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Research article

Characteristics and outcomes of COVID-19 patients admitted to hospital with and without respiratory symptoms

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ABSTRACT

Background: COVID-19 is primarily known as a respiratory illness; however, many patients present to hospital without respiratory symptoms. The association between non-respiratory presentations of COVID-19 and outcomes remains unclear. We investigated risk factors and clinical outcomes in patients with no respiratory symptoms (NRS) and respiratory symptoms (RS) at hospital admission.

Methods: This study describes clinical features, physiological parameters, and outcomes of hospitalised COVID-19 patients, stratified by the presence or absence of respiratory symptoms at

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hospital admission. RS patients had one or more of: cough, shortness of breath, sore throat, runny nose or wheezing; while NRS patients did not.
Results: Of 178,640 patients in the study, 86.4 % presented with RS, while 13.6 % had NRS. NRS patients were older (median age: NRS: 74 vs RS: 65) and less likely to be admitted to the ICU (NRS: 36.7 % vs RS: 37.5 %). NRS patients had a higher crude in-hospital case-fatality ratio (NRS 41.1 % vs. RS 32.0 %), but a lower risk of death after adjusting for confounders (HR 0.88 [0.83–0.93]).
Conclusion: Approximately one in seven COVID-19 patients presented at hospital admission without respiratory symptoms. These patients were older, had lower ICU admission rates, and had a lower risk of in-hospital mortality after adjusting for confounders.

1. Background

Throughout the COVID-19 pandemic, clinical presentation and outcomes have evolved along with virus variants, knowledge of the disease, and levels of care management [1,2]. Early into the pandemic, COVID-19 was predominantly described and managed as a respiratory illness [3–5]. Meanwhile, evidence has accumulated that SARS-CoV-2 infection induces multisystem injury [6–8], affecting cardiovascular, neurological, gastrointestinal, cutaneous, endocrine, renal, musculoskeletal and haematological systems [8–10].

One of the first public health measures to contain transmission of SARS-CoV-2 was identifying febrile patients with respiratory symptoms (RS) and isolating them until laboratory diagnosis was confirmed [11]. However, a proportion of patients with COVID-19 present with no respiratory symptoms (NRS) [12]. A large proportion of COVID-19 patients require in-hospital treatment and have at least one extrapulmonary manifestation during their acute infection [13–16]. However, the clinical outcomes and factors associated with non-respiratory presentations have not been explored systematically [14].

This study attempted to bridge this knowledge gap by characterising the risk factors and clinical outcomes of patients admitted to the hospital with NRS and RS using the ISARIC-WHO database. We hypothesise that the presumed multisystem involvement in patients with NRS is associated with poor prognosis. This information can be relevant to optimise case management and provide helpful information to clinicians treating patients with COVID-19.

2. Methods

We used the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) - World Health Organization (WHO) Clinical Characterisation Protocol (CCP) for Severe Emerging Infections prospective observational data collection platform for hospitalised patients [17]. Participating sites collected the data prospectively using the ISARIC case report forms (CRFs) built on Research Electronic Data Capture (REDCap, version 8.11.11; Vanderbilt University, Nashville, TN, USA), hosted by the University of Oxford (Oxford, UK). Data were also collected on local databases in other settings and submitted for harmonisation and storage at the University of Oxford. Data were converted to Study Data Tabulation Model standards (version 1.7; Clinical Data Interchange Standards Consortium, Austin, TX, USA) to integrate data collected on locally hosted databases with data collected on the ISARIC database. All investigators retain full rights to their data. The protocol, CRFs, and study information are available on the ISARIC website (https://isaric.org/).

The ISARIC-WHO CCP was approved by the WHO ethics review committee (RPC571 and RPC572). Local ethics approval was obtained for each participating country and site according to local requirements.

2.1. Study population

We included patients admitted to the hospital between 30th January 2020 and 30th December 2022 with clinically diagnosed (i.e., symptoms and findings of SARS-CoV-2 pneumonia seen in thoracic diagnostic images) or laboratory-confirmed (i.e., positive reverse transcription polymerase chain reaction) SARS-CoV2 infection according to American Thoracic Society and Infectious Disease Society of America (ATS/IDSA) COVID-19 guidelines [18]. Patients with data on the type of oxygen supplementation status received at any time during their hospitalisation and data on the presence or absence of respiratory symptoms during the first 24 h of admission were included in the study. We excluded patients with missing age or sex, those with missing or unknown respiratory symptoms, and those with missing or negative SARS-CoV-2 status. Sex was defined as the sex assigned at birth and was categorised into male or female.

2.2. Variables and measurement

The following variables were included in the analysis: age, sex, comorbidities, complications, country of recruitment and its region according to the World Bank criteria (https://data.worldbank.org/country), vital signs during the first 24 h of admission, treatments, and clinical outcome, that is, in-patient death, and loss to follow up. The key outcome of interest was in-hospital mortality. Patients presenting with one or more symptoms of cough, shortness of breath, sore throat, runny nose or wheezing at the time of hospital admission, irrespective of other symptoms, were classified in the RS group. Regardless of other symptoms, patients not presenting with these respiratory symptoms were classified in the NRS group. Patients who were lost follow-up (i.e., transferred to another hospital or receiving ongoing care) were not considered for fatal outcomes analyses.

2.3. Statistical methods

We used descriptive statistics to summarise patient demographics and baseline characteristics. For continuous variables, characteristics were reported as medians and interquartile ranges (IQRs). For categorical variables, counts and percentages were reported. Patient characteristics were compared between the NRS and RS patient groups.

The administration of oxygen therapy at any time during hospitalisation by oxygen delivery methods – basic oxygen therapy, a high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), and extracorporeal membrane oxygenation (ECMO) – was compared between the NRS and RS patient groups. The overall baseline median (IQR) oxygen saturation (SpO_2) levels, stratified by age groups, were also compared between the two groups.

We used the Cox proportional hazards model after testing for proportional hazards in the survival analysis to assess the associations of non-respiratory symptoms with the hazard of death. We assessed the proportional hazards assumption using scaled Schoenfeld residuals. Hazard ratios (HRs) and 95 % CIs were estimated for the entire hospitalisation duration and restricted to a shorter hospitalisation duration of 7 and 14 days. Models were adjusted for age (in ten-year age bands), sex, all comorbidities and risk factors, and stratified by country. We grouped countries with less than 50 individuals into a single category.

Comorbidities and risk factors included HIV/AIDS, asthma, cardiac disease, chronic kidney disease, chronic neurological disorder, chronic pulmonary disease, dementia, diabetes, hypertension, liver disease, malignant neoplasm, malnutrition, obesity, smoking, transplantation, rheumatologic disorder and immunosuppression. Immunosuppression was defined according to specific criteria outlined in the case record form for patients who had (i) Pre-admission medication including immunosuppressants such as oral corticosteroids (excluding low-dose hydrocortisone); (ii) People identified as part of clinically extremely vulnerable groups; (iii) People who underwent bone marrow or stem cell transplants within the previous 6 months or were currently under immunosuppression medication; and (iv) People receiving immunosuppressive therapies sufficient to significantly increase risk of infection.

Patients were censored if they were lost to follow-up, which in our dataset could mean they were transferred to another facility or were receiving ongoing care at the time of most recent data collection. Time from symptom onset to time of death or censoring (time to last known to be alive), whichever occurred earlier, was used as the timescale. Patients were considered at risk from 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). All statistical analyses were performed using the R statistical programming language, version 4.0.2, and packages *survival, ggplot2*, and *finalfit*.

3. Results

We included a total of 178,640 patients (Fig. 1) from 66 countries.

