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Understanding the Factors Affecting COVID-19 Mortality in Italy: Does a Relationship Exist With a Sharp Increase in Intensive Care Unit Admissions?

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Original Research

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Abstract

Objective: The present study aims to explore whether a relationship exists between the immediate sharp increase in intensive care unit (ICU) admissions and the mortality rates in Italy.
Methods: Official epidemiological data on coronavirus disease (COVID-19) were employed. The forward lagged (0, 3, 7, 14 days) daily variations in the number of deaths according to the number of days after the outbreak started and the daily increases in ICU admissions were estimated.
Results: A direct relationship between the sharp increase of ICU admissions and mortality rates has been shown. Furthermore, the analysis of the forward lagged daily variations in the number of deaths showed that an increase in the daily number of ICU admissions resulted in significantly higher mortality after 3, 7, and 14 days. The most pronounced effect was detected after 7 days, with 250 deaths (95% CI: 108.1-392.8) for the highest increase in the ICU admissions, from 100 to 200.
Conclusions: These results would serve as a warning for the scientific community and the health care decision-makers to prevent a quick and out-of-control saturation of the ICU beds in case of a relapse of the COVID-19 outbreak.

The coronavirus disease (COVID-19) outbreak posed severe challenges to the health care systems of the countries worldwide. The dramatic and unexpected sharp increase of the demand for health care assistance led to a shortage of the health care resources in a short time, especially for what concerns intensive care units (ICUs).[1,2]

Italy is the first European country where the COVID-19 started spreading,[3] initially from 2 Northern regions, Lombardia and Veneto, and then to the rest of Italy.[4] Since the beginning of the epidemic, the regional governments had to face the potential local health care systems crisis related to the outbreak. Previous experience of such a health crisis was only in Wuhan city, China, whose health care system is not comparable with the Italian ones.

At the beginning of the epidemic, preliminary Italian data about the outbreak show a dramatic situation, including higher mortality rates[5] and a higher proportion of severely ill patients treated with invasive ventilation in the ICUs[1] compared to those of China. Understanding factors that affect the high ICU admission rates and the high mortality rates is of primary importance to improve health care resources planning.

The present study aims to explore whether a relationship exists between the immediate sharp increase in ICU admissions and the mortality rates in Italy, with a focus on 2 Italian regions, Lombardia and Veneto.

Although Lombardia and Veneto are the 2 Italian regions where the virus first spread, the evolution of the epidemic in Lombardia was different from the evolution of the epidemic in Veneto. Soon after the starting of the outbreak, it has become clear that the proportions of COVID-19 patients hospitalized and those of patients admitted to the ICUs were markedly different among these 2 Italian regions.[6] Such differences are probably the result of 2 different approaches of health care governance and outbreak management. The Italian National Health Service (NHS) provides universal coverage free of charge by tax funding that is, in-hospital care and general practitioners consultation, or at a minimal charge, that is, drugs purchase and outpatient visits. However, the NHS is regionally based, meaning that the management of the regional health care systems falls within the competence of each Italian region, in a common framework established by the national government. Consequently, slightly different strategies have been put forward to organize the regional health care systems during the COVID-19

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Table 1. Number of cases, deaths, and ICU admissions according to weeks. The number of weekly events is reported both as absolute values and over 100 000 inhabitants. The data are reported for Italy (Panel 1), Veneto (Panel 2), and Lombardia (Panel 3)

