International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC)

A global federation of clinical research networks, providing a proficient, coordinated, and agile research response to outbreak-prone infectious diseases

COVID-19 Report: 02 April 2020

Summary

The results in this report have been produced using data from the ISARIC COVID-19 database. For information, or to contribute to the collaboration, please contact ncov@isaric.org

Up to the date of this report, data have been entered for **5533** individuals from **216** sites across **25** countries.

We thank all of the data contributors for collecting standardised data during these extraordinary times. We plan to issue this report of aggregate data weekly for the duration of the SARS-CoV-2/COVID-19 pandemic.

Please note the following caveats. Information is incomplete for the many patients who are still being treated. Note that we received more cases of severely ill individuals than people with relatively less severe illness; outcomes from these data, such as the proportion dying, must therefore not be used to infer outcomes for the entire population of people who might become infected. Many of the included cases are from the United Kingdom. Additional caveats are provided in the in the 'Caveats' section below.

The analysis detailed in this report only includes individuals for whom data collection commenced on or before 19 March 2020. We have applied a 14-day rule to focus analysis on individuals who are more likely to have a recorded outcome. By excluding patients enrolled during the last 14 days, we aim to reduce the number of incomplete data records and thus improve the generalisability of the results and the accuracy of the outcomes. However, this limits our analysis to this restricted cohort despite the much larger volumes of data held in the database.

The cohort comprises **1123** individuals, including 621 males and 413 females – sex is unreported for 89 cases.

The median age (calculated based on reported age) is 68 years. The minimum and maximum observed ages are 0 and 97 years respectively.

Outcomes have been recorded for 519 patients, consisting of 346 recoveries and 173 deaths. Follow-up is ongoing for 571 patients.

The observed mean duration for the number of days from hospital admission to outcome (death or discharge) is 6.5 days, with a standard deviation (SD) of 5.7. These estimates are based on all cases which have complete records on length of hospital stay (N = 550).

The observed mean number of days from (first) symptom onset to hospital admission is 6.9 (SD: 5.9).

The symptoms on admission represent the policy for hospital admission and containment at that time plus, whatever the case definition was. As time passes for most countries these will change. The four most common symptoms at admission were fatigue and malaise alongside cough, history of fever and shortness of breath.

251 patients were admitted at some point of their illness into intensive care unit (ICU). The observed mean duration (in days) from hospital admission to ICU is 2.9 (SD: 4.5) – estimated from records on cases with complete date records on hospital admission and ICU entry (N = 177).

The duration of stay in the ICU has a mean of 6.9 days (SD: 4.7 days) – estimated on only those cases with complete records for ICU duration or ICU start/end dates (N = 67). Of these 251 patients who were admitted into ICU, 51 died, 157 are still in hospital and 26 have recovered and been discharged. Outcome records are unavailable for 17 cases

107 patients received non-invasive mechanical ventilation (NIV). The mean duration from admission to receiving NIV is 4 days (SD: 7 days) – estimated from records on cases with complete records on dates of hospital admission and NIV onset (N = 96).

The mean duration for NIV is 1.3 days (SD: 1.6 days) – estimated based on only those cases which have complete NIV duration records (N = 46).

154 patients received invasive mechanical ventilation (IMV). The mean duration from admission to receiving IMV is 2.4 days (SD: 3.3 days) – estimated from records on cases with complete records on dates of hospital admission and IMV onset (N = 148).

The mean and SD for the duration of IMV – estimated based on all 33 cases with complete records on IMV stays – is 8.4 days and 4.9 days respectively.

Of patients with complete details of treatments received, 56.9% received an antibiotic and 25.7% received antivirals. These treatment categories are not mutually exclusive since some patients received multiple treatments. 43.0% of patients received some degree of oxygen supplementation: of these, 11.5% received NIV and 29.5% IMV.

Of patients admitted into ICU with complete details of treatments, 91.9% received antibiotics and 43.2% antivirals; and 82.9% received some degree of oxygen supplementation, of which 20.7% was NIV and 62.1% IMV.

Patient Characteristics

Figure 1: Age and sex distribution of patients. Bar fills are outcome (death/discharge/ongoing care) at the time of report.

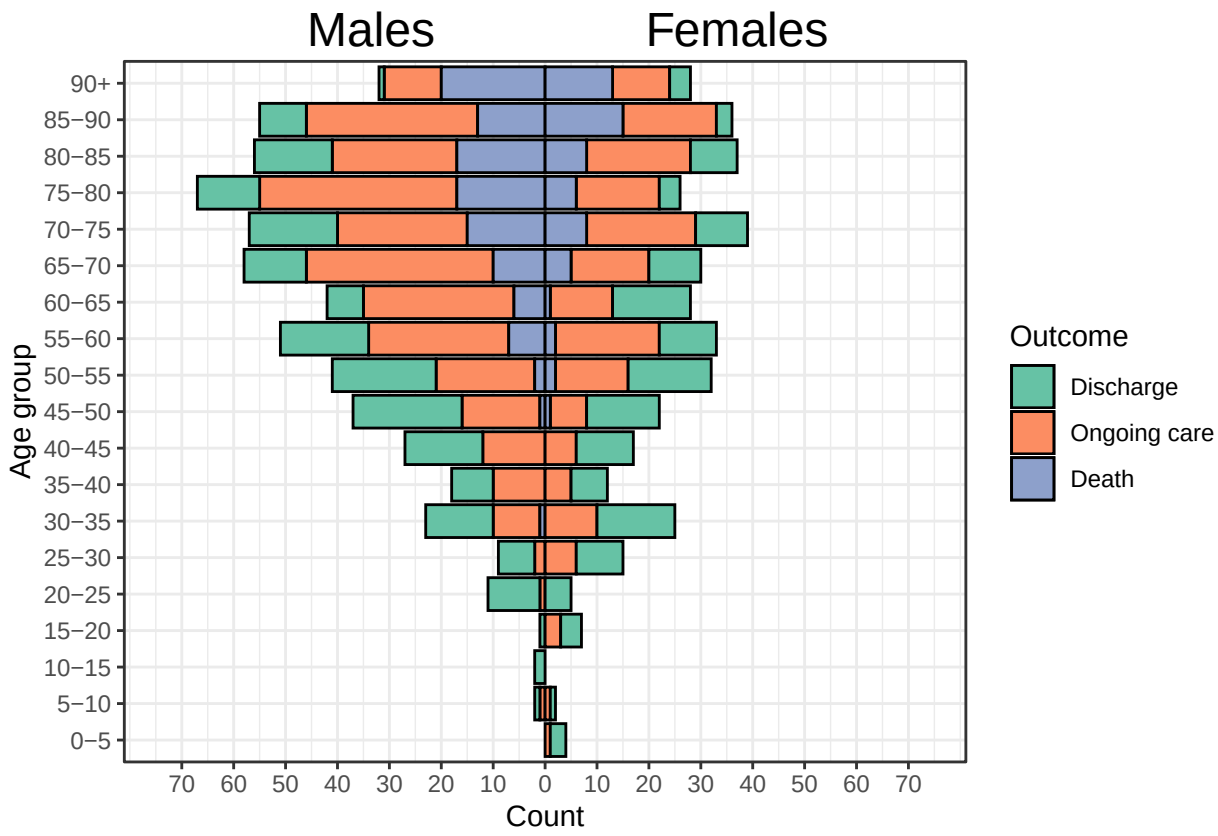


Figure 2: Top: Frequency of symptoms seen at admission amongst COVID-19 patients. Bottom: The distribution of combinations of the four most common symptoms, amongst all patients for whom this data was recorded. Filled and empty circles below the x-axis indicate the presence or absence of each comorbidity. The "Any other" category contains all remaining symptoms in the top plot.

