Original Paper

Impact of Long SARS-CoV-2 Omicron Infection on the Health Care Burden: Comparative Case-Control Study Between Omicron and Pre-Omicron Waves

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Abstract

Background: Following the initial acute phase of COVID-19, health care resource use has escalated among individuals with SARS-CoV-2 infection.

Objective: This study aimed to compare new diagnoses of long COVID and the demand for health services in the general population after the Omicron wave with those observed during the pre-Omicron waves, using similar assessment protocols for both periods and to analyze the influence of vaccination.

Methods: This matched retrospective case-control study included patients of both sexes diagnosed with acute SARS-CoV-2 infection using reverse transcription polymerase chain reaction or antigen tests in the hospital microbiology laboratory during the pandemic period regardless of whether the patients were hospitalized. We included patients of all ages from 2 health care departments that cover 604,000 subjects. The population was stratified into 2 groups, youths (<18 years) and adults (≥18 years). Patients were followed-up for 6 months after SARS-CoV-2 infection. Previous vaccination, new diagnoses, and the use of health care resources were recorded. Patients were compared with controls selected using a prospective score matched for age, sex, and the Charlson index.

Results: A total of 41,577 patients with a history of prior COVID-19 infection were included, alongside an equivalent number of controls. This cohort encompassed 33,249 (80%) adults aged ≥18 years and 8328 (20%) youths aged <18 years. Our analysis identified 40 new diagnoses during the observation period. The incidence rate per 100 patients over a 6-month period was 27.2 for vaccinated and 25.1 for unvaccinated adults (P=.09), while among youths, the corresponding rates were 25.7 for vaccinated and 36.7 for unvaccinated individuals (P<.001). Overall, the incidence of new diagnoses was notably higher in patients compared to matched controls. Additionally, vaccinated patients exhibited a reduced incidence of new diagnoses, particularly among women (P<.001) and younger patients (P<.001) irrespective of the number of vaccine doses administered and the duration since the last dose. Furthermore, an increase in the use of health care resources was observed in both adult and youth groups, albeit with lower figures noted in vaccinated individuals. In the comparative analysis between the pre-Omicron and Omicron waves, the incidence of new diagnoses was higher in the former; however, distinct patterns of diagnosis were evident. Specifically, depressed mood (P=.03), anosmia (P=.003), hair loss (P<.001), dyspnea (<0.001), chest pain (P=.04), dysmenorrhea (P<.001), myalgia (P=.011),

weakness (P<.001), and tachycardia (P=.015) were more common in the pre-Omicron period. Similarly, health care resource use, encompassing primary care, specialist, and emergency services, was more pronounced in the pre-Omicron wave.

Conclusions: The rise in new diagnoses following SARS-CoV-2 infection warrants attention due to its potential implications for health systems, which may necessitate the allocation of supplementary resources. The absence of vaccination protection presents a challenge to the health care system.

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KEYWORDS

Omicron; long COVID; post–COVID-19; diagnostics; primary care; specialist; emergency department; hospitalization

Introduction

The all-cause disease burden worldwide in 2020 and 2021 was the highest in the past 3 decades, mainly due to the consequences of the SARS-CoV-2 pandemic [1]. In fact, the worldwide population was profoundly affected not only by the acute infection, resulting in increased morbidity and mortality [2], but also by persistent symptoms after the initial acute phase of illness or the impact on organ systems with the emergence of new diseases [3-12]. As a result, health care resource use has escalated among individuals with SARS-CoV-2 infection. Ongoing viral mutations and the introduction of vaccines may result in varying degrees of impact, and periodic assessment of the disease burden may help to better define strategies to mitigate the impact.

Rapid dissemination of various SARS-CoV-2 variants and the introduction of vaccines have raised expectations of altered impacts on long COVID. Subsequent to the prevalence of the Alpha and Delta variants during the initial pandemic waves in the pre-Omicron period, SARS-CoV-2 Omicron (PANGO B.1.1.529) swiftly propagated across Europe from December 2021 to February 2022. Clinically, the Omicron variant induced less severe acute illness than its predecessors, and certain studies reported a reduced incidence of postacute-phase impacts [13-19], both in adults and in children [20-24]. Nevertheless, conflicting data have surfaced in the literature [25], and the potential influence of prior vaccination remains uncertain [26-28]. Evaluating the genuine repercussions of SARS-CoV-2 infection in the realm of long COVID following the acute phase proves intricate due to myriad factors. Discrepancies in defining criteria, observation durations, encompassed medical conditions, and symptom dynamics may account for disparities among reported studies. Assessing the tangible effect on the health care resource burden following the acute infection episode holds paramount significance, given its implications for the resources that health care systems must allocate. One effective approach to gauge this impact is to leverage the data available in electronic health records (EHRs), which serve as a valuable source of information regarding the health care resource demands placed on health systems by encompassing a wealth of data on diagnoses, medication usage, and health care resource requirements [29].

Based on the EHRs of 2 health care departments (HCDs) in the Valencian Community of more than 600,000 inhabitants, this study aimed to compare new diagnoses of long COVID and the demand for health services in the general population after the Omicron variant wave with those observed during the pre-Omicron Alpha and Delta waves using similar assessment protocols for both periods. In addition, it sought to elucidate the potential influence of vaccination in mitigating these effects in different age groups.

Methods

Study Design and Participants

A case-control study with retrospective observation of health care data collected from ABUCASIS, the EHR of the Valencia Community was conducted. Administrative data, diagnoses, all prescriptions and dispensations of subsidized treatments, and the use of health services are linked in a database that integrates all health care interventions. In this study, the data included observations of patients with SARS-CoV-2 infection from a total of 604,000 subjects from 2 different HCDs (centers A and B).

