BMJ Open Hypertension is the major predictor of poor outcomes among inpatients with COVID-19 infection in the UK: a retrospective cohort study

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ABSTRACT

Objective To assess the impact of diabetes, hypertension and cardiovascular diseases on inpatient mortality from COVID-19, and its relationship to ethnicity and social deprivation.

Design Retrospective, single-centre observational study
Setting Birmingham, UK.

Participants 907 hospitalised patients with laboratory-confirmed COVID-19 from a multi-ethnic community, admitted between 1 March 2020 and 31 May 2020.

Main outcome measures The primary analysis was an evaluation of cardiovascular conditions and diabetes in relation to ethnicity and social deprivation, with the end-point of inpatient death or death within 30 days of discharge. A multivariable logistic regression model was used to calculate HRs while adjusting for confounders.

Results 361/907 (39.8%) died in hospital or within 30 days of discharge. The presence of diabetes and hypertension together appears to confer the greatest mortality risk (OR 2.75; 95% CI 1.80 to 4.21; $p < 0.001$) compared with either condition alone. Age > 65 years (OR 3.32; 95% CI 2.15 to 5.11), male sex (OR 2.04; 95% CI 1.47 to 2.82), hypertension (OR 1.69; 95% CI 1.10 to 2.61) and cerebrovascular disease (OR 1.87; 95% CI 1.31 to 2.68) were independently associated with increased risk of death. The mortality risk did not differ between the quintiles of deprivation. High-sensitivity troponin I was the best predictor of mortality among biomarkers (OR 4.43; 95% CI 3.10 to 7.10). Angiotensin-receptor blockers (OR 0.57; 95% CI 0.33 to 0.96) and ACE inhibitors (OR 0.65; 95% CI 0.43 to 0.97) were not associated with adverse outcome. The Charlson Index of Comorbidity scores were significantly higher in non-survivors.

Conclusions The combined prevalence of hypertension and diabetes appears to confer the greatest risk, where diabetes may have a modulating effect. Hypertension and cerebrovascular disease had a significant impact on inpatient mortality. Social deprivation and ethnicity did not have any effect once the patient was in hospital.

INTRODUCTION

Since the outbreak in December 2019 originating in Wuhan, China, the COVID-19 caused by SARS-CoV-2 has spread rapidly across the world, with over a million deaths as of 2 November 2020.¹ Since the first reported

Strengths and limitations of this study

- A detailed and reliable collection of data in line with real world evidence during the first surge of this current pandemic using hospital data with an accurate record of comorbidities.
- Uniform clinical care received by all patients as practised across the country demonstrating for the first time that hypertension is more important than diabetes.
- A representative sample of the black, Asian and minority ethnic communities living in the UK.
- The data on biomarkers were incomplete as every patient did not have every test as there was no national guidance at the time.

case on 31 January 2020 in the UK, COVID-19 has spread rapidly across the country with over 50 000 deaths as of 30 November 2020.²

While transmission of any infection is related to the propensity of the agent to spread easily and quickly, the establishment of infection and its severity thereof is determined by host factors and the ability of the host to fight off the infection. For the majority of individuals that contract SARS-CoV-2, the infection is mild, and they do not require medical attention. However, some individuals develop a severe infection and require hospitalisation for treatment. Depending on the severity of the disease, patients may be admitted to the intensive therapy unit (ITU), treated with medication only and/or given respiratory support. It has been suggested from clinical studies that the pre-existing comorbidities particularly cardiovascular disease, diabetes and hypertension are highly likely to be contributing factors.³ There have also been data that suggest individuals from black, Asian, and minority ethnic (BAME) communities or areas of social deprivation are at a disproportionately greater risk of death from SARS-CoV-2.⁴

Birmingham, UK has a large multi-ethnic community with a distribution of 57.9% Caucasian, 23.7% Asian including Chinese, 7.2% Afro-Caribbean and 11.1% representing mixed and other ethnic groups.⁵ A substantial proportion of people from BAME live in the inner city of Birmingham, with a high prevalence of chronic diseases, particularly diabetes (10.5% in Birmingham compared with the UK national prevalence of 8.9%) and cardiovascular disease (3.0% in Birmingham compared with 3.1% for England).⁶

We therefore undertook detailed analyses of the patients' clinical characteristics including their pre-existing comorbidities, to examine in particular the impact of diabetes, hypertension, cardiovascular diseases and cardiovascular drug therapy on inpatient COVID-19 mortality, and the relationship to ethnicity and social deprivation.

