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1 Clinical characteristics and outcomes of critically ill patients
2 with COVID-19 admitted to an intensive care unit in London: a
3 prospective observational cohort study

4

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18 Abstract

19 Background

20 Cohorts of severely ill patients with COVID-19 have been described in several countries around the
21 globe, but to date there have been few published reports from the United Kingdom (UK).
22 Understanding the characteristics of the affected population admitted to intensive care units (ICUs)
23 in the UK is crucial to inform clinical decision making, research and planning for future waves of
24 infection.

25

26 Methods

27 We conducted a prospective observational cohort study of all patients with COVID-19 admitted to a
28 large UK ICU from March to May 2020 with follow-up to June 2020. Data were collected from health
29 records using a standardised template. We used multivariable logistic regression to analyse the
30 factors associated with ICU survival.

31

32 Results

33 Of the 156 patients included, 112 (72%) were male, 89 (57%) were overweight or obese, 68 (44%)
34 were from ethnic minorities, and 89 (57%) were aged over 60 years of age. 136 (87%) received
35 mechanical ventilation, 77 (57% of those intubated) were placed in the prone position and 95 (70%
36 of those intubated) received neuromuscular blockade. 154 (99%) patients required cardiovascular
37 support and 44 (28%) required renal replacement therapy. Of the 130 patients with completed ICU
38 episodes, 38 (29%) died and 92 (71%) were discharged alive from ICU. In multivariable models, age
39 (OR 1.13 [95% CI 1.07-1.21]), obesity (OR 3.06 [95% CI 1.16-8.74]), lowest P/F ratio on the first day of

40 admission (OR 0.82 [95% CI 0.67-0.98]) and PaCO₂ (OR 1.52 [95% CI 1.01-2.39]) were independently
41 associated with ICU death.

42

43 Conclusions

44 Age, obesity and severity of respiratory failure were key determinants of survival in this cohort.

45 Multiorgan failure was prevalent. These findings are important for guiding future research and

46 should be taken into consideration during future healthcare planning in the UK.

47 Introduction

48 The global pandemic of coronavirus disease 2019 (COVID-19), the illness caused by infection with
49 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected tens of millions of
50 people and led to over one million deaths(1). The proportion of patients with severe illness requiring
51 admission to an intensive care unit (ICU) has been reported at between 4% and 32%(2), and
52 concerns that ICU capacity may be overwhelmed have weighed heavily in policy considerations such
53 as the implementation of lockdowns and social distancing(3).

54

55 Cohorts of patients critically ill with COVID-19 have been described by authors from several
56 countries, including China(4,5), Italy(6), Sweden(7) and the United States(8–10). From these studies
57 we have learnt important lessons including the preponderance of males being affected, the
58 association of increasing age with mortality, and the high prevalence of co-morbidities such as
59 hypertension, diabetes and obesity. Patients most severely affected by COVID-19 are likely to be
60 admitted to an ICU; understanding the demographic pattern of these patients and factors related to
61 important clinical outcomes is essential. To date, peer-reviewed analysis of such patients in the
62 United Kingdom (UK) has been limited to large scale epidemiological studies or focussed studies in
63 small samples. We therefore conducted a prospective observational cohort study to better
64 understand the clinical characteristics and outcomes of patients admitted to an ICU in the UK with
65 severe COVID-19. Detailed analysis of this cohort is vital to gain insight into the factors associated
66 with outcomes, guide planning for future waves of infection, and to inform clinical decision making
67 and research.

68

69 Methods

70 Study design and participants

71 We performed a prospective observational cohort study at the Royal Free Hospital(11), a 520 bed
72 teaching hospital in London, UK. The Royal Free Hospital is one of four designated centres for
73 managing patients with airborne high consequence infectious diseases in the UK(12) and was the
74 second hospital in the country to admit a patient with confirmed COVID-19. We enrolled all patients
75 with laboratory confirmed SARS-CoV-2 infection admitted to the ICU from the first case until the cut-
76 off date for this study, 6 May 2020. This date was chosen because there were no further ICU
77 admissions in the subsequent two weeks. Patients were identified by daily review of the ICU
78 admission database. Follow-up was right-censored on 10 June 2020, giving at least 28 days' follow-
79 up in every patient. The initial capacity of the ICU was 34 patients; this was scaled up to 70 patients
80 at the height of the pandemic.

