Changes in hospital mortality in the first wave of COVID-19 in the UK using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study.

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Introduction

There is growing evidence of a decline in COVID-19 mortality rates, both in hospital and in the community.[2,4,5] There could be several potential reasons for the fall, particularly in hospital mortality. One explanation is that the case-mix of patients presenting to hospital has changed towards a younger and less comorbid demographic, who were at lower risk of dying. National UK lockdown and effective shielding measures of vulnerable at risk populations may have reduced transmission of the virus. Advice regarding seeking medical help may have resulted in earlier presentation to hospital. Familiarity with the virus may have led to better management of patients with the virus through improved ward and ICU care.[6,7] Corticosteroids have been shown to reduce mortality in patients with severe COVID-19. [8,9]

We aimed to investigate this phenomenon using the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK).[10] This protocol was activated on 17 January 2020 to recruit COVID-19 patients admitted to hospitals in England, Scotland and Wales participating in the Coronavirus Clinical Information Network (CO-CIN).[11] ISARIC has been prepared for outbreaks like COVID-19 for the past 8 years with the intent that it provide data and samples for near real-time analysis.[10] During the COVID-19 outbreak, analysis of CCP-UK cohort in the first wave allowed development of the pragmatic ISARIC 4C Mortality Score for hospitalised COVID-19 patients in readiness to aid management decisions in wave 2.[12]

We aimed to describe change over time of hospital mortality within 28 days of admission in hospitalised COVID-19 patients across the UK and explore potential drivers for these changes, by assessing the patient characteristics, the severity of illness and the treatment they received during their hospital admission.

Methods

Study design and setting

We undertook a prospective cohort study using participants in the ISARIC WHO CCP-UK cohort who were admitted in the first wave - weeks ending 15 March to 2 August 2020. National strategy changed from containment to admission based on clinical need on 12th March.[13] There were 309 participating hospitals across England, Wales and Scotland, including acute with general care hospitals, long-term community care hospitals and residential mental health hospitals.

Participants and study size

Recruited patients were admitted to hospital with high likelihood or confirmed COVID-19 from assumed community acquired infection. Site training emphasised that only patients who tested

positive (using reverse transcriptase polymerase chain reaction) for COVID-19 were eligible for enrolment. All patients were admitted at least six weeks prior to data extraction to allow for sufficient 28 day follow up.

We restricted participants to the adult population (≥18yrs) from acute with general care hospitals. Community hospitals providing long-term treatment and residential mental health hospitals were excluded since the patient populations were very different and were therefore not comparable.

Exclusions: We excluded patients whose outcome was dated before they were admitted, as well as patients where sex was not available and patients aged over 110 years. We excluded 'nosocomial' infection as patients with onset of COVID-19 symptoms more than 5 days after they were admitted to hospital for a separate condition.[14] For the main manuscript, we excluded patients without an outcome date.

Variables

Data were extracted from routine healthcare records and recorded onto case report forms on a REDCap database. Under the Control of Patient Information (COPI) notice for urgent public health research, collection of this routine demographic and clinical data from medical records did not require consent in England and Wales. [15] In Scotland, a waiver for consent was obtained from the Public Benefit and Privacy Panel. [16]

Exposures

The main exposure of interest was the week of admission to hospital, defined using the ISO week date. This was also categorised into three equal time-periods: 11 to 17 (weeks ending 15 March to 26 April), 18 to 24 (weeks ending 3 May to 14 June) and 25 to 31 (weeks ending 21 June to 2 August).

Variables

Variables were split into four main groups: patient characteristics, severity of illness and level of respiratory support, and treatments.

Patient characteristics: patient age (<50yrs, 50-69yrs, 70-79yrs, 80yrs+), sex (Female, Male), self-reported ethnicity (South Asian, East Asian, Black, Other Ethnic Minority and White) [17] and health worker. Comorbidities were asthma, diabetes, chronic cardiac disease (excluding hypertension), chronic haematologic disease, chronic kidney disease, chronic neurological disorder, chronic pulmonary disease (excluding asthma), dementia, HIV/AIDS, malignancy, malnutrition, mild to severe liver disease, clinician-assigned obesity and rheumatologic disorder. These were used to construct the number of comorbidities (0, 1, 2+).

Severity of illness: we used the physiological components of the ISARIC 4C Score [12] in the first 24 hours of hospital admission: respiratory rate (breaths/min), peripheral oxygen saturation on room air (%), Glasgow coma scale, urea (mmol/L) and C reactive protein (mg/dL). To capture the patterns in accessing hospital treatment we calculated the number of days between symptom onset to admission (onset ≥21 days were assumed to be errors).

Level of respiratory support (online supplement for definitions): Patients were categorised as managed on the ward or in critical care. Maximum level of respiratory support was categorised into: no respiratory support, oxygen (via face mask or nasal cannulae, high flow nasal oxygen (HFNO)), non-invasive ventilation (NIV), and invasive mechanical ventilation (IMV). We assumed that all patients in ICU and all patients receiving IMV also received oxygen. Within critical care only, we included whether the patient was proned or received extra corporeal membrane oxygenation (ECMO).