METHODS

Study design and oversight

This is a retrospective, single-centre observational study supported by Sandwell and West Birmingham National Health Service (NHS) Trust Research and Development Department with ethical approval from NHS Health Research Authority and Health and Care Research Wales (HCRW) (IRAS Project ID: 284293; REC Reference 20/SC/0248). The study included patients across two hospital sites; City Hospital and Sandwell Hospital, both of which treated COVID-19-infected patients during the 2020 pandemic.

Study population

The study included all adult patients (>17 years of age) admitted to inpatient medical wards between 1 March 2020 and 31 May 2020. This was the first height of the current pandemic. All patients had positive swab tests for SARS-CoV-2 and had been an inpatient for at least 24 hours. The throat and nasal swab specimens were processed using real-time reverse transcriptase-PCR (RT-PCR). Patients diagnosed as positive but not admitted into the hospital or not admitted to an internal medicine ward were excluded. Patients with symptoms suggestive of COVID-19 but with a negative test were also excluded from this study. Data collection began on an individual's first hospital admission and continued for a period of 30 days after discharge, as it was felt that death within 30 days of discharge was likely to be related to the outcome while an inpatient.

Data source

Demographic, clinical, laboratory and outcome data were extracted electronically from patients' electronic health-care records (EHR) (in use by the Trust since October 2019) and related laboratory databases for hospital admissions by the Trusts' informatics department. Laboratory data are also routinely uploaded to these data servers and linked with the EHR. The accuracy of the retrieved dataset

was manually checked and validated by two authors (AB and BL) by directly accessing the patients' case-record entries prior to de-identification.

Patients' postcodes were used to retrieve data on their Index of Multiple Deprivation (IMD) from the UK government Ministry of Housing, Communities and Local Government. The IMD is the official measure of relative deprivation in England. Indices of Deprivation 2019 used for this study is the most up-to-date deprivation index published (online supplemental appendix).⁷ We used the Charlson Index of comorbidity as a composite measure of patients' comorbidities as a simple means to quantify the effect of comorbid illnesses, and account for the aggregate effect of multiple concurrent disease processes on clinical outcome, such as mortality.⁸

Data collection

Data on patients' demographic characteristics, comorbidities, cardiovascular drug therapy, serum biomarkers, admission to ITU, date of admission and discharge from hospital, and date of death were retrieved for analyses. The clinical information included age, sex, ethnicity, blood pressure, body mass index (BMI) on admission, coexisting medical conditions, the Charlson Index of comorbidity and the use of ACE inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), statins, anticoagulant and antiplatelet therapy on admission. Ethnicity data was self-reported. Smoking status was not available. The serum biomarkers used for analyses were high-sensitivity (hs)-troponin I, serum ferritin, C reactive protein (CRP), lactate dehydrogenase (LDH) and prothrombin time. hs-troponin I and serum ferritin were measured by chemiluminescent microparticle immunoassay on the Abbott Architect. Measurement of LDH and CRP was by immunoturbidimetric assay, performed on the Abbott Architect. International normalised ratio was calculated from prothrombin time measured on the Instrumentation Laboratory ACL TOP. The Modification of Diet in Renal Disease formula was used to calculate estimated glomerular filtration rate (eGFR).

Statistical analyses

The primary analysis was an evaluation of cardiovascular conditions, such as ischaemic heart disease (IHD), hypertension, cerebrovascular disease, atrial fibrillation (AF) and diabetes in relation to ethnicity and social deprivation, with the end-point of inpatient death or death within 30 days of discharge. Continuous variables are presented as means and SD or as medians with IQR as appropriate. Parametric data were compared using independent t-test and Mann-Whitney U test was used for non-parametric data. Transformation of values of biomarkers was necessary prior to statistical analysis where the data did not conform to a normal distribution. Where more than two groups were present, the groups were compared using analysis of variance. Categorical variables are expressed as frequencies and percentages and compared using χ^2 test or Fischer's exact test. Multiple imputation

