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Impact of the post-COVID-19 condition on health care after the first disease wave in Lombardy

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Background. Lombardy was affected in the early months of 2020 by the SARS-CoV-2 pandemic with very high morbidity and mortality. The post-COVID-19 condition and related public health burden are scarcely known.

Setting and design. Using the regional population administrative database including all the 48,932 individuals who survived COVID-19 and became polymerase-chain-reaction negative for SARS-CoV-2 by 31 May 2020, incident mortality, rehospitalizations, attendances to hospital emergency room, and outpatient medical visits were evaluated over a mid-term period of 6 months in 20,521 individuals managed at home, 26,016 hospitalized in medical wards, and 1611 in intensive care units (ICUs). These data were also evaluated in the corresponding period of 2019, when the region was not yet affected by the pandemic. Other indicators and proxies of the health-care burden related to the post-COVID condition were also evaluated.

Main results. In individuals previously admitted to the ICU and medical wards, rehospitalizations, attendances to hospital emergency rooms, and outpatient medical visits were much more frequent in the 6-month period after SARS-CoV-2 negativization than in the same prepandemic period. Performances of spirometry increased more than 50-fold, chest CT scans 32-fold in ICU-admitted cases and 5.5-fold in non-ICU cases, and electrocardiography 5.6-fold in ICU cases and twofold in non-ICU cases. Use of drugs and biochemical tests increased in all cases.

Conclusions. These results provide a real-life picture of the post-COVID condition and of its effects on the increased consumption of health-care resources, considered proxies of comorbidities.

Keywords: administrative database, clinical sequalae, Lombardy region, long-COVID, polypharmacy, population study, SARS-CoV-2

Introduction

Italy was the first country after China to be hit in the first few months of 2020 (February to May) by the coronavirus disease 2019 (COVID-19) [1] with a very high morbidity and mortality, now totaling more than 160,000 fatalities [2]. This absolute number of deaths puts the country in a prominent position in a gloomy ranking, after the United States (more than 800,000 deaths), Brazil (more than 600,000), India (more than 400,000), and Russia (more than 350,000) at a time when global deaths are nearly 6 million [3]. In Italy, the area to be first and most heavily affected in February to May 2020 for infection number, morbidity, and mortality was Lombardy (35,000 deaths), the largest and most densely populated Northern region (10 million people) [4–6]. The magnitude of the COVID-19 burden on the regional health service may be explained by the large population size, high density of indoor productive activities, and intense trade exchanges with China. The severity of the pandemic may also be explained by factors related to the health-service organization, such as lack of specific expertise on the new infection of

the health-care professionals working within a service that was dramatically challenged by unprecedented mayhem [5–7].

In the first few months of the pandemic, the region's health-care efforts were mainly directed towards the formidable struggle of coping with a previously unknown disease and providing acute care to the many individuals who needed hospital admission and mechanical ventilation in intensive care units (ICUs) [4, 7–9]. More recently, attention was redirected to the clinical and public health consequences in the individuals who recovered from SARS-CoV-2 infection, owing to the potential burden and relevance of the post-COVID condition [10–17].

As a step toward more knowledge [15, 16, 18, 19], we accessed the data available in the administrative population database of the Lombardy region to evaluate the health state of all the survivors of the first COVID-19 wave in the 6-month mid-term period after SARS-CoV-2 polymerase chain reaction (PCR) negativization. In addition, we utilized the database to compare the post-COVID cases regarding their own health state during the corresponding months of the preceding year, 2019, when Lombardy had not yet been exposed to the SARS-CoV-2 infection. Our objective was to gain more understanding of the clinical and public health implications of the post-COVID condition, taking as a model one of the regions affected by the pandemic early and severely.

Patients and methods

Study design

We evaluated three cohorts of SARS-CoV-2 infection survivors: individuals who—after being objectively diagnosed by PCR positivity—were not hospitalized and managed at home, those admitted to ordinary (nonintensive) hospital medical wards, and those managed with mechanical ventilation in ICUs. The data available in the Lombardy Region Health Care administrative database for the post-COVID comparison of these cohorts were incident deaths, hospital admissions, emergency room attendances without hospitalization, and outpatient medical visits. We also compared infection survivors with themselves during the same time period in 2019, when Lombardy was not yet affected by the SARS-CoV-2 pandemic. We compared them not only for the aforementioned events but also for the number and type of dispensed drugs that, together with an array of instrumental and biochemical tests, can be considered proxies and indicators of the post-COVID involvement of body organs and systems.

Data sources

Data on all cases with a PCR SARS-CoV-2-positive swab were obtained from the Lombardy database, which, kept for administrative, reimbursement, and public health purposes, offers a comprehensive picture of the use of health-care services by the region's residents. The database provided data on demographics, drugs dispensed, and hospitalizations of residents who tested positive for SARS-CoV-2 from 15 February to 31 May 2020. It also made available to us demographic characteristics of the individuals who recovered from infection, their 6-month mortality, hospital admissions, attendances to hospital emergency rooms without ensuing admissions, visits to outpatient medical offices, and number and classes of dispensed drugs as well as the imaging, functional, and biochemical tests performed for diagnosis. Our access to the data was possible through an agreement between the Istituto di Ricerche Farmacologiche Mario Negri IRCCS and the Lombardy Welfare Directorate. The structure of this database, regularly updated for administrative and reimbursement purposes, has been described elsewhere [20]. In Italy and Lombardy, health care is publicly funded for all residents irrespective of social class or employment, and each person is assigned a personal identification number kept in the National Civil Registration System connected with the National Health System (NHS). The medication database contains drug name and anatomic therapeutic chemical classification code [21], as well as quantity and dispensation date of the drugs reimbursed by the NHS, but no information is available for a small proportion of them—that is, those dispensed during hospitalization, in nursing homes, or purchased out of pocket. The hospital-related database contains information on admission and discharge dates, deaths, primary diagnoses, up to five co-existing clinical conditions, as well as procedures performed during hospitalization. Diagnoses—uniformly coded in all Italian hospitals according to the 9th International Classification of Diseases, Clinical Modification (ICD-9-CM) [22]—are made by the physicians in charge and validated in each hospital on the basis of the results of clinical, instrumental, and laboratory data. According to Italian law, studies using anonymous data from administrative databases

