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Protective role of vaccination on the development of long COVID: data from a large, multicenter, prospective cohort study

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Abstract

Background Long COVID, a highly heterogeneous syndrome affecting millions of people worldwide, is emerging as an urgent public health threat, but data on the predictors of specific clinical manifestations over long follow-up periods are limited. The aim of this study is to investigate the role of viral variants and other predictors in long COVID incidence and clinical manifestations.

Methods All COVID-19 patients aged > 18 years and hospitalized from March 1 2020 to April 2022 in two Italian University Hospitals were enrolled. Incidence and clinical presentation of long COVID were assessed through structured questionnaires delivered by phone calls. The association between possible risk factors collected during hospitalization and long COVID was reported using an adjusted logistic regression and reported as odds ratios (ORs) with their 95% confidence intervals (CIs).

Results Among 1,012 recruited patients, over a median follow-up of 19 months (IQR: 15–24 months), the cumulative incidence of long COVID was 91.7%, with the most common clinical manifestations involving the respiratory system (80.5%) and the neurological system (77.3%). Among 1,012 recruited patients, over a median follow-up of 19 months (IQR: 15–24 months), the cumulative incidence of long COVID was 91.7%, with the most common clinical manifestations involving the respiratory system (80.5%) and the neurological system (77.3%). Overall, 54% reported long COVID symptomatology between 18 and 24 months. Multivariate analysis suggested that being vaccinated against SARS-CoV-2 was associated with reduced odds of reporting any long COVID symptomatology (OR: 0.34; 95% CI: 0.21–0.58), while infection with the Delta variant was a strong predictor (OR: 9.61, $p < 0.0001$) for the development of post-COVID conditions characterized by neuropsychiatric symptoms.

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Conclusions In this study long COVID symptoms were still highly prevalent after 18–24 months of follow-up and, when compared to wild-type virus, infection with the Delta variant was associated with a higher risk of developing a neurological post-COVID condition.

Keywords Long COVID, Post-acute sequelae of COVID-19, COVID-19 vaccination, Delta variant, Omicron variant

Background

Long COVID, also referred to as " post-acute sequelae of COVID-19", is an emerging global health problem affecting at least 65 million people worldwide [1]. Since its first description, this highly heterogeneous syndrome comprised a wide variety of symptoms, ranging from nasal congestion, abdominal pain, chronic fatigue and long-term cognitive impairment [2].

The principal demographic and clinical characteristics predictors of long COVID in Italy, as established by other studies [3], include the absence of vaccination against COVID-19, infection with pre-Omicron strains, severe COVID-19 disease, and invasive mechanical ventilation. Furthermore, both vaccinated and non-vaccinated persons are at an elevated long-term risk of experiencing acute cardiovascular, thrombotic, and cerebrovascular events [4], as well as new-onset diabetes mellitus [5] and dysautonomia following SARS-CoV2 infection [6]. Key predictors of long COVID in Italy, as determined by previous studies, include the absence of the COVID-19 vaccine, infection with pre-Omicron variants, severe COVID-19 illness, and the use of invasive mechanical ventilation.

The Italian evidence appears to be in accordance with observations in other countries that have experienced an overburdened healthcare system, resulting in subsequent high mortality rates. In an earlier study, Antonelli et al. [7] observed a group of approximately 56,000 adult individuals from the United Kingdom who were diagnosed with SARS-CoV-2 infection between December 2021 and March 2022. They determined that the risk of developing long COVID was consistently lower in patients with SARS-CoV-2 Omicron infection than those infected with the Delta variant. Overall, the risk of long COVID in Omicron cases was significantly lower compared to Delta cases. Specifically, among individuals who were vaccinated over 6 months prior to the infection, the risk was reduced by 74%. For those vaccinated between 3 and 6 months before the infection, the risk decreased by 76%. Lastly, for those who were vaccinated less than 3 months before the infection, the risk was reduced by 50% [7].

Given the almost 700 million COVID-19 cases reported globally [8] – a number that is likely to be grossly underestimated [9, 10] – the socio-economic cost of this condition due to workforce losses is estimated to be substantial [11].

