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Direct impact of 2 years of COVID-19 on chronic disease patients: a population-based study in a large hard-hit Italian region

Daniela Fortuna [iD],[1] Luana Caselli,[1] Elena Berti,[1] Maria Luisa Moro[2]

¹Department of Innovation in Healthcare and Social Services, Emilia-Romagna Region, Bologna, Italy
²Regional Agency for Health and Social Care, Bologna, Italy

Correspondence to
Dr Daniela Fortuna;
daniela.fortuna@regione.emilia-romagna.it

ABSTRACT

Objectives We aimed to provide a region-wide comprehensive account of the direct effects of COVID-19 on chronic disease patients, in terms of disease incidence, severity and mortality, over a 2-year pandemic period (2020–2021).

Design Population-based retrospective study.

Setting/participants Adult patients, affected by at least 1 of 32 prevalent chronic conditions, residing in the Emilia-Romagna Region in Italy, during the years 2020 (N=1 791 189, 47.7% of the overall adult regional population) and 2021 (N=1 801 071, 47.8%).

Results COVID-19 incidence among chronic disease patients was 4.1% (74 067 cases) in 2020 and 7.3% (126 556 cases) in 2021, varying across pathologies, with obesity and dementia showing the highest incidence. Hospitalisation rate for pneumonia or acute respiratory distress syndrome among SARS-CoV-2-positive patients was 15.4%. COVID-19-related excess mortality, that is, deaths from COVID-19 as either main or contributing (1.5% of the total) cause of death, was observed during the three pandemic waves, with observed/expected death ratios ranging from +38% (March 2020) to +11% (December 2021). Increased risks of both COVID-19-related hospitalisation and death were associated with male gender, elderly age and many pre-existing pathologies, including cardiovascular, cerebrovascular and respiratory diseases, neurological and psychiatric disorders, and metabolic dysfunctions. The higher the number of concomitant pathologies, the greater the risk of COVID-19-related adverse outcomes: the likelihood of hospitalisation and death more than doubled for people with more than two comorbidities, compared with those with one underlying condition.

Conclusions This study presents a thorough and up-to-date quantification of the direct impact of COVID-19 on chronic disease patients. The results obtained are particularly relevant considering that people with pre-existing chronic conditions accounted for almost all cases of COVID-19-related hospitalisation (82.6%) and death (91.5%) in a vast region of Italy, among the hardest hit by the pandemic.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used data derived from 15 different regional health databases to explore the association between 32 prevalent chronic conditions and COVID-19-related adverse outcomes.

⇒ We estimated excess mortality directly attributable to COVID-19 over 2 years of the pandemic (2020–2021) comparing observed versus expected mortality among chronic disease patients based on a 3-year prepandemic period.

⇒ This population-based study was conducted at the regional level, and this aspect should be considered when extrapolating and generalising results to other populations.

BACKGROUND

The relationship between COVID-19 and pre-existing conditions has received great attention since the early stages of the pandemic. Many studies have highlighted the association between adverse clinical outcomes of COVID-19 and chronic comorbidities, such as cardiovascular and cerebrovascular diseases, cancer, diabetes, metabolic dysfunctions, obesity, hypertension and chronic lung diseases.[1–15] COVID-19 patients manifest different degrees of clinical symptoms ranging from lack of symptoms to mild, moderate, severe or critical illness requiring hospitalisation.

As the amount of studies about COVID-19 and chronic disease expands, evidence is used to revise the list of underlying medical conditions that put people at higher risk of serious illness or death. For example, the US Centers for Disease Control and Prevention regularly reviews all such studies to update a table of evidence, which classifies pathologies according to their related risk of developing severe COVID-19 outcomes.[16]

Comorbidities are also known to be more prevalent in the elderly. A higher risk of COVID-19-related hospitalisation and death was reported for elderly populations with underlying chronic diseases,[10 11 17 18] emphasising the predictive role of age and the

number of comorbidities in the severe course and poor prognosis of SARS-Cov-2 infection.[1 19–24]

The COVID-19 pandemic has had a major impact in Italy, with 138 099 documented deaths related to SARS-CoV-2 infection as of January 2022, as reported by the Integrated COVID-19 Surveillance System coordinated by the National Institute of Health (ISS).[25] The analysis of the deceased patients for whom it was possible to examine the medical records showed an average number of chronic pathologies of 3.7. Cardiovascular diseases and dementia were the most frequent pre-existing chronic conditions and significantly increased with age.[26] These results, although indicative of the clinical characteristics of SARS-CoV-2 patients who died in Italy, refer to a relatively small sample of 8436 deaths (corresponding to 6% of the total COVID-19-related deaths in Italy) and did not explicitly address the interaction between COVID-19 and previous health conditions.

In Italy, all citizens are registered with the National Health Service and the Italian regions are responsible for the organisation and management of publicly funded healthcare services for their residents. The Emilia-Romagna Region (ERR) has developed an efficient regional information system, based on various healthcare administrative databases, updated monthly, which constitutes a valuable tool to accurately estimate the prevalence, incidence and trends of major diseases over time. In addition, the ERR has been among the most affected Italian regions right since the beginning of the pandemic: to date there are over 19 100 deaths in a resident population of approximately 4 460 000 people.

Using the ERR information system, this study aimed to provide a comprehensive account of the direct effects of COVID-19 on chronic disease patients residing in the region, in terms of incidence, severity and mortality, both during the distinct pandemic waves and overall, considering a period of 24 months starting from the beginning of 2020, when the first COVID-19 cases were identified.

METHODS

Study design and population

This is a population-based retrospective study. The population consisted of adults affected by at least 1 of 32 identified chronic conditions, selected from the total number of people residing in the ERR in the years 2020 and 2021 (total adult residents: 3 755 113 and 3 767 931, respectively). To assess the impact of the pandemic waves, similar reference populations were selected in the previous 3-year period 2017–2019, considering the chronic cases prevalent during each year.

Data sources and patient selection criteria

The present study used data derived from fifteen different regional health databases (online supplemental table 1). We identified 32 prevalent chronic diseases,[27] that are seriously disabling or life-threatening for the patient and require significant dedicated healthcare resources.

Patients with at least one of these conditions were selected based on the anonymous identifier assigned by the region. A summary of the data sources used for the identification of each pathology is detailed in online supplemental table 2; International Classification of Disease, ninth revision, clinical modification (ICD9-CM) diagnosis codes, ATC drug codes and exemption codes used to trace individual conditions in the study population are displayed in online supplemental table 3.

Endpoints and statistical analysis

The effects of the direct impact of COVID-19 on chronic disease patients were addressed by considering the endpoints described below, over three distinct pandemic waves in 2020 and 2021: from March to April 2020, corresponding to the nationwide lockdown imposed by the government; from October 2020 to May 2021; and from October to December 2021.

