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Examining potential Long COVID effects through utilization of healthcare resources: a retrospective, population-based, matched cohort study comparing individuals with and without prior SARS-CoV-2 infection

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Background: A significant proportion of individuals reports persistent clinical manifestations following SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) acute infection. Nevertheless, knowledge of the burden of this condition—often referred to as 'Long COVID'—on the health care system remains limited. This study aimed to evaluate healthcare utilization potentially related to Long COVID. **Methods:** Population-based, retrospective, multi-center cohort study that analyzed hospital admissions and utilization of outpatient visits and diagnostic tests between adults aged 40 years and older recovered from SARS-CoV-2 infection occurred between February 2020 and December 2021 and matched unexposed individuals during a 6-month observation period. Healthcare utilization was analyzed by considering the setting of care for acute SARS-CoV-2 infection [non-hospitalized, hospitalized and intensive care unit (ICU)-admitted] as a proxy for the severity of acute infection and epidemic phases characterized by different SARS-CoV-2 variants. Data were retrieved from regional health administrative databases of three Italian Regions. **Results:** The final cohort consisted of 307 994 previously SARS-CoV-2 infected matched with 307 994 uninfected individuals. Among exposed individuals, 92.2% were not hospitalized during the acute infection, 7.3% were hospitalized in a non-ICU ward and 0.5% were admitted to ICU. Individuals previously infected with SARS-CoV-2 (vs. unexposed), especially those hospitalized or admitted to ICU, reported higher utilization of outpatient visits (range of pooled Incidence Rate Ratios across phases; non-hospitalized: 1.11–1.33, hospitalized: 1.93–2.19, ICU-admitted: 3.01–3.40), diagnostic tests (non-hospitalized: 1.35–1.84, hospitalized: 2.86–3.43, ICU-admitted: 4.72–7.03) and hospitalizations (non-hospitalized: 1.00–1.52, hospitalized: 1.87–2.36, ICU-admitted: 4.69–5.38). **Conclusions:** This study found that SARS-CoV-2 infection was associated with increased use of health care in the 6 months following infection, and association was mainly driven by acute infection severity.

Introduction

A growing body of evidence indicates that a significant proportion of individuals reports clinical manifestations after the acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] This condition is often referred to as 'Long COVID', along with other definitions of prolonged symptoms of COVID-19, including 'Post COVID-19 Condition'.[2,3]

According to a meta-analysis of 194 studies including 735 006 individuals, 45% of SARS-COV-2 infection survivors experienced at least one unresolved symptom at a mean follow-up of 4 months, with higher prevalence in hospitalized than in non-hospitalized populations (52.6% vs. 34.5%, respectively).[4] Other factors, such as female sex, older age, higher body mass index, smoking, pre-existing comorbidities, were found significantly associated with the development of persistent symptoms beyond acute infection.[5] However, research on Long COVID is limited by the lack of a standard clinical framework to assess this condition and by the scarcity of data assessing its burden on the healthcare system. Moreover, signs and symptoms are often evaluated in heterogeneous ways, at varying times and in selected populations, making comparisons of results difficult and offering a partial view of the impact on the health system.

Despite these limitations, it is becoming evident that, beyond acute infection, many individuals show an increased need for hospital admissions,[6,7] dispensed drugs,[7] healthcare visits,[7–11] laboratory tests and imaging.[6] The risk of Long COVID appeared to be higher in individuals with more severe SARS-CoV-2 infection as proxied by the setting of care (SOC) of the acute infection.[12] Nevertheless, data on utilization of health services beyond acute infection according to the degree of severity of SARS-CoV-2 infection are still limited. Furthermore, the progressive introduction of vaccination in the population, the better understanding of disease pathogenesis, the improvements in patient management and treatment and the substitution of the ancestral SARS-CoV-2 virus with milder variants have reduced the incidence of severe COVID-19 and the risk of hospitalization and death.[13] Likewise, the risk of Long COVID and the associated impact on the healthcare system may have changed over time. In fact, the prevalence of Long COVID appeared higher among individuals infected with the ancestral variant than among those infected with the Alpha, Delta or Omicron variants.[14]

However, only one study has assessed healthcare utilization in patients with Long COVID based on severity of acute infection[8] and, to the best of our knowledge, none has yet considered it in the different epidemic phases.

This study aimed to evaluate healthcare utilization potentially related to Long COVID in adults, comparing SARS-CoV-2 infected and non-infected individuals, during a 6-month follow-up, accounting for differences in age, sex and comorbidities. A secondary study objective was to evaluate possible differences in healthcare utilization according to both the severity of acute infection and the epidemic phase.

