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Vaccination and Patient Status of Long COVID-19 Hospitalized Patients: A Cohort Observational Study

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Abstract: Long COVID–19 syndrome is another vicious feature of COVID-19 infection, the mechanism remains unidentified. Several observational studies suggest that vaccinations might have protective and therapeutic effect on long COVID-19 and our study aimed to assess the influence of vaccination on COVID-19 patients. We performed an observational cohort study from October 2020 to July 2022, which included 503 patients (291 males and 212 females) with a median age of 65. They were hospitalized due to COVID-19 pneumonia and had persistent symptoms (after 1 month of COVID-19 infection. The clinical and demographic data including vaccination status collected during hospitalization and regular visits at the Community Healthcare Center dr. Adolf Drolc Maribor were analyzed. More non-vaccinated patients acquired long COVID-19 than vaccinated. Patients with type 2 diabetes suffered from long COVID-19 in a smaller percentage than patients without diabetes. Gender, inhalational therapy due to chronic pulmonary disease and the number of complications have significantly influenced long COVID-19 development and the mostly vaccinated patients were older and with asthma/COPD. Our study confirmed that vaccination is a safe and effective measure to prevent the severe progression of acute disease and to lower the incidence of developing long COVID.

Keywords: long -COVID-19 syndrome; vaccination; comorbidities; COVID-19 pneumonia; observational

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has already caused nearly 7 million deaths worldwide and more than 750 million confirmed cases.   Among those, many experience another vicious feature of coronavirus disease 2019 (COVID-19), long COVID-19 syndrome, characterized by various symptoms, that persist four weeks after the acute symptom onset [1]. The symptoms range from chronic fatigue and dyspnea to cognitive problems.

So far, several risk factors for long COVID have been identified, among them most prevailing are older age [1–4], female gender [3], pre-existing comorbidities, [2,4] mostly diabetes mellitus and obesity. Since 2021, interest in the effect of COVID-19 vaccination has been growing, as reflected by more than 550 papers indexed in the Scopus bibliographic database. COVID-19 vaccines could act at three levels: (1) to prevent infection, (2) to reduce the severity of the disease, and (3) to benefit people

who already have long COVID-19. Recent work based on observational studies reports conflicting results or has methodological flaws that prevent firm conclusions about the effect of vaccination on long COVID-19   [5–7].   Those observational studies suggest that vaccination might have protective and therapeutic effects on long COVID-19. Watanabe et all [8] performed a meta-analysis of 12 observational studies involving vaccinated (before and after infection) and unvaccinated patients and report that vaccination before infection was associated with a lower risk of long COVID, while most of those with ongoing long COVID did not experience symptomatic changes following vaccination.

Even though there is solid evidence that vaccination prevents severe course of disease and there are more and more studies showing that vaccination has positive effect on Long COVID-19 [5], there are still some concerns about COVID-19 vaccines [7,9–11], especially while a new generation of vaccines are being developed [12]. As the COVID-19 vaccines have only been recently introduced worldwide, their acceptance still remains a public health challenge, meaning little is known about their long effects [13,14].

Slovenia has 2.1 million inhabitants and the first COVID-19 patient happened in March 2020. By the end of June 2022, 2.284.078 PCR tests were performed in Slovenia, there were a total of 1.039.298 confirmed cases of COVID-19, 1.023.745 patients who recovered from COVID-19, and a total of 6,651 people died. As of June 30, 2022, a total of 1.265.789 patients were vaccinated [15].

1.1. Study objectives

The aim of our study performed on 503 patients that were hospitalized due to COVID-19 pneumonia was (1) to assess the effect of vaccination on long COVID-19 symptoms (i. e. dyspnea, caught, and fatigue) and complications (2) to analyze the odds of association of various patient status variables on onset of long COVID-19, and (3) determine which demographic and health factors were associated with vaccination status of Slovenian COVID patients. Meaning that we examined patients who experienced the presence of dyspnea, fatigue, caught and chest pain that persisted more than 4 weeks. We then followed all the patients that still had any of above mentioned symptoms for 12 months. After all the symptoms were disappeared the patient was cured

2. Materials and Methods

2.1. Study design and settings

This observational cohort study was conducted at the Community Healthcare Center dr. Adolf Drolc Maribor (HCM), Slovenia, from October 2020 to July 2022.

