Original article

Journal of the Intensive Care Society
2022, Vol. 23(1) 34–43

DOI: 10.1177/1751143720971541
journals.sagepub.com/home/jics

Clinical characteristics and outcomes of 85 intensive care patients with Covid-19 in South London: A single centre observational study

Alexander Isted, Angus J McDonnell, Eben Jones, Tomas Grundy, Swarna Jeyabraba, Tariq O Ali, Reza Khorasanee, Aditya Bhalla, Badrun Shurovi, Katie Rowland, Richard Sykes, Soo Yoon, Paul Morillon, Rohini Salvadi Vijayakumar, Jayson Clarke, Charlie Cox, Richard Breeze and Waqas Khaliq

Abstract

Background: In March 2020, Covid-19 secondary to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was declared a global pandemic.

Methods: This retrospective observational study included patients with Covid-19, managed in a single intensive care unit (ICU). We collected data on patient characteristics, laboratory and radiological findings and ICU management. Data are reported as median (interquartile range). Binary logistic regression modelling was used to identify variables at ICU admission associated with mortality.

Results: 85 patients (age 57.3 years [49.4–64.2], 75.3% male) were followed up for 34 days (26–40). The commonest comorbidities were hypertension (51.8%), obesity (48.7%), and type 2 diabetes (31.8%). Covid-19 presented with shortness of breath (89.4%), fever (82.4%), and cough (81.2%), first noted 8 days (6–10) prior to ICU admission. PaO_2/FiO_2-ratios at ICU admission were 8.28 kPa (7.04–11.7). Bilateral infiltrates on chest X-ray, lymphopenia, and raised C-reactive protein and ferritin were typical. 81.2% received invasive mechanical ventilation (IMV). Acute kidney injury occurred in 62.4% with renal replacement therapy required in 20.0%. By the end of the follow-up period, 44.7% had died, 30.6% had been discharged from hospital, 14.1% had been discharged from ICU but remained in hospital and 10.6% remained in ICU. ICU length of stay was 14 days (9–23). Age was the only variable at admission which was associated with mortality. PaO_2/FiO_2-ratio, driving pressure and peak ferritin and neutrophil count over the first 72-hours of IMV all correlated with mortality.

Conclusions: We report the clinical characteristics, ICU practices and outcomes of a South London cohort with Covid-19, and have identified factors which correlate with mortality. By sharing our insight, we hope to further understanding of this novel disease.

Keywords

Covid-19, infections, coronavirus, intensive care, critical care, analysis, survival, pandemics

Introduction

On December 31, 2019, the Chinese World Health Organisation (WHO) Country Office was informed of a cluster of cases of pneumonia of unknown aetiology occurring in Wuhan City, Hubei Province.[1] The aetiological agent – a novel coronavirus – was rapidly identified by metagenomic ribonucleic acid (RNA) sequencing of a bronchoalveolar lavage sample from an early patient.[2] This virus has subsequently been named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing the disease Coronavirus 2019 (Covid-19).[3]

Early epidemiological reports demonstrated evidence of human-to-human transmission,[4] and the United Kingdom reported its first two cases of Covid-19 on January 31, 2020.[5] As of May 2, 2020,

Department of Intensive Care, University Hospital Lewisham, London, UK

Corresponding author:
Alexander Isted, University Hospital Lewisham, London SE13 6LH, UK.
Email: alex.isted@nhs.net

there have been more than 3.2 million cases and 229,000 Covid-19 associated deaths globally.[6]

Groups in China, USA and elsewhere have described their patient cohorts, providing clinicians worldwide an invaluable insight into the clinical characteristics of this novel disease.[7–9]

The authors of this paper are clinicians in the Intensive Care Unit (ICU) at University Hospital Lewisham (UHL), a 470-bed district general hospital in South London. As of April 30, 2020, South London has borne the greatest burden of Covid-19 in the UK with ICU admissions of confirmed cases exceeding 1,200.[10]

In this retrospective observational study, we describe the characteristics, management, and outcomes of patients with Covid-19 who were treated in UHL's ICU. To our knowledge, this is the largest single-centre case series published that describes a cohort of patients managed in an ICU in the United Kingdom.

Methods

Setting and eligibility criteria

This is a single-centre retrospective observational study. University Hospital Lewisham is a district general hospital in South London that serves a population with diverse ethnic and socioeconomic backgrounds. Prior to the Covid-19 pandemic, its ICU had capacity to provide invasive mechanical ventilation (IMV) to up to 10 patients at one time. By the end of the study period this had been expanded to a surge capacity of 31.