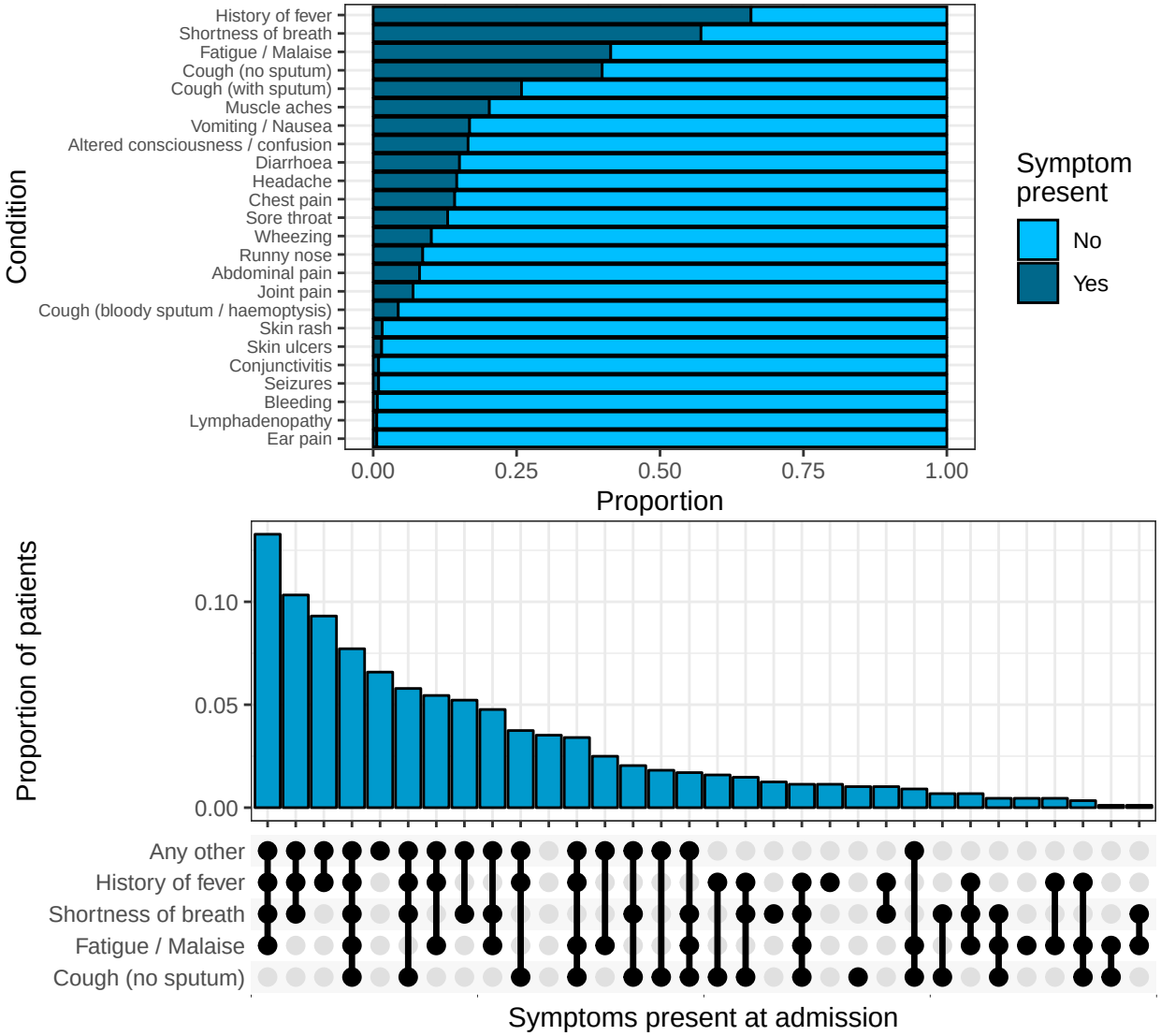
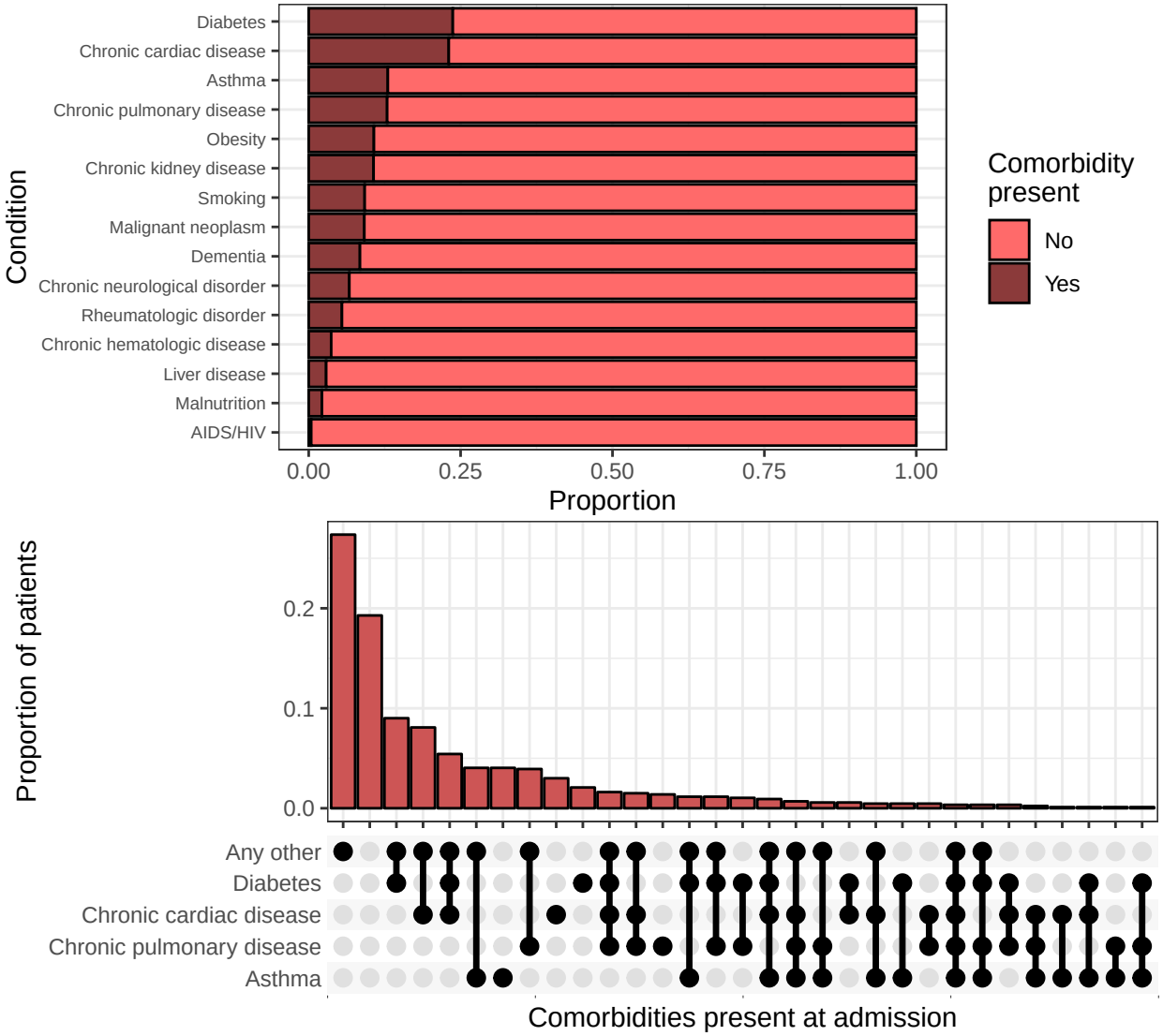


Figure 3: Top: Frequency of comorbidities seen at admission amongst COVID-19 patients. Bottom: The distribution of combinations of the four most common comorbidities, amongst all patients for whom this data was recorded. Filled and empty circles below the x-axis indicate the presence or absence of each comorbidity. The "Any other" category contains all remaining comorbidities in the top plot, and any other comorbidities recorded as free text by clinical staff.



Hospital stays and outcomes

Figure 4: Distribution of length of hospital stay, according to sex. This only includes cases with reported outcomes. The coloured areas indicate the kernel probability density of the observed data and the box plots show the mean and interquartile range of the variable of interest.

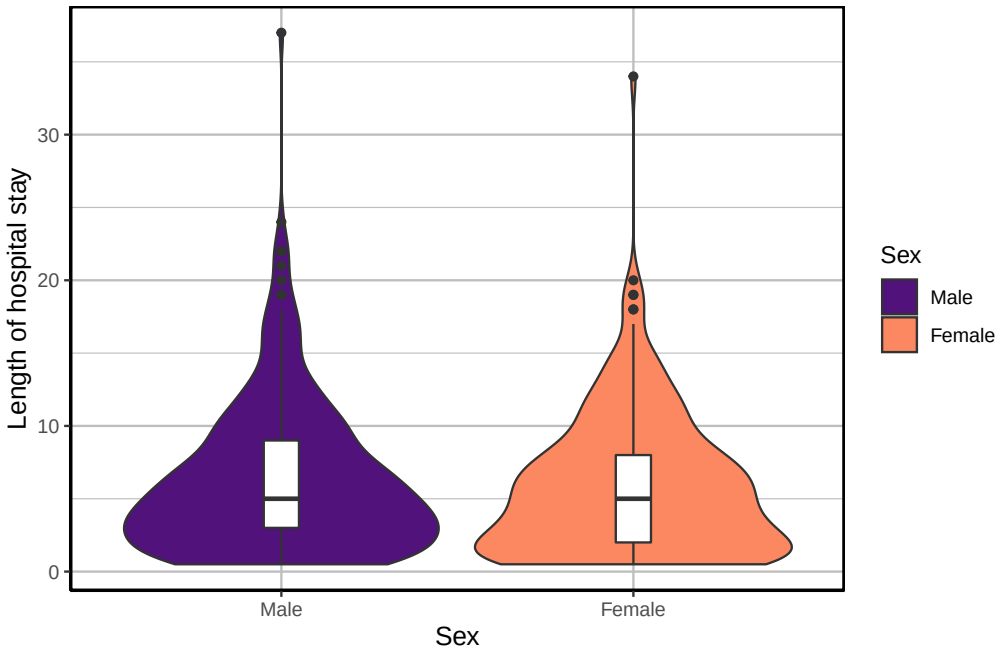


Figure 5: Distribution of length of hospital stay, according to patient age group. This only includes cases with reported outcomes. The coloured areas indicate the kernel probability density of the observed data and the box plots show the mean and interquartile range of the variable of interest.