81

82 A standard operating procedure for identification of patients requiring admission to the ICU was
83 devised in line with the WHO guidance on the management of patients with COVID-19(13). Patients
84 with critical COVID-19 infection, defined as the presence of ARDS, sepsis or septic shock, were
85 admitted to the ICU unless this was contraindicated. Patients with severe COVID-19 infection,
86 defined as respiratory rate > 30 breaths/min; severe respiratory distress; or SpO₂ < 90% on room air,
87 were kept under close observation. In line with guidance issued by the UK National Institute for
88 Health and Care Excellence(14), the Clinical Frailty Score was calculated for every patient admitted
89 to hospital. This, together with a holistic assessment of each patient's condition, including their
90 comorbidities, physiological reserve and their wishes and those of their families, were used to
91 determine when admission to the ICU was likely to be futile. There were no exclusion criteria for the

92 study and there was no sample size calculation; the size of the cohort was determined by the
93 number of patients admitted during the study period.

94

95 Diagnosis of SARS-CoV-2 infection was made using RT-PCR of nasopharyngeal secretions, sputum or
96 endotracheal aspirate. At the beginning of the pandemic all samples were sent to a regional
97 reference laboratory operated by Public Health England; subsequently an in-house assay was
98 developed and this was later supplemented by commercial assays.

99

100 The study was classified as a non-interventional service evaluation using routinely collected patient
101 data and was registered with the institutional audit department. The UK Policy Framework for
102 Health and Social Care does not require ethical approval or explicit patient consent for such studies.

103

104 Procedures

105 We captured routinely collected patient data from paper-based and electronic health records using
106 a standardised template derived from the International Severe Acute Respiratory and emerging
107 Infection Consortium (ISARIC) case report form(15) together with additional variables hypothesised
108 to be relevant, based on the published literature at the start of the study period. The dataset
109 consisted of demographic characteristics (age, sex, self-reported ethnicity and body mass index
110 [BMI]), comorbidities (hypertension, hyperlipidaemia, diabetes, ischaemic heart disease, chronic
111 respiratory disease, smoking status, chronic kidney disease, end-stage renal failure [ESRF] requiring
112 renal replacement therapy), details of the presenting illness including the nature of symptoms and
113 their duration, the initial hospital course prior to ICU admission, physiological variables on hospital
114 and ICU admission and on days 1, 3 and 7 of the ICU admission, details of treatments received on
115 ICU and pathology and radiology reports. We classified cardiovascular and respiratory support
116 according to the definitions used by the UK Intensive Care National Audit and Research Centre(16).

117

118 Statistical Analysis

119 We analysed the data using R version 4.0.0 with RStudio version 1.3.959. All of the authors had
120 unrestricted access to the raw data. Missing data were not imputed. Continuous variables were
121 summarised using medians and interquartile ranges with comparisons between groups using the
122 Wilcoxon rank-sum test. Categorical variables were presented as numbers and percentages with
123 comparisons between groups using the chi-square or Fisher exact tests. p-values have not been
124 adjusted to take account of multiple comparisons.

125

126 We used logistic regression to assess the factors associated with ICU survival. Only patients with
127 completed ICU episodes (i.e. those who died on or were discharged alive from ICU, excluding those
128 who were transferred out to other hospitals) were included in these analyses. We created two sets
129 of models, the first employing patient characteristics and physiology on admission to ICU, and the
130 second using physiology, treatments and complications during the ICU admission. We captured each
131 patient's most extreme physiological variables on days 1, 3 and 7 of the ICU admission. For each
132 model set we performed univariable regressions using variables thought to be associated with
133 survival based on the published literature and clinical experience. From these univariable models we
134 selected those variables found to have a statistically significant association with outcome at the $p <$
135 0.1 level and included them in a multivariable model. For each variable we presented the (adjusted)
136 odds ratio for death together with the associated 95% confidence interval and p value.

137 Results

138 Baseline characteristics

139 Between 2 March and 6 May 2020, 156 patients were admitted to our ICU with COVID-19. 112 (72%)
140 were male, the median (IQR) age was 62 (54 to 70) years and 89 (57%) patients were aged over 60
141 years. The majority of the patients (89 [57%]) were overweight or obese (BMI ≥ 25 kg/m²). With
142 regards to ethnicity, 36 (23%) were Asian and 32 (21%) were Black. 26 patients (17%) had no
143 reported past medical history. The most common comorbidities were hypertension (81 [52%]),
144 dyslipidaemia (56 [36%]) and diabetes mellitus (52 [33%]). Baseline demographic characteristics of
145 the cohort are shown in Table 1 and comorbidities are shown in Figure 1. The number of admissions,
146 discharges, transfers and deaths over time are show in Figure 2. By way of context, 738 patients with
147 a laboratory-confirmed diagnosis of COVID-19 were admitted to the Royal Free Hospital over the
148 same time period. Of the 582 who were not admitted to ICU, the median (IQR) age was 74 (59 to 85)
149 years and 421 (72%) were aged over 60 years. The data for the hospital were derived from an
150 administrative database that did not record clinical characteristics.

