 doi:10.20944/preprints202008.0267.v1

Trends in intensive care for patients with COVID-19 in England, Wales and Northern Ireland

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 doi:10.20944/preprints202008.0267.v1

ABSTRACT

Aim: To report changes in admission rates, patient characteristics, processes of care and outcomes for all patients with COVID-19 admitted to intensive care units (ICUs) in England, Wales and Northern Ireland.

Methods: Population cohort of all 10,287 patients with COVID-19 appearing in the Case Mix Programme national clinical audit from 1 February to 2 July, 2020. Analyses were stratified by time period (pre-peak, peak, post-peak) and geographical region, and multivariable regressions were used to estimate differences in 28-day mortality, adjusting for variation in patient characteristics over time.

Results: Admissions to ICU peaked on 1 April, nine days after commencement of "lockdown", and occurred simultaneously across regions. The number of patients in ICU peaked ten days later. Compared with patients admitted during the pre- and post-peak periods, patients admitted during the peak were younger and had lower levels of prior dependency but more severe respiratory and renal dysfunction. Use of invasive ventilation and renal replacement reduced over time. Twenty-eight-day mortality reduced from 43.5% (95% CI 41.6% to 45.5%) pre-peak to 34.3% (95% CI 32.3% to 36.2%) post-peak; a difference of −8.8% (95% CI: −5.2%, −12.3%) after adjusting for patient characteristics. London experienced the highest admission rate and had higher mortality during the peak period but a greater reduction in post-peak mortality.

Conclusion: Observed trends suggest opposing effects of ICU strain and clinical learning. Further investigation is needed to identify modifiable system factors that could alleviate

 doi:10.20944/preprints202008.0267.v1

strain in future epidemics and changes in clinical practice that contributed to improved patient outcomes.

KEYWORDS

COVID-19; intensive care; trends; United Kingdom; mortality; mechanical ventilation

DECLARATIONS

Funding

No specific funding was provided for this analysis. Dr Shankar-Hari is supported by the National Institute for Health Research Clinician Scientist Award (CS-2016-16-011). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Competing interests

None declared

Ethics approval and consent

The Case Mix Programme has support for the collection and use of patient-identifiable data without consent under Section 251 of the NHS Act 2006 (approval number PIAG 2–10(f)/2005). As a service evaluation, approval from a Research Ethics Committee was not required (UK Health Research Authority).

Availability of data

Access to the CMP data underlying this paper can be requested following guidance here: https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports/Access-Our-Data

 doi:10.20944/preprints202008.0267.v1

Authors' contributions

JD, DH, KR, conceived and designed the study. All authors contributed to the acquisition of data. JD, KT, PFV, DH conducted the analysis of data. All authors contributed to the interpretation of data. JD, PM, DG, MSH, DH, KR, drafted the manuscript. All authors critically reviewed the manuscript and approved the final version to be published and agree to be accountable for all aspects of the work. JD and DH had full access to data and take responsibility for the integrity of the data and the accuracy of the data analysis.

 doi:10.20944/preprints202008.0267.v1

INTRODUCTION

On March 11, 2020, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organisation (WHO).[1] After originating in Wuhan, China,[2] coronavirus disease (COVID-19), spread across the globe. By July 9, 2020, 549,534 deaths across 169 countries had been identified as associated with COVID-19 and the United Kingdom (UK) has reported 44,602 COVID-19 associated deaths.[3]

With reports of approximately 5% of patients with COVID-19 requiring intensive care unit (ICU) admission,[4,5] the UK undertook a number of measures to maximize ICU capacity to deal with the potential increase in ICU admissions. These measures included: increasing the number of overall ICU beds through surge capacity; building of new 'Nightingale' hospitals (specially constructed critical care hospitals as part of the response to COVID-19); cancelling elective surgery; and increasing numbers of available ventilators through re-deployment and purchase.

By July 9, 2020, over 10,000 patients had been reported as admitted to ICU with COVID-19 by the Intensive Care National Audit & Research Centre (ICNARC) via its Case Mix Programme (CMP), the national clinical audit for adult critical care covering England and Wales.[6] Complete, national coverage for England, Wales and Northern Ireland across the National Health Service (NHS) across the first wave of the epidemic by the CMP, provides a unique opportunity to describe trends in admission rates (nationally and regionally), patient characteristics, clinical management and outcomes of patients admitted to ICU with COVID-19. Examining these trends, including the influence patient characteristics had over any changes in outcomes, provides opportunities to learn from changes over time.

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METHODS

Databases

These analyses use patient-level data on critically ill patients with COVID-19 from ICNARC's CMP.[6] The CMP is the national clinical audit for adult critical care that collects case mix and outcome data for individual patient admissions, covering 100% of adult general intensive care units (ICUs; including standalone and combined intensive/high dependency care units) across England, Wales and Northern Ireland. In response to the emerging pandemic, CMP data submission was accelerated for COVID-19 patients to include early submission of data covering the first 24 hours of ICU admission (including patient characteristics and physiology) with subsequent submission of data after ICU discharge (including ICU outcome and duration of organ support) and hospital discharge (including ultimate hospital outcome). In the period prior to ICU/hospital discharge, daily data updates were received.

Participants

CMP patient-level data were extracted for all ICU admissions with confirmed COVID-19 from 1 February 2020 to 1 July, 2020, for England, Wales and Northern Ireland. Multiple ICU admissions for the same patient were linked using a unique national identifier (NHS number) and combined into a single patient record.

Data items

Regional rates of ICU admission were derived using date of admission for a patient's first admission to ICU with a diagnosis of COVID-19 combined with estimates of population size reported by the Office for National Statistics.[7] Caseload was defined as the total number of

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patients with COVID-19 in ICU on each day. 'Region' refer to the NHS Commissioning Regions for the treating hospital.

For analysing trends across the epidemic, variables were selected based on their clinical relevance and categorised to illustrate variation in their distribution over time. *Patient characteristics* included categorised age (≥ 75 years), sex (male), ethnic group (Asian, Black, White, or Other), prior dependency (any level of assistance required with daily activities), severe comorbidity (any from 16 recorded; see Appendix), deprivation (highest quintile; derived from the 2019 English[8] or Welsh Index of Multiple Deprivation[9] (IMD) or from the 2017 Northern Ireland Multiple Deprivation Measure[10] using patient's residential postcode) and body mass (body mass index (BMI) ≥ 30; derived as weight in kg divided by squared height in metres). *Indicators of acute physiological severity* used extreme (lowest/highest) physiology values during the first 24 hours in ICU combined as: overall acute severity of illness (APACHE II acute physiology score ≥ 14; highest quartile); acute kidney injury (KDIGO - Kidney Disease Improving: Global Outcomes, stage 2 or 3[11]); and PaO_2/FIO_2 ratio (from arterial blood gas with lowest $PaO_2 \leq 200$ mmHg[12]. Receipt of invasive ventilation within the first 24 hours was indicated by a recorded ventilated respiratory rate in the physiology data and combined with other processes of care collected after discharge from ICU (below).