Methods

Framework and setting

This study is part of the project 'Analysis and Response Strategies for the Long-Term Effects of COVID-19 Infection (Long COVID)' funded by the National Centre for Diseases Prevention and Control of the Italian Ministry of Health, coordinated by the Italian National Institute of Health, and aimed at increasing knowledge and standardizing the management of Long COVID nationwide. The project is conducted with the participation of three Italian Regions: Friuli Venezia Giulia (FVG) representing the North, Tuscany representing the Center and Apulia representing the South of Italy.

Ethics

The research protocol was approved by the Italian National Ethics Committee (AOO-ISS—19/04/2022–0015066 Class: PRE BIO CE 01.00).

Reporting

Reporting followed the REporting of studies Conducted using Observational Routinely collected health Data statement.[15]

Data sources/measurement and data access

Data were obtained from the regional electronic health databases. For the purposes of the analysis, data on age, sex, residence history, discharge diagnosis, comorbidity status (determined using hospital discharge diagnoses and drug prescriptions), results of laboratory tests for diagnosis of SARS-CoV-2 infection (swabs), outpatient visits, instrumental diagnostic examinations and hospital admissions were collected.

Study design

A population-based, retrospective, multi-center, matched cohort study was conducted. Individuals recovered from SARS-CoV-2 infection (exposed) between 21 February 2020 and 23 December 2021 (enrollment period) and non-infected (unexposed) individuals were compared in terms of healthcare utilization, during a 6-month follow-up period.

Participants

Eligibility criteria

The reference population was defined by all individuals aged 40 years or older from the three above-mentioned Italian Regions, residing uninterruptedly in the Region from 1 January 2015 to 31 December 2019. The exposed cohort included confirmed SARS-CoV-2 cases (according to National guidelines[16–18]) whose negative swab (i.e. reverse transcription polymerase chain reaction or antigen test) fell within the enrollment period, assuming the negative test as a proxy for recovery from acute SARS-CoV-2 infection. Individuals without a negative lab test following acute infection were considered negative 21 days after the first positive test. The unexposed cohort included individuals who never tested SARS-CoV-2 positive during the enrollment period. Individuals could be enrolled only once, either as exposed or unexposed.

Classification of exposure by care setting

The care setting of the acute SARS-CoV-2 infection was assumed as a proxy indicator of disease severity among exposed individuals, who were consequently categorized as (i) non-hospitalized, (ii) admitted in intensive care unit (ICU-admitted) and (iii) admitted in a non-ICU ward (hospitalized).

An admission counted as a COVID-19 hospitalization if it occurred within 30 days from the date of the first positive swab and a primary or secondary diagnosis with COVID-19 was listed in the hospital discharge register. Hence, if a person tested positive during a hospital stay, the case was classified as hospitalized or ICU-admitted, as appropriate.

Classification of exposure by epidemic phase

Healthcare utilization was further evaluated by epidemic waves sustained by different SARS-CoV-2 variants. The enrollment period was divided into four phases, defined according to a previous study performed in the Italian population.[13] Phase 1 (21 February–30 June 2020) was characterized by the first epidemic peak and the national lockdown, Phase 2 (1 July 2020–17 February 2021) was marked by a new peak of cases and the introduction of the vaccination campaign against COVID-19. These two phases were characterized by ancestral lineages of SARS-CoV-2. The two subsequent phases were dominated by the Alpha (Phase 3: 18 February–1 July 2021) and Delta (Phase 4: 2 July–23 December 2021) variants, respectively. Individuals were classified according to the time interval in which the date of the negative test (negativization) of exposed individuals fell.

Matching criteria

One unexposed individual was matched (i.e. matching ratio = 1:1) to a corresponding individual of the exposure cohort by sex, age group (40–54, 55–64, 65–74 and 75+) and comorbidity status. Comorbidity status was assessed through the Multisource Comorbidity Score (MCS), a risk-adjustment tool based on assessment of the presence of 34 conditions, evaluated through hospital discharge diagnoses and drug prescriptions from administrative data, which contribute different weights to the aggregate score.[19] The absence of comorbidity corresponds to a 0 MCS score, while the increase in MCS denotes a progressive worsening of comorbidity status.[20] Data from years 2015–19 were used to calculate the MCS for both exposed and unexposed. For matching purposes, scores were grouped into six categories (0, 1–4, 5–9, 10–14, 15–19 and 20+).[20]

Follow-up

For the exposed and the individually matched unexposed, the six-month follow-up period started 28 days after the exposed subjects turned negative. The follow-up period was right censored in the event of death or out-of-Region emigration or re-infection[21] among exposed and in case of first infection after 23 December 2021 for the unexposed. However, data on swabs performed in Tuscany as of January 2022 were not available, and therefore individuals were not properly right censored in case of SARS-CoV-2 test positivity (i.e. first infection or re-infection) since that time.

