The pressure on healthcare system and intensive care utilization during the COVID-19 outbreak in the Lombardy region: a retrospective observational study on 43,538 hospitalized patients

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ABSTRACT

During the spring of 2020, the COVID-19 epidemic caused an unprecedented demand for intensive care resources in Lombardy, Italy. Using data on 43,538 hospitalized patients admitted between February 21 and July 12, 2020, we evaluated variations in intensive care unit (ICU) admissions and mortality over three periods: the early phase (February 20-March 13), the period of highest pressure on healthcare (March 14-April 25, when COVID-19 patients exceeded the ICU pre-pandemic bed capacity), and the declining phase (April 26-July 12).

Compared to the early phase, patients above 70 years of age were admitted less often to an ICU during highest pressure on healthcare (odds ratio OR 0.47, 95%CI: 0.41-0.54) with longer delays (incidence rate ratio IRR 1.82, 95%CI: 1.52-2.18), and lower chances of death in ICU (OR 0.47, 95%CI: 0.34-0.64). Patients under 56 years of age reported more limited changes in the probability (OR 0.65, 95%CI: 0.56-0.76) and delay to ICU admission (IRR 1.16, 95%CI: 0.95-1.42) and an increased mortality (OR 1.43, 95%CI: 1.00-2.07). In the declining phase, all quantities decreased for all age groups.

These patterns may suggest that limited healthcare resources during the peak epidemic phase in Lombardy forced a shift in ICU admission criteria to prioritize patients with higher chances of survival.

Abbreviations:

ICU: intensive care unit, OR: odds ratio, IRR: incidence rate ratio, CI: confidence interval

BACKGROUND

Italy was the first country in the Western hemisphere to be affected by a widespread epidemic of SARS-CoV-2 [1,2], and still has one of the highest cumulative burden of COVID-19 hospitalizations and deaths worldwide [3]. Lombardy, in particular, was the first and by far the hardest-hit Italian region, accounting alone for over half of COVID-19 hospital admissions in Italy [4], despite having about one sixth of the country's population. The explosive spread of SARS-CoV-2 in the region, coupled with the high COVID-19 morbidity, threatened to collapse even one of the most advanced health systems in the country and resulted in the rapid adoption of unprecedented control measures. Despite a rate of critical care beds per inhabitant above the European average [5] and the drastic actions taken, culminated in the national lockdown of March 11, hospitals of Lombardy were put under severe pressure. By mid-March 2020, the bed occupancy due to COVID-19 in Intensive Care units (ICUs) in the region exceeded the pre-crisis total capacity of about 720 beds [6]. The rapid saturation of hospital capacity was predicted by mathematical models in the early phase of the epidemic [7], prompting the emergency expansion of COVID-19 dedicated ICU and hospital beds [8,9], similarly to what previously experienced during the epidemic in Wuhan

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[10]. Hospital taskforces were created following previously established guidelines for preparedness against disastrous influenza epidemics [8, 11], with the aim of increasing the hospital surge capacity (space, staff and supplies) and safely admit a larger number of critically ill patients with COVID-19 [8,9]. Ethics recommendations issued at the beginning of the COVID-19 epidemic in Italy [12] suggested that selective criteria for admission to an ICU should be applied in order to save resources (mainly ICU beds and staff) when these would become scarce, to maximize the benefits for the largest number of people. The careful evaluation of the functional status of any critically ill patient was recommended in order to prioritize for admission to an ICU those patients with greater probability of survival and life expectancy [12].

On April 3rd, 2020, the pre-crisis total ICU capacity had been increased to 1,761 beds, of which 1,381 (78%) were occupied by COVID-19. Since the beginning of April 2020, the ICU bed occupancy started to decrease and by the end of the month fell below the pre-crisis capacity of 720 beds. The case of Italy was later taken as a benchmark to provide indications for hospital surge capacity in European countries [13]. Saturation in healthcare resources had been demonstrated to worsen clinical outcomes for inpatients in pre-pandemic times [14] and later evaluated with respect to the impact of COVID-19 using different perspectives [15,16,17]. Here, we retrospectively investigate the impact of saturation of intensive care resources during the first COVID-19 epidemic wave in Lombardy to elucidate trends in ICU admission probabilities, admission delays, and mortality across different epidemic periods and age groups.