We included all consecutive adult patients with laboratory confirmed Covid-19 admitted to ICU between March 12 and April 14, 2020, who had at least 14 days of follow-up. Laboratory confirmed Covid-19 was defined as a single positive result on a reverse-transcriptase-polymerase chain reaction assay of a specimen collected on a nasopharyngeal swab or non-directed bronchial lavage. At no point during the study period were strict admission criteria to ICU formalised. Decisions were made on a case-by-case basis as per usual practice, and contributing factors included severity of comorbidities and premorbid functional status.

The study included fully anonymised data, retrospectively obtained from routine care and as such ethics approval was not required. Caldicott Guardian approval has been obtained. The 'strengthening of the reporting of observational studies in epidemiology' (STROBE) checklist was adhered to.[11]

Data collection

Data were collected retrospectively from ICU documentation and electronic medical records by doctors working on the unit. Anonymity was maintained using a random patient identifier at the point of tabulation. No imputation was made for missing data. Where inter-hospital transfer was performed, patients were followed up using a shared South London-wide electronic record system in combination with dialogue with the receiving ICU teams.

We collected background data on patient characteristics, comorbidities, regular medications, history of presenting condition, and physiological parameters prior to admission to the ICU. We additionally collected data pertaining to ICU stay, including: ventilatory parameters at predetermined time-points, rescue interventions (e.g. airway pressure release ventilation (APRV), prone positioning, and paralysis), non-respiratory organ support (e.g. vasopressors and renal replacement therapy), and the administration of antibiotics and anti-viral agents.

We collected results of laboratory investigations performed prior to ICU admission and at predetermined time-points following initiation of IMV. Several laboratory parameters (e.g. ferritin, troponin, lactate dehydrogenase [LDH], and D-dimer) emerged as markers of interest during the study period and as such were not collected in all patients.

The Rockwood clinical frailty scale (CFS)[12] and Acute Physiology and Chronic Health Evaluation II (APACHE II)[13] scores were calculated on the day of ICU admission. In determining whether patients had sustained an acute kidney injury (AKI), baseline creatinine was defined as a mean of the three stable creatinine values in the preceding 12-months (where unavailable admission creatinine was used). AKI was staged in accordance with the 2012 Kidney Disease: Improving Global Outcomes criteria.[14] Chest radiograph interpretation was based on a consultant radiologist's formal report. PaO_2/FiO_2-ratios were calculated both pre- and post-intubation. The FiO_2 of 15L oxygen administered via a non-rebreathe mask was considered to be 1.0. For patients using a Venturi device, the stated FiO_2 was used. PaO_2/FiO_2-ratios were not calculated for patients using nasal cannulae in light of unreliable assumption of FiO_2.

Outcomes

The four outcomes at the end of the study period were: death, discharge from hospital, discharge from ICU but remaining in hospital, and remaining in ICU. Duration of IMV and length of stay both in ICU and in hospital were also calculated.

Statistical analysis

Continuous data are presented as median (interquartile range) throughout. Categorical data are presented as frequencies (percentage). Those who survived the study period were compared with non-survivors with respect to: patient characteristics, comorbidities,

regular medications, laboratory and physiological parameters, and ICU interventions. Non-parametric statistical tests were applied throughout (Mann-Whitney U, Fisher's exact test and Chi-squared tests as appropriate). P-values less than 0.05 were deemed statistically significant.

A binary logistic regression analysis was performed to identify clinical characteristics and laboratory parameters on admission to ICU which were associated with the primary outcome of mortality within the study period. Univariate analyses were performed on all variables which were available to clinicians on admission to ICU (including demographics, comorbidities, laboratory findings and APACHE II score). Variables collected over the course of the ICU stay (ventilator data, peak and trough laboratory values, use of organ support etc.) were not considered for the model to maximise its potential utility to clinicians on admission to ICU and to limit multicollinearity. Variables with a P-value of <0.10 on univariate analysis were considered suitable for retention in the model as were variables of particular interest irrespective of P-value (ethnicity, sex and age). Backward stepwise selection was used. Variables retained in the final step of the regression model had a P-value of <0.05. The area under the receiver operator characteristic curve (AUROC) was calculated to establish the discriminative ability of the model.

The statistics are considered to be descriptive in nature. All statistical tests were performed using IBM SPSS Statistics for Macintosh, Version 25.

Results

Patient characteristics

Between March 12 and April 14, a total of 85 patients were eligible for inclusion and were all followed up for a minimum of 14 days. The median follow-up duration was 34 days (26–40). All patients presented via the emergency department with acute respiratory failure as their primary issue on admission. The median duration between hospital presentation to ICU admission was 2 days (1–4). Patient characteristics, comorbidities, regular medications and presenting symptoms of Covid-19 are presented in Table 1.