for missing data was not undertaken. Missing data were encountered with biomarkers which were not used in the primary outcome analyses and would therefore not affect these estimates. A multivariable logistic regression was undertaken for the primary analysis to ascertain the effect of demographic factors, indices of deprivation, coexisting cardiovascular conditions and medications on the likelihood of death. The purpose was to understand the main effects and not to develop a predictive model. Hence, clinically and biologically meaningful variables were considered that were adjusted for confounding. OR and the corresponding 95% CIs were calculated. A separate model was constructed to specifically understand the relative contribution of diabetes and hypertension either isolated or in combination on mortality after adjusting for ethnicity, sex and BMI. In both models the area under the receiver-operating characteristic (ROC) curve was used to assess model fit and therefore the discriminant power of the model.

All statistical analyses were undertaken using STATA/MP V.15.1 (StataCorp). All p values are two-sided and an α -value of 0.05 was considered to indicate statistical significance.

Public and patient involvement

Patients were not involved in setting the research question or outcome measures, nor were they involved in other areas of the study design. The results of this study will be disseminated across both hospital sites with particular attention towards the care of high-risk patients as identified in the analyses.

RESULTS

Study population

A total of 992 patients were admitted as inpatients on the internal medicine wards. Of these, 85 patients were excluded from the analyses due to missing ethnicity data ($n=69$), identifying as mixed ethnicity ($n=15$) or death after the 30-day period ($n=1$) (online supplemental figure S1). A total of 907 patients were included in the final study population and demographic characteristics are shown in table 1.

Of the 907 patients, 546 (60.2%) survived and 361 (39.8%) died. Non-survivors were aged 65 years or older (85.3%; χ^2 73.65; $p<0.0001$) and men (62.0% men vs 38.0% women; χ^2 12.74; $p<0.001$) in univariate analysis (online supplemental table S1). There was an exponential increase in mortality risk with increasing age (online supplemental figure S2). 10.9% (99/907) were admitted to ITU. 60.6% (60/99) of those admitted died in ITU (median age: 63 years; IQR: 56.5–72.5 years) and the majority were men (43/60; 71.7%). 41.7% of non-survivors in ITU were Asian (25/60), 36.7% Caucasian (22/60) and 21.7% Afro-Caribbean (13/60) although the ethnic distribution between the survivors and non-survivors in ITU was not statistically significant ($p=0.304$) (online supplemental table S2).

Analysis of co-morbidities

Overall, non-survivors had a statistically significant greater number of associated comorbidities (comorbidities >6 : 40.7% in non-survivors vs 22.9% in survivors). The mean BMI was slightly lower among non-survivors (-1.0 kg/m²; 95% CI 0.10 to 1.99; $p=0.030$) (table 1). 46.4% of patients in the 70–89-year-age group and 57.8% of those above 90 years had a BMI of <25 kg/m² (online supplemental table S3). 45.9% (416/907) of patients had diabetes, with a greater prevalence among non-survivors (53.7% non-survivors vs 40.7% survivors; χ^2 14.98; $p<0.001$), with the overall prevalence of diabetes being highest among Caucasians (188/416; 45.2%; $p<0.0001$). However, the prevalence of diabetes between ethnic groups among non-survivors was highest for Asian patients (77.3% Asian, 69.4% Afro-Caribbean, 39.3% Caucasian; χ^2 43.29; $p<0.0001$) (table 2, online supplemental table S4). 69.5% (630/907) of patients in the overall cohort had hypertension, with a greater prevalence among non-survivors (79.5% non-survivors vs 62.8% survivors; χ^2 28.51; $p<0.0001$). The overall prevalence of hypertension was highest among Caucasians (356/630; 56.5%; $p=0.054$). The prevalence of hypertension between ethnic groups for non-survivors was not statistically different (86.4% Asian, 82.3% Afro-Caribbean, 75.8% Caucasian; χ^2 4.58; $p=0.101$) (table 2, online supplemental table S5). 38.4% of patients in the overall cohort had both diabetes and hypertension, with 31.1% having hypertension only and 7.5% with only diabetes (figure 1). The combined prevalence of diabetes and hypertension was greater among non-survivors (171/361; 47.4%) compared with survivors (177/546; 32.4%) (online supplemental table S6). Among patients with pre-existing IHD, 4.1% had diabetes, 35.2% had hypertension and 53.2% had both. The corresponding figures for patients with cerebrovascular disease were 6.3% diabetes, 38.6% hypertension and 47.2% for both.