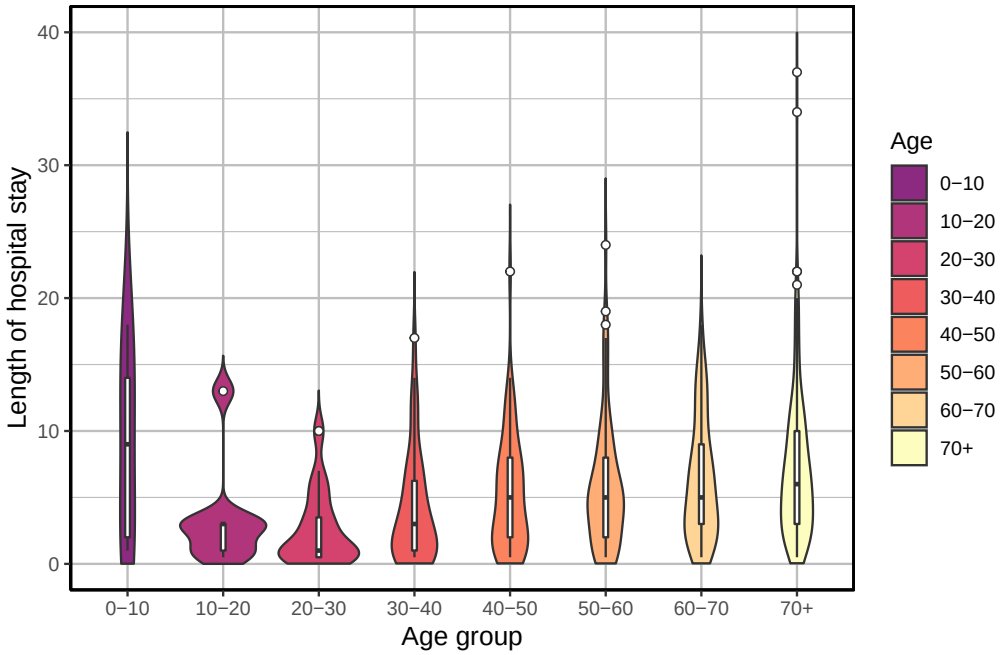


Figure 6: The distribution of patient status by number days after admission. Patients with "Unknown" status have left the site at the time of report but have unknown outcomes due to missing data. Patients with "Ongoing care" are still in site at the time of analysis. The black line marks the end of 14 days; due to the cut-off, only a small number of patients appear in the "ongoing care" category left of this line.

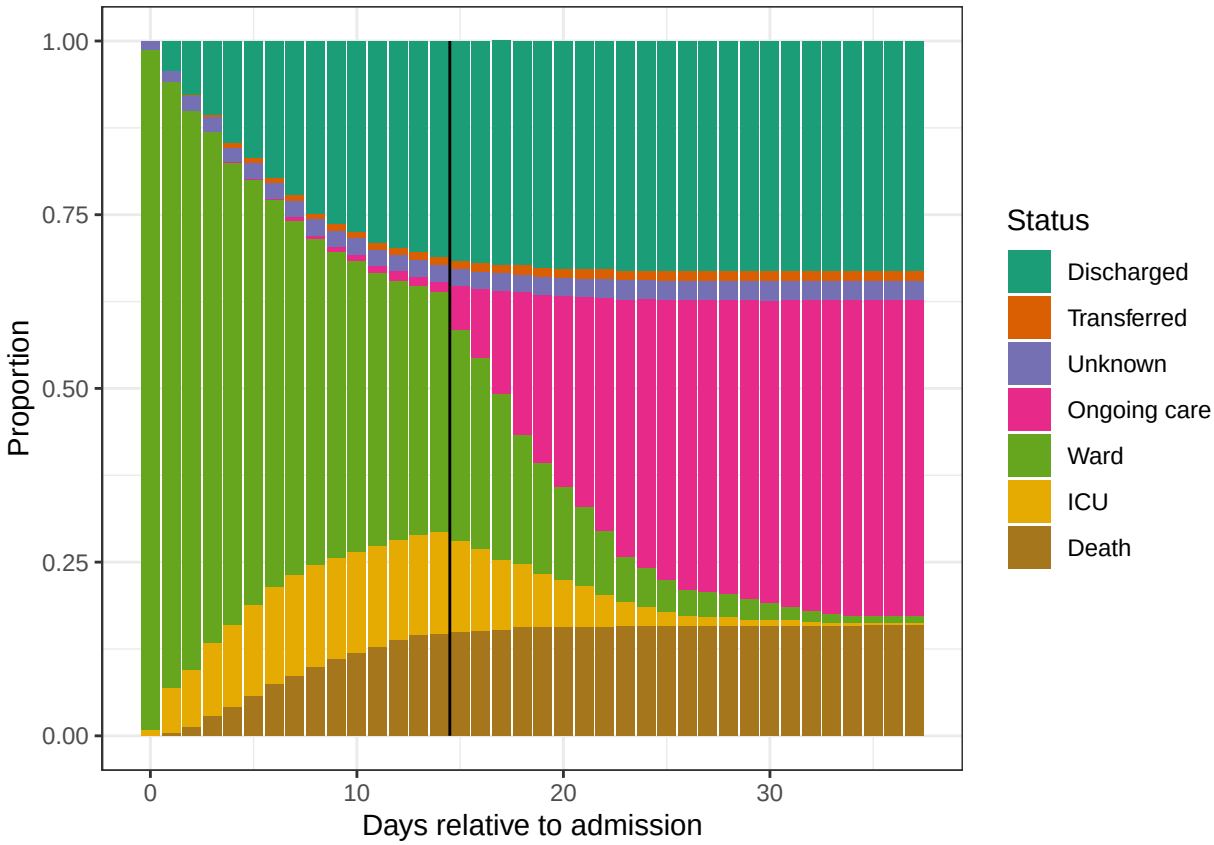
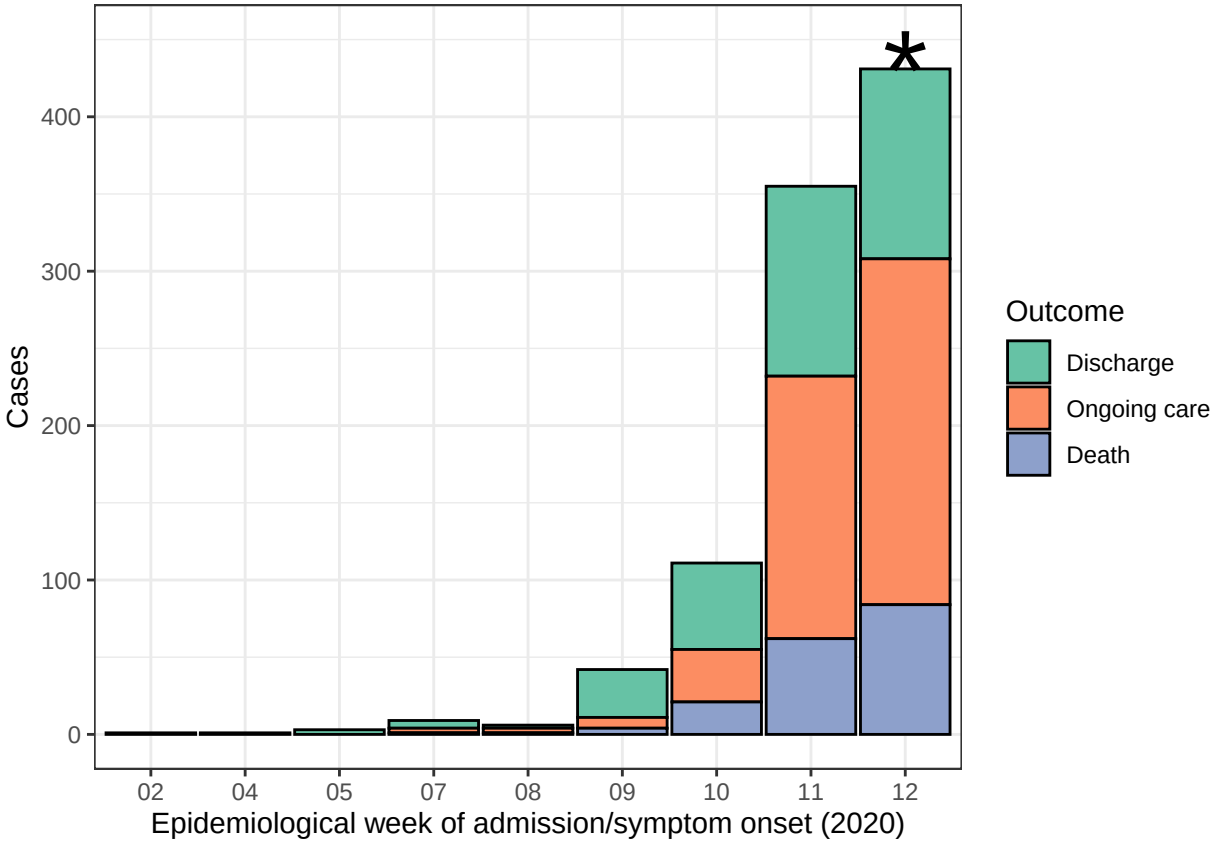


Figure 7: Patient numbers and outcomes by epidemiological week (of 2020) of admission (or, for patients infected in hospital, of symptom onset). The rightmost bar, marked with an asterisk, represents an incomplete week (due to the 14-day cutoff).