METHODS

Our study is based on retrospective data collected on the complete set of 46,554 patients admitted with a laboratory-confirmed SARS-CoV-2 infection to one of the 73 hospitals in

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Lombardy between February 21 and July 12, 2020. Laboratory confirmation of SARS-CoV-2 was defined as a positive result of real-time Reverse Transcriptase–Polymerase Chain Reaction (RT-PCR) assay of nasal and pharyngeal swabs (or, occasionally, from lower respiratory tract aspirates).

The institutional ethics board of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan approved this study and due to the nature of retrospective chart review, waived the need for informed consent from individual patients.

Study population. The analysis focuses on a subset of 43,538 patients, obtained by considering patients who had symptom onset before hospital admission and excluding those with inconsistencies in dates due to data entry (Figure 1).

More than 99.5% of the cohort of patients in our study was followed from hospitalization through either death or discharge. Only 10 (0.2%) among ICU patients were still in hospital at the end of our study period but all of them had already been discharged from the ICU.

Data were collected at hospital admission (age, sex, province of residence, date of symptom onset, date of SARS-CoV-2 diagnosis, date of admission) and throughout the course of the patient's stay (date of admission and discharge from ICUs, if any, date of discharge from hospital, clinical outcome, i.e., recovery or death). Age was grouped into 3 classes (≤ 55 years, 56-69 years and ≥ 70 years), based on the first and third quartile of the age at ICU admission, and treated as a categorical variable. Age cutoffs were set to the first and third quartile of the age at ICU admission in order to guarantee a balanced sample size in each age group. Comorbidities were aggregated in three major groups: cardiovascular diseases, respiratory diseases, and metabolic disorders (see Web appendix 1).

We stratified patients according to the period in which they were hospitalized (see Figure 2):

1) the early phase of the epidemic, from February 21 to March 13, 2020, when the ICU bed

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occupancy by COVID-19 patients was increasing but was still below the pre-crisis capacity of 720 beds; 2) the period of highest pressure on healthcare, from March 14 to April 25, 2020, when the COVID-19 ICU occupancy ranged between 720 and 1,381; 3) the declining phase, from April 26 to July 12, when the COVID-19 ICU occupancy fell again below 720 beds.

Statistical analysis. The outcomes of our analyses are the probability of being admitted to an ICU, the probability of death among ICU patients and the time between hospitalization and admission in ICU.

The time to ICU admission was computed as the time interval between hospitalization and admission to ICU among patients admitted to the ICU.

In descriptive analyses, the probability of ICU admission and death are summarized by sample proportions, while the time between hospitalization and ICU admission by sample means. A sufficient sample size in each category allowed us to compute the 95% CI by assuming the two statistics follow a Normal distribution.

To assess differences across multiple groups, we used one-way ANOVA, followed by post-hoc

Tukey test. Estimated 95% confidence intervals (CI) and p-values are based on the Studentized range statistic, Tukey's 'Honest Significant Difference' method.

In multivariate analyses, we estimated odds ratios (OR) to compare the odds of being admitted to ICU and the odds of dying in ICU in period 2 and 3 against period 1. We also estimated incidence rate ratios (IRR) to compare the delay between hospital and ICU admission between different periods. OR were estimated via logistic regression models adjusted for sex, comorbidities, and province of residence of patients. Negative binomial regressions were used to estimate Incidence Rate Ratios (IRR) adjusting for sex and the

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presence of comorbidities. OR and IRR were computed by exponentiating the estimated models' coefficients. Negative binomial regression was preferred to Poisson regression based on the likelihood ratio test. All models were run separately for subgroups of patients in the three different age classes to account for the interaction between age and both the presence of comorbidities and the period of hospitalization. Sensitivity analyses were conducted to assess the robustness of our results with respect to the definition of the three periods of interests. In particular, we defined the three periods using alternative ICU bed occupancy thresholds of 650 and 800. The statistical significance of the parameters of the logistic and of the negative binomial regressions was assessed through the Wald test. Statistical analysis was performed using R version 3.6.2, and packages "boot", "MASS", "multcomp", "lmtest" and "aod".

