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Association of COVID-19 case fatality rate with disease burden: an ecological analysis in Italy during the first wave

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ABSTRACT

Objectives: In Italy, the case fatality rate (CFR) of coronavirus disease 2019 (COVID-19) during the first wave of the pandemic showed significant geographic heterogeneity. The aim of this study was to explore the possible association between the CFR and measures of disease burden in the Italian regions using an ecological approach.

Methods: Cumulated regional data for the period February 24 to May 11, 2020 were analysed to assess the association of the CFR with the cumulative incidence of COVID-19 and the ratio between the maximum number of COVID-19 patients in intensive care units (ICU) and ICU beds available before the pandemic (ICU load), adjusting for median age of the patients at disease onset, number of nasopharyngeal swabs performed per confirmed case, and prevalence of chronic diseases .

Results: During the study period, the COVID-19 CFR in the Italian regions ranged between 5.0% and 18.4%. On multivariable regression analysis, the CFR was found to be significantly associated with the cumulative incidence (relative rate (RR) 1.02 per 100 cases/1 million increase), median patient age (RR 1.07 per 1 year increase), and ICU load (RR 1.72, 2.18, and 2.57, for >40–70% vs ≤40%, 70–140% vs ≤40%, and ≥140 vs ≤40%, respectively).

Conclusions: A high burden of COVID-19 may contribute to increased disease fatality, possibly as a result of the increasing demand for care of critically ill patients beyond health system capability.

Introduction

Estimates of the case fatality rate (CFR) of coronavirus disease 2019 (COVID-19) varied greatly among countries during the first phase of the pandemic (World Health Organization, 2020). An analysis of data from nine countries found that two-thirds of this heterogeneity was accounted for by differences in age distribution of the cases (Sudharsanan et al., 2020). Other factors, such as the prevalence of comorbidities and rate of detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also contributed to the variability in the CFR (Emanuel et al., 2020). In addition, Ergönül et al. (Ergönül et al., 2020) reported that a larger availability of hospital beds at the country level was associated with a lower CFR. Indeed, it has been suggested that the increased burden on health care systems caused by the sudden increase in number of cases may have contributed to increase the CFR by reducing the standard of care of affected individuals in need of hospital treatment (Emanuel et al., 2020) . Data on this aspect, however, are limited.

In Italy, the incidence and CFR of COVID-19 during the first wave of the pandemic showed significant geographic heterogeneity (ISTAT, 2020). The aim of this study was to explore the possible association between the CFR and measures of disease burden using an ecological approach.

Methods

Italy is administratively divided into 19 regions and two autonomous provinces (PA). On February 24, 2020, the Italian Ministry of Health started a daily collection of new COVID-19 cases, with each region and PA providing the number of deaths, number of hospitalized cases, and number of cases in the intensive

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Table 1
Maximum number of COVID-19 patients in the ICU, number of ICU beds pre COVID-19, and ICU load by region

Region	Maximum number of COVID-19 patients in the ICU	Number of ICU beds pre COVID-19	ICU load[a]
Abruzzo	76	123	61.8
Basilicata	19	49	38.8
Calabria	23	146	15.8
Campania	181	335	54.0
Emilia-Romagna	375	449	83.5
Friuli Venezia Giulia	61	120	50.8
Lazio	203	571	35.6
Liguria	179	180	99.4
Lombardia	1381	861	160.4
Marche	169	115	147.0
Molise	9	30	30.0
PA Bolzano	65	37	175.7
PA Trento	81	32	253.1
Piemonte	453	327	138.5
Puglia	159	304	52.3
Sardegna	31	134	23.1
Sicilia	80	418	19.1
Toscana	297	374	79.4
Umbria	48	70	68.6
Valle d'Aosta	27	10	270.0
Veneto	356	327	108.9

ICU, intensive care unit.
[a] Ratio between the maximum number of COVID-19 patients in the ICU and the number of ICU beds available before the pandemic.

care unit (ICU). According to the regional burden of COVID-19 patients, a proportion of ICUs were dedicated to COVID-19 patients, or, where possible, separate areas for COVID-19 patients were created in ICUs where non COVID-19 patients were also admitted (Pasin et al., 2020). In regions with the highest burden during the peak of the first wave of the pandemic, virtually all ICU beds were dedicated to COVID-19 patients, and non COVID-19 patients were transferred outside the region (Grasselli et al., 2020).