2.2. Participants and variables

We included patients that have been infected with SARS-CoV-2 and developed COVID -19 pneumonia that required hospitalization due to acute hypoxemic respiratory failure. The exclusion criteria were SARS-CoV-2 infection without pneumonia. All patients were checked by physicians at the HCM within 3-4 weeks after discharge from the hospital. Detailed history was taken at the initial evaluation by the physician that included patients' demographics, comorbidities (hypertension, diabetes mellitus, hyperlipidemia, chronic lung disease, obesity, myopathy, secondary infections, hypothyroidism, chronic kidney diseases, stroke, pulmonary embolism) medications used during pre-hospitalization, vaccination status and hospitalization duration. Vaccination against COVID-19 was carried out in accordance with the National vaccination strategy, starting with health workers, persons aged 70 and over, persons aged 60 and over; chronic patients aged 18 to 59 years, and later the rest of the population. All data regarding hospitalization due to COVID-19 pneumonia were collected from the discharge letter from the hospital. The questionnaire about long COVID-19 symptoms was competed by each patient, we focused on the following long COVID symptoms: dyspnea, chest pain, cough, and fatigue. Included patients were regularly checked by physicians at the HCM every 3 months until Long-COVID-19 symptoms disappeared or for the duration of one year. There were no sources of bias in our study. Inclusion and Exclusion criteria are shwn in Table 1.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patients with SARS-CoV-2 infection which developed COVID -19 pneumonia	Patients with SARS-CoV-2 infection without COVID -19 pneumonia
Hospitalized patients due to acute hypoxemic respiratory failure	Non-hospitalized patients

2.3. Study size

Our sample consisted of 503 participants, among them, there were 291 males and 212 females. The post hoc power calculated with G*Power [13] was 0.891.

2.4. Statistical methods

Frequency analysis and its visualization using bar chart were used to determine the effects of vaccination on COVID-19 symptoms and complications [16]. Logistic regression was employed first to analyze odds of association of various patient status variables (Age, BMI, Gender, stay in ICU, steroids, number of complications and number of comorbidities) on long COVID-19 onset, and second to identify demographic and health status factors (Age, BMI, Gender, Type 2 diabetes, Hypothyroidic, Chronic kidney disease, Asthma/COPB, Hyperlipidaemia and Other comorbidities) were influencing patients vaccination status. They were no missing values, because only participants with complete data were selected to be included in the study. The statistical analysis was performed using SPSS Statistics for Windows (version 28.0; IBM Corp., Armonk, NY).

3. Results

As stated above our sample consisted of 503 patients, among them, there were 291 males and 212 females. All patients were followed through the whole study period. The average age was 65.4 ± 12.1 years, with the youngest patient being 19 years and the oldest 98 years of age. The average BMI was 29.1 ± 5.2. The demographic data according to gender is shown in Table 2.

Table 2. The demographic data according to gender.

	Female	Male
Age	66+/-13 (Min=19, Max=98)	65+/-11 (Min=30, Max=92)
BMI	30.6+/-5.8 (Min=19.4, Max=48.9)	29.4+/-11.5 (Min=18.3, Max=29.4)
Number of co-morbidities	1.31+/-1.01 (Min=0, Max=5)	1.28+/-1.06 (Min=0, Max=6)
Vaccinated	23.6	22.7
Diabetes	17.9	31.6
Chronic kidney disease	4.2	4.1
Asthma/COPD	28.8	22.7
Hyperlipidaemia	11.8	13.4
Hypothyroidism	7.1	2.1

3.1. The effect of vaccination on long COVID-19 symptoms

As shown in Table 3. Long COVID-19 patients had more complications, comorbidities, and symptoms associated with long-term COVID-19 during hospitalization. They were also more frequently admitted to ICU and were more frequently treated with ICS. More non-vaccinated patients acquired long COVID-19 than vaccinated. Interestingly, patients with type 2 diabetes suffered from long COVID-19 in a smaller percentage than patients without diabetes.