RESULTS

Among the 43,538 selected patients hospitalized in Lombardy with COVID-19 within July 12, 2020, 3,997 (9.2%) were admitted to an ICU. The median age of hospitalized patients across the three different periods was 68 years (interquartile range 55-79) and the majority of patients were male (59.6%; Table 1). Among patients admitted to ICUs, the median age was 63 (interquartile range 56-70), 78.7% were male and 55.8% had at least one comorbidity. There were 11,906 (27.3%) COVID-19 related deaths among hospitalized patients (see Web Table 1 in Web appendix 2), of which 1,863 among patients admitted to an ICU (46.6% of all ICU admissions and 15.6% of all deaths). Time between key events for patients hospitalized between February 21 and July 12, 2020, are presented in Web table 2 in Web appendix 3. The overall proportion of hospitalized patients that were admitted to an ICU shows a decreasing trend over the course of the epidemic (Figure 3-A and Table 1), from 13.2% (95%CI: 12.6-13.9%) for patients hospitalized during period 1, to 8.4% (95%CI: 8.1-8.7%) in the second period, to 3.1% (95%CI: 2.5-3.7%) in the third period (post-hoc Tukey test p-

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values on the differences in means <0.001). A progressive decrease was observed for the overall ICU mortality as well, from 51.9% (95%CI 49.3-54.5) for patients hospitalized during period 1 to 44.3% (95%CI 43.7-44.9) and 27.6% (95%CI 26.1-29.1) for those hospitalized respectively during the second and third period (post-hoc Tukey test p-values on the differences in means <0.001) (Figure 3-B and Table 1). The delay between hospital and ICU admission, however, was longer for patients hospitalized during highest pressure on healthcare (about 5.8 days (95%CI 5.55-6.14), i.e., 1.18 days (95%CI 0.53-1.83) longer compared to period 1 and 2.6 days (95%CI 065-4.53) longer compared to period 3; post-hoc Tukey test p-values <0.001 and 0.005 respectively; see figure 3-C). Similar qualitative trends over the three periods can be observed for the same quantities within a given age group. However, a comparison of the relative variations within each age group highlights important quantitative differences (see Web table 3 in Web appendix 4, see Web table 4 in Web appendix 5 and see Web table 5 in Web appendix 6).

We therefore report in Fig.3 D-F the OR of being admitted to ICU, the OR of dying in ICU and the IRR for the delay between hospitalization and admission in ICU for patients hospitalized in period 2 and period 3 with respect to those hospitalized during the early phase of the epidemic.

Compared to the early phase (period 1), during the period of highest pressure on healthcare (period 2) the odds of being admitted in ICU decreased much more briskly for patients above 70 years of age than for younger patients (OR 0.47, 95%CI: 0.41-0.54 above 70 years of age, against about 0.64 for ages under 56 or 56-69, Figure 3-D; adjusted for sex, province of residence and presence of comorbidities). The odds of dying in ICU for patients under 56 years of age increased for those hospitalized during highest pressure on healthcare with respect to period 1 (OR 1.43, 95%CI:1.00-2.07, see Figure 3-E and Web table 4 in Web appendix 5); conversely, the risk of patients above 70 years old decreased (OR 0.47, 95%CI: 0.34-0.64, see Figure 3-E and Web table 4 in Web appendix 5). The increase in the delay

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between hospital and ICU admission during highest pressure on healthcare was much more important for patients aged 70 or older (IRR 1.82, 95%CI: 1.51-2.18), compared to younger patients (IRR 1.16 (95%CI 0.95-1.42) for patients under 56 years and 1.11 (95%CI: 0.98-1.27) for patients aged 56-69), Figure 3-F and Web table 5 in Web appendix 6).