To address varying duration of follow-up, a fixed time horizon of 28 days from first ICU admission with COVID-19 was used for the *indicators of processes of care* and *outcome*, with each indicator treated as missing if less than 28 days had elapsed (unless the patient had died or been discharged from hospital before 28 days). Indicators of processes of care included receipt of invasive ventilation (within first 24 hours, and at any point) and of renal replacement (at any point), and duration of each (in calendar days) stratified by mortality at

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28 days. Duration of ICU stay was measured as time from first ICU admission to earliest of either ultimate ICU discharge or 28 days. Patients discharged from acute hospital to a non-acute setting prior to 28 days were assumed to have survived to 28 days.

Statistical analysis

To aid interpretation of trends, the observation window was partitioned into three periods: pre-peak (from first case to three days prior to the observed peak in ICU admissions), peak (to three days after the observed peak in the number of patients in ICU) and post-peak (the remainder). Trends in patient characteristics, processes of care and outcomes were illustrated using linearly weighted moving averages, assigning a weight of 1 for the given date and reducing to one eighth at +/- 7 days.

Patients admitted more recently have higher levels of missing data owing to shorter follow-up and some time lag in data submission. Given that patients with longer duration of ICU or hospital stay are likely to differ from those with shorter duration, data are likely to be missing not at random (MNAR). After reviewing the proportion of missing data in each variable by date of admission, a two-week censoring period was adopted to mitigate the potential influence of missing data. This censoring period is marked on the observed trends and data from this period were excluded from analysis.

Differences between pre-peak, peak and post-peak periods were calculated with exact confidence intervals for differences in proportions, t-tests to derive confidence intervals for differences in means and the Bonett-Price confidence intervals for differences in medians.

Survival was explored using a Kaplan-Meier curve, stratified by time period and censoring patients on the earliest of the most recent date of record update by the treating hospital or

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two weeks prior to data extraction. To further explore the potential influence of changes in patient case mix on mortality, a logistic regression was fitted for 28-day mortality on time period, before and after controlling for a range of variables recorded during the first 24 hours of admission and previously identified as independent risk factors for death in ICU patients with COVID-19.[13] To explore the potential influence of the regional variation in admission rates, the same regression model was fitted for London only and non-London regions combined. For the regression modelling, ten sets of multiply imputed data were created using fully conditional specification. The approach was consistent with that described elsewhere.[13]

All analyses were conducted using Stata 14.2 (StataCorp, Texas).

RESULTS

Admissions to ICU

By 2 July, 12,615 ICU admission records had been received for 10,287 patients with COVID-19. Patient characteristics for this cohort have been reported in detail elsewhere[14] and are summarised in Table 1. Admissions to ICU peaked on April 1 (nine days after lockdown), occurring approximately simultaneously in all regions, and caseload peaked 10 days later (Figure 1). We therefore defined the peak period as 29 March to 14 April.

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Table 1 Characteristics of the cohort

	Median (IQR) [n], or n/n (%)
N	10,287
Patient characteristics and physiology within first 24 h	
Age	60.0 (51.0, 68.0) [10273]
Sex = male	7244/10278 (70.5%)
Dependency prior to hospital admissions, n(%)	
Able to live without assistance in daily activities	9086/10,075 (90.2%)
Some (minor/major) assistance with daily activities	952/10,075 (9.4%)
Total assistance with all daily activities	37/10,075 (0.4%)
Any severe comorbidities [a]	825/10,133 (8.1%)
Immunocompromise [a]	479/10,133 (4.7%)
Quintile of deprivation [a]	
1 (least deprived)	1474/10,122 (14.6%)
2	1637/10,122 (16.2%)
3	1971/10,122 (19.5%)
4	2466/10,122 (24.4%)
5 (most deprived)	2574/10,122 (25.4%)
Body mass index, kg/m^2	28.2 (24.8, 32.9) [9657]
Ethnic group	
Asian	6485/9822 (66.0%)
Black	1527/9822 (15.5%)
White	957/9822 (9.7%)
Other	853/9822 (8.7%)
APACHE II acute physiology score [a]	11 (8, 14) [10041]
ICNARC physiology score [a]	19 (14, 25) [10287]
Acute renal failure (KDIGO stage 2 or 3) [a]	4619/9871 (46.8%)
PaO_2/FIO_2 ratio, mm Hg	118.5 (84.1, 165.0) [9467]
Processes of care and outcome	**Mean (SD) [n], or n/n (%)**
Invasive ventilation [a]	
Within first 24 hrs	5927/9901 (59.9%)
At any point during ICU stay	7197/9866 (73.1%)
Duration among survivors, calendar days [b]	18.4 (9.0) [3913]
Duration among non-survivors, calendar days [b]	10.5 (6.5) [3233]
Renal replacement [a]	
At any point during ICU stay	2680/9866 (27.2%)
Duration among survivors, calendar days [b]	13.8 (9.0) [1300]
Duration among non-survivors, calendar days [b]	6.7 (5.1) [1347]
28-day mortality	3891/9734 (40.0%)
Duration of ICU stay	
Among survivors, calendar days [b]	15.9 (10.4) [5843]
Among non-survivors, calendar days [b]	9.5 (6.7) [3891]

[a] See text for definitions; [b] Durations calculated among survivors or non-survivors at 28 days. Data on outcomes and processes of care treated as missing for patients admitted less than 29 days prior to data extraction (no further censoring applied).