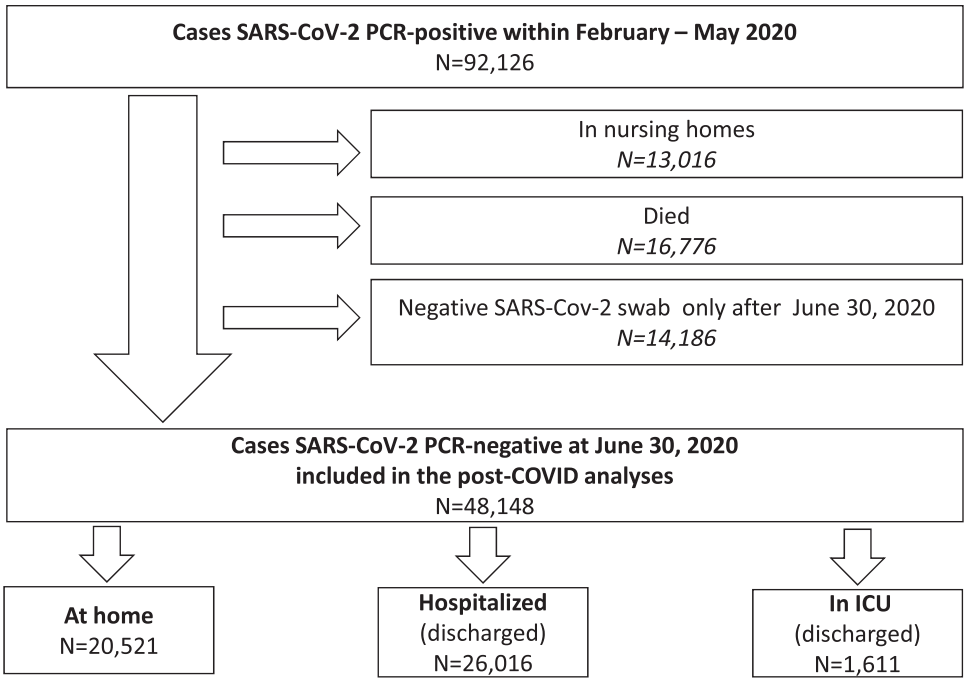


Fig. 1 *Study flow chart.*

that do not involve direct access to individual patient data need no approval from nor notification to an ethics committee/institutional review board, and informed patient consent is not required. All data were managed according to Italian laws on privacy.

Study cohorts

Individuals with a positive PCR test result prior to 31 May 2020 and who survived SARS-CoV-2 infection and became negative prior to 30 June 2020 were included in this analysis and divided into three cohorts: managed at home, discharged alive after hospitalization in medical wards, and in ICU (Fig. 1). Their administrative data were available for a mid-term follow-up period of 6 months up to 31 December 2020, except for data on drug dispensation, which were available for the purpose of the present analysis for only 3 months until 30 September 2020.

Statistical analysis

The main characteristics of the cases are presented as means and standard deviations or medians and interquartile ranges for continuous variables (i.e., age and drug number) and numbers with percentages for categorical variables (all the remaining ones). The three cohorts were compared using logistic regressions adjusted for age, sex, and number of drugs used in 2019. Kaplan–Meier survival curves were plotted, and the log-rank test was employed to assess univariate differences in mortality among the cohorts. Multivariate Cox regression models were adjusted for age, sex, and number of drugs prescribed in 2019, and results were reported as adjusted hazard ratios (aHRs). Differences within the same individuals regarding health-service utilization between 2019 (non-COVID year in Lombardy) and 2020 (first COVID year) were evaluated using the McNemar–Bowker test for paired samples—except for age and number of drugs, for which the Wilcoxon signed-rank test for paired samples was used. To compare changes between the three cohorts, random-intercept logistic regressions were used, except for the total number of drugs. Age, sex, and number of drugs adjusted odds ratios (aORs) were relative to changes in hospitalized or ICU cases with reference to cases treated at home. The total number of drugs was analyzed using a random-intercept linear regression, and age- and sex-adjusted mean difference changes between hospitalized or ICU cases and cases treated at

home were reported. In all case, thereported adjusted mean change/aOR is the estimate of an adjusted interaction representing the increase in the change in hospitalized/ICU patients relative to change in those managed at home. Statistical analysis was performed using JMP Pro 12 (SAS Institute Inc.) and Stata/IC 15 (Stata Inc.).

Results

Cohort characteristics

Figure 1 shows that, from a total of 92,126 SARS-Cov-2 PCR-positive individuals in the period of February to May 2020 during the first infection wave, we excluded those who died before negativization or shortly after negativization, those in nursing homes for whom drug dispensation data are lacking, and those who became PCR negative only after 30 June 2020. Table S1 provides details on the distribution of deaths, nursing home residents, cases with insufficient follow-up, and those individuals who died early after negativization but before June 30. In these subgroups of cases excluded from the general analysis, the mortality rate was 8% in individuals managed at home, 24% in those hospitalized in medical wards, and 43% in those admitted to the ICU. Thus, 48,148 post-COVID cases were included in this analysis. Figure 1 shows that 43% of them were managed at home, 54% in hospital medical wards, and 3% in the ICU with mechanical ventilation. All these cases were followed up for a median period of 259 days (quartiles: 239 and 275).