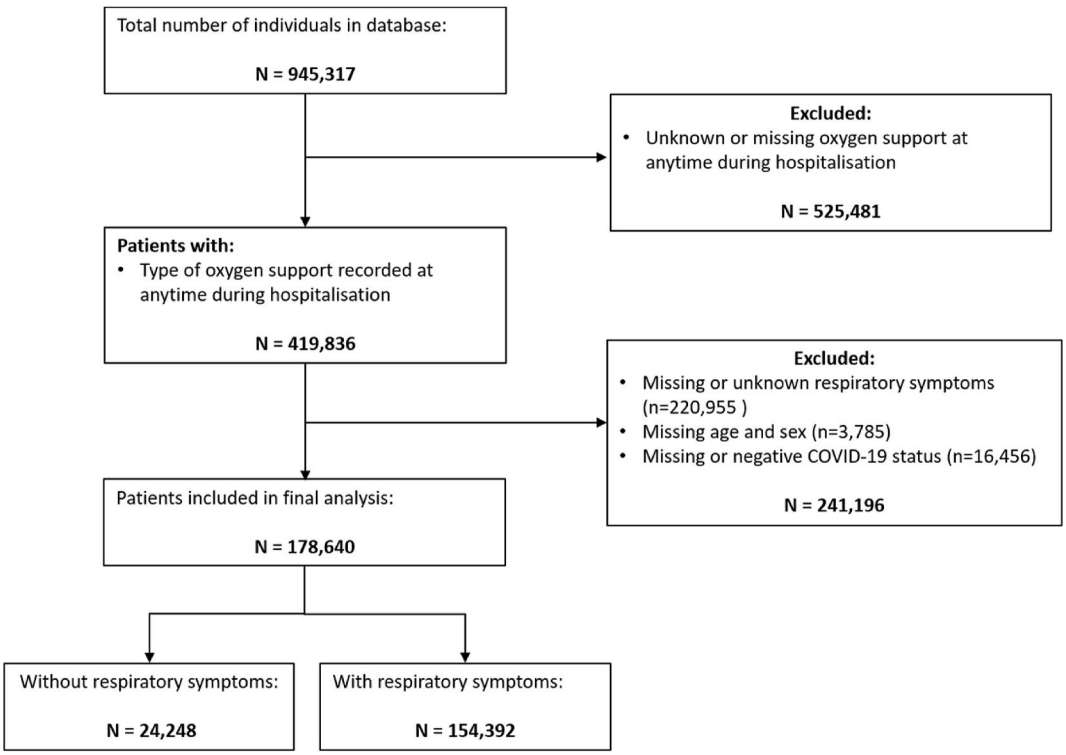

Fig. 1. Flow diagram for the study showing the number of patients included in the analysis.

Most of the patients were from high-income countries (HIC) (87.1 % [155,648/178,640] and the remainder from low-to-middle-income countries (LMIC) (12.9 % [22,992/178,640]) (Table 1). The countries that contributed the majority of the data were the United Kingdom (75.1 % [134,148/178,640]), Pakistan (4.6 % [8264/178,640]), and Spain 2.9 % [5102/178,640]) (Table A.1; Fig. A.1).

The study population included predominantly males (60.0 % [107,144/178,640]). The overall median (IQR) age was 67 (54–79) years (Table 1), with 41.1 % [73,346/178,640] of patients aged between 60 and 79 years. The most frequent comorbidities and risk factors were hypertension (47.8 % [71,908/150,413]), smoking (45.2 % [42,573/94,147]), diabetes (29.2 % [48,826/167,377]), and

Table 1
Baseline characteristics of patients, stratified by respiratory symptoms at hospital admission.

Characteristic	NRS		RS		Total Cohort		*p-value*
	Value (%)	N	Value (%)	N	Value (%)	N	
Sex, *n (%)*							
Female	10,689 (44.1)	24,248	60,807 (39.4)	154,392	71,496 (40.0)	178,640	<0.001
Male	13,559 (55.9)	24,248	93,585 (60.6)	154,392	107,144 (60.0)	178,640	
Age, overall, *Median (IQR)*	74 (60–84)	24,248	65.0 (53–77)	154,392	67 (54–79)	178,640	<0.001
Age, age-groups, *n (%)*							
0 - 19	467 (1.9)	24,248	1406 (0.9)	154,392	1873 (1.0)	178,640	<0.001
20 - 39	1453 (6.0)	24,248	12,502 (8.1)	154,392	13,955 (7.8)	178,640	
40 - 59	4035 (16.6)	24,248	44,121 (28.6)	154,392	48,156 (27.0)	178,640	
60 - 79	9451 (39.0)	24,248	63,895 (41.4)	154,392	73,346 (41.1)	178,640	
>80	8842 (36.5)	24,248	32,468 (21.0)	154,392	41,310 (23.1)	178,640	
Region, *n (%)*							
East Asia & Pacific	289 (1.2)	24,248	1633 (1.1)	154,392	1922 (1.1)	178,640	<0.001
Europe & Central Asia	18,606 (76.7)	24,248	130,273 (84.4)	154,392	148,879 (83.3)	178,640	
Latin America & Caribbean	441 (1.8)	24,248	4417 (2.9)	154,392	4858 (2.7)	178,640	
Middle East & North Africa	143 (0.6)	24,248	1954 (1.3)	154,392	2097 (1.2)	178,640	
North America	399 (1.6)	24,248	5097 (3.3)	154,392	5496 (3.1)	178,640	
South Asia	4262 (17.6)	24,248	10,746 (7.0)	154,392	15,008 (8.4)	178,640	
Sub-Saharan Africa	108 (0.4)	24,248	272 (0.2)	154,392	380 (0.2)	178,640	
Income stratification, *n (%)*							
HIC	19,129 (78.9)	24,248	136,519 (88.4)	154,392	155,648 (87.1)	178,640	<0.001
LMIC	5119 (21.1)	24,248	17,873 (11.6)	154,392	22,992 (12.9)	178,640	
Treatments, *n (%)*							
Vasopressors/Inotropes	2131 (9.0)	23,711	22,433 (15.2)	147,107	24,564 (14.4)	170,818	<0.001
Corticosteroids	10,962 (46.6)	23,535	103,551 (69.4)	149,243	114,513 (66.3)	172,778	<0.001
Intensive care unit	8752 (36.7)	23,834	56,726 (37.5)	151,224	65,478 (37.4)	175,058	0.019
Comorbidities, *n (%)*							
HIV/AIDS	71 (0.3)	22,918	647 (0.5)	134,185	718 (0.5)	157,103	<0.001
Asthma	2002 (8.5)	23,648	20,164 (14.1)	143,489	22,166 (13.3)	167,137	<0.001
Cardiac disease	7318 (30.7)	23,830	36,621 (25.1)	145,976	43,939 (25.9)	169,806	<0.001
Chronic kidney disease	4102 (17.3)	23,652	19,039 (13.3)	143,689	23,141 (13.8)	167,341	<0.001
Chronic neurological disorder	3255 (13.8)	23,606	12,839 (9.0)	143,361	16,094 (9.6)	166,967	<0.001
Chronic pulmonary disease	2943 (12.4)	23,814	24,362 (16.7)	145,618	27,305 (16.1)	169,432	<0.001
Dementia	3252 (14.0)	23,264	10,632 (7.5)	141,130	13,884 (8.4)	164,394	<0.001
Diabetes	6710 (28.5)	23,576	42,116 (29.3)	143,801	48,826 (29.2)	167,377	**0.01**
Hypertension	10,976 (50.0)	21,947	60,932 (47.4)	128,466	71,908 (47.8)	150,413	<0.001
Immunosuppression	377 (3.1)	12,229	2826 (4.2)	66,685	3203 (4.1)	78,914	<0.001
Liver disease	928 (3.9)	23,924	4257 (2.9)	147,818	5185 (3.0)	171,742	<0.001
Malignant neoplasm	2675 (11.2)	23,805	11,995 (8.3)	145,086	14,670 (8.7)	168,891	<0.001
Malnutrition	616 (2.7)	22,465	2110 (1.6)	133,873	2726 (1.7)	156,338	<0.001
Obesity	1989 (9.2)	21,707	24,790 (19.4)	127,711	26,779 (17.9)	149,418	<0.001
Smoking	4639 (47.3)	9801	37,934 (45.0)	84,346	42,573 (45.2)	94,147	<0.001
Transplantation	149 (1.2)	12,485	1045 (1.5)	69,565	1194 (1.5)	82,050	**0.009**
Rheumatologic disorder	2761 (11.8)	23,413	14,074 (10.0)	140,755	16,835 (10.3)	164,168	<0.001
Complications, *n (%)*							
Acute Kidney injury	4133 (18.1)	22,895	25,983 (18.8)	138,315	30,116 (18.7)	161,210	0.009
ARDS	1999 (8.8)	22,756	29,751 (21.8)	136,343	31,750 (20.0)	159,099	<0.001
Coagulation Disorder	701 (3.1)	22,658	6941 (5.2)	134,683	7642 (4.9)	157,341	<0.001
Deep Vein Thrombosis	118 (1.0)	11,730	740 (1.0)	73,346	858 (1.0)	85,076	**1.000**
Hyperglycaemia	1932 (8.6)	22,577	22,332 (16.6)	134,414	24,264 (15.5)	156,991	<0.001
Cardiovascular Events	550 (2.4)	22,609	3913 (2.8)	139,585	4463 (2.8)	162,194	**0.002**
Pancreatitis	186 (0.8)	22,901	415 (0.3)	137,720	601 (0.4)	160,621	<0.001
Pleural Effusion	1388 (6.1)	22,739	8992 (6.6)	135,803	10,380 (6.5)	158,542	**0.004**
Pneumothorax	222 (1.0)	22,771	3094 (2.3)	136,166	3316 (2.1)	158,937	<0.001
Pulmonary Embolism	379 (2.2)	17,030	4653 (4.8)	96,543	5032 (4.4)	113,573	<0.001
Clinical outcomes, *n (%)*							
Loss to follow up	4484 (18.6)	24,062	15,190 (10.1)	150,944	19,674 (11.2)	175,006	<0.001
In-Hospital Mortality	8052 (41.1)	19,578	44,516 (32.0)	139,202	52,568 (33.8)	158,780	