From a pathophysiological standpoint, several mechanisms have been proposed, including the presence of viral reservoirs in several tissues, T-cell exhaustion and prolonged pro-inflammatory dysfunction [1], induced production of auto-antibodies (comprising ACE2 auto-antibodies) [12], reactivation of viruses belonging to the family of *Herpesviridae* (namely EBV and HHV6) [13] and development of persistent fibrinaloid microclots into microcirculatory vessels [14]. However, despite these findings, no approved etiologic treatment for this condition is currently available on the market [15], and the few studies that reported some benefit on symptom control were burdened by severe limitations and thus not generalizable to the overall population [16].

In October 2021, the World Health Organization (WHO) provided a consensus definition of long COVID as a condition lasting at least two months in individuals diagnosed with confirmed or presumptive acute SARS-CoV-2 infection three months before [17]. However, incidence estimates are still highly heterogeneous, ranging from 10 to 12% in vaccinated individuals [18], 10–30% in non-hospitalized cases and up to 70% in hospitalized cases [19], and duration of long COVID-related symptoms after one year from infection is still unclear, but true incidence might have been masked by the adoption of a highly variable set of long COVID definitions, different from the one used in this article and endorsed by the WHO.

Possible risk factors for long COVID incidence are old age, female sex, low socio-economic condition, and prior comorbidities [2, 20, 21], but little or no information is available on the role demographics of specific symptom clusters. Likewise, available data on the incidence of long COVID according to viral variants indicate an increased risk of developing long COVID after infection with the Delta variant compared to the Omicron variant [7, 22]. However, analysis of the incidence of specific clusters of symptoms is not available yet. Given this background, the aim of this prospective cohort study is to investigate the incidence of long COVID, as long as to report the risk of manifesting neurological, respiratory, cardiovascular, dermatological, and gastrointestinal symptoms according to several covariates including demographics, SARS-CoV-2 variants and vaccination status.

Materials and methods

Study population

All patients aged > 18 years and hospitalized in Internal Medicine or Geriatrics Wards from March 1 2020, to April 2022 in the University Hospital (Policlinico) 'P.

Giaccone' in Palermo, Sicily, and in University Hospital of Bari, Apulia, Italy, with a diagnosis of SARS-CoV-2 infection confirmed by the investigation of SARS-CoV-2 nucleic acid on nasopharyngeal swab by means of RT-PCR were enrolled in this study [23]. Five doctors conducted telephone interviews and related data collection between April 2021 and June 2022 after training conducted by the methodology supervisors.

In accordance with the WHO definition of long Covid [17], follow-up was conducted over a period ranging from at least 3 months to, in some cases, up to 24 months from SARS-CoV-2 infection.

No other inclusion criteria are proposed to represent real-life hospitalized people better. The prospective cohort study was approved by the Local Ethical Committee during the session on April 28, 2021 (number 04/2021).

Exposure: risk factors for long COVID

Based on the previous literature on the possible risk factors for long COVID, we included in our analyses: gender (males vs. females), age (categorized in more or less than 65 years), nationality (Italian vs. others), asymptomatic at hospital admission, vaccination against COVID-19 (categorized as yes vs. no), intensive care unit (ICU) admission, SARS-CoV-2 variants (wild type, Omicron variant, Delta variant, Alpha variant). Variants were assessed according to region-specific public epidemiological data [24] and, when available, according to Nucleic acid amplification tests based on reverse transcriptase PCR (RT-PCR) on four molecular targets: Sabercovirus gene E, and SARS-CoV-2 genes P, N and S [25]. The details regarding variants were collected using epidemiological data in Bari and microbiological data in Palermo. Therefore, we had 814 patients whose variants were ascertained using epidemiological information and 198 using microbiological information. All information was collected in the patients' medical records included in the analysis. The variants were ascertained based on the epidemiological and microbiological information available in each center.