Outcomes

For each group (exposed/unexposed), health service utilization was measured in terms of rates (total number of services per person-month) of: (i) outpatient visits for brief and comprehensive medical history examination/evaluation, general or specialist evaluation or comprehensive consultation, performed upon medical prescription (primary care physician visits were not included); (ii) instrumental diagnostic examinations (e.g. electrocardiogram, spirometry, electromyography, polysomnogram, electroencephalogram and walk test) performed upon medical prescription; and (iii) all-cause hospitalizations (ordinary and day hospital).

Additionally, for each health service investigated, the association between healthcare utilization and exposure to SARS-CoV-2 infection was evaluated by comparing utilization rates of exposed to those of matched unexposed by using Incidence Rate Ratios (IRRs).

Statistical analysis

Stratified analyses were performed by SOC of acute infection (non-hospitalized, hospitalized and ICU-admitted) and by epidemic phase. Demographic characteristics (age group and sex) and comorbidity status (MCS category) of participants were described for group of exposure (exposed and unexposed individuals did not differ by age group, sex and MCS category as they are matched 1:1 by these variables). Utilization rates, calculated as the total number of services per person-month, and 95% confidence interval (95% CI) were estimated for outpatient visits, instrumental tests and hospitalizations for all causes, both in aggregate and at the regional level. For each health service, regional IRRs and their 95% CI were estimated with Poisson regression and inverse probability weighting. IRRs were calculated by using rates directly standardized by age and gender using the Italian population census as of 1 January 2020.[22] For each specific SARS-CoV-2 phase and SOC, regional IRRs were pooled through an inverse-variance weighted random-effects meta-analysis (based on the DerSimonian–Laird method).[23] Analyses were performed with STATA (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.) and SAS software (version 9.4 SAS Institute INC., Cary, NC, USA).

Role of the funding source

The funder had no direct role in the study design, data collection, analysis or decision to publish. The authors declare that the manuscript is an honest, accurate and transparent account of the study described and that no important aspects of the study were omitted.

Results

Patients' characteristics

The final matched cohort consisted of 615 988 adults aged 40 years or older, including 307 994 exposed, and 307 994 matched unexposed. For each group (exposed/unexposed), 76 613 (24.9%) were from FVG, 87 316 (28.3%) from Tuscany and 144 065 (46.8%) from Apulia. 98.4% of the exposed and 97.7% of the unexposed were followed for the entire follow-up period. Among exposed individuals, 284 096 (92.2%) were non-hospitalized, 22 381 (7.3%) were hospitalized in a non-ICU ward and 1517 (0.5%) were admitted to the ICU. Females were 52.9% of the total, but this proportion decreased strongly with increasing treatment intensity (53.9%, 41.8% and 31.6% among non-hospitalized, hospitalized and ICU-admitted, respectively). Participants were mostly represented by individuals aged 40–54 (43.7%) and MCS category 1–4 (38.7%). A complete description of the entire cohort is provided in Supplementary table S1.

Use of health services during follow-up

Number of events (count), person-time, crude rates and 95% CI for each outcome are presented in table 1 and figure 1, while data stratified by Region are shown in Supplementary tables S2–S4 and Supplementary figures S1–S3. Likewise, pooled IRRs comparing health service utilization rates for all participants (exposed vs. unexposed) and those stratified by SOC and SARS-CoV-2 phase are presented in table 2, while regional IRRs are available in Supplementary table S5.

Outpatient visits

Exposed individuals (vs. unexposed) reported higher rates of outpatient visits at each phase, and the greater the severity of acute infection (as assessed by SOC), the higher the rate of outpatient visits (figure 1 and table 1). Rates of outpatient visits of ICU-admitted ranged from 0.35 (95% CI 0.30–0.40) to 0.52 (95% CI 0.47–0.57) visits per person-month, whilst those of matched unexposed ranged from 0.11 (95% CI 0.09–0.13) to 0.17 (95% CI 0.14–0.21) visits per person-month (table 1). Although exposed (vs. unexposed) individuals showed higher rates of outpatient visits [overall pooled IRR: 1.87 (95% CI 1.65–2.12)], this association reached statistical significance only among those hospitalized and ICU-admitted during acute infection, with small variations across epidemic phases [pooled IRRs range; non-hospitalized: 1.11 (95% CI 0.89–1.37) to 1.33 (95% CI 0.85–2.08); hospitalized: 1.93 (95% CI 1.74–2.14) to 2.19 (95% CI 1.79–2.67); ICU-admitted: 3.01 (95% CI 1.33–6.82) to 3.40 (95% CI 1.40–8.30)] (table 2). The significant association between exposure and utilization of outpatient visits in the hospitalized and ICU-admitted groups was consistently observed in all three Regions (Supplementary table S5).