Bold p values indicate no statistical significance.
HIC* = High-income country; LMIC** = Low-to-middle income country; ARDS*** = acute respiratory distress syndrome.

cardiac disease (25.9 % [43,939/169,806]) (Table 1). The most frequent complications following admission were acute respiratory distress syndrome (ARDS) (20.0 % [31,750/159,099]) and acute kidney injury (AKI) (18.7 % [30,116/161,210]).

At hospital admission, 13.6 % [24,248/178,640] of patients had no respiratory symptoms. When analysing the cohort per year of the pandemic, the proportion of patients admitted in 2020 with NRS was higher than those admitted in 2021 (2020: 14.6 % [15,320/105,056] vs 2021: 11.1 % [7414/67,054]) (Table A.1).

3.1. Clinical characteristics of patients with NRS and RS

Compared to RS patients, NRS patients were older, with a median (IQR) age of 74 (60–84) vs 65 (53–77) for RS patients. There were more male than female patients in both NRS and RS groups, and more male patients in the RS than the NRS group (NRS: 55.9 % [13,559/24,248] and RS: 60.6 % [93,585/154,392]) (Table 1).

The frequency of some comorbidities and risk factors varied between patients with or without respiratory symptoms: hypertension (NRS: 50.0 % [10,976/21,947] vs RS: 47.4 % [60,392/128,466], $p < 0.001$), smoking (NRS: 47.3 % [4639/9801] vs RS: 45.0 % [37,934/84,346], $p < 0.001$), and cardiac disease (NRS: 30.7 % [7318/23,830] vs RS: 25.1 % [36,621/145,976], $p < 0.001$) were more frequent among patients with NRS; the difference between patients with diabetes was not statistically significant (NRS: 28.5 % [6710/23,576] vs RS: 29.3 % [42,116/143,801], $p = 0.01$). Chronic pulmonary disease and asthma were less frequent among patients with NRS (NRS: 12.4 % [2943/23,814] vs RS: 16.7 % [24,362/145,618], $p < 0.001$; NRS: 8.5 % [2002/23,648] vs RS: 14.1 % [20,164/143,489]), respectively) (Table 1). The distribution of comorbidities and risk factors is presented overall in Fig. 2 and by age groups in Fig. A.2.

3.2. Disease severity, systemic complications and outcomes among patients with NRS and RS

During hospitalisation, NRS patients were less likely to be admitted to the ICU (NRS: 36.7 % [8752/23,834] vs RS: 37.5 % [56,726/151,224], p=0.019); and were less likely to receive vasopressors (NRS: 9.0 %, [2131/23,711] vs RS: 14.4 %, [22,433/147,107], $p < 0.001$), and corticosteroids (NRS: 46.6 %, [10,962/23,535] vs RS: 69.4 %, [103,551/149,243], $p < 0.001$) (Table 1).

Regarding in-hospital complications, patients with NRS had fewer pulmonary dysfunctions such as ARDS (NRS: 8.8 % [1999/22,756] vs RS: 21.8 % [29,751/136,343], $p < 0.001$); and a significantly lower proportion of coagulation disorders (NRS: 3.1 % [701/22,658] vs RS: 5.2 % [6941/134,683]); hyperglycaemia (NRS: 8.6 % [1932/22,577] vs RS: 16.6 % [22,332/134,414]); pulmonary embolism (NRS: 2.2 % [379/17,030] vs RS: 4.8 % [4653/96,543]); and pneumothorax (NRS: 1.0 % [222/22,771] vs RS: 2.3 % [3094/136,166] (all $p < 0.001$), during their hospitalisation. All systemic complications are reported in Table 1. Finally, patients with NRS had a higher in-hospital mortality rate than patients with RS (NRS: 41.1 % [8052/19,578] vs RS: 32.0 % [44,516/139,202], $p < 0.001$) (Table 1).

In the Cox proportional hazards survival analysis, adjusted for age, sex, country, all comorbidities and risk factors, patients with NRS had a lower in-patient mortality risk than patients with RS during their entire hospitalisation (HR [95 % CI] 0.88 (0.83–0.93, p < 0.001) (Table 2; Fig. 3). The in-patient mortality risk remained similar after performing a sensitivity analysis restricted to a shorter hospitalisation duration of 7 and 14 days; however, this was not statistically significant after when restricted to 7 days (Table A.3; Table A.4).

Other risk factors associated with the highest increased mortality risks were pre-existing transplantation (HR 1.34 [1.14–1.57], $p <$

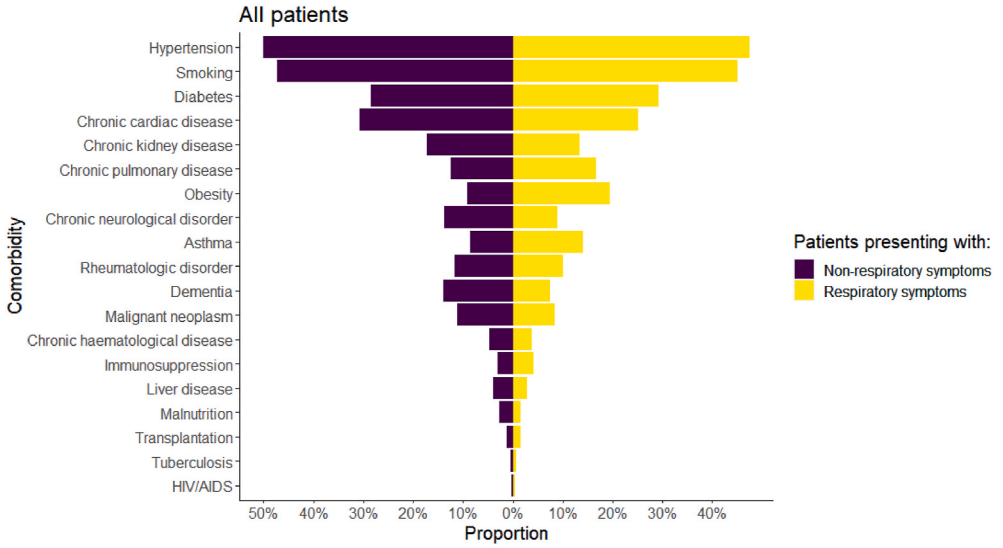

Fig. 2. Frequency of comorbidities for all patients, stratified by respiratory symptoms.

Table 2
Hazard ratios (HR) of death by respiratory symptoms group from Cox Proportional Hazards analysis*.