Incidence of COVID-19: The frequency (and percentage) of COVID-19 cases was calculated based on record linkage with the DB-Covid-19 data source, for each pandemic year (2020 and 2021) and according to the type and number of concomitant chronic diseases, as well as to the demographic characteristics of the patients (by gender and age group).

COVID-19-related hospitalisations: The number of COVID-19 cases hospitalised for pneumonia or acute respiratory distress syndrome (ARDS) was calculated based on the hospital discharge database (SDO). Hospitalisations were analysed monthly, both as absolute numbers and as percentages of the total number of hospitalisations for severe forms of COVID-19.

COVID-19-related deaths: The number of deceased chronic disease patients with COVID-19 as either primary or secondary cause of death in the period 2017–2021 was identified through record linkage with the Regional Mortality Register (REM). Both in-hospital and non-hospital deaths were included.

For a more accurate estimate of COVID-19-related mortality in chronic disease patients, all-cause mortality was also calculated, comparing the trend in the number of observed versus expected daily deaths in the pre-covid period (2017–2019) and during the pandemic (2020–2021), either including or excluding deaths related to COVID-19. The expected trend in the number of deaths was estimated using a negative binomial model, applied to the 2017–2019 data, having as covariates the time trend, the seasonal component expressed by the sine and cosine functions of the trend, the days of the week and the months.[28–30] The model coefficients were then applied to 2020 and 2021 data (using the SAS statement 'store' in the genmod procedure and then the statement 'restore' in the plm procedure). The residual autocorrelation was checked through Ljung-Box test.[31] The estimates obtained are only graphically reported.

To assess the excess mortality directly attributable to COVID-19, the expected mortality in the 2020–2021 period was first obtained, for each month, through a

logistic model relating to the 2017–2019 data and subsequently applying the estimated coefficients on the 2020–2021 population (using the inmodel statement within the SAS logistic procedure). The risk factors included as covariates in the model were age, sex, number and type of chronic diseases. The monthly number of 2020 and 2021 expected (E) deaths was obtained from the sum of the probabilities estimated by the model for each patient. Subsequently, for each month, the number of observed (O) deaths in the 2020–2021 was calculated both for all causes (Otot) and for causes other than COVID-19 (OnoCovid) and related to the expected deaths, obtaining: Otot/E and OnoCovid /E. The difference between Otot/E and OnoCovid/E plus one ((Otot/E–OnoCovid/E) +1) provided the excess mortality directly attributable to COVID-19, expressed as monthly O/E ratio. Values above 1 indicate an increase in mortality, while values below 1 indicate a reduction in mortality. The 95% CI was obtained by multiplying the SE of O/E ratio by 1.96. Observed/expected ratios with 95% CI not containing the value 1 are considered statistically significant.

All analyses were performed using R V.3.6.3 (The R Foundation for Statistical Computing, Wien) and SAS V.9.3 (SAS Institute).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS
The regional context: chronic disease prevalence

In 2020, chronic disease prevalence in the ERR was 47.7% in the overall adult population, corresponding to 1 791 189 patients diagnosed with one to multiple chronic conditions. Similarly, in 2021, chronic disease patients were 1 801 071, 47.8% of the total resident adults. The prevalence of the 32 chronic diseases in 2020 and 2021 is shown in table 1.

COVID-19 incidence

As of December 2021, the cases of COVID-19 recorded in the ERR amounted to 564 213. A substantial fraction of these cases were chronic disease patients (200 623, 35.6%): during the first epidemic wave, the relative share was 61.2% (17 123 out of 27,968). The COVID-19 incidence among patients with one or more underlying health conditions in 2020 was 4.1% (74 067 cases) and it increased to 7.3% in 2021 (126 556 cases). The COVID-19 incidence varied across pathologies, for example, in 2021, it ranged between 11.4% among the prevalent cases of obesity and 5.3% among the osteoporosis/Paget cases (table 1).

COVID-19-related hospitalisations

As of December 2021, the total number of diagnosed COVID-19 patients hospitalised for pneumonia or ARDS was 37 416 out of 564 213 total SARS-CoV-2 cases (6.6%). Among these patients, 30 918 (82.6%) had pre-existing chronic pathologies. The incidence of hospitalisation among all SARS-CoV-2-positive chronic disease patients was 15.4%, while the comparative share among the non-chronic people was 1.8% (N=6525). After adjusting for age and gender, the risk of developing severe forms of COVID-19 among chronic disease patients compared with non-chronic disease patients was 2.15 (95% CI 2.09 to 2.22) times higher in 2020 and 3.20 (95% CI 3.10 to 3.30) times higher in 2021.

Time trend of COVID-19-related hospitalisations (figure 1): During the first wave, a high number of hospital admissions for pneumonia or ARDS among chronic disease patients was observed in March (N=4682, corresponding to 82.5% of all COVID-19 hospitalisations) and April 2020 (N=1599, 83.1%). During the second pandemic wave, the number of hospitalised chronic disease patients increased from October 2020 and reached its peak in March 2021 (N=5547, 83.5% of all COVID-19 hospitalisations).

Characteristics of hospitalised chronic disease patients (table 2): Among SARS-CoV-2-positive chronic disease patients, the risk of developing severe forms of COVID-19 requiring hospitalisation was significantly associated with gender, age, number and type of underlying chronic conditions. The probability of hospitalisation was higher for men than for women (OR 1.57, 95% CI 1.53 to 1.61) and increased proportionally with age, with patients older than 80 years showing a risk up to 11.25 (95% CI 10.26 to 12.34) times higher, compared with the 18–40 years age group.

COVID-19-related hospitalisation rate among SARS-CoV-2-positive chronic disease patients increased for each additional pathology: those with one, two, three, four or more chronic conditions were 6.8%, 13.1%, 19.9% and 32.4%, respectively. Compared with patients with one chronic disease, the risk of developing severe forms of COVID-19 increased by 2.12 (95% CI 2.02 to 2.22) times in patients suffering from two concomitant conditions, 2.62 (95% CI 2.49 to 2.75) times in the case of three pathologies and 3.12 (95% CI 2.93 to 3.32) times for four or more underlying pathologies.

Many chronic conditions were positively associated with the risk of COVID-19-related hospitalisation, including cardiovascular, cerebrovascular and respiratory diseases, metabolic dysfunctions, neurological and liver diseases (table 2). Obesity showed the highest risk (OR 2.53; 95% CI 2.28 to 2.81), dementia was associated with the lowest risk (OR 1.05; 95% CI 1.01 to 1.10).