Table 1 shows that there were age differences among the three cohorts, with cases of younger individuals being more frequently managed at home and older individuals being more frequently hospitalized ($p < 0.001$). Table 1 also shows that in 2019 (non-COVID year), polypharmacy taken as proxy for comorbidities (i.e., five or more daily drugs) was more frequent in patients subsequently hospitalized in 2020 than in those managed at home (aOR: 1.7; 95% confidence interval [CI]: 1.6–1.8) ($p < 0.001$). Moreover, dispensation of drugs of classes A (alimentary tract and metabolism), C (cardiovascular conditions), J (anti-infective), and M (musculoskeletal) was more frequent in hospitalized patients than in those managed at home, and even more so in those hospitalized and mechanically ventilated in the ICU ($p < 0.001$, after adjustment for age, sex, and number of drugs of other classes).

Incident post-COVID events

Pertaining to the events that occurred in the post-COVID period, Table 2 shows that hospitalizations were more frequent in patients admitted to the ICU during the acute phase of infection than in those admitted to medical wards and even more in those managed at home taken as reference (aOR for hospitalized patients: 1.47; 95% CI: 1.36–1.59; aOR for ICU patients: 2.90; 95% CI: 2.49–3.37) ($p < 0.001$). The most frequent ICD diagnoses that led to hospitalizations in the post-COVID period were for diseases of the circulatory and respiratory systems, but also of the kidney and central nervous system. Emergency room attendances were more frequent in cases managed in medical wards than in those managed at home ($p < 0.001$). The raw death rate was higher in cases in medical wards (2.0%) than at home (1.2%) or the ICU (0.7%) ($p = 0.005$). Survival curves (Fig. 2) show that deaths increased in all cohorts but particularly so for patients acutely hospitalized in non-ICU wards, who had the worst survival 300 days post discharge. At univariate analysis, taking as reference patients managed at home, the death hazard ratio was 1.65 (95% CI: 1.41–1.93) for medically hospitalized patients and 0.64 (95% CI: 0.63–1.14) for those admitted to the ICU. However, survival regression corrected for age, sex, and number of drugs reversed these results (death aHR for hospitalized patients: 0.74; 95% CI: 0.63–0.87 and ICU patients: 0.74; 95% CI: 0.41–1.32). Deaths were more frequent in patients aged 70 years or more and treated at home or in medical wards, whereas in those admitted to the ICU there were 10 deaths in patients aged 50–69 years and two in the oldest age range.

Utilization of health-care services

Table 3 shows drug dispensation patterns before and after COVID-19 and compares cases in the July to September 2020 post-COVID period with the corresponding pre-COVID period. Relative to cases managed at home, polypharmacy was more frequent in patients hospitalized in medical wards (aOR: 1.4; 95% CI: 1.2–1.6) and particularly in the ICU (aOR 5.8; 95% CI: 4.3–7.9). The same pattern was observed for the most-represented drug classes—such as those for ailments of the digestive tract and metabolism (A), blood and blood-forming organs (B), and cardiovascular (C), central nervous (N), and respiratory systems (R)—all dispensed more frequently post-COVID in ICU-admitted cases (all aORs equal to or higher than 1.9, p-value for between-cohort comparison <0.001).