Among the 60 patients who died in ITU, an increased prevalence of comorbidities was also observed: 68.3% (41/60) had diabetes, 70.0% (42/60) had hypertension, 28.3% (17/60) had IHD, with a smaller number having AF (13.3%; 8/60) and cerebrovascular disease (8.3%; 5/60). The combined prevalence of diabetes and hypertension was observed among 56.7% (34/60) of the patients who died in ITU.

Antiplatelet therapy was significantly more often prescribed in non-survivors, while the use of ACEIs, ARBs, anticoagulants, statins and antiplatelet agents were similar (table 1).

Analysis of biomarkers

Serum hs-troponin I and CRP levels were significantly elevated in non-survivors (table 1). Serum hs-troponin I, which is highly specific for myocardial injury was found to be the best predictor of outcome after adjusting for IHD, diabetes, AF, cerebrovascular disease and hypertension (OR 4.43; 95% CI 3.10 to 7.10; $p=0.005$. Area under ROC curve for model: 0.84). The eGFR at baseline was lower

Table 1 Patient characteristics with coexisting medical conditions and serum biomarkers among survivors and non survivors of COVID-19 infection*

Characteristic	All patients (N=907)	Survivors (N=546, 60.2%)	Non-Survivors (N=361, 39.8%)	P value
Age—year—mean (SD)	70.9 (16.7)	66.3 (17.6)	77.8 (12.4)	<0.0001
Age ≥65 years— n (%)	627 (69.1)	319 (58.4)	308 (85.3)	<0.0001
Age distribution— n (%)				
17–29 years	16 (1.8)	15 (2.8)	1 (0.3)	
30–49 years	86 (9.5)	81 (14.8)	5 (1.4)	
50–69 years	266 (29.3)	188 (34.4)	78 (21.6)	
70–89 years	454 (50.1)	233 (42.7)	221 (61.2)	
90+ years	85 (9.4)	29 (5.3)	56 (15.5)	
Sex				
Female— n (%)	410 (45.2)	273 (50.0)	137 (38.0)	<0.0001
Male	497 (54.8)	273 (50.0)	224 (62.0)	
Race or ethnicity— n (%)††				
Asian	248 (27.3)	160 (29.3)	88 (24.4)	0.196
Afro-Caribbean	140 (15.4)	78 (14.3)	62 (17.2)	
Caucasian	519 (57.2)	308 (56.4)	211 (58.5)	
Coexisting conditions— . n (%)				
Diabetes	416 (45.9)	222 (40.7)	194 (53.7)	<0.0001
Hypertension	630 (69.5)	343 (62.8)	287 (79.5)	<0.0001
Ischaemic heart disease	293 (32.3)	156 (28.6)	137 (38.0)	0.003
Atrial fibrillation	192 (21.2)	101 (18.5)	91 (25.2)	0.015
Cerebrovascular disease	254 (28.0)	112 (20.5)	142 (39.3)	<0.0001
Charlson Index of comorbidity—n, median (range)	824 5 (1–20)	468 4 (1–20)	356 6 (1–17)	<0.0001
Charlson Index of comorbidity—category (frequency)				
1–3	242	179	63	
4–6	330	182	148	
7–9	161	71	90	
10–12	52	20	32	
13–15	30	10	20	
16–20	9	6	3	
Comorbidities >6 no./total no. (%)	252/824 (30.6)	107/468 (22.9)	145/356 (40.7)	<0.0001
Clinical parameters on admission				
Systolic blood pressure (mm Hg)— n,mean (SD)	904 124.7 (21.4)	544 125.9 (18.5)	360 122.8 (25.1)	0.032
Diastolic blood pressure(mm Hg)— n,mean (SD)	901 69.6 (15.4)	541 72.0 (13.4)	360 66.1 (17.3)	<0.0001
BMI (kg//m ² —mean (SD)	789 27.4 (6.6)	486 27.8 (6.6)	303 26.8 (6.5)	0.030
Estimated GFR—mL/min/1.73m ² —n, mean (SD)	732 62.8 (25.1)	435 67.2 (23.6)	297 56.2 (25.8)	<0.0001
Biomarkers				
hs-troponin I (ng/L)n, median (IQR)	237 26 (9–109)	120 13 (5–42.5)	117 55 (17–166)	<0.0001