Outcomes: long COVID

The incidence of long COVID-19 symptomatology was considered as the primary outcome. We investigated signs or symptoms of long COVID based on some recent systematic reviews [20, 21, 26, 27], i.e., neurological, respiratory, mobility impairment, heart, digestive, skin, or general signs and symptoms. All the questions were posed as yes/no questions by phone. Psychiatric conditions were investigated using the Post-traumatic Stress Disorder Checklist-5 (PCL) for PTSD (post-traumatic stress disorder) [28] and the Hospital Anxiety and Depression Scale (HADS) for detecting anxiety and depression [29], while Voice Handicap Index-10 (VHI-10) was used for voice disorders. All the questions were made via phone calls. In addition to the evaluation provided by the PTSD and/or HADS score, a further evaluation was assessed by a clinician for each participant's data.

The timing of symptom onset was determined using medical history records, and the presence of symptoms from the beginning of infection for a minimum of 3 months was confirmed.

Statistical analyses

All patient records and information were anonymized and de-identified prior to the analysis. The data of the two centers (Bari and Palermo) were homogenized before the analyses. Data on continuous variables were normally distributed according to the Kolmogorov-Smirnov test and then reported as means and standard deviation values (SD) for quantitative measures and percentages for the categorical variables. In the case of non-normal distribution, the data were reported as median with IQR (interquartile) range. Levene's test was used to test the homoscedasticity of variances and, if its assumption was violated, Welch's ANOVA was used.

The association between possible risk factors collected during hospitalization and long COVID was reported using an adjusted logistic regression and reported as odds ratios (ORs) with their 95%CI. Collinearity among factors was analyzed using the variance inflation factor (VIF) of two as the reason of exclusion, but no one of the factors was excluded for this reason. The hierarchical method Ward was performed for cluster analysis which aims to minimize the main variation within groups based on Euclidean distances. The distance of 3 was used as a cut-off for the dendrogram.

All analyses were performed using the SPSS 26.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p-value <0.05.

Results

Among the 1367 patients initially included between the two centers, we excluded 355 patients since they died during the follow-up or since they did not answer the phone calls, finally leaving 1012 people.

The 1012 patients aged a mean of 61.3 ± 17.6 years (range: 18–99), mainly males (55.6%). About half of the patients were vaccinated against COVID-19 (49.2%), mainly with one dose (26.9%). The patients admitted were symptomatic for COVID-19 in 21.4% of the cases and 61 (6.0%) were admitted to the ICU. Overall, 39.7% of the patients were infected by the wild-type variant and 31.4% by the alpha variant.

Over a median of 19 (IQR: 15–24) months, practically all the patients developed a long COVID symptomatology (929 cases, 91.7%). The 83 people who did not report