Panel 1 Italy												
Week	Weekly cases	N of deaths	N of ICU	Weekly cases*100000 inhabitants	Death*100 000 inhabitants	ICU*100 000 inhabitants	Weekly difference in cases	Weekly difference in cases *100 000 inhabitants	Weekly difference in death	Weekly difference in death *100 000 inhabitants	Weekly difference in ICU	Weekly difference in ICU *100 000 inhabitants
24-02 25 02	314	17	61	0.52	0.03	0.1	–	–	–	–	–	–
26-02 03-03	2180	244	796	3.6	0.4	1.31	1866	3.08	227	0.37	735	1.21
04-03 10-03	7647	2145	3935	12.62	3.54	6.49	5467	9.02	1901	3.14	3139	5.18
11-03 17-03	21357	11020	10610	35.25	18.19	17.51	13710	22.63	8875	14.65	6675	11.02
18-03 24-03	37670	33613	19876	62.18	55.48	32.81	16313	26.93	22593	37.29	9266	15.29
25-03 31-03	36616	69623	26599	60.44	114.9	43.9	−1054	−1.74	36010	59.44	6723	11.1
01-04 07-04	29794	106650	27817	49.18	176	45.91	−6822	−11.26	37027	61.12	1218	2.01
08-04 14-04	26902	135696	23965	44.4	224	39.56	−2892	−4.77	29046	47.94	−3852	−6.36
14-04 21-04	21469	162209	19239	35.44	267.7	31.76	−5433	−8.97	26513	43.76	−4726	−7.8
Panel 2 Veneto												
Week	Weekly cases	N of death	N of ICU	Weekly cases*100 000 inhabitants	Death*100 000 inhabitants	ICU*100 000 inhabitants	Weekly difference in cases	Weekly difference in cases *100 000 inhabitants	Weekly differ-ence in death	Weekly difference in death *100 000 inhabitants	Weekly difference in ICU	Weekly difference in ICU *100 000 inhabitants
24-02 25 02	42	2	11	0.07	0	0.02	–	–	–	–	–	–
26-02 03-03	264	15	82	0.44	0.02	0.14	222	0.37	13	0.02	71	0.12
04-03 10-03	549	105	280	0.91	0.17	0.46	285	0.47	90	0.15	198	0.33
11-03 17-03	1848	370	835	3.05	0.61	1.38	1299	2.14	265	0.44	555	0.92
18-03 24-03	3244	1063	1729	5.35	1.75	2.85	1396	2.3	693	1.14	894	1.48
25-03 31-03	3207	2502	2391	5.29	4.13	3.95	−37	−0.06	1439	2.38	662	1.09
01-04 07-04	2770	4198	2302	4.57	6.93	3.8	−437	−0.72	1696	2.8	−89	−0.15
08-04 14-04	2507	5760	1794	4.14	9.51	2.96	−263	−0.43	1562	2.58	−508	−0.84
14-04 21-04	1972	7359	1356	3.25	12.15	2.24	−535	−0.88	1599	2.64	−438	−0.72

Panel 3 Lombardia												
week	Weekly cases	N of death	N of ICU	Weekly cases*100000 inhabitants	Death*100 000 inhabitants	ICU*100 000 inhabitants	Weekly difference in cases	Weekly difference in cases *100 000 inhabitants	Weekly difference in death	Weekly difference in death *100 000 inhabitants	Weekly difference in ICU	Weekly difference in ICU *100 000 inhabitants
24-02 25 02	234	15	44	0.39	0.02	0.07	-	-	-	-	-	-
26-02 03-03	1280	180	593	2.11	0.3	0.98	1046	1.73	165	0.27	549	0.91
04-03 10-03	4271	1528	2426	7.05	2.52	4	2991	4.94	1348	2.22	1833	3.03
11-03 17-03	10429	7495	5016	17.21	12.37	8.28	6158	10.16	5967	9.85	2590	4.27
18-03 24-03	14483	21181	7592	23.91	34.96	12.53	4054	6.69	13686	22.59	2576	4.25
25-03 31-03	12505	41058	9092	20.64	67.77	15.01	−1978	−3.26	19877	32.81	1500	2.48
01-04 07-04	9117	60111	9365	15.05	99.22	15.46	−3388	−5.59	19053	31.45	273	0.45
08-04 14-04	9001	73157	8310	14.86	120.8	13.72	−116	−0.19	13046	21.53	−1055	−1.74
14-04 21-04	6605	84054	6698	10.9	138.7	11.06	−2396	−3.95	10897	17.99	−1612	−2.66

outbreak.[7] For these reasons, these 2 Italian regions would serve as a paradigm to understand how different approaches in the management of the regional ICU systems may affect mortality.