Continued

Table 1 Continued

Characteristic	All patients (N=907)	Survivors (N=546, 60.2%)	Non-Survivors (N=361, 39.8%)	P value
Lactate dehydrogenase (U/L)— n, median (IQR)	181 414 (281–689)	86 381.5 (246–606)	95 437 (297–637)	0.066
Ferritin (µg/L)—n, (IQR)	309 837 (449–1740)	169 841 (445–1740)	140 818.5 (505–1729.5)	0.196
C-reactive protein(mg/L)— n, median (IQR)	511 101 (44–178)	300 73.5 (24–141.5)	211 145.0 (82–238)	<0.0001
INR—n, median (IQR)	479 1.25 (1.14–1.41)	275 1.24 (1.13–1.39)	204 1.27 (1.15–1.43)	0.968
D-dimer(µgFEU/mL)—n, median (IQR)	153 1.66 (0.89–5.71)	80 1.21 (0.61–2.92)	73 2.34 (1.29–8.14)	<0.001
Medications—n (%)				
ACE inhibitors	203 (22.4)	116 (21.3)	87 (24.1)	0.313
Angiotensin receptor blockers	103 (11.4)	67 (12.3)	36 (10.0)	0.285
Statins	459 (50.6)	263 (48.2)	196 (54.3)	0.071
Antiplatelet therapy	290 (32.0)	153 (28.0)	137 (38.0)	0.002
Anticoagulants	186 (20.5)	108 (19.8)	78 (21.6)	0.505

*Values within parentheses represent SD, per cent or range as specified.

†Race and ethnicity were self-reported.

BMI, body mass index; hs, high sensitivity; INR, international normalised ratio.

among non-survivors (mean difference in eGFR -11.0 mL/min/ 1.73m^2 ; 95% CI -14.64 to -7.38 ; $p<0.0001$).

Association with indices of deprivation

88.1% patients admitted with COVID-19 were from the lower two quintiles and 98% from the lower three quintiles of IMD. The predicted probability of death from COVID-19 was highest in the lower quintiles of IMD (0.40, 0.39, 0.41 for IMD quintiles 1, 2 and 3, respectively); the prediction was less accurate for the higher quintiles given the smaller number of patients in these groups (table 3). The odds of dying did not differ between the quintiles of IMD after correcting for sex and ethnicity. The ethnic distribution was similar across the quintiles of deprivation (table 2).

Multivariable logistic regression analysis

A multivariable logistic regression model was used to assess the impact of independent predictors on mortality as the primary outcome analysis. The corresponding OR, 95% CI are shown in figure 2, online supplemental table S7a. Younger age (<65 years), female sex and the use of ACEI and ARBs were associated with a greater chance of survival. An age greater than 65 years (OR 3.32; 95% CI 2.15 to 5.11; $p<0.0001$), male sex (OR 2.04; 95% CI 1.47 to 2.82; $p<0.0001$), presence of hypertension (OR 1.69; 95% CI 1.10 to 2.61; $p=0.017$) and cerebrovascular disease (OR 1.87; 95% CI 1.31 to 2.68; $p=0.001$) were associated with an increased risk of death. Diabetes (OR 1.28; 95% CI 0.91 to 1.80; $p=0.163$) did not appear to have a significant impact when adjusted for confounders, including BMI. There was no statistically significant influence of

ethnicity on the overall model. Exploratory analysis using a reduced model to understand the relative contribution of diabetes and hypertension on mortality, showed the highest OR for patients with diabetes and hypertension (OR 2.75; 95% CI 1.80 to 4.21; $p<0.001$) compared with hypertension alone (OR 1.95; 95% CI 1.26 to 3.02; $p=0.003$), diabetes alone (OR 1.28; 95% CI 0.66 to 2.48; $p=0.463$) or having neither condition (OR=1.00) (online supplemental table S7b).

DISCUSSION

Principal findings

Novel findings were significantly high combined prevalence of diabetes with hypertension among those who died from COVID-19 compared with either condition alone. Advanced age (>65 years), male sex, hypertension and cerebrovascular disease were independently associated with an increased risk of inpatient death with no additional risk of excess mortality from ethnicity or high social deprivation scores.