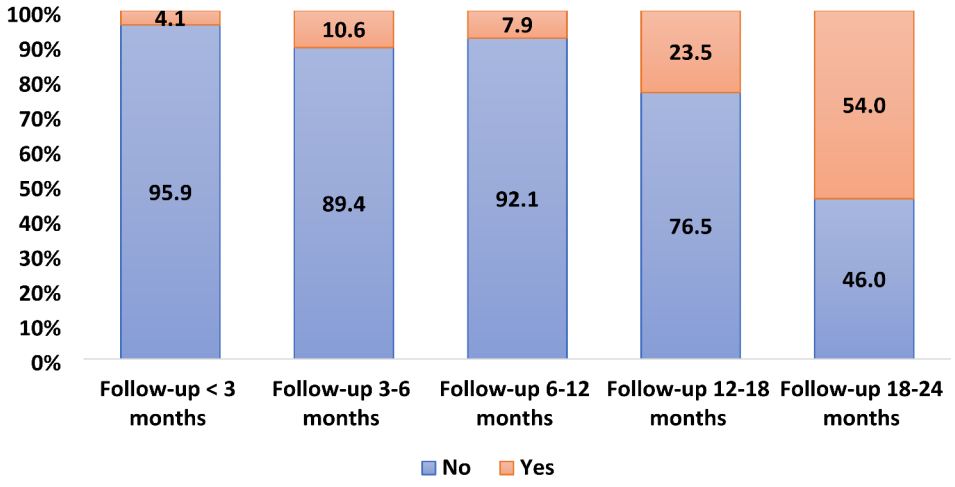

Fig. 1 Prevalence of long COVID symptomatology, by follow-up periods

Table 1 Factors associated with long COVID symptoms

Type of long COVID symptoms	Number of cases	Male sex	Age ≥ 65 years	Italian nationality	Asymptomatic at admission	Vaccination against COVID-19	ICU admission	Omicron variant	Delta variant	Alpha variant
Any	929	1.46 (0.88–2.42)	0.87 (0.52–1.44)	0.40 (0.07–2.17)	1.64 (0.62–4.37)	0.34 (0.21–0.58)***	3.68 (0.49–27.71)	33.88 (0.10-327.10)	3.06 (1.85–33.9)**	1.61 (0.92–2.81)
Neurological	718	1.19 (0.89–1.60)	0.74 (0.55–0.99)*	0.86 (0.44–1.67)	1.40 (0.81–2.42)	1.25 (0.89–1.76)	0.98 (0.55–1.77)	3.38 (1.22–9.39)*	9.61 (3.61–25.61)***	1.13 (0.79–1.60)
Respiratory	748	1.14 (0.84–1.54)	1.00 (0.74–1.36)	0.33 (0.16–0.69)**	1.37 (0.79–2.39)	0.59 (0.42–0.84)**	1.07 (0.57–2.03)	2.08 (0.79–5.54)	2.16 (0.94–4.50)	1.09 (0.75–1.57)
General	515	1.29 (1.00-1.67)*	1.18 (0.91–1.54)	0.65 (0.39–1.10)	0.85 (0.53–1.34)	0.86 (0.63–1.16)	1.41 (0.81–2.44)	1.51 (0.70–3.27)	1.27 (0.68–2.39)	1.56 (1.12–2.17)**
Cardiac	322	1.02 (0.77–1.34)	0.92 (0.69–1.22)	1.09 (0.62–1.89)	1.27 (0-79-2.05)	0.96 (0.69–1.33)	1.06 (0.60–1.33)	1.36 (0.60–3.07)	1.39 (0.71–2.71)	1.37 (0.97–1.95)
Digestive	162	1.64 (1.13–2.37)**	0.89 (0.62–1.29)	0.79 (0.38–1.61)	0.80 (0.41–1.58)	1.43 (0.95–2.16)	1.20 (0.58–2.47)	0.26 (0.08–0.86)*	0.39 (0.15–0.98)*	0.94 (0.61–1.47)
Dermatological	104	0.92 (0.60–1.41)	0.96 (0.62–1.49)	1.27 (0.51–3.20)	1.03 (0.49–2.20)	0.77 (0.47–1.27)	1.40 (0.61–2.24)	0.55 (0.14–2.15)	0.57 (0.19–1.72)	0.40 (0.23–0.70)**
Psychiatric	355	0.96 (0.72–1.28)	0.71 (0.53–0.95)*	1.90 (1.02–3.53)*	0.81 (0.48–1.34)	1.36 (0.97–1.90)	1.04 (0.57–1.92)	1.42 (0.62–3.28)	3.13 (1.54–6.34)**	0.47 (0.33–0.68)***

All the data reported in the cells were odds ratios with their 95% confidence intervals, as result of a multivariable logistic binary regression analysis that included all the factors reported in the Table and time of follow-up, as covariate. *: p-value < 0.05; **: p-value < 0.001; ***: p-value < 0.0001

long COVID were mainly females (51.8%), younger than 65 years (53.0%), Italian (97.6%), and vaccinated against SARS-COV-2 (56.6%). Figure 1 shows the distribution of long COVID by follow-up periods. Among the cases having long COVID, only 4.1% had long COVID during the first three months of the follow-up, whilst more than half (54%) reported long COVID symptomatology between 18 and 24 months. As shown in Table 1, respiratory symptomatology was the most frequent, followed by neurological conditions, followed by dermatological ones. Among the clusters identified in the dendrogram (Fig. 2), the only one with statistical significance was the association between mobility impairment with sore throat, while the others were not aggregated. The cumulative incidence of specific symptoms, stratified per duration of the follow-up period, is provided in Supplemental Table 1.