In this study, cumulated publicly available Italian regional data for the period February 24 to May 11, 2020 were analysed (Github, 2020). The CFR was calculated as the proportion of individuals who died with confirmed COVID-19 of the total reported cases. The correlation coefficient and univariable and multivariable (backward selection, $P = 0.20$) negative binomial regression were used to assess the association between the CFR and the following variables: cumulative incidence of COVID-19, as a measure of the overall disease burden; ratio between the maximum number of COVID-19 patients in the ICU and number of ICU beds available before the pandemic (ICU load), as a proxy for the capacity to care for severely ill patients; median age at disease (ISS, 2020); prevalence of chronic disease including diabetes, cardiovascular disease, and chronic obstructive pulmonary disease (Osservatorio sulla salute 2019); number of SARS-CoV-2 nasopharyngeal swabs performed per COVID-19 case diagnosed, as a proxy for the probability of detecting asymptomatic/mildly symptomatic cases.

All of the variables were considered as continuum measures, except ICU load, which was categorized into three classes according to the distribution in quartiles: ≤40%, >40–70%, 70–140% and ≥140%.

Results

During the period considered, 219 214 cases were reported, with a cumulative incidence of 364 per 100 000 inhabitants. At the regional level, incidence ranged between 58 and 912 per 100 000. Table 1 reports the maximum number of COVID-19 patients in the ICU, the number of ICU beds pre COVID-19, and the ICU load by region; of note, the ICU load varied between a minimum of around 16% and a maximum of 253%.

Overall, the CFR was 14%, ranging among regions between 5.0% and 18.4%. Figure 1a shows a positive correlation between the CFR and the cumulative incidence (panel A) (0.72, 95% confidence interval (CI) 0.55 to 0.88, $P < 0.01$) and the ICU load (panel B) (0.51, 95% CI 0.29 to 0.72, $P < 0.01$). Figure 1b shows a positive correlation between the CFR and median age at disease onset (panel A) (0.87, 95% CI 0.75 to 0.99, $P < 0.01$), and a negative correlation between the CFR and the number of swabs per case (panel B) (−0.79, 95% CI −0.88 to −0.81, $P < 0.01$).

In the univariable analysis, the CFR was associated with the cumulative incidence (relative rate (RR) 1.04 per increase of 100 cases/1 million increase, 95% CI 1.03 to 1.05), ICU load (RR 2.45, 95% CI 1.46 to 4.13 for >40–70% vs ≤40%; RR 9.50, 95% CI 5.65 to 16.00, for 70–140% vs ≤40%; RR 14.19, 95% CI 8.44 to 23.89 for ≥140% vs ≤40%), median age (RR 1.27, 95% CI 1.16 to 1.38 per 1 year increase), and number of nasopharyngeal swabs performed (RR 0.92, 95% CI 0.90 to 0.93 per increase of 1 swab/case), while the prevalence of chronic disease was not associated with the CFR (RR 0.97, 95% CI 0.87 to 1.08 per 1% increase). On multivariable analysis, the cumulative incidence (RR 1.02, 95% CI 1.01 to 1.03 per increase of 100 cases/1 million increase), median age (RR 1.08, 95% CI 1.04 to 1.13 per 1 year increase), and ICU load (RR 1.72, 95% CI 1.31 to 2.27 for >40–70% vs ≤40%; RR 2.18, 95% CI 1.44–3.32 for 70–140% vs ≤40%; RR 2.57, 95% CI 1.57 to 4.21 for ≥140% vs ≤40%) remained significantly associated with the CFR (Table 2).