Ethical Considerations

Exemption from obtaining informed consent was permissible based on the 17th additional provision of Spanish Organic Law 3/2018, dated December 5, which pertains to the protection of personal data and the guarantee of digital rights. This provision legalizes the use of pseudonymized personal data for health-related purposes, particularly in the realm of biomedical research. To harness pseudonymized personal data for the objectives of public health and biomedical research, the following criteria were met: A clear demarcation in terms of both technical and functional aspects was maintained between the research team and individuals responsible for executing the pseudonymization process, as well as safeguarding the information that could potentially facilitate reidentification. Data collection and analysis were carried out considering the protection of patients' privacy by means of a 2-layered method of pseudo anonymization, and the information was managed as aggregated data. Access to pseudonymized data was only permitted for the research team under specific conditions:

- An explicit commitment to maintain confidentiality and abstain from any reidentification endeavors was established.
- Stringent security measures were instituted to forestall reidentification and unauthorized access by third parties.

The research was conducted in full compliance with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016, on the protection of individuals with regard to the processing of personal data and on the free movement of such data. The study also complied with the 17th additional provision of Spanish Organic Law 3/2018 of December 5, the corresponding

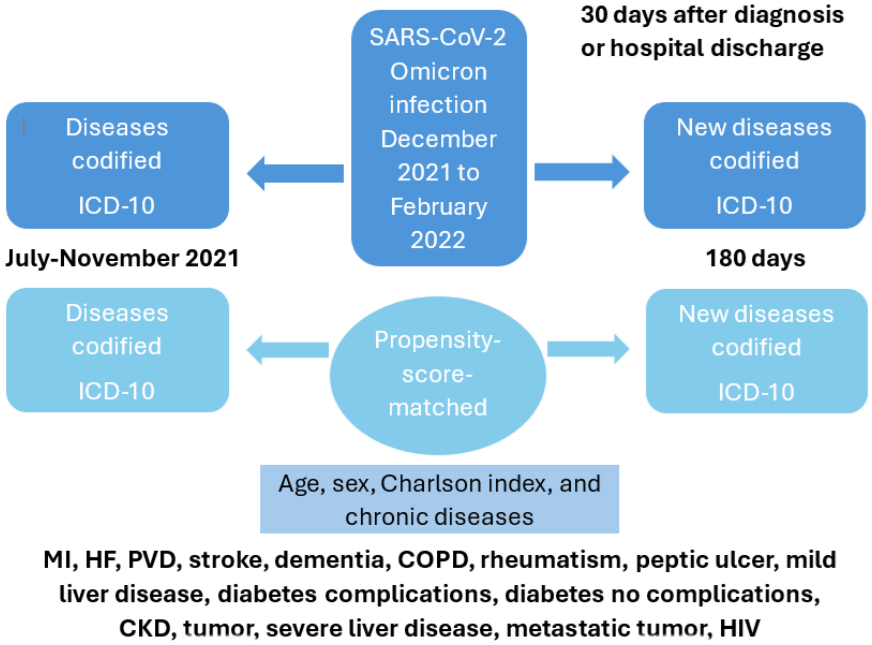
European norms (General Data Protection Regulation [GDPR]) [30], and the applicable sectoral legislation. The information was available for research and pseudo anonymization in accordance with the Spanish Data Protection Act, and the study was approved by the Ethics and Clinical Trials Committee of the Hospital Clinico of Valencia and the Hospital Universitari i Politècnic La Fe of Valencia.

Subjects and Procedures

Cases included patients of both sexes diagnosed with acute SARS-CoV-2 infection using reverse transcription polymerase chain reaction (RT-PCR) or antigen tests in the hospital microbiology laboratory during the SARS-CoV-2 Omicron pandemic period regardless of whether the patients were hospitalized. The population was stratified into 2 groups, youths under the age of 18 years and adults aged ≥18 years.

The study design has been previously detailed [31], with a summary provided in Figure 1. In brief, the cases of Omicron infection included individuals with acute infection diagnosed between December 1, 2021, and February 28, 2022. The observation period for the long COVID phase commenced 30 days following the date of diagnosis, either in primary care or after hospital discharge, and extended for up to 6 months, totaling 180 days. During this period, newly occurring diseases and medications, not present prior to the infection, were meticulously documented within the EHR system. Vaccination details, including the number of doses administered and the time elapsed since the last dose before infection, were also ascertained. Throughout the observation period, the collection of data encompassed the identification of newly diagnosed conditions and prescriptions. Additionally, the use of health care resources, comprising the number of patients and visits to primary care physicians, specialists, emergency rooms, and hospitalization, was extracted from administrative records sourced from primary care health care centers, hospital outpatient clinics, emergency departments, and hospitalization units.

Figure 1. Study design. Cases included patients of both sexes diagnosed with acute SARS-CoV-2 infection, and the same number of matched controls without infection were selected using a propensity score matched for age, sex, previous illnesses, and the same time period as the case index. The observation period for new diagnoses and health care resource use was 6 months after 30 days from virus diagnosis or hospital discharge. CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HF: heart failure; ICD-10: International Classification of Diseases, 10th Revision; MI: myocardial infarction; PVD: pulmonary vascular disease.



The analysis of new diagnoses included an equal number of matched controls who had not been infected with SARS-CoV-2. The control group was generated through propensity score matching (PSM) that incorporated variables such as age, sex, the Charlson index, all preexisting chronic diseases (chronic conditions present prior to the pandemic period, including but not limited to myocardial infarction, heart failure, peripheral artery disease, stroke, dementia, chronic obstructive pulmonary disease, rheumatism, peptic ulcer, liver disease, diabetes, chronic kidney disease, tumor, metastatic tumor, and HIV infection), and the corresponding case's time frame. Data from a prior study conducted using the same methodology during the pre-Omicron period, spanning from March to December 2020, were used to facilitate comparisons regarding the potential impact of Omicron [31].

