Biochemical abnormalities in COVID-19: a comparison of white versus ethnic minority populations in the UK

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ABSTRACT

Aims Public Health England has identified that in COVID-19, death rates among ethnic minorities far exceeds that of the white population. While the increase in ethnic minorities is likely to be multifactorial, to date, no studies have looked to see whether values for routine clinical biochemistry parameters differ between ethnic minority and white individuals.

Methods Baseline biochemical data for 22 common tests from 311 SARS-CoV-2 positive patients presenting to hospital in April 2020 in whom ethnicity data were available was retrospectively collected and evaluated. Data comparisons between ethnic minority and white groups were made for all patient data and for the subset of patients subsequently admitted to intensive care.

Results When all patient data were considered, the ethnic minority population had statistically significant higher concentrations of C reactive protein (CRP), aspartate aminotransferase and gamma-glutamyl transferase, while troponin T was higher in the white group. A greater proportion of ethnic minority patients were subsequently admitted to intensive care, but when the presenting biochemistry of this subset of patients was compared, no significant differences were observed between ethnic minority and white groups.

Conclusion Our data show for the first time that routine biochemistry at hospital presentation in COVID-19 differs between ethnic minority and white groups. Among the markers identified, CRP was significantly higher in the ethnic minority group pointing towards an increased tendency for severe inflammation in this group.

INTRODUCTION

In December 2019, a new highly infectious disease, COVID-19, was first reported in Wuhan, Hubei Province, China.[1 2] The causative agent of COVID-19, SARS-CoV-2, has since spread worldwide resulting in 88 387 352 cases and 1 919 204 deaths as of 10 January 2021, according to a weekly epidemiological update from the WHO.[3]

Severe or fatal COVID-19 infection has been associated with gross changes in clinical biochemistry parameters. To date, common findings include increases of markers of tissue damage (creatine kinase (CK), lactate dehydrogenase (LDH), myoglobin and troponin), inflammation (C reactive protein (CRP), ferritin and procalcitonin), renal impairment (increased creatinine and urea) and liver dysfunction (increases of aminotransferases and bilirubin and decreased albumin).[4 5] Severe COVID-19 infection has also been associated with low serum sodium, potassium and calcium.[6] Biochemical data can be predictive in COVID-19; parameters that are predictive of death include increased CRP, LDH, aspartate aminotransferase (AST), troponin I, creatinine and low albumin.[7–10]

In a review by Public Health England, death rates among black, Asian and other minority ethnicities COVID-19 positive people were shown to be significantly higher than in white British people.[11] Death rates in those of Bangladeshi background were twice as high and for other ethnic minority groups between 10% and 50% higher, after taking into account age, sex, deprivation and region. The cause of these discrepancies is unclear but likely to be multifactorial. We have previously assessed differences in cardiac markers at hospital presentation in ethnic minority and white groups in COVID-19,[12] but to date, no study has investigated whether more broad routine biochemistry profiles differ in this setting, nor whether any differences provide prognostic value. To address these questions, we retrospectively reviewed admission biochemistry for a cohort of COVID-19 positive patients in whom ethnicity data were available. We compared all data between ethnic minority and white groups and in a subset of patients who were subsequently admitted to an intensive care unit (ITU).

METHODS

This retrospective observational study was conducted at King's College Hospital National Health Service Foundation Trust, a busy teaching hospital located in South London. Patients with baseline biochemistry data were included in the analysis if they were admitted between 1 and 28 April 2020 (the period of peak admission rates in London during the first wave of the pandemic), had positive (RT-PCR) SARS-CoV-2 serology and if ethnicity data were available. The first available result after hospital admission for the following 22 biochemical tests were obtained for each patient: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), AST, total bilirubin, adjusted calcium, CK, creatinine, CRP, estimated glomerular filtration rate (eGFR), ferritin, gamma-glutamyl transferase (GGT), LDH, magnesium, sodium, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), procalcitonin, phosphate, potassium, troponin T, total protein and urea. Inclusion of admission biochemical data in

