

COVID-19

Characteristics and outcomes of an international cohort of 600 000 hospitalized patients with COVID-19

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Abstract

Background: We describe demographic features, treatments and clinical outcomes in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) COVID-19 cohort, one of the world's largest international, standardized data sets concerning hospitalized patients.

Methods: The data set analysed includes COVID-19 patients hospitalized between January 2020 and January 2022 in 52 countries. We investigated how symptoms on admission, co-morbidities, risk factors and treatments varied by age, sex and other characteristics. We used Cox regression models to investigate associations between demographics, symptoms, co-morbidities and other factors with risk of death, admission to an intensive care unit (ICU) and invasive mechanical ventilation (IMV).

Results: Data were available for 689 572 patients with laboratory-confirmed (91.1%) or clinically diagnosed (8.9%) SARS-CoV-2 infection from 52 countries. Age [adjusted hazard ratio per 10 years 1.49 (95% CI 1.48, 1.49)] and male sex [1.23 (1.21, 1.24)] were associated with a higher risk of death. Rates of admission to an ICU and use of IMV increased with age up to age 60 years then dropped. Symptoms, co-morbidities and treatments varied by age and had varied associations with clinical outcomes. The case-fatality ratio varied by country partly due to differences in the clinical characteristics of recruited patients and was on average 21.5%.

Conclusions: Age was the strongest determinant of risk of death, with a ~30-fold difference between the oldest and youngest groups; each of the co-morbidities included was

associated with up to an almost 2-fold increase in risk. Smoking and obesity were also associated with a higher risk of death. The size of our international database and the standardized data collection method make this study a comprehensive international description of COVID-19 clinical features. Our findings may inform strategies that involve prioritization of patients hospitalized with COVID-19 who have a higher risk of death.

Key words: COVID-19, SARS-CoV-2, cohort study, risk of death, co-morbidities, symptoms, treatments

Key Messages

- Several studies have investigated the risks of severe illness and death due to infection with SARS-CoV-2, providing estimates of the case-fatality ratio in different settings and risk factors for these outcomes, but these tended to be national studies conducted over a short time period.
- We show how clinical presentation and risks of death and admission to an intensive care unit vary with patient characteristics based on a very large number of patient records from 52 countries, collected using standardized data collection tools.
- Age was the strongest determinant of risk; pre-existing co-morbidities and male sex were also associated with higher risk of death.
- Smoking and obesity are modifiable risk factors that are associated with a higher risk of death.
- Our findings may inform strategies that involve prioritization of patients, globally, who have a higher risk of adverse outcomes if hospitalized with COVID-19, as well as prevention strategies.

Introduction

To respond to COVID-19, policymakers and clinicians need robust data to drive the decision-making processes that save or cost lives. Observational cohort data describing clinical characteristics and the likelihood of severe outcomes can guide health policy development, produce research hypotheses for clinical trials and improve clinical guidelines for patient care.¹ Across the world, multiple cohort studies have described the clinical impact of the COVID-19 pandemic²⁻⁸ but heterogeneity in study features makes combining and comparing the findings challenging.

The Clinical Characterisation Protocol (CCP) developed by the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) and the World Health Organization (WHO)⁹ has helped researchers across the world to collect and analyse clinical data.¹⁰ Thanks to this international co-operation, it has been possible to produce a truly global cohort study using standardized clinical data. The growing data set has been analysed regularly, with results shared via reports,¹¹ and the data set has been used to address specific research questions.^{12,13}

We present data from an international cohort of almost 700 000 patients from 1380 sites across 52 countries. We summarize the demographic features and clinical presentation of hospitalized patients with COVID-19 in low-,

middle- and high-resource settings. We characterize the variability in clinical features in these patients and explore the risk factors associated with mortality, and the need for intensive care and mechanical ventilation, on a global scale. We aimed to report a general description of this international data set 2 years after the beginning of the pandemic, to estimate the frequency of co-morbidities, risk factors, symptoms and use of different treatments, and to estimate the risk of severe clinical outcomes and the associations of various factors with risk of these outcomes.

Methods

Study

We used international prospective observational data of clinical features and outcomes of patients admitted to hospital with COVID-19. The ISARIC/WHO CCP, incorporating Short PeRIod IncideNce sTudy of Severe Acute Respiratory Infection (SPRINT-SARI),¹⁴ is a standardized protocol for investigations of (re-)emerging pathogens of public health interest. All data were stored at a central repository at the University of Oxford, England. Patients with clinically suspected or laboratory-confirmed COVID-19 infection were enrolled in the study. Participating sites used the ISARIC case

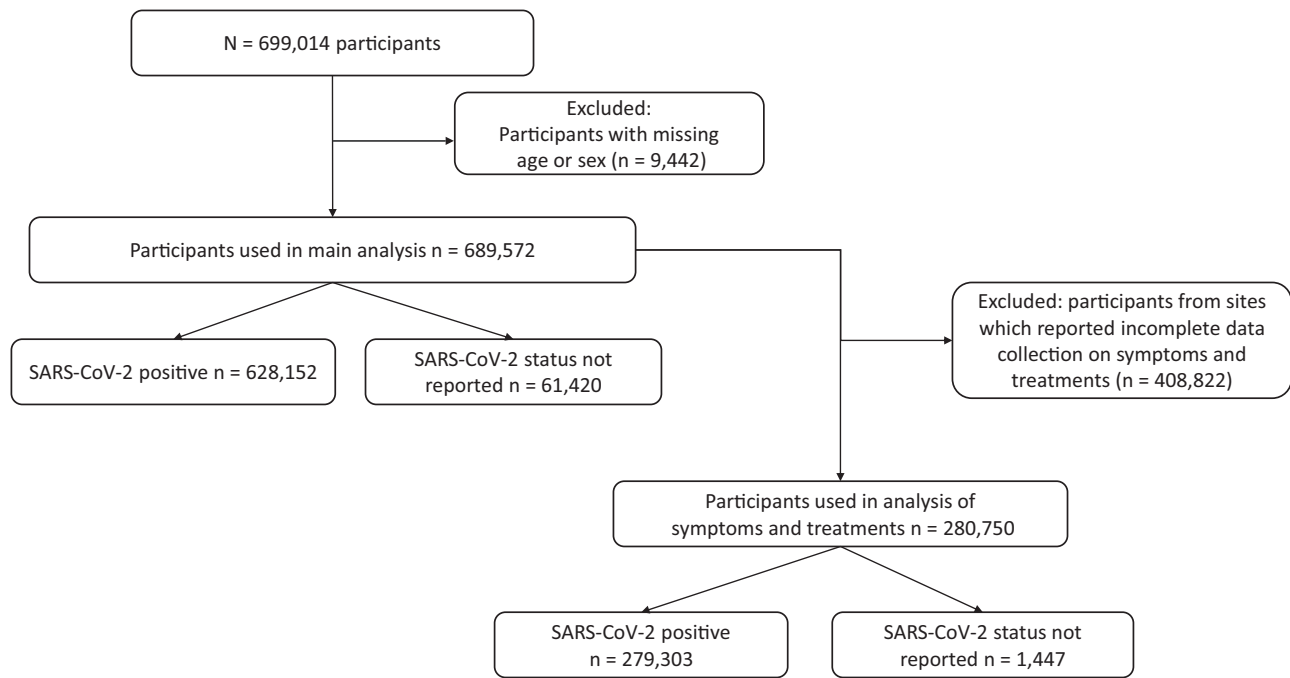


Figure 1 Numbers of participants. 6321 (0.92%) of the participants included in the main analysis were admitted to hospital for isolation

report form¹⁵ to enter data onto a Research Electronic Data Capture (REDCap, version 8.11.11, Vanderbilt University, Nashville, TN) database or used local databases (Supplementary Methods, available as Supplementary data at *IJE* online) before uploading to the central data repository. Centrally collated data were wrangled and mapped to the structure and controlled terminologies of Study Data Tabulation Model (version 1.7, Clinical Data Interchange Standards Consortium, Austin, TX) using Trifacta[®] software. The data collection, aggregation, curation and harmonization process has been previously described.¹⁶ The first patient was enrolled on 30 January 2020. This analysis includes all patients whose data were entered up to 5 January 2022.

Participants

We included hospitalized patients of any age with clinically or laboratory-diagnosed COVID-19. This analysis included patients admitted to hospital in any of the countries which contributed data. It also includes a small subset of asymptomatic patients who were admitted to the hospital purely for isolation (<1%).