Table 1. *Main baseline characteristics of COVID-19 survivors*

Variables	At home $N = 20,521$	Hospitalized $N = 26,016$	Intensive care unit $N = 1611$	P-value[a]
Sex, females, *N* (%)	13,182 (64.2)	11,005 (42.3)	356 (22.1)	
aOR (95% CI)	*1*	*0.40 (0.39–0.42)*	*0.16 (0.14–0.19)*	*<0.001*
Age, median (interquartile range)	50 (40–58)	62 (51–74)	59 (52–66)	<0.001
Difference (95% CI)	-	+7.2 (+7.0; +7.5)	+5.9 (+5.1; +6.6)	
Age groups				<0.001
≤29	2067 (10.1)	925 (3.6)	31 (1.9)	
30–49	7917 (38.6)	4636 (17.8)	248 (15.4)	
50–69	8317 (40.5)	11,458 (44.0)	1114 (69.2)	
70+	2220 (10.8)	8997 (34.6)	218 (13.5)	
Polypharmacy in 2019	3691 (18.0)	10,471 (40.3)	481 (29.9)	
aOR (95% CI)[b]	*1*	*1.7 (1.6–1.8)*	*1.5 (1.3–1.7)*	*<0.001*
Drug classes in 2019 by ATC 1st level classification, *N* (%)				
A	5762 (28.1)	12,322 (47.4)	623 (38.7)	
aOR (95% CI)[b]	*1*	*1.23 (1.17–1.30)*	*1.30 (1.16–1.48)*	*<0.001*
B	2785 (13.6)	7198 (27.7)	300 (18.6)	
aOR (95% CI)[b]	*1*	*1.06 (1.00–1.12)*	*0.94 (0.81–1.09)*	*0.070*
C	4824 (23.5)	13,083 (50.3)	727 (45.1)	
aOR (95% CI)[b]	*1*	*1.41 (1.34–1.49)*	*1.60 (1.42–1.80)*	*<0.001*
D	222 (1.1)	441 (1.7)	21 (1.3)	
aOR (95% CI)[b]	*1*	*1.11 (0.93–1.32)*	*0.92 (0.59–1.46)*	*0.409*
G	953 (4.6)	2791 (10.7)	142 (8.8)	
aOR (95% CI)[b]	*1*	*1.11 (1.02–1.21)*	*0.99 (0.82–1.20)*	*0.029*
H	2289 (11.2)	3964 (15.2)	188 (11.7)	
aOR (95% CI)[b]	*1*	*1.09 (1.03–1.16)*	*1.16 (0.98–1.37)*	*0.011*
J	6700 (32.7)	10,604 (40.7)	584 (36.3)	
aOR (95% CI)[b]	*1*	*1.14 (1.09–1.19)*	*1.15 (1.03–1.28)*	*<0.001*
L	526 (2.6)	1167 (4.5)	40 (2.5)	
aOR (95% CI)[b]	*1*	*1.15 (1.03–1.30)*	*0.90 (0.64–1.25)*	*0.025*
M	2407 (11.7)	5692 (21.9)	280 (17.4)	
aOR (95% CI)[b]	*1*	*1.26 (1.19–1.34)*	*1.40 (1.21–1.61)*	*<0.001*
N	2842 (13.9)	5615 (21.6)	240 (14.9)	
aOR (95% CI)[b]	*1*	*1.10 (1.04–1.17)*	*1.07 (0.92–1.25)*	*0.005*
P	174 (0.9)	284 (1.1)	11 (0.7)	
aOR (95% CI)[b]	*1*	*1.14 (0.92–1.40)*	*1.01 (0.54–1.89)*	*0.441*
R	2297 (11.2)	4062 (15.6)	215 (13.4)	
aOR (95% CI)[b]	*1*	*1.10 (1.04–1.17)*	*1.12 (0.96–1.32)*	*0.007*
S	354 (1.7)	828 (3.2)	37 (2.3)	
aOR (95% CI)[b]	*1*	*0.98 (0.86–1.12)*	*1.10 (0.77–1.55)*	*0.811*
V	172 (0.8)	373 (1.4)	7 (0.4)	
aOR (95% CI)[b]	*1*	*0.71 (0.58–0.87)*	*0.32 (0.15–0.71)*	*<0.001*

Abbreviations: A, alimentary tract and metabolism; aOR, adjusted odds ratio; ATC, anatomic therapeutic chemical; B, blood and blood forming organs; C, cardiovascular system; CI, confidence interval; D, dermatologicals; G, genito-urinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones and insulins; J, anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculoskeletal system; N, nervous system; P, antiparasitic products, insecticides, and repellents; R, respiratory system; S, sensory organs; V, various.

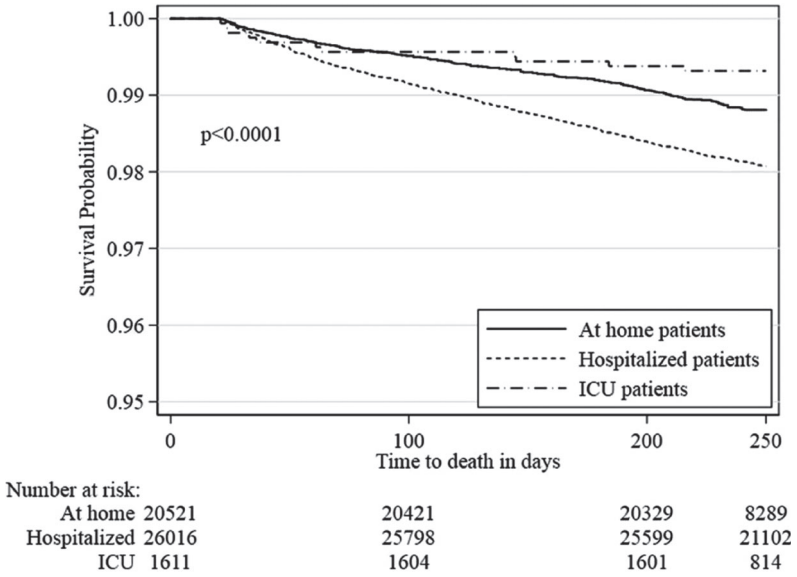
[a]Logistic regression except age (linear regression).

[b]aOR: odds ratios adjusted for age, sex, and number of drugs in 2019. Adjustment for number of drugs of specific classes do not consider drugs of the same class.

Table 2. *Post-COVID condition (emergency room visits, rehospitalizations, and mortality) up to 31 December 2020, 6 months after SARS-CoV-2 polymerase-chain-reaction negativization*

Variables	At home $N = 20,521$	Hospitalized $N = 26,016$	Intensive care unit $N = 1611$	P-value[a]
Cases rehospitalized, N (%)	1079 (5.3)	2830 (10.9)	262 (16.3)	
aOR (95% CI)[b]	*1*	*1.47 (1.36–1.59)*	*2.90 (2.49–3.37)*	*<0.001*
Cases with 2 or more rehospitalizations, N (%)	242 (1.2)	833 (3.2)	89 (5.5)	
aOR (95% CI)[b]	*1*	*1.62 (1.39–1.89)*	*3.75 (2.90–4.84)*	*<0.001*
Cases attending a hospital emergency room without subsequent hospitalization, N (%)	2832 (13.8)	5066 (19.5)	259 (16.1)	
aOR (95% CI)[b]	*1*	*1.50 (1.42–1.58)*	*1.25 (1.08–1.44)*	*<0.001*
Died, N (%)	236 (1.2)	520 (2.0)	12 (0.7)	
aOR (95% CI)[b]	1	0.76 (0.65–0.90)	0.73 (0.40–1.31)	0.005

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.
[a]Logistic regression.
[b]**aOR** (italicized): odds ratios adjusted for age, sex, and number of drugs in 2019.