Treatment

Figure 8: Treatments used. This only includes patients where this information was recorded.

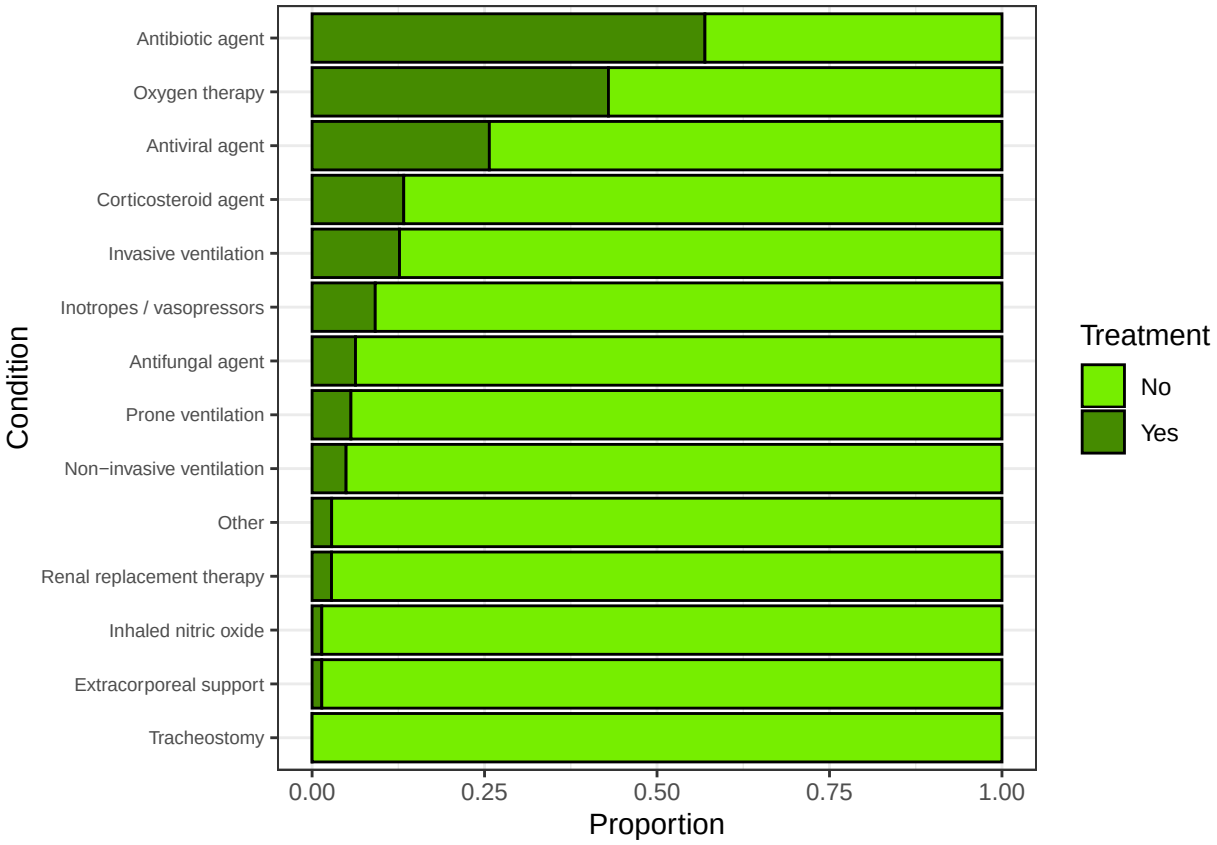
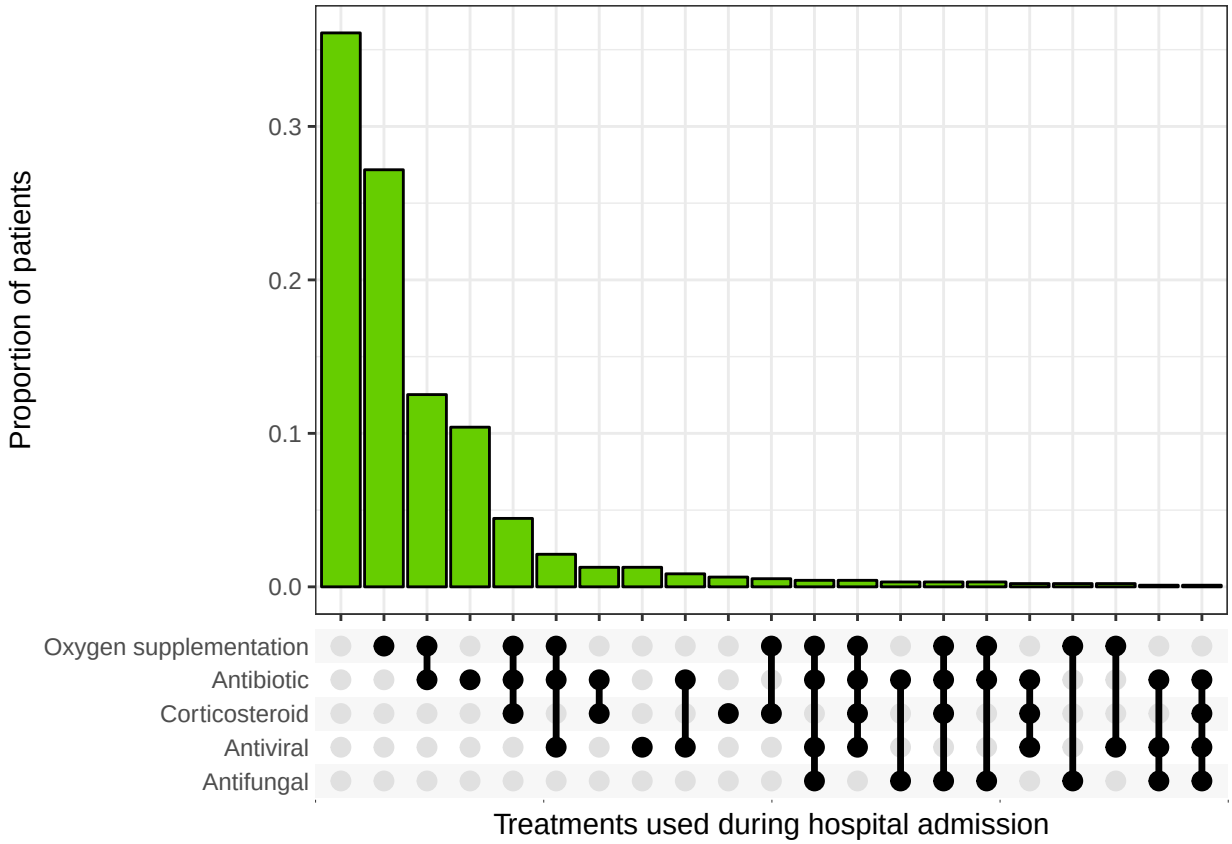


Figure 9: The distribution of combinations of antimicrobial treatments and steroids administered during hospital stay, across all patients with completed hospital stay and recorded treatment data. Filled and empty circles below the x-axis indicate treatments that were and were not administered.



Intensive Care Unit Treatments

These figures include only the ICU patients with complete details of treatments.

Figure 10: Treatments used.