Strengths and limitations of the study

The strengths of this study lie in the detailed and reliable collection of data as part of routine clinical practice in patients admitted to hospital with severe COVID-19 and being able to include robust information on pre-existing comorbidities, ethnicity, demographic data and deprivation scores within a multi-variable model. Specifically, the data would not have been affected by deaths in the community or in care homes. The clinical care received

Table 2 Demographic characteristics and prevalence of cardiovascular conditions among ethnic subgroups COVID-19 infection*

Characteristic	Non-survivors (n, %)			Survivors (n, %)			P value	Asian N=160	Afro-Caribbean N=78	Caucasian N=308	P value
	Asian N=88	Afro-Caribbean N=62	Caucasian N=211	Asian N=160	Afro-Caribbean N=78	Caucasian N=308					
Age (years)—mean (SD)	73.3 (13.1)	77.4 (13.6)	79.7 (11.3)	57.9 (17.5)	66.0 (17.7)	70.7 (16.0)	<0.0001				
Age ≥65 years—n, (%)	68 (77.3)	50 (80.7)	190 (90.1)	61 (38.1)	43 (55.1)	215 (69.8)	<0.0001				
Female sex—n, (%)	24 (27.3)	26 (41.9)	87 (41.2)	68 (42.5)	44 (56.4)	161 (52.3)	0.063				
Coexisting conditions—											
n, (%)											
Diabetes	68 (77.3)	43 (69.4)	83 (39.3)	77 (48.1)	40 (51.3)	105 (34.1)	0.002				
Hypertension	76 (86.4)	51 (82.3)	160 (75.8)	89 (55.6)	58 (74.4)	196 (63.6)	0.018				
Ischaemic heart disease	48 (54.6)	15 (24.2)	74 (35.1)	41 (25.6)	10 (12.8)	105 (34.1)	0.001				
Atrial fibrillation	13 (14.8)	10 (16.1)	68 (32.2)	9 (5.6)	5 (6.4)	87 (28.3)	<0.001				
Cerebrovascular disease	30 (34.1)	22 (35.5)	90 (42.7)	21 (13.1)	14 (18.0)	77 (25.0)	0.009				
Charlson Index of comorbidity >6 no./total no. (%)	35/86 (40.7)	22/60 (36.7)	88/210 (41.9)	18/113 (15.9)	11/71 (15.5)	78/284 (27.5)	0.013				
Clinical parameters on admission											
Systolic blood pressure (mm Hg)—n, mean (SD)	87 122.4 (27.1)	62 130.2 (26.6)	211 120.8 (23.4)	158 124.6 (19.1)	78 130.7 (19.2)	308 125.4 (17.8)	0.034				0.041
Diastolic blood pressure (mm Hg)—no./total no, mm Hg—mean (SD)	87 64.8 (17.5)	62 65.7 (20.2)	211 66.7 (16.3)	157 72.2 (15.2)	78 75.2 (14.5)	306 71.0 (12.0)	0.682				0.050
BMI(kg/m ² —mean (SD)	71 27.4 (5.6)	49 27.3 (6.8)	183 26.4 (6.8)	135 28.4 (6.4)	67 29.2 (7.9)	284 27.3 (6.3)	0.494				0.050
IMD quintile											
1	65 (74.7)	53 (85.5)	140 (66.7)	122 (76.3)	66 (84.6)	198 (64.5)					
2	15 (17.2)	7 (11.3)	38 (18.1)	22 (13.8)	8 (10.3)	63 (20.5)					
3	6 (6.9)	2 (3.2)	30 (14.3)	14 (8.8)	4 (5.1)	33 (10.8)					
4	1 (1.2)	0 (0)	1 (0.5)	1 (0.6)	0 (0)	12 (3.9)					
5	0 (0)	0 (0)	1 (0.5)	1 (0.6)	0 (0)	1 (0.3)					

*Values within parentheses represent SD, per cent or range as specified. BMI, body mass index; IMD, Index of Multiple Deprivation.

Figure 1 The prevalence of diabetes and hypertension among ethnic groups. The percentages within brackets represent the proportion within the respective ethnic groups.

by patients was uniform as the data relates to one centre only. Further, the sample is representative of the BAME communities living in the UK.