Table 3. The differences between vaccinated and nonvaccinated long COVID-19 patients.

	% of Vaccinated patients	% of Non-vaccinated
UCI	15.2	16.7
ICS	23.9	43.1
Stroke	0.3	0
Embolism	7.6	4.9
Thrombosis	1.1	0
Myopathy	24.2	20.6
Secondary infection	13.5	15.7
Vaccination	25.6	21.6
Hypertrichosis	4.8	2.9
Chronic kidney disease	3.4	6.9
Asthma/COPB	22.5	39.2
Other	44.7	52.9
Hyperlipidaemia	54.5	66.7
Dyspnoea	62.6	69.6
Chest pain	20.2	21.6
Cough	46.1	55.9
Tiredness	42.2	44.1

3.2. Odds of association of patient status variables on onset of long COVID-19

Logistic regression analysis of patient status variables presented in Table 4 shows which factors have the largest influence on the occurrence of the long COVID-19. Three were significant, namely gender (women were more than 2.5 times more at risk than men), ICS where the odds of long COVID-19 onset increase by 2.4 times for those who had to be treated with them, and the number of complications, where each complication increases the odds by more than 2.8 times.

Table 4. Influence of patient status during hospitalisation on the onset of long COVID-19.

Patient status variable	Wald	95% CI for lower	95% CI for uper	Significance at 95%	Exp(B)
Age	0.079	0.976	1.033	0.778	1.004
BMI	0.115	0.949	1.078	0.734	1.011
Gender	6.389	1.230	5.151	0.011	2.517
ICU	0.117	0.466	2.960	0.732	1.175
ICS	4.008	1.019	5.732	0.045	2.416
Number of complications	7.801	1.365	5.909	0.005	2.840
Number of comorbidities	0.001	0.703	1.404	0.971	0.994
Vaccination	-0.671	0.372	0.3824	0.071	0.511

3.3. Demographic and health factors associated with vaccination status of Slovenian COVID patients

Finally, logistic regression (Table 5) was used again to analyze which factors have the greatest influence on whether someone was vaccinated or not. Two were significant, namely age (for each year the probability of vaccination has increased by 4.5%) and asthma/COPD, where the presence of asthma/COPD increases the probability almost twice. Other factors were not significant, the strongest was the type 2 diabetes diagnosis, as its presence increases the probability of vaccination by 35%.

Table 5. Factors influencing the vaccination status.

Patient status variable	Wald	95% CI for lower	95% CI for uper	Significance at 95%	Exp(B)
Age	15.877	1.023	1.068	<0.001	1.045
BMI	1.476	0.930	1.017	0.224	0.972
Gender	0.131	0.580	1.455	0.717	0.918
Type 2 diabetes	2.386	0.387	1.119	0.122	0.658
Hypothyroidic	0.092	0.260	2.683	0.762	0.835
Chronic kidney disease	0.743	0.583	4.005	0.389	1.528
Asthma/COPB	8.170	1.242	3.195	0.004	1.992
Hyperlipidaemia	0.559	0.680	2.365	0.454	1.268
Other comorbidities	1.144	0.807	2.076	0.285	1.294

4. Discussion

Our study revealed that vaccination has positive effect on the long COVID symptoms, namely vaccinated patients experienced less symptoms than unvaccinated. The positive effect on long COVID-19 symptoms were also reported in other studies. Strain et al [17] reported that vaccination reduced the number of long COVID 19 patients suffering fatigue, myalgia or chest pain. Another study on more than 16000 US adults revealed that vaccination might be associated with reduction, but not elimination of long COVID-19 risks [18], but another study on 1832 US adults reported significantly higher risk of long COVID.19 symptoms in unvaccinated patients [19]. In a systematic

review including eight studies Notarte et al [20] reported that seven studies showed an improvement in long COVID-19 symptoms. Contrary, Wisnivesky et al [21] based on a study of 453 patients reported no association between vaccination and long COVID-19 symptoms.