the ITU analyses was made if the individual was subsequently transferred to ITU within 28 days of admission. Electronic patient records were accessed for body mass index (BMI) data and to assess for the presence of pre-existing common comorbidities in each patient at baseline (defined as histories of diabetes mellitus, cardiovascular disease (CVD), chronic kidney disease (CKD), hypertension and chronic obstructive pulmonary disease (COPD) or asthma). Patients were classified as 'white' or 'ethnic minority' using the Office for National Statistics list of ethnic groups. All biochemical data were generated using Roche c-702 and e-801 analytical platforms (Roche, Burgess Hill, UK), using blood samples collected into serum separator tubes (Greiner Bio-One Ltd, Stonehouse, UK). All tests are accredited by the United Kingdom Accreditation Service to iso15189. The methods used for ALT and AST included pyridoxal phosphate, with the LDH assay being measured in the L-lactate to pyruvate direction. Test requests on samples for which haemolysis, icteric or lipaemic indices exceeded the manufacturer's limits for that particular test were cancelled and not included in analyses. Biochemical test data were tested for normality using the Kolmogorov-Smirnov test, and with the exception of albumin, adjusted calcium, globulin, LDH, magnesium, potassium and total protein, were found to be not normally distributed so group comparisons of biochemical data were made using a two-tailed Mann-Whitney U test. Data are reported as median (interquartile range (IQR)). Values of $p<0.05$ were taken as statistically significant. The proportion of abnormal results for each test studied was compared using a χ^2 test. Data comparisons were made using R V.3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).[13]

RESULTS

Ethnic minority patients presenting in April 2020 with COVID-19, in comparison with those from white ethnic groups, were younger (median age 65 vs 75 years) and predominantly male (64% vs 52%, table 1). Ethnic minority individuals were more likely to subsequently require ITU admission (19% patients vs 13% white patients, table 1). A history of diabetes mellitus was more common in the ethnic minority group, while CVD history was more common in the white group. Frequencies of hypertension, CKD and respiratory disorders (COPD or asthma) were similar in ethnic minority and white groups (table 1). BMI data were incomplete across the two groups. Of available data (151/211 ethnic minority patients and 70/100 white patients), BMI was similar in the two groups. Median BMI (IQR) in the ethnic minority group was 28.8 kg/m^2 (24.7–33.5) and in the white group 28.7 kg/m^2 (23.3–32.0).

Table 1 Demographic data in ethnic minority and white groups

	Ethnic minority	White
All patient data		
Number	211	100
Age (years)	65 (55–78)	75 (66–84)
Male/female (%)	64/36	52/48
Pre-existing comorbidities (%)		
Diabetes	54	31
CVD	25	50
CKD	31	28
Hypertension	49	49
COPD/asthma	30	27
Patients subsequently admitted to intensive care		
Number (% total)	39 (18)	13 (13)
Age (years)	59 (52–65)	65 (57–71)
Male/female (%)	77/23	77/23

Age data presented as median (IQR).
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

Review of baseline biochemistry data for all patients revealed statistically significant differences between the two groups for a number of common analytes (table 2). Of these results, 86% were obtained on hospital admission day, with 97% of test results being acquired within the first 3 days of the patients hospital stay. The majority of patients in the study had abnormal CRP results; however, CRP concentrations were higher in the ethnic minority group (median value 111.2 mg/L, IQR 66.5–181.1) than in the white group (48.1 mg/L, 22.1–112.9). Increase of this inflammatory marker was not reflected by ethnicity-related differences in procalcitonin, nor ferritin concentration; almost all patients had elevated ferritin. The median cardiac troponin T was higher, and a greater proportion of patients had abnormal results, in the white group than in the ethnic minority group. Median NT-proBNP concentration was also higher in the white group, although this association did not reach statistical significance. Of markers of liver function, AST and GGT were higher in the ethnic minority group but ALP lower. A greater proportion of the ethnic minority population also had AST concentrations falling outside the reference interval. ALT, albumin and total bilirubin were not different between the two groups. No differences between ethnic minority and white groups were noted for sodium, potassium, adjusted calcium or phosphate, nor for markers of renal function (creatinine, eGFR and urea). The tissue damage markers, LDH and CK also showed no ethnicity-specific differences at presentation, with the majority of patients having abnormal values.

When baseline biochemistry data for ethnic minority and white patients that were subsequently admitted to ITU were compared, no statistically significant differences between these groups were observed for any of the analytes studied (table 3).