A similar pattern can be observed when considering a disaggregation by comorbidities rather than by age group (Figure 4). For patients hospitalized in highest pressure on healthcare compared to the first period, the odds of being admitted in an ICU and the odds of dying in an ICU tended to decrease more sharply when a comorbidity was present (Figure 4-D and 4-E), and the delay of admission in an ICU tended to increase more (4-F) after adjusting for age, sex and province of residence.

All findings were robust when considering different ICU bed occupancy thresholds to define the three periods of interest (see Web Figure 1 and Web tables 6-11 in Web appendix 7).

DISCUSSION

In the spring of 2020, the healthcare system of Lombardy was under intense pressure due to the COVID-19 epidemic, with hospital and ICU bed capacity saturated by large numbers of COVID-19 patients. During this period, high risk patients admitted to resource-limited hospitals were transferred to designated hub hospitals in the network with available ICU beds and highly skilled intensive care staff [18]. Even after a coordinated regional effort to massively increase the number of available ICU beds, the occupation reached levels around 80% during the peak of the outbreak at the beginning of April 2020. In addition to the limited availability of beds, the pressure on the healthcare system was aggravated by the shortage of hospital workforce, due to the large number of infections occurring among doctors, nurses and other healthcare professionals [7], and to precautionary quarantines needed to limit hospital transmission.

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In this work, we evaluated the dynamics of ICU admission and mortality over three time periods representing different levels of healthcare resource utilization, as measured by the overall number of ICU beds occupied by COVID-19 patients.

We found that the overall probability of admission to an ICU and the probability of death in ICU decreased continuously over the three considered periods, and this was consistent with similar declines in the overall mortality in hospital (see Web Figure 2 in Web appendix 8). These declines are consistent with a recent study on a large cohort of patients admitted with COVID-19 in US hospitals, which attributed the decline to increasing clinical experience specific to SARS-CoV-2 infection [19]. However, age-specific trends show more subtle patterns. Between the early phase of the epidemics and the period of highest pressure on healthcare, the probability of admission declined by over one half for patients aged 70 years or older, and by only about one third for younger patients. At the same time, the mortality of patients aged 55 years or younger increased by 43% (95%CI: 0-107%) while that of patients above 70 years declined by 53% (95%CI: 36-66%). These trends, together with the observation of a significantly larger increase in waiting times for an ICU bed for elderly patients, may reflect the prioritization of admission criteria in ICU during the period of highest pressure on healthcare towards patients with higher probabilities of survival and higher life expectancy. In fact, such adjustments of admission criteria had been recommended according to ethical principles of disaster medicine to face scarcity of resources during the COVID-19 pandemic [12,20-22]. Stricter criteria for admission of older patients based on the assessed chances of survival likely reduced their observed mortality within ICUs, at a time when the chances of survival for younger patients were worsening. We could reproduce a similar pattern when aggregating patients by the presence of comorbidities, which can be interpreted as another proxy for the frailty of patients as an alternative to age. Just like older patients, during highest pressure on healthcare patients with comorbidities tended to have