COVID-19-related deaths

The number of deaths of chronic disease patients recorded each year in the period 2017–2021 showed an excess of mortality in both 2020 and 2021. In 2020, it exceeded those recorded in 2019 by 7754 (55 060 vs 47 306). According to the REM, 7193 deaths were related to COVID-19, and represented 92.8% of the entire excess

Table 1 Population characteristics and COVID-19 incidence among prevalent chronic diseases (years 2020 and 2021)

Demographic and clinical characteristics	2020				2021			
	Prevalence		COVID-19 Incidence		Prevalence		COVID-19 Incidence	
	N	%	N	%	N	%	N	%
Sex								
Female	988651	55.2	40237	4.1	994421	55.21	68235	6.9
Male	802538	44.8	33830	4.2	806650	44.79	58321	7.2
Age								
18–40	172678	9.64	7871	4.6	173375	9.63	19065	10.9
41–50	210098	11.73	9752	4.6	206607	11.47	20105	9.7
51–60	327912	18.31	14785	4.5	335657	18.64	27385	8.1
61–70	367005	20.49	12436	3.4	371983	20.65	23089	6.2
71–80	383154	21.39	12421	3.2	381495	21.18	19904	5.2
>80	330342	18.44	16802	5.1	331954	18.43	17008	5.1
Chronic disease								
Hyperlipidaemia	578226	15.4	20359	3.5	606907	16.1	35063	5.8
Hypertension	399998	10.6	20539	5.1	387178	10.3	26614	6.9
Rheumatological conditions	369223	9.8	15434	4.2	358503	9.5	25784	7.2
Thyroid pathology	323003	8.6	12476	3.9	331700	8.8	23849	7.2
Neoplasms	286051	7.6	11642	4.1	295421	7.8	18845	6.4
Depression	283753	7.5	12186	4.3	284859	7.6	19001	6.7
Diabetes mellitus	282221	7.5	13153	4.7	287602	7.6	18933	6.6
Prostatic hyperplasia	178728	4.8	7124	4	178987	4.8	10848	6.1
Gout	139673	3.7	5974	4.3	141946	3.8	8903	6.3
COPD	139387	3.7	7047	5.1	127557	3.4	9771	7.7
Reduced vision	134820	3.6	5122	3.8	133953	3.6	7544	5.6
Cardiac arrhythmias	121187	3.2	7571	6.2	118243	3.1	9000	7.6
Ischaemic heart disease	118133	3.1	6272	5.3	114678	3	7971	7
Gastro-oesophageal pathology	114449	3	4884	4.3	116179	3.1	8466	7.3
Epilepsy	100737	2.7	4686	4.7	105194	2.8	7277	6.9
Osteoporosis, Paget	92582	2.5	3408	3.7	88605	2.4	4727	5.3
Psychosis, schizophrenia, bipolar disorder	77638	2.1	4478	5.8	77871	2.1	5217	6.7
Cerebrovascular disease	73130	1.9	5773	7.9	68302	1.8	5343	7.8
Congestive heart failure	69663	1.9	5367	7.7	66993	1.8	5409	8.1
Other cardiovascular pathologies	66343	1.8	5300	5.6	62440	1.7	7198	7.9
Dementia	65098	1.7	7856	12.1	61038	1.6	5544	9.1
Asthma	42754	1.1	2186	5.1	45889	1.2	4471	9.7
Chronic hepatitis	41388	1.1	1704	4.1	40953	1.1	3055	7.5
Crohn, UC	36279	1	1512	4.2	37259	1	2849	7.6
Parkinson	33280	0.9	1796	5.4	32592	0.9	1977	6.1
Migraine	24396	0.6	1121	4.6	24576	0.7	2229	9.1
Chronic renal failure	24073	0.6	1476	6.1	24818	0.7	1811	7.3
Heart valves disease	21085	0.6	1242	5.9	20486	0.5	1419	6.9
Cirrhosis	14233	0.4	786	5.5	13773	0.4	1024	7.4

Continued

Table 1 Continued

Demographic and clinical characteristics	2020				2021			
	Prevalence		COVID-19 Incidence		Prevalence		COVID-19 Incidence	
	N	%	N	%	N	%	N	%
Peripheral vascular disease	13 830	0.4	915	6.6	13 065	0.3	979	7.5
Other neurological diseases	12 921	0.3	723	5.6	13 204	0.4	1041	7.9
Obesity	12 060	0.3	926	7.7	11 367	0.3	1299	11.4
Hearing loss	5082	0.1	218	4.3	4675	0.1	360	7.7
Multimorbidity	1 039 678	27.7	44 982	4.3	1 046 717	27.8	67 055	6.4
1 disease	751 511	42.0	29 085	3.9	754 354	41.9	59 501	7.9
2 diseases	409 856	22.9	15 270	3.7	415 566	23.1	27 255	6.6
3 diseases	256 412	14.3	10 026	3.9	259 610	14.4	15 593	6.0
>3 diseases	373 410	20.9	19 686	5.3	371 541	20.6	24 207	6.5

COPD, Chronic Obstructive Pulmonary Disease; UC, Ulcerative Colitis.

mortality fraction. In 2021, deaths among chronic disease patients were 51 555, with an increase of 4240 deaths compared with 2019. COVID-19-related deaths were 6044, indicating a decrease in deaths from causes other than COVID-19 with respect to 2019 (online supplemental figure 1).

Time trend of all-cause deaths (figure 2A): The trend in all-cause deaths among chronic disease patients from March 2020 onwards reflected the pandemic waves: a high and rapid increase in March and April 2020