Discussion

This analysis showed that in Italy, during the first phase of the pandemic, the CFR of COVID-19 at the regional level was significantly associated with the overall burden and ICU demand due to COVID-19, as well as with age at disease onset.

While most previous studies on the variation in CFR of COVID-19 have involved cross-country comparisons, this analysis was conducted in a single country in which health care standards are defined at the national level, thus it is unlikely that regional differences in the overall quality of care may explain the observed differences in the CFR. However, in most severely hit Italian regions, such as Lombardy, the need for hospital care and in particular ICU

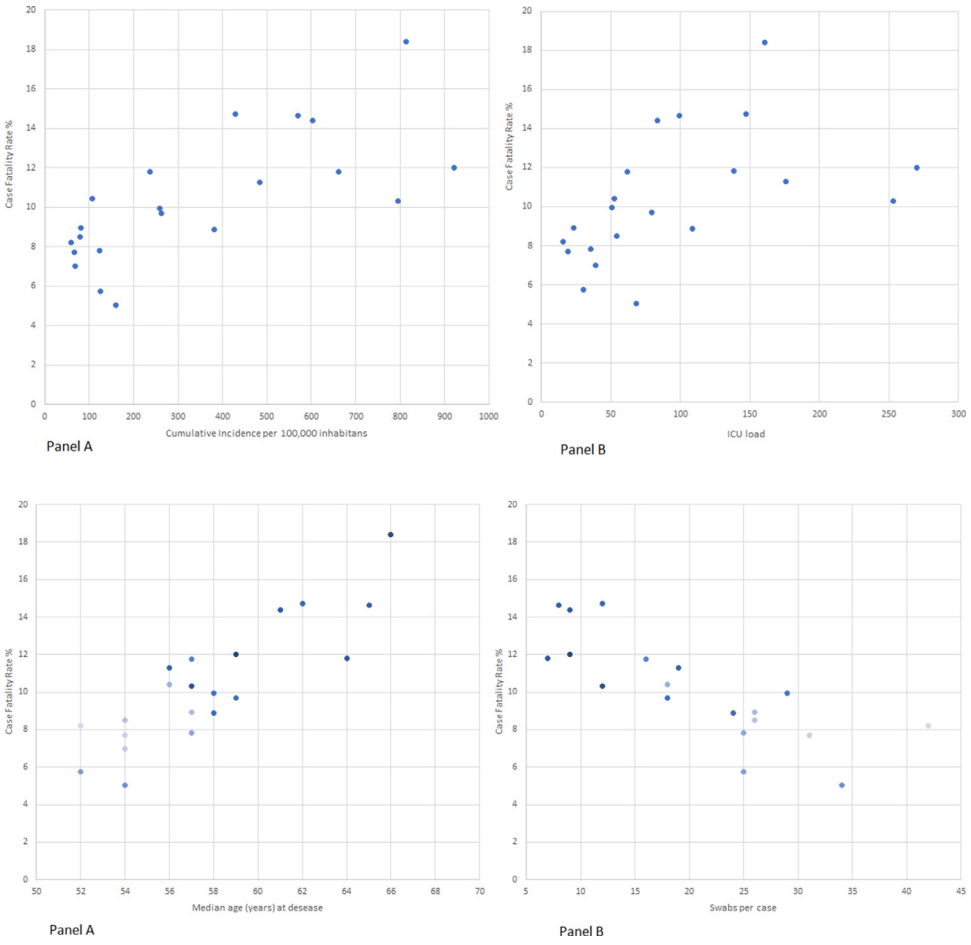

Figure 1. Scatter-plot of the correlation of the CFR with (a) cumulative incidence (panel A) and ICU load (panel B); (b) age (panel A) and number of swabs per case (panel B)—Italian regions (data as at May 11, 2020).