For COVID-19 specific treatments, we recorded only whether patients received any corticosteroids (dexamethasone, hydrocortisone, methylprednisolone and prednisolone), as these were the only treatment so far with proven mortality benefit for COVID-19 in randomised controlled trials. [8,18]

Outcomes

The primary outcome was weekly in-hospital mortality, calculated as the proportion of patients admitted in a given week who died or were palliative discharges within 28 days after admission, out of the total number of patients admitted in the observed week. We used the threshold of 28 days to align with the definition of a COVID-19 death defined by Public Health England. [19]

Secondary outcomes were changes in patient demographics and illness severity for patients managed on the ward and in critical care. Within critical care, we looked separately at oxygen only, NIV, and IMV. Within ward care, we looked at those receiving no respiratory support, oxygen only and NIV.

Missing data and bias

Missing data in comorbidity variables, healthcare worker, respiratory support (receiving oxygen, invasive and non-invasive ventilation), proning and ECMO were classified as 'No'. We performed complete case analysis for other grouped variables.

Statistical methods

The count and percentage of patients within each of the exposure variables were calculated across the three equal width time-periods (weeks 11 to 17, 18 to 24 and 25 to 31). For each variable of interest, the proportion out of the total weekly admissions and the in-hospital fatality rates within 28 days were visualised across the week of admission for each category. We stratified by patient demographics (age, sex, comorbidity count, ethnicity), illness severity (resp rate, SpO_2, GCS, Urea, CRP), and by maximum level of respiratory support (no support, oxygen on ward, NIV on ward, oxygen on critical care, NIV on critical care, IMV).

All analyses were conducted using R (version 3.6.3) using the packages tidyverse, knitr, kableExtra and gridExtra.

Results

All patients

The final cohort contained 63,972 patients (Figure 1), from 247 acute hospitals in England, Scotland and Wales, approximately 48% of all hospital admissions.[2] Admissions peaked in late March and in early April for all age groups and both sexes, and steadily decreased until the end of the study (Figure 2). 29% (N=15,864) of patients managed on the ward died within 28 days of admission and 36% (N=3,317) within critical care (Figure 1).

Patient demographics and severity of illness

The majority of patients admitted throughout the first wave were ≥50yrs (N=55,562 (87%)) (Table 1, Figure 4). There was an increase in the proportion of young people admitted over time (from 13.2% in the first time period to 17.5% in the last time period). There were initially more men admitted than women (60%:40%), but these proportions evened out from mid-April. This was a comorbid population, with over 50% of patients having two or more comorbidities and this increased over time. Patients were mostly 'White' with an increasing proportion of 'South Asian' and a decreasing proportion of 'Black' ethnic groups (Table 2, Figure 4).

There was a clear peak of illness severity in patients admitted around March 30th to April 12th, when people at presentation to hospital had faster respiratory rates, lower peripheral oxygen saturations, higher rates of reduced conscious level and acute kidney injury and inflammation, compared with patients admitted subsequently (Figure 5).

Respiratory support and critical care admission

At the peak of admissions, over 80% of patients admitted to hospital received supplementary oxygen (Figure E1). This reduced consistently over subsequent weeks to around 50% for patients admitted in July onwards (Figure E1).

Most patients were not admitted to critical care, with the proportion of patients being admitted to critical care peaking at the start of the study (N=7,732 (16.3%)) (Table 1). Patients admitted to critical care were younger than patients managed on the ward, and were more likely to be male (Critical care male N = 6,433 (68.9%) vs ward male N = 29,690 (54.3%)) (Tables E2 and E3). Although there were more patients without comorbidity in critical care compared to the ward, patients with two or more comorbidities still accounted for a significant proportion of patients (Critical care N= 3,733 (40%) vs ward comorbid N= 32,531 (60%)) (Tables E2 and E3). The pattern of increasing proportions of younger and more comorbid patients in critical care mirrored that seen on the ward (Tables E2 and E3).

Respiratory support requirements reduced over time for both critical care and ward patients (Figure 6). Within critical care, 64% of those admitted to hospital at the beginning of the pandemic received IMV, which decreased to 29% in those admitted in the last time period (Table E2). As the requirement for IMV fell, the proportion of those requiring NIV substantially increased from 23% to 47% (Table E2). Proning and ECMO were more frequent in patients admitted earlier in the study than later (Figures E2 and E3, Table E2). In comparison, on the ward, NIV proportions remained very low decreasing from 9% to 5% (Table E3). By the end of the first wave, 42.7% of all patients admitted received no respiratory support (ward patients 48.5%) (Table 1 & E3, Figure 6).

Steroid use

The proportion of patients who received steroids increased from 12% (22% in critical care) at the start of the pandemic to 31% (65% in critical care) in June and July (Tables 1 and E2, Figure E4).

Hospital mortality

In-hospital mortality in patients admitted in March and early April fell from 30-35% to 10-15% for patients admitted late July and August. (Figure 3). In-hospital mortality was higher with increasing age, increasing comorbidity count, and male sex, and fell for all demographic categories, most notably in the older and comorbid populations (Figure 3). Markers of increased severity of illness at presentation to hospital were associated with increased in-hospital mortality. Mortality fell for all markers of severity of illness over the course of the first wave (Figure 3). Mortality also fell when stratified by maximum level of respiratory support, except for those patients who received IMV in critical care, or NIV on the ward.