Statistical Analysis

Data were presented in the form of absolute numbers, incidences per 100 patients per 6 months, and percentages, where applicable. To assess differences in the incidence of new diagnoses among patients with Omicron infection, vaccinated individuals, and unvaccinated patients, as well as in comparison to the pre-Omicron period, statistical analyses were conducted using unpaired Student *t* tests and chi-squared tests. The potential long-term effects of vaccination, including the number of vaccine doses and the time elapsed since the last dose to the

time of infection, were evaluated through logistic regression analysis, adjusted for potential confounding factors, such as age and sex. Furthermore, sensitivity analyses were performed by separately analyzing data from the 2 HCDs and comparing the results between them. All statistical analyses were carried out using R version 6.3.1 (R Foundation for Statistical Computing).

Results

General Characteristics of the Study Population

During the study period corresponding to the Omicron wave, a total of 41,577 patients were diagnosed with positive SARS-CoV-2 using RT-PCR or antigen tests. This patient cohort comprised 33,249 (80%) adults aged ≥18 years and 8328 (20%) youths aged <18 years. Prior to the onset of acute infection, 30,199 (90.8%) adults and 4417 (53%) youths had received the vaccine. The general characteristics of the study population are detailed in Table 1 for adults and in Table 2 for youths. Follow-up of the patients extended from 177 to 179 days after 30 days of confirmed infection. Among them, a total of 833 (2%) patients were hospitalized for acute SARS-CoV-2 Omicron infection, including 662 (79.5%) adults and 75 (9%) youths, with 24 (32%) of the latter being vaccinated.

Table 1. General characteristics of adult (≥18 years) study population cases in the 2 HCDs[a] during Omicron and pre-Omicron waves.

Characteristic	Omicron (previous vaccine)		Omicron (no previous vaccine)		Pre-Omicron	
	Center A (n=17,441)	Center B (n=12,758)	Center A (n=1040)	Center B (n=2010)	Center A (n=16,382)	Center B (n=14,199)
Age (years), mean (SD)	46.16 (16.37)	48.78 (18.50)	41.75 (14.81)	40.87 (13.71)	47.63 (17.73)	45.93 (17.10)
Female, n (%)	9832 (56.4)	7110 (55.7)	570 (54.8)	1168 (58.1)	8861 (54.1)	7671 (54.0)
Days of observation, mean (SD)	179 (10.93)	179.58 (6.80)	177.98 (16.04)	177.11 (20.15)	176.06 (20.53)	179.00 (7.68)
Patients hospitalized, n (%)	458 (2.6)	204 (1.6)	78 (7.5)	68 (3.4)	1726 (10.5)	1357 (9.6)
First vaccination, date	June 6, 2021 10089 (57.95)	January 7, 2021 6668 (52.27)	N/A[b]	N/A	N/A	N/A
Patients with new diagnoses, n (%)	3535 (20.3)	2729 (21.4)	223 (21.4)	392 (19.5)	3082 (18.8)	2883 (20.3)
1	2815 (16.1)	2128 (16.7)	171 (16.4)	293 (14.6)	2463 (15.0)	2182 (15.4)
2	574 (3.3)	474 (3.7)	42 (3.9)	71 (3.5)	506 (3.1)	544 (3.8)
3	121 (0.7)	101 (0.8)	8 (0.8)	20 (1.0)	87 (0.5)	116 (0.8)
>3	25 (0.1)	26 (0.2)	2 (0.2)	8 (0.4)	26 (0.2)	41 (0.3)

[a]HCD: health care department.

[b]N/A: not applicable.

Table 2. General characteristics of youth (<18 years) study population cases in the 2 HCDs[a] during Omicron and pre-Omicron waves.

Characteristic	Omicron (previous vaccine)		Omicron (no previous vaccine)		Pre-Omicron	
	Center A (n=2714)	Center B (n=2243)	Center A (n=1824)	Center B (n=1547)	Center A (n=3981)	Center B (n=3605)
Age (years), mean (SD)	12.58 (3.41)	12.17 (3.54)	5.31 (3.87)	5.91 (4.30)	10.23 (4.99)	9.42 (5.19)
Female, n (%)	1377 (50.7)	1123 (50.1)	864 (47.4)	719 (46.5)	1956 (49.1)	1783 (49.0)
Days of observation, mean (SD)	180 (0)	179.91 (3.76)	180 (0)	179.40 (9.01)	179.11 (4.21)	179.26 (3.89)
Patients hospitalized, n (%)	12 (0.4)	12 (0.5)	19 (1.0)	32 (2.1)	23 (0.6)	27 (0.7)
First vaccination, date	October 21, 2021 2243 (82.66)	June 12, 2021 1987 (88.60)	N/A[b]	N/A	N/A	N/A
Patients with new diagnoses, n (%)	511 (18.8)	421 (18.8)	499 (27.4)	404 (26.1)	660 (16.6)	584 (16.2)
1	418 (15.4)	339 (15.1)	387 (21.2)	318 (20.6)	544 (13.7)	463 (12.8)
2	84 (3.1)	70 (3.1)	97 (5.3)	70 (4.5)	95 (2.4)	90 (2.5)
3	8 (0.3)	10 (0.4)	11 (0.6)	13 (0.8)	18 (0.5)	27 (0.7)
>3	1 (0)	2 (0.1)	4 (0.2)	3 (0.2)	3 (0.1)	4 (0.1)

[a]HCD: health care department.

[b]N/A: not applicable.