Death hazard ratios, univariate	**Death hazard ratios**, adjusted for age, sex and number of drugs
- at home: 1	- at home: 1
- hospitalized: HR 1.65 (1.41 - 1.93)	- hospitalized: HR 0.74 (0.63 - 0.87)
- ICU: HR: 0.64 (0.36 - 1.14)	- ICU: 0.74 (0.41 - 1.32)

Fig. 2 *Survival analysis.*

Table 4 shows hospitalizations, emergency room attendances without hospitalization, and outpatient medical visits before and after SARS-CoV-2 infection. Comparing July to September and October to December 2020 with the corresponding months in 2019, these events showed a greater increase in ICU cases. For instance, outpatient medical visits more than doubled for these patients. In the comparison between October and December 2020 and the same period in 2019, hospitalizations and outpatient medical visits increased, indicating that the greater

Table 3. *Drugs dispensed before (July to September 2019) and after SARS-CoV-2 infection (July to September 2020) in the three cohorts of SARS-CoV-2 polymerase chain reaction–positive cases diagnosed up to 31 May 2020*

	At home			Hospitalized				ICU				
	Jul. to Sept. 2019	*Jul. to Sept. 2020*		*Jul. to Sept. 2019*	*Jul. to Sept. 2020*			*Jul. to Sept. 2019*	*Jul. to Sept. 2020*			
Variables	*N* = 20,521, *N* (%)	*N* = 20,521, *N* (%)	Change *p*-value	*N* = 26,016, *N* (%)	*N* = 26,016, *N* (%)	Change *p*-value	Change/aOR relative to at home	*N* = 1611, *N* (%)	*N* = 1611, *N* (%)	Change *p*-value	Change/aOR relative to at home	*P* for aOR
Number of dispensed drugs												
Mean (± standard deviation)	1.2 (2.1)	1.0 (2.0)	*<0.001*	2.5 (3.0)	2.5 (3.0)	*0.009*	**+0.1 (0.1; 0.1)**	1.8 (2.3)	2.7 (2.8)	*<0.001*	**+1.0 (0.9; 1.1)**	*<0.001*
Polypharmacy (5 or more drugs)	1507 (7.3)	1340 (6.5)	*<0.001*	5679 (21.8)	5752 (22.1)	*0.224*	**1.4 (1.2–1.6)**	210 (13.0)	372 (23.1)	*<0.001*	**5.8 (4.3–7.9)**	*<0.001*
Drug classes by ATC 1st level classification, *N* (%) (number of cases with at least one drug in the class)												
A	3359 (16.4)	3208 (15.6)	*0.002*	8805 (33.8)	9342 (35.9)	*<0.001*	**1.2 (1.1–1.4)**	429 (26.6)	659 (40.9)	*<0.001*	**2.0 (1.5–2.6)**	*<0.001*
B	1502 (7.3)	1501 (7.3)	*0.978*	4842 (18.6)	5486 (21.0)	*<0.001*	**1.3 (1.1–1.5)**	181 (11.2)	402 (25.0)	*<0.001*	**3.1 (2.3–4.2)**	*<0.001*
C	3705 (18.1)	3678 (17.9)	*0.506*	11,069 (42.6)	11,346 (43.6)	*<0.001*	**1.0 (0.9–1.1)**	594 (36.9)	812 (50.4)	*<0.001*	**2.0 (1.5–2.7)**	*<0.001*
D	71 (0.4)	62 (0.3)	*0.380*	158 (0.6)	147 (0.6)	*0.455*	**1.0 (0.6–1.7)**	11 (0.7)	11 (0.7)	*1.000*	**1.0 (0.3–2.6)**	*0.960*
G	569 (2.8)	529 (2.6)	*0.044*	2061 (7.9)	2141 (8.2)	*0.015*	**1.3 (1.0–1.6)**	98 (6.1)	130 (8.1)	*0.002*	**1.5 (0.9–2.5)**	*0.061*
H	1014 (4.9)	1053 (5.1)	*0.236*	1846 (7.1)	2098 (8.0)	*<0.001*	**1.1 (0.9–1.3)**	90 (5.6)	159 (9.9)	*<0.001*	**1.4 (0.9–2.1)**	*0.186*
J	1857 (9.1)	1487 (7.3)	*<0.001*	3053 (11.7)	2786 (10.7)	*<0.001*	**1.1 (1.0–1.3)**	172 (10.7)	190 (11.8)	*0.277*	**1.1 (0.9–1.4)**	*0.045*
L	393 (1.9)	424 (2.1)	*0.057*	877 (3.4)	867 (3.3)	*0.700*	**0.7 (0.5–0.9)**	37 (2.3)	31 (1.9)	*0.257*	**0.2 (0.1–0.5)**	*<0.001*
M	980 (4.8)	854 (4.2)	*<0.001*	2729 (10.5)	2372 (9.1)	*<0.001*	**0.9 (0.8–1.0)**	127 (7.9)	114 (7.1)	*0.306*	**0.6 (0.4–0.9)**	*0.012*
N	1740 (8.5)	1763 (8.6)	*0.528*	3706 (14.3)	4228 (16.2)	*<0.001*	**1.3 (1.1–1.5)**	158 (9.8)	306 (19.0)	*<0.001*	**2.7 (1.9–3.9)**	*<0.001*
P	76 (0.4)	72 (0.4)	*0.663*	133 (0.5)	158 (0.6)	*0.045*	**1.4 (0.8–2.4)**	5 (0.3)	5 (0.3)	*1.000*	**0.7 (0.1–4.4)**	*0.415*
R	755 (3.7)	752 (3.7)	*0.915*	1667 (6.4)	1917 (7.3)	*<0.001*	**1.3 (1.1–1.5)**	74 (4.6)	133 (8.3)	*<0.001*	**1.9 (1.2–2.8)**	*0.001*
S	274 (1.3)	193 (0.9)	*<0.001*	586 (2.2)	524 (2.0)	*0.017*	**1.6 (1.1–2.5)**	25 (1.6)	22 (1.4)	*0.405*	**0.9 (0.3–2.7)**	*0.045*
V	110 (0.5)	121 (0.6)	*0.222*	247 (1.0)	529 (2.0)	*<0.001*	**3.5 (2.2–5.6)**	5 (0.3)	57 (3.5)	*<0.001*	**36.4 (8.3–158)**	*<0.001*