Discussion

In-hospital mortality within 28 days after admission substantially decreased throughout the course of the first wave. At the peak of admissions in late March and early April, illness severity at hospital presentation was greatest, and patients presented later from their onset of symptoms. Overall, there was a reduction in the requirement for respiratory support; within this, use of invasive ventilation reduced over time, and non-invasive ventilation increased. By late June/July, nearly half

of all patients admitted required no supplementary oxygen. The reduction in hospital mortality was seen in all demographics, and was not entirely accounted for by the fall in illness severity, changes in case-mix, or use of corticosteroid therapy in patients receiving supplementary oxygen.

ISARIC has recruited patients across the UK, now accounting for approximately half of patients admitted to hospital in the UK with COVID-19. Data was collected from the front door to discharge for patients managed both on the ward and within critical care enabling us to review admissions and mortality for the whole hospital. We did not record treatment escalation plans, but we were able to examine changing case-mixes in the ward and critical care. Due to the nature of the pandemic, there was more missing data than would normally be expected in a prospective cohort study. We were unable to comment on community factors leading up to admission, and indeed those who were not admitted to hospital.

We have demonstrated a reduction in hospital mortality that cannot be fully explained by baseline demographics or measured presenting severity of illness markers. This is consistent with experiences in New York hospitals[20] where mortality also significantly and progressively fell over the course of the study period. Critical care mortality in the UK has also reduced.[21,22] The majority of patients admitted to hospital throughout the first wave were elderly, comorbid and of White ethnicity, and these groups had the highest mortality. Case mix changed over the pandemic, with a rise in the proportion of younger and female patients in the second half who, both in our study and others, have lower mortality rates.[23,24] However this alone could not explain the falls in mortality which were seen in all ages, ethnic groups, and in both sexes. Shielding of vulnerable groups was formally introduced on 23 March[25] and it is possible that earlier patients were more vulnerable but not identifiable in our dataset.

Severity of illness at presentation to hospital fell during the first wave and an increasing proportion of patients required no respiratory support in hospital at all. SARS-CoV-2 infection is transmitted predominately by respiratory droplets, and social distancing as part of the UK lockdown (March 23 2020)[26] along with widespread adoption of masks may have reduced viral load (infectious dose) at point of transmission[27], in turn reducing severity of illness in infected patients.[28] Patients presented earlier in their disease course in later months and length of stay for non-survivors in critical care increased consistent with patients presenting earlier in their illness, and less in-extremis. Our data does not include community factors, however it may be that there were behavioural and structural changes, enabling patients to attend hospitals more easily.

Hospital admissions in the UK peaked in early April, with Intensive Care Unit (ICU) caseload peaking shortly after.[2,3] At the peak there were approximately 3,000 patients admitted to hospital each day in the UK, which gradually fell to a plateau of approximately 100 patients per day by the end of July.[2] The UK has one of the smallest health and care workforces in the world, spending less than the G7 group of advanced economies,[29] and has relatively few hospital and critical care beds compared with other European and North American countries.[29,30] Coming into the pandemic, the UK had high levels of bed occupancy and very little spare capacity.[29] However, during the rapid response to COVID-19 there was a substantial increase in capacity, and national reported occupancy for critical care never exceeded 60%, although this varied significantly at local levels.[20] It is possible that fears regarding extreme surges/scarce resources may have resulted in rationing of critical care interventions during this period. The rapid expansion of critical care beds required redeployment of non-critical care staff, and in some UK regions, increased ratios of nursing staff to patients which may have impacted on early patient outcomes.[31]

During the peak of admissions, and during peak illness severity, a higher proportion of patients were admitted to critical care. Patients in critical care at this time were considerably younger than ward patients, even so, mortality was much higher than for other severe acute respiratory infections such as viral pneumonia.[18] During the peak admission period, the proportion of patients aged >80 years and those with multimorbidity admitted to critical care was lower than subsequently, however, this reflected the demographic pattern also seen in patients admitted to the ward at this time. Mortality was extremely high in those patients aged 80+ years who received invasive ventilation, and the low admission rates potentially reflect judgements regarding benefits and harms of invasive treatment.

The proportion of patients receiving invasive ventilation reduced over time. This is the only group where significant reductions in mortality were not seen after stratifying for patient demographics, severity of illness, and we propose two potential explanations for this paradox. Firstly, there was a change in case mix which was not adequately captured by the variables recorded: we found that a higher proportion of more elderly and comorbid patients were being ventilated later in the pandemic, potentially when there was more critical care capacity. It may be that comorbidity and age were unable to reflect patient frailty. Secondly, practice within critical care changed, with increasing use of NIV over time, and only those presenting in extremis or failing a trial of NIV were ventilated. This may be partly due to the changing case mix, but also due to increasing clinician familiarity with the use of non-invasive as a treatment for severe acute respiratory infections, and an improving ability to identify which patients might benefit, compared with those who needed conventional invasive ventilation. Potentially, early patients who received IMV would later have received NIV and have survived regardless of the mode of ventilation. The later patients receiving IMV were therefore a more severely ill population who had failed to respond to treatments. Ongoing trials comparing the use of NIV and IMV in critically ill patients with COVID-19 will be able to overcome this selection bias and confounding by indication to answer whether patient selection or NIV itself is improving outcomes in critically ill patients with COVID-19.[32] Patients receiving NIV on the ward had higher mortality rates than patients on oxygen and NIV managed in critical care. Along with the higher rates of comorbidity, in particular dementia and chronic pulmonary and cardiac disease, this may reflect a potential ceiling of treatment for patients receiving NIV on the ward.