New Diagnostics

The new diagnoses observed during the follow-up period in patients with SARS-CoV-2 and Alpha and Omicron infections and in controls, regardless of their vaccination status, and the corresponding distribution of the *International Classification of Diseases, 10th Revision* (ICD-10) codes across affected systems are presented in Tables S1-S4 in Multimedia Appendix 1. Among adults, the number of new diagnoses for vaccinated and unvaccinated patients stood at 6642 and 636, respectively, with incidences per 100 patients over 6 months of 27.2 and 25.1, respectively (P=.09). In the case of youths, these numbers were lower, with 1014 diagnoses in vaccinated individuals and 967 in unvaccinated individuals, resulting in incidences of 25.7 and 36.7, respectively (P<.001). In adults, the vaccination status did not appear to significantly influence the number of new diagnoses per patient (P=.09), as indicated by the following percentages: vaccinated (n=4943, 16.4%, had 1 new diagnosis; n=1048, 3.5%, had 2 new diagnoses; n=222, 0.7%, had 3 new diagnoses; and n=51, 0.1%, had more than 3 new diagnoses) and unvaccinated (n=464, 15.5%, had only 1 new diagnosis; n=113, 3.7%, had 2 new diagnoses; n=28, 0.9%, had 3 new diagnoses; and n=10, 0.3%, had more than 3 new diagnoses), as shown in Table 1. Conversely, among youths, a notably higher number of events were observed among the unvaccinated group, with percentages as follows (P<.001): vaccinated (n=757, 15.2%, had 1 new diagnosis; n=154, 3.1%, had 2 new diagnoses; n=18, 0.4%, had 3 new diagnoses; and n=3, 0.1%, had more than 3 new diagnoses in center B) and unvaccinated (n=705, 20.9%, had 1 new diagnosis; n=167, 5%, had 2 new diagnoses; n=24, 0.7%, had 3 new diagnoses; and n=7, 0.2%, had more than 3 new diagnoses), as shown in Table 2. Ultimately, logistic regression analysis revealed a reduced risk of new diagnoses in women (0.39, 95% CI 0.35-0.43, P<.001) and younger patients (0.98, 95% CI 0.98-0.99, P<.001). However, the number of vaccine doses (0.98, 95% CI 0.86-1.11, P=.73) and the time elapsed from the last vaccine dose to infection (1.01, 95% CI 0.99-1.04, P=.42) were not found to be associated with the risk of new diagnoses. Diseases across systems, along with the number and incidence of each disease, are presented in Tables S1 and S2 in Multimedia Appendix 1 for adults and youths, respectively. Incidence data are further detailed in Tables S3 and S4 in Multimedia Appendix 1 for adults and youths, respectively. In the adult population, the most frequently occurring new diagnoses spanned neurophysical, infectious, digestive, respiratory, and musculoskeletal categories. Among the most common diseases were the following: (1) neurophysical conditions included anxiety, insomnia, headache, dizziness, and vertigo; (2) infectious diseases included acute pharyngitis and tonsillitis; (3) digestive conditions included functional dyspepsia, diarrhea, and abdominal pain; (4) respiratory issues included cough; and (5) musculoskeletal ailments included low back pain and weakness. In youths, acute pharyngitis was the most prevalent condition, with no notable difference between vaccinated and unvaccinated individuals.

When comparing the incidence of each new disease between vaccinated and unvaccinated individuals, significant differences were observed in adults for dizziness and giddiness (P=.01) and functional dyspepsia (P=.005). In contrast, among youths, significant differences were found for anxiety disorder (P<.001); dizziness and giddiness (P<.001); headache (P=.025); acute pharyngitis, tonsillitis, and fever (P<.001 for each); dermatitis, unspecified (P=.024); cough (P<.001); functional dyspepsia (P=.009); dysmenorrhea (P=.001); low back pain (P=.004); weakness (P=.033); conjunctivitis (P<.001); and recurrent oral aphthae (P<.001). Further details regarding the statistical

significance of each new diagnosis are provided in Table S5 in Multimedia Appendix 1.

Health Care Resources

The use of health care services, encompassing primary care, specialist consultations, emergency visits, and hospital admissions, among both vaccinated and unvaccinated cases and controls in the adult and youth populations is detailed in Tables 3 and 4, respectively. In vaccinated adults, patients exhibited higher health care service use compared to controls (Table 3). This increase was observed across primary care (n=33,672, 25%, more visits in n=7575, 15%, more patients, *P*<.001), specialist consultations (n=6747, 19%, more visits in n=1875, 17%, more patients, *P*<.001), and emergency admissions (n=1673, 25%, more visits in n=1026, 23%, more patients, *P*<.001). The escalation in resource use was even more pronounced in the unvaccinated population, with primary care visits seeing a 53% (n=6250) increase in visits among 46% (n=958) more patients (*P*<.001), specialist consultations witnessing a 49% (n=1527) surge in visits among 44% (n=413) more patients (*P*<.001), and emergency services experiencing a 27% (n=177) rise in visits among 19% (n=78) more patients (*P*=.002). In vaccinated youths, health care service use was also greater among patients with infection compared to controls, although the differences were smaller than in adults (Table 4). Specifically, there was a 24% (n=4348) increase in primary care visits among 13% (n=1501) more patients (*P*<.001), a 16% (n=417) uptick in specialist consultations among 12% (n=226) more patients (*P*<.001), and a 24% (n=240) rise in emergency visits among 20% (n=137) more patients (*P*<.001). Among unvaccinated youths, health care service use was likewise higher among patients with infection compared to controls, with differences again being smaller than in adults: primary care visits increased by 30% (n=5612) among 20% (n=571) more patients (*P*<.001), specialist consultations surged by 32% (n=667) among 30% (n=262) more patients (*P*<.001), and emergency visits saw a 32% (n=449) rise among 23% (n=190) more patients (*P*<.001).

Overall, hospital admissions were influenced by vaccination status in both adults (*P*<.001) and youths (*P*=.004), with higher demands observed among unvaccinated patients. Among adults, compared to controls, there were 23% (n=292) more patients in the vaccinated group and 48% (n=63) more patients in the unvaccinated group (*P*<.001). Among youths, there were 12% (n=9) more patients in the vaccinated group and 41% (n=44) more patients in the unvaccinated group (*P*<.001 for unvaccinated, *P*=.55 for vaccinated).