(+68.9% and +49.3%, respectively), followed by an equally sharp reduction in May 2020 and again a new increase in November and December 2020 (+37.4% and +36.2%, respectively), corresponding to the second pandemic wave. The numbers remained above the expected trend until May–June 2021, then dropped during the summer months and increased again towards the end of 2021, with the third wave. Overall, the excess in all-cause deaths during the 24-month period was 16.6%. The comparison with the trend in non-COVID-19 deaths suggests a key
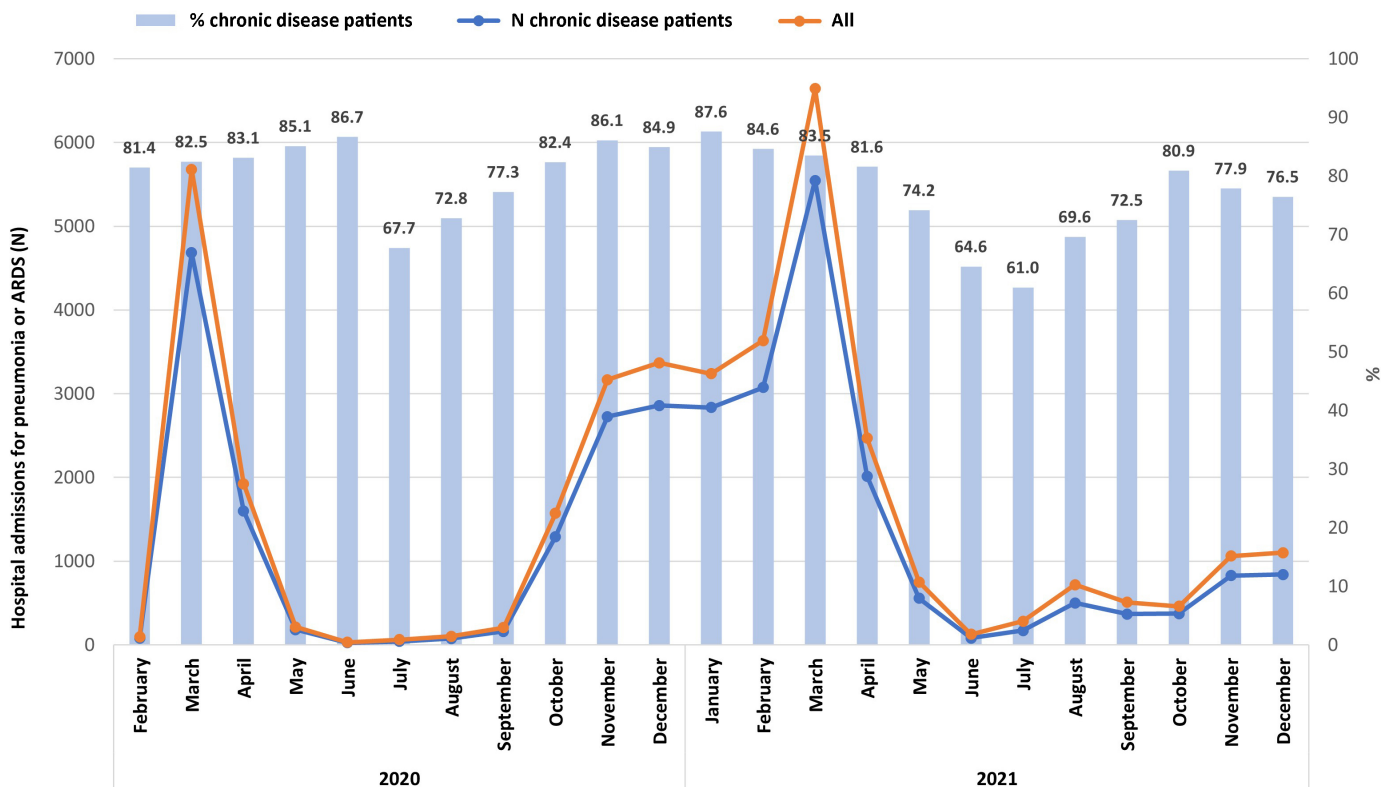

Figure 1 COVID-19-related hospitalisations among all SARS-CoV-2 positive patients and chronic disease patients over time.

Table 2 Characteristics of chronic disease patients associated with increased risk of COVID-19-related hospitalisation

Demographic and clinical characteristics	All SARS-CoV-2 cases	Hospitalisations for pneumonia or ARDS			
	N	N	%	OR	95% CI
Sex					
Female (ref.)	108 864	13 608	12.5	1	
Male	92 085	17 312	18.8	1.57	(1.53 to 1.61)
Age					
18–40 (ref.)	27 048	568	2.1	1	
41–50	29 621	1718	5.8	2.7	(2.45 to 2.97)
51–60	42 247	3929	9.3	3.99	(3.64 to 4.37)
61–70	35 521	5790	16.3	6.29	(5.75 to 6.89)
71–80	32 335	8116	25.1	9.03	(8.24 to 9.88)
>80	33 853	10 799	31.9	11.25	(10.26 to 12.34)
Chronic disease					
Diabetes mellitus	32 086	8746	27.3	1.37	(1.33 to 1.42)
Cardiac arrhythmias	16 571	6064	36.6	1.34	(1.29 to 1.40)
Heart failure	10 776	4288	39.8	1.18	(1.12 to 1.24)
Other cardiovascular diseases	12 498	3310	26.5	1.15	(1.09 to 1.20
Asthma	12 498	734	5.9	1.38	(1.27 to 1.51)
COPD	16 818	4479	26.6	1.28	(1.23 to 1.34)
Gout	14 877	4728	31.8	1.14	(1.10 to 1.19)
Cirrhosis	1810	539	29.8	1.24	(1.10 to 1.39)
Chronic hepatitis	4759	851	17.9	1.13	(1.04 to 1.24)
Cerebrovascular disease	11 116	3778	34	1.14	(1.09 to 1.19)
Neurological disorders	1764	335	19	1.24	(1.08 to 1.41)
Dementia	13 400	4258	31.8	1.05	(1.01 to 1.10)
Parkinson	3773	1166	30.9	1.1	(1.02 to 1.19)
Epilepsy	11 963	2536	21.2	1.09	(1.04 to 1.15)
Obesity	2225	697	31.3	2.53	(2.28 to 2.81)
Multimorbidity					
1 disease (ref.)	88 586	6008	6.8	1	
2 diseases	42 525	5590	13.1	2.12	(2.02 to 2.22)
3 diseases	25 619	5103	19.9	2.62	(2.49 to 2.75)
>3 diseases	43 893	14 217	32.4	3.12	(2.93 to 3.32)

ARDS, acute respiratory distress syndrome; COPD, Chronic Obstructive Pulmonary Disease.

contribution of COVID-19 played in the computation of deaths from all causes in chronic disease patients.

COVID-19-related excess mortality (figure 2B): Adjusting for the clinical and demographic characteristics of the patients such as age, gender and number of chronic conditions, 2020 and 2021 excess mortality directly related to COVID-19 was estimated as O/E death ratio for each month of the pandemic period, based on the prepandemic reference period. A COVID-19-related excess mortality was observed in March, April and May 2020 (+38%, +37% and+8%, respectively), and then again in November 2020 (+28%), remaining statistically significant for several months until May 2021 (+7%). The O/E death ratio then settled around one in the subsequent months until the end of 2021, when a COVID-19-related excess mortality was recorded again (November: +4%, December: +11%), with the third pandemic wave.