The study has some limitations. First, as an observational study the effects of confounding cannot be completely excluded. Second, the data on biomarkers were incomplete and this precluded identification of prognostic indicators of poor outcome. Finally, the predicted probability of a poor outcome is a point estimate at the peak of the pandemic and the predictive accuracy is limited by smaller numbers of patients in the higher quintiles of IMD. Therefore, these figures may not be applicable elsewhere and at other times or to the whole population.

Comparison with other studies

The primary outcome analysis after adjusting for clinically relevant confounders, showed that hypertension had a significant impact on inpatient mortality. Although cerebrovascular disease was also statistically significant, the total numbers of patients with this condition were

small (28.0%). When a separate model was considered adjusting for sex, ethnicity and BMI only, patients were nearly three times more likely to have a poor outcome if both diabetes and hypertension were present; diabetes on its own did not appear to have an impact. Our data may suggest that diabetes possibly has a modulating effect when present along with hypertension, with hypertension being the main predictor for a poor outcome as suggested previously.^{9 10} Given that the major complications of COVID-19 are acute respiratory distress syndrome, kidney injury and thromboembolism, a possible unifying mechanism may be ‘COVID-endotheliopathy’ either occurring de novo in previously healthy individuals, or as a decompensated state with pre-existing endothelial dysfunction in diabetes and hypertension.¹¹ In this study, significantly elevated hs-troponin I seen among non-survivors indicates vascular endothelial or direct myocardial cellular injury, and is known to be an important predictor of mortality.¹² It is likely, that progressive clinical deterioration is related

Table 3 IMD quintiles on clinical outcome of death

IMD quintile	No. died/total (%)	OR*	95% CI*	P value*	Predicted probability of death†	95% CI†	P value†
1	258/644 (40.1)	1			0.40	0.37 to 0.44	<0.0001
2	60/153 (39.2)	0.94	0.65 to 1.35	0.721	0.39	0.31 to 0.46	<0.0001
3	38/89 (42.7)	1.03	0.65 to 1.63	0.895	0.41	0.31 to 0.51	<0.0001
4	2/15 (13.3)	0.22	0.05 to 0.99	0.048	0.13	−0.04 to 0.30	0.129
5	1/3 (33.3)	0.69	0.06 to 7.76	0.766	0.32	−0.20 to 0.84	0.225

*The OR and 95% CI have calculated using a logistic regression model after adjusting for age and gender.

†The predicted probability has been estimated from the logistic model; the 95% CI represent the accuracy of the prediction. IMD, Index of Multiple Deprivation.

Figure 2 Independent predictors of mortality—multivariable logistic regression analysis. The ORs with 95% CIs are presented. This has not been adjusted for multiple testing. ACEI, ACE inhibitor; IMD, Index of Multiple Deprivation.

to the development of widespread endothelial injury and cytokine release resulting in haematological, respiratory and renal complications, many of which may be fatal.^{11 13 14} The use of ARBs and ACEIs were associated with reduced risk of death as shown previously.¹⁰ ARBs increase the levels of angiotensin II, the major substrate for ACE-2, while ACEIs lower levels of angiotensin II.¹⁵ Both drugs limit the harmful effects of angiotensin II on the body and may therefore lessen the cytokine storm and improve outcome. Despite this, it still possible that the effects of ACEI and ARB seen in the multivariate analysis may have been influenced by residual confounding.

A large population-based study in England using information from the National Diabetes Audit compared the associations and risks between the diabetic and non-diabetic population including diabetes subtypes. Hypertension was not included due to a paucity of reliable data.^{16 17} We have not attempted to differentiate between the diabetes subtypes as we feel that using such a classification outside a randomised controlled trial is often unreliable. We did include hypertension and antihypertensive drug therapy particularly the use of ACEI and ARB as the ACE-2 pathway has been known to be responsible for SARS-CoV-2 transmission.¹⁸ The findings in this study are in line with a systematic review published previously on the prevalence of comorbidities in COVID-19 demonstrating clearly the important effects of hypertension on outcome (OR 2.36; 95% CI 1.46 to 3.63) with a statistically non-significant effect due to diabetes (OR 2.07; 95% CI 0.89 to 4.82).¹⁹