Statistical analysis

We excluded patients with missing age or sex from all analyses (Figure 1). Additionally, we excluded from analyses of symptoms or treatments sites that did not record information on these two sets of variables. We calculated medians and interquartile ranges (IQRs) for continuous

variables and proportions for categorical variables. We calculated proportions of patients who met each of the WHO, Centers for Disease Control and Prevention (CDC) of the USA, European Centre for Disease Prevention and Control (ECDC) and Public Health England (PHE) symptom-based case definitions (Supplementary Methods, available as Supplementary data at *IJE* online). We calculated case-fatality ratios (CFRs) overall, by country and by month, using the method suggested by Ghani *et al.*¹⁷ We calculated inverse-variance weighted CFRs by country.

Patients were followed up from hospital admission to death, discharge or censoring, whichever occurred first. Cox proportional hazards models were used to assess the association of demographic variables, co-morbidities and symptoms at admission (unless symptom onset was after admission) with risk of death, admission to an intensive care unit (ICU) or a high-dependency unit (hereafter referred to collectively as ICU) or use of invasive mechanical ventilation (IMV). Individuals were censored if they were lost to follow-up (e.g. transferred to another facility) or remained in hospital on 6 January 2022. Time from symptom onset to the time of death or censoring, whichever occurred earlier, was used as the timescale. Patients were considered at risk from the time of symptom onset or admission, whichever occurred later. For all outcomes, censoring times of discharged patients were modified and set to be equal to the maximum time to censoring/event (to account for informative censoring). For associations with admission to an ICU, the timescale was from symptom onset to the earliest of admission to an ICU, death, discharge and

censoring. The event was admission to an ICU. For associations with receipt of IMV, the timescale was from symptom onset to the earliest of IMV, death, discharge and censoring. The event was IMV. Models were adjusted for age and sex, and stratified by country. We grouped countries with <50 individuals into a single category. Hazard ratios (HRs) and 95% CIs were estimated. We assessed the proportional hazards assumption using scaled Schoenfeld residuals. For explanatory variables with multiple categories (such as age groups), we used quasi-standard errors¹⁸ to facilitate comparisons between any two groups.

We repeated the main analyses for patients with laboratory-confirmed SARS-CoV-2 only, as a sensitivity analysis. For associations of age and sex with risk of death, we also estimated HRs within each country and calculated an overall HR using inverse-variance weighting. For age, sex and co-morbidities, we also estimated associations within the first (2020) and second year (2021) of the pandemic.

In total, 9442 individuals had missing age or sex (Figure 1) and were excluded from the analysis. Missingness for other variables among included patients varied from 2% to 93%. For analyses on the prevalence of co-morbidities, risk factors, symptoms or treatments, 'missing' is shown as a separate category in all tables and figures. For analyses on associations with outcomes, a complete case approach was used.

Analysis was performed using R version 4.1.1 and packages *survival*, *ggplot2*, *qvalc* and *finalfit*.

Patient and public involvement

This was an urgent public health research study in response to a Public Health Emergency of International Concern.

Patients or the public were not involved in the design, conduct or reporting of this rapid response research. ISARIC, ISARIC4C, the National Institute of Communicable Diseases South Africa and other collaborators have public facing websites (isaric.org; isaric4c.net; nicd.ac.za) and social media accounts to disseminate findings. The contributing individuals and institutions engage with print and internet press, television, radio, news and documentary programme makers to share evidence with the public and invite feedback.

Results

Participants' characteristics

In total, 689 572 patients (Figure 1) were included from 1380 sites in 52 countries (Figure 2 and Supplementary Figure S1, available as Supplementary data at *IJE* online). Overall, 91.1% of the participants included in the primary analysis had a positive SARS-CoV-2 PCR test (Table 1); 49.4% were male and the median age was 58 years (range 0 to 119, IQR 30). The median time from the latest of symptom onset or admission to discharge, death or date last known to be alive was 6 (IQR 10) days. Among 679 194 individuals with a known ICU admission status, 15.9% were admitted to an ICU, a third of whom were admitted directly (on the day of hospitalization). Oxygen saturation on presentation to hospital was reported for 34.8% of patients with a median SpO₂ of 96% (IQR 4%).

The majority of patients were recruited in South Africa (59.3%) and 31.1% in the UK (Table 1). Participants' characteristics varied between patients admitted directly to an ICU, those admitted at a later time point and those never admitted (Supplementary Table S1, available as