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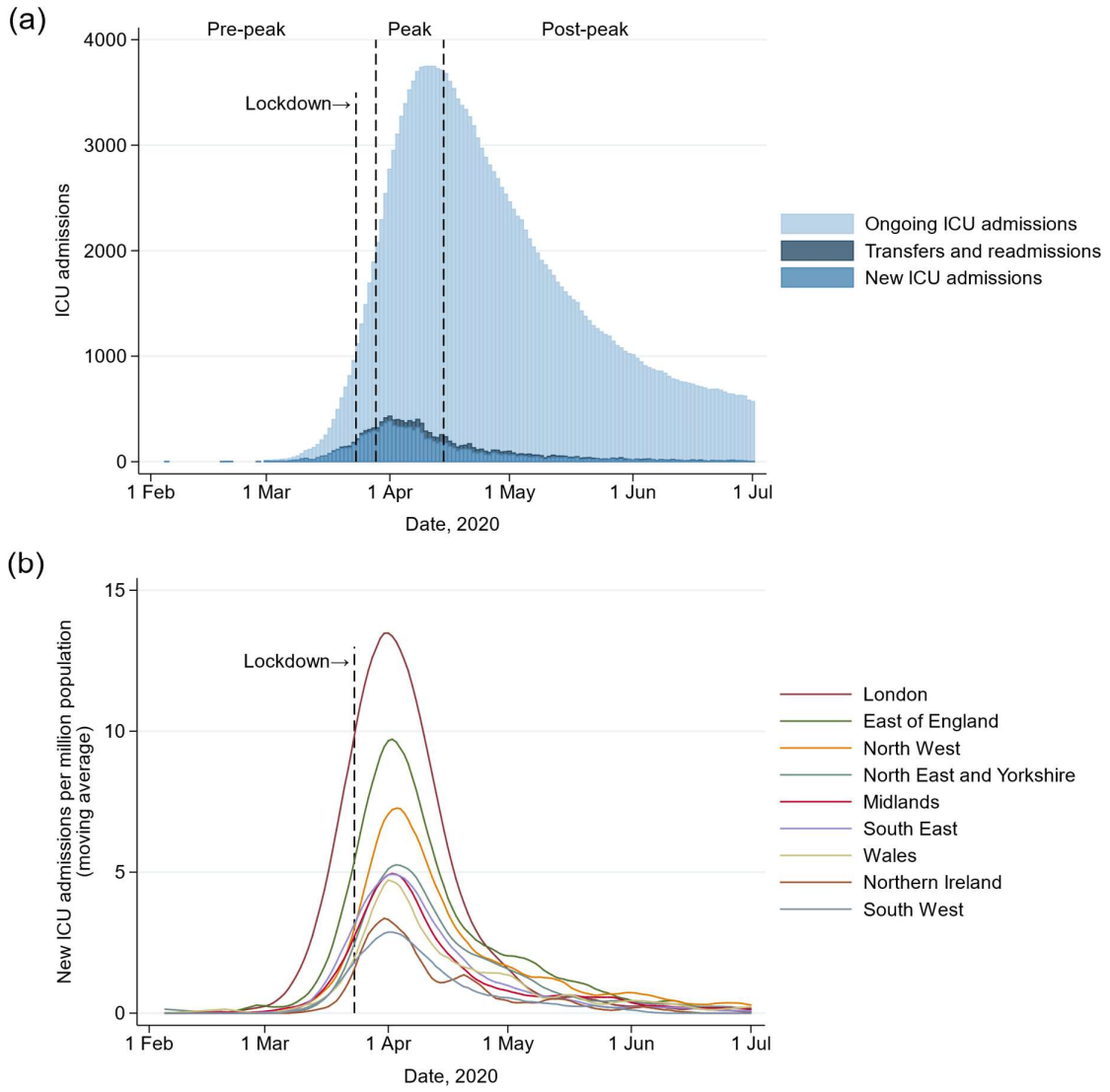

Fig. 1 Admissions to ICU with COVID-19 per day in England, Wales and Northern Ireland

In panel (b), regions are NHS commissioning regions, denominators are ONS estimates of the mid-2019 regional population aged 15 years and over,[7] and moving averages are linearly weighted +/- 7 days.

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Trends in patient characteristics and first 24-hour physiology

Trends in patient characteristics and first 24-hour physiology are illustrated in Figure 2 and summarised by time period in Table 2. Trends in ethnic group are illustrated in eFigure 1, Appendix. The proportion of patients who were male reduced over time, as did the proportion from Black and other minority ethnic groups. Conversely, the proportion with any severe comorbidities, the proportion from the most deprived quintile of postcodes and, to a lesser extent, the proportion who were obese (BMI ≥ 30 kg/m^2), each increased over time. Trends in age ≥ 75 years, any prior dependency and, to a lesser extent, APACHE II acute physiology score ≥ 14, appeared U-shaped, with patients admitted during the peak period being younger and less severely ill, by these measures, when compared with those admitted during pre- and post-peak periods. Conversely, patients admitted during the peak period were more likely to have acute kidney injury (KDIGO stage 2 or 3) and to have more severe respiratory failure (PAO_2/FIO_2 ratio ≤ 200 mmHg).

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Table 2 Patient characteristics and physiology within first 24 h, by time period

	Median (IQR), or n/n (%)			Difference (95% CI)	
	Pre-peak (n = 2420)	Peak (n = 4906)	Post-peak [a] (n = 2856)	Peak vs non-peak	Post-peak vs pre-peak
Age					
Median	61 (51, 70)	59 (51, 67)	59 (50, 67)	-2.0 (-1.3, -2.7)	-2.0 (-1.3, -2.7)
≥ 75 years	322/2420 (13.3%)	398/4906 (8.1%)	280/2856 (9.8%)	-5.2% (-6.7%, -3.6%)	-3.5% (-5.2%, -1.8%)
Sex = male	1763/2418 (72.9%)	3524/4901 (71.9%)	1888/2854 (66.2%)	-1.0% (-3.2%, 1.2%)	-6.8% (-9.2%, -4.3%)
Ethnicity					
Asian	307/2311 (13.3%)	780/4684 (16.7%)	415/2731 (15.2%)	3.4% (1.6%, 5.1%)	1.9% (0.0%, 3.8%)
Black	301/2311 (13.0%)	446/4684 (9.5%)	208/2731 (7.6%)	-3.5% (-5.1%, -1.9%)	-5.4% (-7.1%, -3.7%)
White	1501/2311 (65.0%)	3017/4684 (64.4%)	1905/2731 (69.8%)	-0.5% (-2.9%, 1.8%)	4.8% (2.2%, 7.4%)
Other	202/2311 (8.7%)	441/4684 (9.4%)	203/2731 (7.4%)	0.7% (-0.7%, 2.1%)	-1.3% (-2.8%, 0.2%)
Any prior dependency [b]	233/2395 (9.7%)	373/4796 (7.8%)	367/2790 (13.2%)	-2.0% (-3.4%, -0.5%)	3.4% (1.7%, 5.2%)
Any severe comorbidities [b]	169/2405 (7.0%)	330/4827 (6.8%)	316/2805 (11.3%)	-0.2% (-1.4%, 1.1%)	4.2% (2.7%, 5.8%)
Most deprived quintile [b]	489/2382 (20.5%)	1219/4831 (25.2%)	820/2806 (29.2%)	4.7% (2.7%, 6.7%)	8.7% (6.4%, 11.0%)
Body mass index, kg/m^2					
Median	28.0 (24.9, 32.7)	28.3 (25.0, 32.7)	28.3 (24.7, 33.6)	0.3 (-0.7, 0.0)	0.3 (-0.7, 0.0)
≥ 30	870/2319 (37.5%)	1817/4596 (39.5%)	1066/2654 (40.2%)	2.0% (-0.4%, 4.4%)	2.6% (-0.1%, 5.4%)
APACHE II acute physiology score [b]					
Median	11 (9, 14)	11 (8, 14)	11 (9, 14)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
≥ 14	676/2397 (28.2%)	1301/4760 (27.3%)	887/2792 (31.8%)	-0.9% (-3.1%, 1.3%)	3.6% (1.1%, 6.1%)
KDIGO stage 2 or 3 [b]	1062/2369 (44.8%)	2397/4669 (51.3%)	1140/2740 (41.6%)	6.5% (4.0%, 9.0%)	-3.2% (-5.9%, -0.5%)
PaO_2/FIO_2 ratio, mm Hg					
Median	126.0 (87.7, 173.6)	115.5 (84.0, 159.4)	115.5 (81.0, 171.4)	-10.5 (-6.7, -14.3)	-10.5 (-6.7, -14.3)
< 200	1938/2322 (83.5%)	3924/4487 (87.5%)	2095/2574 (81.4%)	4.0% (2.2%, 5.8%)	-2.1% (-4.2%, 0.1%)

