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Original Article

Impact of Right Ventricular Dysfunction on Mortality in Patients Hospitalized With COVID-19, According to Race

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ABSTRACT

Background: Epidemiologic studies suggest that Black, Asian, and minority ethnic (BAME) patients may be at risk of worse outcomes from coronavirus disease-2019 (COVID-19), but the pathophysiological drivers for this association are unknown. This study sought to investigate the relationship between findings on echocardiography, mortality, and race in COVID-19 pneumonia.

Methods: This was a multicentre, retrospective, observational study including 164 adults (aged 61 ± 13 years; 78% male; 36% BAME) hospitalized with COVID-19 undergoing echocardiography between

RÉSUMÉ

Contexte : Des études épidémiologiques suggèrent que les patients noirs, asiatiques et appartenant à des minorités ethniques (BAME) auraient un risque accru d'aggravation de la maladie à coronavirus 2019 (COVID-19), mais les facteurs physiopathologiques de cette association sont inconnus. Cette étude a cherché à étudier la relation entre les données d'échocardiographie, de mortalité, de l'origine ethnique avec la pneumonie associée à la COVID-19.

Méthodes : Il s'agit d'une étude observationnelle rétrospective multicentrique portant sur 164 adultes (âgés de 61 ± 13 ans; 78 %

As the number of coronavirus disease 2019 (COVID-19) cases rises across the globe, there is evidence from epidemiologic studies that individuals of Black and minority ethnic (BAME) ancestry may be at higher risk of adverse outcomes.[1-3] In the United States, a report from the Centers for Disease Control and Prevention (CDC), compiled using data from 14 states, described a disproportionate increase in the number of African Americans hospitalized for COVID-19.[4] It has been suggested that a clustering of comorbidities (including hypertension, diabetes mellitus, cardiovascular disease, obesity, and chronic lung disease), as well as lower socioeconomic status and greater social deprivation, may be responsible for a higher overall rate of infection. In turn, this might explain the greater number of BAME patients requiring admission to critical care for COVID-19 compared to pre-COVID historic data (2017-2019).[5] UK data from 17.4 million patients suggest, however, that increased risk in BAME patients may be only partly attributable to confounders (including age and sociodemographic characteristics), and that there may be ethnic variation in response to COVID-19 infection.[3] In contrast, in a large US cohort from Louisiana, BAME ancestry was not associated with higher mortality than white race in those already hospitalized with

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Ethics Statement: This study was reviewed and approved by the University Hospitals Birmingham NHS Foundation Trust COVID-19 Related Research and Audit Board.

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See page 99 for disclosure information.

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March 16 and May 9, 2020 at 3 days (interquartile range 2-5) from admission. The primary outcome was all-cause mortality.

Results: After a median follow-up of 31 days (interquartile range 14-42 days), 66 (40%) patients had died. The right ventricle was dilated in 62 (38%) patients, and 58 (35%) patients had right ventricular (RV) systolic dysfunction. Only 2 (1%) patients had left ventricular (LV) dilatation, and 133 (81%) had normal or hyperdynamic LV systolic function. Reduced tricuspid annulus planar systolic excursion was associated with elevated D-dimer ($\rho = -0.18$, $P = 0.025$) and high-sensitivity cardiac Troponin ($\rho = -0.30$, $P < 0.0001$). Reduced RV systolic function (hazard ratio 1.80; 95% confidence interval, 1.05-3.09; $P = 0.032$) was an independent predictor of all-cause mortality after adjustment for demographic and clinical risk factors. Comparing white and BAME individuals, there were no differences in echocardiography findings, biomarkers, or mortality.

Conclusions: In patients hospitalized with COVID-19 pneumonia, reduced RV systolic function is prevalent and associated with all-cause mortality. There is, however, no racial variation in the early findings on echocardiography, biomarkers, or mortality.

d'hommes; 36 % de BAME) hospitalisés pour la COVID-19 et soumis à une échocardiographie entre le 16 mars et le 9 mai 2020, trois jours (écart interquartile 2-5) après leur admission. Le critère principal d'évaluation était la mortalité, toutes causes confondues.

Résultats : Après un suivi médian de 31 jours (intervalle interquartile 14-42 jours), 66 (40 %) patients sont décédés. Le ventricule droit était dilaté chez 62 (38 %) des patients, et 58 (35 %) patients présentaient une dysfonction systolique du ventricule droit (VD). Seuls deux (1 %) patients présentaient une dilatation du ventricule gauche (VG), et 133 (81 %) avaient une fonction systolique VG normale ou en état hyperdynamique. Une réduction du déplacement systolique de l'anneau tricuspide a été associée à un taux de D-dimère élevé ($\rho = -0,18$, $P = 0,025$) et à une Troponine cardiaque de haute sensibilité ($\rho = -0,30$, $P < 0,0001$). Une fonction systolique VD réduite (rapport de risque de 1,80; intervalle de confiance à 95 %, 1,05-3,09 ; $P = 0,032$) était un facteur prédicteur indépendant pour la mortalité, toutes causes confondues, après ajustement pour les facteurs de risque démographiques et cliniques. En comparant les individus blancs et BAME, aucune différence n'a été constatée concernant les résultats d'échocardiographie, les biomarqueurs ou la mortalité.

Conclusions : Chez les patients hospitalisés pour une pneumonie liée à la COVID-19, une réduction de la fonction systolique VD est apparue comme prévalente et associée à la mortalité, toutes causes confondues. Il n'y a cependant aucune influence de l'ethnicité en rapport avec les premiers résultats d'échocardiographie, des biomarqueurs ou de la mortalité.

COVID-19.[6] These discrepant epidemiologic findings support the need for investigation into differences in the pathophysiological response to COVID-19 among BAME individuals infected with COVID-19.

