Title: Trends in hospitalised mortality risk and lengths of stay during the first, second and current waves of COVID-19 in England: a cohort study

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Abstract

Widespread vaccination campaigns have changed the landscape for COVID-19, vastly altering symptoms and reducing morbidity and mortality. We estimate monthly trends in mortality and the impact of vaccination among patients hospitalised with COVID-19 in England, controlling for baseline demographics and hospital load.

Among 259,727 hospitalised individuals, 51,948 (20.0%) experienced mortality in hospital. Hospitalised fatality risk ranged from 40.3% (95% confidence interval 39.4-41.3%) in March 2020 to 8.1% (7.2-9.0%) in June 2021. Older patients and those with multiple co-morbidities were more likely to die or else experienced longer stays prior to discharge. Compared to unvaccinated patients, the hazard ratio for mortality following hospital admission was 0.72 (0.67-0.77) with a first vaccine dose, and 0.58 (0.54-0.62) with a second vaccine dose.

The prognosis for patients hospitalised with COVID-19 in England has varied substantially throughout the pandemic and is influenced by baseline demographic factors, vaccination status, and hospital load at admission.

Main text

Background

It is now well established that a segment of the population who acquire severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the virus responsible for coronavirus disease 2019 (COVID-19), in the community will require hospitalisation, potential escalation to intensive care facilities, and may die in hospital or soon after discharge. COVID-19 has been shown to disproportionately impact older people and those with multiple comorbidities, compared to younger, healthier individuals, and there is now considerable evidence that these factors heavily influence patient prognosis following hospital admission for COVID-19 [1–4].
The extensive vaccination campaign in England during 2021 has dramatically changed the outlook for COVID-19, lessening symptoms and reducing morbidity and mortality [5,6]. Despite widespread and high levels of vaccination, however, individuals continue to experience COVID-19 infection severe enough to require hospitalisation. Several studies have previously examined hospitalised fatality risk (HFR) in England according to baseline demographic factors [1–3,7–9], although limitations exist in the coverage of the data and data quality, and there is little information on hospitalised outcomes in the current context of vaccination across the population. Information on the impact of hospital load on outcomes in England is similarly lacking, nevertheless increased hospital load has been linked to poorer outcomes for COVID-19 in Switzerland [10], and a recent King’s Fund study concluded that a shortage of overnight and acute bed availability prior to the pandemic put hospitals under increased strain [11].

In general, studies of hospital cohorts may include several end-points e.g. death or discharge, with a wide variety of survival analysis techniques available to quantify differences in outcomes between groups of patients, a detailed introduction can be found in e.g. [12]. If the competing risks of events are not independent, and the magnitude of the competing risk is large, the assumptions of conventional survival analysis methods such as Kaplan-Meier and Cox proportional hazards regression may provide biased estimates of risk, or of effect sizes on the rate of events, respectively [13]. In the case of hospitalised mortality for COVID-19, the competing risk of discharge may well be large, e.g. for individuals discharged to palliative care. Two survival analysis techniques which account for these competing risks are Aalen-Johansen cumulative incidence [14] and Fine-Grey regression [15], details of which are included in the supplementary materials.

Another form of bias, often ignored in epidemic studies, is the relationship between the time from infection to symptom onset, and an individual’s eventual outcome: e.g. those who go on to die may experience more rapid onset of symptoms following infection. Since estimates must be conditioned on an observed quantity (e.g. symptom onset date or hospital
admission date) rather than the unobserved infection date, this relationship can introduce bias into results when an epidemic is in a mode of growth or decline [16]. The resulting bias has been termed “epidemic phase bias” and may result in hazards being over or under-estimated.

We aimed to investigate trends in hospitalised mortality and the impact of vaccination, hospital load, and other factors among patients hospitalised with community-onset COVID-19 in England. We apply statistical methods which account for competing outcomes to estimate absolute and relative risks of hospitalised fatality, and lengths of stay in hospital according to outcome, and assess the potential impact of epidemic phase bias.

**Methods**

*Study design and setting*

In this retrospective cohort study we considered data on hospital admissions in England from the start of the COVID-19 pandemic in March 2020 until the end of September 2021, with follow-up until 22nd November 2021.

*Participants*

All patients aged 15 years and older with community-acquired COVID-19 (defined as a positive test for COVID-19 within -14 to 1 days of hospital admission), admitted to hospital in England for COVID-19 or another non-injury related condition between 1st March 2020 and 30th September 2021 were included (n= 259,727). Patient records with inconsistent date information (n=2) or missing demographic information (n=302) were excluded.

*Data sources and outcomes*

The United Kingdom Health Security Agency (UKHSA), alongside NHS England, monitors infectious diseases in England. The NHS England Secondary Uses Service (SUS) dataset contains well completed, accurate information on hospitalisation for COVID-19 in England,
along with identifiers to augment these data through linkage to other routinely collected information. SUS data are reported upon completion of a hospital stay (i.e. at the point of discharge from hospital or death). SUS data were supplemented with information on patients still in hospital though linkage to the Emergency Care Dataset for England (ECDS), which records all emergency care attendances and onwards destinations (i.e. discharge home or admittance to hospital).