Instrumental diagnostic tests

SARS-Cov-2 exposed individuals presented higher rates of instrumental diagnostic tests, and the likelihood of diagnostic procedures appeared to increase in individuals hospitalized or admitted to ICU (figure 1 and table 1). Previously ICU-admitted exposed patients showed rates that ranged from 0.20 (95% CI 0.17–0.24) to 0.46 (95% CI 0.42–0.51) diagnostic tests per person-month, while those for unexposed ranged from 0.05 (95% CI 0.03–0.07) to 0.06 (95% CI 0.04–0.08) diagnostic tests per person-month (table 1). Consequently, exposed (vs. unexposed) of all SOCs of acute infection showed an overutilization of instrumental diagnostic tests [overall pooled IRR: 2.75 (95% CI 2.32–3.26)], especially those hospitalized and ICU-admitted [pooled IRRs range; non-hospitalized: 1.35 (95% CI 1.08–1.69) to 1.84 (95% CI 0.96–3.50); hospitalized: 2.86 (95% CI 1.66–4.92) to 3.43 (95% CI 2.25–5.20); ICU-admitted: 4.72 (95% CI 2.79–8.01) to 7.03 (95% CI 2.72–18.17)] (table 2). The strength of the association seems to decline in later epidemic phases. This significant association between exposure and utilization of instrumental diagnostic tests in the hospitalized and ICU-admitted groups was observed in all three Regions (Supplementary table S5).

Hospitalizations for all causes

Hospitalized or ICU-admitted individuals (vs. unexposed) reported significantly higher hospitalization rates (figure 1 and table 1): for

Table 1 Outpatient visits, instrumental diagnostic tests and hospitalizations during 6-month follow-up period after acute SARS-CoV-2 infection according to SOC and epidemic phase

Setting of care/phase	Exposed				Unexposed			
	Count[a]	person-months	Crude rate[b]	95% CI	Count[a]	person-months	Crude rate[b]	95% CI
				Outpatient visits				
Non-hospitalized								
Phase I	4152	36 426	0.11	(0.11–0.12)	3241	36 865	0.09	(0.08–0.09)
Phase II	71 163	705 730	0.10	(0.10–0.10)	58 618	705 102	0.08	(0.08–0.08)
Phase III	62 590	658 884	0.09	(0.09–0.10)	53 695	658 467	0.08	(0.08–0.08)
Phase IV	17 592	206 819	0.09	(0.08–0.09)	15 928	200 815	0.08	(0.08–0.08)
Hospitalized								
Phase I	1873	8101	0.23	(0.22–0.24)	977	8274	0.12	(0.11–0.13)
Phase II	12 444	48 197	0.26	(0.25–0.26)	6296	48 824	0.13	(0.13–0.13)
Phase III	13 385	56 489	0.24	(0.23–0.24)	6771	57 253	0.12	(0.12–0.12)
Phase IV	2392	11 659	0.21	(0.20–0.21)	1421	11 630	0.12	(0.12–0.13)
ICU-admitted								
Phase I	455	878	0.52	(0.47–0.57)	98	905	0.11	(0.09–0.13)
Phase II	1257	3320	0.38	(0.36–0.40)	453	3423	0.13	(0.12–0.14)
Phase III	1343	3585	0.37	(0.35–0.39)	453	3674	0.12	(0.11–0.13)
Phase IV	216	618	0.35	(0.30–0.40)	107	618	0.17	(0.14–0.21)
				Instrumental diagnostic tests				
Non-hospitalized								
Phase I	2521	36 426	0.07	(0.07–0.07)	1344	36 865	0.04	(0.03–0.04)
Phase II	34 682	705 730	0.05	(0.05–0.05)	25 845	705 102	0.04	(0.04–0.04)
Phase III	29 297	658 884	0.04	(0.04–0.04)	21 378	658 467	0.03	(0.03–0.03)
Phase IV	9640	206 819	0.05	(0.05–0.05)	7378	200 815	0.04	(0.04–0.04)
Hospitalized								
Phase I	1394	8101	0.17	(0.16–0.18)	438	8274	0.05	(0.05–0.06)
Phase II	7380	48 197	0.15	(0.15–0.16)	2625	48 824	0.05	(0.05–0.06)
Phase III	8101	56 489	0.14	(0.14–0.15)	2834	57 253	0.05	(0.05–0.05)
Phase IV	1585	11 659	0.14	(0.13–0.14)	653	11 630	0.06	(0.05–0.06)
ICU-admitted								
Phase I	405	878	0.46	(0.42–0.51)	55	905	0.06	(0.04–0.08)
Phase II	911	3320	0.27	(0.26–0.29)	176	3423	0.05	(0.04–0.06)
Phase III	899	3585	0.25	(0.23–0.27)	179	3674	0.05	(0.04–0.06)
Phase IV	125	618	0.20	(0.17–0.24)	30	618	0.05	(0.03–0.07)
				Hospitalizations				
Non-hospitalized								
Phase I	729	36 426	0.02	(0.02–0.02)	474	36 865	0.01	(0.01–0.01)
Phase II	7756	705 730	0.01	(0.01–0.01)	7181	705 102	0.01	(0.01–0.01)
Phase III	6758	658 884	0.01	(0.01–0.01)	5867	658 467	0.01	(0.01–0.01)
Phase IV	2241	206 819	0.01	(0.01–0.01)	2252	200 815	0.01	(0.01–0.01)
Hospitalized								
Phase I	330	8101	0.04	(0.04–0.05)	164	8274	0.02	(0.02–0.02)
Phase II	1783	48 197	0.04	(0.04–0.04)	823	48 824	0.02	(0.02–0.02)
Phase III	1828	56 489	0.03	(0.03–0.03)	832	57 253	0.01	(0.01–0.02)
Phase IV	395	11 659	0.03	(0.03–0.04)	231	11 630	0.02	(0.02–0.02)
ICU-admitted								
Phase I	62	878	0.07	(0.05–0.09)	14	905	0.02	(0.01–0.02)
Phase II	172	3320	0.05	(0.04–0.06)	42	3423	0.01	(0.01–0.02)
Phase III	273	3585	0.08	(0.07–0.09)	57	3674	0.02	(0.01–0.02)
Phase IV	47	618	0.08	(0.05–0.10)	11	618	0.02	(0.01–0.03)