Elevated circulating levels of D-dimer and high-sensitivity cardiac troponin (HScTn) are both established powerful predictors of in-hospital mortality in patients with COVID-19.[7,8] Patients of Black race are more likely to have a positive D-dimer than whites in conventional thromboembolic disease.[9] Given the postmortem data highlighting the role of diffuse pulmonary small vessel endothelialitis and thrombus formation,[10] together with evidence that injury to the right ventricle (dilatation and dysfunction) is the primary cardiac manifestation of COVID-19 on transthoracic echocardiography (TTE),[11-14] further investigation into the influence of ethnicity on the relationship between these biomarkers, echocardiographic findings, and outcomes is warranted.

In the UK, the Midlands urban catchment area has had a high prevalence of BAME minorities presenting late with COVID-19 disease, many of whom have required admission to the intensive care unit (ICU). The a priori hypothesis of this study is that BAME patients hospitalized with COVID-19 pneumonia develop greater right ventricular injury compared with white individuals, related to differences in fibrin formation and degradation (D-dimer), which is associated with increased early mortality.

Materials and Methods

Study design

This multicentre, retrospective, observational, cohort study included adults aged 18 years or older hospitalized with COVID-19 pneumonia that underwent transthoracic echocardiography (TTE) between March 16 and May 9, 2020. A study CONSORT diagram is available in Figure 1. The conduct and reporting of this study was in line with the principles of the Declaration of Helsinki and guided by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[15] Clinical data were manually extracted from electronic health records. For patients with COVID-19 disease, the need for individual consent was waived by national UK guidance covering research during the COVID-19 pandemic, as the data were collected by members of usual clinical care teams for the primary purposes of clinical need and/or locally approved service evaluation. This study was reviewed and approved by the University Hospitals Birmingham NHS Foundation Trust COVID-19 Related Research and Audit Board.

Study population

Patients were identified after admission to one of 3 UK centers: the Queen Elizabeth Hospital, Birmingham; the New Cross Hospital, Wolverhampton; and Russell's Hall Hospital, Dudley. Before inclusion, all cases were confirmed as having COVID-19 pneumonia through reverse transcriptase polymerase chain reaction (PCR) assays performed on nasopharyngeal swabs, and confirmation of pulmonary infiltrates on chest radiograph. Patients were referred for TTE at the discretion of the clinician responsible for the patient's care, with one or more of the following indications: hemodynamic instability, chest pain, arrhythmia, and electrocardiographic abnormality. In order to minimize the risk of unnecessary exposure to COVID-19 on echocardiographers, a cardiovascular imaging consultant confirmed that each referral

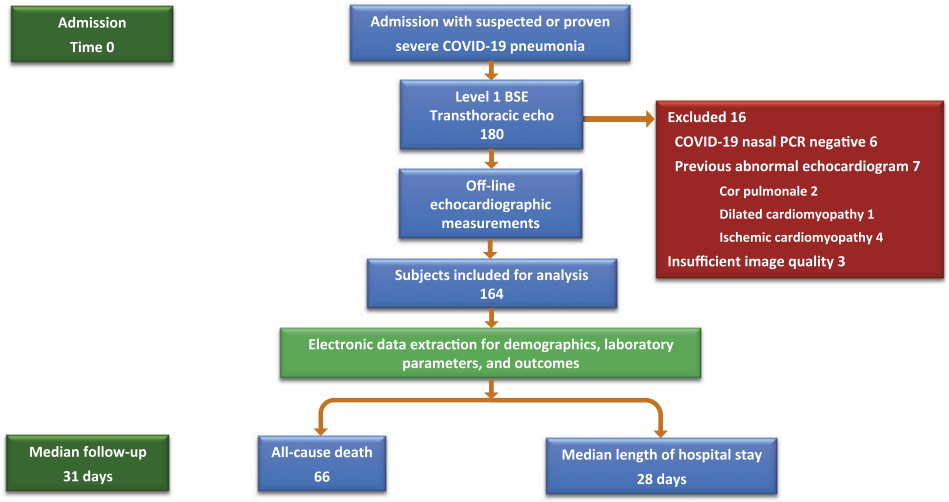

Figure 1. Study CONSORT flow diagram. Of the original 2217 patients admitted with probable coronavirus disease 2019 (COVID-19), a total of 1582 patients subsequently tested positive for COVID-19 on nasopharyngeal throat swab polymerase chain reaction (PCR) testing. BSE, British Society of Echocardiography; echo, echocardiograph.

for inpatient TTE was appropriate. Suspected or proven COVID-19 patients proceeded to TTE only if there was documentation of an elevated high-sensitivity cardiac Troponin level above the reference range for the institution, or if this information was unavailable at the time of triage, in cases in which urgent assessment was needed to guide escalation or withdrawal of care. During the period of study, departmental echocardiographers were available all day and night, and to our knowledge, performed all scanning in COVID-19 patients to the exclusion of other point-of-care ultrasound. Patients with previously abnormal echocardiography and those with images of insufficient quality to make objective RV measurements were excluded.

Clinical data

Demographic and anthropometric data were routinely collected as part of standard clinical care into the patient's electronic record. Standard hematology and biochemistry indices were recorded from the time of admission. Biomarkers including D-dimer, HScTn, and C-reactive protein (CRP) levels were recorded on admission and at peak levels.