Complete information on deaths was obtained through linkage to the UKHSA deaths dataset, containing information on all dates of death for patients with a positive COVID-19 test. Date of vaccination (first and second dose, third doses were not considered as only n=11 hospitalisations had received a third dose during the follow-up period) was obtained through linkage to the National Immunisation Management Service (NIMS). Testing information both for community-acquired COVID-19 infections identified through PCR testing on arrival at hospital (Pillar 1) and PCR testing within the community (Pillar 2) were obtained from the UKHSA Second Generation Surveillance System (SGSS). All data were stored and analysed on UKHSA computers under agreed data governance protocols.

Covariates

Covariates in the linked dataset included vaccination status (no vaccine, <21 days of first dose, ≥21 days after first dose, ≥14 days after second dose), date of hospital admission (aggregated by month), age group, region of residence (Government office region), Charlson comorbidity index (CCI) [17], ethnicity, sex, index of multiple deprivation quintile, and a measure of hospital load. The hospital load measure was defined as the number of COVID-19 admissions at an NHS trust within the 7 days around admission (3 before, same day, and 3 after), as a proportion of the busiest 7-day period at that trust. Hospital load was grouped into: 0-20%, 20-40%, 40-60%, 60-80%, 80-90%, and 90-100%. In relative risk analyses the two key exposure variables of interest considered were vaccination status and month of hospital admission.
Representativeness

Data comprised all new admissions for COVID-19 reported in England. Numbers of reported admissions were compared with the NHS COVID-19 Situation Reports to ensure data were representative. Hospital-onset COVID-19 (i.e. infection occurring in hospital) cases were excluded: those with hospital-onset infection (n=194,888) tended to be older and have longer lengths of stay than the community-onset cases considered in this study.

Bias

Data validation was undertaken between the linked datasets, we found no systematic under-reporting or mis-reporting of patient characteristics and linked information was used to minimise missing data. Censored outcomes and competing risks were explicitly accounted for by the choice of statistical method.

We carried out a sensitivity analysis to assess the potential effect of epidemic phase bias on the estimated hazard ratios in relative risk analyses. Since this bias is caused by conditioning on an observed date later than the date of infection, for this analysis we condition on date of symptom onset, which is nearer to date of infection than date of hospital admission. This should ensure the sensitivity analysis targets bias due to epidemic phase, as opposed to any other factors which may influence time from symptom onset to admission (see Supplementary Information for further details).

Reporting delay

The SUS dataset receives data daily although has significant reporting delay as records are only submitted once a patient leaves hospital (due to discharge or death). Linkage to ECDS was therefore used to ascertain information for patients initially admitted via emergency care who remained in hospital. Among those with completed hospital episodes, 77% were admitted via emergency care.

Statistical methods
Two complementary statistical analyses were undertaken to understand both the absolute and relative risks of hospitalised fatality. We used Aalen-Johansen cumulative incidence estimation to obtain estimates of cumulative HFR and median lengths of stay in hospital for specific sub-sets of the population, unadjusted for other factors [14]. We used stratified Fine-Grey competing risk regression with adjustment for confounders to estimate the association of each risk factor with the cumulative incidence of hospitalised fatality; modelling with proportional hazards a “sub-distribution hazard” of hospitalised fatality derived from the cumulative incidence function [15]. Stratification was used for confounders with non-proportional hazards. See Supplementary Information for further details of these methods.

**Censoring**

To focus our analyses on outcomes following COVID-19 admission, a pragmatic cut-off of 90 days from first positive specimen date was chosen and only those hospital outcomes (death or discharge) occurring within this cut-off were included. All records with outcomes occurring beyond 90 days (n=656) were right-censored at 90 days, meanwhile patients who remained in hospital at the date of data extraction (n=15,460) were right-censored at the shorter of this date or 90 days. To account for palliative discharge, deaths occurring within 14 days of discharge from hospital were classified as deaths rather than discharges and the date of death used as the outcome date. Linkage to UKHSA deaths data enabled these post-hospital discharge deaths to be identified.

**Model implementation**

Statistical models were implemented using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and packages flexsurv 2.0, survival 3.2-12, and matrixStats 0.60.0.

**Results**
Participant characteristics

Table 1 presents patient characteristics for the study population. Among 259,727 people with COVID-19 hospitalised between 15th March 2020 and 30th September 2021, a total of 51,948 (20.0%) died, 191,663 (73.8%) were discharged and the remaining 16,116 (6.2%) remained in hospital at the date of data extraction and/or were right-censored at 90 days. Figure 1 presents weekly hospital admissions for COVID-19 over the study period, with an indication of the first, second, and current (third) waves.

Compared to all people with PCR-confirmed community-acquired COVID-19 infection, those hospitalised for COVID-19 were older (48.4% aged over 65 vs. 10%), more likely to be male (52.1% vs. 47.6%), and to reside in London (18.0% vs. 16.3%). A greater proportion of those hospitalised were of Black ethnicity (5.9% vs 4.2%) and lived in an area of high deprivation (28.1% vs 23.6%), compared to all those with community-acquired COVID-19. Comparative information on comorbidity was not available, although 7.2% of those hospitalised had a CCI score of 5 or more compared to 2.3% among a sample of 657,264 patients 20 years and older registered at English primary care practices in 2005 [18].

Observed hospital outcomes

In unadjusted comparisons, older patients experienced poorer outcomes following hospital admission; almost half (46.5%) of those aged 85+ died in hospital compared to just 0.5% of those aged 15-24. Similarly, males (as compared to females), those living outside of London and the South West, and those with an increased CCI score (compared to lower CCI) were more likely to die in hospital (Supp. Table 1).