Notes: Utilization rates were calculated for exposed and unexposed as the ratio of the number of health services provided during the 6-month follow-up to total person-months, stratified by the care setting of acute SARS-CoV-2 infection (non-hospitalized, hospitalized and ICU-admitted) and by epidemic phase (Phase 1—ancestral, Phase 2—ancestral, Phase 3—Alpha, Phase 4—Delta). Data refer to the three Italian Regions (Friuli Venezia Giulia, Tuscany and Apulia) as a whole. 95% CI, 95% confidence interval; ICU, intensive care unit.
a: Total amount of outpatient visits, instrumental diagnostic tests or hospitalizations performed during the 6-month follow-up.
b: Number of outpatient visits, instrumental diagnostic tests or hospitalizations per person-month.

ICU-admitted patients, hospitalization rates ranged from 0.05 (95% CI 0.04–0.06) to 0.08 (95% CI 0.05–0.10) events per person-month while those for unexposed ranged from 0.01 (95% CI 0.01–0.02) to 0.02 (95% CI 0.01–0.03) events per person-month (table 1). Exposed (vs. unexposed) individuals were more likely to be admitted to the hospital [overall pooled IRR: 1.98 (95% CI 1.66–2.36)], particularly those hospitalized and admitted to ICU during acute infection, with small variations across epidemic phases [pooled IRRs range; non-hospitalized: 1.00 (95% CI 0.69–1.47) to 1.52 (95% CI 0.80–2.90); hospitalized: 1.87 (95% CI 0.89–3.93) to 2.36 (95% CI 1.45–3.82); ICU-admitted: 4.69 (95% CI 2.07–10.65) to 5.38 (95% CI 0.46–62.36)] (table 2). In all Regions hospitalized and ICU-admitted individuals (vs. unexposed) showed a higher susceptibility to hospitalization for all causes after acute SARS-CoV-2 infection (Supplementary table S5).

Discussion

This multi-center, population-based, matched cohort study, conducted on 615 988 adults, with an enrollment period of ~2 years covering different waves of the epidemic, aimed to measure the burden on the healthcare system resulting from the prolonged consequences of SARS-CoV-2 acute infection. During the entire period of observation, exposed (vs. unexposed) reported 2-fold higher rates