Echocardiography

Echocardiography was performed (Sparq 795090CC or Affinity ultrasound systems, both Philips Healthcare, Netherlands) using a phased array S5 probe by experienced, accredited echocardiographers (level 2 proficiency accreditation, British Society of Echocardiography [BSE]) following a modified level 1 focused protocol with assessment of chamber size and function, valvular disease, and likelihood of pulmonary hypertension.[16]

Measurements were performed retrospectively, offline, using the archived images by BSE level 2 accredited observers blinded to the clinical data, in accordance with the 2015 joint guidelines from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[17] The right ventricle was assessed in the RV-focused view. The right ventricle was defined as dilated if the RV basal diameter measured > 41 mm; RV systolic dysfunction was defined as a fractional area change (FAC) $< 35\%$ *or* a tricuspid annular plane systolic excursion (TAPSE) < 17 mm.[17] The echocardiographic probability of pulmonary hypertension was assessed in accordance with American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines.[18] LV size was assessed using the absolute LV end-diastolic dimension according to sex, measured in a parasternal long-axis view.[17] LV systolic function was assessed visually, per BSE level 1 guidance.[16]

Radiology

All patients underwent routine chest radiography. Computed tomography (CT) pulmonary angiography was performed in selected cases at the discretion of the clinical team.

Statistics

The primary outcome measure was all-cause death. Length of hospital stay was examined as a secondary outcome. Statistical analyses were performed with SPSS version 25 (IBM, Armonk, NY). Data are expressed as mean ± standard deviation, median (interquartile range), or frequency (%), unless otherwise stated. The normality of distribution for continuous variables was determined using normality plots and the Kolmogorov-Smirnov test. Baseline characteristics of the population were examined according to ethnicity. The Mann-Whitney *U* test was used to compare continuous nnonparametric data. Contingency table analysis was performed using χ^2 or Fisher's exact tests where appropriate. Kaplan-Meier analysis of outcomes was based on discrete categories of RV function according to accepted thresholds as defined by TAPSE and FAC measurements. The date of hospital admission was used as time zero. Two-sided log-rank tests were used to determine significance. Multivariate Cox proportional hazards models were used to identify the association between time to all-cause death and

Table 1. Baseline demographics, risk factors, laboratory, and clinical characteristics according to ethnicity (N = 164)

Variable	All patients (N = 164)	White (N = 108)	Black, Asian, and minority ethnic (N = 56)	*P*
Baseline demographics and risk factors				
Age, y	61 ± 13	62 ± 14	58 ± 12	0.036
Male	127 (78)	87 (81)	40 (71)	0.19
Ethnicity				
White	108 (66)	108 (100)	0 (0)	—
South Asian	47 (29)	0 (0)	47 (84)	
Afro-Caribbean	9 (5)	0 (0)	9 (16)	
Body mass index, kg/m^2	30.6 ± 6.4	30.4 ± 6.2	30.7 ± 6.7	0.83
Hypertension	68 (41)	39 (36)	29 (52)	0.13
Diabetes mellitus	53 (32)	24 (22)	29 (52)	< 0.001
Current smoker	22 (14)	19 (18)	3 (5)	0.03
Chronic kidney disease	19 (12)	10 (9)	9 (16)	0.34
Previous stroke	12 (7)	7 (7)	5 (9)	0.57
Chronic lung disease	20 (12)	10 (9)	10 (18)	0.11
History of coronary artery disease	21 (13)	11 (10)	10 (18)	0.16
History of malignancy	12 (7)	9 (8)	3 (5)	0.75
Laboratory findings				
Full blood count				
Hemoglobin, g/L	130 ± 25	135 ± 24	122 ± 23	0.003
Platelet count, /mm^3	220 (169-299)	201 (162-284)	244 (185-337)	0.031
White cell count, /mm^3	15.9 (11.8-21.3)	15.8 (11.5-20.9)	16.0 (11.9-21.6)	0.88
Neutrophils, /mm^3	10.3 (6.3-14.6)	10.2 (6.4-14.6)	10.5 (6.1-14.9)	0.74
Lymphocytes, /mm^3	0.98 (0.61-1.60)	0.87 (0.54-1.50)	1.10 (0.72-1.76)	0.026
Neutrophil-to-lymphocyte ratio	10.6 (5.5-18.4)	10.8 (5.8-19.0)	9.5 (5.3-16.7)	0.26
HScTn, peak, ng/L	38 (12-185)	43 (14-196)	33 (10-142)	0.19
D-dimer, on admission, ng/L	884 (482-3782)	934 (518-4464)	878 (438-3184)	0.66
D-dimer, peak, ng/L	4165 (1502-11,938)	4701 (1210-11,938)	3714 (1794-12,305)	0.94
C-reactive protein, on admission, mg/dL	156 (79-257)	147 (77-244)	186 (81-281)	0.29
C-reactive protein, peak, mg/dL	312 (227-393)	305 (216-402)	321 (247-388)	0.48
Chest radiograph findings				
Bilateral pulmonary infiltrates	164 (100)	108 (100)	56 (100)	1.0
During hospital stay				
Vasopressor support	91 (58)	57 (52)	34 (61)	0.56
Invasive mechanical ventilation	120 (73)	77 (74)	43 (77)	0.74
Pulmonary embolism*	7 (4)	5 (5)	2 (4)	1.0
Ventilatory parameters†				
Fraction of inspired oxygen	0.60 ± 0.35	0.60 ± 0.41	0.59 ± 0.22	0.92
PaO2/FiO2, mm Hg	144 ± 56	148 ± 57	138 ± 54	0.41
Positive end-expiratory pressure, cm H_2O	9.0 ± 2.8	9.1 ± 2.6	9.0 ± 3.0	0.93
Outcomes				
Death	66 (40)	49 (45)	17 (30)	0.06
Discharged from hospital	51 (31)	30 (28)	21 (38)	0.20
Length of hospital stay, d	28 (12-35)	26 (12-37)	29 (13-35)	0.98

Values are n (%), mean ± SD, or median (interquartile range), unless otherwise indicated. The normality of distribution for continuous variables was determined using the Kolmogorov−Smirnov test. Continuous data were analyzed using an independent samples Student *t* test if normally distributed, or a Mann-Whitney *U* test if not normally distributed. Categorical data were analyzed using χ^2, or as appropriate, Fisher's exact test.