Hospitalised case-fatality risk

Table 2 and Figure 2A show estimated HFR by month of hospital admission. HFR decreased during the first wave of the pandemic from 40.3% (95% confidence interval: 39.4-41.3%) in March 2020 to 12.3% (10.3-14.8%) in August 2020. During the second wave HFR increased to a peak of 22.8% (22.5-23.2%) in January 2021, although by March 2021 had halved to
10.5% (9.7-11.4%) and was maintained at or below 10% throughout subsequent months (Table 2).

Additional estimates of HFR by month and one a single other covariate (age, sex, ethnicity, region of residence) i.e. unadjusted for all other covariates are included in the Supplementary Information. Males tended to have greater HFR than females, although the extent of this differed by month. There was a clear relationship between age and HFR, with increasing age associated with increased HFR. Those of White ethnicity had greater HFR than those of Asian or Black ethnicity. HFR was slightly elevated for those residing in North of England regions (North East, North West and Yorkshire and Humber) compared to the rest of England (Supp. Tables 2-5).

During the initial months of the study those admitted to hospitals which were experiencing higher load had a greater HFR as compared to those admitted to hospitals with lower activity e.g. during March 2020, HFR was 44.9% (39.6-50.9%) for hospitals at 90-100% of their peak load, compared to 38.8% (36.6-41%) for hospitals at 0-20% of their peak load. This disparity appeared to lessen during subsequent months, although estimates in the 90-100% load category are relatively uncertain (Supp. Table 6).

Length of stay

Table 2 and Figure 2B show estimated median lengths of stay until death or discharge by month of hospital admission. Aside from the first two months of the pandemic (March-April 2020), those with an eventual outcome of death had longer stays in hospital compared to those who were discharged. Trends in length of stay prior to death and discharge followed approximately inverse trends: whilst length of stay prior to discharge decreased throughout the first wave, from 5.9 (5.8-6.0) days in March 2020 to 3.1 (2.9-3.3) days in August 2020, length of stay prior to death increased from 5.6 (5.5-5.6) days to 9.9 (9.2-10.9) days.

During the second wave, lengths of stay prior to discharge initially lengthened, peaking at 5 (5-5.1) days in December 2020, before falling to 2.7 (2.6-2.8) days by June 2021.
Conversely, length of stay prior to death was shortest in January, at 7.5 (7.5-7.6) days, and lengthened to 10.4 (10.1-10.8) days by June 2021.

Examining lengths of stay prior to discharge and death for different subgroups, similar patterns were observed for males and females, although with less pronounced variation among males. Length of stay prior to death estimates were imprecise for younger individuals, due to the small number of events, but for age groups 45-64 and above, the median length of stay prior to death decreased with increasing age. Meanwhile older individuals had longer stays in hospital prior to discharge compared to younger individuals; the median time to discharge among those aged 85+ ranged between 5.1-10.4 days, compared to between 0.8-2.4 days for those aged 0-14 and 15-24 (Supp. Tables 2-5).

Impact of vaccination on HFR

Table 3 shows the impact of vaccination upon HFR, by age group. For all ages, vaccination reduced the HFR, with significant reductions in HFR among those hospitalised >21 days post first vaccine or >14 days post second vaccine. The HFR for a double vaccinated adult aged 75-85 was 22.5% (20.4-24.8%), this compares to 25.3% (24.5-26%) for an unvaccinated adult aged 65-75.

Relative risks

Table 4 and Figure 3 present hazard ratios for hospitalised fatality by month of admission. Controlling for age group, region of residence, vaccination status, sex, ethnicity, IMD quintile, CCI and hospital load, month of hospital admission still remained a significant factor for the prognosis of hospitalised patients. Compared to June 2020, the hazard for hospitalised fatality was increased during March to May 2020, September 2020 to February 2021, and June to September 2021.

Similarly, controlling for month of admission and the factors mentioned above, vaccination status also had a significant effect upon patient prognosis. During January to September 2021, compared to the reference category of unvaccinated, the hazard ratio for hospitalised
mortality was 0.92 (0.88-0.97) for individuals hospitalised <21 days after first vaccination dose, 0.72 (0.67-0.77) for individuals hospitalised ≥21 days after first vaccination dose, and 0.58 (0.54-0.62) for individuals hospitalised ≥14 days after second vaccination dose (Table 5, Figure 4).

There was an increased hazard of hospitalised mortality for those of Asian (1.19 (1.15-1.23)) and Mixed/Other/Unknown ethnicity (1.06 (1.01-1.12)) but reduced for those of Black ethnicity (0.94 (0.89-0.98)) compared to reference category White. Males had a greater hazard compared to females (1.29 (1.27-1.32)), and compared to no comorbidities those with a higher burden of comorbidity had a greater hazard of hospitalised mortality (3.1 (2.98-3.22) for CCI of 5 or above). Those residing in more deprived quintiles had greater hazards for hospitalised mortality (1.13 (1.09-1.16) for the most deprived quintile) compared to a reference of least deprived (Supp. Table 7).

Hazards were also elevated with increased hospital load, to 1.23 (1.17-1.28) for load at 80-90% of the busiest week and 1.21 (1.16-1.27) for load at 90-100% of the busiest week (compared to 0-20% load).

Sensitivity to epidemic phase bias

Supplementary Figure 7 shows the outcome of the shift sensitivity analyses by month of symptom onset, adjusted for the same covariates as above. The greatest effect was observed for the March 2020 hazard ratio estimate, which steadily reduced towards 1 following a shift of c=1, 2, 3 or 4 days. The effect in other months was small, with the previously described monthly trends persisting, although the slight reduction in hazard estimated for the most recent month (September 2021) was no longer apparent.