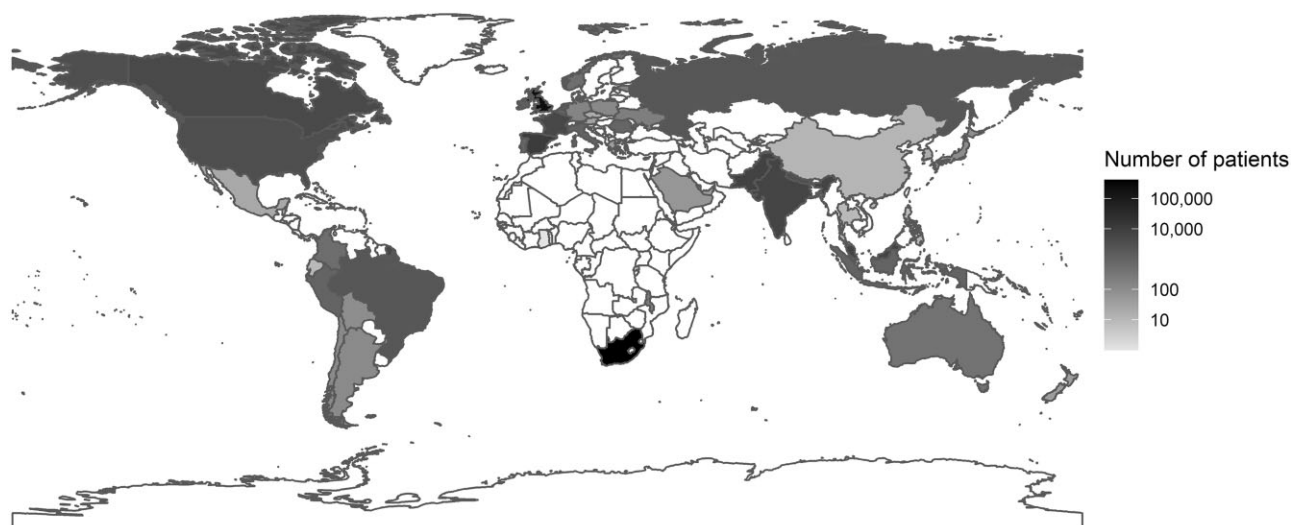


Figure 2 Numbers of patients by country

Table 1 Participants' characteristics

	N recorded (%)		Female	Male	Total
Total N			349 267	340 305	689 572
Age	689 572 (100.0)	Median (IQR)	57.0 (39.0 to 72.0)	58.1 (45.0 to 72.0)	58.0 (42.0 to 72.0)
		0–9	6863 (2.0)	8624 (2.5)	15 487 (2.2)
		10–19	9023 (2.6)	6594 (1.9)	15 617 (2.3)
		20–29	27 684 (7.9)	15 233 (4.5)	42 917 (6.2)
		30–39	44 367 (12.7)	32 124 (9.4)	76 491 (11.1)
		40–49	44 562 (12.8)	48 309 (14.2)	92 871 (13.5)
		50–59	60 856 (17.4)	66 106 (19.4)	126 962 (18.4)
		60–69	56 001 (16.0)	63 357 (18.6)	119 358 (17.3)
		70–79	48 288 (13.8)	54 735 (16.1)	103 023 (14.9)
		80–89	38 383 (11.0)	36 251 (10.7)	74 634 (10.8)
		90+	13 240 (3.8)	8972 (2.6)	22 212 (3.2)
Region	689 572 (100.0)	East Asia and Pacific	2551 (0.7)	5565 (1.6)	8116 (1.2)
		Europe and Central Asia	108 670 (31.1)	133 306 (39.2)	241 976 (35.1)
		Latin America and Caribbean	1451 (0.4)	2618 (0.8)	4069 (0.6)
		Middle East and North Africa	400 (0.1)	608 (0.2)	1008 (0.1)
		North America	3346 (1.0)	4733 (1.4)	8079 (1.2)
		South Asia	5882 (1.7)	11 226 (3.3)	17 108 (2.5)
		Sub-Saharan Africa	226 967 (65.0)	182 249 (53.6)	409 216 (59.3)
Onset to admission (days)	619 812 (89.9)	Median (IQR)	0.0 (0.0 to 3.0)	0.0 (0.0 to 5.0)	0.0 (0.0 to 4.0)
Length of hospital stay (days)	689 572 (100.0)	Median (IQR)	6.0 (2.0 to 11.0)	6.0 (3.0 to 12.0)	6.0 (2.0 to 12.0)
Body mass index (kg/m ²)	18 582 (2.7)	Median (IQR)	27.7 (23.5 to 32.5)	27.3 (24.2 to 30.9)	27.5 (24.0 to 31.2)
Heart rate on admission (b.p.m.)	229 125 (33.2)	Median (IQR)	90.0 (79.0 to 103.0)	90.0 (78.0 to 103.0)	90.0 (79.0 to 103.0)
Systolic blood pressure on admission (mmHg)	236 114 (34.2)	Median (IQR)	128.0 (114.0 to 144.0)	129.0 (116.0 to 143.0)	129.0 (115.0 to 144.0)
Diastolic blood pressure on admission (mmHg)	236 097 (34.2)	Median (IQR)	73.0 (65.0 to 82.0)	75.0 (67.0 to 84.0)	74.0 (66.0 to 83.0)
Temperature on admission (degrees C)	238 084 (34.5)	Median (IQR)	37.0 (36.5 to 37.7)	37.0 (36.5 to 37.8)	37.0 (36.5 to 37.8)
Oxygen saturation on admission (%)	240 068 (34.8)	Median (IQR)	96.0 (93.0 to 98.0)	95.0 (92.0 to 97.0)	96.0 (93.0 to 97.0)
– On oxygen therapy	78 961 (32.9%*)	Median (IQR)	95.0 (92.0 to 97.0)	95.0 (92.0 to 97.0)	95.0 (92.0 to 97.0)
– In room air	150 585 (62.7%*)	Median (IQR)	96.0 (94.0 to 98.0)	96.0 (93.0 to 97.0)	96.0 (93.0 to 98.0)
– Unknown oxygenation status	10 689 (4.5%*)	Median (IQR)	96.0 (93.0 to 98.0)	96.0 (93.0 to 97.0)	96.0 (93.0 to 98.0)
Respiratory rate on admission	229 421 (33.3)	Median (IQR)	20.0 (18.0 to 24.0)	21.0 (18.0 to 26.0)	20.0 (18.0 to 25.0)
Admission to ICU	674 753 (97.9)	Never	300 046 (87.6)	270 984 (81.6)	571 030 (84.6)
		Later admission	30 290 (8.8)	38 720 (11.7)	69 010 (10.2)
		Direct admission	12 212 (3.6)	22 501 (6.8)	34 713 (5.1)
Outcome	689 572 (100.0)	Unknown outcome	28 189 (8.1)	33 706 (9.9)	61 895 (9.0)
		Death	69 878 (20.0)	80 589 (23.7)	150 467 (21.8)
		Discharge	251 200 (71.9)	226 010 (66.4)	477 210 (69.2)
SARS-CoV-2 status	689 572 (100.0)	Positive	314 139 (89.9)	314 013 (92.3)	628 152 (91.1)
		Unknown	35 128 (10.1)	26 292 (7.7)	61 420 (8.9)

*Percentage of individuals with oxygen saturation recorded.

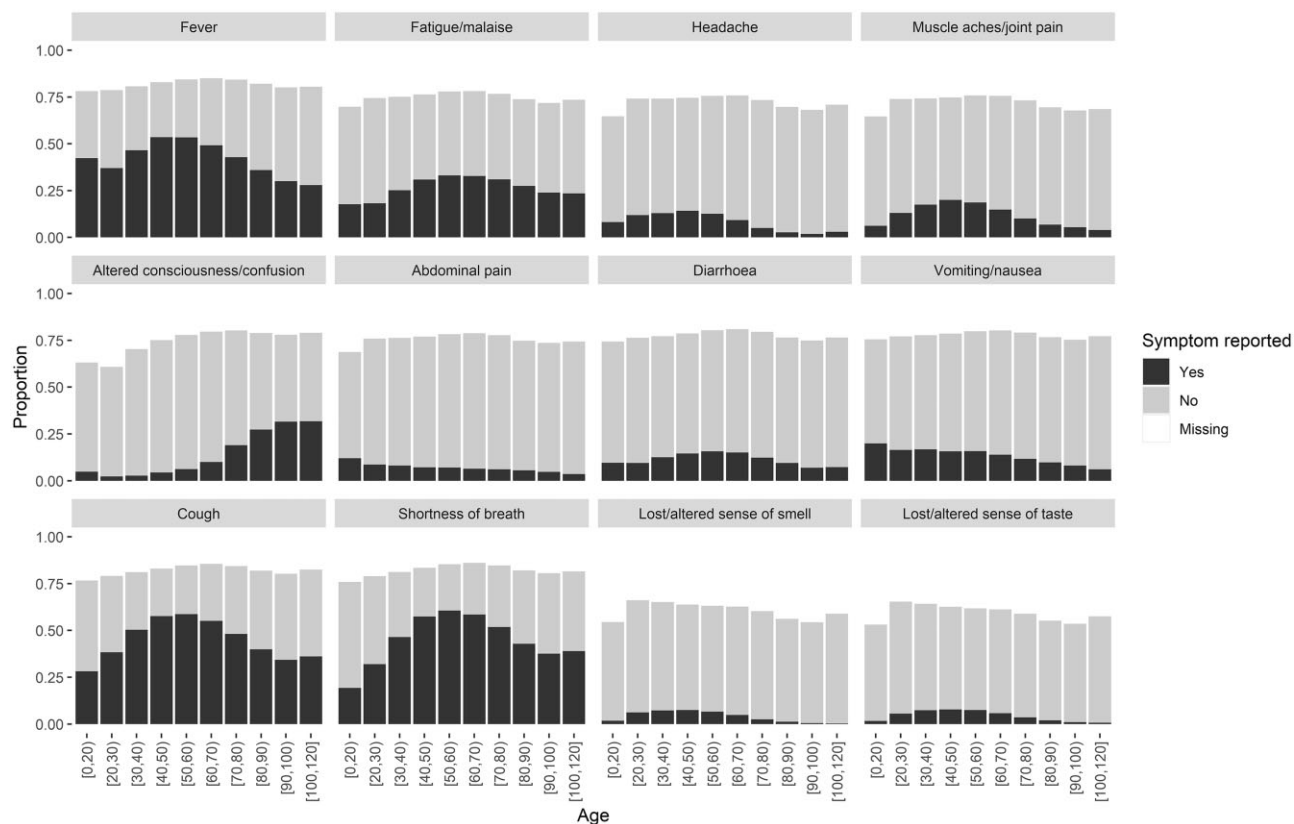


Figure 3 Symptom prevalence by age ($n = 290\,750$)

[Supplementary data](#) at *IJE* online). In particular there were differences in age, region and vital signs (heart and respiratory rate and blood pressure). Anthropometric variables and vital signs varied by age ([Supplementary Table S2](#), available as [Supplementary data](#) at *IJE* online).

Presenting symptoms

The most common symptoms on presentation were shortness of breath (50%), cough (48.5%) and fever (44.3%) ([Figure 3](#) and [Supplementary Table S3](#), available as [Supplementary data](#) at *IJE* online). There was some variation by age and country ([Supplementary Figure S2](#), available as [Supplementary data](#) at *IJE* online). Fatigue/malaise, cough and shortness of breath were most prevalent amongst patients who were 40–70 years old. The prevalence of altered consciousness/confusion increased with age and was reported in 28.4% of patients of >80 years of age. Loss or altered smell or taste were not commonly reported but there was a high proportion of missing values for these two symptoms (39.3% for loss of smell and 40.5% for taste). We have previously described the associations of age and gender with presenting symptoms.¹¹ Prevalence of symptoms by age was similar when we restricted our

analysis to patients with laboratory-confirmed SARS-CoV-2 ([Supplementary Figure S3](#), available as [Supplementary data](#) at *IJE* online) but there were more missing values among individuals with only a clinical diagnosis ([Supplementary Figure S4](#), available as [Supplementary data](#) at *IJE* online). Altered consciousness/confusion, cough, fatigue/malaise, fever, shortness of breath and vomiting/nausea were more frequently reported in patients with laboratory-confirmed SARS-CoV-2 infection than in those with a clinical diagnosis alone ([Supplementary Figure S5](#), available as [Supplementary data](#) at *IJE* online).