Variable	HR (95 % CI, p value)	Total Cohort	
Age group		**Value n (%)**	**N**
0 - 9	*Reference*		
10 - 19	1.20 (0.30–4.79, p = 0.799)	888 (0.5)	171,828
20 - 29	1.99 (0.69–5.72, p = 0.201)	3682 (2.1)	171,828
30 - 39	1.61 (0.58–4.43, p = 0.358)	9776 (5.7)	171,828
40 - 49	3.21 (1.19–8.63, p = 0.021)	17,032 (9.9)	171,828
50 - 59	5.65 (2.11–15.10, p = 0.001)	28,912 (16.8)	171,828
60 - 69	10.13 (3.80–27.04, p < 0.001)	33,530 (19.5)	171,828
70 - 79	16.25 (6.09–43.36, p < 0.001)	36,848 (21.4)	171,828
80 - 89	22.50 (8.43–60.03, p < 0.001)	30,494 (17.7)	171,828
90 - 99	27.53 (10.30–73.57, p < 0.001)	9558 (5.6)	171,828
>100	38.33 (13.52–108.65, p < 0.001)	241 (0.1)	171,828
Sex			
Female	Reference		
Male	1.30 (1.25–1.36, p < 0.001)	102,878 (59.9)	171,828
Symptoms			
Respiratory symptoms	Reference		
Non-respiratory symptoms	0.88 (0.83–0.93, p < 0.001)	23,477 (13.7)	171,828
Comorbidities**			
HIV/AIDS	0.92 (0.60–1.39, p = 0.685)	620 (0.4)	151,214
Asthma	0.99 (0.93–1.05, p = 0.652)	21,356 (13.3)	160,638
Cardiac disease	1.20 (1.15–1.25, p < 0.001)	42,462 (26.0)	163,233
Chronic kidney disease	1.21 (1.15–1.27, p < 0.001)	22,456 (14.0)	160,837
Chronic neurological disorder	1.12 (1.05–1.19, p < 0.001)	15,541 (9.7)	160,485
Chronic pulmonary disease	1.22 (1.16–1.28, p < 0.001)	26,332 (16.2)	162,872
Dementia	1.25 (1.17–1.33, p < 0.001)	13,585 (8.6)	157,938
Diabetes	1.17 (1.12–1.22, p < 0.001)	47,095 (29.3)	160,869
Hypertension	1.02 (0.98–1.07, p = 0.284)	69,044 (47.9)	144,286
Immunosuppression	1.24 (1.12–1.36, p < 0.001)	3151 (4.1)	77,667
Liver disease	1.33 (1.21–1.48, p < 0.001)	4981 (3.0)	165,130
Malignant neoplasm	1.30 (1.23–1.37, p < 0.001)	14,289 (8.8)	162,359
Malnutrition	1.19 (1.06–1.33, p = 0.003)	2593 (1.7)	151,547
Obesity	1.06 (1.00–1.12, p = 0.039)	25,777 (17.8)	144,740
Rheumatologic disorder	0.96 (0.91–1.02, p = 0.224)	16,169 (10.3)	157,739
Smoking	1.07 (1.02–1.11, p = 0.003)	41,366 (45.4)	91,130
Transplantation	1.34 (1.14–1.57, p < 0.001)	1175 (1.5)	80,847

* *Cox proportional hazards model adjusted for age, sex, country, all comorbidities and risk factors.*
** The reference group for comorbidities is not having the particular comorbidity/risk factor.

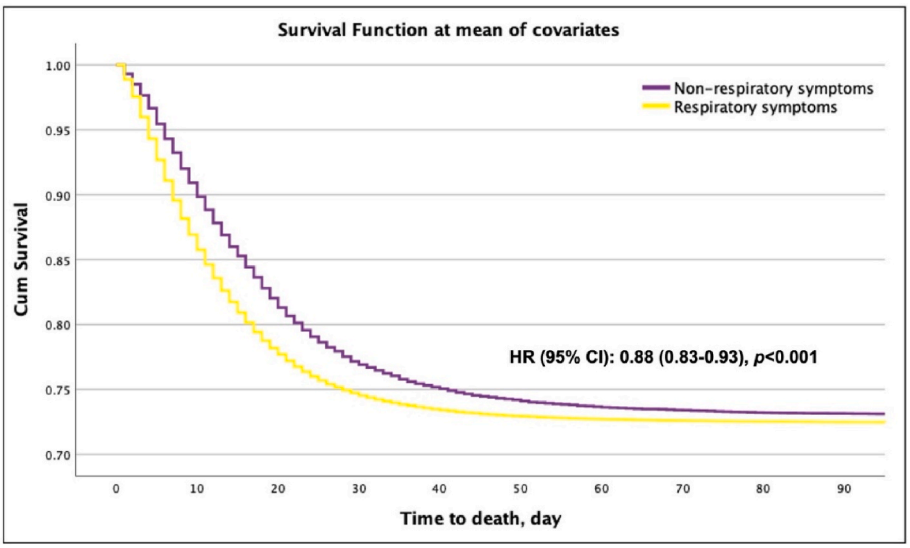

Fig. 3. Kaplan—Meier Plot of patients' outcomes stratified by respiratory symptoms.

Table 3
Physiological parameters of patients during the first 24 h, stratified by respiratory symptoms at hospital admission.

Measure	NRS (n = 24,248)	RS (n = 154,392)	Total Cohort (n = 178,640)	*n (%)*
Physiological parameters, *median* (IQR)				
Oxygen saturation *(SpO_2)*	96 (93–98)	95 (92–97)	95 (92–97)	80,935 (45.3)
Heart rate *(beats/min)*	87 (76–100)	92 (80–105)	91 (80–104)	162,420 (90.9)
Respiratory rate *(breaths/min)*	20 (18–23)	23 (20–28)	22 (20–28)	159,712 (89.4)
Systolic blood pressure *(mmHg)*	130 (115–145)	129 (115–143)	129 (115–143)	163,314 (91.4)
Diastolic blood pressure *(mmHg)*	73 (65–82)	75 (66–83)	74 (66–83)	163,492 (91.5)
Temperature *(°C)*	36.8 (36.4–37.4)	37.2 (36.7–38)	37.1 (36.6–37.9)	162,450 (90.9)

Table 4
Oxygen supplementation at any time during hospitalisation stratified by respiratory symptoms at hospital admission.

Treatment	NRS, *n* (%)	N	RS, *n* (%)	N	Total Cohort, *n* (%)	*p*-value
Basic oxygen therapy	12,771 (52.7)	24,248	66,664 (43.2)	154,392	178,640	<0.001
[a]Any advanced oxygen	11,477 (47.3)	24,248	87,728 (56.8)	154,392	178,640	<0.001
HFNC	5416 (22.6)	23,962	53,648 (35.7)	150,288	174,250	<0.001
NIV	3491 (14.4)	24,232	45,627 (29.7)	153,695	177,927	<0.001
IMV	6052 (25.0)	24,193	35,840 (23.3)	153,551	177,744	<0.001
ECMO	151 (0.6)	24,126	2263 (1.5)	152,002	176,128	<0.001

HFNC = High Flow nasal cannula; NIV = Non-invasive ventilation.
IMV = Invasive mechanical ventilation; ECMO = Extracorporeal membrane oxygenation.
[a] Any advanced oxygen = One or more of HFNC, NIV, IMV, ECMO.

0.001), liver disease (1.33 [1.21–1.48], $p < 0.001$), and malignant neoplasm (1.30 [1.23–1.37], p < 0.001) (Table 2).

3.3. Oxygen saturation at hospital admission and oxygen supplementation during hospitalisation

The overall baseline median (IQR) SpO_2 was higher in NRS patients (NRS: 96 [93–98] vs RS: 95 [92–97], $p < 0.001$ (Table 3; Fig. 4). When stratified by age, NRS patients had higher SpO_2 levels, and the difference between groups also increased by age (Fig. A.3).

We compared the administration of oxygen therapy at any time during hospitalisation by oxygen delivery methods (Table 4). During hospitalisation, basic oxygen therapy was the most frequent form of oxygen therapy used in NRS patients (52.7 % [12,771/24,248]). Patients with NRS were less likely to receive any advanced oxygen therapy (one or more of HFNC, IMV, NIV or ECMO) compared to RS patients (NRS: 47.3 % [11,477/24,248] and RS: 56.8 % [87,728/154,392], $p < 0.001$). However, NRS patients were more likely to receive IMV compared to RS patients (NRS: 25.0 % [6052/24,193] and RS: 23.3 % [35,840/153,551], $p < 0.001$) (Table 4).