Discussion
We examined absolute and relative risks of hospitalised fatality and lengths of stay in hospital during the first year and a half of the COVID-19 pandemic in England. In line with epidemiological studies from UKHSA and others [7,19–21], we found that people with community-acquired COVID-19 who became hospitalised were older, more likely to be male, of Black ethnicity, and to live in areas of high deprivation, as compared to everyone diagnosed with the virus. Among those who were hospitalised, we estimated greater absolute fatality risks for men and older individuals, and HFR also varied according to ethnicity, month of admission, hospital load, and region. Lengths of stay in hospital were similarly influenced by demographic factors, with median lengths of stay prior to death typically longer than those prior to discharge. In relative risk analyses controlling for all measured confounders, baseline comorbidity burden was the strongest predictor of death.

Our estimates suggest a deterioration in survival as hospital load increases, however, there are several potential biases which make this harder to interpret. It has been suggested that during periods of peak hospital load there is likely a modification of intensive care admission criteria, with only the most severe cases being admitted. Meanwhile, individuals with milder disease may be selected for transfer from overloaded hospitals to those with bed availability, due to the lower inherent risk. Hospital load-dependent changes in outcome are not unique to the English setting, with a recent Swiss study estimating poorer patient outcomes at times of increased hospital load; an ICU occupancy of 70% or greater found to be a tipping point at which outcomes became adversely affected [10].

There is now compelling evidence that vaccination reduces the number of individuals being hospitalised [5] and the risk of mortality, regardless of hospital admission [9,22]. We found reduced hospitalised mortality among vaccinated patients, with the reduction most clearly seen among older individuals. For those aged 75 and over, vaccination reduced HFR to approximately the risk of an unvaccinated individual aged 10 years younger. In adjusted estimates, each additional vaccine dose reduced the hazard for fatality by a significant margin, with a 42% (38-46%) estimated reduction in the risk of death for double-vaccinated...
individuals. This is a slightly lower reduction than for all community-acquired PCR-positive COVID-19 cases in England, where a 51% (37-62%) reduced risk of death was estimated for symptomatic patients who had received a single vaccine [5]. This difference may reflect the portion of hospitalised patients who die from other causes, or could be an indication of waning vaccine efficacy among our study population.

After controlling for all measured covariates, including hospital load and vaccination, we continued to estimate monthly variation in outcomes, with apparent seasonal variation in hazards. Whilst seasonal patterns in respiratory pathogens such as influenza and respiratory syncytial virus are well-documented [23,24], a multitude of interlinked factors including changes in national restrictions and the emergence of new variants may have influenced these trends.

**Strengths and limitations**

The use of high-quality hospital surveillance data linked to several other comprehensive data sources is a strength of this study and enabled a broader understanding of the factors influencing hospitalised mortality. For covariates with varying levels of completeness we undertook sensitivity analyses to confirm minimal effects on our estimates (e.g. indication of injury as a factor for emergency care admission), however, there may have been other unmeasured confounders for which we could not account. Using carefully chosen statistical methods we adjusted for competing risks, and the use of a relatively course monthly timescale likely limited the extent to which our study was affected by epidemic phase bias [16].

Data on hospital pathways following admission were unavailable. As such, we were not able to subdivide the hospitalised population by severity of infection and/or need of respiratory support, whether within or outside of intensive care. Treatment data and changes in patient management were similarly unmeasured in our dataset, although the use of therapeutic
agents is likely to have contributed to the reduction in hospital fatality risk, particularly at the start of the pandemic [7,25].

The measure of hospital burden we used considered acute hospital admissions at and around the time of admission as a proxy for bed occupancy. Whilst no single accepted measure of hospital burden exists, overnight bed occupancy is a widely used metric [11], and guidance on bed occupancy was issued to ICUs (e.g. alterations in practice upon reaching 150% and 200% above pre-pandemic baseline) [26]. A limitation of the bed occupancy measure is that it only measures demand and not supply (i.e. staffing levels), or the extent of other hospital pressures. Work to access and integrate measures of supply is ongoing.

Lastly, this study did not consider the significant proportion of patients (up to 40%) who may have acquired COVID-19 nosocomially (in hospital). Fatality risks and lengths of hospital stay for these patients are complicated by other conditions. Whilst these patients were excluded from our estimates, researchers in Scotland have found similar effects of age, sex, and comorbidity upon patient prognosis following nosocomial COVID-19 acquisition [27].

Conclusions

Case-mix, vaccination, and changes in hospital load continue to impact upon patient outcomes and lengths of stay more than 18 months after the pandemic began in England. One of the primary goals of the lockdown measures implemented in England at various times since start of the pandemic has been to protect against hospitals becoming excessively overburdened. Even with these measures in place, being admitted during a period of high hospital load was correlated with poorer outcomes. Meanwhile, vaccinated individuals admitted to hospital for COVID-19 had a significantly reduced risk of mortality, and third (booster) doses may further reduce this risk.
Outcomes following hospitalisation with COVID-19 should continue to be monitored, particularly with the emergence of new variants. The datasets and methods we describe will be vital to estimate future changes in severity.
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Patient and public involvement: This study was a retrospective cohort analysis. The research question, design and data collection were motivated by the response to an urgent public health emergency. The surveillance data were collected by NHS England and the UK Health Security Agency with permissions granted under Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, and without explicit patient permission under Section 251 of the NHS Act 2006. Although patients were not directly involved in the study design, the experiences of clinicians and public health officials interacting with patients informed the design of the data collection.