Table 3. Burden of health care resources (primary care, specialist consultations, emergency room, hospital admissions, and CCU[a] admissions) in the adult study population in the 2 HCDs[b] during the 2 study periods.[c]

Health care resource	Omicron (previous vaccine)		Omicron (no previous vaccine)		Pre-Omicron	
	Center A	Center B	Center A	Center B	Center A	Center B
Primary care visits						
Visits	Cases: 76,957	Cases: 56,855	Cases: 4050	Cases: 7701	Cases: 94,131	Cases: 76,902
	Controls: 56,503	Controls: 43,637	Controls: 1887	Controls: 3614	Controls: 76,702	Controls: 56,563
	Difference: 20,454 (27%)	Difference: 13,218 (23%)	Difference: 2163 (53%)	Difference: 4087 (53%)	Difference: 17,429 (19%)	Difference: 20,339 (26%)
Patients	Cases: 13,360	Cases: 9893	Cases: 735	Cases: 1347	Cases: 14,074	Cases: 11,896
	Controls: 11,346	Controls: 8419	Controls: 401	Controls: 723	Controls: 12,967	Controls: 9905
	Difference: 6101 (15%)	Difference: 1474 (15%)	Difference: 334 (45%)	Difference: 624 (46%)	Difference: 1107 (8%)	Difference: 1991 (17%)
Specialist visits						
Visits	Cases: 19,969	Cases: 15,768	Cases: 1063	Cases: 2054	Cases: 21,439	Cases: 19,892
	Controls: 15,472	Controls: 13,518	Controls: 542	Controls: 1048	Controls: 16,255	Controls: 13,540
	Difference: 4497 (23%)	Difference: 2250 (14%)	Difference: 521 (49%)	Difference: 1006 (49%)	Difference: 5184 (24%)	Difference: 6352 (32%)
Patients	Cases: 6298	Cases: 4728	Cases: 356	Cases: 584	Cases: 6389	Cases: 5331
	Controls: 5200	Controls: 3951	Controls: 167	Controls: 360	Controls: 5106	Controls: 3720
	Difference: 1098 (17%)	Difference: 777 (16%)	Difference: 189 (53%)	Difference: 224 (38%)	Difference: 1283 (20%)	Difference: 1611 (30%)
Emergency room visits						
Visits	Cases: 4081	Cases: 2480	Cases: 265	Cases: 389	Cases: 3503	Cases: 2727
	Controls: 3018	Controls: 1870	Controls: 169	Controls: 308	Controls: 2746	Controls: 1706
	Difference: 1063 (26%)	Difference: 610 (25%)	Difference: 96 (36%)	Difference: 81 (21%)	Difference: 1665 (22%)	Difference: 1021 (37%)
Patients	Cases: 2682	Cases: 1736	Cases: 159	Cases: 247	Cases: 2270	Cases: 1885
	Controls: 2060	Controls: 1332	Controls: 95	Controls: 233	Controls: 1838	Controls: 1227
	Difference: 622 (23%)	Difference: 404 (23%)	Difference: 64 (40%)	Difference: 14 (6%)	Difference: 432 (19%)	Difference: 658 (35%)
Hospital admissions						
Admissions	Cases: 850	Cases: 472	Cases: 43	Cases: 88	Cases: 838	Cases: 603
	Controls: 656	Controls: 374	Controls: 20	Controls: 48	Controls: 792	Controls: 438
	Difference: 194 (23%)	Difference: 98 (21%)	Difference: 23 (53%)	Difference: 40 (45%)	Difference: 46 (5%)	Difference: 165 (27%)
Admissions from emergency	Cases: 303	Cases: 181	Cases: 18	Cases: 42	Cases: 417	Cases: 318
	Controls: 307	Controls: 118	Controls: 10	Controls: 15	Controls: 476	Controls: 208
	Difference: –4 (–1%)	Difference: 63 (35%)	Difference: 8 (44%)	Difference: 27 (64%)	Difference: –59 (–14%)	Difference: 110 (35%)
Admissions scheduled	Cases: 246	Cases: 159	Cases: 10	Cases: 21	Cases: 196	Cases: 110
	Controls: 160	Controls: 136	Controls: 5	Controls: 21	Controls: 160	Controls: 96
	Difference: 86 (35%)	Difference: 23 (14%)	Difference: 5 (50%)	Difference: 0	Difference: 36 (18%)	Difference: 14 (13%)
Patients	Cases: 741	Cases: 436	Cases: 39	Cases: 82	Cases: 672	Cases: 518
	Controls: 555	Controls: 352	Controls: 18	Controls: 45	Controls: 641	Controls: 366
	Difference: 186 (25%)	Difference: 84 (19%)	Difference: 21 (54%)	Difference: 37 (45%)	Difference: 31 (5%)	Difference: 152 (29%)
CCU admissions						

Health care resource	Omicron (previous vaccine)		Omicron (no previous vaccine)		Pre-Omicron	
	Center A	Center B	Center A	Center B	Center A	Center B
Admissions	Cases: 9	Cases: 22	Cases: 1	Cases: 22	Cases: 17	Cases: 15
	Controls: 15	Controls: 11	Controls: 0	Controls: 11	Controls: 36	Controls: 19
	Difference: –6 (–67%)	Difference: 11 (50%)	Difference: 1 (100%)	Difference: 11 (50%)	Difference: 19 (–112%)	Difference: –4 (–27%)
Patients	Cases: 7	Cases: 20	Cases: 1	Cases: 20	Cases: 15	Cases: 14
	Controls: 13	Controls: 10	Controls: 0	Controls: 10	Controls: 33	Controls: 17
	Difference: –6 (–86%)	Difference: 10 (50%)	Difference: 1 (100%)	Difference: 10 (50%)	Difference: –18 (–120%)	Difference: –3 (–21%)

[a]CCU: critical care unit.

[b]HCD: health care department.

[c]Data show the number of cases and controls. The difference is presented as both a numerical value (n) and a percentage calculated as ([cases – controls]/cases) × 100.