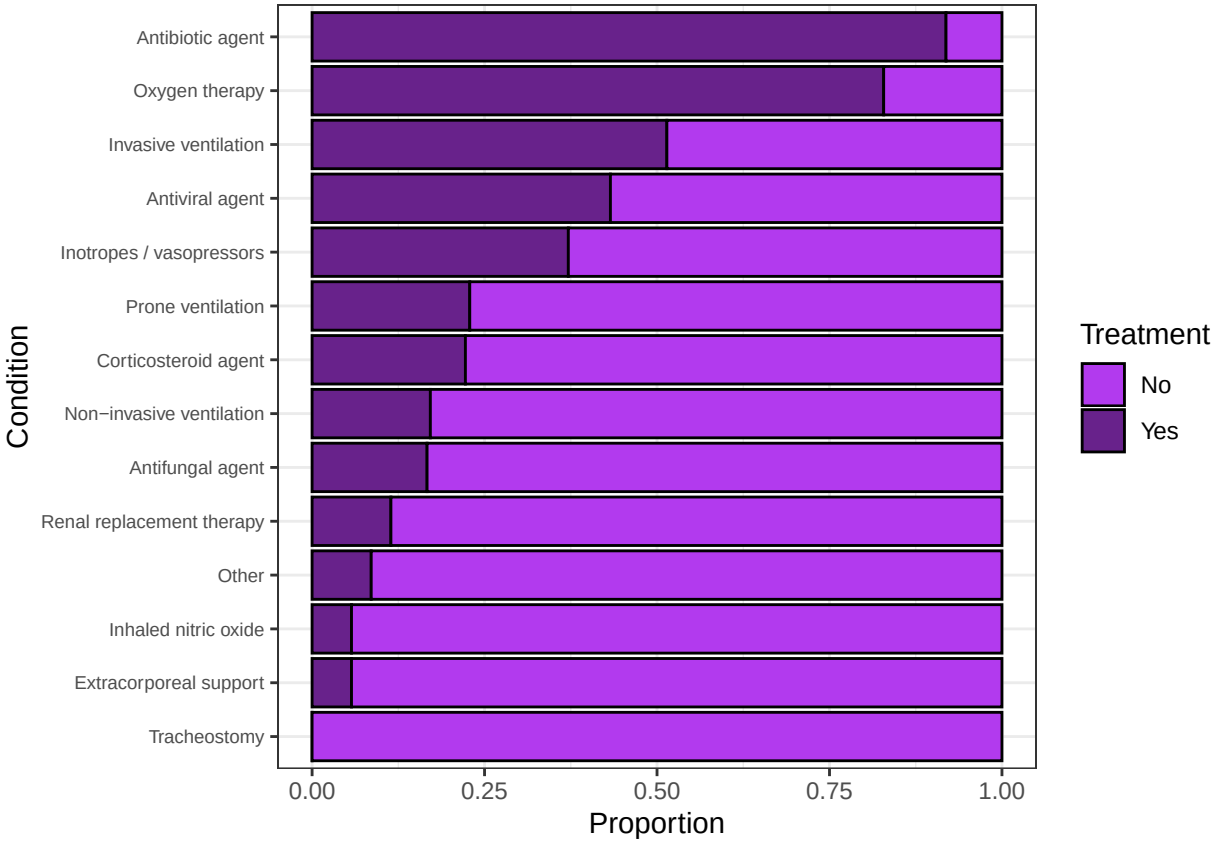


Figure 11: The distribution of combinations of treatments administered during ICU stay. Filled and empty circles below the x-axis indicate treatments that were and were not administered respectively.

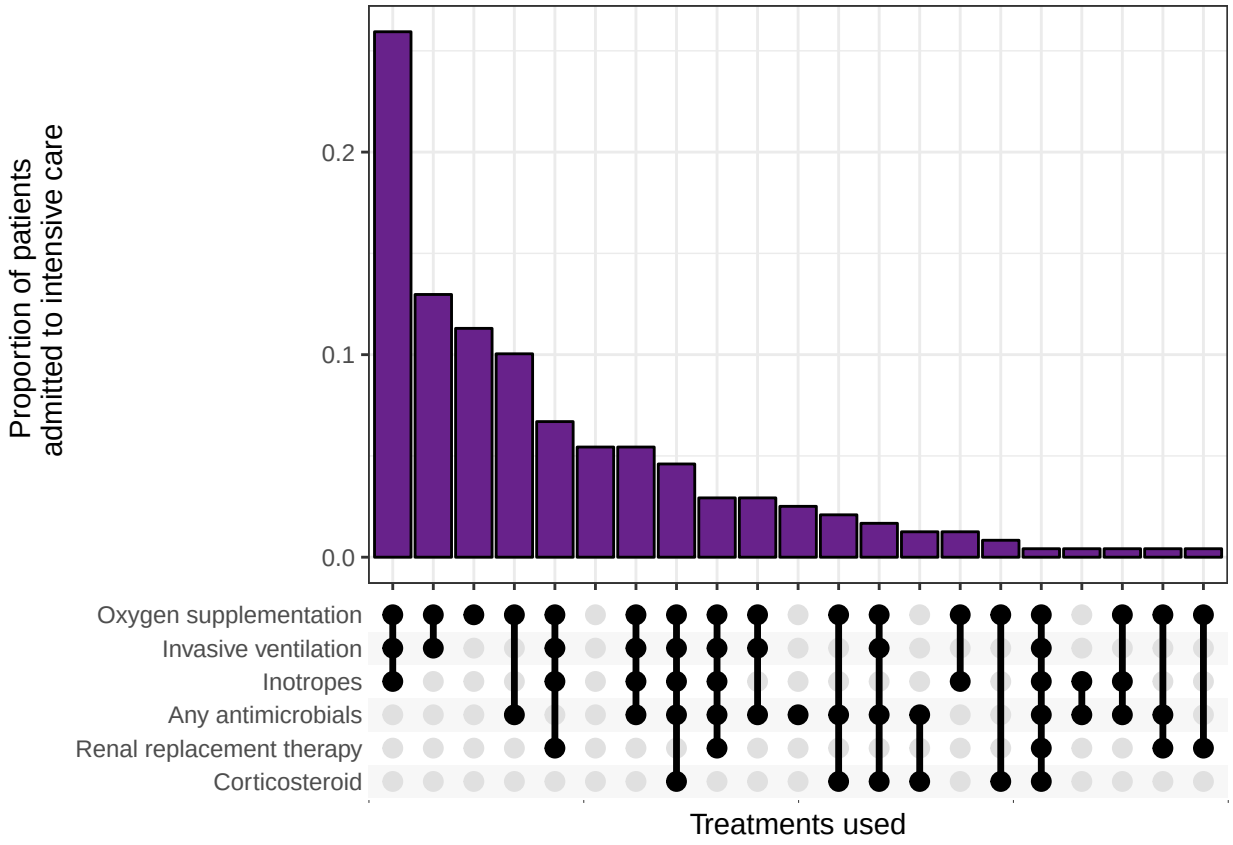
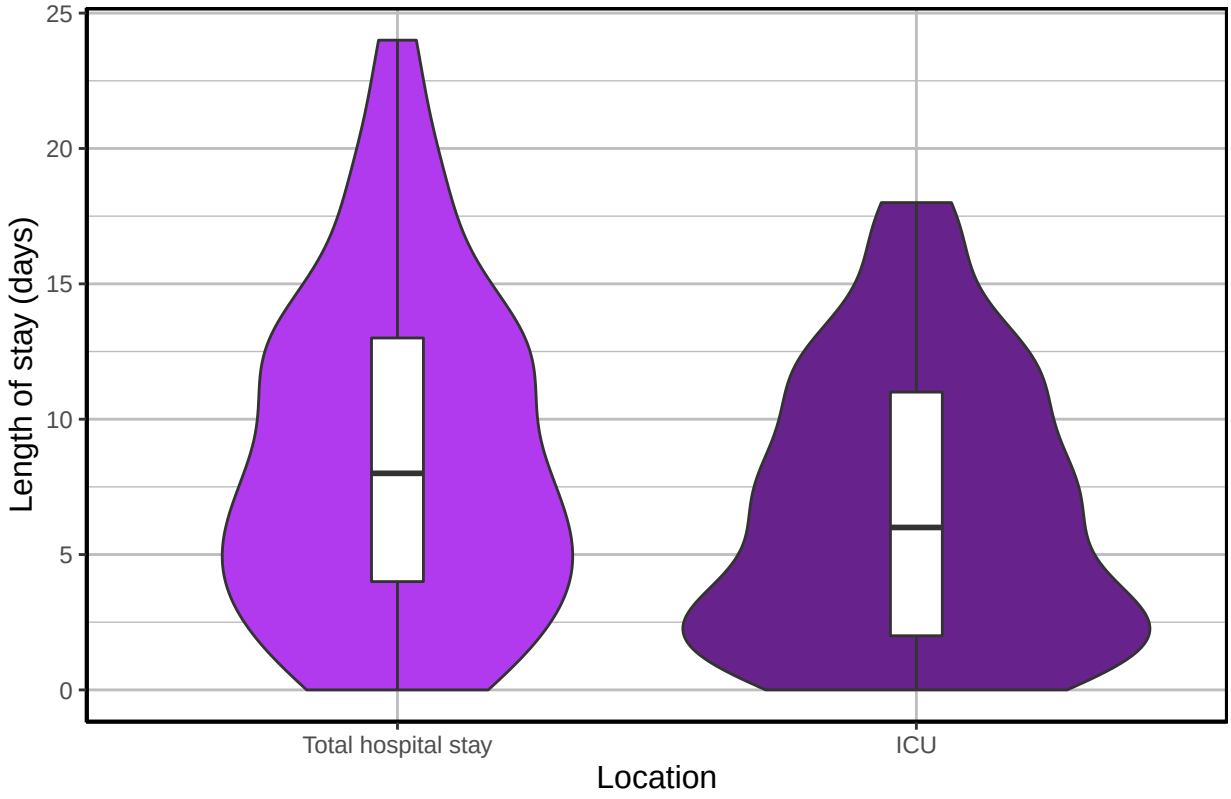


Figure 12 Distribution of lengths of stay for patients who were admitted to ICU: total length of stay for this group and length of stay within intensive care. This only includes cases with reported completed stays. The coloured areas indicate the kernel probability density of the observed data and the box plots show the mean and interquartile range of the variable of interest.



Statistical Analysis

Figure 13: Distribution of time from symptom onset to admission. The blue curve is the Gamma distribution fit to the data. The black dashed line indicates the position of the expected mean. Expected estimates, accounting for unobserved outcomes, are provided in the summary tables at the end of this report.