Data availability: Requests to access non-publicly available data are handled by the UKHSA Office for Data Release (ODR).

Dissemination to participants and related patient and public communities: UKHSA and the MRC Biostatistics Unit have public facing websites and Twitter accounts @UKHSA and @MRC_BSU. UKHSA and the MRC Biostatistics Unit engage with print and internet press, television, radio, news, and documentary programme makers.

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**Transparency statement:** The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Authors’ contributions:** PDK, AMP and DDA conceived the research study. PDK and AMP drafted the manuscript and formatted and verified the datasets. PDK carried out the analyses. All authors provided expert advice and critical review of the manuscript prior to submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. PDK is the guarantor.

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Figures

Figure 1: Observed number of individuals hospitalised with COVID-19, by week of admission, March 2020 to September 2021 with annotations for wave 1, wave 2, and current wave.

![Graph of hospitalisations by week](image)

Figure 2: Hospitalised fatality risk and median* length of stay by month of admission. Estimated by Aalen-Johansen cumulative incidence estimator, for the competing outcomes of death and discharge. Error bars are 95% confidence intervals.

*Median length of stay is a weighted median estimate with weighted ties; when two values satisfy the weighted median requirement, the estimate is the weighted average of the two.
Figure 3: Hospitalised fatality sub-distribution hazard ratio by month of hospital admission, stratified by age group, region of residence and vaccination status, with regression adjustment (main effects) on sex, ethnicity, IMD quintile, hospital load, and CCI. Reference group: June 2020.
Figure 4: Hospitalised fatality sub-distribution hazard ratio by vaccine status for January-September 2021, stratified by age group, region of residence and month of hospital admission, with regression adjustment (main effects) on sex, ethnicity, IMD quintile, hospital load, and CCI. Reference group: Unvaccinated.

Tables

Table 1: Characteristics of the study population compared with all people with PCR-confirmed community-acquired COVID-19 in England.

| Characteristic | Study population (hospitalised for COVID-19 in England) n (%) | All people with PCR-confirmed community-acquired COVID-19 in England n (%) |
|---------------|-------------------------------------------------------------|-----------------------------------------------------------------------|
| **Total**     | 259,727 (100%)                                             | 6,616,231 (100%)                                                     |
| **Age**       |                                                             |                                                                       |
| 0-14          | 6650 (2.6%)                                                 | 892,640 (13.5%)                                                      |
| 15-24         | 8972 (3.5%)                                                 | 1,265,595 (19.1%)                                                   |
| 35-44         | 44,094 (17%)                                                | 2,242,751 (33.9%)                                                   |
| 45-64         | 74,258 (28.6%)                                              | 1,559,808 (23.6%)                                                  |
| 65-74         | 42,307 (16.3%)                                              | 301,356 (4.6%)                                                      |
| 75-84         | 47,783 (18.4%)                                              | 198,201 (3%)                                                       |
| 85+           | 35,663 (13.7%)                                              | 155,880 (2.4%)                                                      |
| **Sex**       |                                                             |                                                                       |
| Male          | 135,419 (52.1%)                                             | 3,151,711 (47.6%)                                                   |
| Ethnicity                  | Male                  | Female                  |
|---------------------------|-----------------------|-------------------------|
| White                     | 195,496 (75.3%)       | 5,100,116 (77.1%)       |
| Asian                     | 32,191 (12.4%)        | 740,194 (11.2%)         |
| Black                     | 15,394 (5.9%)         | 278,773 (4.2%)          |
| Mixed/Other/Unknown       | 16,646 (6.4%)         | 497,148 (7.5%)          |

| Region of residence       | Male                  | Female                  |
|---------------------------|-----------------------|-------------------------|
| London                    | 46,854 (18%)          | 1,077,599 (16.3%)       |
| East Midlands             | 22,571 (8.7%)         | 586,513 (8.9%)          |
| East of England           | 26,323 (10.1%)        | 678,869 (10.3%)         |
| North East                | 15,131 (5.8%)         | 376,600 (5.7%)          |
| North West                | 43,017 (16.6%)        | 1,056,012 (16.3%)       |
| South East                | 32,740 (12.6%)        | 887,116 (13.4%)         |
| South West                | 17,391 (6.7%)         | 496,411 (7.5%)          |
| West Midlands             | 29,808 (11.5%)        | 733,250 (11.1%)         |
| Yorkshire and Humber      | 25,892 (10%)          | 723,861 (11.0%)         |

| Index of multiple deprivation | Male                  | Female                  |
|-------------------------------|-----------------------|-------------------------|
| 1st quintile (most deprived)  | 73,100 (28.1%)        | 1,564,464 (23.6%)       |
| 2nd quintile                 | 59,754 (23%)          | 1,440,534 (21.8%)       |
| 3rd quintile                 | 48,458 (18.7%)        | 1,287,972 (19.5%)       |
| 4th quintile                 | 42,608 (16.4%)        | 1,209,869 (18.3%)       |
| 5th quintile (least deprived)| 35,807 (13.8%)        | 1,113,392 (16.8%)       |

