Impact of Long SARS-CoV-2 Omicron on Health Care Burden: A Case-control Comparative Study with the Pre-Omicron Waves

Josep Redon, Bernardo Valdivieso-Martinez, Victoria Lopez-Sanchez, Inma Sauri, Javier Diaz, Jose Miguel Calderon, Maria Eugenia Gas-Lopez, Laura Lidon, Juliette Philibert, Jose Luis Lopez-Hontangas, David Navarro, Maria Jose Forner

Submitted to: JMIR Public Health and Surveillance
on: October 11, 2023

Table of Contents

Impact of Long SARS-CoV-2 Omicron on Health Care Burden: A Case-control Comparative Study with the Pre-Omicron Waves

Josep Redon[1*] Prof Dr Med; Bernardo Valdivieso-Martinez[2*] Prof Dr; Victoria Lopez-Sanchez[3] PhD; Inma Sauri[4] PharmB; Javier Diaz[4] PhD; Jose Miguel Calderon[1]; Maria Eugenia Gas-Lopez[2] PhD; Laura Lidon[1] MAT; Juliette Philibert[2] PhD; Jose Luis Lopez-Hontangas[2] Prof Dr; David Navarro[5] Prof Dr Med; Maria Jose Forner[5] Prof Dr Med

[1]INCLIVA Research Institute, University of Valencia Valencia ES
[2]University and Polytechnic La Fe Hospital of Valencia Valencia ES
[3]Medical Research Institute Hospital La Fe Valencia ES
[4]INCLIVA RESEARCH INSTITUTE Valencia ES
[5]Hospital Clinico of Valencia Valencia ES
[*]these authors contributed equally

Corresponding Author:
Josep Redon Prof Dr Med
INCLIVA Research Institute, University of Valencia
Menendez y Pelayo, 4
Valencia
ES

Abstract

Background: The global population has been profoundly affected by the SARS-CoV-2 pandemic, resulting in elevated morbidity and mortality. Following the initial acute phase of illness, healthcare resource utilization has escalated among individuals with SARS-CoV-2 infection, attributed to persistent symptoms or the emergence of new illnesses.

Objective: The primary aim of this study was to ascertain the enduring consequences of SARS-CoV-2 virus infection on both the incidence of new diagnoses and the utilization of healthcare resources among patients, within the context of the Omicron pandemic. A case-control investigation was conducted with the aim of drawing comparisons between the Omicron wave and the preceding pre-Omicron waves.

Methods: This matched retrospective cohort study included patients of all ages from two healthcare Departments. Patients were matched on control and were followed-up for 6 months after SARS-CoV-2 infection. Previous vaccination, new diagnosis (CIE10) and use of health care resources were recorded.

Results: In the study, a total of 41,577 patients with a history of prior COVID infection were included, alongside an equivalent number of controls. This cohort encompassed 33,249 adults aged >17 years and 8,328 youths aged <18 years. Notably, our analysis revealed the identification of forty new diagnoses. The incidence rate per 100 patients over a six-month period stood at 27.2 for vaccinated and 25.1 for unvaccinated adults (p=0.09), 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 when compared to 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 utilization of healthcare resources was observed in both adult and adolescent patients, 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. Similarly, healthcare resource utilization, 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 healthcare system.

(JMIR Preprints 11/10/2023:53580)
DOI: https://doi.org/10.2196/preprints.53580

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✔ **Please make my preprint PDF available to anyone at any time (recommended).**

Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.

Only make the preprint title and abstract visible.

No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✔ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v

Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

Impact of Long SARS-CoV-2 Omicron on Health Care Burden. A Case-control Comparative Study with the Pre-Omicron Waves

Bernardo Valdivieso-Martínez [1,2], Javier Lopez-Sanchez[3], Inma Sauri [3], Victoria Lopez-Sanchez [2], Juliette Philibert [2], Jose Miguel Calderon [3], María-Eugenia Gas [2] Jose Luis López-Hontangas [4], David Navarro [5,6], Laura Lidon[3], L Cuenca[7] , Maria Jose Forner [8] and Josep Redon [3,6]

[1] The University and Polytechnic La Fe Hospital of Valencia, Avenida Fernando Abril Martorell, 106 Torre H 1st floor, Valencia, 46026, Spain
[2] The Joint Research Unit in ICT applied to the Reengineering of Socio-Sanitary Processes. The Medical Research Institute Hospital La Fe, Avenida Fernando Abril Martorell, 106 Torre A 7th floor, Valencia, 46026, Spain
[3] BigData Team. INCLIVA Research Institute, University of Valencia, Spain
[4] Department of Microbiology. The University and Polytechnic La Fe Hospital of Valencia, Spain
[5] Department of Microbiology. Hospital Clinico of Valencia, University of Valencia, Spain
[6] PROVAVAC, Generalitat Valenciana, Spain
[7] Politechnic University of Valencia, Spain
[8] Internal Medicine, Hospital Clínico, University of Valencia, Spain
*

Correspondence:
Josep Redon,
INCLIVA Research Institute,
Menendez Pelayo, 4, Valencia 46010. Spain,
josep.redon@uv.es.
Phone number +34 658909676

Abstract:

Background: Following the initial acute phase of illness, healthcare resource utilization has escalated among individuals with SARS-CoV-2 infection
Objective: To compare new diagnoses of Long COVID and demand for health services in the general population after the Omicron variant wave with those observed during the pre-Omicron waves, using similar assessment protocols for both periods in a case-control study. The influence of vaccination were also

analyzed. **Methods:** Cases included patients of both sexes diagnosed with acute SARS-CoV-2 infection by PCR or antigen in the hospital microbiology laboratory during the pandemic periods, regardless of whether the patients were hospitalised or not. This matched retrospective cohort study included patients of all ages from two healthcare Departments who cover 606,000 subjects. The population was stratified into two groups, namely youths under the age of 18 and adults. Patients were followed-up for 6 months after SARS-CoV-2 infection. Previous vaccination, new diagnosis (CIE10) and use of health care resources were recorded**.** Patients with SARS-CoV-2 infection were compared with controls selected using a prospective score matched of age, sex, and Charlson index. **Results:** In the study, a total of 41,577 patients with a history of prior COVID infection were included, alongside an equivalent number of controls. This cohort encompassed 33,249 adults aged >17 years and 8,328 youths aged <18 years. Notably, our analysis revealed the identification of forty new diagnoses during the observational period. The incidence rate per 100 patients over a six-month period stood at 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 when 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 utilization of healthcare resources was observed in both adult and adolescent patients, 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, healthcare resource utilization, encompassing primary care, specialist, and emergency services, was more pronounced in the Pre-Omicron wave. **Conclusion:** 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 healthcare system.

Keywords: Omicron**,** Long-COVID; Post-COVID; Omicron, diagnostics; Primary Care; Specialist; Emergency Department; hospitalization.

