Trends in Risk-Adjusted 28-Day Mortality Rates for Patients Hospitalized with COVID-19 in England

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Early reports showed high mortality from coronavirus disease 2019 (COVID-19). Mortality rates have recently been lower; however, patients are also now younger, with fewer comorbidities. We explored 28-day mortality for patients hospitalized for COVID-19 in England over a 5-month period, adjusting for a range of potentially mitigating variables, including sociodemographics and comorbidities. Among 102,610 hospitalizations, crude mortality dropped from 33.4% (95% CI, 32.9-34.0) in March 2020 to 15.5% (95% CI, 14.1-17.0) in July. Adjusted mortality dropped from 33.4% (95% CI, 32.8-34.1) in March to 17.4% (95% CI, 11.3-26.9) in July. The relative risk of mortality dropped from a reference of 1 in March to 0.52 (95% CI, 0.34-0.80) in July. This demonstrates that the reduction in mortality is not solely due to changes in the demographics of those with COVID-19. *Journal of Hospital Medicine* 2021;16:XXX-XXX. © 2021 Society of Hospital Medicine

The early phase of the COVID-19 pandemic in the United Kingdom (UK) was characterized by uncertainty as clinicians grappled to understand and manage an unfamiliar disease that affected very high numbers of patients amid radically evolving working environments, with little evidence to support them. Early reports indicated high mortality in patients hospitalized with COVID-19.

As the disease became better understood, treatment evolved and the mortality appears to have decreased. For example, two recent papers, a national study of critical care patients in the UK and a single-site study from New York, have demonstrated a significant reduction in adjusted mortality between the pre- and post-peak periods.[1,2] However, the UK study was restricted to patients receiving critical care, potentially introducing bias due to varying critical care admission thresholds over time, while the single-site US study may not be generalizable. Moreover, both studies measured only in-hospital mortality. It remains uncertain therefore whether overall mortality has decreased on a broad scale after accounting for changes in patient characteristics.

The aim of this study was to use a national dataset to assess the casemix-adjusted overall mortality trend in England over the first 5 months of the COVID-19 pandemic.

METHODS

We conducted a retrospective, secondary analysis of English National Health Services (NHS) Hospitals' admissions of patients at least 18 years of age between March 1 and July 31, 2020. Data were obtained from the Hospital Episode Statistics (HES) admitted patient care dataset.[3] This is an administrative dataset that contains data on diagnoses and procedures as well as organizational characteristics and patient demographics for all NHS activity in England. We included all patients with an *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis of U07.1 (COVID-19, virus identified) and U07.2 (COVID-19, virus not identified).

The primary outcome of death within 28 days of admission was obtained by linking to the Civil Registrations (Deaths) - Secondary Care Cut - Information dataset, which includes the date, place, and cause of death from the Office for National Statistics[4] and which was complete through September 31, 2020. The time horizon of 28 days from admission was chosen to approximate the Public Health England definition of a death from COVID as being within 28 days of testing positive.[5] We restricted our analysis to emergency admissions of persons over age 18 years. If a patient had multiple emergency admissions, we restricted our analysis to the first admission to ensure comparability across hospitalizations and to best represent outcomes from the earliest onset of COVID-19.

We estimated a modified Poisson regression[6] to predict death at 28 days, with month of admission, region, source of admission, age, deprivation, gender, ethnic group, and the 29 comorbidities in the Elixhauser comorbidity measure as variables in the regression.[7] The derivation of each of these variables from the HES dataset is shown in Appendix Table 1.

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TABLE. **Selected Demographics and Outcomes by Month of Admission**

Month (No. of patients)	Median age (IQR), y	Male, %	Median Elixhauser comorbidity index (IQR)	Relative risk of death (95% CI)	Crude mortality rate (95% CI), %	Adjusted mortality rate (95% CI), %
March (27,957)	73 (58-83)	58.2	5 (0-10)	(Reference)	33.4 (32.9-34.0)	33.4 (32.8-34.1)
April (49,455)	73 (57-83)	55.3	5 (0-10)	0.95 (0.89-1.00)	31.8 (31.4-32.2)	31.6 (29.8-33.5)
May (16,678)	75 (58-85)	50.1	5 (0-11)	0.73 (0.66-0.80)	25.5 (24.9-26.2)	24.3 (21.9-26.8)
June (6,010)	72 (55-83)	50.7	5 (0-11)	0.61 (0.49-0.76)	20.0 (19.0-21.0)	20.4 (16.4-25.3)
July (2,510)	65 (47-80)	49.9	4 (0-9)	0.52 (0.34-0.80)	15.5 (14.1-17.0)	17.4 (11.3-26.9)

Abbreviations: IQR, interquartile range.