| Month of hospital admission | Male                  | Female                  |
|-----------------------------|-----------------------|-------------------------|
| Mar-20                      | 12,408 (4.8%)         | 31,598 (0.5%)           |
| Apr-20                      | 25,867 (10%)          | 111,629 (1.7%)          |
| May-20                      | 7475 (2.9%)           | 66,563 (1%)             |
| Jun-20                      | 2698 (1%)             | 25,007 (0.4%)           |
| Jul-20                      | 1077 (0.4%)           | 18,905 (0.3%)           |
| Aug-20                      | 911 (0.4%)            | 29,130 (0.4%)           |
| Sep-20                      | 3945 (1.5%)           | 124,294 (1.9%)          |
| Oct-20                      | 15,235 (5.9%)         | 474,083 (7.2%)          |
| Nov-20                      | 23,218 (8.9%)         | 518,220 (7.8%)          |
| Dec-20                      | 31,468 (12.1%)        | 852,653 (12.9%)         |
| Jan-21                      | 60,389 (23.3%)        | 1,068,457 (16.1%)       |
| Feb-21                      | 19,503 (7.5%)         | 289,488 (4.4%)          |
| Mar-21                      | 5809 (2.2%)           | 134,516 (2%)            |
| Apr-21                      | 1929 (0.7%)           | 58,209 (0.9%)           |
| May-21                      | 1370 (0.5%)           | 61,016 (0.9%)           |
| Jun-21                      | 3756 (1.4%)           | 293,512 (4.4%)          |
| Jul-21                      | 13,984 (5.4%)         | 926,889 (14%)           |
| Aug-21                      | 15,578 (6%)           | 775,051 (11.7%)         |
| Sep-21                      | 13,107 (5%)           | 757,011 (11.4%)         |

| Vaccination status at date of admission (for admissions occurring January and July 2021) | Male | Female |
|--------------------------------------------------------------------------------------------|------|--------|
| Unvaccinated                                                                              | N/A  | N/A    |
| <21 days after first dose                                                                  | 10,774 (8%)   | N/A    |
| ≥21 days after first dose                                                                  | 7885 (5.8%)   | N/A    |
| ≥14 days after second dose                                                                 | 19,325 (14.3%) | N/A    |

| Charleson comorbidity index                                                               | Male | Female |
|-------------------------------------------------------------------------------------------|------|--------|
| 0                                                                         | 92,753 (38.8%) | N/A    |
| 1-2                                                                       | 93,436 (39.1%) | N/A    |
| 3-4                                                                       | 35,527 (14.9%) | N/A    |
| 5+                                                                        | 17,190 (7.2%)  | N/A    |

| Hospital load at time of admission (as proportion of busiest week)                       | Male | Female |
|------------------------------------------------------------------------------------------|------|--------|
| 0-20%                                      | 61,406 (23.6%) | N/A    |
| 20-40%                                     | 64,722 (24.9%) | N/A    |
Table 2: Hospitalised fatality risk and median* length of stay in hospital by month of hospital admission. Figures in brackets represent 95% confidence intervals.

| Month of hospital admission | Hospitalised fatality risk | Median length of stay prior to death (days) | Median length of stay prior to discharge (days) |
|----------------------------|---------------------------|------------------------------------------|-----------------------------------------------|
| Mar-20                     | 40.3% (39.4 - 41.3%)      | 5.6 (5.5 - 5.6)                          | 5.9 (5.8 - 6)                                 |
| Apr-20                     | 37.4% (36.7 - 38%)        | 5.2 (5.2 - 5.3)                          | 5.8 (5.8 - 5.9)                               |
| May-20                     | 29.7% (28.6 - 30.8%)      | 6.5 (6.4 - 6.7)                          | 5.6 (5.5 - 5.7)                               |
| Jun-20                     | 20.3% (18.8 - 21.9%)      | 7.7 (7.5 - 8)                             | 4.9 (4.8 - 5.1)                               |
| Jul-20                     | 13.1% (11.1 - 15.3%)      | 10.4 (9.7 - 11)                           | 4.3 (4.2 - 5.1)                               |
| Aug-20                     | 12.3% (10.3 - 14.8%)      | 9.9 (9.2 - 10.9)                          | 3.1 (3.0 - 3.3)                               |
| Sep-20                     | 15.5% (14.4 - 16.7%)      | 9 (8.7 - 9.3)                             | 4.1 (4 - 4.2)                                 |
| Oct-20                     | 19.1% (18.5 - 19.7%)      | 8.5 (8.4 - 8.7)                           | 4.5 (4.5 - 4.6)                               |
| Nov-20                     | 20.7% (20.2, 21.3%)       | 8.4 (8.3 - 8.5)                           | 4.8 (4.8 - 4.9)                               |
| Dec-20                     | 22.5% (22.1 - 23%)        | 8.5 (8.4 - 8.6)                           | 5.0 (5 - 5.1)                                 |
| Jan-21                     | 22.8% (22.5 - 23.2%)      | 7.5 (7.5 - 7.6)                           | 4.9 (4.9 - 4.9)                               |
| Feb-21                     | 17.8% (17.3 - 18.4%)      | 7.8 (7.6 - 7.9)                           | 4.6 (4.5 - 4.6)                               |
| Mar-21                     | 10.5% (9.7 - 11.4%)       | 8.7 (8.4 - 9)                             | 3.6 (3.6 - 3.7)                               |
| Apr-21                     | 8.7% (7.5 - 10.1%)        | 8.6 (8.3 - 9.1)                           | 3.2 (3.1 - 3.3)                               |
| May-21                     | 8.6% (7.2 - 10.3%)        | 10 (9.5 - 10.7)                           | 2.8 (2.7 - 2.9)                               |
| Jun-21                     | 8.1% (7.2 - 9%)           | 10.4 (10.1 - 10.8)                       | 2.7 (2.6 - 2.8)                               |
| Jul-21                     | 8.7% (8.3 - 9.2%)         | 9.9 (9.7 - 10.2)                          | 3.0 (3.0 - 3.1)                               |
| Aug-21                     | 10.7% (10.2 - 11.2%)      | 9.6 (9.4 - 9.8)                           | 3.2 (3.2 - 3.3)                               |
| Sep-21                     | 10.5% (10.0 - 11.1%)      | 7.6 (7.5 - 7.8)                           | 3.6 (3.5 - 3.6)                               |