[a] To mitigate potential influence of data missing not at random, the post-peak period excludes patients admitted during the 14 days prior to data extraction; [b] See text for definitions. Confidence intervals calculated using exact formula for difference in proportions and Bonett-Price formula for difference in medians.

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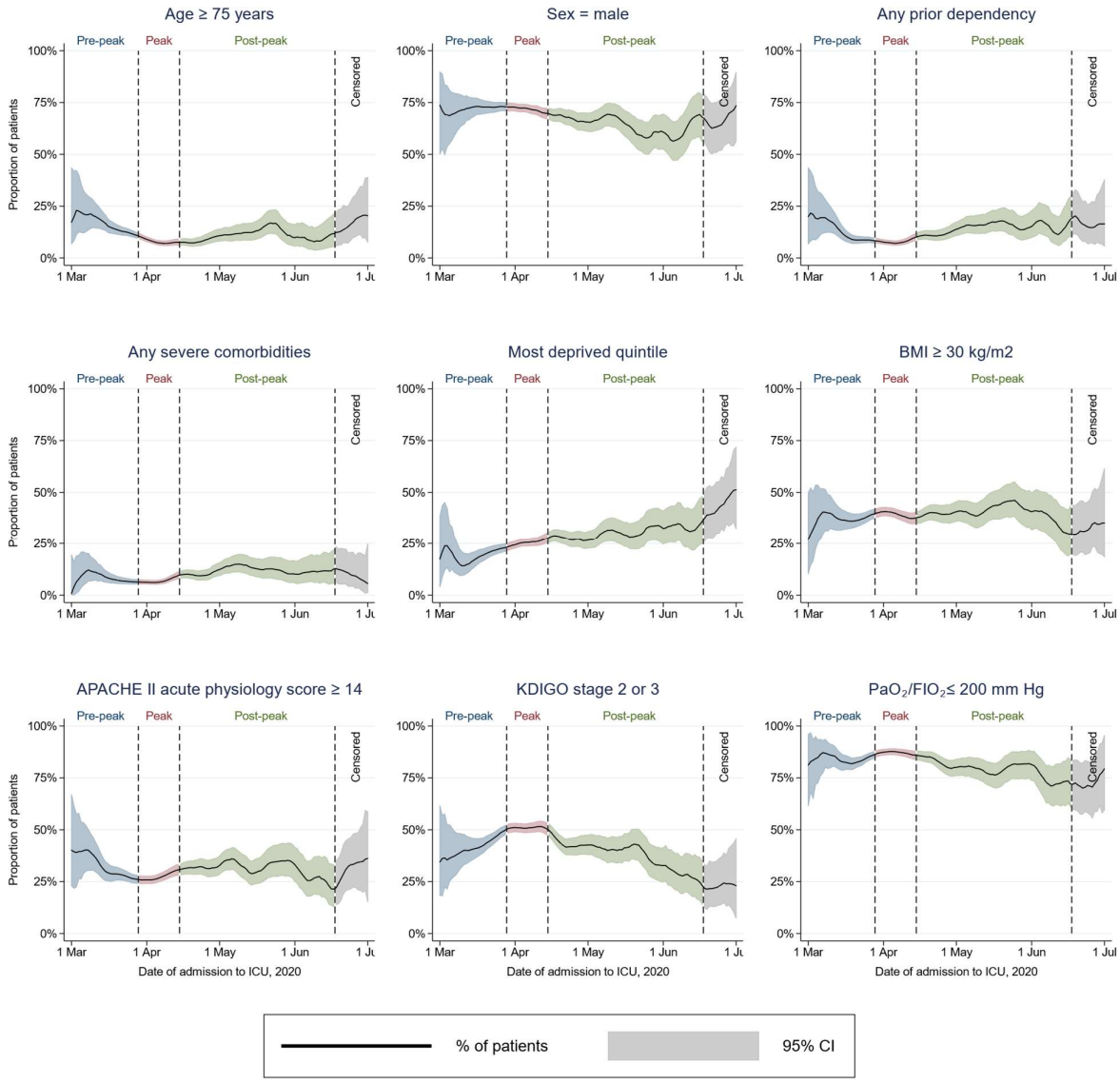

Fig. 2 Trends in patient characteristics at admission to ICU

Lines are moving averages linearly weighted +/- 7 days. See text for definitions.

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Trends in processes of care and outcome

Of the 10,000 patients admitted at least 28 days prior to data extraction, 28-day outcomes were available for 9727 (97.3%). On day 28, 3887 (40.0%) had died, 1725 (17.7%) were still in ICU, 978 (10.1%) had been discharged from ICU but were still in hospital, and 3003 (30.9%) had been discharged from hospital to a non-acute setting (and assumed to have survived to day 28). After censoring, 10,166 patients were included in the Kaplan-Meier analysis (where 28 days of follow-up was not required) and 9713 in other analyses of processes of care and outcome.