CRP, C-reactive protein; HScTn, high-sensitivity cardiac troponin; PO2/FiO2 (also known as the Horowitz or P/F ratio), the ratio of arterial oxygen concentration in mmHg to the fraction of inspired oxygen.

*Diagnosis made in the 48 patients undergoing CT pulmonary angiography.

†Available data in 94 patients.

baseline demographic, clinical risk factors, biomarkers, and echocardiogram results. A *P* value <0.05 was considered statistically significant for all analyses.

Results

Of 2217 patients admitted with suspected or proven COVID-19 pneumonia across the 3 centers, 180 patients were identified as having undergone TTE. Of those, a total of 16 were excluded (6, negative nasopharyngeal reverse transcriptase PCR assay; 7, previous abnormal echocardiogram; 3, poor image quality), leaving 164 subjects for inclusion in the present analysis (Fig. 1). The baseline demographics and clinical characteristics of the study cohort are summarized in Table 1. The mean age was 61 ± 13 years; 78% were male; and 36% were BAME patients. Compared with White patients, BAME subjects were younger, more often female, had diabetes more frequently, and were less likely to be current smokers. Admission hemoglobin levels were lower and platelet count was higher in BAME compared with White patients, although there were no significant differences between groups in neutrophil-to-lymphocyte ratio, D-dimer, HScTn, or CRP levels.

After a median follow up of 31 days (interquartile range: 14-42 days), 66 (40%) patients had died, and of those, 30 (52%) had reduced RV function. Table 2 summarizes the

Table 2. Echocardiographic characteristics (N = 164)

Echocardiographic parameters	All patients (N = 164)	White (N = 108)	Black, Asian, and minority ethnic (N = 56)	*P*
LV size				
Normal	138 (84)	92 (85)	46 (82)	0.06
Dilated	4 (2)	4 (4)	0 (0)	
Small	21 (13)	12 (11)	9 (16)	
LV end-diastolic dimension, mm	40 (29-45)	40 (20-45)	49 (29-43)	0.53
LV systolic function				
Hyper-dynamic	46 (28)	23 (22)	23 (41)	0.35
Normal	87 (53)	61 (57)	26 (46)	
Mildly impaired	24 (15)	18 (17)	6 (11)	
Moderately impaired	2 (1)	1 (1)	1 (2)	
Severely impaired	4 (3)	4 (4)	0 (0)	
LV ejection fraction, %	60 (55-67)	58 (55-66)	62 (59-70)	0.10
RV size				
Normal	102 (62)	64 (59)	38 (68)	0.06
Dilated	62 (38)	44 (41)	18 (32)	
RV basal diameter, mm	40 (37-45)	42 (38-46)	39 (35-43)	0.003
RV systolic function				
Fractional area change, %	40 ± 11	40 ± 8	39 ± 12	0.19
TAPSE, mm	20 ± 5	21 ± 5	20 ± 5	0.55
Fractional area change < 35%	46 (28)	34 (31)	12 (21)	0.18
TAPSE < 17 mm	34 (21)	26 (24)	8 (14)	0.14
Fractional area change < 35% *and* TAPSE < 17 mm	23 (14)	16 (15)	7 (13)	0.65
Pulmonary hypertension				
Low probability	24 (15)	21 (20)	3 (5)	0.16
Intermediate probability	27 (16)	18 (11)	9 (16)	
High probability	27 (16)	18 (11)	9 (16)	
Unable to estimate*	85 (52)	50 (47)	35 (63)	0.25
Peak TR velocity†	2.9 ± 0.5	3.0 ± 0.6	2.9 ± 0.4	0.76
Pericardial effusion	13 (8)	6 (11)	7 (7)	0.50

Values are n (%), mean ± standard deviation, or median (interquartile range), unless otherwise indicated.

LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

The normality of distribution for continuous variables was determined using the Kolmogorov–Smirnov test. Continuous data were analyzed using an independent samples Student *t* test if normally distributed, or a Mann-Whitney *U* test if not normally distributed. Categorical data were analyzed using χ^2, or as appropriate, Fisher's exact test.

*Due to an incomplete tricuspid regurgitation continuous wave Doppler signal.

†In the 79 patients with measurable tricuspid regurgitation continuous wave Doppler signal.

echocardiographic findings for all patients. The median time between admission and TTE imaging was 3 days (IQR: 2-5). RV systolic dysfunction was present in 58 (35%) patients, and it was associated with increased mortality on Kaplan-Meier analysis (Fig. 2). There was a higher proportion of subjects (28% vs 21%) with globally reduced RV function (as defined by FAC < 35%) than with reduced longitudinal RV function (as defined by TAPSE < 17 mm). Across all groups, impaired longitudinal RV systolic function assessed by TAPSE was associated with the highest mortality (Fig. 3). The right ventricle was dilated in 62 (38%) patients. Although a higher number of deaths occurred in patients with RV dilatation, there was no significant difference in time to all-cause death by Kaplan-Meier analysis (log-rank test, $P = 0.246$). In contrast, there was a low prevalence of abnormalities in LV size and function; only 2 (1%) patients had LV dilatation, and in 133 (81%) patients, LV systolic function was either normal or hyper-dynamic.

Comparing White and BAME individuals, there were no differences in the requirements for mechanical ventilation or vasopressor support. There were also no significant differences between groups in echocardiography measures. The median RV basal dimension was smaller in BAME than in White patients, although a greater proportion of BAME subjects were female. There was no difference in mortality or hospital length of stay between the White and BAME groups.