Deprivation was measured by the Index of Multiple Deprivation (IMD), a methodology used widely within the UK to classify relative deprivation.[8] To control for clustering, hospital system (known as Trust) was added as a random effect. Robust errors were estimated using the sandwich package.[9] Modified Poisson regression was chosen in preference to the more common logistic regression because the coefficients can be interpreted as relative risks and not odds ratios. The model was fitted using R, version 4.0.3, geepack library.[10] We carried out three sensitivity analyses, restricting to laboratory-confirmed COVID-19, length of stay ≥3 days, and primary respiratory disease.

For each month, we obtained a standardized mortality ratio (SMR) by fixing the month to the reference month of March 2020 and repredicting the outcome using the existing model. We calculated the ratio of the sum of observed and expected deaths (obtained from the model) in each month, comparing observed deaths to the number we would have expected had those patients been hospitalized in March. We then multiplied each period's SMR by the March crude mortality to generate monthly adjusted mortality rates. We calculated Poisson confidence intervals around the SMR and used these to obtain confidence intervals for the adjusted rate. The binomial exact method was used to obtain confidence intervals for the crude rate. Multicollinearity was assessed using both the variance inflation factor (VIF) and the condition number test.[7] All analyses used two-sided statistical tests, and we considered a *P* value < .05 to be statistically significant without adjustment for multiple testing. The study was exempt from UK National Research Ethics Committee approval as it involved secondary analysis of anonymized data.

RESULTS

The dataset included 115,643 emergency admissions from 179 healthcare systems, of which 103,202 were first admissions eligible for inclusion. A total of 592 patients were excluded due to missing demographic data (0.5%), resulting in 102,610 admissions included in the analysis. Peak hospitalizations occurred in late March to mid April, accounting for 44% of the hospitalizations (Table). Median length of stay for patients who died was 7 days (interquartile range [IQR], 3-12). The median age and number of Elixhauser comorbidities decreased in July. The proportion of men decreased between May and July. Additional data are provided in Appendix Table 2 (length of stay, percentage of in-hospital deaths, and estimated percentage occupancy) and Appendix Table 3 (cause of death by month).

The modified Poisson regression had a C statistic of 0.743 (95% CI, 0.740-0.746) (Appendix Table 4). The VIF and condition number test found no evidence of multicollinearity.[11]

Adjusted mortality dropped each month, from 33.4% in March to 17.4% in July (Figure). The relative risk of death declined progressively to a minimum of 0.52 (95% CI, 0.34-0.80) in July, compared to March. The three sensitivity analyses did not materially change the results (Appendix Figure 1). Appendix Figure 2 shows that the crude mortality tended to decrease with time across all age groups.

Admission from another hospital and being female were associated with reduced risk of death. Admission from a skilled nursing facility and being older than 75 years were associated with increased risk of death. Ten of the 29 Elixhauser comorbidities were associated with increased risk of mortality (cardiac arrhythmia, peripheral vascular disease, other neurological disorders, renal failure, lymphoma, metastatic cancer, solid tumor without metastasis, coagulopathy, fluid and electrolyte disorders, and anemia). Deprivation and ethnic group were not associated with death among hospitalized patients.

DISCUSSION

Our study of all emergency hospital admissions in England during the first wave of the COVID-19 pandemic demonstrated that, even after adjusting for patient comorbidity and risk factors, the mortality rate dropped by approximately half over the first 5 months. Although the demographics of hospitalized patients changed over that period (with both the median age and the number of comorbidities dropping), this does not fully explain the drop in mortality. It is therefore likely that the drop is due, at least in part, to an improvement in treatment and/or a reduction in hospital strain.

For example, initially the use of corticosteroids was controversial, in part due to previous experience with severe acute respiratory syndrome and Middle East respiratory syndrome (in which a Cochrane review demonstrated no benefit but potential harm). However, this changed as a result of the Randomized Evaluation of Covid-19 Therapy