Note: Change *p*-value: McNemar test, except for the number of dispensed drugs (Wilcoxon signed-rank for paired data). Change/aOR: difference in the mean change of hospitalized/ICU patients relative to the change of at-home patients (for mean of dispensed drugs); odds ratio of polypharmacy/taking a drug in the relative classes in 2020 versus 2019 for hospitalized/ICU patients relative to the ratio in at-home patients. All values corrected for age, sex, and number of drugs. Corrections for single ATC classes ignore the specific class in the number of drugs used for covariate.

Abbreviations: A, alimentary tract and metabolism; aOR, adjusted odds ratio; ATC, anatomic therapeutic chemical; B, blood and blood forming organs; C, cardiovascular system; D, dermatologicals; G, genito-urinary system and sex hormones; H, systemic hormonal preparations, excluding sex hormones and insulins; ICU, intensive care unit; J, anti-infectives for systemic use; Jul. to Sept., July to September; L, antineoplastic and immunomodulating agents; M, musculoskeletal system; N, nervous system; P, antiparasitic products, insecticides, and repellents; R, respiratory system; S, sensory organs; V, various.

Table 4. *Hospitalizations, emergency room attendances, and outpatient medical visits before (July to December 2019) and after SARS-Cov-2 infection (July to December 2020) in the three cohorts of polymerase chain reaction–positive cases diagnosed up to 31 May 2020*

	At home			Hospitalized				ICU				
Variables	*N* = 20,521, *N* (%)	*N* = 20,521, *N* (%)	Change *p*-value	*N* = 26,016, *N* (%)	*N* = 26,016, *N* (%)	Change *p*-value	aOR relative to at home	*N* = 1611, *N* (%)	*N* = 1611, *N* (%)	Change *p*-value	aOR relative to at home	*P* for aOR
Number of patients who had at least one instance of hospitalization												
	Jul. to Sept. 2019	*Jul. to Sept. 2020*		*Jul. to Sept. 2019*	*Jul. to Sept. 2020*			*Jul. to Sept. 2019*	*Jul. to Sept. 2020*			
N (%)	494 (2.4)	492 (2.4)	0.973	1043 (4.0)	1316 (5.1)	<0.001	**1.3 (1.1–1.5)**	31 (1.9)	102 (6.3)	<0.001	**2.7 (1.7–4.3)**	<0.001
	Oct. to Dec. 2019	*Oct. to Dec. 2020*		*Oct. to Dec. 2019*	*Oct. to Dec. 2020*			*Oct. to Dec. 2019*	*Oct. to Dec. 2020*			
N (%)	663 (3.2)	420 (2.1)	<0.001	1404 (5.4)	1064 (4.1)	<0.001	**1.2 (1.0–1.3)**	42 (2.6)	75 (4.7)	0.002	**2.4 (1.6–3.7)**	<0.001
Number of patients who had at least an emergency room attendance without a subsequent hospitalization												
	Jul. to Sept. 2019	*Jul. to Sept. 2020*		*Jul. to Sept. 2019*	*Jul. to Sept. 2020*			*Jul. to Sept. 2019*	*Jul. to Sept. 2020*			
N (%)	1420 (6.9)	1207 (5.9)	<0.001	2246 (8.7)	2106 (8.1)	0.022	**1.1 (1.0–1.2)**	106 (6.6)	128 (8.0)	0.113	**1.2 (0.9–1.6)**	0.151
	Oct. to Dec. 2019	*Oct. to Dec. 2020*		*Oct. to Dec. 2019*	*Oct. to Dec. 2020*			*Oct. to Dec. 2019*	*Oct. to Dec. 2020*			
N (%)	1405 (6.9)	1040 (5.1)	<0.001	2312 (8.9)	1535 (5.9)	<0.001	**0.9 (0.8–1.0)**	95 (5.9)	79 (4.9)	0.230	**1.0 (0.7–1.4)**	0.022
Number of patients who visited a specialist at least once												
	Jul. to Sept. 2019	*Jul. to Sept. 2020*		*Jul. to Sept. 2019*	*Jul. to Sept. 2020*			*Jul. to Sept. 2019*	*Jul. to Sept. 2020*			
N (%)	4605 (22.4)	4639 (22.6)	0.657	8452 (32.5)	11,141 (42.8)	<0.001	**1.7 (1.6–1.8)**	400 (24.8)	1033 (64.1)	<0.001	**6.5 (5.4–7.8)**	<0.001
	Oct. to Dec. 2019	*Oct. to Dec. 2020*		*Oct. to Dec. 2019*	*Oct. to Dec. 2020*			*Oct. to Dec. 2019*	*Oct. to Dec. 2020*			
N (%)	5066 (24.7)	4636 (22.6)	<0.001	9589 (36.9)	10,101 (38.8)	<0.001	**1.3 (1.2–1.3)**	436 (27.1)	875 (54.3)	<0.001	**4.2 (3.5–5.0)**	<0.001

Note: Change *p*-value: McNemar test.