Our results show that the significant risk factors for developing long COVID-19 are female gender, required inhalation therapy (due to existing chronic pulmonary disease or severe COVID-19 pneumonia with bronchoconstriction that required therapy) and complications during hospitalization – severity of acute disease. This finding is in line with several other studies regarding long COVID [8,22–24]. Our study   results are also comparable to Romero-Rodrigez et all [25] who reported that hospitalization, ICU admission, history of pneumonia, and vaccination were predictive factors (positive or negative) for the presence or absence of long-COVID symptoms. Similarly Hamdh and Nazzal [26] report that the odds ratio of non-vaccinated patients was almost seven times higher than the odds ratio of vaccinated patients regarding the occurrence of long-COVID symptoms.

Finally, our study identified two factors that significantly increase the probability that a patient was vaccinated, namely patient age (every year increases the probability for vaccination for 4.5%) and if patient has had asthma or chronic obstructive pulmonary disease (COPD) which increased the probability of vaccination for almost 100%. Presence of diabetes was also an important however not statistically significant factor which increased the probability of vaccination for 35%. The reason for the above finding might be that in Slovenia, according to the course of COVID-19 pandemic and medical data that were collected during the first and second wave COVID-19 infections, when vaccination was not yet available, the age and comorbidities, especially type 2 diabetes and obesity, were the risk factors for severe acute COVID-19   infection with several possible complications as well as risk factor for developing long COVID [27]. According to these data, the main goal for vaccination strategy was to vaccinate the population with highest risk for developing severe acute disease as well as long COVID, older patients and patients with comorbidities and especially patients with chronic pulmonary diseases [28]. Similar reasons to those found in our study were reported in various studies [29–32]. Contrary no association between demographic factors an attitude toward vaccination were reported for US adults [33].

Our study has some limitations, firstly we were able to include a relative small number of patients, who developed COVID-19 pneumonia requiring hospitalization during the study period and who were vaccinated, because vaccination was not available at the beginning of the COVID - 19 pandemic. However we must also take into account that Slovenia is a small country, but the sample size is still comparable to some other studies enumerated above. Additionally, it might be possible that many COVID-19 pneumonia hospitalizations were prevented due to the vaccination of the population with highest risks. The limitation is also that the patients came from northeast Slovenia, which means that it is not possible to generalize the results. On the other hand, the strength of the study is in the results itself, as similar studies have not yet been conducted in Slovenia. Therefore, we added new knowledge which is now routinely used in healthcare practice.

5. Conclusion

Pandemics, as COVID-19 showed, that they can have the potential to result in serious global health threats and crises. Management of such kind of crisis presents a serious challenge due to the number of affected people, differences in legal, administrative, health procedures, political cultures, and the lack of evidence. In this regard our study contributed some important new knowledge. Consequently, the results of our study were also used in the EU project STAMINA [34], where the goal was to overcome the above challenges and support efficient and effective pandemic management by using real world data. In the project participated 26 different institutions from 16 countries with the aim to inform decision-makers and legislation in the field of solving and managing pandemic crises. It was our study that provided the key inputs for a more precise definition of the duration of Long COVID-19 in Slovenia and the evidence how the vaccination against COVID-19 affected the course of the disease.

According to the study results we can conclude that vaccination is a safe and effective measure to prevent severe progression of acute disease, as well as to lover the incidence for developing long

COVID. Data from our study that is based on clinical practice in the real-world healthcare system environment are comparable to those of similar studies performed worldwide.

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