DISCUSSION

For the first time, we have shown that there are significant differences at hospital presentation between ethnic minority and white populations in results for a number of routine biochemistry tests. The results of this study are therefore important because they may contribute towards a greater understanding of why ethnic minority individuals are at increased risk of death due to COVID-19. The most striking finding from our study is the increase at presentation of CRP in ethnic minority individuals versus white individuals. CRP measurement is now well established as a marker of disease severity in COVID-19.[14] Zhang *et al*[15] showed that in 140 hospitalised patients with confirmed SARS-CoV-2 infection, in non-severe disease, CRP concentrations ranged from 9.5 to 52.1 mg/L, while in severe disease, values ranged from 20.6 to 87.1 mg/L. In another study, 56.4% of patients with non-severe COVID-19 had CRP above the reference interval, which rose to 81.5% in those with severe disease.[16] Around 20% of patients infected with SARS-CoV-2 progress to having associated life-threatening complications involving acute inflammation associated with a cytokine storm, coagulopathy, septic shock and multiple organ failure.[17] Increased concentrations of interleukin-6 (IL-6) are associated with severe COVID-19 and positively correlate with adverse outcomes.[18 19] The increased concentrations of IL-6 directly result in the liver increasing synthesis of CRP.[18] The results from this study raise the interesting possibility that the higher concentrations of CRP in ethnic

Table 2 Biochemistry at presentation (all patient data)

	Number of results		Test result (median (IQR))			Abnormal results (%)		
Test	Ethnic minority	White	Ethnic minority	White	P value	Ethnic minority	White	P value
Albumin (g/L)	211	100	37.0 (34.0–39.5)	37.5 (34.0–41.0)	0.247	30	33	0.668
ALP (IU/L)	209	100	74.0 (57.0–98.0)	84.0 (63.0–102.5)	0.039	12	17	0.302
ALT (IU/L)	104	33	41.0 (27.8–58.0)	32.0 (17.0–70.0)	0.078	29	27	1.000
AST (IU/L)	206	99	52.0 (35.2–76.0)	40.0 (28.0–71.5)	0.008	75	56	0.001
Total bilirubin (µmol/L)	211	100	9.0 (6.5–13.0)	9.0 (6.0–14.0)	0.617	6	6	1.000
Adjusted calcium (mmol/L)	183	81	2.3 (2.2–2.4)	2.3 (2.2–2.4)	0.537	19	22	0.604
CK (IU/L)	63	31	270.0 (111.5–1139.0)	163.0 (63.5–725.0)	0.447	67	52	0.236
Creatinine (µmol/L)	211	100	106.0 (80.0–159.5)	100.0 (76.8–138.5)	0.208	40	35	0.442
CRP (mg/L)	209	98	111.2 (66.5–181.1)	48.1 (22.1–112.9)	<0.001	97	93	0.153
eGFR (mL/min/1.73 m^2)	210	99	58.0 (34.0–78.8)	55.0 (38.5–86.0)	0.447	56	65	0.222
Ferritin (µg/L)	91	35	916.0 (579.0–1815.5)	1046.0 (386.5–1859.0)	0.208	90	86	0.699
GGT (IU/L)	209	100	57.0 (32.0–99.0)	41.0 (23.0–83.2)	0.030	51	40	1.000
LDH (IU/L)	48	12	467.0 (351.2–631.2)	503.5 (457.5–634.0)	0.432	92	92	1.000
Magnesium (mmol/L)	183	81	0.9 (0.8–1.0)	0.8 (0.8–1.0)	0.028	28	32	0.582
Sodium (mmol/L)	211	100	137.0 (134.0–140.0)	137.0 (134.0–140.30)	0.521	35	35	1.000
NT-proBNP (ng/L)	34	13	221.5 (90.8–1077.5)	427.0 (141.0–1678.0)	0.274	66	77	0.448
Procalcitonin (µg/L)	28	8	1.2 (0.4–11.4)	0.7 (0.3–2.5)	0.594	100	100	N/A
Phosphate (mmol/L)	181	81	1.0 (0.8–1.2)	1.0 (0.9–1.2)	0.145	36	30	0.395
Potassium (mmol/L)	208	98	4.2 (3.8–4.7)	4.3 (3.9–4.8)	0.215	24	19	0.502
Troponin T (ng/L)	122	45	19.0 (8.2–52.2)	35.0 (16.0–74.0)	0.023	62	82	0.024
Total protein (g/L)	210	100	71.0 (67.0–74.0)	68.5 (64.0–71.2)	<0.001	12	13	0.929
Urea (mmol/L)	211	99	7.0 (4.6–14.3)	8.7 (5.9–13.9)	0.059	64	67	0.738