Introduction

The global all-cause disease burden in 2020 and 2021 was the highest in the last three decades, mainly due to the consequences of the SARS-CoV-2 pandemic [1]. In fact, the global population was profoundly affected not only by the acute infection, resulting in increased morbidity and mortality [2], but also after the initial acute phase of illness due to persistent symptoms or the impact on organ systems with the emergence of new diseases [3-12]. As a result, health care resource utilization 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 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, Omicron variant induced less severe acute illness than its predecessors, and certain studies reported a reduced incidence of post-acute phase impacts [13-19], both in adults and children [20-24]. Nevertheless, conflicting data have surfaced in the literature [25], and the potential influence of prior vaccination remains uncertain [26-28].Valuating 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 healthcare resource burden following the acute infection episode holds paramount significance, given its implications for the resources that healthcare 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 healthcare resource demands placed on health systems by encompassing a wealth of data on diagnoses, medication usage, and healthcare resource requirements [29].

Based on the electronic health records (EHRs) of two health departments in the Valencian Community of more than 600,000 inhabitants, this study aimed to compare new diagnoses of Long COVID and 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

Design and participants

Case-control study with retrospective observation of health care data collected in ABUCASIS, the EHR of the Community of Valencia. Administrative data, diagnoses, all prescriptions and dispensations of subsidised treatments, and use of health services are linked in a database that integrates all health care interventions. In the present study, the data included the observation of patients with SARS-COVID infection from a total of 604,000 subjects from two different Health Care Departments (HCDs).

Ethical consideration

The exemption from obtaining informed consent was permissible based on the seventeenth additional provision of Spanish Organic Law 3/2018, dated December 5th, which pertains to the protection of personal data and the guarantee of digital rights. This provision legalizes the utilization 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 those individuals responsible for executing the pseudonymization process, as well as safeguarding the information that could potentially facilitate re-identification. Data collection and analysis have been carried out taking into account the protection of patients' privacy by means of a two-layered method of pseudo-anonymisation, and the information is managed as aggregated data.

The research was conducted in full compliance with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Likewise, compliance with the seventeenth additional provision on the processing of health data of Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights and the applicable sectoral legislation is guaranteed. The information was available for the research, pseudo-anonymisation in accordance with the Spanish Data Protection Act, and with the approval of the study by the Ethics and Clinical Trials Committee of the Hospitals Clinico of Valencia and The University and Polytechnic La Fe Hospital of Valencia. The

Spanish Law 3/2018 of Data Protection and Guarantee of Digital Rights and the corresponding European norms (GDPR) [30] were followed.

Subjects and Procedures

Cases included patients of both sexes diagnosed with acute SARS-CoV-2 infection by PCR or antigen in the hospital microbiology laboratory during the pandemic period with SARS-CoV-2 Omicron, regardless of whether the patients were hospitalised or not. The population was stratified into two groups, namely youths under the age of 18 and adults.

The study design has been previously detailed in a publication [31], with a summary provided in Figure 1. In brief, the selection of cases for Omicron infection encompassed 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 observational period, the collection of data encompassed the identification of newly diagnosed conditions and prescriptions. Additionally, the utilization of healthcare 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.

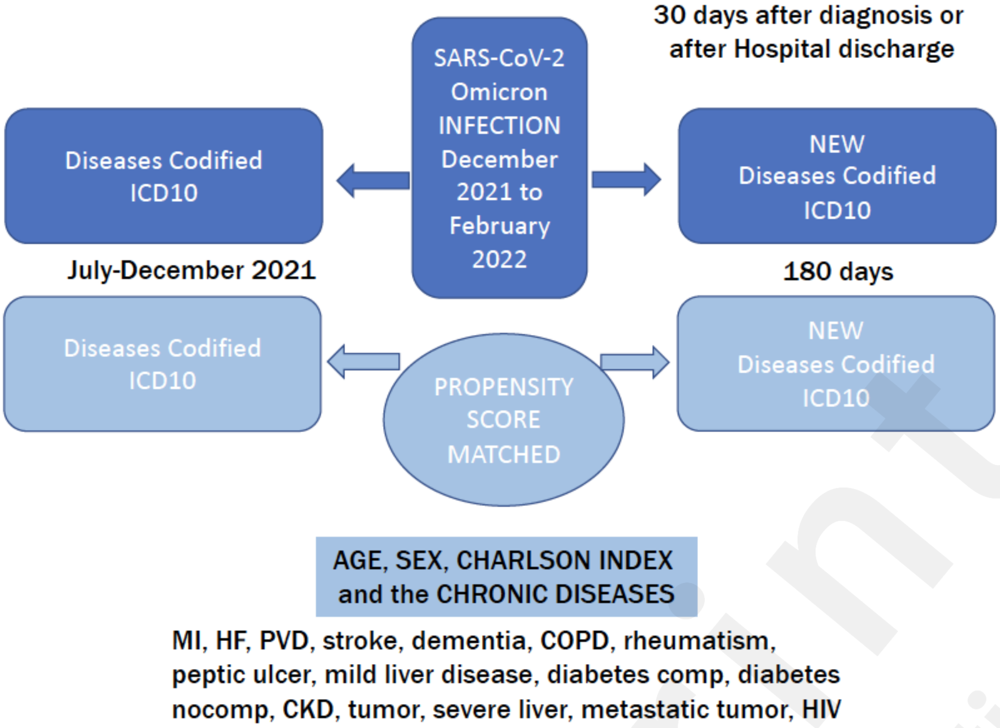


Figure 1. Study design. Cases included patients of both sexes diagnosed with acute SARS-CoV-2 infection, and the same number of matched controls without infection were selected by a propensity score for age, sex, previous illnesses and the same time period as the case index. The observation period for new diagnoses and health care use was 6 months after 30 days from virus diagnosis or hospital discharge.

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 a propensity score matching (PSM) procedure that incorporated variables such as age, sex, Charlson index, all pre-existing 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 timeframe. Data from a prior study conducted using the same methodology during the pre-Omicron period, spanning from March 2020 to December 2020, were utilized to facilitate comparisons regarding the potential impact of Omicron. [31]

Statistical analysis

Data have been 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 two HCDs and comparing the results between them. All statistical analyses were carried out using R version 6.3.1. The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing the report.

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 RT-PCR or antigen tests. This patient cohort comprised 33,249 adults aged >17 years and 8,328 youths aged <18 years. Prior to the onset of acute infection, 30,199 adults and 4,417 youths had received the vaccine. The general characteristics of the study population are detailed in Table 1 for both adults and youths. Follow-up of the infected patients extended from 177 to 179 days after 30 days of confirmed infection. Among them, a total of 833 patients (2%) were hospitalized for acute SARS-CoV-2 Omicron infection, including 662 adults and 75 youths (0.09%), with 24 of the latter being vaccinated.