151

152 Figure 1: Comorbidities at hospital admission

153 Figure 2: Admissions, discharges, transfers and death over time

154

155 **Table 1: Baseline characteristics of the population**
 156

Characteristic	N = 156 ¹
Gender	
Female	44 (28%)
Male	112 (72%)
Age	62 (54, 70)
Age Group	
Under 20	0 (0%)
20 to 40	8 (5.1%)
40 to 60	59 (38%)
60 to 80	86 (55%)
80+	3 (1.9%)
Ethnicity	
White	73 (47%)
Black	32 (21%)
Asian	36 (23%)
Other	15 (9.6%)
BMI Group	
Under 18.5	0 (0%)
18.5 to 25	67 (43%)
25 to 30	58 (37%)
30 to 40	20 (13%)
40+	11 (7.1%)

¹Statistics presented: n (%); median (IQR)

157

158 Patients reported, on average, a one week history of symptoms at the time of hospital admission
 159 (median 7 days, IQR 5 to 10 days). The most common symptoms at the time of admission were
 160 breathlessness (127 [81%]), cough (125 [81%]) and fever (122 [78%]). The range of symptoms on
 161 admission is presented in Figure 3. 109 (70%) patients were initially admitted to a ward. For these
 162 patients, the median (IQR) length of stay prior to ICU admission was 55 (29 to 87) hours.

163

164 Figure 3: Symptoms at hospital admission

165 Physiology

166 Patients were profoundly hypoxaemic on admission to ICU, with a median ratio of arterial partial
167 pressure of oxygen (PaO₂) to inspired fraction of oxygen (FiO₂) (P/F ratio) of 17.1 (IQR 13.2 to 21.3)
168 kPa (approximately 125 mmHg). Compared to those patients who survived to ICU discharge, those
169 who died had persistently lower P/F ratios (15.8 versus 17.9, p=0.017 on day 1), lower arterial pH
170 (7.3 versus 7.4, p=0.031 on day 1) and higher arterial partial pressure of carbon dioxide (PaCO₂) (6.0
171 versus 5.5 kPa, p=0.040 on day 1) on days 1, 3 and 7 of admission. Furthermore, those patients who
172 died had higher peak inspiratory pressure (PIP) on days 3 and 7; this was predominantly driven by a
173 reduction of PIP in the group who survived and a rise of PIP in the group who died, reflecting
174 changes in lung compliance over time. Patients who survived had lower peak noradrenaline doses
175 on day 3 (0.10 versus 0.15 mcg/kg/min, p=0.030) and day 7 (0.07 versus 0.15 mcg/kg/min, p=0.003).
176 Patients who died had higher positive cumulative fluid balance on the third (1,962 versus 1,350 ml,
177 p=0.045) and seventh (4,645 versus 1,332 ml, p<0.001) days of admission compared to those who
178 survived. There were no differences between those who died and those who survived in the lowest
179 recorded mean arterial blood pressure or highest temperature. Physiological measures for patients
180 with completed ICU episodes are presented in Table 2.