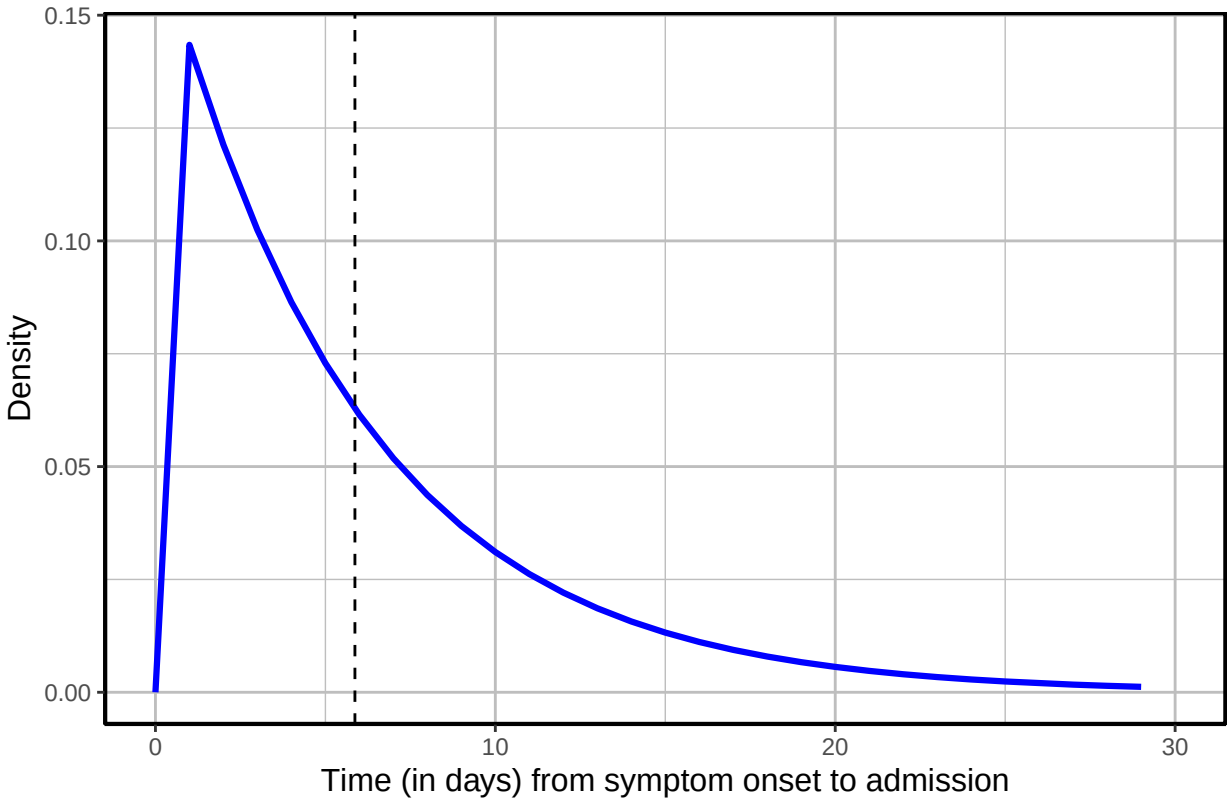


Figure 14: Distribution of time from admission to an outcome - either death or recovery (discharge). The blue curve is the Gamma distribution fit to the data. The black dashed line indicated the position of the expected mean.

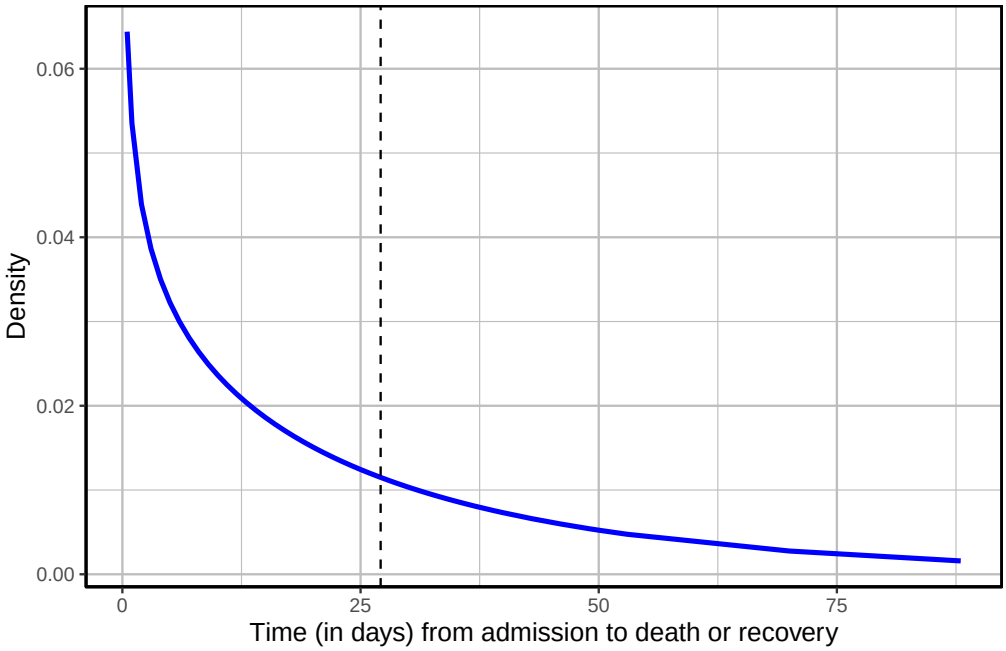
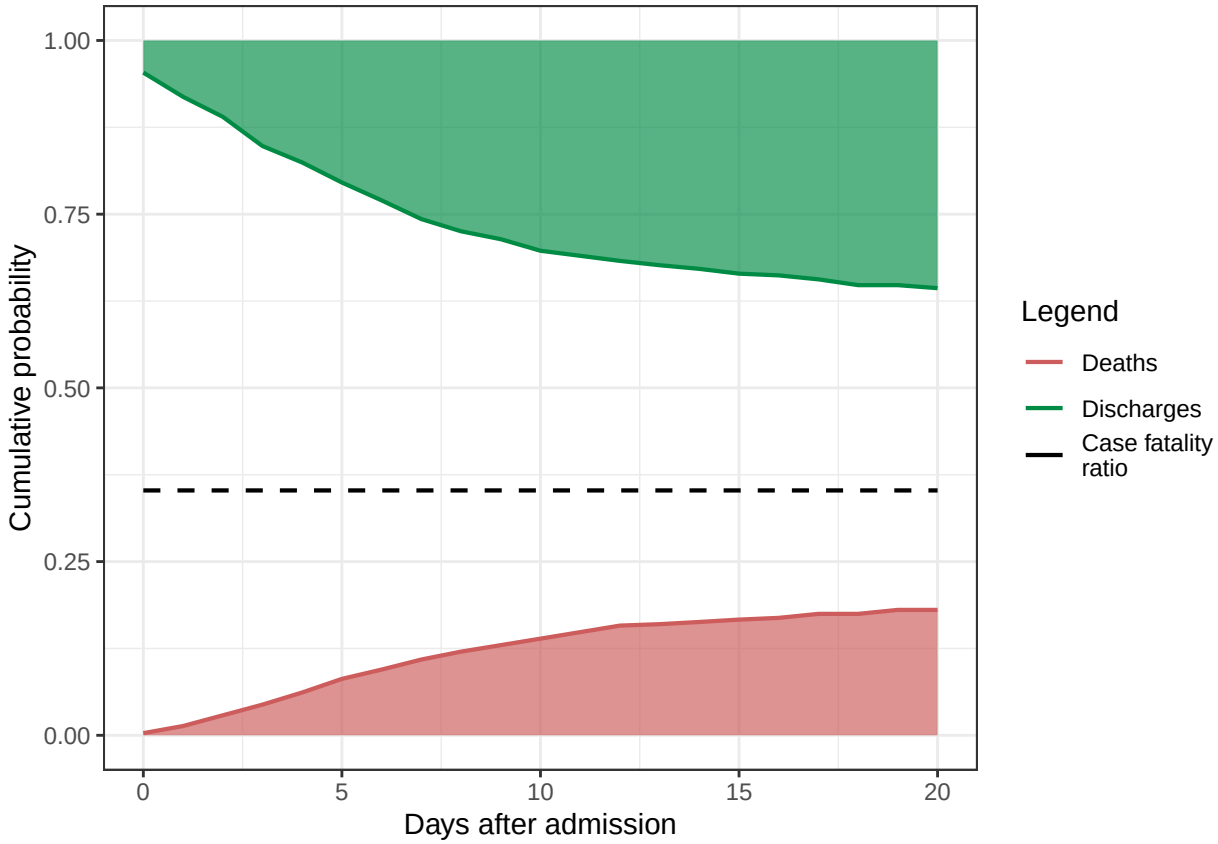

0.06
0.04
0.02
0.00
Density
0
25
50
75
Time (in days) from admission to death or recovery

Figure 15: Nonparametric probabilities of death (red curve) and recovery (green curve) over time. The black line indicates the case fatality ratio (black). The method used here considers all cases, irrespective of whether an outcome has been observed. For a completed epidemic, the curves for death and recovery meet. Estimates were derived using a nonparametric Kaplan-Meier–based method proposed by Ghani *et al.* (2005).