Note: Interaction change/OR: odds ratio of using a medical service in 2020 versus 2019 for hospitalized/ICU patients relative to the ratio in at-home patients. All values adjusted for age, sex, and number of drugs.

Note: aOR: odds ratio of a hospitalization, emergency room attendance, or outpatient medical visit in 2020 versus 2019 for hospitalized/ICU patients relative to the ratio in at-home patients, adjusted for age, sex, and number of drugs.

Abbreviations: aOR, adjusted odds ratio; ICU, intensive care unit; Jul. to Sept., July to September; Oct. to Dec., October to December.

use of regional health service facilities continued even after the first three months following SARS-Cov-2 negativization. Moreover, in comparison with cases managed at home, the risk of hospitalization and outpatient medical visits increased in both previously hospitalized and ICU cases. Negative changes between 2019 and 2020 may be partially due to incomplete retrieval of administrative data in the final period of 2020 (October to December) and perhaps also due to less hospital-bed availability due to the surge in October 2020 of the second COVID-19 wave.

Utilization of imaging, instrumental, and biochemical tests

Tables S2 and S3 show that use of spirometry increased in ICU patients from as few as eight cases in July to September 2019 to as many as 425 in the same period in 2020, a more than 50-fold increase. Electrocardiograms (ECG) showed a 5.6-fold increase in ICU cases and a twofold increase in those in medical wards. The corresponding increases for chest CT scans were 32-fold and 5.5-fold. A statistically significant increased rate of use of spirometry and chest CT scans was also observed in cases managed at home from July to September and October to December 2019 compared to the corresponding periods in 2020. For spirometry, the rate increased from 0.6% to 2.2% and from 0.8% to 1.4%, respectively, and for chest CT scans from 0.7% to 2.7% and from 0.9% to 2.3%, respectively. Moreover, regarding all the periods considered, comparing the likelihood of performing imaging and functional instrumental tests before and after COVID-19 in cases hospitalized in medical wards or ICUs versus those managed at home, there was a 1.2- to 3.4-fold increase in medically hospitalized cases and a 3.0- to 28.0-fold increase in those in ICUs, the greatest increase being observed for spirometry and chest CT scans. Moreover, the use of biochemical tests increased in all cohorts between the corresponding pre- and post-COVID periods (July to September 2019 and 2020), but more markedly in ICU cases than in those managed at home or in medical wards (between-cohort differences for all biochemical tests: $p < 0.001$). Between October to December 2019 and October to December 2020, the pattern for all the aforementioned tests was the same as for the comparison between July to September 2019 and 2020. All visits and diagnostic tests were more frequent in cases hospitalized in medical wards and ICUs, even though differences were somewhat less marked than those between July to September 2019 and 2020.

Pertaining to biochemical tests, in comparison with the corresponding pre-COVID-19 period (2019), there was a large increase for both, cases hospitalized and those managed at home (all p-values <0.001 for the July to September period for cases treated at home and for both periods for the other two cohorts). The increase was observed for all biochemical tests, but particularly for C-reactive protein, creatinine, prothrombin time, D-dimer, and complete blood counts. Finally, the aORs for using more biochemical tests after COVID-19 in patients hospitalized compared to those managed at home ranged from 0.9 to 1.5 and in patients admitted to the ICU from 1.3 to 11.9. The highest increases were observed for D-dimer, lactate dehydrogenase (LDH), prothrombin time, and C-reactive protein.

Discussion

The post-COVID-19 condition, also called long COVID, is still a partially defined entity [15–19], notwithstanding the initiative of the WHO Health Emergency Programme to summon a two-round Delphi consensus, which provided a clinical case definition and newly included this condition in the International Classification of Disease (ICD) with specific codes [23]. A systematic review and meta-analysis of 33 studies on the prevalence of post-COVID symptoms was carried out including 15,244 individuals hospitalized at the time of acute illness and 9011 nonhospitalized individuals [24]. More than 60% of the individuals who recovered from infection were still symptomatic, with fatigue and dyspnea being the most prevalent complaints [24]. A retrospective cohort study in the UK that included 42,780 individuals discharged from NHS hospitals during the first COVID-19 wave until 31 August 2020 showed that during a post-discharge follow-up of 5 months, approximately one third of the individuals needed rehospitalization and one third died [14]. Moreover, the post-COVID rate of multiorgan dysfunction was higher than expected in the general UK population, with the risk of adverse outcomes not limited to older people. Another large population-based study from the UK employed the database stemming from 1392 general practices (GP) and including 456,002 individuals diagnosed with COVID-19 mainly during the second SARS-CoV-2 infection wave (until 14 February 2021) [25]. During a follow-up period

of up to 9.2 months, the GP consultations for post-infection sequelae differed between patients admitted to the hospital during acute infection and those managed in the community. The most common post-COVID outcomes in hospitalized patients were venous thromboembolism, muscle/joint pain, and dyspnea, while in cases handled in the community the prevailing symptoms recorded during GP visits were anxiety, depression, and gastrointestinal symptoms, in addition to loss of smell and taste [25].