Laboratory and radiological findings

The laboratory and radiological findings closest to the time of ICU admission are detailed in Table 2. All patients were in acute respiratory failure with a median PaO_2 of 7.88 kPa (6.76–9.19) despite high concentrations of inspired oxygen, typically via a non-rebreathe mask or 60% Venturi device. Median PaO_2/FiO_2-ratios at ICU admission were 8.28 kPa (7.04–11.7). The sensitivity of the initial Covid-19 viral PCR nasopharyngeal swab was 78.8% (similar to sensitivity values reported in a recent meta-analysis)[15] with the remainder testing positive on either subsequent swab or non-directed bronchial lavage.

Intensive care management: Ventilatory

Ventilatory ICU management is detailed in Table 3. The initial strategy of IMV was as follows. Pressure-controlled ventilation with a peak end-expiratory pressure of 10–12 cmH_2O, a respiratory rate of up to 20 breaths per minute, an inspiratory to expiratory time ratio between 1:1.0 and 1:1.5 with the lowest possible driving pressure titrated to achieve an acceptable minute ventilation and a target pH of 7.30 or greater. FiO_2 was titrated to a target PaO_2 of greater than 8 kPa. In the latter part of the study period a trial of continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) was routinely performed.

Ventilatory parameters at predetermined intervals following commencement of IMV are outlined in Supplementary Table 1. Median PaO_2/FiO_2-ratios were consistently in keeping with acute respiratory distress syndrome within the initial 72-hours of IMV.[16]

Intensive care management: Non-ventilatory

Additional non-ventilatory ICU management is detailed in Table 3, including cardiovascular and renal support. Other general principles of ICU care included early enteral feeding, electrolyte correction, protection of pressure areas and venous thromboembolism chemoprophylaxis. Initial daily fluid balance targets were typically neutral to 500 mL negative, however this strategy moved to a more personalised fluid balance target in the latter part of the study period. Data were not collected on these in the interest of rationalising the number of variables.

Empirical broad-spectrum antibiotics were used in line with local guidelines. Oseltamivir was initially given until negative influenza viral PCR was obtained, however in the latter half of the study period this was deemed unnecessary.

Serial laboratory findings are detailed in Supplementary Table 2. Values were recorded from the commencement of IMV at specific time-points, however an overall peak value was taken for all patients including those who did not receive IMV.

Thirty-seven patients (43.5%), all receiving IMV at the time, were transferred to one of three neighbouring teaching hospitals with large pre-Covid-19 ICU capacity. Capacity transfers made up the 81.1% (30/37), four were transferred to a unit with an on-site renal team, two for extracorporeal membrane oxygenation, and one for primary percutaneous coronary intervention. Median time from ICU admission to transfer was 4 days (2–6).

Table 1. Pre-admission patient characteristics.

Patient characteristics		
Age (years)		57.3 (49.4–64.2)
Male sex		64/85 (75.3%)
Ethnicity	White	28/85 (32.9%)
	Black, African, Caribbean & Black British	37/85 (43.5%)
	Asian & Asian British	9/85 (10.6%)
	Mixed, 'other' & not declared	11/85 (12.9%)
	Black, Asian and Minority Ethnic (BAME) (including mixed, 'other' and not declared)	57/85 (67.1%)
Comorbidities		
Hypertension		44/85 (51.8%)
Diabetes mellitus	Type 1	2/85 (2.4%)
	Type 2	27/85 (31.8%)
	Any	29/85 (34.1%)
BMI ($kg.m^{-2}$) [n = 71][a]		29.7 (26.4–32.9)
Obese (BMI 30 $kg.m^{-2}$ and above)		38/78[a] (48.7%)
Chronic kidney disease	Overall	11/85 (12.9%)
	Stage 2	0/11 (0%)
	Stage 3	6/11 (54.5%)
	Stage 4	2/11 (18.2%)
	Stage 5	3/11 (27.3%)
Active malignancy		1/85 (1.2%)
Heart failure		2/85 (2.4%)
Chronic obstructive pulmonary disease		2/85 (2.4%)
Asthma		11/85 (12.9%)
Smoking history (current or previous)		25/82 (30.4%)
Rockwood clinical frailty scale	1	9/85 (10.6%)
	2	47/85 (55.3%)
	3	20/85 (23.5%)
	4	7/85 (8.2%)
	5 and above	2/85 (2.4%)
Regular medications		
Regular non-steroidal anti-inflammatory drug		2/85 (2.4%)
Angiotensin converting enzyme inhibitor		14/85 (16.5%)
Angiotensin II receptor antagonist		12/85 (14.1%)
Oral hypoglycaemic agent		25/85 (29.4%)
Insulin		9/85 (10.6%)
Regular oral steroid		4/85 (4.7%)
Other immunosuppressant or immunomodulator		7/85 (8.2%)
Symptoms		
Symptom duration		8 (6–10)
Fever (perceived or measured by patient)		70/85 (82.4%)
Shortness of breath		76/85 (89.4%)
Cough		69/85 (81.2%)
Coryza		7/85 (8.2%)
Vomiting		7/85 (8.2%)
Diarrhoea		10/85 (11.8%)
Headache		9/85 (10.6%)
Foreign travel in the last 30 days		7/85 (8.2%)
Personal contact Covid-19 features and/or positive test result		21/85 (24.7%)

Data are recorded as median (interquartile range) or number/total (percentage) as appropriate. BMI = Body Mass Index.
[a]Numerical height and weight data were available for 71 patients. A further seven patients had high BMI documented as a comorbidity hence the discrepancy in denominator between the two BMI variables.