Management of COVID-19 has also developed in the past eight months. Corticosteroids[8,9] and antivirals have shown benefit in subgroups of the hospital population, and trials of other treatments including anticoagulation, anti-virals, convalescent plasma and non-invasive ventilation are ongoing.[8,9] Until 16 June 2020 steroids were used predominantly in trial settings, and it may be that the reduction in mortality seen in the trials[8,18] was not reflected here because patients were allocated them, rather than for specific respiratory support. However no effect from steroids was seen in the critical care population, where all patients were on supplementary oxygen. This highlights the critical importance of suitably-powered blinded randomised controlled trials for drug evaluation even in outbreak situations.

Conclusion

In-hospital mortality rates for patients with COVID-19 fell in the UK over the course of the first wave. This fall persisted after stratifying for illness severity, changes in patient case-mix and treatment received. Patients were most severely unwell at hospital presentation at the start of the pandemic and presented later in their disease course. At the peak of admissions, NHS trusts were stretched beyond capacity, and the reduction in caseload enabled safer staffing. Community and hospital practice changed, in particular the use of NIV increased dramatically, and many patients have been

included in drug and other treatment trials, which may help to explain the fall in mortality and inform future waves.

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Tables

Table 1: Baseline characteristics of patients admitted to hospital with SARS-CoV-2 infection, stratified by time (N=63,972).

Type	Characteristic	1 - Weeks 11 to 17 9 Mar to 26 Apr 2020	2 - Weeks 18 to 24 27 Apr to 14 Jun 2020	3 - Weeks 25 to 31 15 Jun to 2 Aug 2020
	Total	47453 (74.2%)	13744 (21.5%)	2775 (4.3%)
Patient characteristics	**Country**			
	England	43326 (91.3%)	12579 (91.5%)	2589 (93.3%)
	Scotland	2140 (4.5%)	534 (3.9%)	33 (1.2%)
	Wales	1987 (4.2%)	631 (4.6%)	153 (5.5%)
	Age (grouped)			
	<50	6261 (13.2%)	1663 (12.1%)	486 (17.5%)
	50-69	14284 (30.1%)	3261 (23.7%)	734 (26.5%)
	70-79	10675 (22.5%)	3015 (21.9%)	590 (21.3%)
	80+	16233 (34.2%)	5805 (42.2%)	965 (34.8%)
	Age (continuous)			
	Median (IQR)	73.2 (IQR=24.8)	76.9 (IQR=23.5)	73.5 (IQR=25.9)
	Mean (SD)	70.1 (SD=16.7)	72.6 (SD=17.3)	69 (SD=18.6)
	Sex			
	Female	19837 (41.8%)	6659 (48.5%)	1353 (48.8%)
	Male	27616 (58.2%)	7085 (51.5%)	1422 (51.2%)
	Ethnic group			
	White	33993 (71.6%)	10832 (78.8%)	1922 (69.3%)
	South Asian	2279 (4.8%)	530 (3.9%)	296 (10.7%)
	East Asian	398 (0.8%)	41 (0.3%)	12 (0.4%)
	Black	2015 (4.2%)	236 (1.7%)	41 (1.5%)
	Other Ethnic Minority	3340 (7%)	681 (5%)	229 (8.3%)
	Unknown	5428 (11.4%)	1424 (10.4%)	275 (9.9%)
	Number of comorbidities			
	0	10789 (22.7%)	2014 (14.7%)	507 (18.3%)
	1	11389 (24.0%)	2463 (17.9%)	546 (19.7%)
	2+	25275 (53.3%)	9267 (67.4%)	1722 (62.1%)
	Health worker	2419 (5.1%)	738 (5.4%)	77 (2.8%)
Severity of illness	**Asymptomatic**	2446 (5.2%)	2117 (15.4%)	785 (28.3%)
	Symptom onset (days)*			
	Median (IQR)	4.0 (IQR=7.0)	2.0 (IQR=7.0)	3.0 (IQR=7.0)
	Mean (SD)	5.0 (SD=5.2)	4.1 (SD=5.2)	4.1 (SD=4.9)
	Length of stay (days)			
	Median (IQR)	8.0 (IQR=11.0)	9 (IQR=13)	8 (IQR=12)
	Mean (SD)	11.0 (SD=12.6)	12.2 (SD=11.9)	10.6 (SD=9.7)
	ISARIC 4C Score			
	Low (0-3)	2056 (4.3%)	726 (5.3%)	196 (7.1%)
	Intermediate (4-8)	7469 (15.7%)	2020 (14.7%)	506 (18.2%)
	High (9-14)	16509 (34.8%)	5416 (39.4%)	1042 (37.5%)
	Very high (15+)	5055 (10.7%)	1321 (9.6%)	156 (5.6%)
	Unknown	16364 (34.5%)	4261 (31%)	875 (31.5%)
	Respiratory rate (breaths/min)			
	<20	13066 (27.5%)	5303 (38.6%)	1131 (40.8%)
	20-30	23791 (50.1%)	6232 (45.3%)	1197 (43.1%)
	≥30	8433 (17.8%)	1670 (12.2%)	305 (11%)
	Unknown	2163 (4.6%)	539 (3.9%)	142 (5.1%)
	Peripheral oxygen saturation on room air (%)			
	≥92	34345 (72.4%)	10970 (79.8%)	2259 (81.4%)
	<92	10667 (22.5%)	2224 (16.2%)	378 (13.6%)
	Unknown	2441 (5.1%)	550 (4%)	138 (5%)
	Glasgow coma score			
	15	35403 (74.6%)	10857 (79%)	2323 (83.7%)
	<15	6645 (14%)	1911 (13.9%)	250 (9%)
	Unknown	5405 (11.4%)	976 (7.1%)	202 (7.3%)
	Urea (mmol/L)			
	<7	17581 (37%)	5250 (38.2%)	1195 (43.1%)
	7-14	12785 (26.9%)	3858 (28.1%)	757 (27.3%)