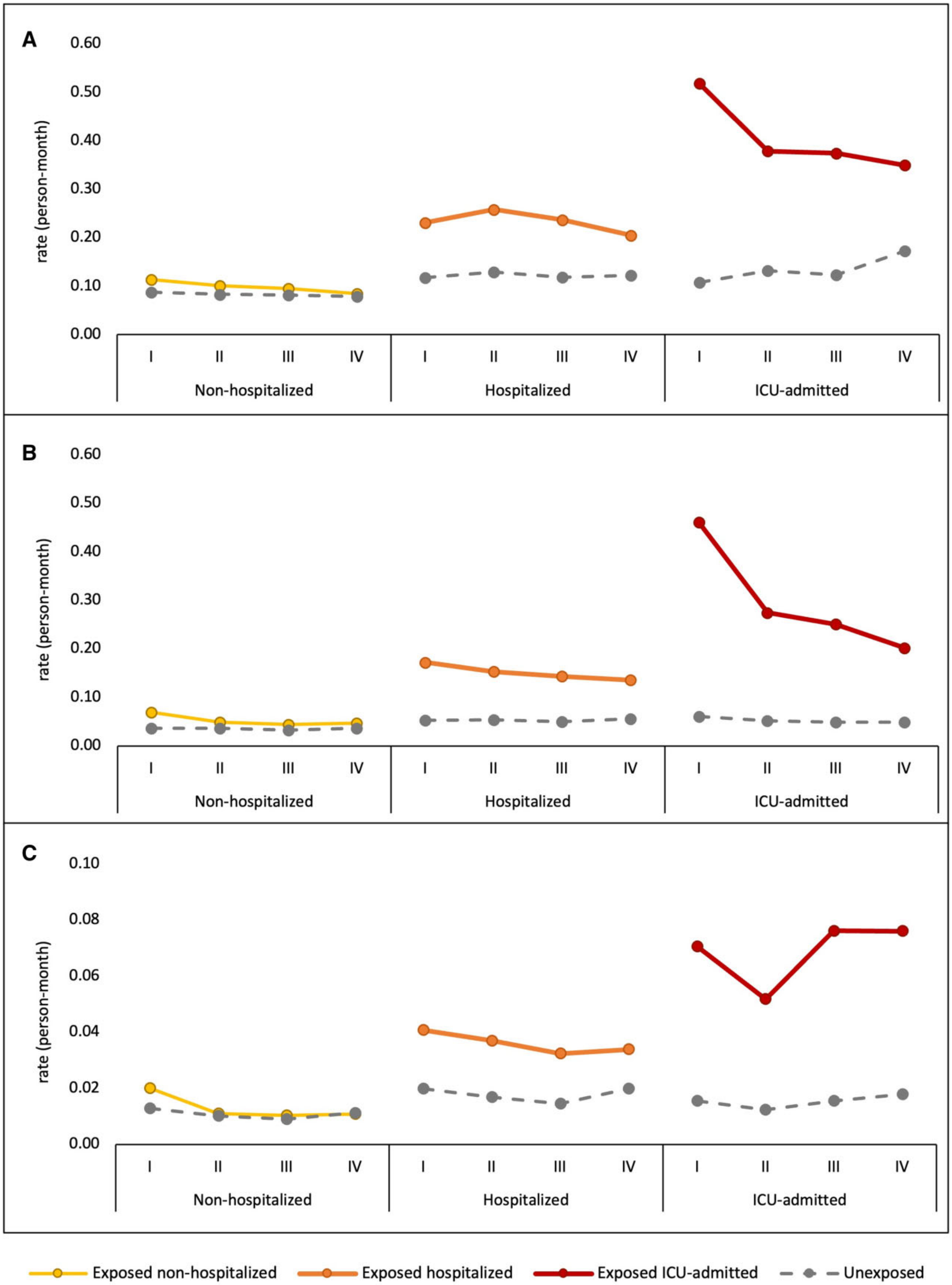

Figure 1 Rates of outpatient visits (a), instrumental diagnostic tests (b) and hospitalizations (c) of exposed (continuous line) and unexposed (dashed line) during 6-month follow-up period after acute SARS-CoV-2 infection. Comparison of healthcare utilization rates between previously SARS-CoV-2 infected individuals and matched uninfected individuals during the 6-month follow-up period after acute infection. Utilization rates of outpatient visits, instrumental diagnostic tests and hospitalizations were calculated as the ratio of the number of health services provided during follow-up to total person-months, stratified by the care setting of acute SARS-CoV-2 infection (non-hospitalized, hospitalized and ICU-admitted) and by epidemic phase (Phase 1—ancestral, Phase 2—ancestral, Phase 3—Alpha, Phase 4—Delta). Data refer to the three Italian Regions (Friuli Venezia Giulia, Tuscany and Apulia) as a whole. ICU, intensive care unit

Table 2 Pooled IRRs of outpatient visits, instrumental diagnostic tests and hospitalizations, stratified by SARS-CoV-2 phase and care setting of the acute infection

Setting of care/phase	Outpatient visits		Instrumental diagnostic tests		Hospitalizations	
	Pooled IRR[a]	95% CI	Pooled IRR[a]	95% CI	Pooled IRR[a]	95% CI
Non-hospitalized						
Phase I	1.33	(0.85–2.08)	1.84	(0.96–3.50)	1.52	(0.80–2.90)
Phase II	1.25	(0.98–1.59)	1.42	(1.08–1.86)	1.12	(0.77–1.63)
Phase III	1.17	(0.99–1.38)	1.37	(1.09–1.72)	1.11	(0.77–1.60)
Phase IV	1.11	(0.89–1.37)	1.35	(1.08–1.69)	1.00	(0.69–1.47)
Hospitalized						
Phase I	2.08	(1.68–2.58)	3.43	(2.25–5.20)	1.91	(1.25–2.92)
Phase II	2.19	(1.79–2.67)	3.35	(2.22–5.05)	2.36	(1.45–3.82)
Phase III	2.06	(1.79–2.38)	3.10	(2.33–4.12)	2.13	(1.24–3.67)
Phase IV	1.93	(1.74–2.14)	2.86	(1.66–4.92)	1.87	(0.89–3.93)
ICU-admitted						
Phase I	3.40	(1.40–8.30)	7.03	(2.72–18.17)	4.76	(2.08–10.87)
Phase II	3.11	(2.49–3.88)	5.64	(3.89–8.18)	4.69	(2.07–10.65)
Phase III	3.21	(2.64–3.90)	6.17	(4.18–9.13)	5.22	(1.58–17.18)
Phase IV	3.01	(1.33–6.82)	4.72	(2.79–8.01)	5.38	(0.46–62.36)
Overall	1.87	(1.65–2.12)	2.75	(2.32–3.26)	1.98	(1.66–2.36)