Trends in processes of care and outcome are illustrated in Fig. 3 and summarised by time period in Table 3. Receipt of invasive ventilation reduced over time, both within the first 24 hours and at any point during ICU stay. Duration of invasive ventilation increased during the peak period among survivors but remained stable among non-survivors. Receipt of renal replacement also reduced over time and duration of renal replacement also increased slightly during the peak among survivors. Duration of ICU stay reduced over time among survivors but remained stable among non-survivors.

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Table 3 Processes of care, by time period

	Mean (SD), or n/n (%)			Difference (95% CI)	
	Pre-peak (n = 2420)	Peak (n = 4906)	Post-peak [a] (n = 2387)	Peak vs non-peak	Post-peak vs pre-peak
Invasive ventilation [b]					
Within first 24h	1804/2376 (75.9%)	2891/4698 (61.5%)	1209/2741 (44.1%) [c]	-14.4% (-16.6%, -12.2%)	-31.8% (-34.3%, -29.3%)
At any point	2021/2415 (83.7%)	3603/4842 (74.4%)	1444/2345 (61.6%)	-9.3% (-11.2%, -7.4%)	-22.1% (-24.6%, -19.6%)
Duration among survivors, calendar days	17.4 (9.0)	19.1 (8.9)	18.1 (9.2)	1.7 (1.0, 2.3)	0.7 (-0.1, 1.5)
Duration among non-survivors, calendar days	10.5 (6.1)	10.6 (6.6)	10.2 (7.1)	0.1 (-0.4, 0.6)	-0.3 (-1.0, 0.3)
Renal replacement [b]					
At any point	760/2415 (31.5%)	1332/4842 (27.5%)	538/2345 (22.9%)	-4.0% (-6.2%, -1.7%)	-8.5% (-11.0%, -6.0%)
Duration among survivors, calendar days	13.4 (8.3)	14.4 (9.2)	13.0 (9.3)	0.9 (-0.2, 2.1)	-0.4 (-1.8, 0.9)
Duration among non-survivors, calendar days	6.5 (4.8)	6.8 (5.1)	6.9 (5.3)	0.4 (-0.3, 1.0)	0.4 (-0.3, 1.2)
Duration of ICU stay					
Among survivors, days	16.6 (9.9)	16.3 (10.5)	14.6 (10.4)	-0.3 (-0.9, 0.4)	-2.0 (-2.7, -1.3)
Among non-survivors, days	9.6 (6.3)	9.6 (6.7)	9.0 (7.1)	0.0 (-0.5, 0.5)	-0.6 (-1.2, 0.0)

[a] To mitigate potential influence of data missing not at random, the post-peak period excludes patients admitted during the 42 days prior to data extraction (28 days of follow-up plus 14 days of censoring); [b] See text for definitions. [c] Because invasive ventilation within first 24h was recorded alongside patient characteristics and 24-hour physiology, a larger sample was available for the post-peak period. Durations calculated among survivors or non-survivors at 28 days. Confidence intervals calculated using exact formula for difference in proportions and *t*-statistics for difference in means.

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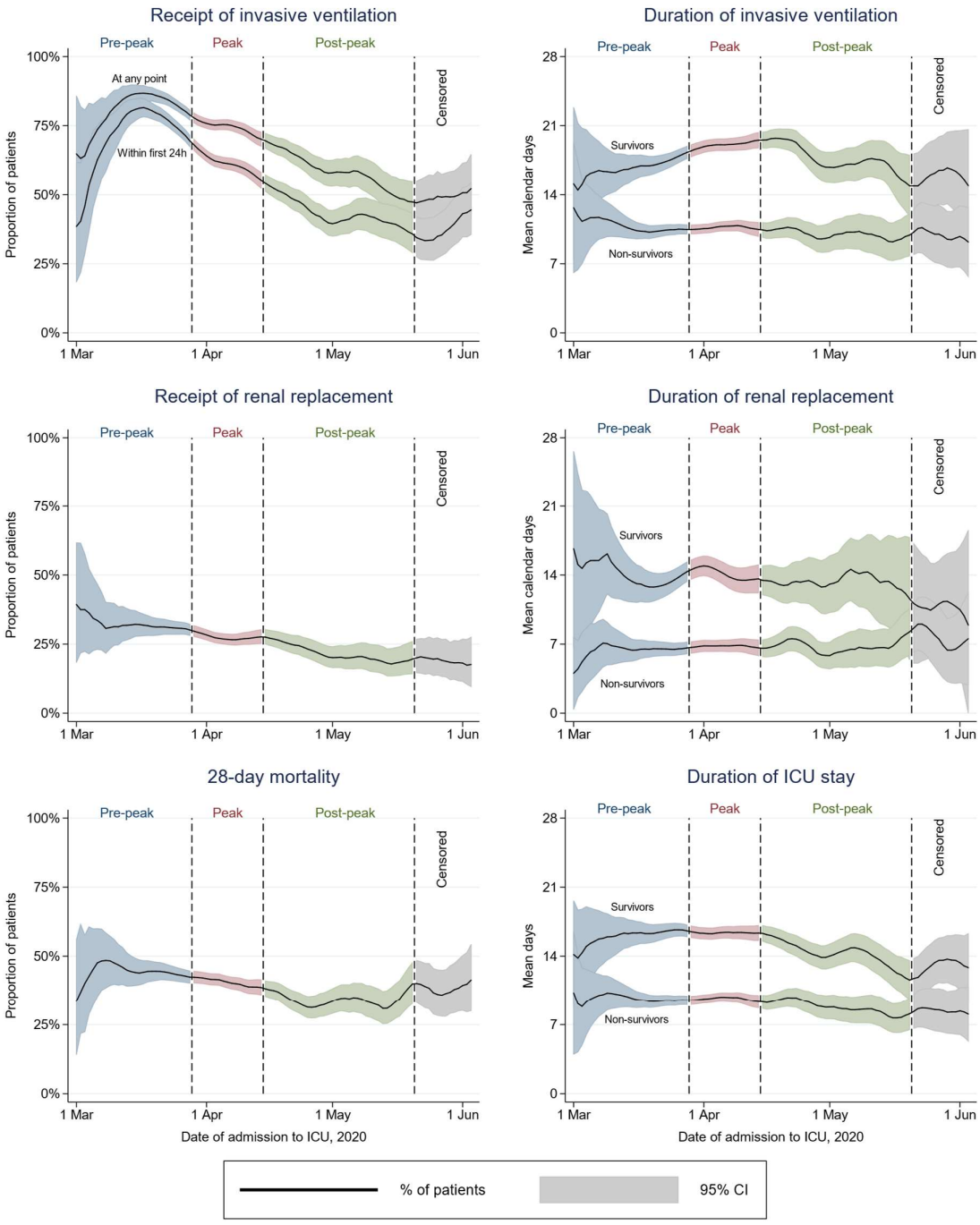

Fig. 3 Trends in 28-day mortality, duration of ICU stay and organ support

Lines are moving averages linearly weighted +/- 7 days. Durations calculated by survival at 28 days. See text for definitions.