Overall, 50–70% of patients met each of the international symptom-based case definitions. These proportions were higher among those with laboratory-confirmed SARS-CoV-2 infection (CDC met by 64.0% vs 33.7% among laboratory-confirmed and clinically diagnosed, respectively, ECDC 68.7% vs 31.3%, PHE 61.3% vs 33.7%, WHO 49.2% vs 30.2%) ([Supplementary Figure S6](#), available as [Supplementary data](#) at *IJE* online). Individuals aged 40–70 years were more likely to meet each of the four case definitions based on symptoms than patients at the extremes of the age distribution ([Figure 4](#)). Adults with laboratory-confirmed SARS-CoV-2 infection were more likely to meet one of the four case definitions

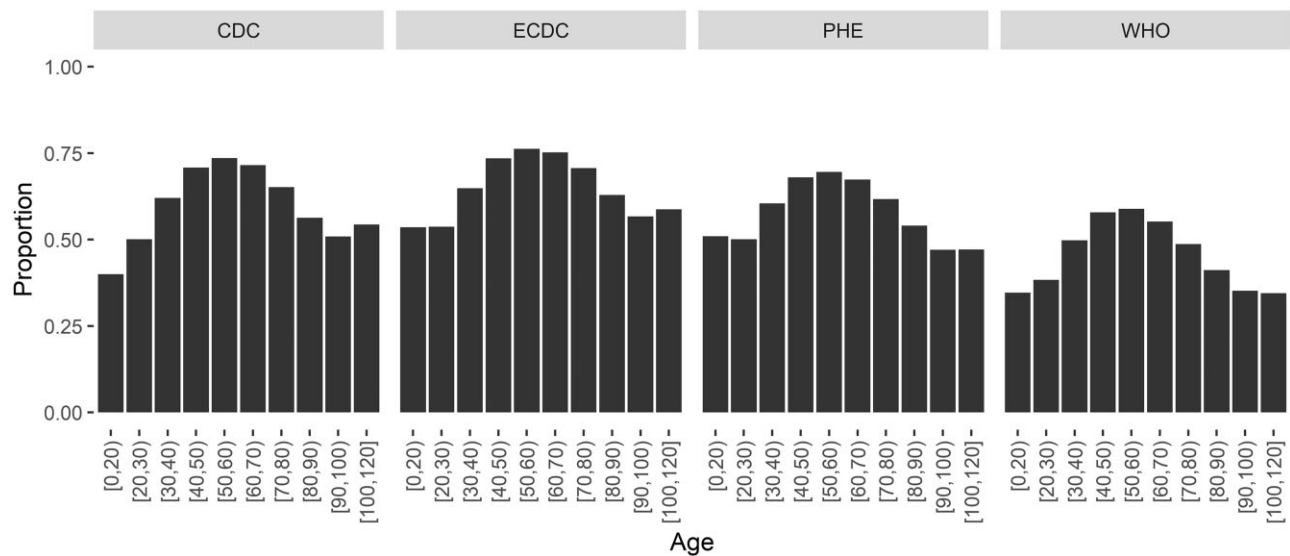


Figure 4 Proportions meeting each symptom definition by age ($n=290750$). CDC, Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; PHE, Public Health England; WHO, World Health Organization

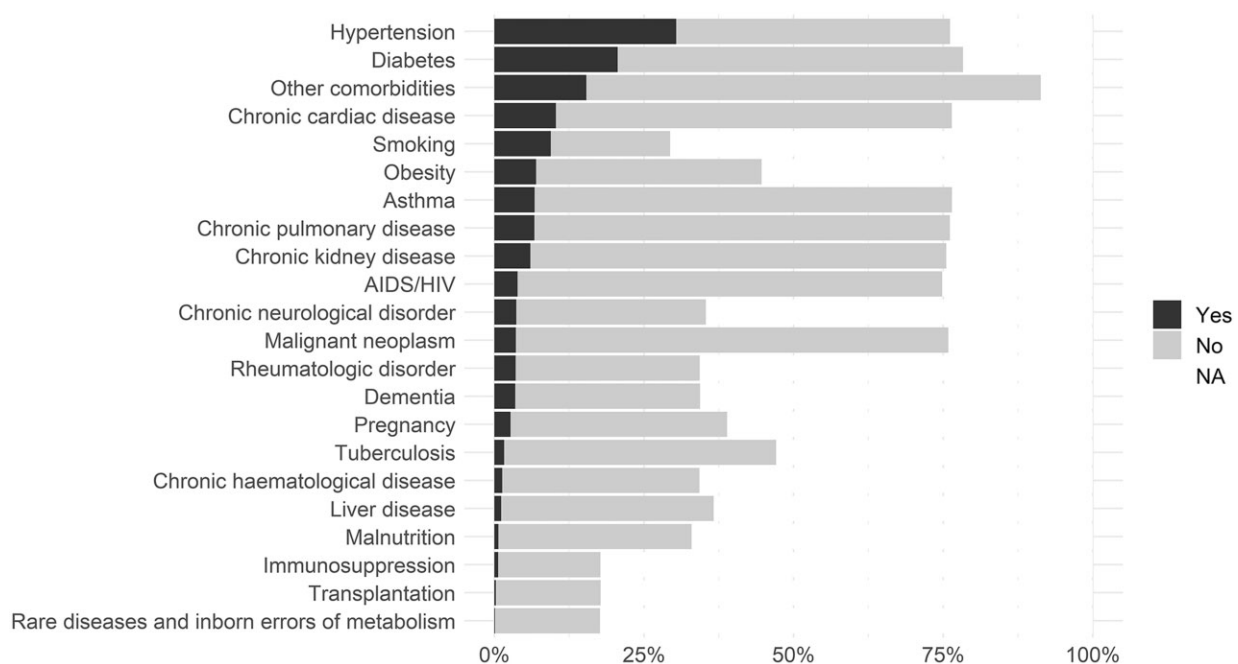


Figure 5 Prevalence of pre-existing co-morbidities and risk factors ($n=689572$)

based on symptoms than those with only a clinical diagnosis of SARS-CoV-2 infection, but the opposite was true amongst patients aged <20 years (Supplementary Figure S7, available as Supplementary data at *IJE* online).

Routine blood test results are shown in Supplementary Table S4 (available as Supplementary data at *IJE* online). The median white blood cell count (7.2×10^9 ; IQR 5.4 – 9.8×10^9 cells per litre) was normal but the median lymphocyte count was low (0.9×10^9 ; IQR 0.6 – 1.3×10^9 cells per litre) among participants with available data. The median C-reactive protein was high (74.0; IQR 30.0–

138.0 mg/litre) but the median liver transaminase and median urea levels were unremarkable. Several median values for routine blood test results varied with age; with increasing age, the median lymphocyte count was lower, whereas the median urea was higher (Supplementary Figure S8, available as Supplementary data at *IJE* online).

Pre-existing co-morbidities and risk factors

The most common pre-existing co-morbidities were hypertension, diabetes and chronic cardiac disease (Figure 5

Table 2 Oxygen supplementation among patients who received at least one type of oxygen supplementation

	N recorded (%)		Female	Male	Total
Total N (%)			72 484 (40.4)	106 964 (59.6)	179 448
Extracorporeal membrane oxygenation	173 972 (96.9)	No	69 984 (99.1)	102 052 (98.7)	172 036 (98.9)
		Yes	603 (0.9)	1333 (1.3)	1936 (1.1)
Ever received invasive mechanical ventilation	176 135 (98.2)	No	58 745 (82.5)	78 950 (75.2)	137 695 (78.2)
		Yes	12 462 (17.5)	25 978 (24.8)	38 440 (21.8)
Ever received non-invasive ventilation	177 313 (98.8)	No	56 111 (78.3)	76 922 (72.8)	133 033 (75.0)
		Yes	15 594 (21.7)	28 686 (27.2)	44 280 (25.0)
High-flow nasal cannula	163 908 (91.3)	No	45 488 (68.5)	62 879 (64.5)	108 367 (66.1)
		Yes	20 891 (31.5)	34 650 (35.5)	55 541 (33.9)
Oxygen therapy via mask	45 (0.0)	No	17 (89.5)	21 (80.8)	38 (84.4)
		Yes	2 (10.5)	5 (19.2)	7 (15.6)
Nasal oxygen therapy	45 (0.0)	No	0 (0.0)	2 (7.7)	2 (4.4)
		Yes	19 (100.0)	24 (92.3)	43 (95.6)
Other or unspecified type of oxygen supplementation	87 328 (48.7)		38 922 (100.0)	48 406 (100.0)	87 328 (100.0)
Number of types of oxygen supplementation	92 120 (51.3)	1	20 998 (62.6)	33 792 (57.7)	54 790 (59.5)
		2	9240 (27.5)	17 672 (30.2)	26 912 (29.2)
		3	3203 (9.5)	6836 (11.7)	10 039 (10.9)
		4	121 (0.4)	258 (0.4)	379 (0.4)

*Extracorporeal membrane oxygenation, invasive mechanical ventilation, non-invasive ventilation or high-flow nasal cannula.