higher reductions in their probability of admission to an ICU and with extended delays, as well as a higher increase in survival rates compared to patients without comorbidities. The analysis of ICU admission patterns is made complex by the superposition of multiple dynamic factors, such as the varying level of pressure on the healthcare system and the progressive improvement of clinical and pharmaceutical practices. A limitation of this study was the definition of pressure on healthcare solely on the basis of ICU bed occupancy (Figure 2). Further data to better characterize different aspects of pressure on hospital management (e.g., the availability of ventilators, healthcare staff, drugs used for COVID-19 therapy, personal protective equipment; or the progressive expansion of ICU bed capacity over time and the percent of existing beds occupied by COVID-19 patients), were not available. In addition, we did not have information about inter-hospital referrals which might provide further insight in the dynamics of pressure on healthcare system for individual hospitals [18]. We note that the observed patterns may be influenced, at least in part, by other mechanisms than the changing in admission criteria only. For example, it is possible that the health conditions of patients appearing at the hospital have changed over time, affecting waiting times in ICU. In the cohort under study, individual data on the severity of patients at hospital admission and during their hospital stay were available for a very small fraction of patients and could not be included in the analysis. Similarly, we did not have granular information on the individual therapeutic course, on possible changes in therapeutic approaches over time and on the use of life support measures. Of note, as of April 22, 2020, about 87% of ICU patients in Lombardy received invasive mechanical ventilation, while the remaining were assisted with non-invasive respiratory support [23]. We acknowledge that the experience in the treatment of COVID-19 patients in ICU and the physician-to-patient and nurse-to-patient ratios varied widely among the hospitals [23] and over the course of the epidemic, i.e. the increasing caution about early intubation among COVID-19 critical patients [24], and this represents a possible confounder of our analysis. Information on individual comorbidities was

coarsely represented by three macro categories (cardiovascular, respiratory, and metabolic) that contained diverse conditions with a heterogeneous level of prognostic relevance. For this reason, only the binary information on the presence or absence of a given type of comorbidity was used in the regression models. In Web figures 3 and 4 in Web appendix 9, we report a sensitivity analysis showing that the observed trends are confirmed when considering individual categories of comorbidity. All results about mortality in ICU refer to deaths in individuals with a SARS-CoV-2 diagnosis, but we do have data on the specific cause; however, the majority of these fatal outcomes were attributable to COVID-19 complications [25]. Hospital outbreaks of SARS-CoV-2, especially in the early days, may have played a role in altering transmission dynamics, but we believe that this was not a major source of bias for ICUs, on which our study is focused. Finally, to estimate the probability of ICU admission and delay between hospitalization and ICU admission we have considered only patients admitted to an ICU. As such, we acknowledge a possible bias in these as we are not accounting for patients who died in hospital without being admitted to an ICU. Indeed, our data does not allow us to assess whether these patients would have been admitted to an ICU or not under different circumstance. The pervasive use of personal protective equipment and strict infection prevention protocols in pre-pandemic times has likely reduced the transmission of SARS-CoV-2 in ICUs; indeed, a serological study on healthcare workers in Lombardy found significantly lower SARS-CoV2 seroprevalence among ICU doctors and nurses compared to staff in other hospital wards [26].

Many studies have focused on risk factors associated with COVID-19 related mortality [27,28,29,30] and ICU admission [30] among hospitalized patients. A positive association between the proportion of occupied ICU beds and the increase of COVID-19 deaths was identified before, but in a setting that was quite far from saturation of resources (average ICU occupation 20%) [31]. Our work adds to recent studies [15,16,17], which identified negative

associations between the pressure on the healthcare system during the COVID-19 epidemic and improvements in patients' outcome.

The use of complete hospitalization data from 43,538 COVID-19 patients in Lombardy, the largest and hardest-hit Italian region, allowed sufficient statistical power to characterize subtle age-specific trends in intensive care admission criteria and mortality during the COVID-19 pandemic. The saturation of available healthcare resources following the rapid upsurge of cases and its impact on ICU utilization may have played a role in the high mortality risk observed during the first COVID-19 epidemic wave in Lombardy [32] and in the excess mortality observed especially among adults over 75 years of age in municipalities of Northern Italy [33]. Our analysis stresses the importance of epidemiological surveillance and modeling [7] to support the prompt implementation of interventions and social distancing measures to limit the transmission of a newly emerging virus and avoid the saturation of healthcare resources, which can ultimately result in higher losses.

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Table 1. Characteristics of patients hospitalized and admitted to an Intensive Care Unit due to COVID-19 symptoms between February 21 and July 12, 2020, Lombardy region, Italy.