The peak HScTn correlated with reduced TAPSE ($\rho = -0.30$, $P < 0.0001$) and increased RV basal diameter ($\rho = 0.22$, $P = 0.007$), although there was no significant association with LV function. Higher D-dimer levels were also associated with lower TAPSE ($\rho = -0.18$, $P = 0.025$) and lower FAC ($\rho = -0.17$, $P = 0.045$), and there was an inverse association between neutrophil-to-lymphocyte ratio and TAPSE ($\rho = -0.24$, $P = 0.004$, respectively). Levels of CRP did not correlate with any RV parameters. There was no significant association between the Horowitz ratio (PaO2/FiO2 ratio), a marker of adult respiratory distress syndrome severity, and measures of RV size and function (TAPSE, FAC, or RV basal diameter).

In multivariable Cox regression analysis, age (HR, 1.05; 95% CI, 1.03-1.08; $P < 0.001$) and reduced RV systolic function (HR, 1.80; 95% CI, 1.05-3.09; $P = 0.032$) were the only factors independently associated with all-cause mortality after adjustment for sex, peak HScTn, diabetes mellitus, hypertension, chronic lung disease, and malignancy (Table 3). To date, only 51 patients (31%) have been discharged from the hospital.

Baseline demographics, risk factors, laboratory, and clinical characteristics according to the presence of RV systolic

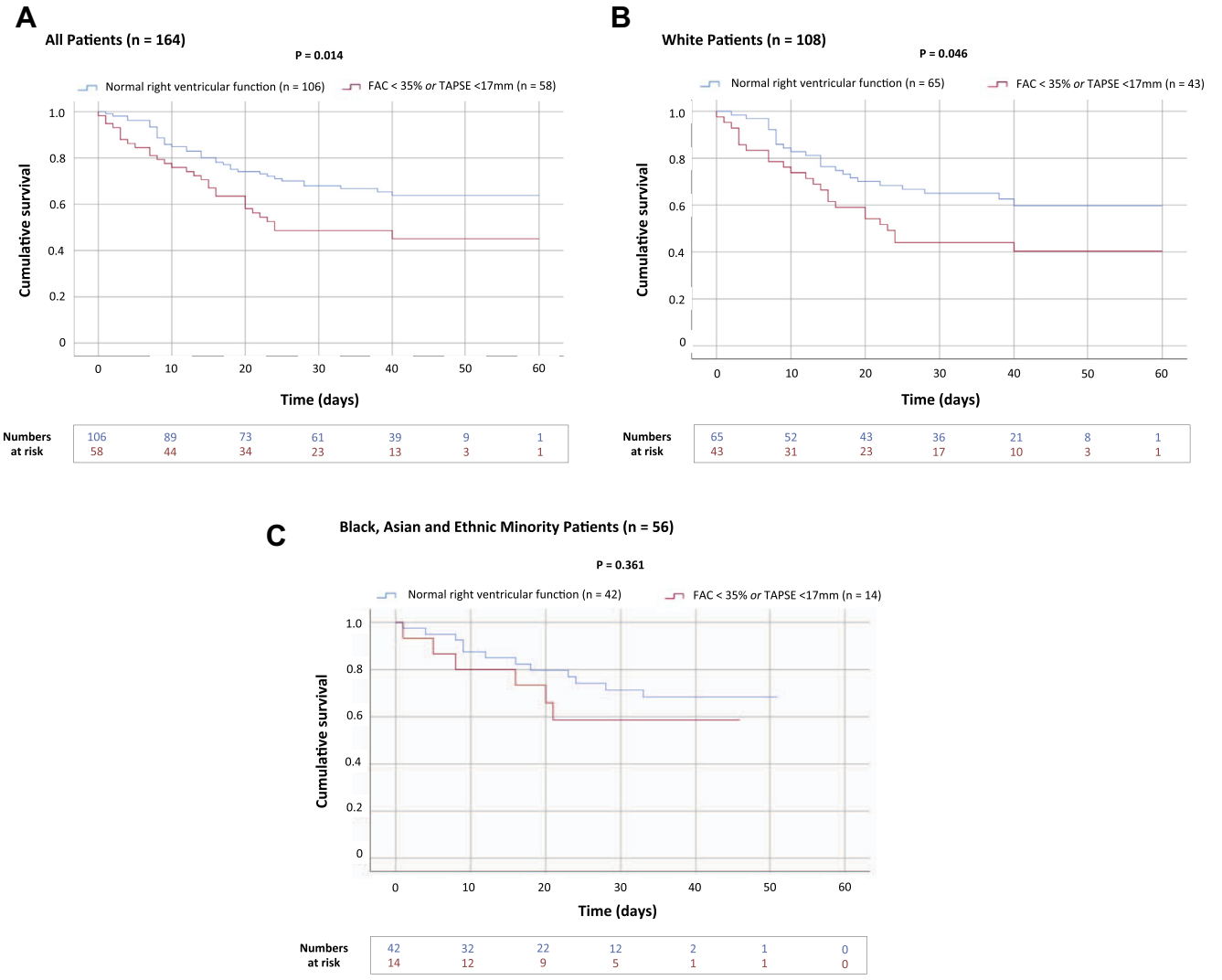

Figure 2. Kaplan-Meier curves for unadjusted cumulative survival from all-cause death among (**A**) all patients, (**B**) White patients, and (**C**) Black, Asian, and minority ethnic patients dichotomized according to right ventricular systolic function. Two-sided log rank tests were used to determine significance. FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion.

dysfunction are presented in Table 4. Patients characterized with reduced RV function demonstrated significantly higher levels of D-dimer and an elevated neutrophil:lymphocyte ratio on admission, as well as higher peak HScTn levels. There was no association between the requirement for mechanical ventilation and RV dysfunction. In patients that required ventilation, however, those subjects with reduced RV function had a numerically lower PaO2/FiO2 ratio coupled to higher FiO2 and positive end-expiratory pressure requirements, although these results did not meet statistical significance. CT pulmonary angiography was performed in 48 of the 164 patients (29%), and pulmonary embolism was detected more frequently among patients with abnormal RV function ($P = 0.04$).