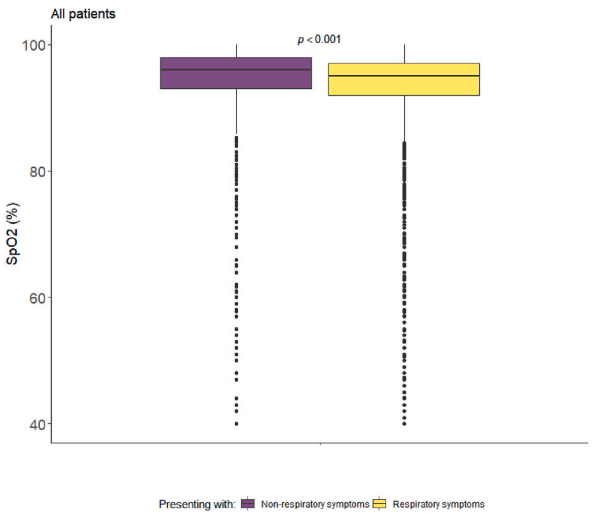

Fig. 4. Boxplots of oxygen saturation (SpO_2) for all patients, stratified by respiratory symptoms.

4. Discussion

In this large multicentre and prospective cohort, we found that around one in seven hospitalised patients diagnosed with SARS-CoV-2 had no respiratory symptoms of cough, shortness of breath, sore throat, runny nose or wheezing at hospital admission. Compared to those who presented with RS, patients with NRS were older and more likely to suffer from comorbidities other than asthma and chronic pulmonary disease. During hospitalisation, those with NRS were less likely to receive treatment with vasopressors, corticosteroids, and admission to the ICU; however, they developed respiratory failure comparable to those with RS. Notably, the risk for in-hospital mortality was lower in patients with NRS after adjusting for confounders.

COVID-19 has a broad clinical spectrum [10], though its principal manifestation is respiratory [19,20]. Hence, respiratory symptoms have been a critical criterion for identifying SARS-CoV-2 infection [21]. Thus, patients with lung comorbidities have been prioritised during vaccination campaigns for patient care since they are at a higher risk of developing more severe respiratory symptoms [22–24]. This can be attributable to the already dysregulated pulmonary physiology [25,26]. In contrast, at least in the initial phases of COVID-19, patients without apparent respiratory symptoms may be overlooked [8,9,27]. Observational studies have found that almost 30 % of patients manifest atypical symptoms, increasing the risk of misdiagnosis and leading to delays in healthcare, the development of multiorgan failure, and worse clinical outcomes [28–31]. Our results show that most patients with NRS admitted to the hospital required supplementary oxygen at some point during their hospital stay, and almost a third were admitted to ICU, which aligns with prior data [28–31].

One of the main results of our study is that patients with NRS had higher crude in-hospital mortality risk but lower risk than RS patients after adjusting for confounders. Some small prior studies have shown that atypical (most frequently patients with NRS) COVID-19 symptoms are frequent in older patients and are associated with higher mortality [29,32]. Hariyanto et al. and Raymond Pranata et al., in a systematic review and meta-regression, found a significant association of extrapulmonary symptoms, such as delirium with death (OR 1.90 [1.55–2.33], $p < 0.00001$ and 1.50 [1.16, 1.94], $p = 0.002$, respectively). This relationship was not significantly influenced by age, sex, hypertension, diabetes, and dementia [33,34]. Additionally, patients with NRS could develop profound hypoxemia without dyspnoea, called “silent or happy hypoxemia”, which may deteriorate rapidly without warning and has been associated with increased mortality [35]. However, this association remains controversial [36–38].

Early during the pandemic, respiratory symptoms and fever were used to detect patients with possible SARS-CoV-2 infection. However, we found that both patients presenting with and without respiratory symptoms early into the course of COVID-19 could subsequently develop respiratory failure and systemic complications, require oxygen support and die. Targeting patients with respiratory symptoms and/or reduced oxygen saturation will overlook those cases. Jiayi Tan et al., in a systematic review and meta-analysis, found that some public health interventions, such as stroke education campaigns on stroke symptom recognition and intention to call emergency medical services increased the estimated pool risk ratio (RR) for symptoms recognition (RR 1.20) and intention to reach emergency services (RR 1.19) [39].

Our study has strengths and limitations that should be recognised. Firstly, our study population was composed mainly of patients in HICs, which limits the generalisability of these results. Secondly, we do not have complete data on respiratory symptoms, nor extrapulmonary symptoms (i.e., gastrointestinal, cardiac, neurological, among others), during hospitalisation. Therefore, we cannot investigate the association of the progression and impact of respiratory symptoms, nor extrapulmonary symptoms, with outcomes in patients who present with RS or NRS. Moreover, our study had limited data on SARS-CoV-2 variants which restricted our ability to analyse their impact on COVID-19 disease progression. Future studies that incorporate detailed variant data are essential to provide a more in-depth understanding of their impact on COVID-19 patients admitted to hospital with and without respiratory symptoms. Finally, throughout the COVID-19 pandemic, hospitalised patients were treated with a wide range of medications and supportive care protocols, which may bias the factors associated with fatality using observational study methodologies in a fluctuating setting. However, including large numbers of patients over a long period adds to the robustness of our data. To our knowledge, this is one of the largest cohorts comparing patients with NRS and RS globally.

In conclusion, while many COVID-19 patients are hospitalised with respiratory symptoms, about one in seven do not have obvious respiratory symptoms on admission. These NRS patients are usually older and have multiple chronic conditions often unrelated to pulmonary comorbidities. While in the hospital, these patients are less likely to be admitted to the ICU and less likely to receive vasopressors and corticosteroids. About two in five patients may die, but their risk for in-hospital mortality is lower than those presenting with respiratory symptoms after adjusting for confounders. Therefore, more strategies should be implemented to identify patients with COVID-19 and to prevent fatal outcomes in this at-risk population.

Ethics and consent statement

This observational study required no change to clinical management. The ISARIC-WHO Clinical Characterisation Protocol was approved by the World Health Organization Ethics Review Committee (RPC571 and RPC572 on 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) and the Scotland A Research Ethics Committee (Ref 20/SS/0028) for the United Kingdom, representing the majority of the data. Requirement for consent was waived by the confidentiality advisory group of UK Health Regulations Authority and approved by the sponsor.

Other institutional and national approvals were obtained by participating sites as per local requirements. Regionally appropriate decisions regarding a waiver or requirement of patient consent and/or assent were made by each committee and implemented at the sites.

Data availability

The data that underpin this analysis are highly detailed clinical data on individuals hospitalised with COVID-19. Due to the sensitive nature of these data and the associated privacy concerns, they are available via a governed data access mechanism following review of a data access committee. Data can be requested via the IDDO COVID-19 Data Sharing Platform (http://www.iddo.org/covid-19). The Data Access Application, Terms of Access and details of the Data Access Committee are available on the website. Briefly, the requirements for access are a request from a qualified researcher working with a legal entity who have a health and/or research remit; a scientifically valid reason for data access which adheres to appropriate ethical principles. The full terms are at: https://www.iddo.org/document/covid-19-data-access-guidelines. A small subset of sites who contributed data to this analysis have not agreed to pooled data sharing as above. In the case of requiring access to these data, please contact the corresponding author in the first instance who will look to facilitate access.

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Tirupakuzhi Vijayaraghavan: Investigation, Writing – review & editing. **Prasan Kumar Panda:** Writing – review & editing, Investigation. **Ignacio Martin-Loeches:** Writing – review & editing, Investigation. **Shinichiro Ohshimo:** Writing – review & editing, Investigation. **Arie Zainul Fatoni:** Investigation, Writing – review & editing. **Peter Horby:** Conceptualization, Writing – review & editing. **Jake Dunning:** Writing – review & editing, Conceptualization, Investigation, Methodology, Writing – original draft. **Jordi Rello:** Writing – review & editing, Investigation. **Laura Merson:** Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Amanda Rojek:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization, Methodology. **Michel Vaillant:** Writing – original draft, Methodology, Investigation, Conceptualization, Writing – review & editing. **Piero Olliaro:** Writing – original draft, Methodology, Investigation, Conceptualization, Writing – review & editing. **Luis Felipe Reyes:** Methodology, Writing – original draft, Writing – review & editing, Conceptualization, Investigation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:IML declared lectures for Gilead, Thermofisher, MSD; advisory board participation for Fresenius Kabi, Advanz Pharma, Gilead, Accelerate, Merck; and consulting fees for Gilead outside of the submitted work.