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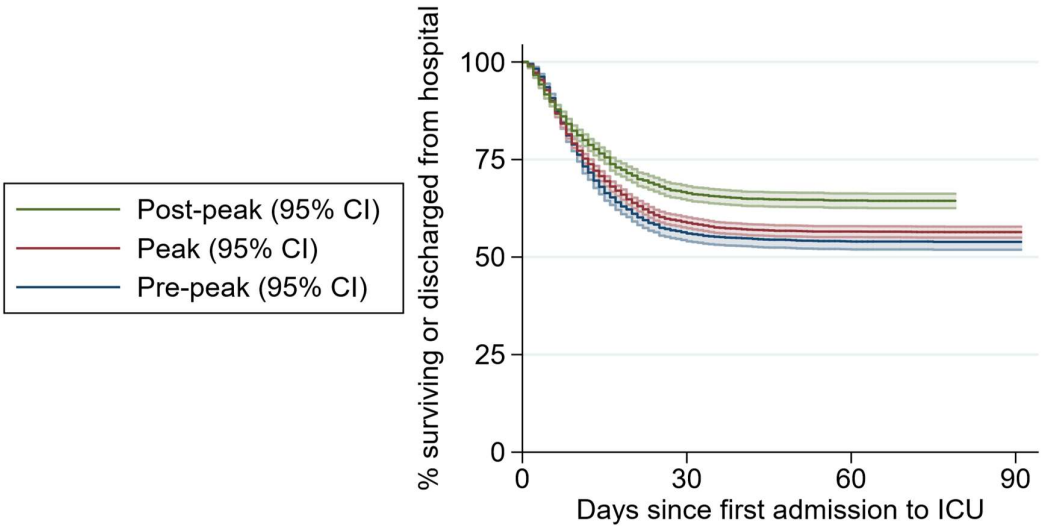
Survival is illustrated in Fig. 4 and results from analysis of 28-day mortality are summarised in Table 4. Twenty-eight-day mortality decreased from 43.5% (95% CI 41.6% to 45.5%) pre-peak to 34.4% (95% CI 32.3% to 36.2%) post-peak overall. A greater decrease in mortality was observed in London compared to other regions but after an initial, small increase in mortality during the peak period (Table 4). Differences in mortality over time were similar before and after controlling for a wide range of patient and physiological risk factors for mortality (all coefficients from the regression models can be found in eTable 1, Appendix).



Post-peak, at risk	2856	1566	895	0
Post-peak, censored	0	386	1016	1910
Peak, at risk	4895	2796	2613	988
Peak, censored	0	105	182	1801
Pre-peak, at risk	2415	1341	1267	1189
Pre-peak, censored	0	15	40	116

Fig. 4 Survival to hospital discharge, by time period

Kaplan-Meier analysis includes 10,166 patients admitted more than two weeks prior to data extraction on 2 July, after excluding 16 patients with missing outcomes dates. Patients were censored on the earliest of: last record update by hospital or two weeks prior to data extraction. Patients discharged from hospital were treated as surviving to end of follow-up.

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Table 4 Differences in 28-day mortality, by time period

	Overall (n = 9713)	London (n = 2910)	Non-London (n = 6803)
Available case analysis			
28 mortality (%)			
Pre-peak	1,044/2,401 (43.5 %)	402/958 (42.0 %)	642/1,443 (44.5 %)
Peak	1,967/4,794 (41.0 %)	613/1,392 (44.0 %)	1,354/3,402 (39.8 %)
Post-peak	790/2,295 (34.4 %)	147/473 (31.1 %)	643/1,822 (35.3 %)
Multiply imputed analysis			
28 mortality (95% CI)			
Pre-peak	43.5% (41.6%, 45.5%)	42.0% (38.9%, 45.2%)	44.5% (42.0%, 47.1%)
Peak	40.9% (39.5%, 42.3%)	43.8% (41.2%, 46.4%)	39.7% (38.1%, 41.4%)
Post-peak	34.3% (32.3%, 36.2%)	31.2% (27.1%, 35.3%)	35.1% (32.9%, 37.3%)
Unadjusted OR (95% CI) [a]			
Peak vs pre-peak	0.90 (0.81, 0.99)	1.07 (0.91, 1.27)	0.82 (0.72, 0.93)
Post-peak vs pre-peak	0.68 (0.60, 0.76)	0.62 (0.50, 0.79)	0.67 (0.58, 0.78)
Adjusted OR (95% CI) [b]			
Peak vs pre-peak	0.97 (0.86, 1.08)	1.11 (0.91, 1.35)	0.90 (0.78, 1.05)
Post-peak vs pre-peak	0.70 (0.61, 0.81)	0.54 (0.41, 0.71)	0.73 (0.61, 0.87)
Adjusted risk difference (95% CI) [c]			
Peak vs pre-peak	-0.6% (-3.5%, 2.4%)	3.2% (-1.8%, 8.2%)	-2.4% (-6.0%, 1.3%)
Post-peak vs pre-peak	-8.8% (-12.3%, -5.2%)	-14.8% (-21.2%, -8.4%)	-7.8% (-12.1%, -3.4%)

OR: Odds ratio. Periods are based on the date of first admission to ICU (pre-peak = before 29 March; peak = 29 March to 15 April; post-peak = 16 April to 21 May (patients admitted after 21 May were censored to minimise potential influence of data missing not at random). [a] Estimated using univariable logistic regression; [b] Results were adjusted for: age, sex, ethnicity, quintile of deprivation, body mass index, any dependency prior to hospital admission, immunocompromise, sedated for entire of first 24h, highest temperature, lowest systolic blood pressure, highest heart rate, highest respiratory rate, PaO_2/FIO_2, highest blood lactate concentration, highest serum creatinine, highest serum urea, lowest haemoglobin concentration, lowest platelet count (see eTable 1, Appendix, for values of all coefficients). [c] Derived from differences in the average marginal predicted risk of 28-day mortality for a patient with mean values for all covariates, compared to an equivalent patient admitted during the pre-peak period.