Table 2: Physiological measurements over time, stratified by ICU survival

Characteristic	Overall, N = 156	Died, N = 38 ¹	Surviving, N = 118 ¹	p-value ²
Lowest P/F Ratio				
Day 1	17.1 (13.2 to 21.3)	15.8 (12.1 to 18.3)	17.9 (13.6 to 22.3)	0.017
Day 3	17.7 (13.9 to 23.6)	16.1 (12.7 to 18.7)	18.2 (14.4 to 24.6)	0.006
Day 7	17.6 (13.6 to 23.2)	12.9 (10.1 to 16.3)	19.2 (15.8 to 24.2)	<0.001
pH at the time of lowest P/F Ratio				
Day 1	7.4 (7.3 to 7.4)	7.3 (7.3 to 7.4)	7.4 (7.3 to 7.4)	0.031
Day 3	7.4 (7.3 to 7.4)	7.3 (7.3 to 7.4)	7.4 (7.4 to 7.4)	<0.001
Day 7	7.4 (7.3 to 7.4)	7.4 (7.3 to 7.4)	7.4 (7.4 to 7.5)	<0.001
PaCO₂ at the time of the lowest P/F Ratio (kPa)				
Day 1	5.7 (5.1 to 6.5)	6.0 (5.3 to 6.5)	5.5 (5.0 to 6.4)	0.040
Day 3	6.1 (5.4 to 6.9)	6.8 (6.1 to 7.8)	5.8 (5.2 to 6.6)	<0.001
Day 7	5.9 (5.2 to 6.8)	6.3 (5.4 to 7.2)	5.8 (5.0 to 6.6)	0.029
PEEP at the time of the lowest P/F ratio (cmH₂O)				
Day 1	10.0 (10.0 to 12.0)	10.0 (10.0 to 12.5)	10.0 (10.0 to 12.0)	0.5
Day 3	10.0 (9.0 to 12.0)	12.0 (10.0 to 12.5)	10.0 (8.0 to 12.0)	0.056
Day 7	10.0 (8.0 to 12.0)	10.0 (8.2 to 12.4)	10.0 (8.0 to 12.0)	0.055
PIP at the time of the lowest P/F Ratio (cmH₂O)				
Day 1	27.0 (23.0 to 29.0)	27.0 (24.0 to 29.0)	26.0 (23.0 to 29.0)	0.4
Day 3	26.0 (21.8 to 29.0)	27.0 (24.2 to 30.0)	26.0 (21.0 to 28.0)	0.034
Day 7	25.0 (20.0 to 30.0)	30.0 (25.0 to 33.0)	24.0 (18.8 to 28.0)	<0.001
Cumulative fluid balance in 24 hours (ml)				
Day 1	648 (99 to 1334)	850 (450 to 1386)	600 (4 to 1220)	0.062
Day 3	1700 (318 to 3022)	1962 (1250 to 3620)	1350 (-22 to 2590)	0.045
Day 7	1888 (56 to 4726)	4645 (2963 to 6485)	1332 (-309 to 3493)	<0.001
Mean arterial blood pressure (mmHg)				
Day 1	68 (63 to 75)	68 (63 to 75)	68 (63 to 75)	0.9
Day 3	68 (65 to 75)	65 (65 to 75)	68 (65 to 75)	0.7
Day 7	71 (65 to 80)	70 (60 to 75)	74 (65 to 80)	0.2
Maximum noradrenaline dose in 24 hours (mcg/kg/min)				
Day 1	0.11 (0.07 to 0.17)	0.13 (0.08 to 0.24)	0.11 (0.07 to 0.16)	0.2
Day 3	0.11 (0.07 to 0.18)	0.15 (0.09 to 0.26)	0.10 (0.06 to 0.15)	0.030
Day 7	0.10 (0.05 to 0.16)	0.15 (0.10 to 0.27)	0.07 (0.04 to 0.13)	0.003
Maximum temperature in 24 hours (°C)				
Day 1	38.0 (37.2 to 38.8)	38.2 (37.4 to 38.8)	37.9 (37.2 to 38.8)	0.4
Day 3	37.7 (37.1 to 38.5)	37.8 (37.1 to 38.2)	37.7 (37.2 to 38.5)	0.3
Day 7	37.5 (37.2 to 37.9)	37.4 (37.1 to 37.9)	37.5 (37.2 to 37.9)	0.6

¹Statistics presented: median (IQR)²Statistical tests performed: Wilcoxon rank-sum test

Patients who were transferred out or who were still on ICU at the time of analysis were classed as Surviving

184 Treatments received on ICU

185 136 (87%) patients were intubated for mechanical ventilation during their ICU admission, with this
186 occurring less than one hour after ICU admission in 104 (67%) patients. 77 (57% of those intubated)
187 patients were placed in the prone position for mechanical ventilation at some point during their ICU
188 stay, while 95 (70% of those intubated) received neuromuscular blockade (over and above that given
189 at the time of intubation). The median (IQR) time to administration of neuromuscular blockade was
190 24 hours (0 to 48) and the median (IQR) time to prone positioning was 48 hours (0 to 96). 52 (38% of
191 those intubated) patients ultimately underwent tracheostomy insertion to facilitate weaning from
192 the ventilator; this occurred a median (IQR) of 15.8 days (12.6 to 21) after ICU admission.