Table 4. Burden of health care resources (primary care, specialist consultations, emergency room, hospital admissions, and CCU[a] admissions) in the adult study population in the 2 HCDs[b] during the 2 study periods.[c]

Health care resource	Omicron (previous vaccine)		Omicron (no previous vaccine)		Pre-Omicron	
	Center A	Center B	Center A	Center B	Center A	Center B
Primary care visits						
Visits	Cases: 9525	Cases: 8578	Cases: 10,595	Cases: 8375	Cases: 14,801	Cases: 14,195
	Controls: 6808	Controls: 6947	Controls: 7344	Controls: 6014	Controls: 13,045	Controls: 9769
	Difference: 2717 (29%)	Difference: 1631 (19%)	Difference: 3251 (31%)	Difference: 2361 (28%)	Difference: 1756 (12%)	Difference: 4426 (31%)
Patients	Cases: 2094	Cases: 1814	Cases: 1519	Cases: 1303	Cases: 2988	Cases: 2665
	Controls: 1758	Controls: 1649	Controls: 1248	Controls: 1003	Controls: 2681	Controls: 1952
	Difference: 1336 (16%)	Difference: 165 (9%)	Difference: 271 (18%)	Difference: 300 (23%)	Difference: 307 (10%)	Difference: 713 (27%)
Specialist visits						
Visits	Cases: 1714	Cases: 1624	Cases: 1066	Cases: 988	Cases: 2493	Cases: 2243
	Controls: 1442	Controls: 1479	Controls: 661	Controls: 726	Controls: 2065	Controls: 1710
	Difference: 272 (16%)	Difference: 145 (9%)	Difference: 405 (38%)	Difference: 262 (27%)	Difference: 428 (17%)	Difference: 533 (24%)
Patients	Cases: 768	Cases: 649	Cases: 458	Cases: 409	Cases: 1008	Cases: 847
	Controls: 622	Controls: 569	Controls: 314	Controls: 291	Controls: 885	Controls: 633
	Difference: 146 (19%)	Difference: 80 (12%)	Difference: 144 (31%)	Difference: 118 (29%)	Difference: 123 (12%)	Difference: 214 (25%)
Emergency room visits						
Visits	Cases: 550	Cases: 439	Cases: 796	Cases: 612	Cases: 675	Cases: 610
	Controls: 400	Controls: 349	Controls: 521	Controls: 439	Controls: 486	Controls: 418
	Difference: 150 (27%)	Difference: 90 (21%)	Difference: 275 (35%)	Difference: 173 (28%)	Difference: 189 (28%)	Difference: 192 (31%)
Patients	Cases: 390	Cases: 311	Cases: 479	Cases: 361	Cases: 468	Cases: 431
	Controls: 300	Controls: 264	Controls: 332	Controls: 318	Controls: 367	Controls: 315
	Difference: 90 (23%)	Difference: 47 (15%)	Difference: 147 (31%)	Difference: 43 (12%)	Difference: 101 (22%)	Difference: 116 (27%)
Hospital admissions						
Admissions	Cases: 32	Cases: 39	Cases: 44	Cases: 55	Cases: 62	Cases: 84
	Controls: 25	Controls: 52	Controls: 23	Controls: 32	Controls: 32	Controls: 57
	Difference: 9 (22%)	Difference: –13 (–33%)	Difference: 21 (48%)	Difference: 23 (42%)	Difference: 30 (48%)	Difference: 27 (32%)
Admissions from emergency	Cases: 15	Cases: 11	Cases: 20	Cases: 19	Cases: 24	Cases: 39
	Controls: 14	Controls: 14	Controls: 10	Controls: 19	Controls: 7	Controls: 21
	Difference: 1 (7%)	Difference: –3 (–27%)	Difference: 10 (50%)	Difference: 0	Difference: 17 (71%)	Difference: 18 (46%)
Admissions scheduled	Cases: 5	Cases: 17	Cases: 7	Cases: 23	Cases: 17	Cases: 26
	Controls: 2	Controls: 19	Controls: 6	Controls: 10	Controls: 4	Controls: 24
	Difference: 3 (60%)	Difference: –2 (–12%)	Difference: 1 (14%)	Difference: 13 (57%)	Difference: 13 (76%)	Difference: 2 (8%)
Patients	Cases: 31	Cases: 36	Cases: 39	Cases: 51	Cases: 51	Cases: 72
	Controls: 23	Controls: 52	Controls: 22	Controls: 31	Controls: 31	Controls: 49
	Difference: 8 (26%)	Difference: –16 (–44%)	Difference: 17 (44%)	Difference: 20 (39%)	Difference: 20 (39%)	Difference: 23 (32%)
CCU admissions						

Health care resource	Omicron (previous vaccine)		Omicron (no previous vaccine)		Pre-Omicron	
	Center A	Center B	Center A	Center B	Center A	Center B
Admissions	Cases: 0	Cases: 2	Cases: 0	Cases: 2	Cases: 0	Cases: 1
	Controls: 0	Controls: 1	Controls: 0	Controls: 1	Controls: 0	Controls: 5
	Difference: 0	Difference: 1 (50%)	Difference: 0	Difference: 1 (50%)	Difference: 0	Difference: –4 (–400%)
Patients	Cases: 0	Cases: 2	Cases: 0	Cases: 2	Cases: 0	Cases: 1
	Controls: 0	Controls: 1	Controls: 0	Controls: 1	Controls: 0	Controls: 4
	Difference: 0	Difference: 1 (50%)	Difference: 0	Difference: 1 (50%)	Difference: 0	Difference: –3 (–300%)

[a]CCU: critical care unit.

[b]HCD: health care department.

[c]Data show the number of cases and controls. The difference is presented as both a numerical value (n) and a percentage calculated as ([cases – controls]/cases) × 100.