Outcomes

After a follow-up period of 34 days (26–40), 38 patients (44.7%) had died, 26 (30.6%) had been discharged from hospital, 12 (14.1%) had been discharged from ICU but remained in hospital and nine (10.6%) remained in ICU.

Sixteen (18.8%) were managed with CPAP/NIV alone (this representing the ceiling of treatment for six patients), nine (56.3%) of whom had been

Table 2. Investigation results at intensive care unit admission.

Laboratory findings		
Haemoglobin (g/L)		133 (122–144)
White blood cells ($\times 10^9$/L)		8.9 (7.0–12.6)
Neutrophils ($\times 10^9$/L)		7.6 (5.5–10.7)
Lymphocytes ($\times 10^9$/L)		0.9 (0.6–1.1)
Lymphocytopenia (Lymphocyte count $<1.0 \times 10^9$/L)		50/85 (58.9%)
Platelets ($\times 10^9$/L)		228 (188–285)
International normalised ratio		1.3 (1.2–1.4)
Urea (mmol/L) [n = 55]		6.3 (4.1–9.4)
Creatinine (μmol/L)		93 (72–109)
C-reactive protein (mg/L)		182 (121–249)
Alanine aminotransferase (IU/L) [n = 79]		37 (25–58)
Ferritin (μg/L) [n = 46]		1952 (862–3330)
HbA1c (mmol/mol) [n = 42]		45 (37–68)
Arterial blood gas (closest available to admission to ICU)		
PaO2 (kPa)		7.88 (6.76–9.19)
PaCO2 (kPa))		4.58 (3.89–5.20)
SaO2 (%)		92 (87–95)
PaO_2/FiO_2 ratio (kPa)		8.28 (7.04–11.7)
Other investigations		
First Covid-19 viral PCR nasopharyngeal swab positive		67/85 (78.8%)
Bilateral pulmonary infiltrates on admission chest radiograph		85/85 (100%)
CT scan used to guide diagnosis		0/85 (0%)
Calculated indices		
APACHE II score		14.5 (12–17)
Acute kidney injury (AKI)		10/85 (11.8%)
Stage of AKI	1	2/10 (20.0%)
	2	4/10 (40.0%)
	3	4/10 (40.0%)

Data are recorded as median (interquartile range) or number/total (percentage) as appropriate. Denominator is 85 unless otherwise stated. All values and calculated indices are those closest available to time of ICU admission ± 72 hours with the exception of HbA1c which was included if within six-months of admission. APACHE II score = Acute physiology and chronic health evaluation II score; HbA1c = Glycated Haemoglobin; ICU = Intensive Care Unit.

discharged home, five (31.3%) had been discharged from ICU and remained in hospital, and two (12.5%) died with CPAP/NIV as their ceiling of treatment. The majority of patients were managed with IMV (81%) which was administered for a median duration of 12 days (8–19). Of those who survived to discharge home, the median duration of IMV was 16 days (11–31),

The median ICU length of stay for all patients, including non-survivors, was 14 days (9–23) and for those who survived to discharge home was 14 days (10–20).

Factors associated with survival

Patients were grouped into survivors (47/85) and non-survivors (38/85) at the end of the follow-up period.

Univariate analysis was performed on all variables available to clinicians at point of ICU admission (Supplementary Table 3). Age was significantly lower in survivors (53.1 years [44.6–62.7] versus 59.9 [53.6–66.2], p = 0.002). No significant differences were seen in sex, racial background, comorbidities, regular medications, APACHE II score, Rockwood CFS, admission laboratory investigations or admission PaO_2/FiO_2 ratio.

The variables selected for inclusion in the regression model were: age, BMI, sex and racial background. Non-white ethnicities were amalgamated into a Black, Asian and Minority Ethnic (BAME) group. The Hosmer and Lemeshow Test significance was >0.05 demonstrating good fit. The model explained 15.4% (Nagelkerke R^2) of the variance in mortality and correctly classified 60.6% of cases. Age was the only variable to be retained in the model (odds ratio 1.069, 95% CI 1.017–1.123, p = 0.008). The AUROC for age was 0.694.