Table 1. General characteristics of study population cases in the two Centers during Omicron and Pre-Omicron waves, split in adults >17 year and youths <18 year old. Omicron period is split in the subjects with or without vaccine

	OMICRON PREVIOUS VACCINE	OMICRON NO PREVIOUS VACCINE	PRE-OMICRON

	CENTER A	CENTER B	CENTER A	CENTER B	CENTER A	CENTER B
			ADULTS >17 yr			
Number	17441	12758	1040	2010	16382	14199
Age (yr)	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 (%)	9832 (56.4%)	7110	570 (54.8%)	1168	8861 (54.1%)	7671 (54.0%)
Days of observation	179 ± 10.93	179.58 ± 6.80	177.98 ± 16.04	177.11 ± 20.15	176.06 ± 20.53	179.00 ± 7.68
Hospital (ns)	458	204	78	68	1726	1357
First vaccination	2021-06-06 ± 57.95	2021-01-07 ± 52.27	NA ± NA	NA ± NA	NA ± NA	NA ± NA
Patients with new diagnostics	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%	2182 ; 15,4%
2	574 ; 3,3%	474 ; 3,7%	42 ; 4%	71 ; 3,5%	506 ; 3,1%	544 ; 3,8%
3	121 ; 0,7%	101 ; 0,8%	8 ; 0,8%	20 ; 1%	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%
			YOUTHS <18 yr			
Number	**2.714**	**2.243**	**1.824**	**1.547**	**3981**	**3605**
Age (yr)	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 (%)	1377 (50.7%)	1123	864 (47.4%)	719	1956 (49.1%)	1783 (49%)
Days of observation	180 ± 0	179.91 ± 3.76	180 ± 0	179.40 ± 9.01	179.11 ± 4.21	179.26 ± 3.89
Hospital (ns)	12	12	19	32	23	27
First vaccination	2021-10-21 ± 82.66	2021-06-12 ± 88.60	NA ± NA {0 0%}	NA ± NA {0 0%}	NA ± NA {0 0%}	NA ± NA {0 0%}
Patients with new diagnostics	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%

New diagnostics

The new diagnoses observed during the follow-up period in patients with SARS-CoV-2 and Alpha Omicron infection and controls, regardless of their vaccination status, and the corresponding distribution of CIE-10 codes across affected systems are presented in Supplementary Tables 1a, 1b, 2a and 2b. Among adults, the number of new diagnoses for vaccinated and unvaccinated patients stood at 6,642 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 1,014 diagnoses in vaccinated individuals and 967 in unvaccinated individuals, resulting in incidences of 25.7 and 36.7, respectively (*P*=<.001). Regarding adults, vaccination status did not appear to significantly influence the number of new diagnoses per patient, as indicated by the following percentages: vaccinated (16.4% had one new diagnosis, 3.5% had two, 0.7% had three, and 0.1% had more than three) and unvaccinated (15.2% had only one, 3.7% had two, 0.9% had three, and 0.3% had two or more) (*P*=.09). Conversely, among youths, a notably higher number of events were observed among the unvaccinated group, with percentages as follows: vaccinated (15.2% had one new diagnosis, 3.1% had two, 0.4% had three, and 0.1% had more than three) and unvaccinated (20.9% had one new diagnosis, 5.0% had two, 0.7% had three, and 0.2% had two or more) (*P*<.001). Ultimately, the 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, is presented in Supplementary Tables 1a and 1b for adults and youths. Incidence data are further detailed in Supplementary Table 2a and Table 2b. 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: i) neurophysical conditions included anxiety, insomnia, headache, dizziness, and vertigo; ii) infectious diseases comprised acute pharyngitis and tonsillitis; iii) digestive conditions encompassed functional dyspepsia, diarrhea, and abdominal pain; iv) respiratory issues involved cough; and v) 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 Supplementary Table 3.

Health Care Resources

The utilization of healthcare services, encompassing primary care, specialist consultations, emergency visits, and hospital admissions, among both vaccinated and unvaccinated cases and controls in the adult and adolescent populations, is detailed in Tables 2a and 2b. In vaccinated adults, cases exhibited higher healthcare service utilization when compared with controls. This increase was observed across primary care (25% more visits in 15% more patients, *P*<.001), specialist consultations (19% more visits in 17% more patients, *P*<.001), and emergency admissions (25% more visits in 23% more patients, *P*<.001). The escalation in resource utilization was even more pronounced in the unvaccinated population, with primary care visits seeing a 53% increase in visits among 46% more patients (*P*.001), specialist consultations witnessing a 49% surge in visits among 44% more patients (*P* <.001), and emergency services experiencing a 27% rise in visits among 19% more patients (*P*=.002). In vaccinated youths, healthcare service utilization was also greater among infected patients when compared to controls, although the differences were smaller than in adults. Specifically, there was a 24% increase in primary care visits among 13% more patients (*P*<.001), a 16% uptick in specialist consultations among 12% more patients (*P*<.001), and a 24% rise in emergency visits among 20% more patients (*P*<.001). Among unvaccinated youths, healthcare service utilization was likewise higher among infected patients in comparison to controls, with differences again being smaller than in adults: primary care visits increased by 30% among 20% more patients (*P*<.001), specialist consultations surged by 32% among 30% more patients (*P*<.001), and emergency visits saw a 32% rise among 23% 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% more patients in the vaccinated group and 48% more in the unvaccinated group (*P*<.001). Among youths, there were 12% more patients in the vaccinated group and 41% more in the unvaccinated group (*P*<.001 for unvaccinated, *P*=.55 for vaccinated).

Comparison with the data from the Pre-Omicron SARS-CoV-2 waves

The general characteristics of the study population, along with the occurrence of new diagnoses and the healthcare burden associated with Omicron and Pre-Omicron, are presented in the corresponding tables for adults and youths. In adults, it was observed that 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 (<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. Conversely, cough (*P*<.001), diarrhea (*P*=.03), 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 healthcare services was similar between the Omicron and Pre-Omicron periods, with the exception of musculoskeletal complaints.

Overall, the utilization of healthcare 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 healthcare services was greater among the unvaccinated population than in the Pre-Omicron period.

Table 2a. Burden of the Health Care resources, number of visits in Primary Care, Specialists, Emergency room, Hospital and Critical Care Unit admissions, in the study population >17-year-old in the two Centers during the two periods included in the study. Omicron period is split in the subjects with or without vaccine

	OMICRON PREVIOUS VACCINE						OMICRON NO PREVIOUS VACCINE						PRE - OMICRON					
	CENTER A			CENTER B			CENTER A			CENTER B			CENTER A			CENTER B		
	Case	**Control**	**%**	**Case**	**Control**	**%**	**Case**	**Control**	**%**	**Case**	**Control**	**%**	**Case**	**Control**	**%**	**Case**	**Control**	**%**
Number	**17441**	**17435**		**12758**	**12770**		**1040**	**1047**		**2010**	**2004**		**16382**	**16389**		**14199**	**14214**	
Primary Care Visits																		
Number of visits	76957	56503	27%	56855	43637	23%	4050	1887	53%	7701	3614	53%	94131	76702	19%	76902	56563	26%
Number of patients	13360	11346	15%	9893	8419	15%	735	401	45%	1347	723	46%	14074	12967	8%	11896	9905	17%
Specialist Visit																		
Number of visits	19969	15472	23%	15768	13518	14%	1063	542	49%	2054	1048	49%	21439	16255	24%	19892	13540	32%
Number of patients	6298	5200	17%	4728	3951	16%	356	167	53%	584	360	38%	6389	5106	20%	5331	3720	30%
Emergency Room																		
Number of visits	4081	3018	26%	2480	1870	25%	265	169	36%	389	308	21%	3503	2746	22%	2727	1706	37%
Number of patients	2682	2060	23%	1736	1332	23%	159	95	40%	247	233	6%	2270	1838	19%	1885	1227	35%
Hospital Admision																		
Number of admissions	850	656	23%	472	374	21%	43	20	53%	88	48	45%	838	792	5%	603	438	27%
Adm.from Emergency	303	307	-1%	181	118	35%	18	10	44%	42	15	64%	417	476	-14%	318	208	35%
Adm. scheduled	246	160	35%	159	136	14%	10	5	50%	21	21	0%	196	160	18%	110	96	13%