193

194 The majority of patients admitted to ICU required organ support in addition to mechanical
195 ventilation. 119 (76%) patients required a single vasopressor drug while 35 (23%) patients required
196 multiple vasopressor or inotropic medications. 44 (28%) patients required renal replacement
197 therapy (continuous venovenous haemofiltration or haemodialysis), for a median (IQR) duration of 8
198 (4 to 22) days. All patients received broad-spectrum antibiotics for the empirical treatment of super-
199 added bacterial pneumonia. Details of organ support are presented in Table 3.

200

201 8 (5.1%) patients were enrolled in a randomised control trial of remdesivir versus placebo
202 (clinicaltrials.gov registration number NCT04292899) and 15 (9.6%) patients were enrolled in the
203 COVACTA trial of tocilizumab versus placebo (clinicaltrials.gov registration number NCT04320615).

204

205 **Table 3: Organ support received on ICU**

206

Characteristic	N = 156 ¹
Cardiovascular support (ICNARC definition)	
Advanced	35 (22%)
Basic	119 (76%)
None	2 (1.3%)
Missing	0 (0%)
Respiratory support (ICNARC definition)	
Advanced	141 (90%)
Basic	15 (9.6%)
None	0 (0%)
Missing	0 (0%)
Renal replacement therapy	44 (28%)
Number of days of renal replacement therapy	8 (4 to 22)

¹Statistics presented: n (%); median (25% to 75%)

207

208 Thromboembolic complications

209 82 (53%) patients underwent clinically indicated computed tomography pulmonary angiography
 210 (CTPA) to diagnose or exclude pulmonary thromboembolism (PE). Criteria for CTPA included
 211 hypoxaemia out of keeping with the appearance of the lung fields on chest radiography, extremely
 212 high D-dimer or a D-dimer that rose or remained static despite improvement of other inflammatory
 213 markers, failure to improve despite 48 hours' prone position ventilation, new onset dysrhythmia, or
 214 evidence of right heart strain on ECG or echocardiography. 44 patients (54% of those who
 215 underwent CTPA) were diagnosed with PE; the majority of these were lobar or segmental. Right
 216 heart strain was present in 15 patients (33% of those who underwent CTPA). Thromboembolic
 217 complications are presented in Table 4.

218

219 **Table 4: Thromboembolic complications**

220
221

Characteristic	N = 156 ¹
CTPA performed	82 (53%)
PE diagnosed on CTPA	44 (54%)
Level of PE	
Pulmonary trunk	6 (14%)
Lobar	10 (23%)
Segmental	22 (50%)
Subsegmental	6 (14%)
RV strain on CTPA	15 (33%)

RV = Right ventricular

Percentages are of the parent group

¹Statistics presented: n (%)

222

223 Outcomes

224 Of the 156 total admissions to ICU with COVID-19, 38 (24%) patients died on ICU, 23 (15%) patients
 225 were transferred out to other hospitals, 92 (59%) patients were discharged alive from ICU and the
 226 remaining 3 (2%) patients were still on ICU at the time of follow-up. Of the 23 patients transferred
 227 out, one patient was transferred to the regional referral centre for extracorporeal membrane
 228 oxygenation and 22 patients were sent to other hospitals to balance patient capacity in London. Of
 229 the 92 patients discharged from ICU 82 (89%) were subsequently discharged from hospital and one
 230 died on the ward. Considering all patients, including those transferred out, 116 (74%) patients
 231 survived to 30 days following ICU admission. Survival, stratified by age group and sex, is shown in
 232 Figure 4. The 23 patients transferred out to other hospitals and 3 patients still on ICU have been
 233 excluded from the analysis of outcomes. Of the 130 patients with completed ICU episodes, who
 234 were included in the logistic regression models, 92 (71%) patients survived and the median length of
 235 stay was 11.8 (6.6 to 28.7) days.

236

237 Figure 4: Survival stratified by age and sex

238 In the first set of logistic regression models (Table 5), that employed patient characteristics on
 239 admission to ICU, age (OR 1.12 [95% CI 1.07-1.18]), Asian ethnicity (OR 2.57 [95% CI 1.02-6.57]),
 240 overweight or obese BMI (OR 1.90 [95% CI 0.87-4.33]), lowest P/F ratio on the first day of admission
 241 (OR 0.91 [95% CI 0.84-0.97]) and PaCO₂ at the time of the lowest P/F ratio on the first day of
 242 admission (OR 1.40 [95% CI 1.02-1.95]) were associated with increased odds of death in univariable
 243 regression models, at a significance level of p < 0.1. Arterial pH at the time of the lowest P/F ratio on
 244 the first day of admission was significantly associated with death in the statistical sense although the
 245 effect size was negligible. In a multivariable model age (OR 1.13 [95% CI 1.07-1.21]), obesity (OR 3.06
 246 [95% CI 1.16-8.74]), lowest P/F ratio on the first day of admission (OR 0.90 [95% CI 0.81-0.98]) and
 247 PaCO₂ (OR 1.52 [95% CI 1.01-2.39]) remained significant at the p < 0.05 level.