Characteristics of chronic disease patients who died from COVID-19: In the 2-year pandemic period considered (2020–2021), COVID-19 as primary cause of death among chronic disease patients was the third in terms of frequency (11 635 deaths, 10.9%), following cardiovascular diseases (31 165, 29.2%) and malignant tumours (24 685, 23.2%). Notably, COVID-19 was a contributing cause
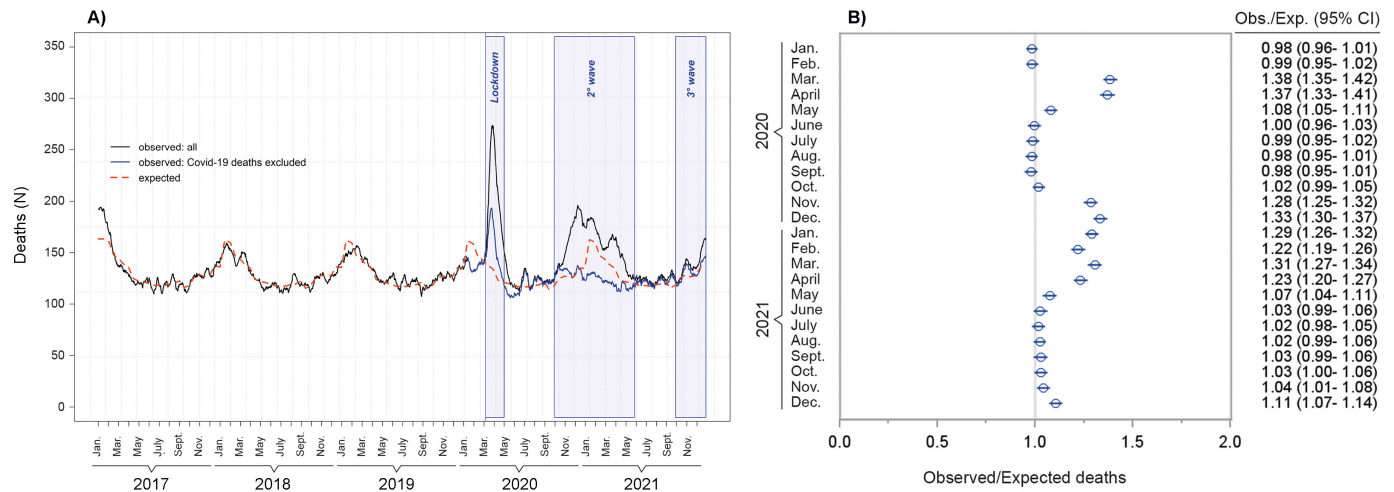
Figure 2 Observed versus expected trend in the number of deaths among chronic disease patients, either including or excluding COVID-19 cases (period 2017–2021) (A), and monthly excess mortality among chronic disease patients directly attributable to COVID-19 (period 2020–2021) (B).

of death in 1602 cases (1.5% of the total), and mostly in association with deaths from cardiovascular diseases (567 cases) and malignant tumours (351 cases). The main causes of deaths with relative distribution frequencies are listed in online supplemental table 4. Chronic disease patients who died from COVID-19 (as either main or secondary cause of death) were 13 237, corresponding to 12.4% of the total number of all-cause deaths in the chronic population and to 91.5% of all regional COVID-19 deaths. The time course of COVID-19-related deaths among chronic disease patients was mostly coincident with that of the total COVID-19 deaths (online supplemental figure 2).

Table 3 shows the main demographic and clinical characteristics of SARS-CoV-2-positive chronic disease patients, associated with increased risk of COVID-19 death. Risk was higher for men than for women (OR 1.99, 95% CI 1.89 to 2.09) and considerably increased with advancing age: chronic disease patients aged 60 and over had a markedly enhanced risk of dying from COVID-19, compared with those between 18 and 40 years old. This risk became extremely high in people over eighty, since 22.3% of these patients died from COVID-19-related complications.

Multimorbidity was another important risk factor for COVID-19 death: compared with people with one underlying condition, the risk of death was 1.44 (95% CI 1.32 to 1.56), 1.86 (95% CI 1.71 to 2.03) and 2.20 (95% CI 2.00 to 2.42) times higher for those with 2, 3 or more comorbidities, respectively.

In addition, increased risks of death from COVID-19 were associated with different pathologies, with obesity and dementia showing the strongest associations (OR 2.50, 95% CI 2.12 to 2.95 and OR 1.76, 95% CI 1.67 to 1.86, respectively).

DISCUSSION
To our knowledge, this is the first and most up-to-date population-based study that thoroughly investigated the direct impact of 2 years of pandemic on people with pre-existing medical conditions, who represent the subgroup of patients most vulnerable to SARS-CoV-2-related adverse outcomes.[1 3 7 8 13 14] Taking advantage of the large ERR administrative health database, this study estimated the incidence of severe forms of COVID-19 and related risk factors, on about 1 800 000 chronic disease patients per year, residing in one of the Italian regions most affected by the COVID-19 pandemic.

The decision to focus our study on chronic disease patients is well supported by the result that most of the patients who were hospitalised (82.6%) or died (91.5%) from complications related to COVID-19 in the ERR had underlying chronic conditions. COVID-19 was indeed the third cause of death among chronic disease patients during the pandemic. In addition, COVID-19-related deaths, that is, deaths with COVID-19 as main or contributing (1.5% of the total) cause, represented almost the entire excess mortality fraction (92.8% in 2020 and 100% in 2021, alongside a reduction in mortality from causes other than COVID-19). The trend in the number of deaths directly attributable to COVID-19, net of expected annual fluctuations and patient characteristics, clearly showed a significant excess of mortality during the first and second waves with peaks up to +38% and +33%, respectively, and, to a lesser extent, also at the end of the 2021 (+11%). These results highlighted the persistent effects of the three pandemic waves on chronic disease patients.

There has been evidence since the beginning of the pandemic that males are at a significantly higher risk of severe forms of COVID-19 than females and, also in the present work, male gender was associated with increased risk of both COVID-19-related hospitalisation and death, probably due to the fundamental differences observed in the immune system that are unfavourable in males compared with females for the early response to SARS-CoV-2 infection.[32]

Table 3 Characteristics of chronic disease patients associated with increased risk of COVID-19-related death

Demographic and clinical characteristics	All SARS-CoV-2 cases	COVID-19 deaths			
	N	N	%	OR	95% CI
Sex					
Female (ref.)	108 705	5182	4.8	1	
Male	92 351	6296	6.8	1.99	(1.89 to 2.09)
Age					
18–40 (ref.)	27 001	19	0.1	1.00	
41–50	29 926	83	0.3	3.81	(2.31 to 6.28)
51–60	42 264	289	0.7	8.35	(5.24 to 13.30)
61–70	35 604	916	2.6	26.80	(16.98 to 42.30)
71–80	32 393	2614	8.1	72.33	(45.92 to 113.93)
>80	33 868	7557	22.3	178.47	(113.32 to 281.07)
Chronic disease					
Diabetes mellitus	32 086	3232	10.1	1.13	(1.08 to 1.19)
Cardiac arrhythmias	16 571	3558	21.5	1.37	(1.29 to 1.44)
Heart failure	10 776	2925	27.1	1.44	(1.36 to 1.52)
Peripheral vascular disease	1894	460	24.3	1.48	(1.31 to 1.66)
Ischaemic heart disease	14 243	2512	17.6	1.36	(1.28 to 1.44)
COPD	16 818	2076	12.3	1.16	(1.10 to 1.23)
Gout	14 877	2187	14.7	1.16	(1.09 to 1.22)
Cirrhosis	1810	232	12.8	1.67	(1.40 to 2.00)
Cerebrovascular disease	11 116	2342	21.1	1.17	(1.10 to 1.24)
Neurological disorders	1764	153	8.7	1.50	(1.23 to 1.83)
Dementia	13 400	3577	26.7	1.76	(1.67 to 1.86)
Parkinson	3773	692	18.3	1.20	(1.09 to 1.32)
Epilepsy	11 963	1098	9.2	1.12	(1.04 to 1.21)
Psychosis, schizophrenia, bipolar disorder	9695	1234	12.7	1.20	(1.11 to 1.29)
Obesity	2225	223	10.0	2.50	(2.12 to 2.95)
Neoplasms	30 487	2625	8.6	1.21	(1.15 to 1.28)
Chronic renal failure	3287	624	19.0	1.54	(1.39 to 1.71)
Multimorbidity					
1 disease (ref.)	88 790	1138	1.3		
2 diseases	42 618	1550	3.6	1.44	(1.32 to 1.56)
3 diseases	25 672	1815	7.1	1.86	(1.71 to 2.03)
>3 diseases	43 976	6975	15.9	2.20	(2.00 to 2.42)

COPD, Chronic Osbstructive Pulmonary Disease.