Number of patients	741	555	25%	436	352	19%	39	18	54%	82	45	45%	672	641	5%	518	366	29%
CRITICAL CARE UNIT (CCU)																		
CCU number	9	15	67%	22	11	50%	1	0	100%	22	11	50%	17	36	112%	15	19	-27%
CCU patients	7	13	86%	20	10	50%	1	0	100%	20	10	50%	15	33	120%	14	17	-21%

Table 2b. Burden of the Health Care resources, number of visits in Primary Care, Specialists, Emergency room, Hospital and Critical Care Unit admissions, in the study population <18-year-old in the two Centers during the two periods included in the study. Omicron period is split in the subjects with or without vaccine

	OMICRON PREVIOUS VACCINE						**OMICRON NO PREVIOUS VACCINE**						**PRE - OMICRON**					
	CENTER A			**CENTER B**			**CENTER A**			**CENTER B**			**CENTER A**			**CENTER B**		
	Case	**Control**	**%**	**Case**	**Control**	**%**	**Case**	**Control**	**%**	**Case**	**Control**	**%**	**Case**	**Control**	**%**	**Case**	**Control**	**%**
Number	**2714**	**2720**		**2243**	**2231**		**1824**	**1817**		**1547**	**1553**		**3981**	**3974**		**3605**	**3590**	
Primary Care Visits																		
Number of visits	9525	6808	29%	8578	6947	19%	10595	7344	31%	8375	6014	28%	14801	13045	12%	14195	9769	31%
Number of patients	2094	1758	16%	1814	1649	9%	1519	1248	18%	1303	1003	23%	2988	2681	10%	2665	1952	27%
Specialist Visit																		
Number of visits	1714	1442	16%	1624	1479	9%	1066	661	38%	988	726	27%	2493	2065	17%	2243	1710	24%
Number of patients	768	622	19%	649	569	12%	458	314	31%	409	291	29%	1008	885	12%	847	633	25%
Emergency Room																		
Number of visits	550	400	27%	439	349	21%	796	521	35%	612	439	28%	675	486	28%	610	418	31%
Number of	390	300	23%	311	264	15%	479	332	31	361	318	12%	468	367	22%	431	315	27%

patients									%									
Hospital Admision																		
Number of admissions	32	25	22%	39	52	-33%	44	23	48 %	55	32	42%	62	32	48%	84	57	32%
Adm. from Emergency	15	14	7%	11	14	-27%	20	10	50 %	19	19	0%	24	7	71%	39	21	46%
Adm. scheduled	5	2	60%	17	19	-12%	7	6	14 %	23	10	57%	17	4	76%	26	24	8%
Number of patients	31	23	26%	36	52	-44%	39	22	44 %	51	31	39%	51	31	39%	72	49	32%
CRITICAL CARE UNIT (CCU)																		
CCU number	0	0	0%	2	1	50%	0	0	0%	2	1	50%	0	0	0%	1	5	-400%
CCU patients	0	0	0%	2	1	50%	0	0	0%	2	1	50%	0	0	0%	1	4	-300%

Sensitive analysis

The concordance of new diagnoses within the two 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 two HCDs were, to some extent, attributed to the distinct protocols employed by each HCD. However, these discrepancies were not deemed significant in terms of their overall impact.

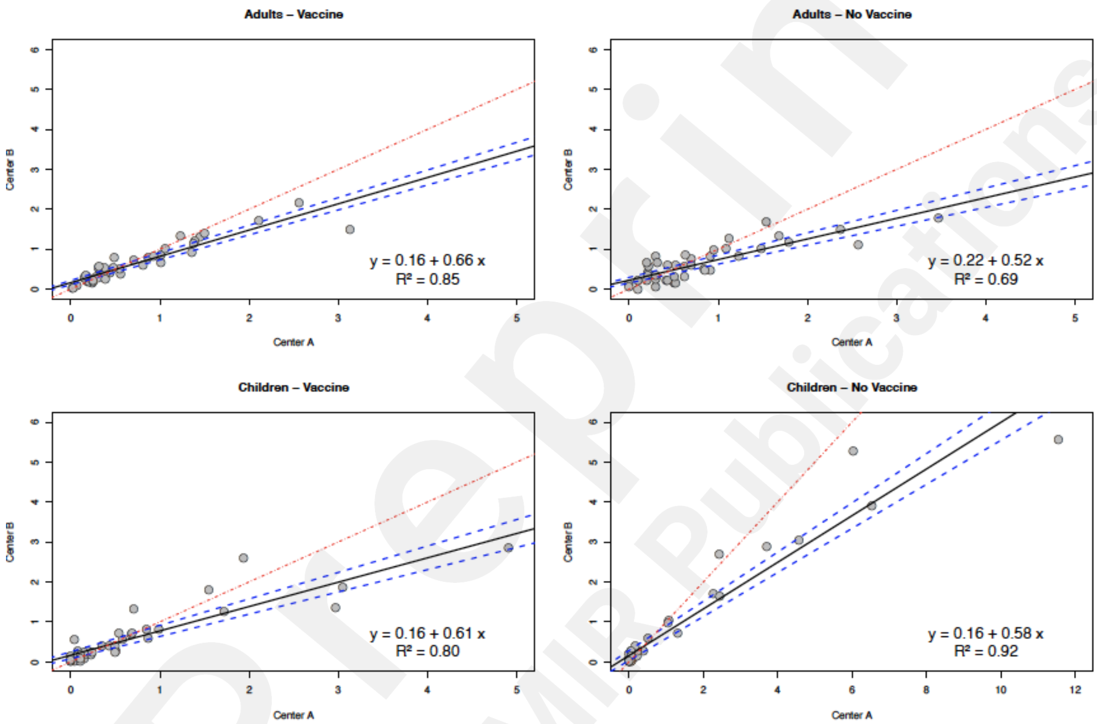


Figure 2. Correlation of New Diagnoses Between Two Health Care Areas in Study Population Aged >17 and <18 Years Old. Black line is the regression line of the number of diagnostics in the two HCDs. Blue broken line 95 CI. Red line is the reference.

Discussion

The analysis of the long-term impact of SARS-CoV-2 Omicron infection following the acute phase was conducted using electronic health records (EHRs) sourced from two distinct HCDs, comprising data from the medical records of these health departments. Notably, vaccinated Omicron patients 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 healthcare services compared to their unvaccinated counterparts, a pattern observed across both adult and adolescent 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 like diarrhea, conjunctivitis, and low back pain exhibited higher incidence rates in the Omicron period. Despite the increase in healthcare resource utilization during the Omicron period, it remained significantly lower when compared to the Pre-Omicron period. Notably, among adults, the increment in healthcare resource usage was more pronounced in unvaccinated patients and during the Pre-Omicron period when contrasted with the vaccinated population.