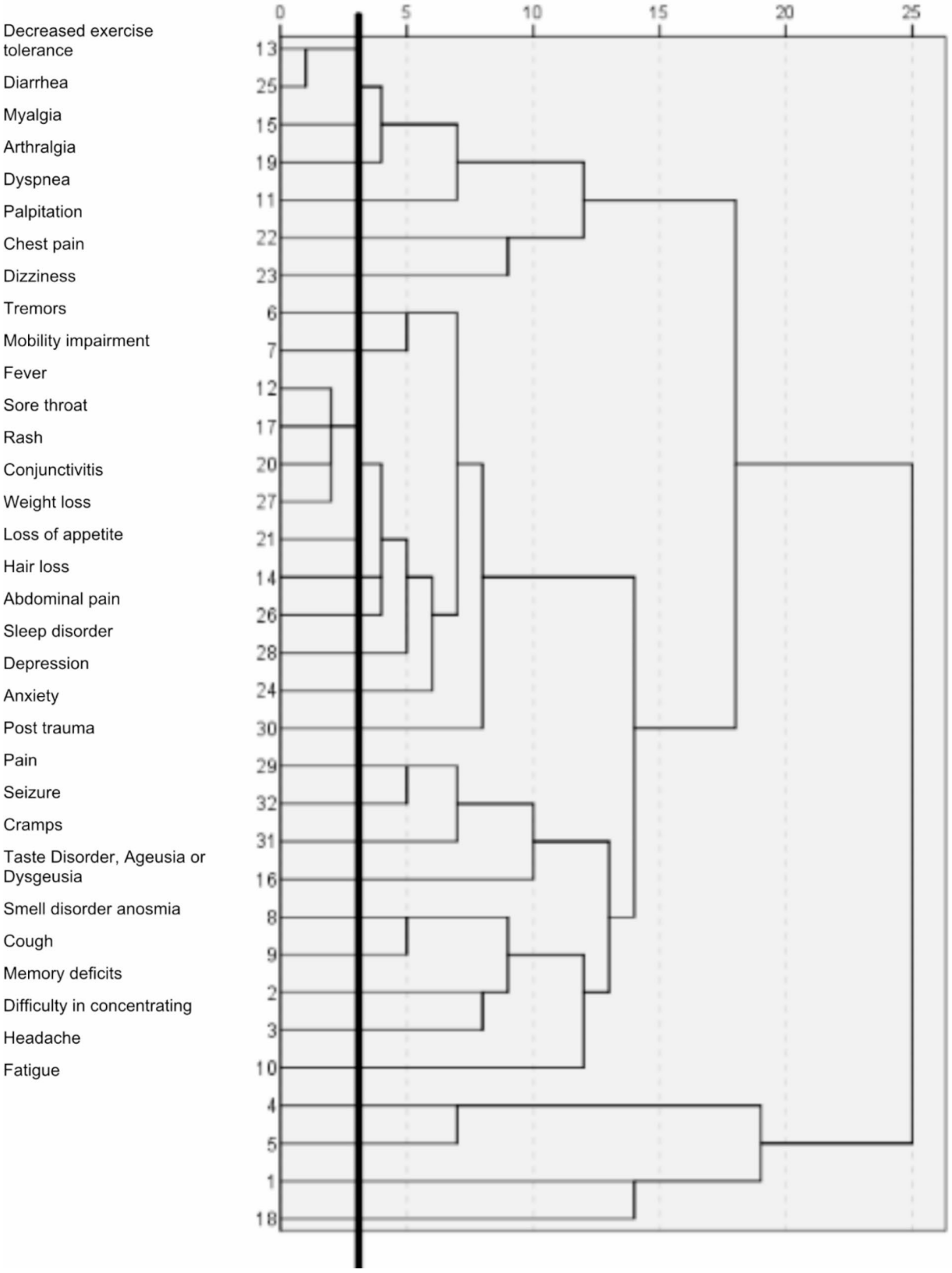

Fig. 2 Single linkage dendrogram for long COVID signs and symptoms. Values on the vertical axis are points from the initial data set. Black nodes and numbers on the dendrogram tree represent the internal nodes formed by the linkage algorithm. Values on the horizontal axis are the distances between combined objects