Also, age as a prognostic factor for severe SARS-CoV-2 infection has been extensively described, and this effect may be partly explained by the increased risk of concurrent diseases with advancing age.[9 20 23 24] Much of the chronic population in this study was represented by older patients, with nearly 40% over the age of seventy, and almost 60% suffering from more than one chronic condition. We found that both hospitalisations and deaths increased significantly with age and, notably, most of COVID-19-related deaths involved chronic disease patients over the age of 80, whose risk of death was considerably higher than that of all other age groups.

Furthermore, in line with the existing literature highlighting potential interactions between COVID-19 and various diseases, our results showed that patients with certain underlying medical conditions were at increased risk of severe COVID-19-related outcomes. Risks were higher for patients with a variety of pre-existing pathologies, including cardiovascular, cerebrovascular, and

respiratory diseases, neurological and psychiatric disorders, and metabolic dysfunctions.

Obesity was one of the most important risk factors for the chronic population under study, as it more than doubled the likelihood for both COVID-19-related hospitalisation and death. This result supports current evidence[3 10 14] that reports obesity as a major health issue, leading to many other comorbidities and directly affecting the prognosis of COVID-19 symptoms and mortality.[33] We also found that patients with diabetes were at higher risk of COVID-19 severity and mortality. Diabetes mellitus, frequently coexisting with obesity, is known to be associated to a greater risk of critical illness and fatal cases.[34 35]

Recent studies confirmed that clinical outcomes are worse in COVID-19 patients with pre-existing cardiovascular disease.[3 14 17 36–38] In the present work, patients with cardiac arrhythmias, heart failure, peripheral vascular disease and ischaemic heart disease, showed increased risk of developing severe forms of COVID-19, either requiring hospitalisation or leading to death. Despite the high prevalence of hypertension in this chronic population and several early reports suggesting it may represent a risk factor for susceptibility to SARS-CoV-2 infection and worse COVID-19 prognosis, we found that hypertension was not significantly associated with any clinical outcomes. A lack of association was also observed in other recent studies,[11 39 40] suggesting that hypertension is rather a condition influenced by older age and interacting with other cardiovascular risk factors, and therefore, may not play an independent role in the disease course. Patients with comorbid cardiac and cerebrovascular pathologies may experience increased rates and severity of infectious diseases, such as COVID-19; however, both disease groups have also been shown to be independently associated with poor prognosis of COVID-19,[41] as we also observed here: cerebrovascular disease by itself presented some increased risk for both COVID-19-related hospitalisation and death.

The association between chronic respiratory disease and COVID-19 adverse outcomes is controversial. Chronic Obstructive Pulmonary Disease (COPD) has consistently been described as an important risk factor, regardless of age and other associated comorbidities.[42 43] In contrast, the influence of asthma appears to depend on its severity: patients with mild-to-moderate asthma did not present with a significantly poorer COVID-19 prognosis compared with patients without asthma.[44–46] According to our results, both asthma and COPD increased the risk of COVID-19-related hospitalisation, whereas only COPD was positively related with death. This finding is consistent with previous studies that found asthma to be associated with an increased level of in-hospital care, but not with an increased risk of death, except for patients with severe asthma.[47 48] However, in our analysis, the different levels of asthma severity were pooled together, and this may have affected the size of the observed association with COVID-19.

Neoplasms were found to be a relevant risk factor for COVID-19-related death. Patients with cancer are vulnerable to SARS-CoV-2 infection due to their compromised immune system. Moreover, much of their routine care has been reprioritised, with subsequent delays in diagnosis and treatment. Thus, these patients particularly suffered from both direct and indirect effects of the pandemic[49] and, although the type of tumour, duration and therapy may modulate COVID-19 severity, cancer has been shown to critically increase the risk of disease progression and mortality.[10 14 50]

Pre-existing mental and neurological disorders in the chronic population under study were also associated with an increased risk of poor COVID-19 outcomes, mostly with mortality. Like patients with cancer, people with dementia, Parkinson's disease, epilepsy and psychiatric diseases, have been considerably affected by the disruption of their routine care during the pandemic period. There is a strong evidence that the rate of COVID-19-related deaths has been particularly high among cognitively impaired people, who have experienced a significant worsening of symptoms.[51 52] A recent comprehensive meta-analysis showed that pre-existing mood and cognitive dysfunctions were predictors of increased risk of COVID-19 severity and mortality.[53] The caring of people with dementia during the pandemic was complicated by various factors, which may partly explain the finding that these patients, while showing a significantly higher risk of COVID-19-related death, did not show any relevant association with increased hospitalisations. First, many people with dementia live in long-term care facilities, where the risk of death increased about four times during the pandemic and the several restrictions applied to prevent the spreading of SARS-CoV-2 infection also had unintended consequences, including the disruption in the continuity of care.[54] Second, the cognitive impairment of these patients may lead to the disease being diagnosed only at an advanced stage, which would no longer benefit from hospital intervention.[54 55] Third, the shift in the management of care priorities limited the access of these patients to hospital care.[55] In settings with shortage of resources, such as Italy, guidelines were issued that excluded certain patients from intensive care approaches in favour of people with a better chance of recovery.[56] As a result, the care needs of older people with dementia were considered less of a priority.

Other underlying medical conditions, such as chronic renal failure, cirrhosis, chronic hepatitis, that we found to be associated with negative COVID-19 outcomes, have been shown to exacerbate COVID-19 symptoms and progression. The impact of chronic kidney and liver diseases on COVID-19 severity has been consistently highlighted in the literature.[10 14 57–59]

Finally, although the interplay between COVID-19 and rheumatological diseases is controversial, recent literature points to an increased risk of COVID-19 mortality in people with gout.[60 61] Our results also indicated some positive association between gout and COVID-19-related hospitalisation and death.

Overall, these findings are consistent with the underlying medical conditions indicated by the CDC as being at higher risk for severe COVID-19.[62]

We also observed a strong association between the multimorbidity and the risks of COVID-19-related outcomes: the higher the number of concomitant pathologies, the greater the risk. The likelihood of hospitalisation and death more than doubled for people with more than two comorbidities, compared with those with one underlying condition. Consistent with the available national data collected since the first months of the pandemic by the ISS,[26] and as already reported by other studies,[5 11 12 15] we confirmed that multiple coexisting diseases were contributing factors for severe COVID-19 illness and mortality.