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APPENDIX A

Table A.1
Demographics of patients, stratified by respiratory symptoms.

Characteristic	NRS Value (%)	RS Value (%)	Total Cohort Value (%) N	
Year of admission				
2020	15,320 (63.4)	89,736 (58.2)	105,056 (58.9)	178,297
2021	7414 (30.7)	59,640 (38.7)	67,054 (37.6)	178,297
2022	1433 (5.9)	4754 (3.1)	6187 (3.5)	178,297
Country				
United Kingdom	17,580 (72.5)	116,568 (75.5)	134,148 (75.1)	178,640
Pakistan	1954 (8.1)	6310 (4.1)	8264 (4.6)	178,640
Spain	385 (1.6)	4717 (3.1)	5102 (2.9)	178,640
Nepal	752 (3.1)	2717 (1.8)	3469 (1.9)	178,640
India	1556 (6.4)	1719 (1.1)	3275 (1.8)	178,640
United States	173 (0.7)	2578 (1.7)	2751 (1.5)	178,640
Canada	226 (0.9)	2519 (1.6)	2745 (1.5)	178,640
Brazil	300 (1.2)	2328 (1.5)	2628 (1.5)	178,640
Italy	92 (0.4)	2180 (1.4)	2272 (1.3)	178,640
France	95 (0.4)	1529 (1.0)	1624 (0.9)	178,640
Netherlands	72 (0.3)	1552 (1.0)	1624 (0.9)	178,640
Peru	68 (0.3)	1189 (0.8)	1257 (0.7)	178,640
Ireland	119 (0.5)	818 (0.5)	937 (0.5)	178,640
Portugal	106 (0.4)	756 (0.5)	862 (0.5)	178,640
Indonesia	58 (0.2)	751 (0.5)	809 (0.5)	178,640
Kuwait	32 (0.1)	771 (0.5)	803 (0.4)	178,640
Belgium	70 (0.3)	533 (0.3)	603 (0.3)	178,640
Russian Federation	23 (0.1)	501 (0.3)	524 (0.3)	178,640

(*continued on next page*)

Table A.1 (*continued*)

Characteristic	NRS Value (%)	RS Value (%)	Total Cohort Value (%) N	
Colombia	43 (0.2)	472 (0.3)	515 (0.3)	178,640
Norway	19 (0.1)	424 (0.3)	443 (0.2)	178,640
Malaysia	151 (0.6)	222 (0.1)	373 (0.2)	178,640
Qatar	22 (0.1)	317 (0.2)	339 (0.2)	178,640
Australia	32 (0.1)	291 (0.2)	323 (0.2)	178,640
Libya	11 (0.0)	270 (0.2)	281 (0.2)	178,640
Ukraine	0 (0.0)	210 (0.1)	210 (0.1)	178,640
South Africa	8 (0.0)	184 (0.1)	192 (0.1)	178,640
United Arab Emirates	7 (0.0)	168 (0.1)	175 (0.1)	178,640
Romania	26 (0.1)	145 (0.1)	171 (0.1)	178,640
Argentina	14 (0.1)	156 (0.1)	170 (0.1)	178,640
Philippines	33 (0.1)	125 (0.1)	158 (0.1)	178,640
Saudi Arabia	45 (0.2)	98 (0.1)	143 (0.1)	178,640
Bolivia	4 (0.0)	137 (0.1)	141 (0.1)	178,640
Germany	8 (0.0)	122 (0.1)	130 (0.1)	178,640
Chile	6 (0.0)	104 (0.1)	110 (0.1)	178,640
Israel	20 (0.1)	82 (0.1)	102 (0.1)	178,640
New Zealand	3 (0.0)	98 (0.1)	101 (0.1)	178,640
Egypt	0 (0.0)	94 (0.1)	94 (0.1)	178,640
Ghana	57 (0.2)	36 (0.0)	93 (0.1)	178,640
Syrian Arab Republic	1 (0.0)	92 (0.1)	93 (0.1)	178,640
Estonia	0 (0.0)	87 (0.1)	87 (0.0)	178,640
Austria	4 (0.0)	77 (0.0)	81 (0.0)	178,640
Gambia	40 (0.2)	31 (0.0)	71 (0.0)	178,640
Japan	4 (0.0)	61 (0.0)	65 (0.0)	178,640
China	6 (0.0)	53 (0.0)	59 (0.0)	178,640
Palestine, State of	4 (0.0)	49 (0.0)	53 (0.0)	178,640
Greece	4 (0.0)	19 (0.0)	23 (0.0)	178,640
Mexico	0 (0.0)	21 (0.0)	21 (0.0)	178,640
Czechia	3 (0.0)	13 (0.0)	16 (0.0)	178,640
Korea, Republic of	1 (0.0)	15 (0.0)	16 (0.0)	178,640
Guinea	2 (0.0)	12 (0.0)	14 (0.0)	178,640
Lao PDR	0 (0.0)	13 (0.0)	13 (0.0)	178,640
Honduras	6 (0.0)	6 (0.0)	12 (0.0)	178,640
Jordan	1 (0.0)	10 (0.0)	11 (0.0)	178,640
Poland	0 (0.0)	9 (0.0)	9 (0.0)	178,640
Turkey	0 (0.0)	9 (0.0)	9 (0.0)	178,640
Congo	0 (0.0)	4 (0.0)	4 (0.0)	178,640
Ecuador	0 (0.0)	4 (0.0)	4 (0.0)	178,640
Thailand	0 (0.0)	4 (0.0)	4 (0.0)	178,640
Iraq	0 (0.0)	3 (0.0)	3 (0.0)	178,640
Sudan	0 (0.0)	3 (0.0)	3 (0.0)	178,640
Senegal	1 (0.0)	1 (0.0)	2 (0.0)	178,640
Hungary	0 (0.0)	2 (0.0)	2 (0.0)	178,640
Taiwan	1 (0.0)	0 (0.0)	1 (0.0)	178,640
Cameroon	0 (0.0)	1 (0.0)	1 (0.0)	178,640
Gibraltar	0 (0.0)	1 (0.0)	1 (0.0)	178,640
Sweden	0 (0.0)	1 (0.0)	1 (0.0)	178,640

Table A.2
General symptoms at admission, stratified by respiratory symptoms.

Variable	NRS		RS		Total Cohort	
	Value (%)	N	Value (%)	N	Value (%)	N
Conjunctivitis	41 (0.2)	24,090	443 (0.3)	128,763	484 (0.3)	152,853
Ear pain	24 (0.1)	22,449	359 (0.3)	105,267	383 (0.3)	127,716
Headache	928 (3.9)	24,036	15,737 (12.2)	128,518	16,665 (10.9)	152,554
Lost/altered sense of smell	224 (1.0)	21,699	9528 (8.8)	108,566	9752 (7.5)	130,265
Lost/altered sense of taste	318 (1.5)	21,708	11,387 (10.7)	106,209	11,705 (9.2)	127,917
Chest pain	889 (3.7)	24,187	22,020 (16.0)	137,793	22,909 (14.1)	161,980
Abdominal pain	2072 (8.6)	24,121	9188 (6.8)	134,226	11,260 (7.1)	158,347
Joint pain	1571 (6.5)	24,030	27,231 (21.2)	128,510	28,802 (18.9)	152,540
Fatigue	4521 (18.8)	24,028	62,837 (46.5)	135,011	67,358 (42.4)	159,039
Fever	7070 (29.3)	24,130	101,835 (69.0)	147,679	108,905 (63.4)	171,809
Vomiting/nausea	2991 (12.4)	24,185	23,593 (17.0)	138,867	26,584 (16.3)	163,052
Diarrhoea	2085 (8.6)	24,168	25,406 (18.2)	139,405	27,491 (16.8)	163,573
Severe Dehydration	1284 (14.2)	9016	7126 (12.2)	58,293	8410 (12.5)	67,309
Skin rash	452 (1.9)	24,085	2414 (1.8)	131,269	2866 (1.8)	155,354