DISCUSSION

We report trends in critical care admissions, patient characteristics, and outcomes, covering the whole of England, Wales and Northern Ireland. Our analysis indicated that regional epidemic peaks in ICU admissions occurred simultaneously, with the highest epidemic peak

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in London. Patient characteristics, such as the proportions of older patients, male patients, obese patients and patients from deprived areas, and illness severity, differed during the peak period when compared with the pre- and post-peak periods. There was a substantial reduction in the proportion of patients receiving invasive mechanical ventilation as the epidemic progressed. An even greater reduction was seen in the proportion of patients invasively ventilated during the first 24 hours, indicating later commencement of invasive ventilation over time. Mortality at 28 days improved over time and ICU length of stay appeared to be reducing towards the end of the wave. After adjustment for patient characteristics, 28-day mortality was significantly lower in the post-peak period compared with the pre-peak period.

In our study, London had the highest epidemic peak. It is well recognized that highest peaks occur in cities with major national and international transport hubs. Such cities generally have higher population densities, greater levels of deprivation, many hospital networks[15] with healthcare workers and greater proportion of population classed as *essential* workers[16]. Cities such as London will also have seen more numbers of people travelling into them, out of them and within them. All of which have been reported as factors associated with COVID-19 illnes.[17-19]

The United Kingdom has a substantially lower ICU bed capacity, per capita, than many other European countries or North America.[20-22] Despite the increase in ICU bed capacity in response to the anticipation of COVID-19, our data highlight that patient case mix and perhaps clinical management (such as invasive ventilation and renal replacement therapy) changed during the peak of the wave. Furthermore, it appears now that the decreasing

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trend in use of invasive ventilation was due to changing clinical management rather than patient characteristics or equipment availability.[23-25]

Logistic regression modelling demonstrated that the reduction in mortality was not explained by changing case mix. There is the potential that earlier detection, earlier intervention[26] and learning have contributed to improved outcomes over time. Large numbers of informal information-sharing networks, both within the UK and internationally, contributed to rapid learning during the course of the epidemic. The care of critically ill patients, particularly technical aspects of this care such as mechanical ventilation, has been shown to be subject to volume effects.[27] When restricted to London, where the epidemic peak was greatest, admission during the peak period was associated with a non-significant increase in 28-day mortality compared with the pre-peak period. This is consistent with a potential effect of increased strain on patient outcomes.[28]

This study benefited from a rapid response to the emerging epidemic through the existence of the CMP: a platform able to adapt rapidly; a well-defined and unchanged dataset; and a network of trained data collectors across all ICUs in England and Wales who submitted high-quality clinical data, daily. This response was informed by lessons learned during the H1N1 pandemic.[29,30] Using the CMP ensured high coverage, reducing potential selection bias.

The main risk to validity of the trends described in this study is the observed trends in data completeness over time. This risk was mitigated by censoring more recent records and multiple imputation for the regression analysis, but the residual implications are unclear. Even though we collected the data prospectively through well-established mechanisms, we may not have captured some critically ill patients, especially if those patients were treated outside of the ICU.

 doi:10.20944/preprints202008.0267.v1

In conclusion, this study highlights changes in patient characteristics, clinical management and outcomes over time during the UK epidemic that warrant further study. After adjusting for patient characteristics, there were substantial improvements in mortality over the course of the epidemic.

ACKNOWLEDGEMENTS

The authors thank all of the ICU data clerks who submitted accelerated data to the CMP and the CMP Data Coordinators who increased capacity to process records rapidly.

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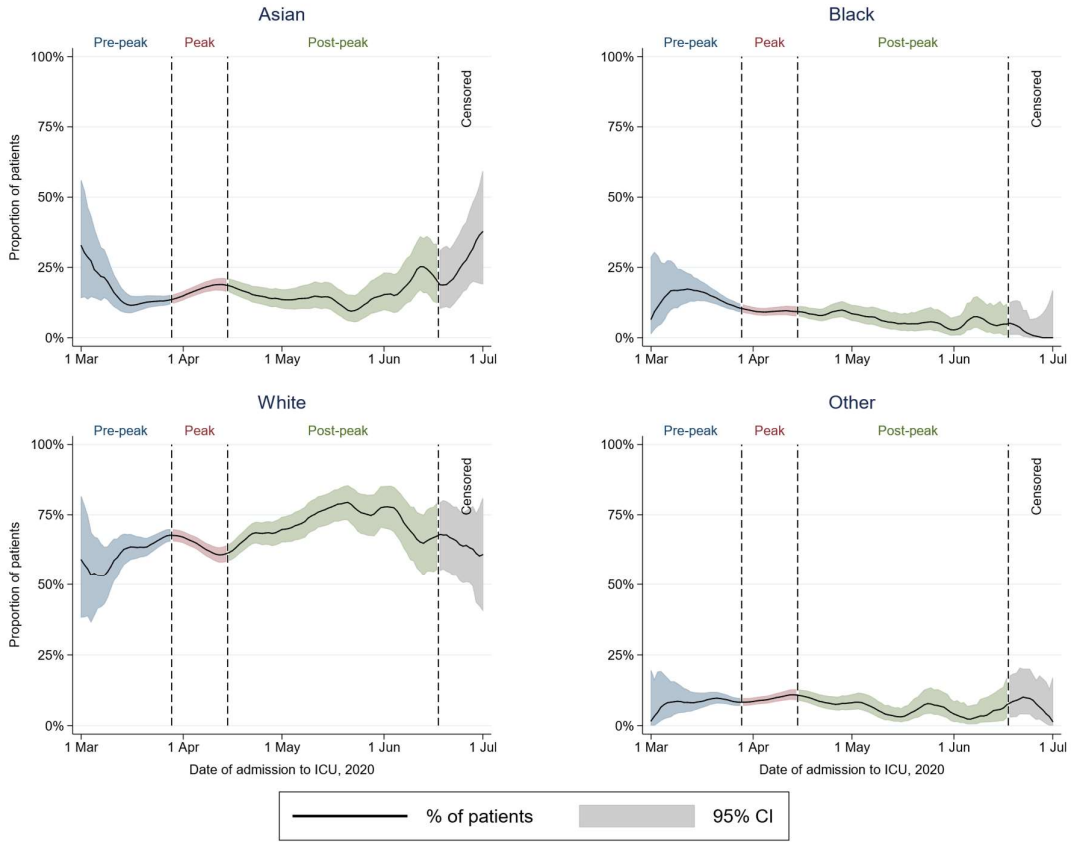
APPENDIX: SUPPLEMENTARY FIGURE AND TABLE



eFigure 1Trends in ethnic group

Lines are moving averages linearly weighted +/- 7 days. Durations calculated by survival at 28 days. See text for definitions.