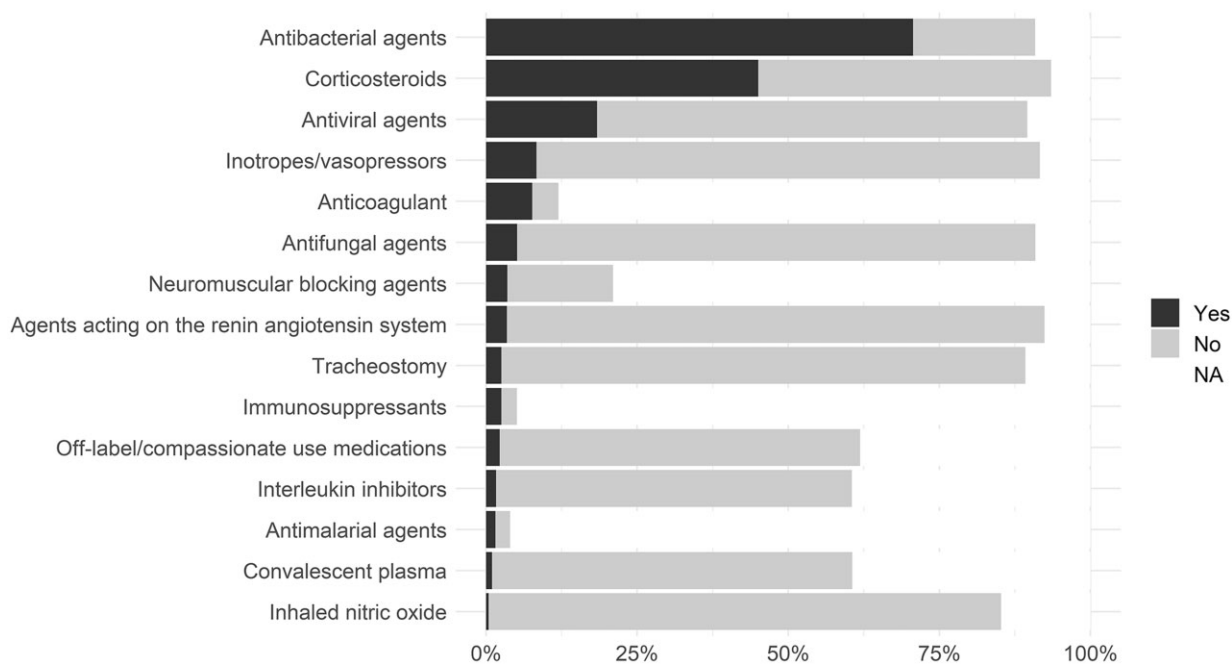


Figure 6 Proportion who have received each treatment (n = 290 750)

and [Supplementary Table S5](#), available as [Supplementary data](#) at *IJE* online). Among 538 974 individuals with data available for any five or more co-morbidities or risk factors, 165 987 (30.8%) had no co-morbidities reported. The prevalence of most co-morbidities varied by age ([Supplementary Figure S9](#), available as [Supplementary](#)

[data](#) at *IJE* online). The prevalence of chronic cardiac disease, chronic kidney disease, dementia, hypertension and rheumatologic disorder increased with age. The prevalence of diabetes was highest in individuals aged 60–80 years. There were 26 776 patients with HIV infection, 11 384 with tuberculosis and 5044 with both; 25 368 of the

patients with HIV infection and 11 137 patients with tuberculosis were from South Africa. Obesity was reported for 48 077 participants, smoking for 65 056 and pregnancy for 18 669.

Treatments

Of 275 051 patients with available data on oxygen therapy (98.0% of individuals included in the treatment analyses), 179 448 (65.2%) received oxygen therapy at any time during hospitalization, which was delivered via a high-flow nasal cannula to 55 541 (19.8%), by non-invasive ventilation (NIV) to 44 280 (15.8%) and IMV to 38 440 (13.7%) (Table 2). Type of oxygen supplementation received was not specified for 48.7%. As might be expected, a proportion of patients received multiple types of oxygen delivery systems during their admission [37 330 (20.8%)]. For instance, 41.8% of those receiving IMV also received oxygen delivered via NIV.

The most used treatments were oxygen therapy, antibacterial agents and corticosteroids (Figure 6 and Supplementary Table S6, available as Supplementary data at *IJE* online). The proportion of patients receiving antibacterial agents increased with age, as did the proportion receiving corticosteroids up to ages 70–80 years (Supplementary Figure S10, available as Supplementary data at *IJE* online). Information on antibacterial treatment was available for 255 031 patients, 198 295 (77.8%) of

whom received antibacterial agents; 126 391 of 262 385 of patients with data available (48.2%) received corticosteroids. The use of corticosteroids increased after the publication of results of the RECOVERY trial¹⁹ in June 2020 (Supplementary Figure S11, available as Supplementary data at *IJE* online), in particular among patients who received oxygen supplementation, in line with the trial results.

CFR

The CFR varied by country (Figure 7), likely because of the different features of different sites in different countries where patients of different disease severity may be admitted. The weighted average CFR was 0.215 [standard error (SE) 0.000462]. Among patients for whom reporting commenced in the ICU, the CFR was 0.469 (SE 0.00287). Among patients admitted to the ICU but for whom reporting did not commence in the ICU, the CFR was 0.341 (SE 0.00178). The CFR was 0.214 (SE 0.00048) among patients with laboratory-confirmed SARS-CoV-2 and 0.231 (SE 0.00161) among patients with clinically diagnosed COVID-19. The CFR varied over time during the study, as did patient recruitment at different sites (Supplementary Figure S12, available as Supplementary data at *IJE* online). Admission criteria likely varied by country and time, contributing to the heterogeneity in illness severity. Death and discharge rates increased over the first 40 days from

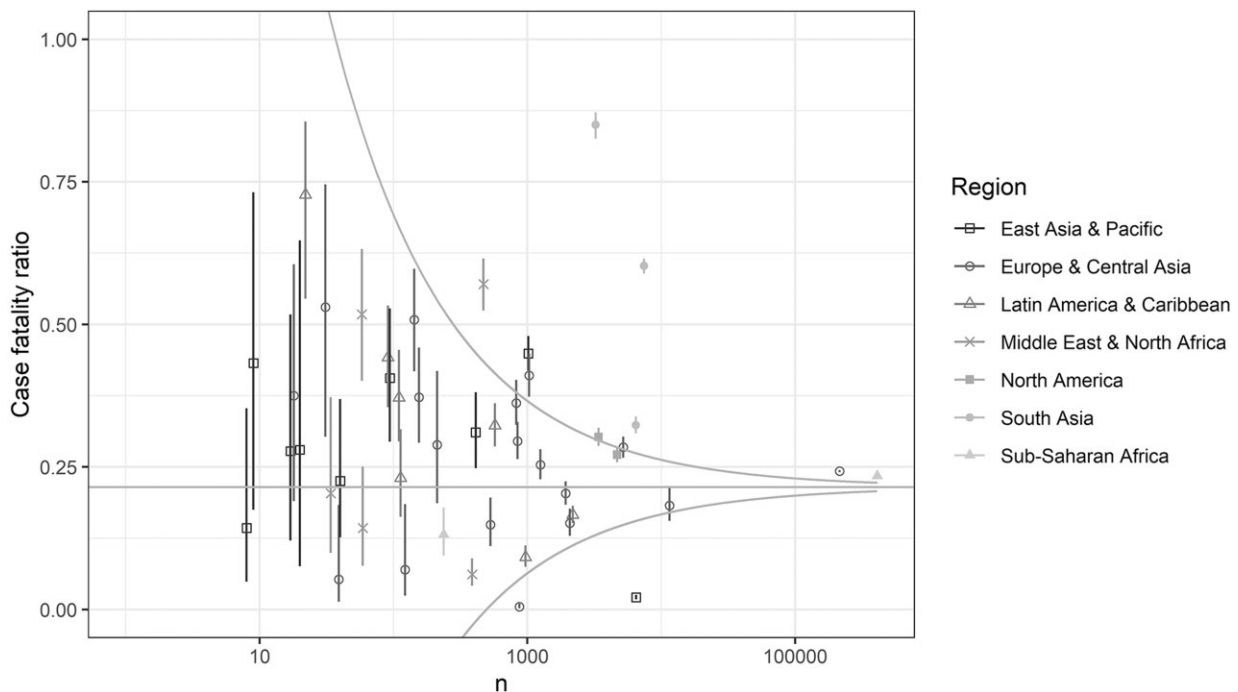


Figure 7 Case-fatality ratio by country. Each point is a country and points are coloured and have different shapes by region. The horizontal line is the inverse-variance weighted average case-fatality ratio. The funnel plot shows the 95% confidence limits. The x-axis is on a log₁₀ scale

hospital admission (or symptom onset if this occurred after admission) (Supplementary Figure S13, available as Supplementary data at *IJE* online).

