Heliyon 10 (2024) e40409

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

The impact of vaccination status on post-acute sequelae in hospitalized COVID-19 survivors using a multi-disciplinary approach: An observational single center study

Lucia Ilaria Birtolo [1], Gianluca Di Pietro [1], Antonella Ciuffreda [1], Riccardo Improta [1], Sara Monosilio [1], Silvia Prosperi [1], Sara Cimino [1], Nicola Galea [2], Paolo Severino [1], Gioacchino Galardo [3], Maria Chiara Colaiacomo [4], Patrizia Pasculli [5], Angelo Petroianni [6], Paolo Palange [6], Claudio Maria Mastroianni [5], Laura de Vito [7], Carlo Catalano [2], Francesco Pugliese [8], Maria Rosa Ciardi [5], Paola Celli [8], Roberto Badagliacca [1], Francesco Fedele [1], Carmine Dario Vizza [1], Viviana Maestrini [1], Massimo Mancone [1,*], on behalf ofPoliclinico Umberto I COVID-19 Group

[1] *Department of Clinical, Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, "Policlinico Umberto I" Hospital, Rome, Italy*
[2] *Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, "Policlinico Umberto I" Hospital, Rome, Italy*
[3] *Emergency Department - "Policlinico Umberto I" Hospital, Rome, Italy*
[4] *Radiology DEA Department, Sapienza University of Rome, "Policlinico Umberto I" Hospital, Rome, Italy*
[5] *Department of Public Health and Infectious Diseases, Sapienza University of Rome, "Policlinico Umberto I" Hospital, Rome, Italy*
[6] *Department of Public Health and Infectious Diseases, Division of Pulmonary Medicine, Sapienza University of Rome, "Policlinico Umberto I" Hospital, Rome, Italy*
[7] *"Policlinico Umberto I" Hospital, Rome, Italy*
[8] *Department of Anaesthesia and Intensive Care Medicine, Sapienza University of Rome, "Policlinico Umberto I" Hospital, Rome, Italy*

ARTICLE INFO

Keywords:
Long-COVID19
mRNA vaccines
Hospitalized
Survivors
Sequalae

ABSTRACT

Background: COVID-19 vaccines reduced mortality, hospitalizations and ICUs admissions. Conversely, the impact of vaccination on Long COVID-19 syndrome is still unclear. This study compared the prevalence of post-acute sequelae at short and long-term follow-up among hospitalized unvaccinated and vaccinated COVID-19 survivors through a multidisciplinary approach. *Methods:* After 2 months from discharge, unvaccinated and vaccinated COVID-19 survivors underwent a follow-up visit at a dedicated "post-COVID-19 Outpatient Clinic". The follow-up visit

Abbreviations: ATS, American Thoracic Society; ABG, arterial blood gas analysis; ARDS, Acute Respiratory Distress Syndrome; AF, Atrial Fibrillation; CPAP, Continuous Positive Airway Pressure; CVD, Cardiovascular Disease; (CCT), Chest Computed Tomography; CMR, Cardiac Magnetic Resonance; CCTA, Coronary Computed Tomography Angiography; COVID-19, Coronavirus Disease 19; ECG, electrocardiogram; HFNC, High Flow Nasal Cannula; Hs-cTNT, high-sensitive cardiac troponin T; ICA, Invasive Coronary Angiography; ICU, intensive unit care; MACCEs, major adverse cardiac and cerebrovascular events; mRNA, messenger ribonucleic acid; TTE, transthoracic echocardiogram; 6MWT, Six minutes walking test; WHO, World Health Organization.

* Corresponding author: Department of Clinical, Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Italy, Viale del Policlinico, 155, 00161 Rome, Italy

E-mail address: massimo.mancone@uniroma1.it (M. Mancone).

https://doi.org/10.1016/j.heliyon.2024.e40409
Received 22 January 2024; Received in revised form 12 November 2024; Accepted 13 November 2024
Available online 15 November 2024

included a cardiovascular evaluation, blood tests, chest computed tomography, 6-min walking test (6MWT), spirometry. A one-year telephone follow-up was performed to assess re-hospitalizations, death and long-lasting symptoms. An additional 1:1 case-control matching analysis adjusted for baseline characteristics was performed.