Table 1 reports the factors associated with long COVID symptoms. Taking into consideration the presence of any long COVID symptomatology, vaccination against COVID-19 significantly decreased this risk (OR=0.34; 95%CI: 0.21–0.58, $p<0.0001$), while, compared to the wild type variant, the delta variant increased the risk of long COVID of more than 3 times (OR=3.06; 95%CI: 1.85–33.9; $p=0.003$). Considering neurological signs and symptoms, the presence of these conditions was lower in older people, while omicron and delta variants substantially increased 3 and 10 times the risk of neurological issues during the follow-up time. The vaccination against COVID-19 substantially decreased the risk of respiratory conditions (OR=0.59; 95%CI: 0.42–0.84; $p=0.002$), whilst the male sex and the Alpha variant were associated with a higher presence of general long COVID signs/symptoms (Table 1). Digestive issues were more present in males and less present in patients previously affected by omicron and delta variants, whilst the Alpha variant was associated with a significantly lower risk of dermatological and psychiatric conditions. Additionally, individuals who were previously impacted by the Omicron variant exhibit a higher prevalence of neurological symptoms, whereas general symptoms are more prevalent in those affected by the Alpha variant. Italian nationality was found to be significant as a predictor of psychiatric long COVID symptoms. (Table 1).

Discussion

In this study, over an active follow-up period ranging from 3 to 24 months, we found the incidence density of signs and symptoms suggestive of long COVID of 91.7%, with clinical manifestations involving most commonly the respiratory and neurological systems. Incidence density among hospitalized patients was substantially higher than the one found by two recent meta-analyses [16, 20], which reported a pooled incidence of any post-COVID of 54% and 51%. However, consistent with our study, the most commonly reported complaints were respiratory and neurological symptoms. Likewise, the proportion of patients lamenting fatigue was higher than the one reported in a meta-analysis conducted by Ceban et al. that analyzed studies published as of June 2021 [30]. (36%).

Data collection for this study concluded in June 2022. Consequently, the higher prevalence of fatigue observed in our sample could be attributed to the longer duration of the development of long COVID symptoms. Additionally, the increased prevalence may be influenced by the effect of newer variants, which were more prevalent during the period of our observation compared to previous studies.

Interestingly, however, the median follow-up period reported in the abovementioned meta-analysis was lower (6- and 2.8-months vs. 19 of our study) and, in our study, the highest proportion of patients reporting any post-COVID condition peaked when follow-up calls were conducted after 18–24 months (Fig. 1). However, it should be noted that follow-up calls were distributed over a long period of time and not repeated and, therefore, rather than assuming that long COVID incidence increases over time, this finding might indicate that some complaints are more likely to be reported after some months after acute infection.

Contrary to other cohort studies [31, 32], being female was not associated with significantly increased odds of developing long COVID, but, conversely, the male sex predicted the manifestation of long-COVID-related constitutional and gastrointestinal symptoms. Similarly, in this study, having more than 65 years of age at the time of acute SARS-CoV-2 infection was not a predictor of long COVID but, in contrast with other studies [2, 21, 30], was found to be protective for manifesting neuro-psychiatric symptoms at multivariable logistic regression analysis. However, it should be noted that no association was found between sex or age and incidence density of any post-COVID condition and, as discussed, the unexpectedly high proportion of patients reporting long COVID symptoms at 18–24 months of follow may have played a role in influencing the results.

Consistently with a large cohort study [18] and a systematic review [33], being vaccinated at the time of acute infection was strongly associated with reduced odds of reporting any symptom at least 3 months after being hospitalized for COVID-19. Importantly, to our knowledge, this is the first study evaluating the role of vaccination on long COVID incidence in hospitalized patients up to two years after acute infection and controlling for several covariates, including age, sex, and viral variants. More in detail, our analysis found that vaccination conferred a 66% and 41% reduction of reporting, respectively, any symptom and any respiratory symptom characteristic of long COVID. This finding supports the idea that the benefits of vaccination are not limited to the prevention of symptomatic infection and progression towards severe disease [34] but extend beyond breakthrough infection and possibly last for a prolonged period of time. Mechanisms underlying this post-acute risk reduction are not yet understood, but, since the incidence of long COVID appears to be influenced by the severity of acute infection [1], it may be a consequence of the fact that vaccinated individuals may have experienced a more favorable clinical course during hospitalization.