Associations with death

The risk of death was higher for males than for females (Figure 8). Older age was associated with a significantly higher risk of death, with a HR of 1.49 (95% CI 1.48,

1.49) per 10 years higher age, adjusting for sex and stratifying by country, with individuals aged 90–100 years having an HR of 17.45 (95% CI 16.54, 18.40) compared with the group aged 20–30 years (Supplementary Figure S14, available as Supplementary data at *IJE* online). Males had a significantly higher risk of death than females, with an HR of 1.23 (95% CI 1.21, 1.24), adjusting for age (in 10-year groups) and stratifying by country. There was evidence of deviation from the proportional hazards assumption for both variables. There was no particular trend over follow-up for the magnitude of the association of age with death, but the magnitude of the association of male sex with death appeared to increase with increasing time from admission (or symptom onset for patients who developed symptoms after admission). A model stratified by sex was fitted to estimate associations of age with death taking this time-varying association of sex into account. HRs for age estimated by the two models were very similar. HRs were also estimated by sex and age, stratifying (allowing different baseline hazards) by country (Figure 9). HRs for age (Supplementary Figure S15, available as Supplementary data at *IJE* online) and sex (Supplementary Figure S16, available as Supplementary data at *IJE* online) varied by country. Country-specific HRs for a 10-year increase in age varied from 1.15 (Italy; 95% CI 1.05, 1.26) to 3.50 (Poland; 1.19, 10.29), with a pooled estimate of 1.49 (1.48, 1.49), which is the same as the estimate from the

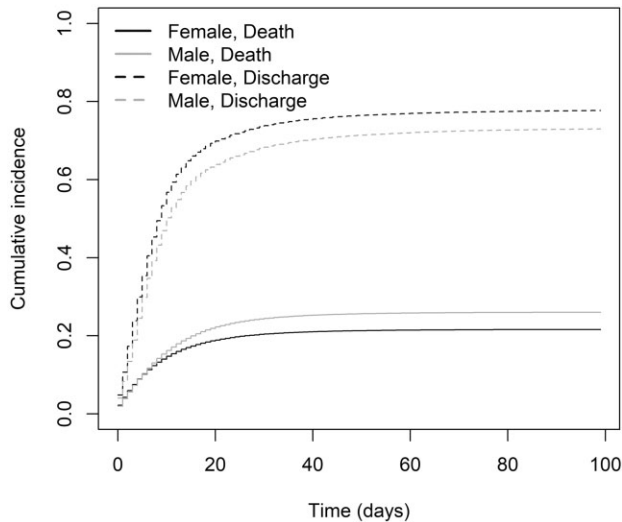


Figure 8 Cumulative incidence curves of death and discharge by sex ($n = 689\,572$)

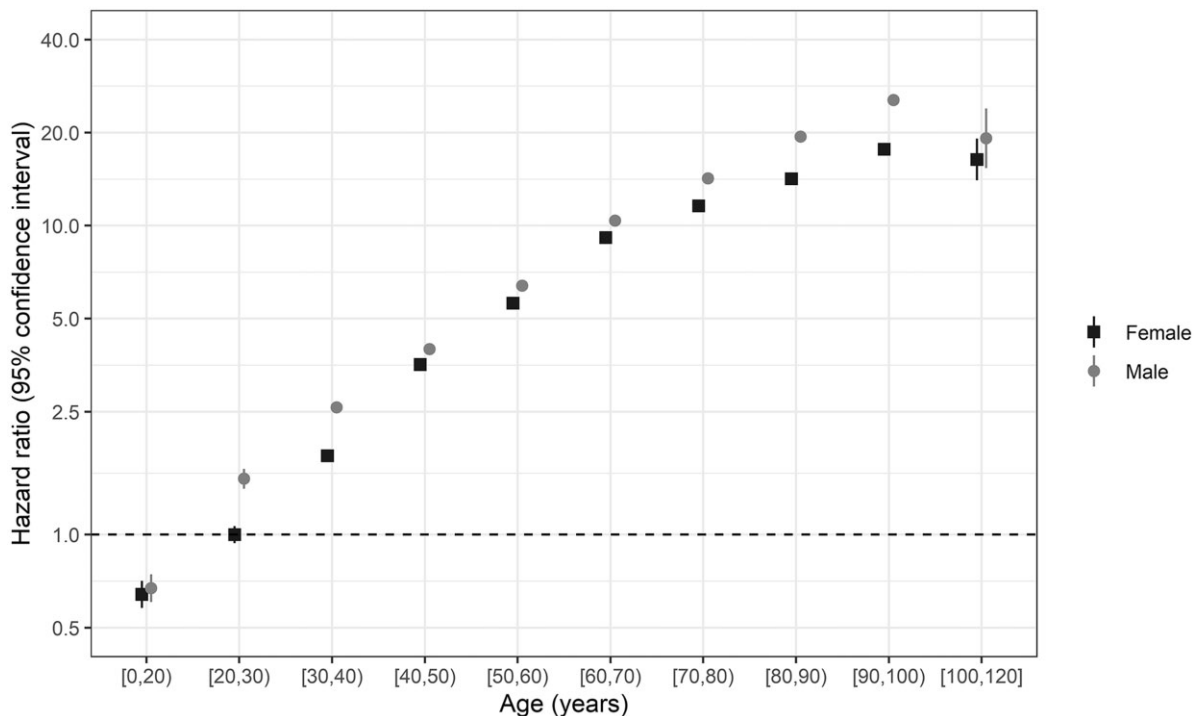


Figure 9 Hazard ratios and 95% confidence intervals for death by age group and sex ($n = 689\,572$). The model is stratified by country. The reference group is females of age [20,30). The y -axis is plotted on a logarithmic scale

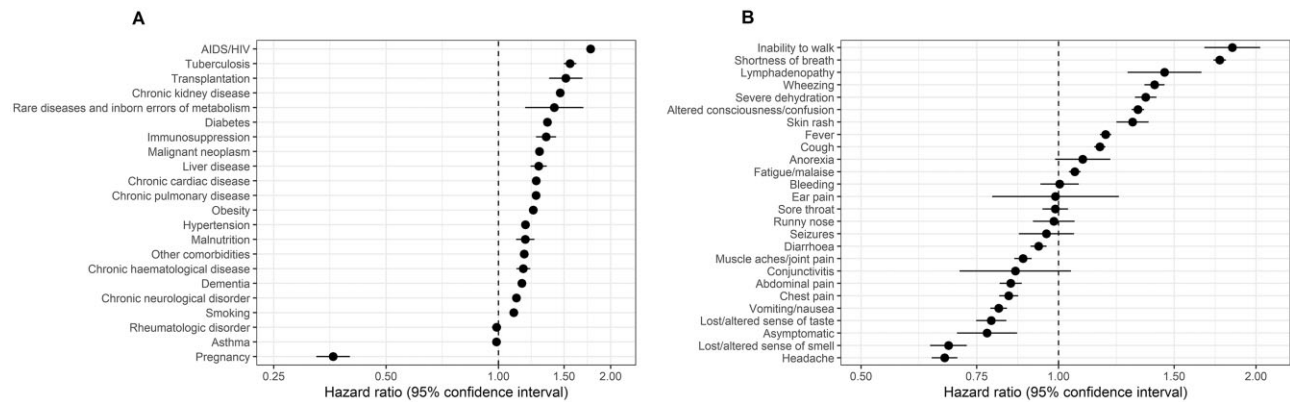


Figure 10 Associations of (A) co-morbidities ($n=689\,572$) and (B) symptoms ($n=290\,750$) with risk of death. Dots are hazard ratios and lines are 95% confidence intervals of death by each variable at a time (the reference group is not having the particular symptom/comorbidity/risk factor). Models were adjusted for age and age², stratified by sex and country

main analysis. For sex (males vs females), HRs were between 0.61 (Malawi; 95% CI 0.28, 1.31) and 3.57 (Japan; 1.05, 12.07), with a weighted average of 1.26 (1.25, 1.27) [compared with 1.23 (1.21, 1.24) in the main analysis]. When fitting a model including age (continuous) and sex, and stratified by country, within each year of the pandemic, HRs (95% CI) per 10 years of higher age were 1.50 (1.49, 1.51) for 2020 and 1.47 (1.47, 1.48) for 2021, and for males vs females 1.31 (1.29, 1.33) and 1.20 (1.19, 1.22), respectively.