*Median length of stay is a weighted median estimate with weighted ties; when two values satisfy the weighted median requirement, the estimate is the weighted average of the two.

Table 3: Hospitalised fatality risk by vaccine status at hospital admission and age group.

Figures in brackets represent 95% confidence intervals. Estimates are replaced with a dash (-) where insufficient information was available.
| Age group | Unvaccinated or <21 days after first vaccination dose | <21 days after first vaccination dose | ≥21 days after first vaccination dose | ≥14 days after second vaccination dose |
|-----------|------------------------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------|
| [0,15)    | 0.2% (0.1 - 0.4%)                                      | -                                   | -                                   | -                                    |
| [15,25)   | 0.3% (0.2 - 0.5%)                                      | 1.3% (0.3 - 5.3%)                   | -                                   | -                                    |
| [25,45)   | 1.7% (1.5 - 1.9%)                                      | 2.1% (1.3 - 3.5%)                   | 1.2% (0.7 - 2.2%)                   | -                                    |
| [45,65)   | 10.1% (9.8 - 10.5%)                                    | 8.7% (7.5 - 10.1%)                  | 6.1% (4.9 - 7.7%)                   | 7.5% (6.2 - 9%)                      |
| [65,75)   | 25.3% (24.5 - 26%)                                     | 22.5% (20.5 - 24.7%)                | 18.2% (15.6 - 21.1%)                | 14.9% (12.9 - 17.2%)                 |
| [75,85)   | 38.6% (37.7 - 39.6)                                    | 34.5% (32.8 - 36.2%)                | 26.2% (24.1 - 28.5%)                | 22.5% (20.4 - 24.8%)                 |
| [85,Inf]  | 49.9% (48.7 - 51.1%)                                   | 47% (45.2 - 48.9%)                  | 37.7% (35.4 - 40.2%)                | 32% (29.1 - 35.2%)                   |

Table 4: Hospitalised fatality sub-distribution hazard ratio by month of hospital admission, stratified by age group, region of residence and vaccination status, with regression adjustment (main effects) on sex, ethnicity, IMD quintile and CCI. Figures in brackets represent 95% confidence intervals.
Table 5: Hospitalised fatality sub-distribution hazard ratio by vaccine status at hospital admission, stratified by age group, region of residence and month of hospital admission, with regression adjustment (main effects) similarly on sex, ethnicity, IMD quintile and CCI. Figures in brackets represent 95% confidence intervals.

| Vaccination status                                | Hazard ratio     |
|---------------------------------------------------|------------------|
| Unvaccinated                                      | 1 (reference category) |
| <21 days after first vaccination dose              | 0.92 (0.88 - 0.97) |
| ≥21 days after first vaccination dose              | 0.72 (0.67 - 0.77) |
| ≥14 days after second vaccination dose             | 0.58 (0.54 - 0.62) |
Supplementary Information: Statistical methods

Epidemic phase bias

Epidemic phase bias may occur if there exists a relationship between the time from infection to symptom onset, and an individual's eventual outcome. E.g. if those who go on to die experience more rapid onset of symptoms following infection.

To correct for this bias, a time shift of $c$ days should be added to records with the outcome of interest (e.g. mortality), where $c$ is the mean difference in time from infection to symptom onset date between those experiencing the outcome and those not, as proposed by Seaman et al. [1]. As the value of $c$ is typically unknown, sensitivity analysis with differing values of $c$ can be used to assess the susceptibility of results to this bias.

For the sensitivity analysis in this study we shifted the date of symptom onset backwards in time by $c = 0, 1, 2, 3, 4$ days for those who died, to mitigate against the effect of more rapid symptom onset for those with more severe illness, where the shift $c$ represents the average difference in time from infection to symptom onset between those patients who died and those who did not. The effect of this shift is shown in Supplementary Figure 7.

Aalen-Johansen estimator

The Aalen-Johansen estimator is the standard non-parametric estimate of the cumulative incidence function for competing risk [2], also described as the matrix version of the Kaplan-Meier estimator.

Let the transition hazard from state $i \in S$ to state $j \in S, i \neq j$ be defined as:

$$\alpha_{i,j}(t) dt = P(X_{t+dt} = j \mid X_t = i)$$

and let $A(t)$ be the matrix of cumulative transition hazards:

$$A_{i,j}(t) = \int_0^t \alpha_{i,j}(u) du, \quad A_{i,i}(t) = -\sum_{j \neq i} A_{i,j}(t)$$
then, defining as \( P_{i,j}(s, t) = P(X_t = j \mid X_s = i) \), for \( i, j \in S, s \leq t \) the probability that an individual in state \( s \) at time \( i \) will be in state \( t \) at time \( j \), the Aalen-Johansen estimator is given by the matrix of transition probabilities:

\[
P(s, t) = \prod_{s, t}(1 + dA(u))
\]

The cumulative incidence function is a special case of the Aalen-Johansen estimate where:

\[
C_k(t) = \int_0^t \alpha_k(u)S(u)du
\]

\( \alpha_k \) is the incidence function for outcome \( k \), and \( S(u) \) is the overall survival curve.