In order to evaluate the potential impact of viral infection itself on newly diagnosed cases and healthcare resource utilization, 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 infected and non-infected individuals to varying degrees. The current study employed 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 utilized data extracted from the Electronic Health Records (EHR) [31] and serves as a basis for comparison between the Omicron and pre-Omicron periods.

The results of the present study suggest that the impact on new diagnoses and healthcare resource utilization 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 healthcare 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 the SARS-CoV-2 virus [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 healthcare resources than their counterparts in the vaccinated population [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 the present study, the time elapsed between the last vaccine dose and infection does 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 encompassed a wide range of symptoms, including fatigue, headache, loss of smell, cough, and neurological symptoms [37]. This data was corroborated by a report from the UK, where persistent symptoms were frequently

18

observed in English schoolchildren, regardless of their SARS-CoV-2 test results. Additionally, certain 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 underscored that symptomatology can vary depending on the viral variant. This observation was reaffirmed in the present 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 adolescent population, as differences between vaccinated and unvaccinated individuals were much more apparent than in adult.

An essential aspect that has received insufficient attention in the majority of LONG COVID studies pertains to the utilization of outpatient and hospital resources [34,40]. In this analysis, it is imperative not only to document the patient numbers but also to evaluate resource utilization within a controlled PSM framework. The observed escalation in the healthcare 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. While the demand for resources was more substantial in the Pre-Omicron era than in the Omicron period, the increment in Omicron 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-Cov2- 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.

Both the strengths and limitations of the study merit consideration. The assessment of new diagnoses in both adolescent 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 does 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 electronic health records (EHRs). Despite efforts to minimize these limitations, the study was restricted to patients with the necessary records for analysis.

In conclusion, the attention to be paid to the emergence of new diagnoses after omicron infection should be emphasized 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.

20

Regardless of the severity of acute infections and the reinforced immunological status achieved through vaccination and/or prior infections, the potential repercussions on LONG COVID, and subsequently on the demands placed on healthcare systems, may necessitate additional resources. Vaccination plays a crucial role in mitigating the challenges faced by the healthcare system.

21

Author Contributions:

Conceptualization, B.V.-M. and J.R.; methodology, I.A. B.V.-M., J.R., I.S., J.M.C., V.L.S; software, J.P., J.M.C., M.E.G. and J.D.; validation, J.L.L.-H., D.N. and M.J.F.; formal analysis, I.A.,J.P., J.M.C., M.E.G, LL and J.D.; writing—review and editing, B.V.-M., M.E.G and J.R. All authors have read and agreed to the published version of the manuscript.

Funding:

The study was funded by Conselleria de Innovación, Universidades, Ciencia y Sociedad Digital (Grant number GVA-COVID19/2021/065).

Institutional Review Board Statement:

The research was carried out in full compliance with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Likewise, compliance with the seventeenth additional provision on the processing of health data of Organic Law 3/2018 of 5 December on the Protection of Personal Data and the guarantee of digital rights and the applicable sectoral legislation is guaranteed. The information was available for research, pseudo-anonymized in accordance with the Spanish Law of Data Protection, and with the approval for its study by the Committee for Ethics and Clinical Trials of the Hospitals Clinico of Valencia (data of approval 10 October 2021) and The University and Polytechnic La Fe Hospital of Valencia (data of approval 18 October 2021). Spanish Law 3/2018 of Data Protection and Guarantee of Digital Rights and corresponding European norms (GDPR) [27] were followed.

Informed Consent Statement:

The exemption from obtaining informed consent was permissible based on the seventeenth additional provision of Spanish Organic Law 3/2018, dated December 5th, which pertains to the protection of personal data and the guarantee of digital rights. This provision legalizes the utilization 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 those individuals responsible for executing the pseudonymization process, as well as safeguarding the information that could potentially facilitate re-identification. Access to pseudonymized data was only permitted for the research team under specific conditions:

i) An explicit commitment to maintain confidentiality and abstain from any re-identification endeavors was established.

ii) Stringent security measures were instituted to forestall re-identification and unauthorized access by third parties.

Data Availability Statement:

The data presented in this study are available in the article and supplementary material.

Conflicts of Interest:

The authors declare no conflict of interest. The funders had 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.

References

1. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analys for the Global Burden of Disease Study 2021. Lancet. 2024:S0140-6736(24)00757-8. doi: 10.1016/S0140-6736(24)00757-8.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W, China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382:727-733. doi: 10.1056/NEJMoa2001017.
3. Daugherty SE, Guo Y, Heath K, Dasmariñas MC, Jubilo KG, Samranvedhya J, Lipsitch M, Cohen K. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study, BMJ. 2021;373:n1098. doi: 10.1136/bmj.n1098.
4. Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, Husain L, Greenhalgh T. Persistent symptoms after Covid-19: qualitative study of 114 “long Covid” patients and draft quality principles for service. BMC Health Services Research. 2020;20(1):1144. doi: 10.1186/s12913-020-06001-y.
5. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis, Sci Rep. 2021;11(1):16144-16144. doi: 10.1101/2021.01.27.21250617.
6. Al-Aly Z, Xie Y, Bowe B, High-dimensional characterization of post-acute sequelae of COVID-19, Nature.2021;594(7862):259-64. doi: 10.1038/s41586-021-03553-9.
7. Ghosn J, Piroth L, Epaulard O, Le Turnier P, Mentré F, Bachelet D, Laouénan C. Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort, Clin Microbiol Infect.2021;27:1041,e1-1041,e4,. doi: 10.1016/j.cmi.2021.03.012.
8. Datta SD, Talwar A, Lee JT. A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications. JAMA. 2020;324:2251-2252. doi: 10.1001/jama.2020.22717.
9. Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, Gibbs KW, Erickson HL, Steingrub JS, Smithline HA, Gong MN, Aboodi MS, Exline MC, Henning DJ, Wilson JG, Khan A, Qadir N, Brown SM, Peltan ID, Rice TW, Hager DN, Ginde AA, Stubblefield WB, Patel MM, Self WH, Feldstein LR; IVY Network Investigators; CDC COVID-19 Response Team; IVY Network Investigators. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. MMWR Morb Mortal Wkly Rep. 2020;69:993-998. doi: 10.15585/mmwr.mm6930e1.

10. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehrawat TS, Ahluwalia N, Bikdeli B, Dietz D, Der-Nigoghossian C, Liyanage-Don N, Rosner GF, Bernstein EJ, Mohan S, Beckley AA, Seres DS, Choueiri TK, Uriel N, Ausiello JC, Accili D, Freedberg DE, Baldwin M, Schwartz A, Brodie D, Garcia CK, Elkind MSV, Connors JM, Bilezikian JP, Landry DW, Wan EY. Post-acute COVID-19 syndrome. Nat Med. 2021;27:601-615. doi: 10.1038/s41591-021-01283-z.
11. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324:603-605. doi: 10.1001/jama.2020.12603.
12. Golzardi M, Hromić-Jahjefendić A, Šutković J, Aydin O, Ünal-Aydın P, Bećirević T, Redwan EM, Rubio-Casillas A, Uversky VN. The Aftermath of COVID-19: Exploring the Long-Term Effects on Organ Systems. Biomedicines. 2024;12:913. doi: 10.3390/biomedicines12040913.
13. Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. Lancet. 2022;399(10343):2263-2264. doi: 10.1016/S0140-6736(22)00941-2.
14. Wise J. Covid-19: Long covid risk is lower with omicron than delta, researchers find. BMJ. 2022;377:o1500. doi: 10.1136/bmj.o1500.
15. Wilson C. Long covid risk with omicron may be half that of delta. New Sci. 2022;254(3392):12. doi: 10.1016/S0262-4079(22)01099-5.
16. Morioka S, Tsuzuki S, Suzuki M, Terada M, Akashi M, Osanai Y, Kuge C, Sanada M, Tanaka K, Maruki T, Takahashi K, Saito S, Hayakawa K, Teruya K, Hojo M, Ohmagari N. Post COVID-19 condition of the Omicron variant of SARS-CoV-2. J Infect Chemother. 2022;28:1546-1551. doi: 10.1016/j.jiac.2022.08.007.
17. Liao X, Guan Y, Liao Q, Ma Z, Zhang L, Dong J, Lai X, Zheng G, Yang S, Wang C, Liao Z, Song S, Yi H, Lu H. Long-term sequelae of different COVID-19 variants: The original strain versus the Omicron variant. Glob Health Med. 2022;4(6):322-326. doi: 10.35772/ghm.2022.01069.
18. Bhandari S, Rankawat G, Joshi S, Tiwaskar M, Lohmror A, Bhandari S. Post-COVID Syndrome: The Stranger Ghost of Culprit COVID-19. J Assoc Physicians India. 2023;71:11-12. doi: 10.5005/japi-11001-0193.
19. Couzin-Frankel J. New Long Covid cases decline with Omicron. Science. 2023;379(6638):1174-1175. doi: 10.1126/science.adh9054.
20. Lokanuwatsatien T, Satdhabudha A, Tangsathapornpong A, Bunjoungmanee P, Sinlapamongkolkul P, Chaiyakulsil C, Sritipsukho P, Tantiyavarong P. Prevalence and associating factors of long COVID in pediatric patients during the Delta and the Omicron variants. Front Pediatr. 2023;11:1127582. doi: 10.3389/fped.2023.1127582.
21. Buonsenso D, Morello R, Mariani F, De Rose C, Mastrantoni L, Zampino G, Valentini P. Risk of long Covid in children infected with

Omicron or pre-Omicron SARS-CoV-2 variants. Acta Paediatr. 2023;112:1284-1286. doi: 10.1111/apa.16764.
22. Chen H, Zhang L, Zhang Y, Chen G, Wang D, Chen X, Wang Z, Wang J, Che X, Horita N, Seki N. Prevalence and clinical features of long COVID from omicron infection in children and adults. J Infect. 2023;86:e97-e99. doi: 10.1016/j.jinf.2023.02.015.
23. Pinto Pereira SM, Nugawela MD, Stephenson T, Foret-Bruno P, Dalrymple E, Xu L, Whittaker E, Heyman I, Ford T, Segal T, Chalder T, Ladhani SN, Mensah AA, McOwat K, Simmons R; CLoCk Consortium; Shafran R. Post-Covid-19 condition (Long Covid) in children and young people 12 months after infection or reinfection with the Omicron variant: a prospective observational study. Sci Rep. 2024;14:9957. doi: 10.1038/s41598-024-60372-4.
24. Noij LCE, Blankestijn JM, Lap CR, van Houten MA, Biesbroek G, der Zee AM, Abdel-Aziz MI, van Goudoever JB, Alsem MW, Brackel CLH, Oostrom KJ, Hashimoto S, Terheggen-Lagro SWJ. Clinical-based phenotypes in children with pediatric post-COVID-19 condition. World J Pediatr. 2024. doi: 10.1007/s12519-024-00805-2.
25. Du M, Ma Y, Deng J, Liu M, Liu J. Comparison of Long COVID-19 Caused by Different SARS-CoV-2 Strains: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2022;19:16010. doi: 10.3390/ijerph192316010.
26. Hernández J, Dehesa-Canseco F, Vázquez-López AB, Reséndiz-Sandoval M, Caire-Juvera G, Solís-Hernández M, Valenzuela O, Gómez-Gil B, Mata-Haro V. Neutralization of Omicron BA.1, BA.5.1.6, BQ.1.3 and XBB1.1 induced by heterologous vaccination Ad5-nCoV and mRNA-1273. Signal Transduct Target Ther. 2023;8:174. doi: 10.1038/s41392-023-01447-y.
27. Luo J, Zhang J, Tang HT, Wong HK, Lyu A, Cheung CH, Bian Z. Prevalence and risk factors of long COVID 6-12 months after infection with the Omicron variant among nonhospitalized patients in Hong Kong. J Med Virol. 2023;95:e28862. doi: 10.1002/jmv.28862.
28. AlBahrani S, AlBarrak A, AlGubaisi N, Alkurdi H, Alburaiki D, AlGhamdi A, AlOthaiqy M, Tayeb S, Tayeb N, Abdraboh S, Khairi A, Alshareef L, AlHarbi A, AlRabeeah S, Alqahtani AS, Alqahtani JS, Hakami FH, Al-Maqati TN, Alkhrashi SA, Almershad MM, AlAbbadi A, Hakami MH, Faqihi O, Altawfiq KJA, Jebakumar AZ, Al-Tawfiq JA. Self-reported long COVID-19 symptoms are rare among vaccinated healthcare workers. J Infect Public Health. 2023;16:1276-1280. doi: 10.1016/j.jiph.2023.05.037.
29. Brannock MD, Chew RF, Preiss AJ, Hadley EC, Redfield S, McMurry JA, Leese PJ, Girvin AT, Crosskey M, Zhou AG, Moffitt RA, Funk MJ, Pfaff ER, Haendel MA, Chute CG; N3C; RECOVER Consortia. Long COVID risk and pre-COVID vaccination in an EHR-based cohort study from the RECOVER program. Nat Commun. 2023;14(1):2914. doi: 10.1038/s41467-023-38388-7.
30. The EU General Data Protection Regulation GDPR. Available online: https://gdpr-info.eu/
31. Valdivieso-Martínez B, Sauri I, Philibert J, Calderon JM, Gas ME, Diaz J, López-Hontangas JL, Navarro D, Forner MJ, Redon J. Impact of Long-