Racial background (BAME versus white) was not statistically significant in the regression model. Mortality by racial background was as follows: Black 16/37 (43.2%), white (13/28) (46.4%), Asian 4/9 (44.4%), and 'other' 5/11 (45.5%). When BAME patients were compared with white patients, the mortality is 25/57 (43.9%) versus 13/28 (46.4%). Age among different racial backgrounds was as follows: white 63.5 years (49.1–68.3), Black 55.6 (52.1–62.8), Asian 38.8 (31.8–59.1), other 57.3 (56.5–59.5). These did not differ significantly (p = 0.092). Median

Table 3. Intensive care management.

ICU management: ventilatory		
IMV prior to or on arrival to ICU		49/85 (57.6%)
Trial of CPAP/NIV	Overall	36/85 (42.4%)
	Subsequently intubated	20/36 (55.6%)
	Not intubated	16/36 (44.4%)[a]
Duration of CPAP/NIV (days)	Overall	2.4 (1.0–5.0)
	Subsequently intubated	1.5 (0.8–2.5)
	Not intubated	3.1 (1.4–7.1)
Received IMV at some point during ICU stay		69/85 (81.2%)
Duration of IMV (hours)	Overall	12 (8–19)
	Survivors	16 (11–31)
Paralysis in first 72 hours of IMV		28/69 (40.6%)
APRV in first 72 hours of IMV		14/69 (20.3%)
Prone positioning in first 72 hours of IMV		16/69 (23.2%)
Tracheostomy		13/69 (18.8%)
Day of IMV, tracheostomy performed		14 (9–17)
Reintubation required		5/69 (7.2%)
ICU management: non-ventilatory		
Empirical broad-spectrum IV antibiotics		83/85 (97.6%)
Empirical oseltamivir		41/85 (48.2%)
Noradrenaline infusion in first 72 hours of ICU	Low-dose (<0.1 mcg/kg/min)	44/85 (51.8%)
	High-dose (>0.4 mcg/kg/min)	7/85 (8.2%)
Second-line vasopressor/ inotrope in first 72 hours of ICU		0/85 (0%)
Acute kidney injury in first 72 hours of IMV	All	45/85 (52.9%)
	Stage 1	19/45
	Stage 2	11/45
	Stage 3	15/45
Acute kidney injury over course of ICU stay		
	All	53/85 (62.4%)
	Stage 1	16/53 (30.2%)
	Stage 2	12/53 (22.6%)
	Stage 3	28/53 (52.8%)
Continuous renal replacement therapy		17/85 (20.0%)
Inter-hospital transfer		37/85 (43.5%)
Indication for inter-hospital transfer	Capacity	30/37 (81.1%)
	Extra-corporeal membrane oxygenation	2/37 (5.4%)
	Other	5/37 (13.5%)
Day of ICU admission of inter-hospital transfer		4 (2–6)

Data are recorded as median (interquartile range) or number/total (percentage) as appropriate. Denominator is 85 unless otherwise stated. Duration of CPAP does not include breaks.

APRV: Airway Pressure Release Ventilation; CPAP: Continuous Positive Airway Pressure; ICU: Intensive Care Unit; IMV: Invasive Mechanical Ventilation; NIV: Non-Invasive Ventilation.

[a]14/16 were discharged from ICU and 2/16 of whom died with CPAP/NIV as their ceiling of care. In total six patients had a ceiling of care of CPAP/NIV.

age of the BAME group was 56.6 (51.7–62.6). Age was not significantly different between white and BAME groups ($p = 0.077$).

At the point of ICU admission, there were no significant differences in laboratory findings between survivors and non-survivors, however differences arose between peak values in the first 72-hours of IMV. Peak ferritin within the first 72-hours of IMV was lower in survivors (1311 [788–3049] versus 3213 [1534–5927], $p = 0.024$) as was peak neutrophil count within the first 72-hours of IMV (9.8 [7.4–12.9] versus 12.0 [10.3–14.4], $p = 0.006$). Peak C-reactive protein and trough lymphocyte count within the first 72-hours of IMV were not associated with survival. Survival was not affected by presence of an AKI at admission or within the first 72-hours of IMV, nor with renal replacement therapy use.

Among patients who received IMV, driving pressure was significantly greater in non-survivors at 24 hours (18 [16–22] versus 16 [14–19], $p = 0.036$) and at 72 hours (18 [14–20] versus 15 [12–20], $p = 0.041$). PaO_2/FiO_2 ratio was significantly lower in non-survivors at 24 hours (17.8 [13.4–26.1] versus 23.8 [18.7–31.1], $p = 0.012$) and at 72 hours (16.8 [14.2–21.0] versus 22.0 [16.9–28.2], $p = 0.024$). Further data on driving pressures and PaO_2/FiO_2 ratios at additional time points following commencement of IMV can be found in Supplementary Table 1.