	>14	6572 (13.8%)	1869 (13.6%)	286 (10.3%)
	Unknown	10515 (22.2%)	2767 (20.1%)	537 (19.4%)
	C-reactive protein (mg/dL)			
	<50	11714 (24.7%)	4775 (34.7%)	1037 (37.4%)
	50-99	9400 (19.8%)	2397 (17.4%)	442 (15.9%)
	≥100	17948 (37.8%)	3736 (27.2%)	684 (24.6%)
	Unknown	8391 (17.7%)	2836 (20.6%)	612 (22.1%)
Respiratory support and treatments	**Threshold of care**			
	ICU	7732 (16.3%)	1275 (9.3%)	333 (12%)
	Ward	39721 (83.7%)	12469 (90.7%)	2442 (88%)
	Respiratory support			
	None	9314 (19.6%)	4780 (34.8%)	1184 (42.7%)
	Oxygen only	28023 (59.1%)	7170 (52.2%)	1221 (44%)
	Non-invasive	5158 (10.9%)	1240 (9%)	272 (9.8%)
	Invasive	4958 (10.4%)	554 (4%)	98 (3.5%)
	Steroids			
	Yes	5650 (11.9%)	1841 (13.4%)	854 (30.8%)
	No	12858 (27.1%)	6507 (47.3%)	1712 (61.7%)
	Unknown	28945 (61%)	5396 (39.3%)	209 (7.5%)

W/E – Week ending
* Symptom onset summary statistics based on patients with symptoms up to 3 weeks before admission only