COVID on Health Care Burden: A Case-Control Study. J Clin Med. 2023,12:5768. https://doi.org/10.3390/jcm12185768.
32. Hedberg P, Nauclér P. Post-COVID-19 Condition After SARS-CoV-2 Infections During the Omicron Surge vs the Delta, Alpha, and Wild Type Periods in Stockholm, Sweden. J Infect Dis. 2024;229:133-136. doi: 10.1093/infdis/jiad382.
33. Magnusson K, Kristoffersen DT, Dell'Isola A, Kiadaliri A, Turkiewicz A, Runhaar J, Bierma-Zeinstra S, Englund M, Magnus PM, Kinge JM. Post-covid medical complaints following infection with SARS-CoV-2 Omicron vs Delta variants. Nat Commun. 2022;13:7363. doi: 10.1038/s41467-022-35240-2.
34. Hedberg P, Granath F, Bruchfeld J, Askling J, Sjöholm D, Fored M, Färnert A, Naucler P. Post COVID-19 condition diagnosis: A population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection. J Intern Med. 2023;293:246-258. doi: 10.1111/joim.13584.
35. Diexer S, Klee B, Gottschick C, Xu C, Broda A, Purschke O, Binder M, Frese T, Girndt M, Hoell JI, Moor I, Gekle M, Mikolajczyk R. Association between virus variants, vaccination, previous infections, and post-COVID-19 risk. Int J Infect Dis. 2023;136:14-21. doi: 10.1016/j.ijid.2023.08.019.
36. Hammel IS, Tosi DM, Tang F, Pott H, Ruiz JG. Frailty as a risk factor for post-acute sequelae of COVID-19 among US veterans during the Delta and Omicron waves. J Am Geriatr Soc. 2023;71:3826-3835. doi: 10.1111/jgs.18584.
37. Izquierdo-Pujol J, Moron-Lopez S, Dalmau J, Gonzalez-Aumatell A, Carreras-Abad C, Mendez M, Rodrigo C, Martinez-Picado J. Post COVID-19 Condition in Children and Youths: An Emerging Problem. Front Pediatr. 2022;10:894204. doi: 10.3389/fped.2022.894204.
38. Warren-Gash C, Lacey A, Cook S, Stocker D, Toon S, Lelii F, Ford B, Ireland G, Ladhani SN, Stephenson T, Nguipdop-Djomo P, Mangtani P; COVID-19 Schools Infection Survey 2 Study Group. Post-COVID-19 condition and persisting symptoms in English schoolchildren: repeated surveys to March 2022. BMC Infect Dis. 2023;23:201. doi: 10.1186/s12879-023-08203-1.
39. Yildirim Arslan S, Avcu G, Sahbudak Bal Z, Arslan A, Ozkinay FF, Kurugol Z. Evaluation of post-COVID symptoms of the SARS-CoV-2 Delta and Omicron variants in children: a prospective study. Eur J Pediatr. 2023;182:4565-4571. doi: 10.1007/s00431-023-05134-6.
40. Leahy J, Bajracharya R, Altonen B, Ferreira-Ortiz M, Silvera L, Astua AJ. Post-discharge Healthcare Usage and Costs From March 2020 Through the Omicron Surge for Individuals Hospitalized With COVID-19. Cureus. 2023 15:e50663. doi: 10.7759/cureus.50663.
41. Buonsenso D, Piazza M, Boner AL, Bellanti JA. Long COVID: A proposed hypothesis-driven model of viral persistence for the pathophysiology of the syndrome. Allergy Asthma Proc. 2022;43:187-193. doi: 10.2500/aap.2022.43.220018.
42. L'Huillier AG, Pagano S, Baggio S, Meyer B, Andrey DO, Nehme M, Guessous I, Eberhardt CS, Huttner A, Posfay-Barbe KM, Yerly S, Siegrist CA, Kaiser L, Vuilleumier N. Autoantibodies against apolipoprotein A-1 after COVID-19 predict symptoms persistence. Eur J Clin Invest. 2022;52:e13818. doi: 10.1111/eci.13818.

27

28

Legend of figures:

Figure 1. Study design.

Figure 2. Correlation of New Diagnoses Between Two Health Care Areas in Study Population Aged >17 and <18 Years Old. *Black line* is the regression line of the number of diagnostics in the two HCDs. *Blue broken line* 95 CI. *Red line* is the reference.

29

Supplementary Files

Untitled.
URL: http://asset.jmir.pub/assets/3f5ef985c3d9e48867d2d720750558f4.docx

Untitled.
URL: http://asset.jmir.pub/assets/45041e0ce829f1553350ccdcff7df0d1.docx

Untitled.
URL: http://asset.jmir.pub/assets/f14e521a2b8725b436fbeb7185c8b17b.pdf

Untitled.
URL: http://asset.jmir.pub/assets/d01b1bdb3017035736ebeff62b6c7aab.docx

Untitled.
URL: http://asset.jmir.pub/assets/8cddcc932e44f9f90be76e98b377cdac.docx

Untitled.
URL: http://asset.jmir.pub/assets/f05751f4125e6fb3be6d78dce263f4af.docx

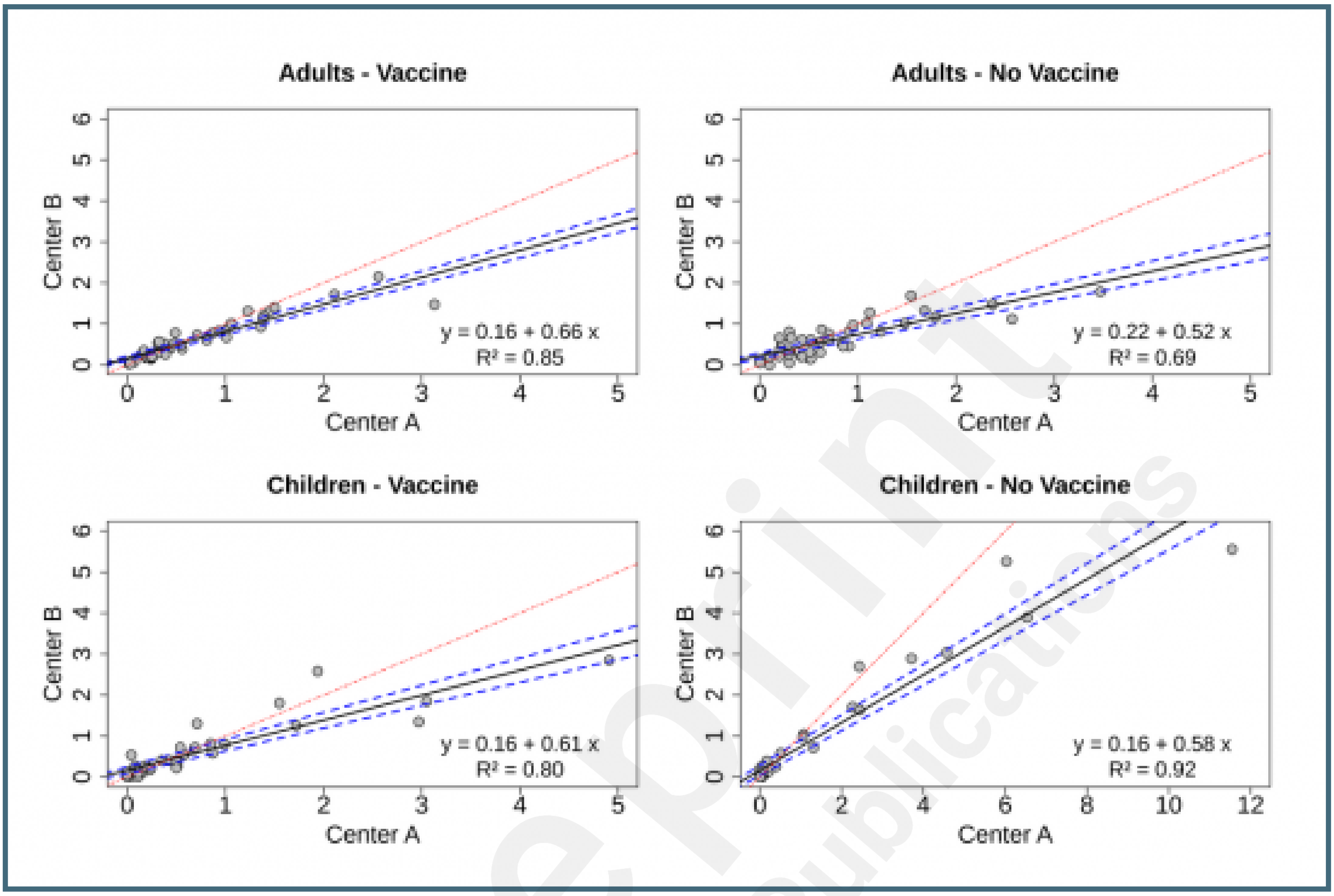
Untitled.
URL: http://asset.jmir.pub/assets/59a5aed178818435b74cb1a3ed20ff15.docx