Discussion

This study has demonstrated the chief echocardiographic abnormalities in patients with severe COVID-19 pneumonia and elevated HScTn level, including RV dilatation and impaired RV systolic function, whereas LV function is usually preserved or hyperdynamic. Reduced RV systolic function is an independent predictor of all-cause mortality, outperforming conventional risk factors including sex, hypertension, and diabetes mellitus, with a nearly 2-fold increase in mortality hazard. This series is the first to explore the influence of race on the cardiac response to acute COVID-19 as defined by echocardiography. There were no significant differences between White and BAME individuals in outcomes, RV dysfunction, or biomarker evidence of myocardial necrosis or fibrin turnover.

No increase in mortality in hospitalized BAME patients was demonstrated in our study. This result is in keeping with a recent US report from Louisiana, which showed that although Black race was associated with higher odds of hospital admission than White race, after adjustment for differences in sociodemographic and baseline comorbidity, it was not associated with increased in-hospital mortality.[6] This finding is also consistent with a more contemporaneous report

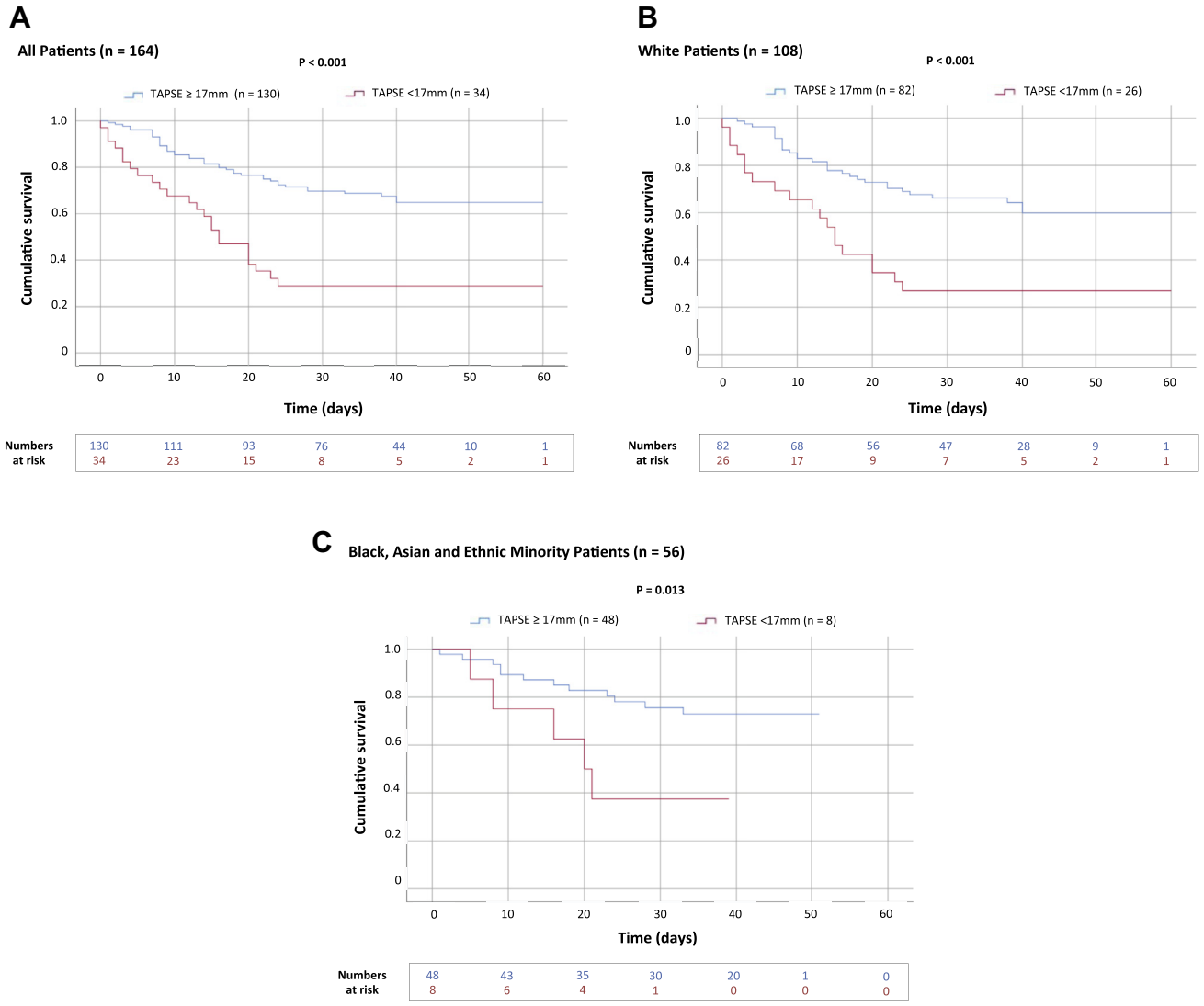

Figure 3. Kaplan-Meier curves for unadjusted cumulative survival from all-cause death among (**A**) all patients, (**B**) White patients, and (**C**) Black, Asian, and minority ethnic patients dichotomized according to tricuspid annular plane systolic excursion (TAPSE) <17 mm. Two-sided log rank tests were used to determine significance.