Comparison With the Data From Pre-Omicron SARS-CoV-2 Waves

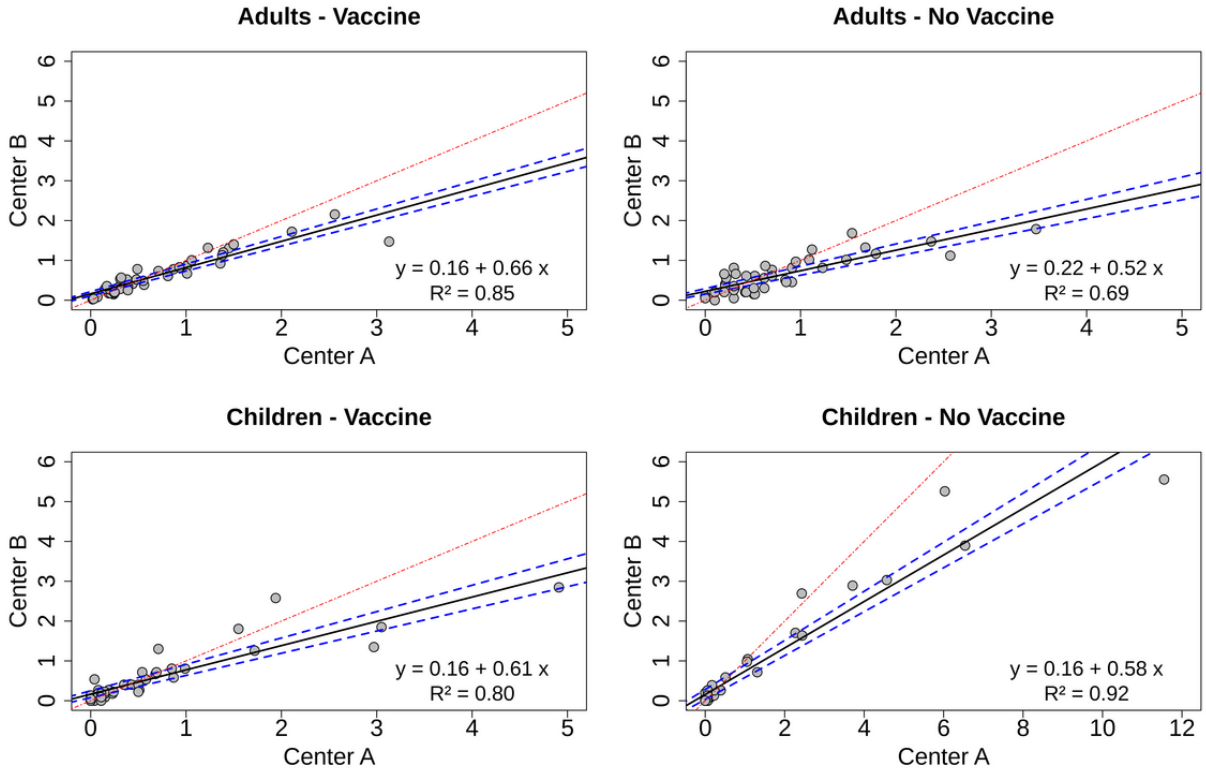
The general characteristics of the study population, along with the occurrence of new diagnoses and the health care burden associated with Omicron and pre-Omicron waves, are presented in Tables 3 and 4 for adults and youths, respectively. In adults, the prevalence of certain diagnoses in the pre-Omicron period was higher than in the Omicron period. Specifically, depressed mood (P=.03), anosmia (P=.003), hair loss (P<.001), dyspnea (P<.001), chest pain (P=.04), dysmenorrhea (P<.001), myalgia (P=.011), weakness (P<.001), and tachycardia (P=.015) were more common in the pre-Omicron period. Conversely, cough (P<.001), diarrhea (P=.03), low back pain (P<.001), and conjunctivitis (P<.001) were more prevalent in the Omicron period. In youths, anosmia (P=.003) was found to be more common in the pre-Omicron period. Despite these differences in frequency, the burden of long COVID complaints on health care services was similar between the Omicron and pre-Omicron periods, with the exception of musculoskeletal complaints.

Overall, the use of health care resources was higher during the pre-Omicron period in both adults (primary care, P<.001; specialist, P<.001; emergency, P<.001) and youths (primary care, P<.001; specialist, P<.001; emergency, <.001). Furthermore, the demand for health care services was greater among the unvaccinated population in the Omicron period than in the pre-Omicron period.

Sensitivity Analysis

The concordance of new diagnoses within the 2 HCDs was subjected to analysis. Figure 2 displays the correlation coefficient within each of the Omicron subgroups, comprising vaccinated and unvaccinated adults and youths. The disparities observed between the 2 HCDs were, to some extent, attributed to the distinct protocols used by each HCD. However, these discrepancies were not deemed significant in terms of their overall impact.

Figure 2. Correlation of new diagnoses between 2 health care areas in the study populations aged ≥18 and <18 years old. The black line is the regression line of the number of diagnoses in the 2 HCDs. The blue broken line is the 95% CI. The red line is the reference. HCD: health care department.



Discussion

Principal Findings

The analysis of the long-term impact of SARS-CoV-2 Omicron infection following the acute phase was conducted using EHRs sourced from 2 distinct HCDs, comprising data from the medical records of these HCDs. Notably, vaccinated patients with Omicron infection exhibited a reduced incidence of new diagnoses, particularly among females and younger individuals, irrespective of the number of vaccine doses administered and the interval between the last dose and infection. In the case of youths, vaccination also contributed to a decrease in the incidence of new diagnoses. Additionally, vaccinated patients displayed a reduced demand for health care services compared to their unvaccinated counterparts, a pattern observed across both adult and youth populations.

Furthermore, it was observed that the overall number of new diagnoses was higher during the pre-Omicron period in comparison to the Omicron period. Specific conditions, such as depressed mood, anosmia, alopecia, dyspnea, chest pain, dysmenorrhea, myalgia, weakness, and tachycardia, were more prevalent during the pre-Omicron period, whereas conditions such as diarrhea, conjunctivitis, and low back pain exhibited higher incidence rates in the Omicron period. Despite the increase in health care resource use during the Omicron period, it remained significantly lower when compared to the pre-Omicron period. Notably, among adults, the increment in health care resource usage was more pronounced in unvaccinated patients and during the pre-Omicron period when contrasted with the vaccinated population.