248

249 **Table 5: Relationships between factors on admission to ICU and outcome**

250

Characteristic	N	Univariable			Multivariable		
		OR ¹	95% CI ¹	p-value	OR ¹	95% CI ¹	p-value
Age on admission	130	1.12	1.07, 1.18	<0.001	1.13	1.07, 1.21	<0.001
Gender	130						
Female							
Male		1.27	0.54, 3.17	0.6			
Ethnicity	130						
White							
Black		0.87	0.30, 2.38	0.8	2.11	0.59, 7.60	0.2
Asian		2.57	1.02, 6.57	0.046	2.94	0.94, 9.78	0.068
Other		0.25	0.01, 1.45	0.2	0.41	0.02, 3.18	0.5
BMI	130						
Normal Weight							
Overweight or Obese		1.90	0.87, 4.33	0.10	3.06	1.16, 8.74	0.029
Smoking status	117	0.67	0.40, 1.08	0.12			
Any comorbidity	130	1.29	0.46, 4.21	0.7			
Lowest P/F ratio on first ICU day	126	0.91	0.84, 0.97	0.006	0.90	0.81, 0.98	0.016
pH at time of lowest P/F ratio	126	0.01	0.00, 1.09	0.058			
PaCO ₂ at time of lowest P/F ratio	126	1.40	1.02, 1.95	0.041	1.52	1.01, 2.39	0.050

¹OR = Odds Ratio, CI = Confidence Interval

251

252 In the second set of logistic regression models (Table 6), that evaluated events during ICU admission,
 253 age (OR 1.12 [95% CI 1.07-1.18]), lowest P/F ratio across days 1, 3 and of ICU admission (OR 0.80
 254 [95% CI 0.71-0.88]), highest PaCO₂ across days 1, 3 and of ICU admission (OR 2.00 [95% CI 1.43-
 255 2.89]), highest positive end-expiratory pressure (PEEP) across days 1, 3 and of ICU admission (OR
 256 1.15 [95% CI 0.99-1.35]), highest peak inspiratory pressure (PIP) across days 1, 3 and of ICU
 257 admission (OR 1.15 [95% CI 1.04-1.29]), peak noradrenaline dose across days 1, 3 and of ICU
 258 admission (OR 32.2 [95% CI 3.97-341]) and receiving neuromuscular blockade (OR 5.82 [95% CI 2.36-
 259 16.6]) or receiving prone position ventilation (OR 3.37 [95% CI 1.54-7.73]) were associated with
 260 increased odds of death in univariable models, at a significance level of $p < 0.1$. In a multivariable
 261 model age (OR 1.17 [95% CI 1.09-1.27]), lowest P/F ratio (OR 0.82 [95% CI 0.67-0.98]) and peak
 262 noradrenaline dose (OR 33.0 [95% CI 1.61-860]) remained significantly associated with death at the
 263 $p < 0.05$ level.

264

265 **Table 6: Relationships between factors during ICU admission and outcome**

266

Characteristic	N	Univariable			Multivariable		
		OR ¹	95% CI ¹	p-value	OR ¹	95% CI ¹	p-value
Age on admission	130	1.12	1.07, 1.18	<0.001	1.17	1.09, 1.27	<0.001
Lowest P/F ratio during ICU admission	127	0.80	0.71, 0.88	<0.001	0.82	0.67, 0.98	0.036
Lowest pH ratio during ICU admission	127	0.00	0.00, 0.01	<0.001			
Highest PaCO ₂ during ICU admission	127	2.00	1.43, 2.89	<0.001	1.30	0.74, 2.34	0.4
Lowest PaO ₂ during ICU admission	127	0.70	0.45, 1.06	0.11			
Highest PEEP during ICU admission	117	1.15	0.99, 1.35	0.072	0.94	0.73, 1.20	0.6
Highest PIP during ICU admission	112	1.15	1.04, 1.29	0.010	1.05	0.87, 1.27	0.6
Highest noradrenaline dose during ICU admission	128	32.2	3.97, 341	0.002	33.0	1.61, 860	0.027
Highest temperature during ICU admission	128	1.12	0.97, 1.70	0.3			
Intubated	130	2.46	0.76, 11.0	0.2			
Neuromuscular blockade	130	5.82	2.36, 16.6	<0.001	6.48	0.96, 53.4	0.064
Prone position ventilation	130	3.37	1.54, 7.73	0.003	0.76	0.16, 3.56	0.7
PE diagnosed during admission	73	1.28	0.48, 3.49	0.6			
Renal replacement therapy	130	1.66	0.74, 3.65	0.2			