In our population, the proportion of vaccinated individuals is relatively low. The administration of dosages has luckily increased. The current vaccination rate in Italy, as reported by the WHO [35], is as follows: 50,581,311 individuals have received at least one dose of

the vaccine. In comparison, 49,484,582 individuals have received a complete primary series [3].

From the prevention perspective, this demonstrates the necessity of implementing an effective and enduring vaccination campaign. Another peculiar finding of this study is that cumulative incidence and clinical presentation of long COVID was influenced by viral variants. Compared to the wild-type, the Delta variant was strongly associated with markedly increased odds of complaining neuro-psychiatric symptoms and any post-COVID condition. This is relevant since the Delta variant was associated with increased disease severity [36], but the association found here was controlled, among other factors, also for ICU admission, age, and for being asymptomatic at diagnosis (a circumstance that is common in the case of nosocomial transmission). A similar association was found between the Omicron variant and neurological symptoms but with weaker strength of association. These findings may be influenced by the fact that odds ratios were calculated in comparison to the wild-type variant, widely prevalent in Italy during the first year of the pandemic (up to December 2020 [35]) and, therefore, at the time of follow-up calls, some long COVID symptoms may have resolved. Nevertheless, ' 'it's worth noting that both the strength of the association and involvement of neurological symptoms, which are expected to be lifelong [1], suggest that the Delta variant may have played a role in increasing the risk of developing neuro-psychiatric post-COVID conditions.

Several studies conducted in Northern Italy, the part of the country which experienced during the first waves of the pandemic the greatest incidences of the spread of viruses and the highest mortality rate, investigated the impact of long COVID on mental health, implying a significant correlation between Italian nationality and long COVID-related psychiatric symptoms [37].

A study by Cecchetti et al. attests to a wide range of persistent psychiatric disturbances, including post-traumatic stress disorder (PTSD), depression, and anxiety in patients hospitalized for COVID-19 [38].

Mental health sequelae may be relevant and long-lasting for COVID-19 survivors, as shown by Gramaglia et al. also in the pediatric population, particularly when specific risk factors are prevalent [39].

In a meta-analysis by Di Gennaro et al. [2]. the prevalence of psychiatric conditions was 20.3% among the 65,156 individuals in 117 cohorts. The incidence of all four signs and symptoms included in this cluster (post-traumatic stress disorder (PTSD), depression, sleep disorder, anxiety) had an incidence of over 10%.

In addition, it is necessary to evaluate, the fact that the risk was inferred in comparison to infection from wild-type virus, which circulated on a completely unvaccinated population, supports the assumption that infection from the Delta variant, and possibly also from the Omicron variant, pose a true risk for developing neurological long COVID symptoms. In this regard, a subject of debate is the mechanism behind the decrease in vaccine effectiveness observed during large-scale vaccination campaigns against the Delta variant. This reduction may be attributed to the virus's ability to escape the immune system more effectively due to an extra viral mutation at position 417 in the receptor-binding domain (RBD) region [40]. Future studies should further explore the role of variants in shaping the risk of long COVID clinical presentation and investigate potential underlying mechanisms that may explain this association.

This study has several strengths. On the one hand, the presence of any long COVID-related symptomatology was with an active, operator-initiated contact to all COVID patients admitted in the two study centers. On the other hand, in line with the Newcastle-Ottawa Risk of bias assessment for cohort studies [41], the population was truly representative, data of exposed and non-exposed individuals were drawn from the same cohort, exposure was assessed through secured medical records, and outcomes were assessed after a long enough follow-up period and controlled for multiple covariates. To our knowledge, this is also the first study exploring predictors of specific long COVID symptoms after up to two years of follow-up.