We acknowledge that this study has some limitations. First, this population-based study, although large, was conducted at the regional level, and this aspect should be considered before extrapolating and generalising the results to other populations. Second, restrictive measures and hospital management changed significantly throughout the pandemic, and it should also be noted that, since March 2021, Italy implemented a national COVID-19 vaccination campaign primarily targeting categories considered to be priority, which included people aged over eighty and with pre-existing medical conditions. Therefore, it is possible that these measures and the vaccine uptake influenced the estimated associations between COVID-19 outcomes and the underlying diseases. Third, the associations reported here do not indicate any causal effect as well as the estimated impact of multimorbidity over the clinical outcomes did not reflect the specific contribution and nature of each pathology, which had equivalent weight in our analyses. Also, as this is a retrospective study based on administrative data, reporting errors in COVID-19-related diagnosis or death may have occurred, especially during the first phase of the pandemic, when the understanding of the clinical presentation of the disease was still evolving and testing rates were low. However, our results include all-cause excess deaths, and this indicator accounted for possible misreporting errors.

CONCLUSION

While our understanding of how chronic disease may increase the risk of severe COVID-19 is still evolving and more clinical research is needed on the exact underlying mechanisms,[13 14 21] we confirm that male gender, age, multimorbidity and most of the prevalent chronic diseases were positively associated with adverse COVID-19-related outcomes. Furthermore, we provide additional relevant information on the time trend of excess mortality specifically related to COVID-19 among chronic disease patients.

The global COVID-19 infection is now gradually evolving from a pandemic to an endemic stage; however, it is still ongoing and older people and those with pre-existing pathologies remain at greatest risk. Therefore, the present results are valuable for future healthcare planning and management of chronic populations.

ORCID iD
Daniela Fortuna http://orcid.org/0000-0003-0927-7199

REFERENCES

1 Clark A, Jit M, Warren-Gash C, *et al*. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a Modelling study. *The Lancet Global Health* 2020;8:e1003–17.

2 Harrison SL, Fazio-Eynullayeva E, Lane DA, *et al*. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the united states: A federated electronic medical record analysis. *PLoS Med* 2020;17:e1003321.

3 Ejaz H, Alsrhani A, Zafar A, *et al*. COVID-19 and Comorbidities: deleterious impact on infected patients. *J Infect Public Health* 2020;13:1833–9.

4 Zádori N, Váncsa S, Farkas N, *et al*. The negative impact of Comorbidities on the disease course of COVID-19. *Intensive Care Med* 2020;46:1784–6.

5 Ge E, Li Y, Wu S, *et al*. Association of pre-existing comorbidities with mortality and disease severity among 167,500 individuals with COVID-19 in canada: A population-based cohort study. *PLOS ONE* 2021;16:e0258154.

6 Gude-Sampedro F, Fernández-Merino C, Ferreiro L, *et al*. Development and validation of a Prognostic model based on Comorbidities to predict COVID-19 severity: a population-based study. *Int J Epidemiol* 2021;50:64–74.

7 Hacker KA, Briss PA, Richardson L, *et al*. COVID-19 and chronic disease: the impact now and in the future. *Prev Chronic Dis* 2021;18:E62.

8 Gasmi A, Peana M, Pivina L, *et al*. Interrelations between COVID-19 and other disorders. *Clin Immunol* 2021;224:108651.

9 Martos-Benítez FD, Soler-Morejón CD, García-Del Barco D. Chronic Comorbidities and clinical outcomes in patients with and without COVID-19: a large population-based study using national administrative Healthcare open data of Mexico. *Intern Emerg Med* 2021;16:1507–17.

10 Gao Y-D, Ding M, Dong X, *et al*. Risk factors for severe and critically ill COVID-19 patients: A review. *Allergy* 2021;76:428–55.

11 Semenzato L, Botton J, Drouin J, *et al*. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. *Lancet Reg Health Eur* 2021;8:100158.

12 Adab P, Haroon S, O'Hara ME, *et al*. Comorbidities and COVID-19. *BMJ* 2022;377:1431.

13 Bellou V, Tzoulaki I, van Smeden M, *et al*. Prognostic factors for adverse outcomes in patients with COVID-19: a field-wide systematic review and meta-analysis. *Eur Respir J* 2022;59:2002964.

14 Bigdelou B, Sepand MR, Najafikhoshnoo S, *et al*. COVID-19 and preexisting Comorbidities: risks, synergies, and clinical outcomes. *Front Immunol* 2022;13:890517.

15 Kompaniyets L, Pennington AF, Goodman AB, *et al*. Underlying medical conditions and severe illness among 540,667 adults hospitalized with COVID-19. *Prev Chronic Dis* 2020;18.

16 Centers for Disease Control and Prevention (US). Science brief: evidence used to update the list of underlying medical conditions associated with higher risk for severe COVID-19. In: *CDC COVID-19 Science Briefs*. Atlanta (GA), 2020.

17 Emami A, Javanmardi F, Pirbonyeh N, *et al*. Prevalence of underlying diseases in hospitalized Paitents with COVID-19: a systematic review and Meta- analysis. *Arch Acad Emerg Med* 2020;8:e35.

18 Sanyaolu A, Okorie C, Marinkovic A, *et al*. Comorbidity and its impact on patients with COVID-19. *SN Compr Clin Med* 2020;2:1069–76.

19 Polidori MC, Sies H, Ferrucci L, *et al*. COVID-19 mortality as a fingerprint of biological age. *Ageing Res Rev* 2021;67:101308.

20 Liu D, Zheng Y, Kang J, *et al*. Not only high number and specific Comorbidities but also age are closely related to progression and poor prognosis in patients with COVID-19. *Front Med* 2022;8:736109.

21 Liu D, Yuan X, Gao F, *et al*. High number and specific Comorbidities could impact the immune response in COVID-19 patients. *Front Immunol* 2022;13.

22 Henkens MTHM, Raafs AG, Verdonschot JAJ, *et al*. Age is the main determinant of COVID-19 related in-hospital mortality with minimal impact of pre-existing Comorbidities, a retrospective cohort study. *BMC Geriatr* 2022;22:184.

23 Tisminetzky M, Delude C, Hebert T, *et al*. Age, multiple chronic conditions, and COVID-19: A literature review. *The Journals of Gerontology* 2022;77:872–8.

24 Wanhella KJ, Fernandez-Patron C. Biomarkers of ageing and frailty may predict COVID-19 severity. *Ageing Res Rev* 2022;73:101513.

25 EpiCentro. Coronavirus - news [Internet], Available: https://www.epicentro.iss.it/coronavirus/aggiornamenti [Accessed 7 Dec 2022].

26 EpiCentro. Characteristics of COVID-19 patients dying in Italy [Internet]. 2022. Available: https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-analysis-of-deaths

27 Fortuna D, Berti E, Moro ML. Multimorbidity epidemiology and health care utilization through combined Healthcare administrative databases. *Epidemiol Prev* 2021;45:62–71.