Characteristics	Intensive Care Unit patients								Hospitalized patients							
	Period 1 (*n* = 1435)		Period 2 (highest pressure) (*n* = 2457)		Period 3 (*n* = 105)		Total (*n* = 3997)		Period 1 (*n* = 10841)		Period 2 (highest pressure) (*n* = 29288)		Period 3 (*n* = 3409)		Total (*n* = 43538)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Sex																
Female	267	19	533	22	42	40	842	21	3755	34	11934	41	1873	55	17562	40
Male	1168	81	1916	78	63	60	3147	79	7086	66	17345	60	1532	45	25963	60
Missing	0	0	8	0	0	0	8	0	0	0	9	0	4	0	13	0
Age																
Under 56	311	22	624	25	19	18	954	24	2585	24	7548	26	1130	34	11263	26
56-69	701	49	1284	52	40	38	2025	51	3034	28	7899	27	572	17	11505	26
Over 69	423	29	548	22	46	44	1017	25	5222	48	13840	47	1707	50	20769	48
Missing	0	0	1	0	0	0	1	0	0	0	1	0	0	0	1	0
Province of residence																
Bergamo	352	25	491	20	15	14	858	21	2652	24	4999	17	517	15	8168	19
Brescia	253	18	407	17	15	14	675	17	2540	23	6086	20	521	15	9147	21
Como	21	1	115	5	8	8	144	4	140	1	1006	3	142	4	1288	3
Cremona	193	13	133	5	0	0	326	8	1331	12	1922	6	148	4	3401	8
Lecco	34	2	73	3	3	3	110	3	290	2	956	3	109	3	1355	3
Lodi	157	11	59	2	2	2	218	5	961	8	859	3	182	5	2002	5
Mantua	30	4	52	6	5	4	87	2	223	4	739	8	105	5	1067	2
Milan	223	16	655	27	37	35	915	23	1534	14	7098	24	978	29	9610	22
Monza Brianza	59	2	154	2	4	5	217	5	352	2	2075	2	171	3	2598	6
Pavia	71	1	143	0	9	3	223	6	552	0	1709	0	213	1	2474	6
Sondrio	8	5	43	6	0	9	51	1	52	5	497	5	66	6	615	1
Varese	22	1	102	2	4	0	128	3	113	0	1083	2	208	2	1404	3
Other outside Lombardy	10	2	11	4	3	4	24	1	61	1	101	3	28	6	190	0
Missing	2	0	19	1	0	0	21	1	40	0	158	0	21	1	219	1
Cardiological comorbidities																
No	639	45	1262	51	66	63	1967	49	4586	42	13036	44	2344	69	19966	46
Yes	796	55	1195	49	39	37	2030	51	6255	57	16252	55	1065	31	23572	54