Some limitations should be acknowledged. First, follow-up visits were performed once and not repeated after pre-defined periods, thus not allowing us to infer the dynamics of the onset and potential resolution of long COVID symptomatologic clusters. Second, variants were identified using both molecular methods and aggregated epidemiological data. However, even when only epidemiological data was used, it should be noted that, in Italy, a variant replacement has always occurred in a short time after the new variant identification, which was usually less than one month [42], and this approach was consistent with the one used by other studies [43] and by major national databases [22] Third, outcome data were self-reported and collected by phone calls, and no clinical examination was performed to confirm the diagnosis. Fourth, the study design did not include controlling for non-infected patients. In interpreting the results of our analysis, it is crucial to acknowledge a notable limitation related to the confirmation of variants. Only 24% (198 out of 814) of the identified variants were confirmed through PCR. Regrettably, there is no access to data pertaining to precise specifics of participants' vaccination schemes, such as the brand of the vaccine, the number of doses administered, and the availability of booster doses. Unfortunately, it was not possible to incorporate the data detailing the differences between the two centers and the potential impact of these discrepancies on the study's

outcomes. These implementations could enhance the relevance of future studies and potentially guide directions for further research.

With a view to the future perspective, there is absolutely a need to guarantee the reliance on molecular techniques, such as PCR, for variant validation, which is a well-established standard due to its precision and specificity. Despite these limitations, our computational analysis provides valuable insights and highlights the need for a comprehensive approach that combines computational predictions with experimental validation for a more robust understanding of genetic variation in our study population.Some crucial confounders, such as medical conditions, smoking, alcohol, substance use/abuse, and obesity, were not considered, limiting our results.

Strengths and limitations

- The follow-up is long, investigating symptoms of long COVID until 18–24 months after the infection.
- This study analyses data from a very large sample.
- This study analyzes a broad spectrum of symptoms in two different hospitals in Southern Italy.
- The evaluation of symptoms long COVID-related was performed by phone questionnaire, minimizing the Hawthorne effect of a face-to-face interview. Nonetheless, the use of phone conversations may provide a limitation that could hinder the development of a connection, the precise understanding of facial expressions and body language, as well as the capacity to focus owing to the possible existence of other factors in the participant's environment.
- The analysis of the effects of SARS-CoV-2 reinfections in our population was not feasible, potentially introducing confusion regarding the implications of newer variants.This study mainly focuses on the Italian population, so the findings may not apply to other ethnic groups.
- In a relevant number of interviewers, data on admission to ICU during hospitalization is not known.
- The use of yes/no questions prevents obtaining information about the degree or specific of the studied variables or symptoms.It was not possible to conduct a comparative and descriptive study of the two groups.

Conclusions

In our cohort of hospitalized patients, after a median follow-up period of 19 months, the cumulative incidence of long COVID was unexpectedly high, and its clinical presentation was dominated by neurological and respiratory manifestations.

At the same time, infection with the Delta and Omicron variants was observed in individuals who had received vaccines against SARS-CoV-2. Vaccination was strongly associated with decreased odds of developing any post-COVID condition. In contrast, infection with Delta and Omicron variants was predictive of emergent neurological symptoms.

Further investigation may include the impact of clinical characteristics and pre-existing comorbidities, not only in the acute phase of the infection 444546 but also as predictors of vulnerability to developing Long COVID [47] Additional studies investigating the dynamics of specific long COVID symptoms over time, as well as more evidence exploring the role of viral variants in the incidence of post-COVID conditions predominated by neurological symptoms are urgently needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10226-1.

Supplementary Material 1

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Author contributions

M.C., G.R, G.G., A.L., S.L., L.L., L.T.S., A.I., V.P., G.C., L.C., submitted patients questionnaires by telephone and collected data. N.V. dealt with the statistical analysis. G.G., L.F, F.D.G., F.V.S., N.V.,D.M.,D.F.B.,A.S., wrote the manuscript. F.D.G.F.V.S. and N.V prepared tables and figures.M.L.F.,M.B. A.S. reviewed and edited. All authorshave read and agreed to final version the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the University of Palermo during the session of the 28th of April 2021 (number 04/2021). The study is in accordance with the declaration of Helsinki relevant institutional guidelines. Informed consent was obtained from each participant and/or their legal guardian(s) who received information verbally and read the information letter.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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