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eTable 1 Multivariable logistic regression models for 28-day mortality, overall and by London/non-London

	Overall (n = 9713)	London (n = 2910)	Non-London (n = 6803)
Period (vs pre-peak)			
Peak	-0.035 (-0.151, 0.081)	0.102 (-0.094, 0.297)	-0.102 (-0.250, 0.045)
Post-peak	-0.353 (-0.496, -0.210)	-0.612 (-0.885, -0.339)	-0.317 (-0.492, -0.143)
Age (years) – RCS (42,60,75)			
Spline base variable 1	0.035 (0.030, 0.048)	0.035 (0.019, 0.052)	0.042 (0.030, 0.054)
Spline base variable 2	0.030 (0.020, 0.041)	0.039 (0.020, 0.058)	0.027 (0.014, 0.039)
Male sex (vs female)	0.048 (-0.073, 0.164)	0.169 (-0.055, 0.394)	0.006 (-0.136, 0.149)
Ethnicity (vs white)			
Asian	0.424 (0.279, 0.569)	0.532 (0.291, 0.773)	0.369 (0.178, 0.560)
Black	0.049 (-0.123, 0.223)	0.138 (-0.118, 0.395)	0.162 (-0.114, 0.440)
Mixed/other	-0.065 (-0.243, 0.122)	-0.028 (-0.304, 0.247)	0.018 (-0.245, 0.282)
Quintile of deprivation (vs 1, least deprived)			
2	-0.001 (-0.178, 0.176)	0.006 (-0.365, 0.377)	-0.011 (-0.212, 0.190)
3	0.001 (-0.167,0.169)	-0.241 (-0.595, 0.113)	0.097 (-0.096, 0.291)
4	0.117 (-0.043, 0.270)	-0.041 (-0.367, 0.286)	0.167 (-0.023, 0.359)
5 (most deprived)	0.231 (0.071, 0.391)	-0.022 (-0.386, 0.341)	0.296 (0.115, 0.478)
Body mass index (kg m^{-2})	0.010 (0.002,0.016)	0.011 (-0.001, 0.024)	0.008 (-0.001, 0.017)
Any dependency prior to hospital admission	0.543 (0.377, 0.709)	0.514 (0.181, 0.847)	0.555 (0.360, 0.749)
Immunocompromise	0.559 (0.330, 0.789)	0.774 (0.362, 1.181)	0.494 (0.205, 0.782)
Sedated for entire of first 24h	0.306 (0.182, 0.430)	0.342 (0.123, 0.561)	0.291 (0.137, 0.445)
Highest temperature (°C)	0.004 (-0.042, 0.050)	-0.039 (-0.126, 0.047)	0.021 (-0.034, 0.077)
Lowest systolic blood pressure (mmHg)– RCS (78,95,121)			
Spline base variable 1	-0.013 (-0.019, -0.006)	-0.012 (-0.023, -0.001)	-0.014 (-0.022, -0.006)
Spline base variable 2	0.011 (0.002, 0.019)	0.013 (-0.002, 0.028)	0.011 (-0.000, 0.021)
Highest heart rate (min^{-1})	0.009 (0.006, 0.011)	0.009 (0.004, 0.013)	0.009 (0.006, 0.012)
Highest respiratory rate (min^{-1})	0.010 (0.004, 0.016)	0.011 (0.001, 0.022)	0.010 (0.003, 0.017)
PaO2/FiO2 (kPa)	-0.047 (-0.052, -0.040)	-0.044 (-0.054, -0.033)	-0.049 (-0.056, -0.041)
Highest blood lactate concentration (mmol l^{-1}) – RCS (0.9,1.4,2.5)			
Spline base variable 1	0.665 (0.465, 0.865)	0.267 (-0.126,0.661)	0.859 (0.614, 1.105)
Spline base variable 2	-0.615 (-0.844, -0.386)	-0.181 (-0.623,0.260)	-0.825 (-1.109, -0.542)
Highest serum creatinine (µmol l^{-1}) – RCS (46,72,101,327)			
Spline base variable 1	-0.006 (- .013, 0.001)	-0.015 (-0.029, -0.001)	-0.003 (-0.011, 0.005)
Spline base variable 2	0.237 (0.092, 0.382)	0.475 (0.188,0.763)	0.136 (-0.043, 0.315)
Spline base variable 3	-0.472 (-0.754, -0.191)	-0.940 (-1.490, -0.386)	-0.271 (-0.618, 0.075)
Highest serum urea (mmol l^{-1}) – RCS (3.5,7.0,16.6)			
Spline base variable 1	0.076 (0.037, 0.115)	0.038 (-0.034,0.111)	0.098 (0.052, 0.143)
Spline base variable 2	-0.099 (-0.152, -0.046)	-0.072 (-0.173,0.028)	-0.121 (-0.183, -0.060)
Lowest haemoglobin concentration (g l^{-1})	-0.020 (-0.048, 0.008)	0.046 (-0.004,0.097)	-0.054 (-0.090, -0.018)
Lowest platelet count ($\times 10^9$ l^{-1}) – RCS (134,232,375)			
Spline base variable 1	-0.004 (-0.005, -0.003)	-0.004 (-0.006, -0.002)	-0.005 (-0.006, -0.003)
Spline base variable 2	0.003 (0.002, 0.005)	0.003 (0.001, 0.006)	0.004 (0.002, 0.005)
Intercept	-3.162 (-5.204, -1.119)	-1.186 (-4.985, 2.612)	-3.809 (-6.292, -1.324)

All estimates are conditional log odds ratios estimated using multivariable logistic regression with multiple imputation for missing data, and separate models for patients admitted anywhere (Overall), in London, or in any region other than London (Non-London). RCS (k_1,…,k_j) indicates restricted cubic spline with knots at positions k_1 to k_j, corresponding to the following base variables for prognostic factor x:

Spline base variable 1 = x

Spline base variable i+1 = $[\max((x - k_i)^3, 0) - (k_j - k_i) \times \max((x - k_{j-1})^3, 0)/(k_j - k_{j-1}) + (k_{j-1} - k_i) \times \max((x - k_j)^3, 0)/(k_j - k_{j-1})]/(k_j - k_1)^2$; i =1, … , j−2