Untitled.
URL: http://asset.jmir.pub/assets/ff164037f814a502ae5566e278cda61c.docx

Supplementary file.
URL: http://asset.jmir.pub/assets/3a3b5e9f23279aa3a4c036440c809bc9.docx

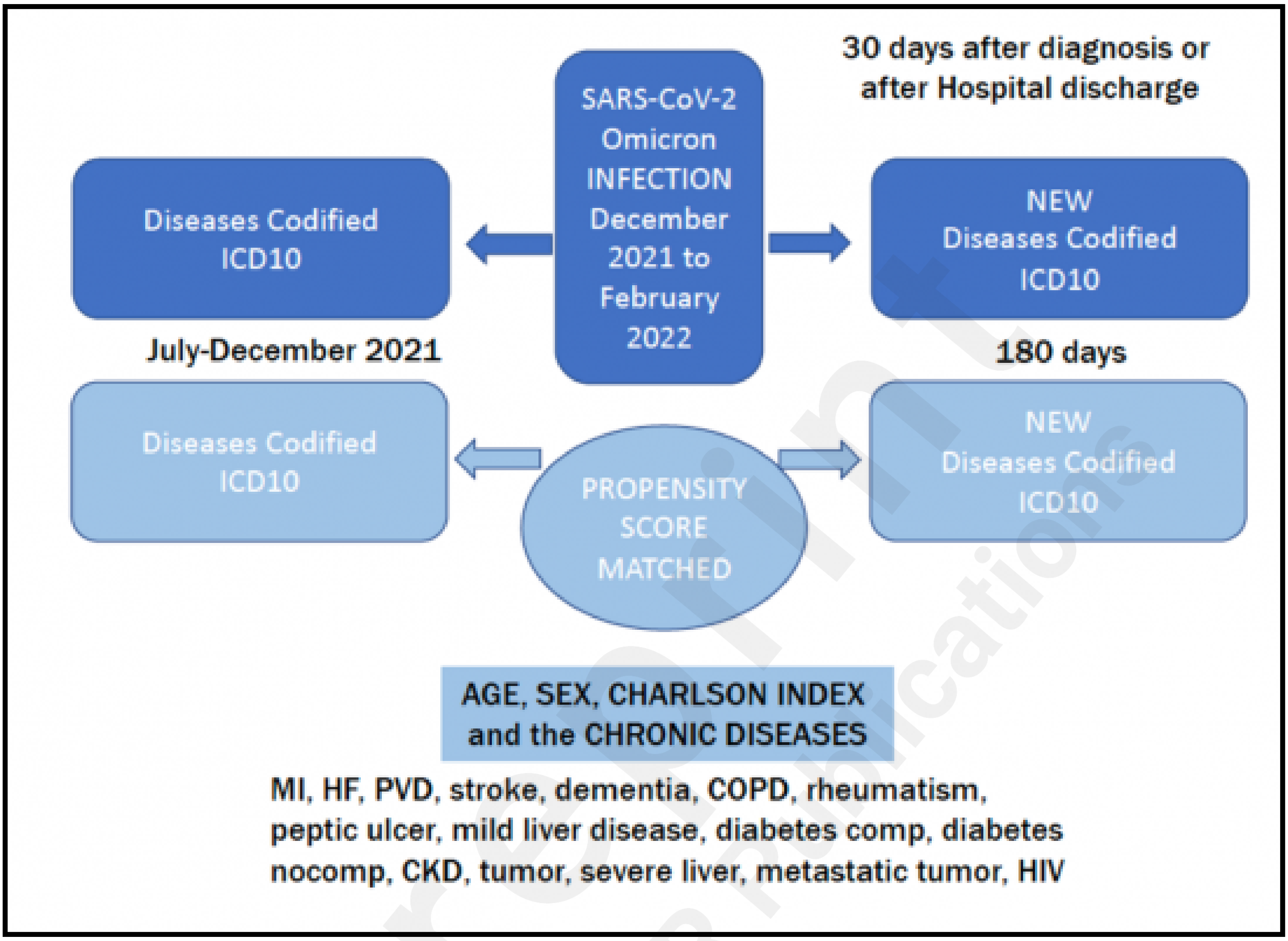
Untitled.
URL: http://asset.jmir.pub/assets/41072e073be69aceaf47da6cf4f15613.docx

Figures



Adults - Vaccine
Center B
Center A
y = 0.16 + 0.66 x
R² = 0.85
Adults - No Vaccine
Center B
Center A
y = 0.22 + 0.52 x
R² = 0.69
Children - Vaccine
Center B
Center A
y = 0.16 + 0.61 x
R² = 0.80
Children - No Vaccine
Center B
Center A
y = 0.16 + 0.58 x
R² = 0.92

Study design.



Related publication(s) - for reviewers eyes onlies

Untitled.

URL: http://asset.jmir.pub/assets/47e2f446059499fe37e38a39f4908395.pdf

Untitled.

URL: http://asset.jmir.pub/assets/47452385c7c66471ea597abcbc59611c.pdf

File with tracker changes.

URL: http://asset.jmir.pub/assets/36831bd6339bf2509abf2de75284c249.pdf

Untitled.

URL: http://asset.jmir.pub/assets/a380d376aed6b8f7a192f402835a913e.pdf

File with tracked changes.

URL: http://asset.jmir.pub/assets/a8fa3794b9596941f8e08333d1704c06.pdf

Untitled.

URL: http://asset.jmir.pub/assets/3872870d3609d8b1441af3a077410745.pdf