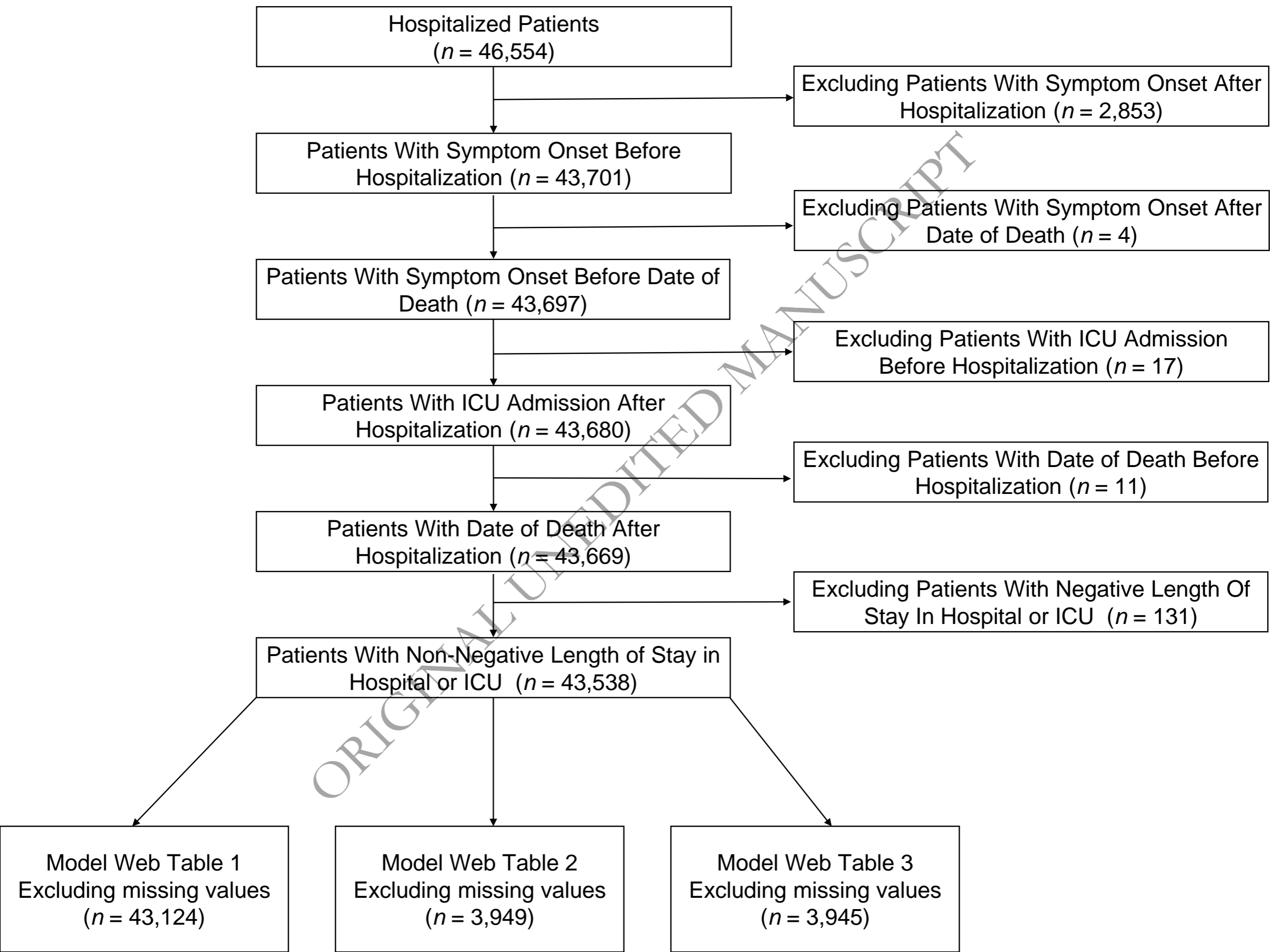|																
Respiratory comorbidities																
No	1344	94	2333	95	97	92	3774	94	9812	90	26781	91	3210	94	39803	91
Yes	91	6	124	5	8	8	223	6	1029	10	2507	8	199	6	3735	9
Metabolic Disorders																
No	1177	82	2050	83	87	83	3314	83	8826	82	24025	82	3055	90	35906	82
Yes	258	18	407	17	18	17	683	17	2015	18	5263	18	354	11	7632	18
Outcome																
Dead	745	52	1089	44	29	28	1863	47	3509	32	7942	27	455	13	11906	27
Discharged	690	48	1361	55	72	69	2123	53	7322	67	21278	73	2830	83	31430	72
Still in hospital	0	0	6	0	4	4	10	0	6	0	61	0	123	3	190	0
Missing	0	0	1	0	0	0	1	0	4	0	7	0	1	0	12	0

Abbreviations:

Figures

Figure 1. Flowchart on the selection of the study population.

Figure 2. Daily occupancy of ICU beds in Lombardy between February and July 2020, and definition of periods for the statistical analysis. Lighter grey bars refer to Period 1 (early phase), middle grey to Period 2 (healthcare strain) and darker grey to Period 3 (declining phase). The dashed black line refer to the pre-crisis ICU capacity of 720 beds.