**Fine-Grey proportional hazards regression**

The Fine-Grey model estimates the hazard of a competing event (so-termed the sub-distribution hazard) among the risk set of those yet to experience an event of the type of interest by time \( t \) [3]. The risk set therefore consists of both those who have yet to experience any event; and those who have yet to experience the event of interest (e.g. death) but have experienced a competing event (e.g. discharge).

The subdistribution hazard is defined as the instantaneous risk of dying (from a cause \( k \) given that the individual has not already died:

\[
h_k(t) = \lim_{\delta \to 0} \left\{ \frac{P(t \leq T < t + \delta t, K = k \mid T > t \text{ or } (T \leq t \text{ and } K \neq k))}{\delta t} \right\}
\]

Fine-Grey regression links the subdistribution hazard to the Aalen-Johansen cumulative incidence estimator through the relationship:

\[
h_k(t) = - \frac{d \log(1 - C_k(t))}{dt}
\]

Covariate effects on the sub-distribution hazard can then be interpreted as covariate effects on the cumulative incidence, or marginal probability, of a competing event (in this case hospitalised fatality).
Stratification

Stratified survival analyses enable appropriate adjustment for important confounders, by allowing the baseline hazard to vary across strata [4]. Stratification is a similar principle to matched designs, except rather than a 1:n ratio of cases to controls, as many (a:b for a and b both ≥ 1) cases and controls as possible within each strata are used.

For the regression on month of admission, stratification was by age group, region of residence and vaccination status, with regression adjustment (main effects) on sex, ethnicity, IMD quintile and CCI. For the regression on vaccination status, stratification was by age group, region of residence and month of hospital admission, with regression adjustment (main effects) similarly on sex, ethnicity, IMD quintile and CCI.

Consistency in model estimates

Supplementary figure 8 demonstrates the high degree of agreement between the Aalen-Johansen and Fine-Grey model estimates.

References for Supplementary Information

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Supplementary Information: Supplementary Figures

Supplementary figure 1: Hospitalised fatality risk and median length of stay by month of admission and gender. Estimated by Aalen-Johansen cumulative incidence estimator, for the competing outcomes of death and discharge. Error bars are 95% confidence intervals.
Supplementary figure 2: Hospitalised fatality risk and median length of stay by month of admission and age group. Estimated by Aalen-Johansen cumulative incidence estimator, for the competing outcomes of death and discharge. Error bars are 95% confidence intervals.
Supplementary figure 3: Hospitalised fatality risk and median length of stay by month of admission and ethnicity. Estimated by Aalen-Johansen cumulative incidence estimator, for the competing outcomes of death and discharge. Error bars are 95% confidence intervals.
Supplementary figure 4: Hospitalised fatality risk and median length of stay by month of admission and region of residence. Estimated by Aalen-Johansen cumulative incidence estimator, for the competing outcomes of death and discharge. Error bars are 95% confidence intervals.
Supplementary figure 5: Hospitalised fatality risk and median length of stay by month of admission and measure of hospital load. Estimated by Aalen-Johansen cumulative incidence estimator, for the competing outcomes of death and discharge. Error bars are 95% confidence intervals.
Supplementary figure 6: Hospitalised fatality sub-distribution hazard ratios for sex, ethnicity, IMD quintile, hospital load and CCI, stratified by age group, region of residence and vaccination status, with regression adjustment (main effects) on month of admission (shown in Figure 2).
Supplementary figure 7: Hospitalised fatality sub-distribution hazard ratio by month of hospital admission, stratified by age group, region of residence and vaccination status, with regression adjustment (main effects) on sex, ethnicity, IMD quintile, hospital load, and CCI. Reference group: June 2020.

Supplementary figure 8: Aalen-Johansen and Fine-Grey cumulative fatality estimates for first 60 days following hospital admission for selected months. Figure shows high degree of agreement between the two models.
**Supplementary Information: Supplementary Tables**

All tables in Supplementary Excel workbook.

Supplementary table 1: Hospital outcomes according to patient characteristic.

Supplementary table 2: Hospitalised fatality risk and length of stay in hospital by month of hospital admission and sex.

Supplementary table 3: Hospitalised fatality risk and length of stay in hospital by month of hospital admission and age group. Estimates are replaced with a dash (-) where insufficient information was available.

Supplementary table 4: Hospitalised fatality risk and length of stay in hospital by month of hospital admission and ethnicity.

Supplementary table 5: Hospitalised fatality risk and length of stay in hospital by month of hospital admission and region of residence.

Supplementary table 6: Hospitalised fatality risk and length of stay in hospital by month of hospital admission and measure of hospital load. Estimates are replaced with a dash (-) where insufficient information was available.

Supplementary table 7: Hospitalised fatality sub-distribution hazard ratio by patient characteristic, stratified by age group, PHE centre of residence and month of hospitalisation, with regression adjustment (main effects) on sex, ethnicity, IMD quintile, CCI and hospital load.