levels of plasma VWF are a known thrombotic risk factor and excessive cardiovascular mortality and plasma VWF levels are known to be lower in patients with blood group O perhaps due to excessive proteolytic

degradation, which may have a bearing on clinical outcomes in blood group O patients. [1,5,28,29,30,31,35,36,37]

- **Genetic mutations, blood group and risk of SARS-CoV -19 and severity of illness**

A large meta-analysis of two case control studies in Spain and Italy on genetic susceptibility to SARS-CoV-19 confirmed replicating gene cluster at locus 3p21.31comprising of six genes (SLC6A20,LZTFL1,CCR9,FYCO1,CXCR6 and XCR1) which may make us susceptible to SARS-Cov-19 infection. They demonstrated that the frequency of the risk allele of the lead variant at 3p21.31 (rs11385942 gene GA or G) was higher among patients who received mechanical ventilation than among those who received oxygen supplementation only. This risk allele is associated with reduced expression of CXCR6 but increased expression of SLC6A20 and LZTLF1in lung epithelium. The same study also showed replicating gene cluster at locus 9q34.2 (rs657152 A or C) that showed higher risk in blood Group A with respiratory failure than other blood groups as well as protective effect in blood group O [34]. One of these genes SLC6A20, encodes the sodium–imino acid (proline) transporter 1 (SIT1) and functionally interacts with ACE-2 receptor [38,39]. Other genes at this locus encode CC motif chemokine receptor 9 (CCR9) and the C-X-C motif chemokine receptor 6 (CXCR6) which is important for regulation of specific location of lung-resident memory CD8 T cells during immune response to various pathogens like influenza viruses [40]. This may also explain the severity of disease in patients with blood group A patients.

Ethnic origin, blood group and risk of infection with SARS-CoV -19

There is paucity of data on ethnic correlation with blood groups. Leaf et al also looked at ethnicity and blood groups and found correlation with blood group A in Caucasians only in whom blood group A was overrepresented, whether this could be explained by genetic polymorphism remains unknown. Our study was done on multi-ethnic population however we did not have full data on ethnicity [4].

To conclude since the spread of SARS-CoV-19 infection, several studies have looked at susceptibility of patients with different ABO and Rh blood groups. Majority of these studies have shown some association with ABO Rh blood groups and SARS-CoV-19 infection but only few have shown an impact on severity of illness and mortality. Many of these studies are limited in sample size, lack data on critically ill patients and ethnicity. These studies have all been retrospective and hence likely affected by selection bias. It is difficult to come to a firm conclusion from these studies including ours as also majority of the other COVID -19 studies also lack data on blood grouping. But it does seem that blood group A and Rh positive patients may be more susceptible to the impact of SARS-Cov-19 thus these groups should be observed more closely and ensure appropriate focused care to limit further events.

This study has limitations inherent to its retrospective design. First, the reliance on previously collected data may introduce selection bias, as the dataset was not specifically designed to address our research objectives. This also limits the ability to control for potential confounding variables, as not all relevant data may have been available or consistently recorded. We did not include patients admitted to intensive care due to lack of information of blood groups. They were obviously more severely ill and could have given us more valuable information. There is also an overall selection bias because not all COVID-19 patients admitted to hospital had blood groups done Second, the accuracy and completeness of the data depend on the quality of documentation in the original records, which may be subject to errors or omissions. This could affect the reliability of key variables and outcomes. Furthermore, the low number of patients in the AB group may limit the statistical power to detect significant differences or draw robust conclusions. Small sample sizes increase the risk of type II errors and may not adequately represent the variability within the population

Conclusion:

Our findings suggest a tendency toward heightened inflammatory reactions in patients with blood groups A and B, as well as Rh-positive blood types, though no significant differences in mortality were observed between the groups. We acknowledge that the small size of our study limits the ability to draw definitive conclusions for the wider population. However, it provides valuable insights into the potential effects of blood groups on clinical outcomes and inflammatory responses to SARS-CoV-19 infection. It may be that this group of patients should have more focused care. Given the current context, where the COVID-19 pandemic has subsided and infection rates are minimal, prospective data collection is unlikely. Therefore, a larger, multicenter retrospective study would be beneficial. Such an analysis, particularly one including patients admitted to intensive care units, could further validate and expand upon these findings, providing a more comprehensive understanding of the relationship between blood group types and COVID-19 outcomes

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Conflict of Interest

No conflict of interest.

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