To evaluate the potential impact of the viral infection itself on newly diagnosed cases and health care resource use, the inclusion of a control group becomes essential. This is because many of the newly diagnosed conditions or symptoms may not be directly caused by the virus but could instead result from factors such as stress, anxiety, or pandemic-related restrictions, affecting both individuals with and without infection to varying degrees. This study used a control group selection method based on a stringent PSM approach, which closely resembled the methodology used in a previous study conducted by our research team during the pre-Omicron pandemic waves. This earlier study used data extracted from EHRs [31] and served as a basis for comparison between the Omicron and pre-Omicron periods.

The results of this study suggest that the impact on new diagnoses and health care resource use following a less severe acute infection with the Omicron variant decreases when compared to previous pandemic waves involving other SARS-CoV-2 variants, aligning with findings from prior research [32]. However, complaints requiring health care services remain comparable, with potential differences in musculoskeletal symptoms [33]. Several factors may contribute to the reduced risk of sequelae associated with Omicron, including variances in the inherent characteristics of different SARS-CoV-2 variants in causing long-term health issues, the severity of acute infection [34], and variations in vaccination coverage and population immunity to SARS-CoV-2 [19,34,35]. Previous studies have indicated that COVID-19 vaccination

and prior infections are associated with a lower risk of developing long COVID events [29,34]. Notably, the population vaccinated before the onset of acute infection exhibits fewer new diagnoses and requires fewer health care resources than its unvaccinated counterpart [36]. Currently, the effect of vaccination in reducing the risk of long COVID appears to be more prominent among women and younger individuals. Furthermore, in this study, the time elapsed between the last vaccine dose and infection did not appear to significantly impact the risk reduction. It is worth noting that individuals with a previous infection prior to the case index were excluded from the study.

The specific effects on youths have been investigated in various studies. A meta-analysis included [37] a wide range of symptoms, including fatigue, headache, loss of smell, cough, and neurological symptoms. These data were corroborated using a report from the United Kingdom, where persistent symptoms were frequently observed in English schoolchildren regardless of their SARS-CoV-2 test results. Additionally, specific symptoms, such as loss of smell and taste, were more commonly reported among those with a positive test history [38]. Furthermore, specific to youths, some studies have underscored that symptomatology can vary depending on the viral variant. This observation was reaffirmed in this study, where the impact of pre-Omicron variants was more pronounced compared to Omicron [39]. Notably, the influence of the immune response stimulated by vaccination was significant in this youth population, as differences between vaccinated and unvaccinated individuals were much more apparent than in adults.

An essential aspect that has received insufficient attention in the majority of long COVID studies pertains to the use of outpatient and hospital resources [34,40]. In this analysis, it was imperative not only to document patient numbers but also to evaluate resource use within a controlled PSM framework. The observed escalation in the health care burden, comparing cases to controls, manifested in both adults and youths, albeit with lower figures among the latter group. Across both periods, Omicron and pre-Omicron, an upsurge in visits to general practitioners, specialists, and emergency departments, as well as an increase in the necessity for hospital admissions, were noted. Although the demand for resources was more substantial in the pre-Omicron period than in the Omicron period, the demand increment in the Omicron period was also noteworthy when compared to the control group.

Several pathogenesis models have been proposed to elucidate the persistence of symptoms or the emergence of new diagnoses after SARS-CoV-2 infection. One hypothesis suggests that the persistence of the virus or a viral component [41] might exacerbate the immune response, leading to elevated levels of proinflammatory cytokines. This could potentially explain organ damage and the enduring presence of symptoms such as fatigue, headache, and olfactory dysfunction [37,42]. Furthermore, another proposed mechanism involves molecular mimicry between autoantigens and spike epitopes [42]. Nevertheless, distinguishing between functional complaints attributable to the virus and those resulting from social limitations poses a challenge in many long COVID sequelae.

Strengths and Limitations

Both the strengths and limitations of the study merit consideration. The assessment of new diagnoses in both youth and adult cases within the general population, alongside propensity score–matched controls, facilitated the measurement of the impact of COVID-19 infection. Robust comparator data for the assessment of new diagnoses and treatments were obtained, not only through the selection of cases and controls, but also through the identification of prior diagnoses. It is important to note that the study did not encompass a clinical evaluation of the new diagnoses; however, characterizing these new diagnoses was not the primary objective of this study. Finally, it is worth acknowledging the limitations inherent in EHRs. Despite efforts to minimize these limitations, the study was restricted to patients with the necessary records for analysis.

Conclusion

In conclusion, attention must be paid to the emergence of new diagnoses after Omicron infection, in preparation for potential future waves of SARS-CoV-2 infection. The virus's successive mutations introduce the possibility of new waves, which may vary in terms of incidence within the general population or specific risk groups. Regardless of the severity of acute infections and the reinforced immunological status achieved through vaccination or prior infections or both, the potential repercussions for long COVID, and, subsequently, for the demands placed on the health care system, may necessitate additional resources. Vaccination plays a crucial role in mitigating the challenges faced by the health care system.

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Data Availability

The data presented in this study are available in the paper and multimedia appendices.

Authors' Contributions

BV-M and JR were responsible for conceptualization; BV-M, JR, IS, JMC, and VLS for methodology; JP, JMC, MEG, and JD for software; JLL-H, DN, and MJF for validation; JP, JMC, MEG, LL, and JD for formal analysis; and BV-M, MEG-L, and JR for writing—review and editing All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared. The funders played no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Multimedia Appendix 1

Supplementary tables.
[DOCX File , 79 KB-Multimedia Appendix 1]

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Abbreviations

CCU: critical care unit
EHR: electronic health record
HCD: health care department
ICD-10: International Classification of Diseases, 10th Revision
PSM: propensity score matching
RT-PCR: reverse transcription polymerase chain reaction

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