Table 2
Univariable and multivariable analysis of factors associated with the COVID-19 case fatality rate in Italy, February 24 to May 11, 2020

	Univariable			Multivariable		
	RR	*P*-value	95% CI	RR	*P*-value	95% CI
Cumulative incidence (per 100 cases/1 million increase)	1.04	<0.01	1.03–1.05	1.02	<0.01	1.01–1.03
Swabs per confirmed case (per 1 swab increase)	0.92	<0.01	0.90–0.93	NI		
Median age at disease (per 1 year increase)	1.27	<0.01	1.16–1.38	1.08	<0.01	1.04–1.13
ICU load						
>40–70% vs ≤40%	2.45	<0.01	1.46–4.13	1.72	<0.01	1.31–2.27
70–140% vs ≤40%	9.50	<0.01	5.65–16.00	2.18	<0.01	1.44–3.32
≥140 % vs ≤40%	14.19	<0.01	8.44–23.89	2.57	<0.01	1.57–4.21
Prevalence of chronic disease (per 1% increase)	0.97	0.575	0.87–1.08	NI		

RR, relative rate; CI, confidence interval; ICU, intensive care unit; NI, not included.

beds for COVID-19 patients rapidly exceeded the pre-existing capacity (Grasselli et al., 2020). The care of critically ill patients with COVID-19 is a complex task in which interventions in several areas are needed. These include infection control practices, hemodynamic and ventilatory support, and COVID-19-specific therapy (Alhazzani et al., 2020). It can be hypothesized that unmeasured variations in the application of these interventions, possibly linked to variations in the patient burden (Rubinson, 2021) , may in part explain the variation in CFR.

The results of the present study are also consistent with the results of a study conducted in the United States, in which a higher ICU patient load was found to be associated with increased COVID-19 in-hospital mortality (Bravata et al., 2021).

In a previous study in China, it was observed that Hubei Province, which had the highest COVID-19 incidence during the first wave of the pandemic, also had the highest CFR when compared to the other provinces, and it was postulated that this could be attributed to differences in case ascertainment (Leung et al., 2020). In the adjusted estimates in the present study, no association was found between the CFR and testing rates, suggesting that it is unlikely that differences in the availability of and approaches to SARS-CoV-2 testing may account for the regional variability in the CFR. Indeed, the testing policy in Italy followed national guidelines, although it is possible that in areas with the highest incidence, even severely ill patients were not tested for SARS-CoV-2, as suggested by the significant numbers of excess deaths recorded in these areas (Piccininni et al., 2020).

A major limitation of this analysis is that the CFR overestimates the true infection fatality rate. Moreover, an ecological approach was used, which is subject to bias due to the lack of individual data (Wakefield, 2008). It should be noted that the study data were aggregated at a regional level and therefore it was not possible to standardize them by age and sex. Nonetheless, the results of this study are consistent with an analysis of Italian national surveillance data (ISS, 2021), which also showed a positive correlation between the standardized CFR and standardized incidence. In that analysis, however, the COVID-19 burden on ICUs was not analysed.

The health status of the population has been widely demonstrated to represent a risk factor for COVID-19 mortality (Epicentro, 2020). In particular, diseases such as hypertension, heart disease, and diabetes can increase the risk of death by up to three times (Robinson et al., 2021). In our analysis, the prevalence of the population with at least one chronic disease in each region was used, and these data do not seem to show any effect on the CFR . Possible explanations for this finding could be that we used data from all of the population, not adjusted for age, data from a sample survey, and data not specific to particular comorbidities.

In conclusion, this analysis suggests that the rapid increase in incidence of COVID-19 may have contributed to an increased disease fatality. The study findings underscore the need for the timely adoption of mitigation measures during subsequent epidemic waves in order to ensure appropriate care for all affected patients and to limit mortality.

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Ethical approval

This study was performed with data from routine surveillance activity and did not require ethical clearance.

Conflict of interest

None.

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