Overall, HIV infection [HR 1.77 (95% CI 1.72, 1.81), adjusting for age, age² and sex, and stratifying by country] and tuberculosis [1.56 (1.50, 1.62)] were associated with the highest relative risks of death; there was no evidence of an interaction ($P=0.18$). Since many patients with these co-morbidities were from South Africa, we assessed the associations separately among patients from South Africa and patients from all other countries by fitting a model including HIV, tuberculosis, age and age stratified by sex and country. The associations with risk of death did not significantly differ between patients from South Africa and patients from other countries, although estimates were numerically higher for patients from South Africa: respectively for HIV HR (95% CI) 1.52 (1.47, 1.58) and 1.18 (0.83, 1.69) and for tuberculosis 1.35 (1.29, 1.41) and 1.18 (0.82, 1.70). All reported co-morbidities were associated with a higher risk of death, except rheumatologic disorder and asthma for which there was no evidence of an association (Figure 10 and Supplementary Table S7, available as Supplementary data at *IJE* online). Obesity was associated with a higher risk of death [HR 1.24 (1.21, 1.27)]. Smoking was also associated with a higher risk of death [1.10 (1.07, 1.12)]. Pregnancy was associated with a lower risk of death [HR 0.37 (0.33, 0.41) among females aged

15–45 years, adjusting for age, age² and stratifying by country]. There were small differences in the magnitude of associations of co-morbidities with risk of death between calendar years (Supplementary Figure S17, available as Supplementary data at *IJE* online).

Inability to walk [HR 1.84 (95% CI 1.67, 2.03), adjusting for age, age² and sex, and stratifying by country], shortness of breath [1.76 (1.72, 1.80)], lymphadenopathy [1.45 (1.27, 1.65)], wheezing [1.40 (1.35, 1.45)], severe dehydration [1.36 (1.31, 1.41)], altered consciousness/confusion [1.32 (1.29, 1.35)], skin rash [1.30 (1.22, 1.37)], cough [1.16 (1.13, 1.18)], fever [1.18 (1.16, 1.20)] and fatigue/malaise [1.06 (1.04, 1.08)] were associated with a higher risk of death (Figure 10 and Supplementary Table S8, available as Supplementary data at *IJE* online). In general, gastrointestinal, musculoskeletal symptoms and loss of or altered taste or smell were associated with a lower risk of dying; e.g. nausea/vomiting had a HR of 0.81 (0.79, 0.83), abdominal pain 0.84 (0.81, 0.88), diarrhoea 0.93 (0.91, 0.96) and muscle aches/joint pain 0.88 (0.86, 0.91).

Associations with admission to an ICU and with use of IMV

The risk of admission to an ICU increased with age after age 30 years and started decreasing from age 60 years, with patients aged >80 years being unlikely to be admitted to an ICU. Men were more likely to be admitted to an ICU overall, with a HR of 1.17 (1.15, 1.18). There was evidence of non-proportional hazards, indicating that the relative risk changed with time since symptom onset (or hospitalization). There were similar patterns for risk of IMV (Figure 11). There was some variation in risks by age in different countries (Supplementary Figure S18, available as Supplementary data at *IJE* online).

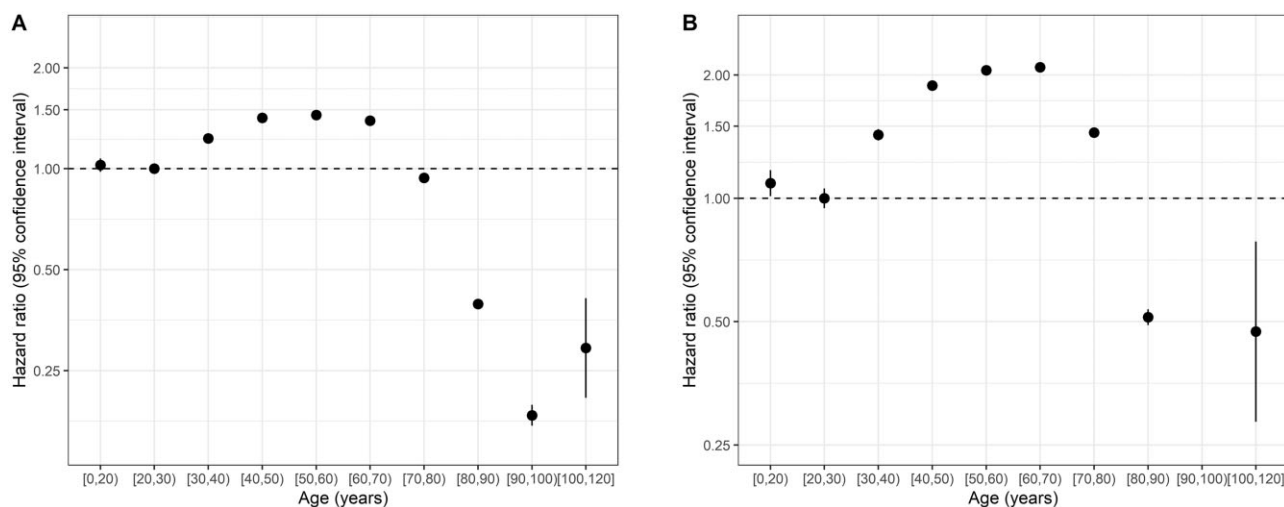


Figure 11 Hazard ratios and 95% confidence intervals for (A) admission to an intensive care unit and (B) use of invasive mechanical ventilation by age ($n = 689\,572$)

Discussion

The ISARIC international cohort study included at the time of these analyses standardized data on almost 700 000 patients from 1380 sites across 52 countries. To our knowledge, this is the most extensive in-hospital COVID-19 cohort study in the world. The size and breadth of the study allow us to evaluate the contribution of individual risk factors to outcomes such as death, admission to an ICU and use of mechanical ventilation. The value of the international cohort design is its capacity to cover the breadth of COVID-19 characteristics unencumbered by differences in classification and reporting. Furthermore, our international cohort design allowed us to explore risk factors that are globally uncommon, or uncommon in cohorts from high-income countries. For example, our data set is the largest prospective cohort study of COVID-19 patients with HIV infection, tuberculosis, malnutrition, pregnancy and transplantation. Although the study population includes children and we have presented some of their characteristics, a detailed analysis of the children population is beyond the scope of this paper.

Across the cohort, the most common presenting symptoms were fever, shortness of breath and cough. Among other symptoms reported, the most common were altered consciousness in older patients and gastrointestinal symptoms in younger patients. Our data show that about one-third of patients do not meet one of the four most widely used case definitions at the time of hospitalization, particularly those in the younger and older age groups. These differences are relevant when defining testing or isolation and for early detection of new clusters and variants. Although case definitions must be simple, age-specific definitions may improve sensitivity. This has implications also for case

management; about one-third of patients did not require any oxygen therapy during their hospitalization.

Our study confirms that the strong association between age and risk of death from COVID-19 is a global phenomenon. The elderly are at a significantly higher risk of death from COVID-19. Every decade of life adds a 50% risk of dying, with those aged >90 years having a 17-fold higher risk than 20- to 30-year-olds. Although similar results were shown globally for non-hospitalized cases,^{20,21} our study reproduces these results globally and amongst hospitalized patients. There were differences between the sexes, with men having an increased risk of death around one-third higher than the corresponding female 10-year age group. A meta-analysis published early in the pandemic showed that male patients had an odds ratio (OR) of 2.84 (95% CI 2.06, 3.92) for intensive treatment unit admission and an OR of 1.39 (1.31, 1.47) for death compared with females, despite not having a higher risk of infection.²² A US study of hospitalized patients also reported a higher risk of death among males.²³ Such age- and sex-specific CFRs with a global perspective are critical to understanding the global in-hospital burden of COVID-19. The pattern holds across lower- and higher-income countries. Interestingly, non-respiratory presentations were associated with lower risk of death.