Results: Between June 2020 and June 2022, a total of 458 unvaccinated and vaccinated patients (229 per group) underwent the follow-up visit. Vaccinated patients had lower rates of ICU admissions (1.7 % vs 9.6 %, p= <0.001) and severe respiratory complications requiring intubation (1.3 % vs 7 %, p = 0.002) or non-invasive ventilation such as high-flow nasal oxygen therapy (1.7 % vs 7.9 %, p = 0.02), CPAP (1.3 % vs 20.1 %, p= < 0.001), and low-flow oxygen therapy (3.5 % vs 63.3 %, p= <0.001) compared to unvaccinated ones. At 2-month follow-up, vaccinated patients **had** fewer persistent ground-glass opacities (2.6 % vs 52.8 %, p= <0.001) or consolidations (0.9 % vs 8.3 %, p= <0.001). Additionally, unvaccinated patients experienced more frequent myocarditis (4.8 % vs 0.9 %, p = 0.013) and pulmonary embolism (1.8 % vs 0 %, p = 0.042) and exhibited more significant respiratory impairment as evidenced by desaturation during the 6MWT (10.2 % vs 3.5 %, p = 0.005) and altered spirometry (14 % vs 8.7 %, p = 0.043) compared to vaccinated ones. At one-year, unvaccinated patients reported more symptoms such as dyspnea (20.5 % vs 10 %, p = 0.002), psychological symptoms (10 % vs 3.5 %, p = 0.005) and chronic rhinosinusitis/cough (6,6 % vs 2,6 %, p = 0.04) as compared to vaccinated ones. The 1:1 case-control matching analysis also confirmed these results.

Conclusions: COVID-19 vaccines improve short-term outcomes and may reduce Long COVID-19 prevalence.

1. Introduction

The outbreak of the COVID-19 pandemic has resulted in millions of deaths worldwide since March 2020 [1]. Acute Respiratory Distress Syndrome (ARDS) is one of the most severe clinical manifestations, particularly common in unvaccinated patients [2].

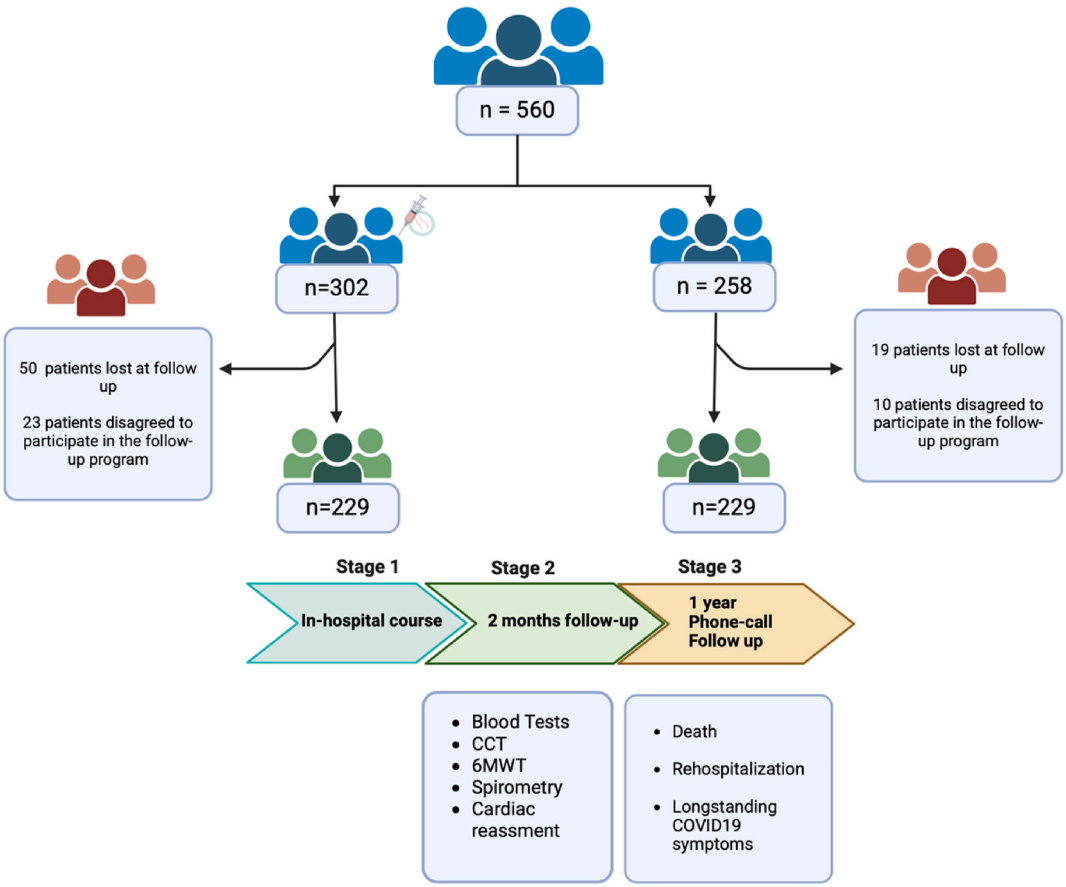


Fig. 1. Protocol of the study.