Figures

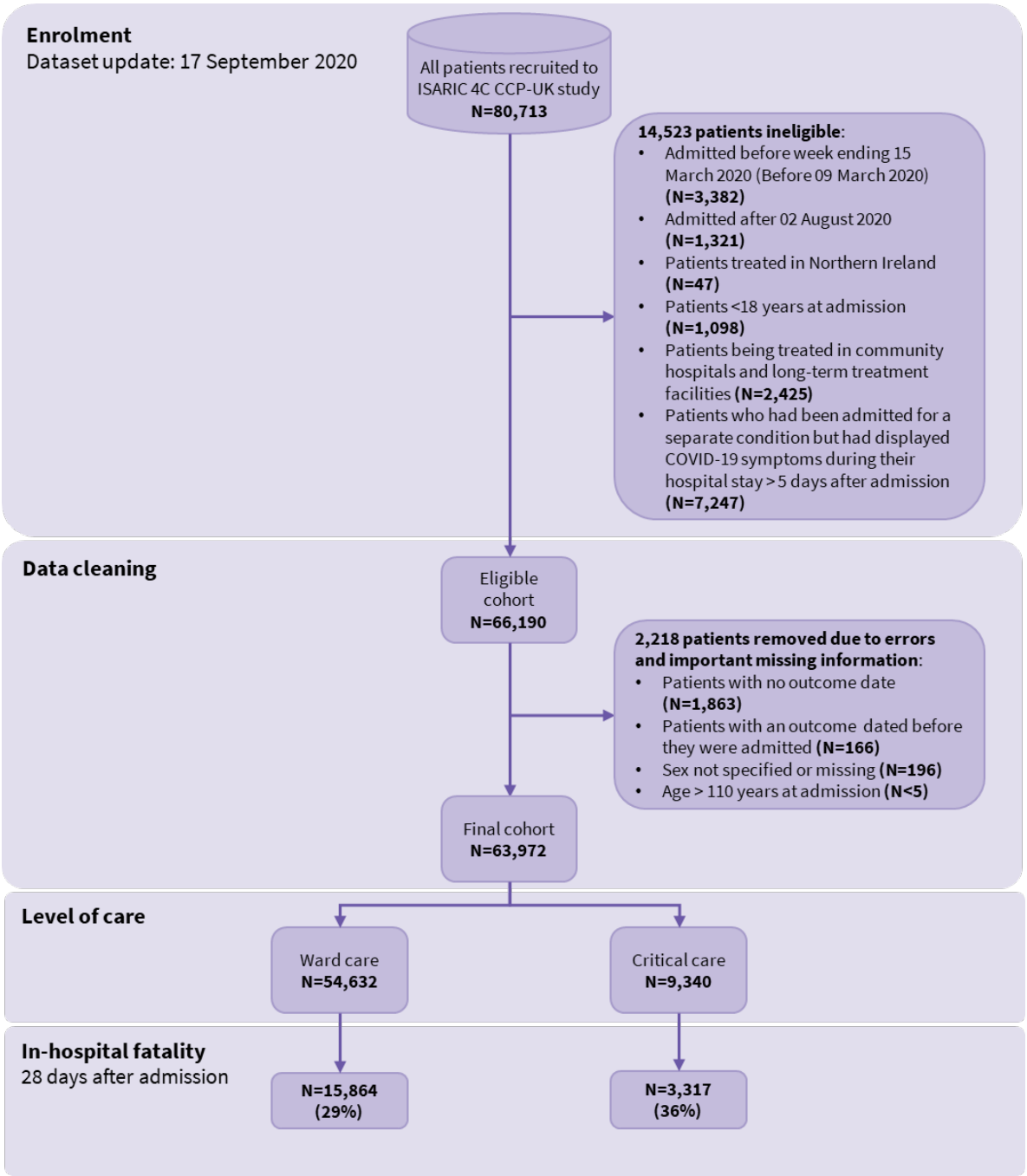

Figure 1: Consort diagram

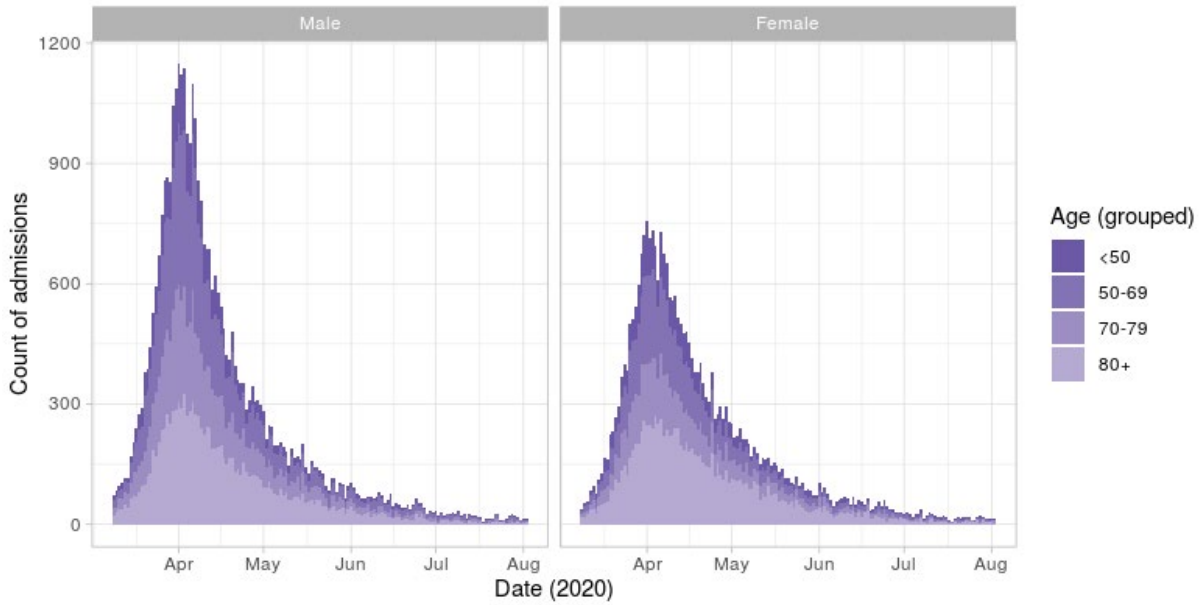

Figure 2: Daily admissions from 9 March to 2 August 2020, split by age and sex

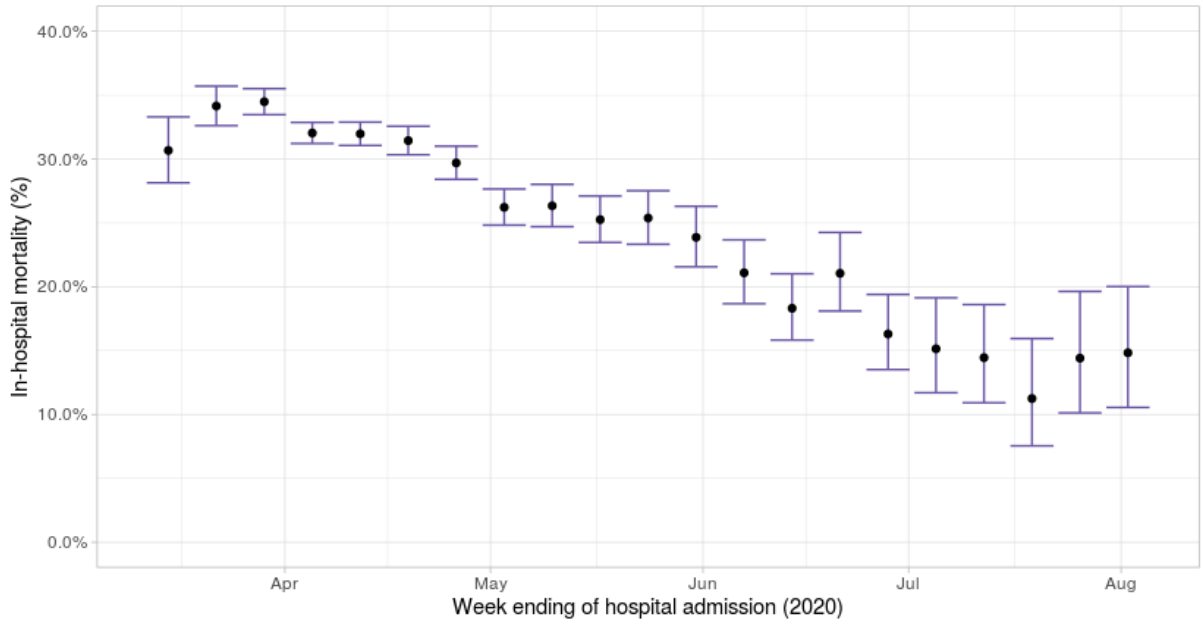

Figure 3: Unadjusted weekly in-hospital mortality and 95% confidence intervals for patients admitted with SARS-CoV-2 from 9 March 2020 to 