Country Comparisons

Figure 16: Number of sites per country.

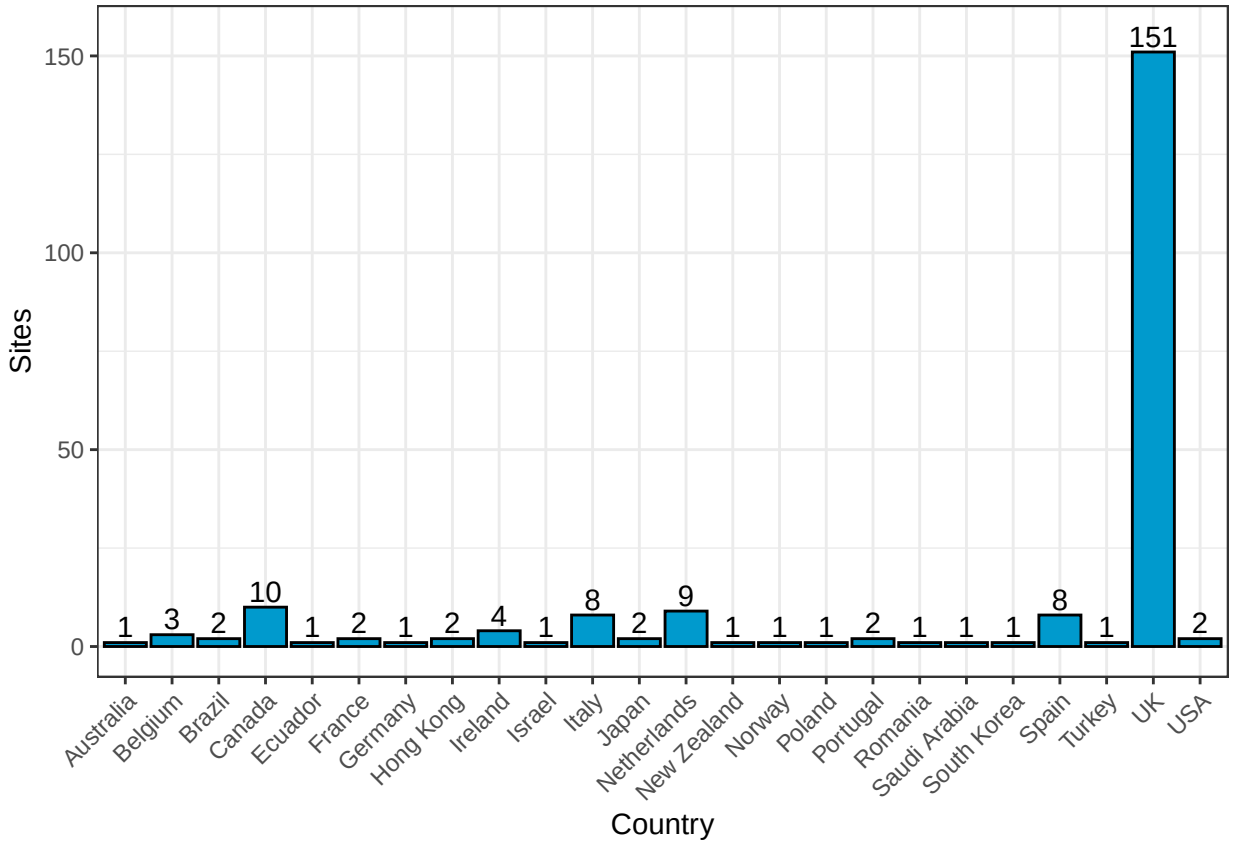
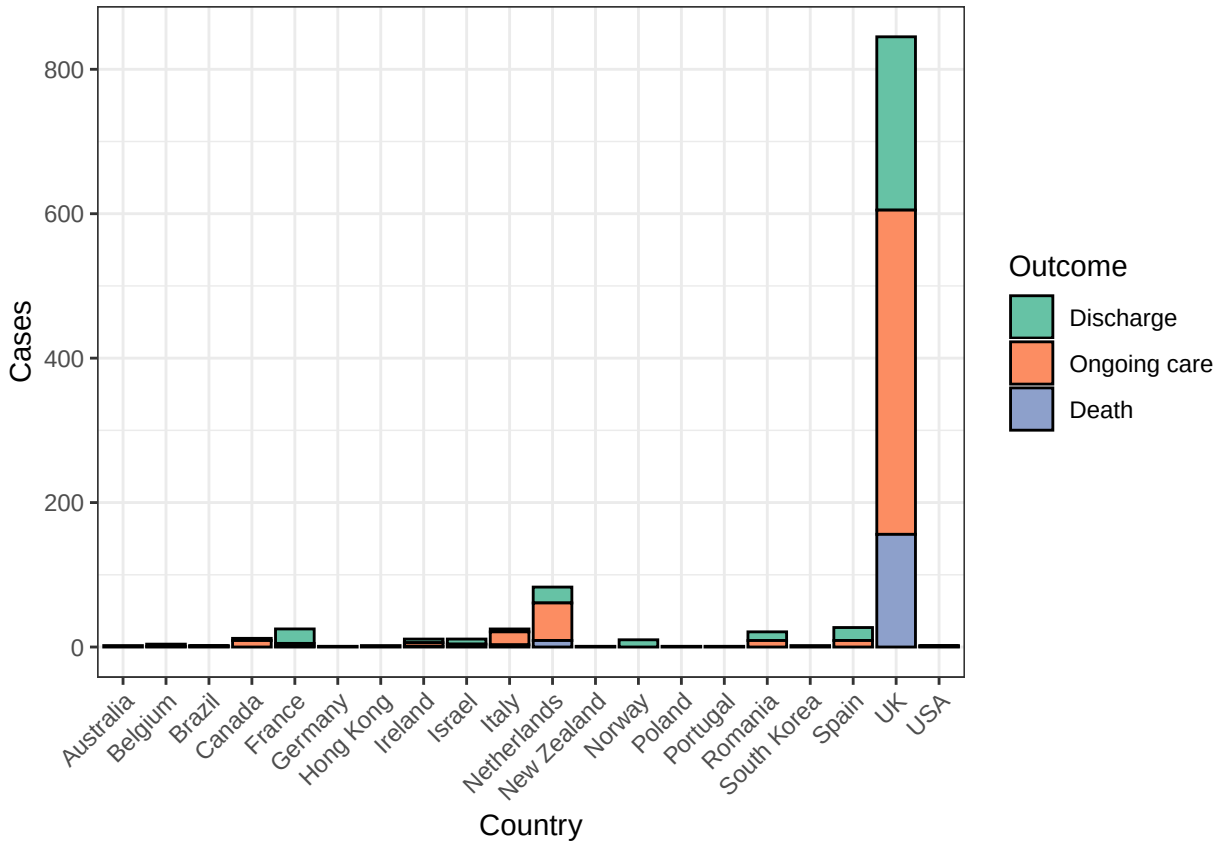
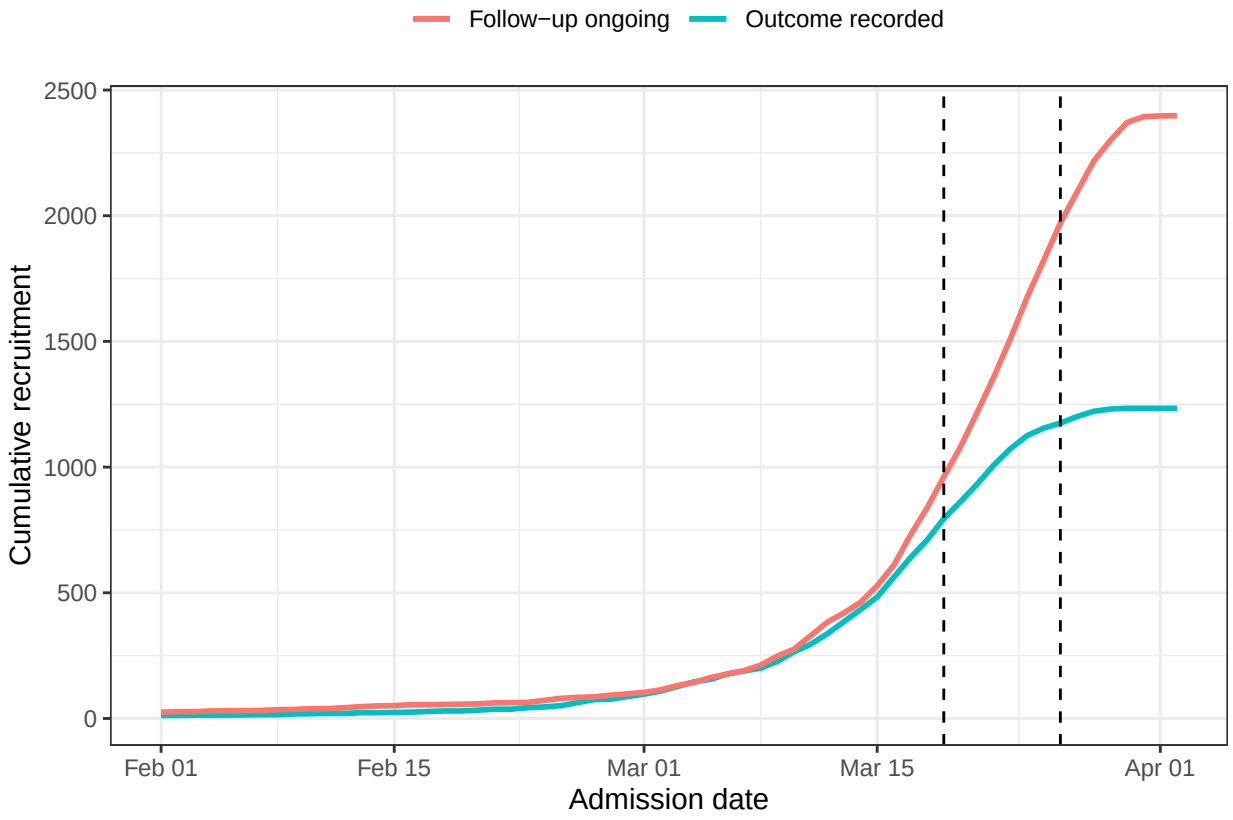