Methods

The source of data for COVID-19 ICU admissions, deaths, and swabs was the Italian Civil Protection Department of the Council of Ministers Presidency (https://github.com/pcm-dpc/COVID-19), while the resident population data have been retrieved from the National Italian Statistics Institute (www.istat.it). The time series of ICU admissions have been considered until April 22, 2020. In Italy, the regional policies for the diagnosis of COVID-19 infection are heterogeneous, providing different levels of inclusion of the general population. For this reason, the regional estimates of ICU per 100 000 inhabitants were computed using a weighted ratio estimator.

Statistical Analysis

The weekly total number of deaths and ICU admissions were reported in absolute values and over 100 000 inhabitants. The data were displayed for Italy, Lombardia, and Veneto.

The ICU admissions (ie, daily variation in ICU admissions) over 100 000 inhabitants, in comparison with the number of deaths (daily variation in deaths) over 100 000 inhabitants, were represented in a plot together with a Local Polynomial Regression Smoothing curve (LOESS).[8]

The forward lagged (0, 3, 7, 14 days) daily variations in the number of deaths according to the number of days after the outbreak started and the daily increases in ICU admissions were estimated via the Ordinary Least Square (OLS) method. The non-linearity of the effects was modeled using a Restricted Cubic Spline (RCS) approach.[9] The estimated effects were reported according to different increases in ICU occupation, together with relative SE and 95% CI.

The model estimates were reported according to different variations in ICU daily admissions:

1. The effects of daily death variations for Italy were evaluated for an increase of ICU admissions ranging from 0 to 50, 50 to 100, and 100 to 250. The time effect was estimated from the 11th to the 30th epidemic day.
2. An increase in ICU admissions ranging from 0 to 5, 5 to 10, and 10 to 20 was instead considered for Veneto. The time effect was computed from the 9th to the 26th epidemic day.
3. For Lombardia, the effect on daily death variations was evaluated for an increase of ICU occupations ranging from 0 to 20, 20 to 40, and 40 to 60. The time effect was estimated from the 11th to the 30th epidemic day.

Computations were performed using R 3.5.2[10] with rms[11] package.

Results

Table 1 shows descriptive data on weekly COVID-19 ICU admissions and the number of deaths from the beginning of the outbreak to April 21. The ICU admission rates in Italy showed an increasing trend until April 7, with 45.91 ICU admissions per 100 000 inhabitants in the week between April 1 and April 7. Conversely, the mortality rates increased until the last observation week included

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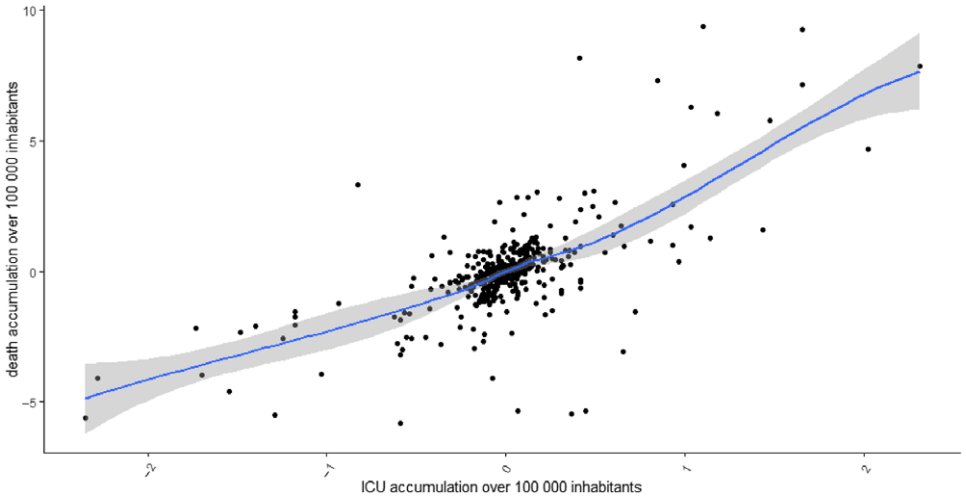

Figure 1. ICU admissions (daily variation in ICU admission) over 100 000 inhabitants versus death (daily variation in deaths) over 100 000 inhabitants.

in the study (April 14-21). Lombardia and Veneto showed the same pattern observed for Italian data. However, both ICU admissions and mortality rates were found to be markedly higher in Lombardia compared to Veneto in all of the weeks considered.