The majority of the inpatients who died were elderly. While over 85% of non-survivors were above 65 years of age, the 70–89-year-age group was the worst affected (61% mortality). Age is a non-modifiable biological factor and the increased susceptibility to viral infection with advancing years, is well known.²⁰ Further, the susceptibility of older patients to COVID-19 infection has been consistently shown in epidemiological studies in the USA,²¹ China⁹ and Italy.²² Women had a lower mortality rate even among those admitted to ITU, with the mean age of women significantly lower among those who survived (80.0±11.6 years in non-survivors vs 68.9±18.4 years in survivors). This difference in sex with regards to survival has been previously observed with other coronavirus infections including COVID-19.^{9 23} The reasons for this difference may partly be due to higher levels of oestrogens in women linked to greater adaptive and innate immunity,²⁴ and higher levels of androgens in men, which may lead to upregulation of type II transmembrane serine protease (TMPRSS2), the main peptide implicated in viral transmission.²⁵

It has been suggested that COVID-19 affects certain ethnic groups more than others, particularly BAME patients in the UK.^{16 17 26 27} However, this association has recently been refuted with no noticeable difference between Caucasian and Afro-Caribbean patients on inpatient mortality.²⁸ We similarly did not find any significant difference with inpatient mortality among ethnic groups when controlling for other comorbidities. There was however a non-statistical trend to worse outcome in Afro-Caribbean patients (OR 1.27; 95% CI 0.78 to 2.05) and a

high critical-care mortality among Asian patients (41.7%) in this study. The lack of a significant difference between ethnic groups may also be related to a small sample size. While we witnessed a greater number of admissions from the lower quintiles of social deprivation, there was no indication that deprivation was an independent predictor of poor outcome. The predicted probability for poor outcome was similar among the deprivation quintiles. Sociocultural practices where communities have small-group gatherings may account for higher risks of transmission, but cannot necessarily explain excess mortality after hospital admission which implies a severe and more progressive infection and a poor immune response from the host to fight off the infection.

We did not include GFR in our multivariable model as clinical experience suggests that GFR declines on admission in many patients with COVID-19, and recovers soon after; hence, it would be incorrect to use it within a model to identify risk factors of disease outcome. We could not associate obesity as an independent risk factor; the BMI among non-survivors was lower than survivors as majority of them were elderly. In our study 46.4% of patients in the 70–89-year-age group and 38.7% in the entire cohort had a BMI <25 kg/m². The elderly (>70 years) with a proportionately higher mortality had lower BMI (<27 kg/m²). It is well known that there is a general decline in muscle and fat mass with age. The association of obesity to poor outcome among a cohort of patients with COVID-19 in France was adjusted only for age and sex in the multivariable model.²⁹ Additionally, a meta-analysis linking obesity to a variety of poor outcome measures did not report the selection criteria used nor the heterogeneity observed among the selected studies.³⁰

Implications

This study will help us to focus our clinical attention to all high-risk patients with COVID-19 admitted to hospital particularly those with hypertension with or without associated diabetes. While it has been suggested that optimising blood pressure and glycaemic control may have a benefit in improving outcome, such intervention trials with COVID-19 to our knowledge do not exist. We would be less concerned about the concomitant use of statins, ACEI and ARBs.

CONCLUSIONS

This study is a representative sample of the UK population, within a local health economy. It has demonstrated that increased mortality in COVID-19 is closely linked to hypertension either singly or in combination with diabetes. BMI alone did not appear to have an independent effect on outcome as most patients were elderly. Ethnicity may be a confounding factor in such patients as communicable diseases showing predilection for a particular ethnic group warrants clear scientific reasoning. At this point it is safe to implicate hypertension as an important risk factor especially with its association with the renin-angiotensin-aldosterone system supported by the results from a meta-analysis.¹⁹

Future research

We did observe a trend to worse outcome in patients of Afro-Caribbean descent although this was not statistically significant and may be due to proportionately smaller number of patients in this study. As TMPRSS2 is regulated by androgens, and Afro-Caribbean men ethnically have high levels of free testosterone,³¹ this epigenetic association may have a bearing on risk of COVID-19, and would be an area for future research. Further understanding of the RAAS pathway in COVID-19 would also be an interesting area for future research.

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