Figure 3. Impact of period of hospital admission on the probability of admission to an ICU, the probability of death in ICU and the delay between hospital and ICU admission, by age group. A) Proportion of hospitalized patients admitted to ICU stratified by period of hospital admission. B) Proportion of non-survivors among ICU patients stratified by period of hospital admission. C) Delay between hospital and ICU admission stratified by period of hospital admission. Colored bars represent sample means and grey lines 95% CIs. D) Adjusted odds ratio of being admitted to an ICU. E) Adjusted odds ratio of dying in ICU. F) Adjusted incidence rate ratios on the delay between hospitalization and ICU admission. The reference period for panels D-F is period 1. Colored dots represent mean estimates and lines 95% CIs. The grey shaded area highlights the period of healthcare (HC) strain (March 14 - April 25, 2020).

Figure 4. Impact of period of hospital admission on the probability of admission to an ICU, the probability of death in ICU and the delay between hospital and ICU admission, by presence of any comorbidities. A) Proportion of hospitalized patients admitted to ICU stratified by period of hospital admission. B) Proportion of non-survivors among ICU patients stratified by period of hospital admission. C) Delay between hospital and ICU admission stratified by period of hospital admission. Colored bars represent sample means and grey lines 95% CIs. D) Adjusted odds ratio of being admitted to an ICU. E) Adjusted odds ratio of dying in ICU. F) Adjusted incidence rate ratios on the delay between hospitalization and ICU admission. The reference period for panels D-F is period 1. Colored dots represent mean estimates and lines 95% CIs. The grey shaded area highlights the period of healthcare (HC) strain (March 14 - April 25, 2020).

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┌─────────────────────────────────┐
│      Hospitalized Patients       │
│        (n = 46,554)              │
└─────────────────────────────────┘
                │          ┌──────────────────────────────────────────┐
                │─────────▶│ Excluding Patients With Symptom Onset After│
                │          │      Hospitalization (n = 2,853)           │
                ▼          └──────────────────────────────────────────┘
┌─────────────────────────────────┐
│ Patients With Symptom Onset Before│
│    Hospitalization (n = 43,701)   │
└─────────────────────────────────┘
                │          ┌──────────────────────────────────────────┐
                │─────────▶│ Excluding Patients With Symptom Onset After│
                │          │       Date of Death (n = 4)                │
                ▼          └──────────────────────────────────────────┘
┌─────────────────────────────────┐
│ Patients With Symptom Onset Before│
│   Death (n = 43,697)              │
└─────────────────────────────────┘
                │          ┌──────────────────────────────────────────┐
                │─────────▶│ Excluding Patients With ICU Admission      │
                │          │   Before Hospitalization (n = 17)          │
                ▼          └──────────────────────────────────────────┘
┌─────────────────────────────────┐
│ Patients With ICU Admission After │
│     Hospitalization (n = 43,680)  │
└─────────────────────────────────┘
                │          ┌──────────────────────────────────────────┐
                │─────────▶│ Excluding Patients With Date of Death Before│
                │          │       Hospitalization (n = 11)             │
                ▼          └──────────────────────────────────────────┘
┌─────────────────────────────────┐
│ Patients With Date of Death After │
│    Hospitalization (n = 43,669)   │
└─────────────────────────────────┘
                │          ┌──────────────────────────────────────────┐
                │─────────▶│ Excluding Patients With Negative Length Of │
                │          │  Stay In Hospital or ICU  (n = 131)        │
                ▼          └──────────────────────────────────────────┘
┌─────────────────────────────────┐
│ Patients With Non-Negative Length │
│  of Stay in Hospital or ICU       │
│       (n = 43,538)                │
└─────────────────────────────────┘
```

| Model Web Table 1 Excluding missing values (n = 43,124) | Model Web Table 2 Excluding missing values (n = 3,949) | Model Web Table 3 Excluding missing values (n = 3,945) |