Overall there was no difference in mortality between those who had a trial of CPAP/NIV

(16/36 (44.4%)) and those who were intubated prior to or on arrival to ICU (22/49 (44.9%), p = 0.967). Within the group of patients to receive a trial of CPAP/NIV, mortality was high in those who subsequently required intubation (14/20 [70.0%]). Of those who had a noradrenaline requirement in excess of 0.4 mcg/kg/min, 6/7 (85.7%) died versus 32/78 (41.0%) of those without (p = 0.005).

Discussion

This single-centre retrospective observational study described 85 patients with acute respiratory failure secondary to laboratory-confirmed Covid-19, managed in a South London district general hospital's ICU. We describe our cohort's clinical characteristics, ICU management with a focus on the initial 72-hours of IMV, and outcomes after a follow-up period of at least 14 days.

Our cohort was relatively young (median age 57.3 [49.4–64.2]) and three-quarters male, in keeping with nationwide audit data.[10] A greater proportion of patients in our cohort were Black compared with 2011 local census data (43.5% versus 27.2%).[17] Conversely, proportionally fewer White patients were seen in our cohort compared with census data (32.9% versus 53.6%). These trends mirror those seen both more widely in the UK and internationally, with postulated causes including relative prevalences of comorbidities like hypertension and diabetes and socioeconomic factors such as increased housing density.[18,19] The functional baseline of the cohort was reasonable, with 89.4% having a Rockwood CFS of 3 or less. A score of 3 denotes: "managing well – people whose medical problems are well controlled but are not regularly active beyond routine walking".[12]

The majority (80.0%) had one or more comorbidities, the commonest being hypertension (51.8%), obesity (48.7%), and diabetes mellitus type 2 (31.8%). These comorbidities were more common in our cohort than in the local population as a whole (hypertension 19.9%; obesity 24%; diabetes mellitus 9.7%).[20–22] It is currently unclear whether these comorbidities play a role in the pathophysiology of severe disease, or merely represent associations (e.g. by becoming more prevalent with increasing age). There is a suggestion that Covid-19 causes an endotheliitis, and pre-existing hypertension and diabetes may further contribute to the endothelial dysfunction.[23] Obesity poses general challenges for IMV, including increased atelectasis and a requirement for greater driving pressures to overcome reduced thoracic compliance and abdominal splinting.[24] It is also possible that metabolic dysfunction contributes to the pathophysiology of Covid-19.[25]

The clinical presentation of Covid-19 mirrored that seen in similar studies: shortness of breath, fever and cough in the majority of cases with a significant minority experiencing gastrointestinal disturbance.[26–29] The median duration from symptom onset to ICU admission was 8 days (6–10). Recent history of foreign travel was uncommon and the majority of patients had no known unwell contacts. All patients presented via the emergency department and were found to be in acute respiratory failure, with a profoundly low PaO_2/FiO_2-ratio (8.28 kPa [7.04–11.7]), values consistent with ARDS according to the Berlin definition (the inherent limitations of PaO_2/FiO_2-ratio calculation in the spontaneously ventilating patient and the median preceding symptom duration of eight days notwithstanding).[16] Bilateral pulmonary infiltrates on chest radiograph were universal.

At the point of ICU admission, lymphopenia (58.9%) and markedly raised CRP (182 [121–249]) and ferritin (1952 [862–3330]) were typical. These derangements were sustained throughout the first 72 hours of IMV. In keeping with other case series, elevated LDH and D-dimer were near-universal in those tested. However, unlike some similar case series, we did not find that the degree of derangement of these values was associated with increased risk of non-survival, possibly due to our sample size.[30–34] These markers are non-specific, and an evidence base is needed if they are to inform and improve patient care.

Our respiratory support strategy evolved over the study period. Initially, all patients who remained markedly hypoxic despite high flow supplemental oxygen delivered via non-rebreathe or Venturi mask were intubated prior to or on arrival to ICU. What began as a strategy to 'bridge' patients until stretched staff and resources could be made available to safely intubate them and admit to ICU, a 'trial of CPAP/NIV' gradually became adopted as an alternative to intubation in certain patients. In the absence of an evidence base, this was driven by several factors: the observed lack of improvement in intubated patients; concerns of our resources becoming exhausted by rapidly increasing demand; and informal anecdotal reports from colleagues in the UK and abroad in favour of CPAP/NIV.

Eligibility for a trial of CPAP/NIV was determined clinically on an individual patient basis. Factors in favour of intubation over a trial of CPAP/NIV included: high work of breathing, rapidly deteriorating clinical trajectory, altered mentation and patient issues which may affect prolonged facemask compliance. CPAP/NIV also represented a ceiling of treatment in several patients who were felt not to be suitable for IMV.