P values <0.05 were taken as statistically significant.
N/A=χ^2 test was not applicable to data where only abnormal results were recorded.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

minority patients at hospital presentation may mark an increased susceptibility to severe inflammation during their COVID-19 disease course. These differences appear not to be accounted for by a genetic predisposition of ethnic minority individuals to higher CRP levels; median value of CRP in blacks was 3.0 mg/L versus 2.3 mg/L in whites in one study of healthy individuals.[20] The absence of differences between the ethnic minority and white groups for the two other markers of inflammation studied (procalcitonin and ferritin) supports the hypothesis of a specific increased susceptibility to cytokine-mediated adverse incidents in the ethnic minority population.[21] Pre-existing comorbidities including CVD, COPD, diabetes and hypertension are established risk factors for severe disease in the pandemic.[22] Many of these comorbidities are known to promote a pro-inflammatory state, but of these, only diabetes mellitus prevalence was higher in the ethnic minority group than in the white group in our study. It is hypothesised that existing diabetes mellitus may accentuate the inflammation associated with viral infection[23]; therefore, the increased prevalence of diabetes in the ethnic minority group in our study may be a contributory factor to the increased CRP concentrations at presentation in this group. Like CRP, diabetes has also been shown to be significantly associated with in-hospital mortality.[24]

Liver injury in COVID-19 is also associated with disease severity.[25] It is characterised by increased transminases, with increase of AST dominating over ALT.[5] In our study, AST tended to be higher in the ethnic minority population than in the white population, while ALT did not show any difference between the two groups. However, the increases of transminases seen in both groups were generally mild and unlikely to represent significant liver injury. Although GGT tended to be higher in the ethnic minority population, this difference is likely related to known ethnic differences in this marker.[26] We have previously reported higher troponin T and NT-ProBNP in the white population than in ethnic minorities,[12] although the latter association did not reach statistical significance. Likely contributory factors to these findings are that the white population were older with a higher prevalence of CVD. Elevated troponin has been associated with worse outcomes in COVID-19.[27]

In our cohort, although non-white ethnicity and male gender were predictive of ITU admission, no statistically significant differences in biochemistry at presentation were noted for those who were subsequently admitted to ITU compared with the white population, including for CRP. This may suggest that there is no difference in the pathological mechanisms underlying severe COVID-19 that are reflected by routine biochemistry, but that ethnic minority subjects are at an increased risk of developing them.[19] Of course, the association between ethnic minority and severe COVID-19 disease is likely to be complex and incorporate multiple demographic and socioeconomic factors not already captured in this study. In one study, Raisi-Estabragh *et al*[28] suggested that both the sex and ethnic patterns of COVID-19 are not adequately explained by variation in cardiometabolic factors, 25(OH)-vitamin D concentrations or socioeconomic factors; clearly, there is a need for more research required to define the mechanism of increased ethnic minority risk.

This study has some limitations. Although the facts that 86% of total test results were obtained on admission day and 97% within 3 days of admission would argue against the possibility of differences in care between ethnic groups while in hospital, we cannot exclude the possibility that biochemical differences

Table 3 Biochemistry at hospital presentation in patients subsequently admitted to intensive care