from the Office for National Statistics that, after accounting for confounders (including age, measures of self-reported health, and sociodemographic characteristics), suggests South Asian women are at no more risk of dying from COVID-19 than white individuals, and although elevated risk may persist in South Asian men, the residual attributable mortality is small.[19] Our data are consistent and suggest that once patients reach the intensive care unit (or even hospital) with COVID-19, factors other than ethnicity have a greater influence on outcome. Certainly, the risk profile of our patients was worse than that in the larger epidemiologic studies, with a high demand for mechanical ventilation (73%) and an in-patient mortality rate of 40%. Rather than in-hospital differences in acute medical care, the disparities in risk and outcomes of COVID-19 in BAME groups may be attributed to social deprivation and a greater likelihood of living in densely populated areas and dwellings, increasing their risk of initial exposure. The lack of impact of ethnicity on mortality in our study could also reflect selection bias; our BAME group was significantly younger, more often female, and less likely to smoke than the White group. In the current study, the right ventricle measured smaller among BAME patients compared with measurements among White patients, likely reflecting the higher proportion of women, but no other significant differences in RV response were found. There are both UK and international data indicating smaller ventricular volumes in South Asian populations, but the larger studies have focused on the LV dimensions at rest, and there are no data that investigate differences in myocardial response under stress.[20,21]

Our finding of RV injury with relative LV sparing in severe COVID-19 pneumonia is consistent with a previous smaller echocardiographic study of 120 consecutive patients treated in Wuhan.[12] Using receiver operator curve analysis, Li et al.[12] demonstrated RV free wall strain (RVFWS) was a more accurate marker of mortality than conventional indices such as

Table 3. Multivariate predictors of in-patient all-cause mortality

Variable	All-cause death	
	Hazard ratio (95% CI)	*P*
Age, y	1.05 (1.03-1.08)	< 0.001
Gender, female	0.52 (0.88-3.25)	0.12
Diabetes	0.84 (0.63-1.12)	0.23
Hypertension	2.51 (0.64-9.91)	0.19
Chronic lung disease	1.36 (0.83-2.23)	0.22
History of malignancy	1.75 (0.93-3.23)	0.08
Right ventricular dysfunction	1.80 (1.05-3.09)	0.032
HScTn, ng/L	1.00 (1.00-1.00)	0.75

Variables were simultaneously entered into a multivariate Cox regression model.

Age and high-sensitivity cardiac Troponin were entered as continuous variables.

All other variables were entered as categorical variables.

CI, confidence interval; HScTn, high-sensitivity cardiac Troponin.

FAC and TAPSE, corroborating earlier data on the sensitivity of this marker.[22] Although RVFWS may be more sensitive, we made a pragmatic decision before the arrival of COVID-19 in the UK to perform a limited level 1 study and minimize the time spent by echocardiographers with infected patients, an approach that has subsequently been adopted by major imaging societies.[23,24] Furthermore, RVFWS could not be obtained in 24 of 120 subjects in the Wuhan study, which also identified cutoffs for FAC and TAPSE well within the normal range (TAPSE <23 mm; FAC <43.5%) to discriminate those at higher risk. In contrast, we adopted thresholds of normality for RV parameters of systolic function (FAC <35% and TAPSE <17 mm) agreed on by consensus, and these provided robust prognostication in the current study acquired as part of a rapid, focused study. In a recent Italian study of non-ICU patients (n = 200) hospitalized with COVID-19, the presence of pulmonary hypertension but not RV dysfunction was associated with a higher rate of mortality or ICU admission.[25] The absence of an association between RV dysfunction and adverse outcome contrasts with the present study; however, this discrepancy may relate to their cohort being less sick, with a lower requirement for mechanical ventilation (4%), lower event rates (19 deaths), and a shorter median follow-up period (9 days).

Levels of D-dimer and HScTn were both elevated across the cohort and associated with reduction in RV longitudinal function. D-dimer is the fibrin degradation product released upon cleavage of cross-linked fibrin by plasma and is routinely used for diagnosis of disseminated intravascular coagulation and venous thromboembolism. Given the increasing evidence for thromboembolism and the adverse outcomes associated with COVID-19,[26] the implication is that RV injury in our cohort may have been secondary to pulmonary thrombosis. CT pulmonary angiography was only performed in a small proportion of this cohort at the discretion of the clinician, and it is, therefore, impossible to confirm or refute this. Recent postmortem data, however, confirm widespread small pulmonary arteriolar fibrin thrombi and widespread alveolar capillary thrombi specific to COVID-19, compared to influenza cases, supporting the concept that RV dilatation is partly due to pressure overload.[10] Moreover, although previous data have found that patients of Black race are more likely to have a positive D-dimer than Whites,[9] no ethnic differences were found in our study. Elevated HScTn was also associated with RV injury in our cohort, without evidence of either LV dysfunction or regional wall motion abnormalities to suggest type 1 or type 2 myocardial infarction. HScTn is a vital prognostic marker in COVID-19, with multiple potential causes, including myocarditis, stress cardiomyopathy, coronary microvascular ischemia, and tachycardiomyopathy.[27] Our findings are supported by a systematic echocardiographic study from Tel Aviv, which suggested that for the majority of patients admitted with COVID-19, RV rather than LV injury is the more likely explanation for a raised HScTn.[28] An echocardiographic study including 82 critical care patients has suggested pulmonary hypertension rather than RV dysfunction has a more robust association with increased in-hospital mortality, although the authors concede the presence of elevated pulmonary pressures are likely multifactorial and could relate to hypoxemia-related pulmonary vasoconstriction and increased positive end-expiratory pressure.[29] In our cohort, although there was echocardiographic evidence of an intermediate or high likelihood of pulmonary hypertension in about a quarter of subjects, the association does not appear strong enough to suggest that RV injury was due solely to increased afterload.