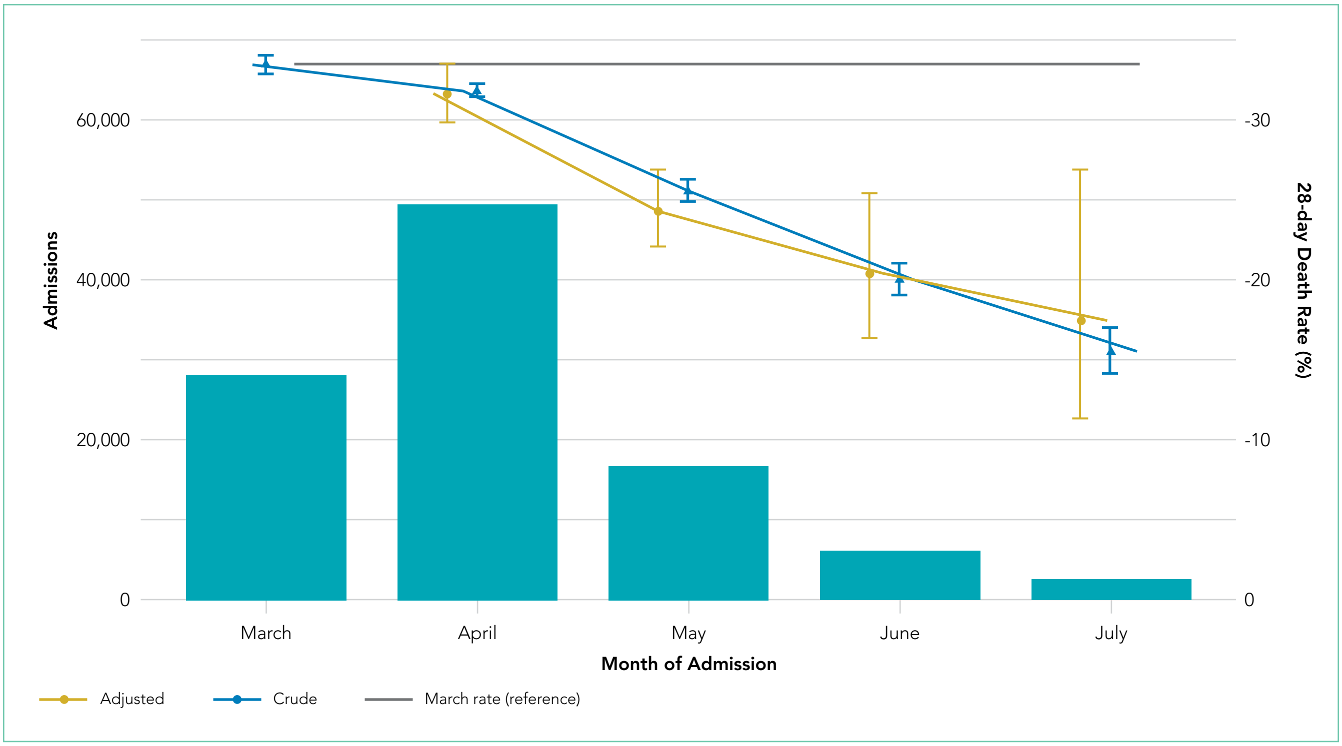

FIG. Adjusted and Unadjusted Mortality Rates by Month of Admission

(RECOVERY) trial,[12] which showed a significant survival benefit. One of the positive defining characteristics of the COVID-19 pandemic has been the intensive collaborative research effort combined with the rapid dissemination and discussion of new management protocols. The RECOVERY trial randomly assigned more than 11,000 participants in just 3 months, amounting to approximately 15% of all patients hospitalized with COVID-19 in the UK. Its results were widely publicized via professional networks and rapidly adopted into widespread clinical practice.

Examples of other changes include a higher threshold for mechanical ventilation (and a lower threshold for noninvasive ventilation), increased clinician experience, and, potentially, a reduced viral load arising from increased social distancing and mask wearing. Finally, the hospitals and staff themselves were under enormous physical and mental strain in the early months from multiple factors, including unfamiliar working environments, the large-scale redeployment of inexperienced staff, and very high numbers of patients with an unfamiliar disease. These factors all lessened as the initial peak passed. It is likely, therefore, that the reduction in adjusted mortality we observed arises from a combination of all these factors, as well as other incremental benefits.

The factors associated with increased mortality risk in our study (increasing age, male gender, certain comorbidities, and frailty [with care home residency acting as a proxy in our study]) are consistent with multiple previous reports. Though not the focus of our analysis, we found no effect of ethnicity or deprivation on mortality. This is consistent with many US studies that demonstrate that the widely reported effect of these factors is likely due to differences in exposure to the disease. Once patients are hospitalized, adjusted mortality risks are similar across ethnic groups and deprivation levels.

The strengths of this study include complete capture of hospitalizations across all hospitals and areas in England. Likewise, linking the hospital data to death data from the Office for National Statistics allows complete capture of outcomes, irrespective of where the patient died. This is a significant strength compared to prior studies, which only included in-hospital mortality. Our results are therefore likely robust and a true observation of the mortality trend.

Limitations include the lack of physiologic and laboratory data; having these would have allowed us to adjust for disease severity on admission and strengthened the risk stratification. Likewise, although the complete national coverage is overall a significant strength, aggregating data from numerous areas that might be at different stages of local outbreaks, have different management strategies, and have differing data quality introduces its own biases.

Furthermore, these results predate the second wave in the UK, so we cannot distinguish whether the reduced mortality is due to improved treatment, a seasonal effect, evolution of the virus itself, or a reduction in the strain on hospitals.

CONCLUSION

This nationwide study indicates that, even after accounting for changing patient characteristics, the mortality of patients hospitalized with COVID-19 in England dropped significantly as the outbreak progressed. This is likely due to a combination of incremental treatment improvements.

Disclosures: The authors have nothing to disclose.

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