2 August 2020. Divided into 3 equal time periods (Weeks 11 to 17, 18 to 24 and 25 to 31). Confidence intervals calculated via exact method.

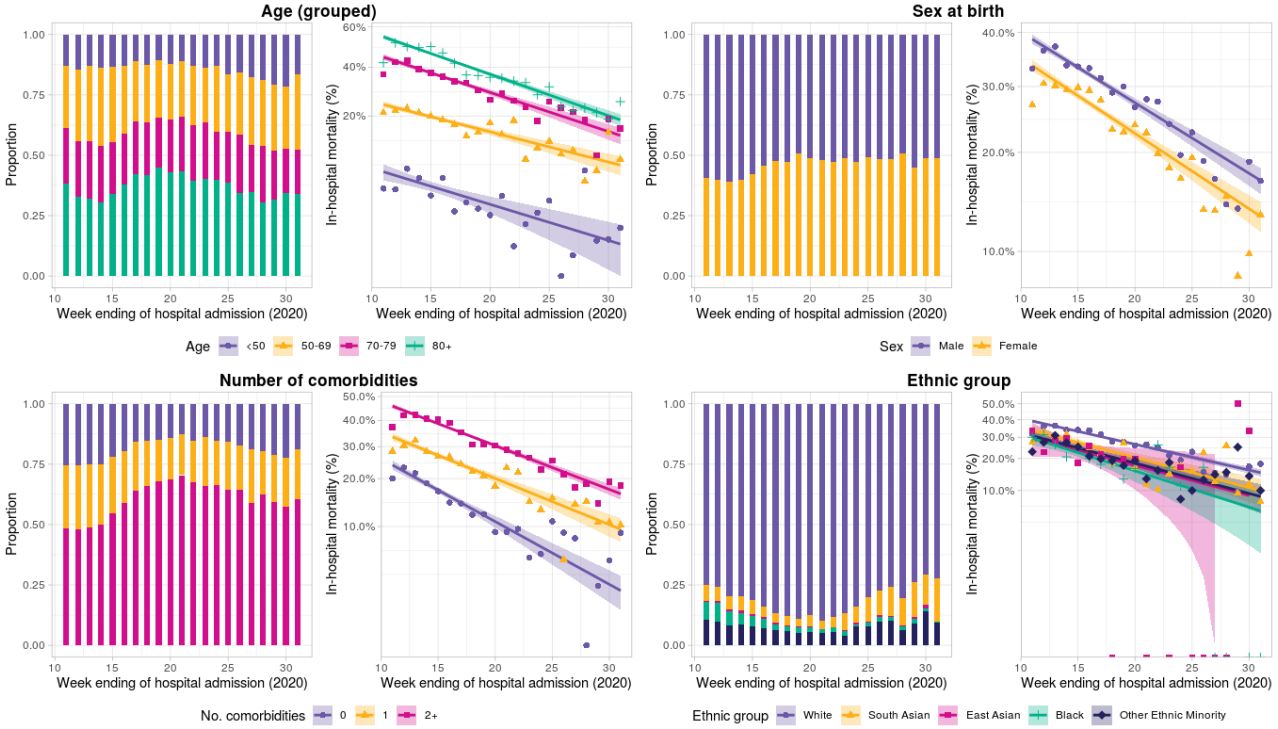

Figure 4: (Left) Patients admitted to hospital with SARS-CoV-2 by time stratified by patient characteristics (%). (Right) In-hospital mortality by time stratified by patient characteristics (%).