28 Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a Tutorial. *Int J Epidemiol* 2017;46:348–55.

29 Wagner AK, Soumerai SB, Zhang F, *et al*. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;27:299–309.

30 Bhaskaran K, Gasparrini A, Hajat S, *et al*. Time series regression studies in environmental epidemiology. *Int J Epidemiol* 2013;42:1187–95.

31 Ljung GM, Box GEP. On a measure of lack of fit in time series models. *Biometrika* 1978;65:297–303.

32 Peckham H, de Gruijter NM, Raine C, *et al*. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun* 2020;11:6317.

33 Rottoli M, Bernante P, Belvedere A, *et al*. How important is obesity as a risk factor for respiratory failure, intensive care admission and death in hospitalised COVID-19 patients? results from a single Italian centre. *Eur J Endocrinol* 2020;183:389–97.

34 Drucker DJ. Diabetes, obesity, metabolism, and SARS-Cov-2 infection: the end of the beginning. *Cell Metabolism* 2021;33:479–98.

35 Smati S, Tramunt B, Wargny M, *et al*. Relationship between obesity and severe COVID-19 outcomes in patients with type 2 diabetes: results from the CORONADO study. *Diabetes Obes Metab* 2021;23:391–403.

36 Yang J, Zheng Y, Gou X, *et al*. Prevalence of Comorbidities and its effects in patients infected with SARS-Cov-2: a systematic review and meta-analysis. *Int J Infect Dis* 2020;94:91–5.

37 Chung MK, Zidar DA, Bristow MR, *et al*. COVID-19 and cardiovascular disease: from bench to bedside. *Circ Res* 2021;128:1214–36.

38 Pina A, Castelletti S. COVID-19 and cardiovascular disease: a global perspective. *Curr Cardiol Rep* 2021;23:135.

39 Iaccarino G, Grassi G, Borghi C, *et al*. Age and Multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian society of hypertension. *Hypertens Dallas Tex* 1979;76:366–72.

40 Gallo G, Calvez V, Savoia C. Hypertension and COVID-19: Current evidence and perspectives. *High Blood Press Cardiovasc Prev* 2022;29:115–23.

41 Pranata R, Huang I, Lim MA, *et al*. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19– systematic review, meta-analysis, and meta-regression. *J Stroke Cerebrovasc Dis* 2020;29:104949.

42 jie GW, hua LW, Zhao Y, *et al*. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020.

43 Halpin DMG, Criner GJ, Papi A, *et al*. Global initiative for the diagnosis,Management, and prevention of chronic obstructive lung disease. The 2020 GOLD science committee. *Am J Respir Crit Care Med* 2021;203:24–36.

44 Adir Y, Saliba W, Beurnier A, *et al*. Asthma and COVID-19: an update. *Eur Respir Rev* 2021;30:210152.

45 Chiner-Vives E, Cordovilla-Pérez R, de la Rosa-Carrillo D, *et al*. Short and long-term impact of COVID-19 infection on previous respiratory diseases. *Arch Bronconeumol* 2022;58 Suppl 1:39–50.

46 He Z, Zhong N, Guan W-J. Impact of chronic respiratory diseases on the outcomes of COVID-19. *Archivos de Bronconeumología* 2022;58:5–7.

47 Williamson EJ, Walker AJ, Bhaskaran K, *et al*. Factors associated with COVID-19-related death using Opensafely. *Nature* 2020;584:430–6.

48 Bloom CI, Drake TM, Docherty AB, *et al*. Risk of adverse outcomes in patients with underlying respiratory conditions admitted to hospital with COVID-19: a national, Multicentre prospective cohort study using the ISARIC WHO clinical Characterisation protocol UK. *Lancet Respir Med* 2021;9:699–711.

49 Zarifkar P, Kamath A, Robinson C, *et al*. Clinical characteristics and outcomes in patients with COVID-19 and cancer: a systematic review and meta-analysis. *Clinical Oncology* 2021;33:e180–91.

50 Venkatesulu BP, Chandrasekar VT, Girdhar P, *et al*. A systematic review and meta-analysis of cancer patients affected by a novel Coronavirus. *JNCI Cancer Spectr* 2021;5:pkaa102.

51 Toniolo S, Scarioni M, Di Lorenzo F, *et al*. Dementia and COVID-19, a Bidirectional liaison: risk factors,Biomarkers, and optimal health care. Bonanni L, editor. *J Alzheimers Dis* 2021;82:883–98.

52 Vai B, Mazza MG, Delli Colli C, *et al*. Mental disorders and risk of COVID-19-related mortality, Hospitalisation, and intensive care unit admission: a systematic review and meta-analysis. *Lancet Psychiatry* 2021;8:797–812.

53 Liu L, Ni S-Y, Yan W, *et al*. Mental and neurological disorders and risk of COVID-19 susceptibility, illness severity and mortality: A systematic review, meta-analysis and call for action. *EClinicalMedicine* 2021;40:101111.

54 Bianchetti A, Rozzini R, Bianchetti L, *et al*. Dementia clinical care in relation to COVID-19. *Curr Treat Options Neurol* 2022;24:1–15.

55 Canevelli M, Palmieri L, Raparelli V, *et al*. Prevalence and clinical correlates of dementia among COVID-19-related deaths in Italy. *Alzheimers Dement (Amst)* 2020;12:e12114.

56 COVID. Raccomandazioni Di Etica Clinica per L'Ammissione a Trattamenti Intensivi E per La Loro Sospensione, in Condizioni Eccezionali Di Squilibrio Tra Necessità E Risorse Disponibili. 2020. Available: https://www.sicp.it/wp-content/uploads/2020/03/SIAARTI-Covid19-Raccomandazioni-di-etica-clinica.pdf

57 Oyelade T, Alqahtani J, Canciani G. Prognosis of COVID-19 in patients with liver and kidney diseases: an early systematic review and meta-analysis. *Trop Med Infect Dis* 2020;5:80.

58 Fitero A, Bungau SG, Tit DM, *et al*. Comorbidities, associated diseases, and risk assessment in COVID-19-A systematic review. *Int J Clin Pract* 2022;2022:1571826.

59 Jdiaa SS, Mansour R, El Alayli A, *et al*. COVID–19 and chronic kidney disease: an updated overview of reviews. *J Nephrol* 2022;35:69–85.

60 Topless RK, Gaffo A, Stamp LK, *et al*. Gout and the risk of COVID-19 diagnosis and death in the UK Biobank: a population-based study. *Lancet Rheumatol* 2022;4:e274–81.

61 Tai V, Robinson PC, Dalbeth N. Gout and the COVID-19 pandemic. *Curr Opin Rheumatol* 2022;34:111–7.

62 CDC. Coronavirus disease 2019 (COVID-19) [Internet]. 2020.
Available: https://www.cdc.gov/coronavirus/2019-ncov/science/ science-briefs/underlying-evidence-table.html