¹OR = Odds Ratio, CI = Confidence Interval

267 Discussion

268 In this prospective observational cohort study, we found that patients admitted to the ICU of a
269 London teaching hospital were mostly male, aged over 60 years and with a high prevalence of
270 comorbidities. A substantial proportion were from ethnic minorities. Patients were critically ill with
271 severe hypoxaemia, almost all received mechanical ventilation, the vast majority required
272 cardiovascular support and there were high rates of renal failure and thromboembolic
273 complications.

274

275 Our study is one of the two largest single centre analyses, published to date, describing cohorts of
276 critically ill patients with COVID-19 in Europe(7,17). Larsson and colleagues(7) reported on the
277 characteristics and outcomes of 260 patients admitted to ICU at the Karolinska Institute in
278 Stockholm, although almost one quarter of patients did not have a completed ICU episode at the
279 time of analysis and their study lacked detailed information on physiological variables and
280 treatments received on ICU. The UK Intensive Care National Audit and Research Centre (ICNARC) has
281 published regular reports throughout the pandemic(16), summarised in a recent peer-reviewed
282 publication(18). These analyses have been limited to physiological data from the first 24 hours of
283 admission and have lacked detailed information on symptoms and disease-specific therapies
284 received on ICU, such as prone position ventilation. Other reports from the UK include a study using
285 administrative data to evaluate differences in mortality between hospitals(19), a study focussing on
286 the use of risk scores to predict outcome in patients admitted to ICU with COVID-19(20), an analysis
287 of the demographic characteristics of a small cohort of patients admitted to ICU(21), and a highly
288 selected case-control series(22) published on the preprint server medRxiv.org. A large retrospective,
289 telephone-based cohort study from Lombardy, Italy(6) conducted a comprehensive analysis of
290 comorbidities, respiratory physiology and the use of prone position ventilation although their study
291 was again limited to data from the first 24 hours of admission and only 42% of patients had a

292 completed ICU episode at the time of publication. Two recent systematic reviews(17,23) have
293 summarised the available data from cohort studies around the world.

294

295 The demographic characteristics of our patient cohort – almost three quarters male, more than half
296 overweight or obese, more than 40% from ethnic minorities, more than half aged over 60 years –
297 closely mirror those seen in other studies(6–8,10,18). The prevalence of comorbidities was high,
298 with only 16% reporting no past medical history. Data from all ICUs in England, Wales, and Northern
299 Ireland, as reported by ICNARC(18), found that 70% of patients were male, 74% were overweight or
300 obese, and 36% were from ethnic minorities, with a median age of 60. These findings closely mirror
301 those seen at our institution. Large cohort studies from New York City(8), Atlanta(10), Lombardy(6)
302 and Stockholm(7) reached similar conclusions. It is noteworthy that raised BMI was associated with
303 increased mortality in this current study, even after adjustment for possible confounding factors in a
304 multivariable logistic regression model, with Asian ethnicity almost reaching the threshold for
305 statistical significance. The proportion of patients of Asian or Black ethnicity admitted to our ICU
306 with COVID-19 is much higher than would be expected given the makeup of the local population(24).
307 Further research is urgently required to understand the mechanisms underpinning these
308 observations, which have been consistently noted in a number of studies(18,21,25–27).

309

310 The patients admitted to our ICU had severe hypoxaemic respiratory failure. Almost all patients
311 required intubation and mechanical ventilation, in keeping with the New York(8), Atlanta(10),
312 Lombardy(6) and Stockholm(7) cohorts, although the requirement for invasive ventilation was much
313 higher than reported in Chinese studies(4,5,28–30). This may reflect differences in the use of non-
314 invasive ventilation between countries and the settings within the hospital where these therapies
315 are provided, and highlights the importance of considering regional data when planning for potential
316 future waves of the pandemic.