Notes: The pooled association between healthcare utilization and exposure to SARS-CoV-2 infection was evaluated by comparing utilization rates of exposed to those of matched unexposed by using pooled IRRs. Pooled IRRs are stratified by the care setting of acute SARS-CoV-2 infection (non-hospitalized, hospitalized and ICU-admitted) and by epidemic phase (Phase 1—ancestral, Phase 2—ancestral, Phase 3—Alpha, phase 4—Delta). IRR, incidence rate ratios; 95% CI, 95% confidence interval; ICU, intensive care unit.

a: Pooled IRR obtained from meta-analysis of IRRs of the three Italian Regions (Friuli Venezia Giulia, Tuscany and Apulia). Meta-analysis was performed using random-effects inverse-variance model with DerSimonian–Laird estimate of tau.[2]

of outpatient visits and hospitalizations and nearly 3-fold higher rates of instrumental diagnostic procedures during the 6-month follow-up after acute infection. These results appear consistent with findings from other studies on higher healthcare utilization among individuals recovered from SARS-CoV-2 infection.[7–11] According to a cohort study conducted in the USA on 127 859 patients with a SARS-CoV-2 positive test, SARS-CoV-2 infection was associated with a 4% increase in healthcare utilization over a 6-month period, mainly for virtual encounters and emergency department visits, with the greatest overutilization in the first 3 months following acute infection.[10]

Our results also suggest that overutilization increases according to the individuals' SOC, as proxy of acute disease severity. While the overutilization observed for non-hospitalized individuals was limited, hospitalized and ICU-admitted patients reported 2-fold and 3-fold higher rates of outpatient visits, 3-fold and over 4-fold higher rates of instrumental diagnostic tests and 2-fold and over 4-fold higher hospitalization rates. This pattern may be explained by the fact that individuals hospitalized during acute SARS-CoV-2 infection are more likely to experience at least one unresolved symptom than non-hospitalized individuals[4,24] and the burden of individual sequelae increases according to the severity of acute infection.[25] Results are consistent with findings from a study conducted on 181 384 individuals previously infected with SARS-CoV-2 and on 4 397 509 non-infected, which found that the burden of post-acute sequelae of SARS-CoV-2 infection, defined as the presence of at least one more sequela compared with individuals without SARS-CoV-2 infection, increased with intensity of treatment during acute infection (at 6 months was 4.4%, 21.7%, 36.5% among non-hospitalized, hospitalized and ICU-admitted individuals, respectively).[25] Furthermore, hospitalized patients were found to have longer persistence of symptoms, possibly leading to a greater use of health services. Specifically, those patients reported 4 and 8 weeks longer median duration of fatigue than non-hospitalized individuals, respectively.[26] In our study, the association between SARS-CoV-2 infection and outpatient visits and hospitalizations did not show significant variability among the different epidemic waves, which were characterized by different SARS-CoV-2 variants. However, with regard to diagnostic tests, the association was stronger in early waves. This result may be explained by a higher prescription of tests in the early epidemic, when the long-term effects of SARS-CoV-2 infection were more uncertain and accurate diagnostics were needed to better frame this condition.

Furthermore, while it appears quite evident that the frequency and the severity of COVID-19 post-acute sequelae are directly associated with the severity of acute infection, results for non-hospitalized individuals appear also relevant, especially in terms of burden on healthcare, since they represent the majority of people exposed to SARS-CoV-2 infection.[25]

The study has several strengths. We used large regional electronic health care databases from different geographical areas of the country. With an enrollment period of almost 2 years, our study presents, to the best of our knowledge, the longest observation period across the COVID-19 pandemic compared with other studies on healthcare utilization among individuals recovered from SARS-CoV-2 infection.[7–11] In addition, only a few studies on healthcare utilization have stratified the analysis according to the SOC of SARS-CoV-2 infection[9] and, as far as we know, this is the first that accounted for different epidemic phases. Furthermore, to account for confounders, exposed and unexposed cohorts were matched by sex, age and comorbidities. Findings from analysis of utilization of three different measures of health care service utilization (hospitalizations, visits and instrumental examinations) add valuable evidence of the impact of Long COVID on health care services, and these data constitute relevant information also for pharmacoeconomic assessments of the cost impact associated with the post-acute consequences of infection.