(*continued on next page*)

Table A.2 (*continued*)

Variable	NRS		RS		Total Cohort	
	Value (%)	N	Value (%)	N	Value (%)	N
Bleeding	559 (2.3)	24,124	1735 (1.3)	133,709	2294 (1.5)	157,833
Confusion	5275 (21.9)	24,091	23,117 (16.5)	139,827	28,392 (17.3)	163,918
Seizures	496 (2.1)	24,117	997 (0.7)	136,215	1493 (0.9)	160,332
Lymphadenopathy	62 (0.3)	23,952	607 (0.5)	128,575	669 (0.4)	152,527

Table A.3
Hazard ratios (HR) of death by symptoms group from Cox Proportional Hazards analysis[a], restricted to 7 days hospitalisation

Variable	HR (95 % CI, p value)	Total Cohort	
Age group		**Value n (%)**	**N**
0–9	Reference		
10–19	1.21 (0.30–4.85, p = 0.785)	888 (0.5)	171,828
20–29	2.03 (0.71–5.83, p = 0.189)	3682 (2.1)	171,828
30–39	1.63 (0.59–4.49, p = 0.345)	9776 (5.7)	171,828
40–49	3.26 (1.21–8.75, p = 0.019)	17,032 (9.9)	171,828
50–59	5.76 (2.15–15.38, p < 0.001)	28,912 (16.8)	171,828
60–69	10.29 (3.85–27.46, p < 0.001)	33,530 (19.5)	171,828
70–79	16.22 (6.08–43.27, p < 0.001)	36,848 (21.4)	171,828
80–89	22.13 (8.29–59.05, p < 0.001)	30,494 (17.7)	171,828
90–99	26.95 (10.09–72.03, p < 0.001)	9558 (5.6)	171,828
>100	35.96 (12.68–101.97, p < 0.001)	241 (0.1)	171,828
Sex			
Female	Reference		
Male	1.29 (1.24–1.35, p < 0.001)	102,878 (59.9)	171,828
Symptoms			
Respiratory symptoms	Reference		
Non-respiratory symptoms	0.91 (0.86–0.96, p = 0.001)	23,477 (13.7)	171,828
Comorbidities[b]			
HIV/AIDS	0.92 (0.61–1.40, p = 0.696)	620 (0.4)	151,214
Asthma	0.98 (0.93–1.04, p = 0.599)	21,356 (13.3)	160,638
Cardiac disease	1.19 (1.14–1.24, p < 0.001)	42,462 (26.0)	163,233
Chronic kidney disease	1.21 (1.15–1.27, p < 0.001)	22,456 (14.0)	160,837
Chronic neurological disorder	1.11 (1.04–1.18, p = 0.001)	15,541 (9.7)	160,485
Chronic pulmonary disease	1.21 (1.16–1.27, p < 0.001)	26,332 (16.2)	162,872
Dementia	1.23 (1.15–1.31, p < 0.001)	13,585 (8.6)	157,938
Diabetes	1.16 (1.12–1.22, p < 0.001)	47,095 (29.3)	160,869
Hypertension	1.02 (0.98–1.06, p = 0.363)	69,044 (47.9)	144,286
Immunosuppression	1.24 (1.13–1.37, p < 0.001)	3151 (4.1)	77,667
Liver disease	1.34 (1.21–1.49, p < 0.001)	4981 (3.0)	165,130
Malignant neoplasm	1.29 (1.22–1.36, p < 0.001)	14,289 (8.8)	162,359
Malnutrition	1.16 (1.03–1.30, p = 0.011)	2593 (1.7)	151,547
Obesity	1.06 (1.00–1.12, p = 0.043)	25,777 (17.8)	144,740
Rheumatologic disorder	0.96 (0.90–1.02, p = 0.146)	16,169 (10.3)	157,739
Smoking	1.07 (1.02–1.11, p = 0.002)	41,366 (45.4)	91,130
Transplantation	1.34 (1.14–1.57, p < 0.001)	1175 (1.5)	80,847

[a] *Cox proportional hazards model adjusted for age, sex, country, all comorbidities and risk factors.*
[b] The reference group for comorbidities is not having the particular comorbidity/risk factor.

Table A.4
Hazard ratios (HR) of death by symptoms group from Cox Proportional Hazards analysis[a], restricted to 14 days hospitalisation

Variable	HR (95 % CI, p value)	Total Cohort	
Age group		**Value n (%)**	**N**
0–9	Reference		
10–19	1.20 (0.30–4.80, p = 0.796)	888 (0.5)	171,828
20–29	2.00 (0.70–5.75, p = 0.198)	3682 (2.1)	171,828
30–39	1.61 (0.58–4.44, p = 0.356)	9776 (5.7)	171,828
40–49	3.21 (1.20–8.64, p = 0.021)	17,032 (9.9)	171,828
50–59	5.65 (2.11–15.09, p = 0.001)	28,912 (16.8)	171,828
60–69	10.10 (3.79–26.96, p < 0.001)	33,530 (19.5)	171,828
70–79	16.13 (6.04–43.03, p < 0.001)	36,848 (21.4)	171,828
80–89	22.25 (8.34–59.37, p < 0.001)	30,494 (17.7)	171,828
90–99	27.17 (10.17–72.60, p < 0.001)	9558 (5.6)	171,828
>100	37.90 (13.37–107.46, p < 0.001)	241 (0.1)	171,828
Sex			
Female	Reference		
Male	1.30 (1.25–1.35, p < 0.001)	102,878 (59.9)	171,828

(*continued on next page*)

Table A.4 (*continued*)

Variable	HR (95 % CI, p value)	Total Cohort	
Symptoms			
Respiratory symptoms	Reference		
Non-respiratory symptoms	0.88 (0.84–0.93, p < 0.001)	23,477 (13.7)	171,828
Comorbidities[b]			
HIV/AIDS	0.90 (0.59–1.36, p = 0.609)	620 (0.4)	151,214
Asthma	0.99 (0.93–1.05, p = 0.662)	21356 (13.3)	160638
Cardiac disease	1.20 (1.15–1.25, p < 0.001)	42462 (26.0)	163233
Chronic kidney disease	1.21 (1.15–1.27, p < 0.001)	22456 (14.0)	160837
Chronic neurological disorder	1.12 (1.05–1.19, p = 0.001)	15541 (9.7)	160485
Chronic pulmonary disease	1.22 (1.16–1.28, p < 0.001)	26332 (16.2)	162872
Dementia	1.24 (1.17–1.33, p < 0.001)	13585 (8.6)	157938
Diabetes	1.17 (1.12–1.22, p < 0.001)	47095 (29.3)	160869
Hypertension	1.02 (0.98–1.07, p = 0.282)	69044 (47.9)	144286
Immunosuppression	1.23 (1.12–1.36, p < 0.001)	3151 (4.1)	77667
Liver disease	1.34 (1.21–1.48, p < 0.001)	4981 (3.0)	165130
Malignant neoplasm	1.29 (1.23–1.37, p < 0.001)	14289 (8.8)	162359
Malnutrition	1.17 (1.04–1.31, p = 0.007)	2593 (1.7)	151547
Obesity	1.06 (1.00–1.12, p = 0.051)	25777 (17.8)	144740
Rheumatologic disorder	0.96 (0.91–1.02, p = 0.214)	16169 (10.3)	157739
Smoking	1.07 (1.02–1.11, p = 0.002)	41366 (45.4)	91130
Transplantation	1.34 (1.14–1.58, p < 0.001)	1175 (1.5)	80847

[a] *Cox proportional hazards model adjusted for age, sex, country, all comorbidities and risk factors.*

[b] The reference group for comorbidities is not having the particular comorbidity/risk factor.