With this background of knowledge, we chose to analyze the data stemming from an administrative health-care database of an early and heavily affected region in order to understand the clinical and public health implications of the post-COVID condition, convinced of the comprehensiveness and real-life significance of this approach. After having accrued the data of all the infected individuals, we chose to analyze three cohorts of cases objectively diagnosed with SARS-CoV-2 who survived the infection. Assuming that those managed at home were less compromised than those who needed hospital admission in medical wards offering noninvasive methods of ventilation or needing mechanical ventilation in the ICU, this severity gradient is supported by our finding that individuals managed at home were younger than those hospitalized and less affected by comorbidities before developing COVID-19, as witnessed by their lower use in 2019 of polypharmacy and classes of drugs taken as proxies of corresponding comorbidities.

The comparison of the three cohorts of survivors before and after infection indicates that more events occurred and more use of regional health service facilities was needed by those who had been admitted to the ICU, and that in cases managed at home there was a lower rate of rehospitalizations than in those hospitalized in the ICU or medical wards. Their less-stormy post-COVID condition is also witnessed by a lower need to attend hospital emergency rooms and outpatient medical visits.

In patients who had been admitted to the ICU and needed mechanical ventilation, a persistent involvement, particularly of the respiratory, circulatory, and urinary systems, was evident by more frequent rehospitalizations for related ICD diagnoses and the high use of such functional and imaging diagnostic tests as spirometry/chest CT scan and ECG/echocardiography. Moreover, in the 6-month post-infection period, previously medically hospitalized and ICU patients were frequent users of polypharmacy and drugs of the alimentary and metabolic (A), hematological (B), cardiovascular (C), neuropsychiatric (N), and respiratory (R) classes. These proxies of comorbidities indicate that the post-COVID condition involves multiple organs and body systems [14, 15, 17–19].

Pertaining to biochemical tests, those more frequently done post COVID examined renal and liver functions (creatinine and transaminases) and blood cells and the coagulation system (prothrombin time and D-dimer) [26, 27]. The increased use of multiple diagnostic tests and procedures in individuals who survived COVID-19 may be due to overall worsening of their health condition and the post-COVID condition, but also to the anxiety created by their SARS-CoV-2 infection despite recovery.

We acknowledge that this study—based on data stemming from an administrative database—has limitations, mainly related to the fact that data could not be audited and that a number of clinical details were not available. For instance, while the main ICD diagnoses that led to post-COVID hospitalizations are known, reasons for visits to hospital emergency rooms and outpatient medical offices are not detailed in the population database. In addition, we have no direct information on the main signs and symptoms in the post-COVID period. The organs and body systems most frequently involved can only be indirectly inferred from the drugs dispensed and the instrumental and biochemical tests performed. Furthermore, we were unable to evaluate the post-COVID prevalence of such frequently reported subjective symptoms as fatigue, insomnia, confusion, breathlessness, ageusia, and anosmia, even though a questionnaire developed in collaboration with the main Italian daily newspaper and administered to more than 5000 patients and their significant next of kin helped to gather this information [28].

Additional limitations must be mentioned. The Lombardy region may not be representative of other global regions hit by the pandemic, because it is likely that the quality of medical care offered in these regional settings was affected by the high degree of saturation of non-ICU and ICU hospital wards as well as by the sudden occurrence and rapid growth of the contagion. Furthermore, since we chose to analyze the post-COVID cases after PCR negativization, the three cohorts do not

represent the whole cohort (dead and survivors) of those infected and treated in the three settings during the index period. We do not know, for instance, if the mean age of the survivors was the same as those who died in the three settings, so that the death rates may be biased due to a different selection of patients admitted or not admitted and the treatments received. The relatively low rate of post-COVID deaths in those admitted to the ICU may be due to a higher rate of mortality during ICU stay [29], so that those who survived mechanical ventilation and became available for the post-COVID follow-up are likely to represent the healthiest among those admitted to the ICU.

Notwithstanding these limitations, a strength of this study is the large number of cases, the real-life approach, as well as that infected cases were their own control in the corresponding period of the year before the onset of the pandemic. It is also a strength that the Lombardy Region health-care administrative database supplied objective and comprehensive data on the usage of health-care resources such as hospitalizations, attendances to hospital emergency room, outpatient visits, instrumental and biochemical tests, and drugs dispensed through the NHS.

In conclusion, this population-based study establishes that in nearly 50,000 individuals who recovered from the first wave of the SARS-CoV-2 infection, the post-COVID condition is associated with deaths, rehospitalizations, and utilization of the regional health resources, and the associated burden is relevant for public health [17, 30–35]. The regional database also offered the opportunity to compare the mid-term health state of recovered individuals with their own state in the same period in 2019, when the viral infection and related disease had not yet appeared. A solid and unequivocal finding is that in 2019, these individuals were less frequently hospitalized than in the corresponding 6-month post-COVID period in 2020 and had less frequently attended hospital emergency rooms as well as outpatient medical offices. Their health-care burden was also less prominent pertaining to indirect indicators and proxies of illness such as drug prescriptions and the performance of imaging and functional diagnostic tests. Admittedly, these results pertain to the first pandemic wave and may not apply to the subsequent waves, when the regional health-care system was more prepared to tackle COVID-19, and even more so to the most recent waves that occurred after the start of the vaccination campaign in the early months of 2021.

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Conflict of interests

All the authors declare no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Causes of exclusion from the analysis.
Table S2. Imaging and functional instrumental tests performed before (July-December 2019) and after infection (July-December 2020) in the three cohorts of cases SARS-CoV-2 PCR positive within 31 May 2020.
Table S3. Biochemical tests performed before (July-December 2019) and after SARS-Cov-2 infection (July-December 2020) in the three cohorts of cases PCR-positive within 31 May 2020. ■