SARS-CoV2 affects the respiratory system predominantly, but cardiovascular involvement is also frequently observed. Indeed, 28 % of COVID-19 hospitalized unvaccinated patients had new cardiovascular conditions, with myocarditis being the most common [3].

After the recovery phase, post-acute long-lasting symptoms were also observed, leading to the proposal of a new pathological condition called "Long-COVID Syndrome". This condition usually occurs three months after the SARS-CoV2 infection, lasts at least two months and is not associated with instrumental abnormalities [4,5].

Although COVID-19 vaccines have significantly reduced the rates of hospitalizations, admissions to intensive care units and deaths worldwide, the impact of vaccination on Long-Covid Syndrome remains unclear [5]. To clarify this issue, this study aimed to compare the prevalence of post-acute sequelae at short and long-term follow-up in hospitalized unvaccinated and vaccinated COVID-19 survivors using a multidisciplinary approach.

2. Methods

This is a prospective observational follow-up study conducted at "Sapienza" University of Rome- "Policlinico Umberto I″, an academic Hospital Hub for COVID-19 patients in Rome. A dedicated "post-COVID-19 Outpatient Clinic" has been created to monitor discharged COVID-19 patients.

From June 2020 to June 2022, we recruited adult Italian hospitalized patients who were discharged from the hospital with a diagnosis of COVID-19 and agreed to participate in the follow-up program. The enrolled patients were divided into two groups based on their vaccination status. Specifically, vaccinated patients were enrolled from June 2021, in line with the Italian government's vaccination campaign. In the meantime, we enrolled unvaccinated patients who were hospitalized both before and after the vaccination campaign. Vaccinated patients were admitted to hospital for low oxygen requirements as assessed by a general practitioner or for low oxygen saturation as self-assessed.

We excluded patients who did not have a need for hospitalization and were therefore under the care of general practitioners.

All COVID-19 survivors were invited to attend a two-month follow-up visit and a telephone follow-up one year after hospital discharge to evaluate short and long-term sequelae of COVID-19, respectively (Fig. 1). During the follow-up visit, all patients underwent blood sample collection (Supplementary Table 1), arterial blood gas analysis (ABG), Chest Computed Tomography (CCT), a 6-min walking test (6MWT), spirometry, and a new cardiovascular evaluation.

Cardiovascular evaluation included clinical reassessment, high-sensitive cardiac troponin T (hs-cTnT) assay, resting 12-lead electrocardiogram (ECG) and transthoracic echocardiogram (TTE). Further tests such as Cardiac Magnetic Resonance (CMR), Coronary CT angiography (CCTA), Invasive Coronary Angiography (ICA) and 24-h Holter ECG monitoring were requested if clinically indicated. Cardiovascular disease (CVD) was defined as the persistence of a cardiovascular condition that occurred during the hospitalization for COVID-19 or the occurrence of new onset cardiovascular disease during the follow-up evaluation. CVD did not include pre-existing cardiovascular conditions before COVID-19.

ECG was recorded with the patient in the supine position during quiet respiration at 25 mm/s, using a Cardioline Delta 3 Plus. TTE was performed by Versana Active (General Electric Healthcare) according to standard guidelines and protocols [6,7] (Supplementary Table 2). 6MWT was performed following American Thoracic Society (ATS) guidelines and current recommendations [8–10].

CT scans were performed using Philips Ingenuity CT Scanner and were reviewed by two senior experienced radiologists blinded to clinical and laboratory data, and consensus was reached. Persistent radiological abnormalities were defined as ground glass appearance or consolidation at two months of follow-up.

For comorbidities, CDC-defined high-risk conditions for severe COVID-19 were considered [11]. One year after the COVID-19 diagnosis, all survivors were contacted by phone call to evaluate the occurrence of death, re-hospitalization and long-lasting COVID-19-related symptoms.