A direct relationship has been shown between the sharp increase of ICU admissions and mortality rates (Figure 1 and Figure S1, Supplementary Material). Furthermore, the analysis of the forward lagged (0, 3, 7, 14 days) daily variations in the number of deaths according to the increases in ICU daily admissions showed that an increase in the daily number of ICU admissions resulted in a significantly higher number of deaths after 3, 7, and 14 days. The most pronounced effect was detected after 7 days, with 250 deaths (95% CI: 108.1-392.8) for the highest increase in the ICU admissions, from 100 to 200 (Table 2, Figure S2).

The analysis of Veneto data did not detect any significant effect in the forward lagged (0, 3, 7, 14 days) daily variations in the number of deaths. Conversely, in line with Italian data, Lombardia data showed that the daily increase in the ICU admissions resulted in a significant increase in the daily variation of the number of deaths, especially after 7 and 14 days. An increase in ICU admissions from 0 to 20 resulted in 112.9 deaths (95% CI: 28.56-197.2) after 7 days and an increase in ICU admissions from 20 to 40 resulted in 74 new deaths (95% CI: 28.29-119.7) after 7 days.

Discussion

The results of the present study show a strong relationship between the immediate sharp increase of ICU admissions and mortality rates in Italy. These results are confirmed by the analysis of data of 2 Italian regions, Lombardia and Veneto, where the epidemic outbreak has started. Lombardia presented both higher ICU admissions and higher mortality compared to Veneto and showed a significant effect of the daily increase in the ICU admissions on the forward lagged daily variation in the number of deaths, especially after 7 and 14 days. This is consistent with the literature showing that the median ICU length of stay is 9 days (interquartile range, 6-13),[1] and mortality continued to increase after the peak of ICU admissions.

Literature has already shown that the ICU bed shortage resulted in higher COVID-19 mortality, especially at the beginning of the outbreak.[12] The value added by the present study is that the daily variation itself of the ICU admission is associated with higher mortality rates. The results of this study may have an important impact on the organization of health care systems during the COVID-19 outbreak. They highlight the need for preventing the sharp increase in ICU admissions. Such findings could be explained by the fact that the hospital resources available were not able to face the quick increase of ICU admissions, likely affecting the quality of care. As an example, the ICU capacity has been increased soon after the start of the outbreak,[13] but trained personnel have not been increased to treat the increase of critically ill patients.

Several factors could affect the immediate and sharp increase of ICU admissions, including both non-modifiable (eg, the age structure of the population, comorbidities, the severity of the underlying disease) and modifiable factors. Among modifiable factors, the virus transmission speed could be affected by the adoption of containment measures at the community level, which have been proven to be effective.[14] However, ICU admissions may also depend on the actions taken by the health care decision-makers. An analysis of the testing strategies for COVID-19 used by Lombardia and Veneto shows that the testing strategy is associated with hospital admission, in favor of a wide testing strategy, including also mild/asymptomatic subjects, as the one adopted by the Veneto region.[15,16] Such findings could be explained by the fact that testing also asymptomatic and mildly symptomatic patients allows for a prompt quarantine for those subjects and for better clinical monitoring that would be helpful in preventing the worsening of symptoms. Finally, the ICU admission rates would also be affected by the organization of the health care system itself. As an example, the Lombardia region's health care organization is characterized by the shortage of community health facilities, resulting in a physiologically higher hospital admission rate.