Limitations

Selection bias is an inherent limitation of this study's retrospective observational design. These findings, therefore, can be generalized only to those patients presenting with severe COVID-19 pneumonia and elevated HScTn level. The decision to include only those patients with positive reverse transcriptase PCR assays for COVID-19 means those subjects with false-negative nasopharyngeal PCR swab results have been excluded. We acknowledge the difficulties in estimating pulmonary pressures using echocardiography in critically ill patients requiring mechanical ventilation; thus, we have not calculated estimated pulmonary artery systolic pressures, but in accordance with European Society of Cardiology guidelines, offer an echocardiographic estimation of pulmonary hypertension. Finally, it is possible that some patients with RV dysfunction suffered undiagnosed thromboembolic disease, because the decision to perform CT pulmonary angiography was based on physician discretion.

Conclusions

The major effect of COVID-19 pneumonia on cardiac structure and function is RV injury associated with elevated HScTn; in contrast, the left ventricle is affected much less often. Reduced RV systolic dysfunction is independently associated with all-cause mortality and also with increased HScTn and elevated D-dimer levels, reflecting increased fibrin formation and degradation. There are no differences in echocardiographic findings, biomarker evidence of myocardial necrosis or fibrin turnover, or mortality between BAME and White patients hospitalized with severe COVID-19 disease.

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Table 4. Baseline demographics, risk factors, laboratory, and clinical characteristics according to right ventricular (RV) systolic function (N = 164)

Variable	All patients (N = 164)	Normal RV systolic function (n = 106)	Impaired RV systolic function (n = 58)	*P*
Baseline demographics and risk factors				
Age, y	61 ± 13	62 ± 13	61 ± 14	0.62
Gender, male	127 (78)	78 (74)	49 (84)	0.12
Ethnicity				
White	108 (66)	64 (60)	44 (76)	0.06
Black, Asian and minority ethnic	56 (34)	42 (40)	14 (24)	
Body mass index, kg/m^2	30.6 ± 6.4	30.6 ± 6.6	30.4 ± 6.2	0.87
Hypertension	68 (41)	50 (47)	18 (31)	0.09
Diabetes mellitus	53 (32)	37 (35)	16 (28)	0.34
Chronic kidney disease	19 (12)	12 (11)	7 (12)	0.75
Previous stroke	12 (7)	10 (9)	2 (3)	0.22
Current smoker	22 (13)	15 (14)	7 (12)	0.69
Chronic lung disease	20 (12)	16 (15)	4 (7)	0.13
History of coronary artery disease	21 (13)	16 (15)	5 (9)	0.24
History of malignancy	12 (7)	8 (8)	4 (7)	1.00
Laboratory findings				
Full blood count				
Hemoglobin, g/L	130 ± 25	129 ± 23	132 ± 28	0.45
Platelets, /mm^3	220 (169-299)	224 (170-296)	206 (169-315)	0.73
White cell count, /mm^3	15.9 (11.8-21.3)	15.0 (11.1-19.6)	17.7 (13.7-24.4)	0.025
Neutrophils, /mm^3	10.3 (6.3-14.6)	9.6 (5.5-13.3)	13.1 (8.0-19.9)	0.001
Lymphocytes, /mm^3	0.98 (0.61-1.60)	0.97 (0.16-1.52)	1.00 (0.61-1.90)	0.74
Neutrophil-to-lymphocyte ratio	10.6 (5.5-18.4)	9.1 (5.2-16.6)	12.4 (6.8-20.8)	0.030
HScTn, peak, ng/L	38 (12-185)	32 (11-131)	49 (21-252)	0.036
D-dimer, on admission, ng/L	884 (482-3782)	739 (368-3015)	2050 (609-8705)	0.014
D-dimer, peak, ng/L	4165 (1502- 11,938)	4075 (1557-11,938)	4495 (1043-11,938)	0.63
CRP, on admission, mg/dL	156 (79-257)	155 (78-244)	157 (81-292)	0.70
CRP, peak, mg/dL	312 (227-393)	301 (226-378)	333 (214-409)	0.33
Chest radiograph findings				
Bilateral pulmonary infiltrates	164 (100)	106 (100)	58 (100)	1.00
During hospital stay				
Vasopressor support	91 (58)	59 (57)	32 (55)	0.76
Invasive mechanical ventilation	120 (73)	77 (73)	43 (74)	0.84
Pulmonary embolism*	7 (4)	2 (2)	5 (9)	0.04
Ventilatory parameters†				
Fraction of inspired oxygen	0.60 ± 0.35	0.58 ± 0.39	0.64 ± 0.21	0.47
PaO_2/FiO_2, mm Hg	144 ± 56	148 ± 53	135 ± 61	0.30
Positive end-expiratory pressure, cm H_2O	9.0 ± 2.8	8.8 ± 2.9	9.6 ± 2.4	0.19
Outcomes				
Death	66 (40)	36 (34)	30 (52)	0.027
Discharged from hospital	51 (31)	39 (37)	12 (17)	0.07
Length of hospital stay, d	28 (12-35)	28 (11-35)	29 (15-41)	0.56

Values are n (%), mean ± SD, or median (interquartile range), unless otherwise indicated.

VThe normality of distribution for continuous variables was determined using the Kolmogorov−Smirnov test. Continuous data were analyzed using an independent samples Student *t* test if normally distributed, or a Mann-Whitney *U* test if not normally distributed. Categorical data were analyzed using χ^2, or as appropriate, Fisher's exact test.

CRP, C-reactive protein; HScTn, high-sensitivity cardiac troponin; PO_2/FiO_2 (also known as the Horowitz or P/F ratio), the ratio of arterial oxygen concentration in mmHg to the fraction of inspired oxygen.

*Diagnosis made in the 48 patients undergoing CT pulmonary angiography.

†In the 73 patients requiring mechanical ventilation.

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The authors have no conflicts of interest to disclose.

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