Overall, we have observed that mortality was similar in those who were intubated at or prior to arrival to ICU and those who received a trial of CPAP/NIV. However, this comparison should be interpreted with caution since those who received a trial of CPAP/NIV included patients who were more clinically stable than those intubated at or on arrival to ICU, and patients

who had a ceiling of treatment of CPAP/NIV in place.

There are clear advantages such as avoidance of the risks of intubation, invasive ventilation, sedation and paralysis and a reduced demand on ICU nurses. However, despite the use of viral filters, concerns remain regarding droplet and aerosol spread and its implications on staff and other patients. The role for CPAP/NIV in Covid-19 remains unclear and further investigation into this clinical dilemma is warranted.

Our cohort had a substantial incidence of renal dysfunction, with 62.4% sustaining an AKI over the course of their ICU stay, and 20.0% requiring renal replacement therapy. The burden of renal dysfunction is not fully understood, but we speculate that our initial practice of keeping patients' fluid balance mildly negative to support their ventilation may have contributed.

At a median of 34 days of follow-up (26–40), 44.7% of our cohort had died, in line with national audit data.[10] A secondary objective of the study was to highlight patient characteristics and laboratory findings which may have a role in prognostication in Covid-19. Parameters of interest were compared between non-survivors (44.7%) and those who remained alive at the end of the follow-up period (55.3%).

Besides increased age, no clinical characteristics or admission laboratory parameters were associated with mortality in our cohort. It is notable that while racial background was not associated with mortality, there was a trend towards patients of a BAME background, particularly those of Asian background being younger than white patients.

Following admission to ICU, lower PaO_2/FiO_2-ratios, increased driving pressures and a higher peak ferritin and neutrophil count over the first 72-hours of IMV were all associated with increased mortality. Elevated ferritin has been associated with mortality in Covid-19 in several studies[28,30] and has been postulated to be a marker of a hyperinflammatory process, possibly secondary haemophagocytic lymphohistiocytosis.[35] Notably, ferritin was more closely associated with non-survival than CRP, an acute phase protein used to quantify inflammation more routinely in clinical practice. PaO_2/FiO_2-ratio, a well-established diagnostic criterion for ARDS, was significantly lower in non-survivors at a range of time points following commencement of IMV (6-, 12-, 24- and 72-hours)[16] (Supplementary Table 1).

Tools that aid prognostication at the time of referral to ICU are currently lacking but could prevent patients from receiving futile interventions and could facilitate the appropriate allocation of resources. The sharing of data and experiences from a single centre such as ours is a step in the right direction, but the authors recognise the need for pooling of datasets to address the shortfall of sample size.

Strengths and Limitations

To our knowledge, this is the largest single-centre case series describing a cohort of Covid-19 patients in a UK ICU setting. We present a wide array of clinical data from our cohort and provide a valuable insight into a district general hospital setting, which is often under-represented in the literature compared to tertiary centres.

This study builds on the ICNARC report data which has been an invaluable resource in appreciating the scale of the burden of Covid-19 in ICU nationally.[10] However, given its broad scope, it lacks granularity in certain areas such as comorbidities and organ support. Our study offers a detailed insight into a cohort with respect to clinical characteristics, laboratory, radiological findings and ICU management – in particular regarding respiratory support. We also propose a range of variables which appear to correlate with survival and warrant further investigation.

Several factors influenced the heterogeneity of this cohort. Due to the emerging nature of Covid-19, local practice evolved over the study period. For example, a trial of CPAP/NIV was increasingly utilised in the latter part of the study period. Additionally, interhospital transfer was routinely used to balance surges in demand and capacity across London. Finally, biochemical markers of potential prognostic value (e.g. ferritin, D-dimer, and LDH) identified in other studies were incorporated into monitoring of our patients in the latter part of this study.

As with all single-centre observational studies, generalisability of our findings cannot be assumed. Our sample size is large for a single ICU, but is small when placed in the context of the national and international burden of Covid-19. Given the range of variables of interest, interpretation should be cautioned in light of the risk of type-1 error. Our study has a number of potential sources of bias. Firstly, data were collected by the team responsible for the care of patients. Secondly, the reliability of data is contingent on the quality of clinical documentation. Finally, while we were able to obtain the majority of data from receiving hospitals, some data points were impractical to obtain expediently.

During the study period, a number of factors placed our ICU under unprecedented strain including and not limited to: high patient caseload, concerns about risk to staff and personnel working in unfamiliar environments. Data on operational factors such as staff redeployment, doctor- and nurse-to-patient ratios, drug and equipment shortages and use of suboptimal equipment (such as anaesthetic machines as ventilators) were not recorded. These factors likely represent hidden confounders and further research into their relative impact on patient outcomes would be of value.