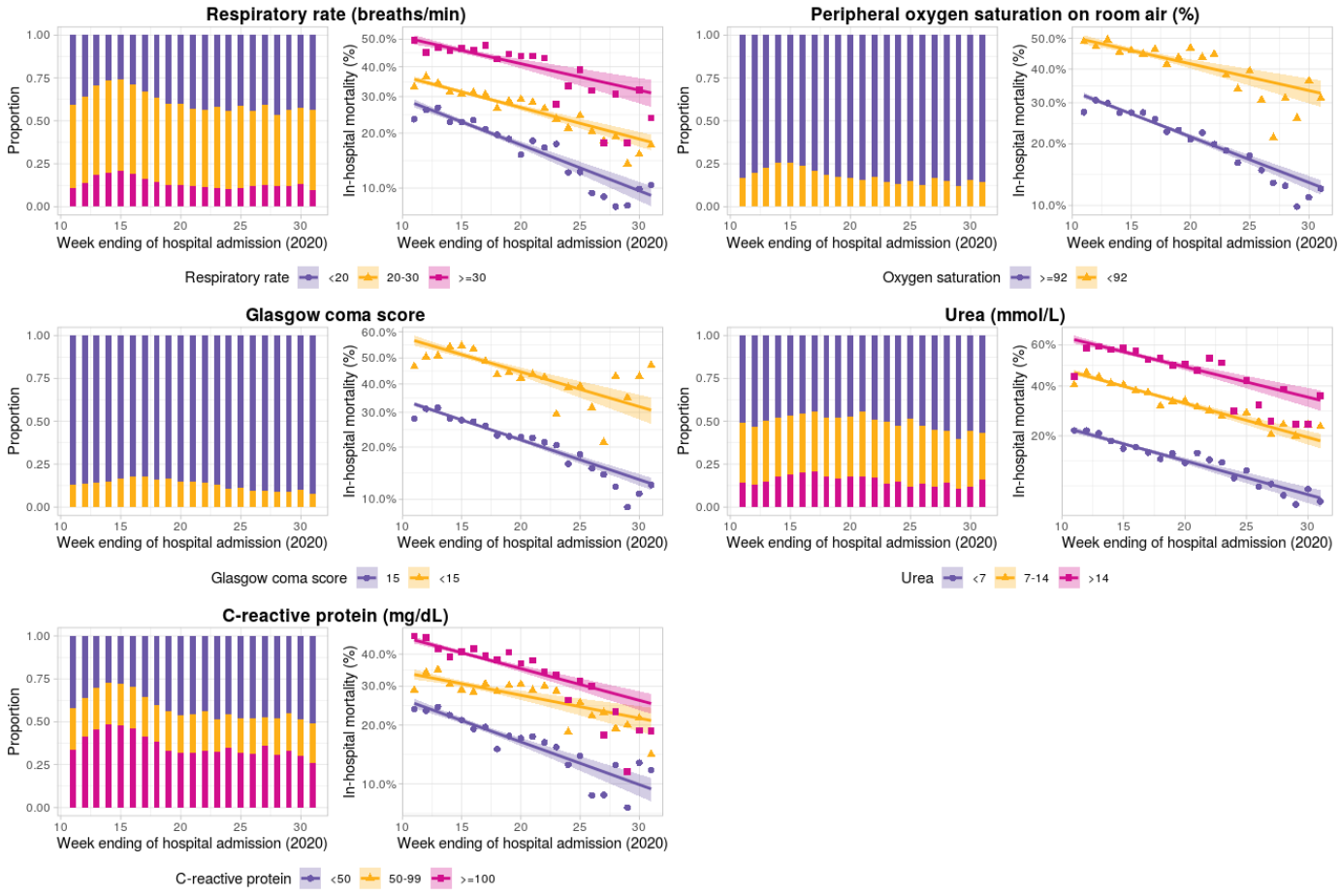

Figure 5: (Left) Proportion of markers of severity of illness at admission to hospital by week of admission. (Right) In-hospital mortality rate per category by week of admission. Unknown measurements are excluded from this figure.

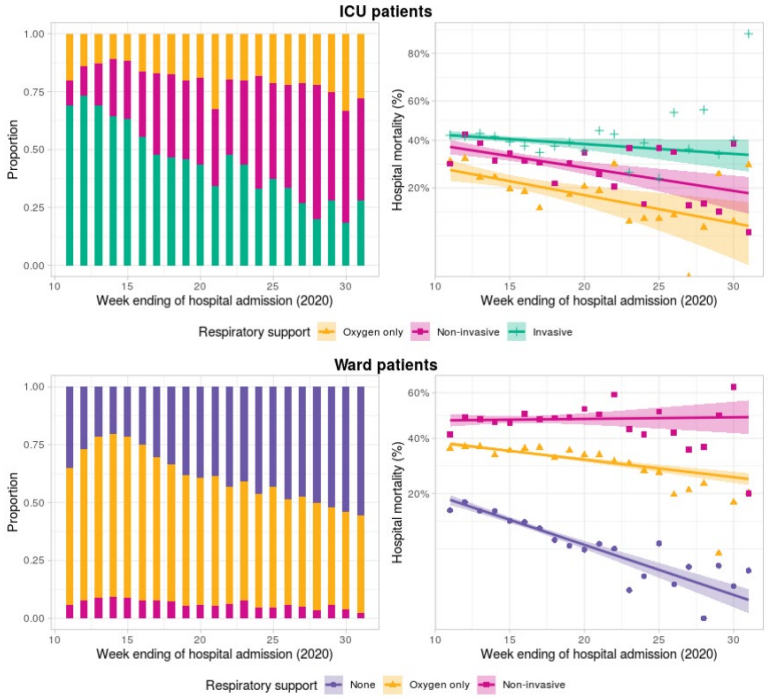

Figure 6: Respiratory support within ICU (top) and ward (bottom). (Left) Proportion of respiratory support treatments by week of admission. (Right) In-hospital mortality rate per category by week of admission.