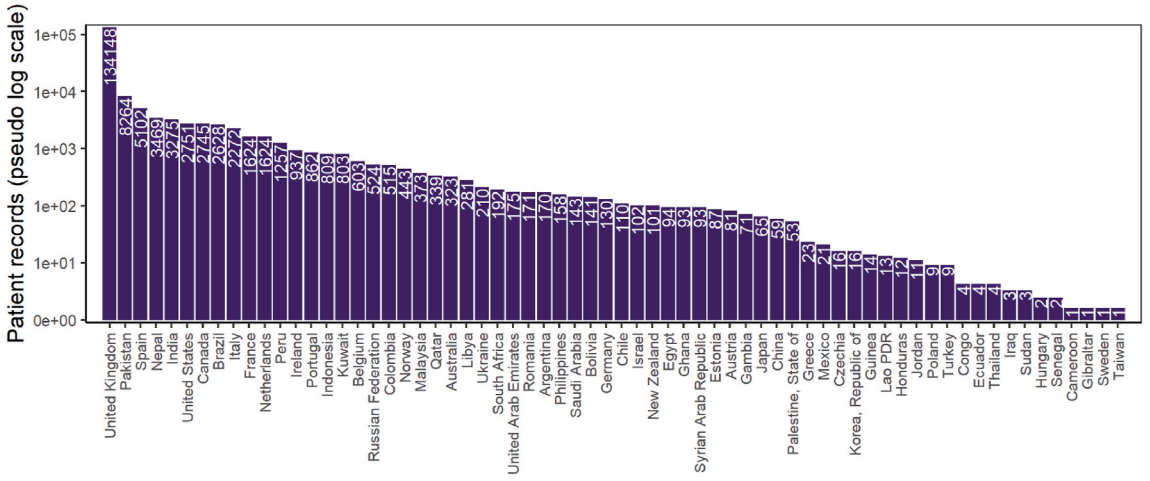

Fig. A.1. Countries included in the analysis.

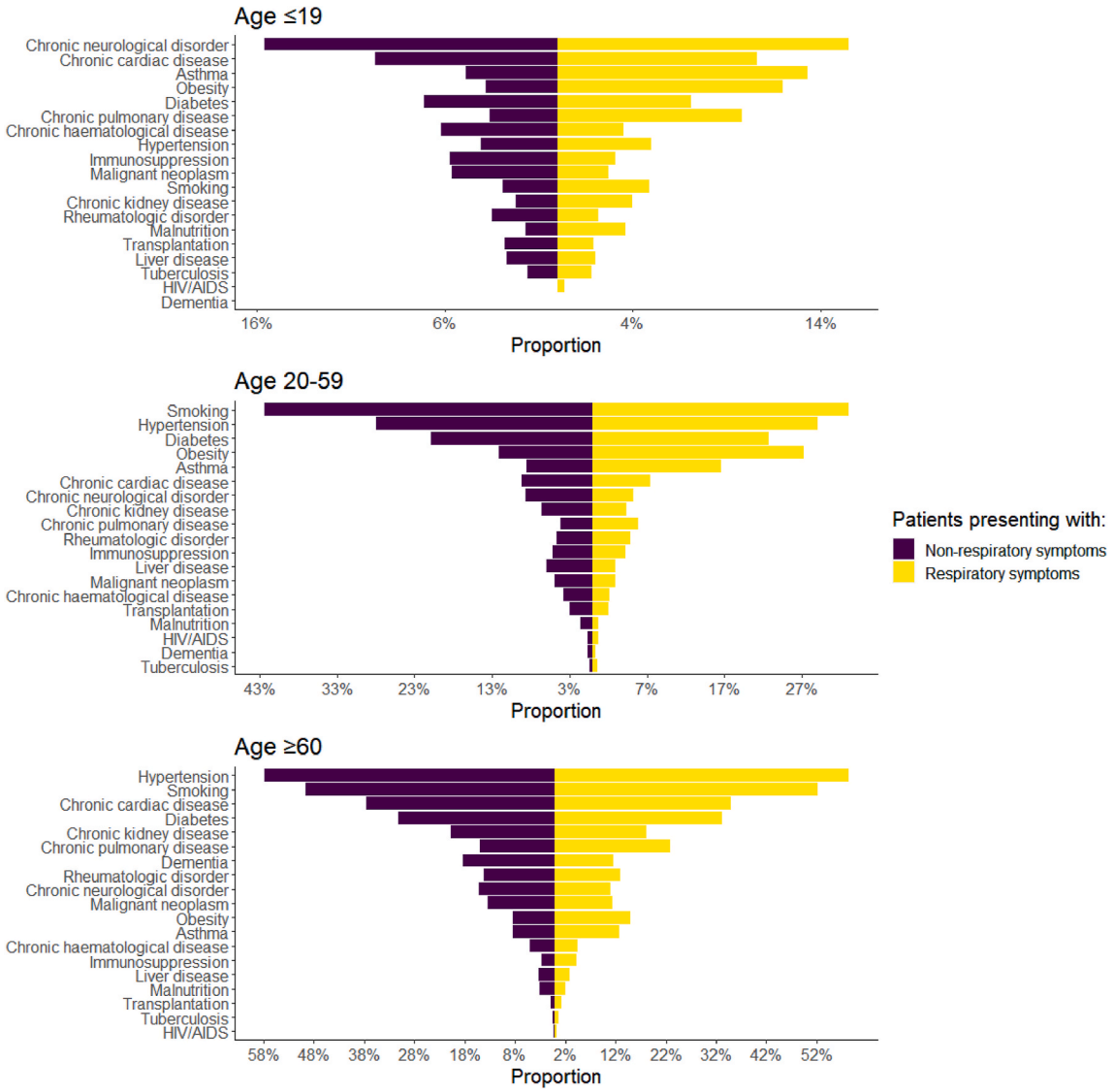

Fig. A.2. Frequency of comorbidities for different age groups, stratified by respiratory symptoms.

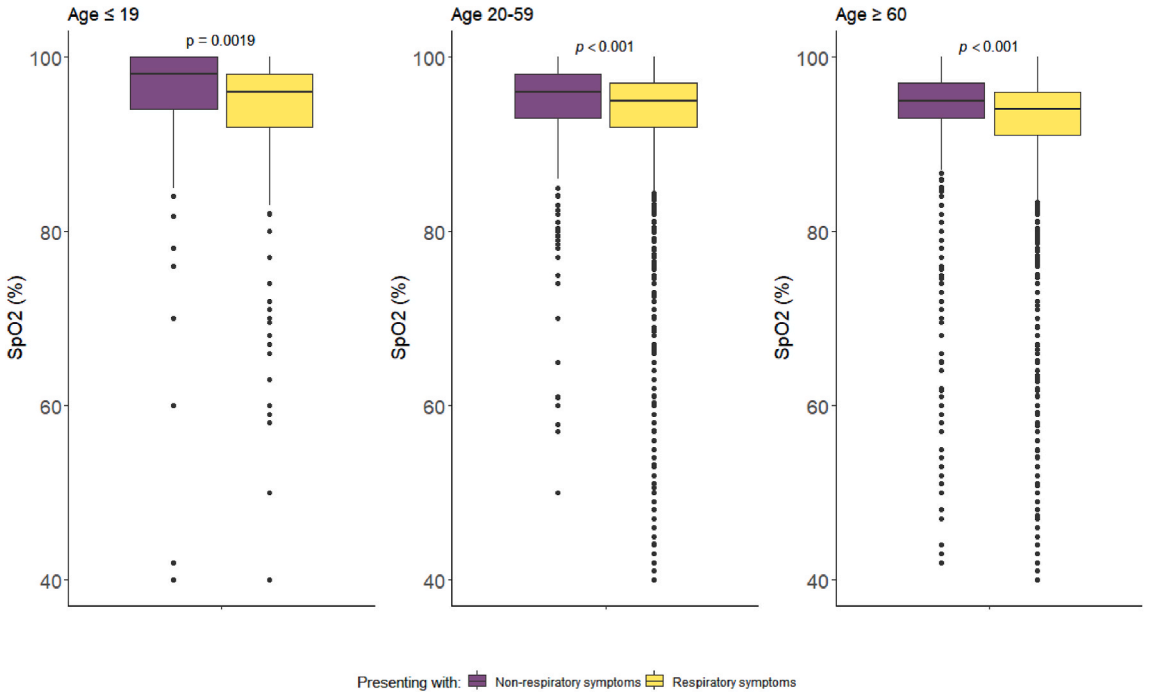

Fig. A.3. Boxplots of oxygen saturation (SpO2) for different age groups, stratified by respiratory symptoms.

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