	Number of results		Test result (Median (IQR))			Abnormal results (%)		
Test	Ethnic minority	White	Ethnic minority	White	P value	Ethnic minority	White	P value
Albumin (g/L)	39	13	38.0 (34.0–39.0)	35.0 (32.0–37.0)	0.167	28	38	0.729
ALP (IU/L)	39	13	81.0 (57.0–107.0)	83.0 (74.0–132.0)	0.459	21	31	0.704
ALT (IU/L)	36	10	44.5 (30.0–68.5)	76.0 (41.0–154.5)	0.432	36	50	0.667
AST (IU/L)	39	13	68.0 (48.5–136.0)	65.0 (44.0–183.0)	0.966	87	77	0.657
Total bilirubin (µmol/L)	39	13	8.0 (7.0–13.0)	11.0 (8.0–18.0)	0.203	5	23	0.175
Adjusted calcium (mmol/L)	39	13	2.3 (2.2–2.4)	2.3 (2.2–2.3)	0.958	23	31	0.853
CK (IU/L)	29	10	632.0 (161.0–1687.0)	142.5 (83.2–1174.2)	0.311	79	40	0.054
Creatinine (µmol/L)	39	13	110.0 (81.0–211.0)	130.0 (110.0–182.0)	0.310	41	62	0.335
CRP (mg/L)	39	13	157.0 (111.4–257.1)	168.4 (40.9–251.8)	0.616	100	100	N/A
eGFR (mL/min/1.73 m^2)	39	13	59.0 (28.0–83.0)	39.0 (32.0–58.0)	0.295	51	85	0.073
Ferritin (µg/L)	34	10	1054.5 (718.0–1981.0)	1822.0 (1018.2–2507.5)	0.245	97	90	0.937
GGT (IU/L)	39	13	91.0 (46.0–136.0)	66.0 (48.0–100.0)	0.512	72	69	1.000
LDH (IU/L)	28	6	522.5 (399.8–687.0)	500.5 (402.2–672.2)	0.878	96	100	1.000
Magnesium (mmol/L)	39	13	0.9 (0.9–1.0)	1.0 (0.8–1.1)	0.657	33	46	0.618
Sodium (mmol/L)	39	13	136.0 (134.0–139.0)	137.0 (136.0–138.0)	0.367	38	23	0.501
NT-proBNP (ng/L)	23	5	400.0 (164.5–1867.0)	427.0 (126.0–3916.0)	0.676	74	80	1.000
Procalcitonin (µg/L)	22	8	1.6 (0.5–11.8)	0.7 (0.3–2.5)	0.241	100	100	N/A
Phosphate (mmol/L)	39	13	1.1 (0.8–1.5)	1.2 (1.0–1.7)	0.336	46	54	0.873
Potassium (mmol/L)	39	13	4.4 (4.0–4.9)	4.7 (3.8–5.4)	0.695	28	38	0.729
Troponin T (ng/L)	35	12	24.0 (14.5–54.0)	32.0 (16.0–90.2)	0.472	74	92	0.389
Total protein (g/L)	39	13	72.0 (67.0–73.0)	66.0 (60.0–71.0	0.044	8	15	0.786
Urea (mmol/L)	39	13	8.6 (5.0–15.2)	17.6 (9.9–19.1)	0.076	59	85	0.178

P values <0.05 were taken as statistically significant.
N/A=χ^2 test was not applicable to data where only abnormal results were recorded.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

are not contributed to by variance in the disease stage at which different ethnic groups accessed hospital care. In the patients who were admitted to ITU during their hospital stay, the number of results for some tests may be too low to identify true differences between the two groups. The outcomes of ITU patients (requirement for mechanical ventilation/continuous positive airway pressure support and morbidity/mortality) were also not available to allow interrogation of the biochemistry with respect to endpoint. In addition, the majority of the ethnic minority group were of black ethnicity (149/211 of all ethnic minority cases, all ethnic minority individuals in ITU), so caution is advised in making generalisations across all non-white ethnic groups. Finally, for some tests in the study, such as procalcitonin, only a small number of tests were performed overall.

Take home messages

- In the UK, it has been shown that ethnic minorities have poorer outcomes in COVID-19 relative to those of the white population, including an increased risk of death.
- In this study, we show that there are significant differences between ethnic minority and white populations in routine clinical biochemistry parameters at presentation to hospital with COVID-19.
- Among the markers identified, C reactive protein was significantly higher in the ethnic minority group, pointing towards an increased tendency for severe inflammation in this group, which may contribute towards the poorer outcomes in this group reported previously.

In conclusion, the major finding of this study is that ethnic minority patients have higher CRP concentrations at presentation, indicating a more severe acute inflammation. This may augment existing comorbidities characterised by chronic inflammation that may be more prevalent in the ethnic minority population such as diabetes, pointing towards an increased tendency for severe inflammation in this group.

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