Figure 17: Distribution of patients by country and outcome


800
600
400
200
0
Cases
Australia
Belgium
Brazil
Canada
France
Germany
Hong Kong
Ireland
Israel
Italy
Netherlands
New Zealand
Norway
Poland
Portugal
Romania
South Korea
Spain
UK
USA
Country
Outcome
Discharge
Ongoing care
Death

Recruitment

Figure 18: Cumulative recruitment of participants, separated by whether follow-up is ongoing or an outcome has been recorded. The first dashed black line indicates the exclusion date for this report: patients recruited after this date have not been included. The second black line is the exclusion date for next week's report.



Background

In response to the emergence of novel coronavirus (COVID-19), ISARIC launched a portfolio of resources to accelerate outbreak research and response. All data collection tools are designed to address the most critical public health questions, have undergone extensive review by international clinical experts, and are free for all to use. Resources are available on the ISARIC website.

The ISARIC-WHO COVID-19 Case Record Form (CRF) enables the collection of standardised clinical data to inform patient management and the public health response. These forms should be used to collect data on suspected or confirmed cases of COVID-19. The CRF is available in multiple languages and is now in use across dozens of countries and research consortia, who are contributing data to these reports.

To support the rapid implementation of standardised data collection and reporting, ISARIC hosts a data platform that includes an electronic data capture system, a secure repository and an analytic framework. Data are entered to a web-based REDCap data management system, securely stored, and used to inform regular reports as above. Data contributors are invited to input on the methods and contents of the reports, and are provided with the R code to execute analysis on their own data in the platform. For more information, visit the ISARIC website.

Following the launch of this these open resources, ISARIC received a massive response from the health and research communities. ISARIC supports researchers to retain control of the data and samples they collect. All decisions regarding data use are made by the institutions that enter the data. We keep our contributors informed of any plans and welcome their input to ensure that we are generating the best science and promoting the interests of your patients, your institutions and your public health authorities. Feedback and suggestions are welcome at ncov@isaric.org.

Methods

Patient details were submitted electronically by participating sites to the ISARIC database. Relevant background and presenting symptoms were recorded on the day of study recruitment. Daily follow-up was then completed until recovery or death. A final form was completed with details of treatments received and outcomes. All categories that represent fewer than five individuals have been suppressed to avoid the potential for identification of participants.

Graphs have been used to represent the age distribution of patience by sex and status (dead, recovered & still in hospital), the prevalence of individual symptoms - and combinations of them - on admission, the prevalence of individual comorbidities - and combinations of them - on admission, the length of hospital stay by sex and age group and the distribution of patient statuses by time since admission. In addition, the number of cases recruited by country and site, as well as the case count by status, has been represented.

Using a non-parametric Kaplan-Meier-based method (Ghani *et al.*, 2005), the case- fatality ratio (CFR) was estimated, as well as probabilities for death and recovery. This method estimates the CFR with the formula $a/(a+b)$, where a and b are the values of the cumulative incidence function for deaths and recoveries respectively, estimated at the last observed time point. In a competing risk context (i.e. where there are multiple endpoints), the cumulative incidence function for an endpoint is equal to the product of the hazard function for that endpoint and the survival function assuming a composite endpoint. It is worth noting that this method assumes that future deaths and recoveries will occur with the same relative probabilities as have been observed so far. Binomial confidence intervals for the CFR were obtained by a normal approximation (See Ghani *et al.*, (2005)).

A survival analysis was performed to test whether significant differences exist in the length of hospital stay by sex.

To obtain estimates for the distributions of time from symptom onset to hospital admission and the time from admission to outcome (death or recovery), Gamma distributions were fitted to the observed data, accounting

for unobserved outcomes. Parameters were estimated by a maximum likelihood procedure and confidence intervals for the means and variances were obtained by bootstrap.

All analysis were performed using the R statistical software (R Core Team, 2019).

Caveats

Patient data are collected and uploaded from start of admission, however a complete patient data set is not available until the episode of care is complete. This causes a predictable lag in available data influenced by the duration of admission which is greatest for the sickest patients, and accentuated during the up-phase of the outbreak.

Summary Tables

Table 1: Patient Characteristics

Description	Value
Size of cohort	1123
By sex	
Male	621
Female	413
Unknown	89
By Status	
Dead	173
Recovered (discharged alive)	346
Still in hospital	571
By age group	
0-10	8
10-20	11
20-30	42
30-40	82
40-50	105
50-60	165
60-70	162
70+	447
Unknown	101

Table 2: Prevalence of Symptoms, Comorbidities and Treatments

Symptoms	**Present**	**Absent**	**Unknown**
Abdominal pain	77	694	352
Bleeding	7	758	358
Chest pain	135	631	357
Confusion	157	625	341
Conjuctivitis	9	669	445

Symptoms	Present	Absent	Unknown
Cough	520	225	378
Diarrhoea	143	636	344
Ear pain	6	630	487
Fatigue	393	339	391
Fever	631	255	237
Headache	138	533	452
Joint pain	66	576	481
Lymph	6	653	464
Myalgia	192	483	448
Rash	15	671	437
Runny nose	82	583	458
Seizures	9	748	366
Shortness of breath	548	411	164
Comorbidities			
AIDS/HIV	4	894	225
Asthma	127	788	208
Chronic cardiac disease	225	695	203
Chronic haematologic disease	36	872	215
Chronic neurological disorder	65	841	217
Chronic pulmonary disease	126	792	205
Dementia	82	830	211
Diabetes	231	742	150
Liver disease	28	881	214
Malignant neoplasm	89	819	215
Malnutrition	21	851	251
Obesity	104	758	261
Chronic kidney disease	104	810	209
Rheumatologic disorder	53	849	221
Smoking	68	473	582
Other risk factors	286	558	279
Treatment			
Antibiotic agent	82	62	979
Antifungal agent	9	134	980
Antiviral agent	37	107	979
Corticosteroid agent	19	124	980
Extracorporeal support	2	139	982
Inhaled nitric oxide	2	139	982
Inotropes / vasopressors	13	128	982
Invasive ventilation	154	786	183
Non-invasive ventilation	107	825	191
Oxygen therapy	413	515	195
Prone ventilation	8	133	982
Renal replacement therapy	4	137	982
Tracheostomy inserted	0	141	982
Other	4	135	984
Extracorporeal membrane oxygenation (ECMO)	10	515	190

Table 3: Key time variables.

Unlike the observed mean, the estimation process of the **expected mean** accounts for all cases, irrespective

of whether an outcome has been observed. The expected mean is 'NA' for those variables for which parameter estimation could not be performed, due to the high proportion of unobserved end dates.

Time (in days)	Observed mean	Observed SD	Observed median	Expected mean (95% CI)
Length of hospital stay	6.5	5.7	5	27.1 (25.5, 29.3)
Symptom onset to admission	6.9	5.9	4	5.9 (5.5, 6.2)
Admission to ICU entry	2.9	4.5	1	2.9 (2.7, 3.1)
Duration of ICU	6.9	4.7	6	NA
Admission to IMV	2.4	3.3	1	2.4 (2.2, 2.5)
Duration of IMV	8.4	4.9	9	NA
Admission to NIV	4	7	1	4 (3.8, 4.4)
Duration of NIV	1.3	1.6	0.5	59.5 (55.9, 69.2)

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- Mark Pritchard
- Clark Russell
- Calum Semple
- Louise Sigfrid

- All those who contributed the data, which enabled this report.

References

1. A. C. Ghani, C. A. Donnelly, D. R. Cox, J. T. Griffin, C. Fraser, T. H. Lam, L. M. Ho, W. S. Chan, R. M. Anderson, A. J. Hedley, G. M. Leung (2005). Methods for Estimating the Case Fatality Ratio for a Novel, Emerging Infectious Disease, *American Journal of Epidemiology*, 162(5), 479 - 486. doi:10.1093/aje/kwi230.
2. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.