We found five co-morbidities to be strongly associated with risk of death. The most substantial risk factor was HIV infection. There was a high proportion of people living with HIV (PLWH) in this cohort. Whilst retrospective health records analyses have been performed previously,^{24,25} this is the most extensive international cohort study of COVID-19 in PLWH. A recent cohort study performed in South Africa²⁶ demonstrated that PLWH had an adjusted OR of death of 1.34 (95% CI 1.27, 1.43). Our

study reinforces these findings and suggests that a higher risk is observed in other countries as well. Unfortunately, we have no further detail on how well controlled the HIV infection was or on the levels of immunocompromise for PLWH in our study. The second strongest association with the risk of death was a diagnosis of tuberculosis. To our knowledge, this is also the largest international cohort of patients co-infected with SARS-CoV-2 and tuberculosis (>5000 patients); however other studies have reported a higher risk of death among patients with COVID-19 and tuberculosis.^{26,27} There have been few studies on the effect of COVID-19 on transplant patients. The 1606 transplant patients included in our data set make it one of the largest cohorts to date. Overall, risk of death was 52% higher in transplant patients and 34% higher in those on immunosuppressive therapies. Several studies have shown that tobacco smoking is associated with worse COVID-19 outcomes.^{28,29} We found a 10% higher risk of death among smokers; however, smoking information was available only on ~30% of patients and detailed information on the quantity and duration of smoking were not available. Obesity is a recognized risk factor for hospitalization and poor outcomes in patients with COVID-19 and has been one of the conditions for which individuals are prioritized for access to vaccines and treatments. Obesity was associated with a 24% increase in risk; obesity status was available for ~45% of patients. Both smoking and obesity are potentially modifiable risk factors that could be targeted by public health measures. Our results suggest pregnancy is associated with a lower risk of death among people admitted to hospital, which appears to contrast with other studies suggesting an increased risk of death, intubation or ICU admission for pregnant women.³⁰ However, the UK Obstetric Surveillance System found that 55% of hospital admissions for pregnant women with COVID-19 were for the purpose of giving birth,³¹ whereas very few other elective and semi-elective admissions were taking place during the pandemic; this is likely to have increased the proportion of pregnant women in hospital with less severe COVID-19 compared with the broader cohort, confounding our observed lower risk of death for pregnant women.

Globally, CFRs were much higher in the 5% of patients who were admitted to an ICU on the first day of their admission than those who required an ICU later during their admission. The risk of admission to an ICU increased with age, but then started decreasing from age 60 years, with patients aged >80 years being very unlikely to be admitted to an ICU. It has been suggested that patients who have severe illness and are not treated in an ICU have poorer outcomes.³² This may reflect decisions to admit patients to an ICU during periods when resources were limited, taking

into account their overall health. Compared with other studies, these results are consistent for patients aged <60 years but not for those aged >60 years. For example, in a study from the USA³³ and in a separate meta-analysis,³⁴ elderly patients were more likely to be admitted to an ICU than their younger counterparts;³⁵ this may reflect geographical variation in clinical practice.

This international cohort study overcomes some of the traditional problems of multicentre observational studies by using standardized variables and outcome measures. Our data are likely to be of value in modelling and health system planning. For example, we note the greatly increased risk of death amongst patients with tuberculosis and malnutrition in our cohort and protecting such individuals from COVID-19 must be a critical public health priority for countries with high prevalence rates of these conditions. Equally concerning is our finding of increased risk of death amongst PLWH. Many PLWH reside in sub-Saharan Africa and our data may indicate a phenomenon that is currently hidden due to under-testing for SARS-CoV-2³⁶ across Africa.

Limitations

Whereas our study includes a broad range of data from different countries, various sites have different levels of data completeness. For example, we cannot evaluate the proportion of patients with HIV infection or tuberculosis who were taking appropriate, effective treatments. We have no further detail on the type of organ received by the transplantation cohort. Missing data may have affected the estimates of prevalence of symptoms, co-morbidities and other patient characteristics, as well as estimates of associations between these and risks of outcomes. We presented missing data in each variable in tables and figures. Specifically for symptoms and treatments, data from South Africa were not available and aggregated estimates might largely reflect data from the UK. Whereas we have produced a summary of the associations of risk factors with outcomes in COVID-19, pandemics are complex, dynamic phenomena. There is variation in the amount and completeness of data between countries and between sites within each country. Although we have adjusted for potential confounders, inclusion of patients in the data varies by country/site, which may lead to bias in estimates of association and of absolute risks such as CFR. Our findings will increasingly be influenced by the provision of vaccination, which we have not examined in this study, and effective treatments, as well as the variability in access to these measures in the global context. We do not include data on SARS-CoV-2 variants of concern in this paper. The majority of submitted case records come from two countries: the

UK and South Africa; however, there were 22 countries with data on >500 patients.

Conclusion

This paper represents the largest international cohort of hospitalized COVID-19 patients published to date. We demonstrate several associations of global importance, including an increased risk of death in patients with HIV and tuberculosis. Co-morbidities were associated with a higher risk of death, each associated with up to a 2-fold increase. Smoking and obesity were also associated with a higher risk of death. Age was most strongly associated with risk of death, with a ~30-fold difference between the oldest and youngest groups. These findings may be used to inform strategies that involve prioritization of high-risk patients hospitalized with COVID-19 and prevention strategies. The ISARIC global collaboration continues to collect standardized data which will enable continued data-led comparisons as the world implements vaccination, treatment and public health control strategies.

Notes

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Hattem; Carolien van Netten; Frank van Someren Greve; Ilonka van Veen; Hugo Van Willigen; Noémie Vanel; Henk Vanoverschelde; Pooja Varghese; Michael Varrone; Shoban Raj Vasudayan; Charline Vauchy; Shaminee Veeran; Aurélie Veislinger; Sebastian Vencken; Sara Ventura; Annelies Verbon; James Vickers; José Ernesto Vidal; César Vieira; Deepak Vijayan; Joy Ann Villanueva; Judit Villar; Pierre-Marc Villeneuve; Andrea Villoldo; Gayatri Vishwanathan; Benoit Visseaux; Hannah Visser; Chiara Vitiello; Harald Vonkeman; Fanny Vuotto; Suhaila Abdul Wahab; Noor Hidayu Wahab; Nadirah Abdul Wahid; Marina Wainstein; Wan Fadzlina Wan Muhd Shukeri; Chih-Hsien Wang; Steve Webb; Katharina Weil; Tan Pei Wen; Sanne Wesselius; T. Eoin West; Murray Wham; Bryan Whelan; Nicole White; Paul Henri Wicky; Aurélie Wiedemann; Surya Otto Wijaya; Keith Wille; Suzette Willems; Virginie Williams; Calvin Wong; Yew Sing Wong; Teck Fung Wong; Natalie Wright; Gan Ee Xian; Lim Saio Xian; Kuan Pei Xuan; Ioannis Xynogalas; Siti Rohani Binti Mohd Yakop; Masaki Yamazaki; Yazdan Yazdanpanah; Nicholas Yee Liang Hing; Cécile Yelnik; Chian Hui Yeoh; Stephanie Yerkovich; Toshiki Yokoyama; Hodane Yonis; Obada Yousif; Saptadi Yulianto; Akram Zaaqoq; Marion Zabbe; Kai Zacharowski; Masliza Zahid; Maram Zahran; Nor Zaila Binti Zaidan; Maria Zambon; Miguel Zambrano; Alberto Zanella; Konrad Zawadka; Nurul Zaynah; Hiba Zayyad; Alexander Zoufaly; David Zucman; Mazankowski Heart Institute; The Western Australian COVID-19 Research Response.

Ethics approval

Ethics Committee approval was given by the WHO Ethics Review Committee (RPC571 and RPC572, 25 April 2013). Institutional approval was additionally obtained by participating sites including the South Central—Oxford C Research Ethics Committee in England (Ref. 13/SC/0149), the Scotland A Research Ethics Committee (Ref. 20/SS/0028) for the UK and the Human Research Ethics Committee (Medical) at the University of the Witwatersrand in South Africa as part of a national surveillance programme (M160667), which collectively represent the majority of the data. Other institutional and national approvals are in place as per local requirements.

Data availability

The ISARIC-WHO CCP, case report form and consent forms are openly available on the ISARIC website at <https://isaric.org/research/covid-19-clinical-research-resources/clinical-characterisation-protocol-ccp/>. The statistical analysis plan is openly available on the ISARIC website at <https://isaric.org/research/covid-19-clinical-research-resources/accessing-covid-19-clinical-data/approved-uses-of-platform-data/>. Most individual patient data are available to researchers approved by the Data Access Committee. The data

inventory, application form and terms of access for the COVID-19 Data Platform, hosted by the Infectious Diseases Data Observatory (IDDO), are available at <https://www.iddo.org/covid19/data-sharing/accessing-data>. All individual participant data are available to individuals from sites who have contributed to the ISARIC COVID-19 Platform via the ISARIC Partner Analysis Scheme. See details via this link: <https://isaric.org/research/isaric-partner-analysis-frequently-asked-questions/>.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

Author contributions are available as a Supplementary file at *IJE* online.

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