This study also has several limitations. Firstly, our study included only individuals over 40 years old, and this limits the generalizability of the results to the younger population. However, the adult population excluded from the study appears to be at less risk for Long COVID. According to a recent systematic review and meta-analysis, individuals aged 40–69 years and ≥70 years are at equally high risk of persistent symptoms after SARS-CoV-2 infection compared with adults younger than 40 years.[5] Secondly, the follow-up period was limited to 6 months and the impact over a longer period of time remains unclear. Moreover, data on laboratory tests for SARS-CoV-2 were assessed for all adults residing in the three Regions but some cases of individuals actually infected with SARS-CoV-2 may not have been detected or reported to the Regional surveillance and therefore classified as unexposed. This misclassification due to under-diagnosis or under-reporting may have varied over time. According to an Italian study, infection ascertainment has changed across phases, with the highest ascertainment ratio during the second phase (40.5%).[13] Furthermore, the date of negativization, assumed as a proxy for recovery from acute SARS-CoV-2 infection, was also used for individual's classification by phase. This may have introduced some misclassification, which, however, could have occurred even considering the date of the positive laboratory test, since we had no genome sequencing data. Finally, although the association between overuse of health services and intensity of treatment during acute infection is consistent with other findings on relation between Long COVID and SOC,[4,9,12,24–26] results for exposed with ICU-admitted as SOC could be partially related to post-intensive care syndrome, a condition that can lead to the onset of new or worsening problems in ICU-survivors.[27] Finally, data for Phase 4 are likely to be incomplete for both outcomes and laboratory testing of SARS-CoV-2 due to limitations in database availability and consolidation. The dramatic increase in SARS-CoV-2 incidence rates, which occurred especially during the Omicron phase covering all or part of the follow-up of Phase 4 individuals, may have exceeded the laboratories' capacity for analysis for some periods. This may have led to an under-diagnosis of cases. In addition, data on swabs taken from January 2022 onward were not available for Tuscany, making right censoring unfeasible in the case of SARS-CoV-2 infection. Despite this limitation, we decided not to exclude Tuscany from meta-analysis of Phase 4 as the results appeared consistent across Regions (see Supplementary table S5). In addition, although the association between utilization of health services and Long COVID may also vary according to sex, as females appear to be more prone to use medical care services,[28] the results regarding sex as risk factor for Long COVID are still conflicting[5,29] and this study did not aim to examine this relationship.

Conclusion

SARS-CoV-2 infection was associated with increased utilization of healthcare resources in the 6 months after acute infection. This association appeared strongest among individuals with severe infection, causing hospital or ICU admission, and seems consistent across epidemic phases. These results add some evidence on the burden on the health care system caused by the post-acute consequences of acute infection that may be related to Long COVID and constitute relevant information for assessing the cost impact of Long COVID on health care systems.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Conflicts of interest: None declared.

Author contributions

C.F. and L.B. had full access to data from the Apulia Region; L.C. and Y.B. had full access to data from the Friuli Venezia Giulia Region; B.B., F.P. and P.F. had full access to data from the Tuscany Region. The above authors take responsibility for the integrity of the data and the accuracy of their analysis. S.B. and G.O. obtained funding. G.O. supervised the project work. G.O., S.B., P.F., F.B., L.B., M.F., M.G., F.Pri., T.Gri., T.Gra., D.T. and M.V. contributed to the conception and design of the study. V.R., C.F., P.F., F.B., L.B., F.Pro., L.C. and Y.B. contributed to the data acquisition and analysis. All authors contributed to interpretation of results. Y.B., L. C. and V.R. drafted the manuscript. All authors contributed to the review of the manuscript for intellectual content. M.V., M.G., T.Gri., T.Gra. and D.T. provided administrative, technical and material support. All authors approved the final version of the manuscript.

Data availability

The Italian Ministry of Health holds the ownership of the data used for analysis and therefore can be made available with the legal permission of the Italian Ministry of Health. Also, according to Italian law, anonymized data can only be shared if there is no potential for the reidentification of individuals (https://www.garanteprivacy.it). Thus, the data underlying this study are available on request once collapsed. Data access requests should be addressed to the corresponding author.

Key points

- This retrospective cohort study showed that individuals previously infected by SARS-CoV-2—especially those hospitalized or admitted to ICU—were associated with higher healthcare utilization over a 6-month follow-up.
- During the observation period, ICU-admitted patients (vs. uninfected) showed on average 3-fold higher rates of outpatient visits and over 4-fold higher rates of instrumental diagnostic tests and hospitalizations.
- The association between SARS-CoV-2 infection and outpatient visits and hospitalizations did not show significant variability between the different epidemic waves, which were characterized by different SARS-CoV-2 variants.
- Findings from this study provide information that may be relevant to pharmacoeconomic assessments of the impact of costs associated with the post-acute consequences of SARS-CoV-2 infection.

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