Conclusions

Covid-19 represents an unprecedented global challenge and sharing experience and insights from the 'front line' are essential in our response. ICU capacity, while expanding on an incomparable scale, remains a finite and invaluable resource as the Covid-19 pandemic continues. Decisions surrounding admission to ICU, treatment escalation planning and withdrawal of care should be informed by the best available evidence, which at present remains limited. Appropriate allocation of ICU resources hinges on evidence-based prognostication and may lessen the psychological burden to clinicians making daily life-and-death decisions.

We have cautiously identified several variables which were associated with mortality in our cohort including: age, PaO_2/FiO_2-ratio, driving pressure and peak ferritin and neutrophil count over the first 72-hours of IMV. The associations seen in this descriptive study cannot be assumed to be causative, but merit further investigation in studies with larger cohorts over a more prolonged follow-up period.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Alexander Isted https://orcid.org/0000-0001-9634-0832

Supplemental material

Supplemental material for this article is available online.

References

1. World Health Organization (WHO). Novel coronavirus (2019-nCoV) situation report – 1. *WHO Bulletin*, 21 January 2020.
2. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature* 2020; 579: 265–269.
3. World Health Organization (WHO). *Naming the coronavirus disease (COVID-19) and the virus that causes it*. Geneva: World Health Organization, 2020.
4. Shereen MA, Khan S, Kazmi A, et al. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res* 2020; 24: 91–98.
5. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020; 382: 1199–1207.
6. World Health Organization (WHO). Coronavirus disease (COVID-19) situation report-103 [Internet]. 202AD [cited 2020 May 2], https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200502-covid-19-sitrep-103.pdf?sfvrsn=d95e76d8_4 (accessed 26 October 2020).
7. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020; 8(5): 475–481.
8. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA* 2020; 323(18): 1775–1776.
9. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle Region — case series. *Lancet Respir Med* 2020; 382: 2012–2022. https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases (2020, accessed 26 October 2020).
10. Intensive Care National Audit and Research Centre. *ICNARC report on COVID-19 in critical care* 01 May 2020 [Internet]. https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports (2020, accessed 26 October 2020).
11. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61(4): 344–349.
12. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173(5): 489–495.
13. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13(10): 818–829.
14. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron - Clin Pract* 2012; 120 (4): 179–84.
15. Lisboa Bastos M, Tavaziva G, Abidi SK, et al. Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis. *BMJ* 2020; 370: m2516.
16. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012; 38(10): 1573–1582.
17. Office of National Statistics. 2011 Census second release, December 2012, Lewisham Council [Internet]. [cited 2020 Apr 18], https://lewisham.gov.uk/inmyarea/census-2011 (2018, accesses 26 October 2020).
18. Yancy CW. COVID-19 and African Americans. *JAMA*. 2020; 323(19): 1891–1892.
19. Aldridge RW, Lewer D, Katikireddi SV, et al. Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data. *Wellcome Open Res*. 2020; 5: 88.
20. Hypertension prevalence estimates for local populations, Public Health England, [Internet]. 2016, https://www.gov.uk/government/publications/hypertension-prevalence-estimates-for-local-populations (2016, accessed 26 October 2020).
21. Diabetes prevalence estimates for local populations, Public Health England [Internet]. 2015, https://www.gov.uk/government/publications/diabetes-prevalence-estimates-for-local-populations (2015, accessed 26 October 2020).
22. Department of Health. Obesity in Adults, Department of Health [Internet]. 2014 [cited 2020 Apr 20], https://

data.london.gov.uk/dataset/obesity-adults (2014, accessed 26 October 2020).
23. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395(10234): 1417–1418.
24. De Jong A, Chanques G and Jaber S. Mechanical ventilation in obese ICU patients: from intubation to extubation. *Crit Care* 2017; 21(1): 63.
25. Kassir R. Risk of COVID-19 for patients with obesity. *Obes Rev* 2020; 21: e13034.
26. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 2020; 80(4): 388–393.
27. Wu J, Liu J, Zhao X, et al. Clinical characteristics of imported cases of coronavirus disease 2019 (COVID-19) in Jiangsu Province: a multicenter descriptive study. *Clin Infect Dis* 2020; 71(15): 706–712.
28. Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect* 2020; 80(5): E1–E6.
29. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. *N Engl J Med* 2020; 382: 2372–2374.
30. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; 46(5): 846–848.
31. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; 323 (11): 1061–1069.
32. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020; 395(10229): 1054–1062.
33. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382: 1708–1720.
34. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180(7): 934–943.
35. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* 2020; 395(10229): 1033–1034.