According to the World Health Organization (WHO) definition, Long-COVID-19 syndrome was considered in individuals with a history of suspected or confirmed SARS-CoV-2 infection, with persisting symptoms usually after three months, lasting at least two months and without alternative diagnosis [4].

Long-lasting COVID-19-related symptoms included: dyspnea, palpitations, anger, asthenia, hair loss, attention deficit, gastrointestinal symptoms, psychological disturbs, and respiratory symptoms.

Patients who reported cardiovascular symptoms at one-year follow-up were invited to perform an additional follow-up visit at the dedicated "post-COVID-19 Outpatient Clinic". The study was approved by the Ethics Committee of "Policlinico Umberto I″ Hospital-"Sapienza" University of Rome (number 109/2020 approved on April 07, 2020). The study was conducted in accordance with the Declaration of Helsinki. A written informed consent was obtained from the patients before evaluation. Patients also consented to have their internal scans published.

2.1. Statistical analysis

Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 29). Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were presented as numerical values and percentages. Continuous variables were compared using the student's t-test if normally distributed, and the Mann-Whitney non-parametric test in other cases. Categorical variables were compared using the Chi-square test. A p-value less than 0.05 was considered significant.

Study power was based on an 80 % probability of persistent COVID-19 related symptoms at one year. The primary analysis is performed using a chi-squared test comparison with a 2-sided significance level of 0.05. Recent literature estimates an increased risk of at least 15 % of persistent COVID-19 related symptoms at one year in unvaccinated patients compared with vaccinated patients. The

sample size was considered to be approximately 116 patients (58 per group), assuming a 20 % loss to follow-up.

To compensate for the lack of proper statistical design and randomization in observational studies such as this one, an additional 1:1 case-control matching with a caliper width of 0.2 was performed for both groups using SPSS v.29. Vaccination status was the dependent variable; independent variables were those baseline characteristics that showed a statistically significant difference between vaccinated and unvaccinated patients and other variables considered clinically relevant. The final variables included in the case-control matching were: age, dyslipidemia, diabetes, current smoking, heart failure, chronic obstructive pulmonary disease (COPD), atrial fibrillation, and chronic kidney disease.

2.2. Outcomes

The primary end-point was 1 year persistency of COVID-19 related symptoms. Secondary outcomes were: CT scans and pulmonary functional abnormalities at 2-months follow-up; cardiovascular events including Pericarditis, Myocarditis, New onset Atrial Fibrillation (AF) and Pulmonary Embolism at 2 months.

3. Results

3.1. Baseline characteristics and clinical presentation

During the study period, 560 patients were admitted for COVID-19 in our tertiary level institution. Of them, 33 patients disagreed to participate in the follow-up program, whereas 69 patients were lost at follow-up. Finally, a total of 458 COVID-19 survivors who agreed to participate in the follow-up program were included in the analysis from June 2020 to June 2022 (n = 229 unvaccinated and n = 229 vaccinated patients) (Fig. 1). Vaccinated patients were found to be older (age 57.28 ± 14 vs 60.9 ± 15, p = 0.009) and had more cardiovascular risk factors compared to unvaccinated ones, including dyslipidemia (38.9 % vs 27.9 %, p = 0.013) and a smoking habit (17.9 % vs 9.2 %, p = 0.006). A higher prevalence of comorbidities such as COPD (14.8 % vs 6.5 %, p = 0.005), atrial fibrillation (11.8 % vs 5.8 %, p = 0.023), heart failure (5.7 % vs 0.9 %, p = 0.004), and chronic kidney disease (11.4 % vs 2.6 %, p= <0.001) were reported. Other baseline characteristics are summarized in Table 1.

Vaccinated patients had lower rates of Intensive Care Unit (ICU) admissions (1.7 % vs 9.6 %, p= <0.001) and fewer severe respiratory complications requiring intubation (1.3 % vs 7 %, p = 0.002) or non-invasive ventilation such as high-flow nasal oxygen therapy (1.7 % vs 7.9 %, p = 0.02) and Continuous Positive Airway Pressure (CPAP) (1.3 % vs 20.1 %, p= < 0.001) compared to unvaccinated ones. Table 2 provides further information about on the types of vaccines administered to vaccinated patients, whereas Table 3 provides additional details about in-hospital course.