317

318 More than half of the intubated patients on our ICU required neuromuscular blockade and/or prone
319 position ventilation; the use of these therapies was much higher than reported in early studies(6,8),
320 although was similar to the findings of a more recent report from Norway(31). The association
321 between neuromuscular blockade and prone position ventilation and death in univariable models is
322 likely to reflect confounding by indication, whereby the most severely unwell patients, with
323 refractory hypoxaemia, were more likely to be receive neuromuscular blockade and/or be placed in
324 the prone position. Although there is high quality evidence of a mortality benefit from prone
325 position ventilation in patients with ARDS(32), it is unclear whether this extends to patients with
326 COVID-19. In the event of another wave of infection further studies are required to address this
327 important question. Furthermore, the intense resource commitment required to safely ventilate
328 large numbers of patients in the prone position should be borne in mind when planning for any
329 future outbreaks of COVID-19 infection.

330

331 The majority of patients admitted to our ICU had multiorgan failure, defined as the requirement for
332 at least two of respiratory, cardiovascular or renal support, with almost three quarters requiring at
333 least one vasoactive drug and more than one quarter requiring renal replacement therapy. The high
334 prevalence of acute kidney injury in patients with COVID-19 has been widely reported (4,8,18,33)
335 and requires urgent further investigation to understand the mechanisms involved. Similarly, high
336 rates of renal replacement therapy have been reported in other UK ICUs(18) and in cohorts from
337 New York(8), Dublin(34) and Stockholm(7) but not China(30,35). The requirement for multiorgan
338 support must be borne in mind when it comes to planning for further waves of infection; it is clear
339 that a focus on ICU ventilators, for example, will not be sufficient. Adequate plans to provide
340 vasopressor and inotropic drugs by infusion, along with renal replacement therapy, must be made.

341

342 A greater than expected number of patients in our cohort were diagnosed with a PE and more than
343 one third of these had CT evidence of right ventricular dysfunction. Thromboembolic complications

344 have been widely reported in patients with COVID-19(36,37), including in patients admitted to
345 ICU(38). Further work is required to understand the role of screening for PEs in patients admitted to
346 ICU with COVID-19, and determine the most effective treatment strategy.

347

348 Strengths of our study include its relatively large sample size, the complete ascertainment of all
349 patients admitted to ICU with COVID-19 at our institution, the prospective design using a
350 standardised, internationally recognised data collection tool, the granular and highly curated dataset
351 collected on each patient through manual chart review, and follow-up for at least 28 days in every
352 patient.

353

354 Our study had a number of limitations. Like all observational designs it is subject to confounding and
355 associations between exposures and outcomes should not be interpreted as causal relationships.

356 The population admitted to ICU was a subset of those presenting to and admitted to hospital.

357 Upstream triage of patients and the criteria used to identify those patients requiring (and suitable
358 for) ICU admission will have affected the composition of our cohort and potentially the relationships
359 between exposures and outcomes. The criteria used for ICU admission are likely to have varied
360 between institutions and at different time points during the pandemic. As such, the findings in our
361 cohort may differ from those in other studies, and they may not represent the entire population of
362 patients severely ill with COVID-19. The lack of data concerning the population admitted to our
363 hospital but not our ICU limits our ability to explore this inclusion bias in more detail, although it is
364 reassuring to note the similarities between our findings and those of other cohorts. Physiological
365 data were recorded on paper charts and as such only a small subset of observations could be
366 digitised for analysis. A number of patients were transferred out of the hospital for logistical reasons
367 and we were unable to gather information beyond their survival status once they left our ICU. This is
368 likely to have biased in favour of increased mortality since the most stable patients were chosen for
369 transfer. Although patients were transferred to our hospital from across London the local population

370 is not representative of London as a whole in terms of its ethnic and sociodemographic makeup. We
371 have not controlled for multiple analyses and the possibility of type I error cannot be excluded.

372

373 Conclusions

374 In this large cohort of hypoxaemic critically ill patients admitted to an ICU in London with COVID-19,
375 we demonstrated that age, obesity and degree of hypoxaemia were independently associated with
376 increased odds of death. There was a strong signal towards an association between Asian ethnicity
377 and death in univariable analyses. Multiple organ failure requiring support was common as was the
378 diagnosis of PE. In the event of further waves of this pandemic in the UK, sufficient plans must be in
379 place to cope with this expected pattern of disease and studies must be ready to explore the links
380 between obesity, ethnicity and survival.

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386

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