Conclusion

This study shows a clear relationship between the immediate sharp increase in ICU admissions and mortality rates in Italy. These results would serve as a warning for the scientific community and the health care decision-makers in order to prevent a quick and out-of-control saturation of the ICU beds in case of a relapse of the COVID-19 outbreak.

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Table 2. Estimated forward lagged (0, 3, 7, 14 days) daily variation in the number of deaths according to the days since the outbreak started and daily increases in ICU occupations. The estimated effects (effect daily deaths) are reported according to different ICU occupation increases (identified in the columns labeled high and low) together with SE and 95% CI

Panel 1 Italy							
Lag	Variable	Low	High	Effect daily deaths	SE	Lower.0.95	Upper.0.95
lag 0	Delta ICU	0	50	−8.74	35.6	−81.01	63.53
lag 0	Days	10.75	30.25	534.7	30.95	471.8	597.5
lag 0	Delta ICU	50	100	−4.62	22.42	−50.13	40.89
lag 0	Delta ICU	100	250	10.93	43.34	−77.06	98.91
lag 3	Delta ICU	0	50	37.68	35.89	−35.19	110.5
lag 3	Delta ICU	50	100	46.2	22.6	0.31	92.09
lag 3	Delta ICU	100	250	134.1	43.7	45.38	222.8
lag 7	Delta ICU	0	50	99.75	34.1	30.53	169
lag 7	Delta ICU	50	100	95.31	21.47	51.72	138.9
lag 7	Delta ICU	100	250	250.4	70.12	108.1	392.8
lag 14	Delta ICU	0	50	169.4	39.61	88.94	249.8
lag 14	Delta ICU	50	100	137.5	24.95	86.88	188.2
lag 14	Delta ICU	100	250	157.6	81.47	−7.81	323
Panel 2 Veneto							
Lag	Variable	Low	High	Effect in deaths daily variation	SE	Lower.0.95	Upper.0.95
lag 0	Delta ICU	0	5	5	0.73	−3.59	5.06
lag 0	Days	9.25	25.75	16.5	19.36	14.92	23.81
lag 0	Delta ICU	5	10	5	0.18	−2.85	3.2
lag 0	Delta ICU	10	20	10	−2.53	−6.14	1.08
lag 3	Delta ICU	0	5	5	−3.25	−8.9	2.41
lag 3	Delta ICU	5	10	5	−2.59	−6.54	1.36
lag 3	Delta ICU	10	20	10	−1.81	−6.53	2.91
lag 7	Delta ICU	0	5	5	3.22	−2.9	9.34
lag 7	Delta ICU	5	10	−40	10.44	−21.2	42.08
lag 7	Delta ICU	10	20	10	−0.74	−5.85	4.36
lag 14	Delta ICU	0	5	5	6.34	−0.69	13.37
lag 14	Delta ICU	5	10	−40	11.88	−24.48	48.24
lag 14	Delta ICU	10	20	10	0.26	−5.6	6.13
Panel 3 Lombardia							
lag	variable	Low	High	Diff.	Effect	Lower.0.95	Upper.0.95
lag 0	Delta ICU	0	20	20	52.99	−22.12	128.1
lag 0	days	10.75	30.25	19.5	253.7	196.8	310.6
lag 0	Delta ICU	20	40	20	19.84	−20.87	60.56
lag 0	Delta ICU	40	60	20	−29.62	−76.41	17.16
lag 3	Delta ICU	0	20	20	77.94	2.54	153.3
lag 3	Delta ICU	20	40	20	42.42	1.54	83.29
lag 3	Delta ICU	40	60	20	−10.6	−57.57	36.37
lag 7	Delta ICU	0	20	20	112.9	28.56	197.2
lag 7	Delta ICU	20	40	20	74	28.29	119.7
lag 7	Delta ICU	40	60	20	15.98	−36.53	68.5
lag 14	Delta ICU	0	20	20	101.7	23.31	180.1
lag 14	Delta ICU	20	40	20	81.07	38.55	123.6
lag 14	Delta ICU	40	60	20	50.31	4.52	96.09

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