3.2. Two-months follow-up

Two months after COVID-19, cardiovascular involvement was registered in 7.4 % (n = 34) of COVID-19 survivors (Table 4). Specifically, unvaccinated patients experienced more frequent myocarditis (4.8 % vs 0.9 %, p = 0.013) (Fig. 2A–H) and pulmonary embolism (1.8 % vs 0 %), p = 0.042) (Fig. 3). Persistent ground-glass opacities (52.8 % vs 2.6 %, p= <0.001) or consolidations (8.3 % vs 0.9 %, p= <0.001) were more frequent in unvaccinated patients as compared to vaccinated ones (Fig. 4). During clinical examination, unvaccinated individuals exhibited more significant respiratory impairment as evidenced by desaturation (<90 % SpO2) during the 6-min walk test (10.2 % vs 3.5 %, p = 0.005) and altered spirometry results with at least mild ventilatory deficiency (14 % vs 8.7 %, p = 0.043). Other 2-month follow-up findings are reported in Table 5 (see Fig. 5).

Table 1
Baseline characteristics of enrolled populations.

	Vaccinated (n = 229)	Unvaccinated (n = 229)	p-value
Age, years old (±SD)	60.9 ± 15	57.28 ± 14	**0.009**
Male, n (%)	107 (46.7 %)	124 (54.1 %)	0.112
Hypertension, n (%)	109 (47,6 %)	108 (47.1 %)	0.925
Diabetes, n (%)	39 (17 %)	30 (13.1 %)	0.248
Dyslipidaemia, n (%)	89 (38.9 %)	64 (27.9 %)	**0.013**
Actual smoking, n (%)	41 (17.9 %)	21 (9.2 %)	**0.006**
Heart failure, n (%)	13 (5.7 %)	2 (0.9 %)	**0.004**
COPD, n (%)	34 (14.8 %)	15 (6.5 %)	**0.005**
AF, n (%)	27 (11.8 %)	13 (5.8 %)	**0.023**
Cancer, n (%)	22 (9.6 %)	29 (12.7 %)	0.276
CKD, n (%)	26 (11.4 %)	6 (2.6 %)	**<0.001**
IHD, n (%)	24 (10.5 %)	13 (5.8 %)	0.065

Abbreviations- AF: Atrial Fibrillation; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; IHD: Ischemic Heart Disease.

Table 2
Vaccine types in the vaccinated population.

	Unvaccinated (n = 229)	Vaccinated (n = 229)
BNT162b2, n (%)	–	145 (63,3 %)
mRNA-1273, n (%)	–	79 (34,5 %)
ChAdOx1-S, n (%)	–	5 (2,2 %)

Table 3
Clinical in-hospital outcomes.

	Vaccinated (n = 229)	Unvaccinated (n = 229)	p-value
Intensive unit care, n (%)	4 (1.7 %)	22 (9.6 %)	**<0.001**
Intubation, n (%)	3 (1.3 %)	16 (7 %)	**0.002**
HFNC, n (%)	4 (1.7 %)	18 (7.9 %)	**0.02**
CPAP, n (%)	3 (1.3 %)	46 (20.1 %)	**<0.001**
Pulmonary Embolism, n (%)	1 (0.4 %)	1 (0.4 %)	0.906
NSTE-ACS, n (%)	0 (0 %)	1 (0.4 %)	0.311
STE-ACS, n (%)	0 (0 %)	1 (0.4 %)	0.311

Abbreviations- CPAP: Continuous Positive Airway Pressure; HFNC: High Flow Nasal Cannula; NSTE-ACS: Non ST elevation Acute Coronary Syndrome; STE-ACS: ST elevation Acute Coronary Syndrome.

Table 4
Clinical and radiological short-term outcomes at 2-months follow up – Overall data.

	Patients (n = 458)
Pericarditis, n(%)	8 (1.8 %)
Myocarditis, n(%)	13 (2.9 %)
New onset AF, n(%)	6 (1.3 %)
Pulmonary Embolism, n(%)	4 (0.9 %)
Ground Glass at CCT, n(%)	108 (23,6 %)
Consolidation at CCT, n (%)	37 (8.1 %)
Pleural effusion at CCT, n (%)	12 (2.6 %)
Desaturation during 6MWT, n (%)	29 (6.3 %)
At least mild ventilatory deficiency at spirometry, n (%)	53 (11.6 %)
LVEF, % (±SD)	59.4 ± 6.5

Abbreviations- AF: Atrial Fibrillation; CCT: Chest Computed Tomography; LVEF: Left Ventricular Ejection Fraction; 6MWT: Six minutes walking test.

3.3. One year follow-up

One year after COVID-19, all the patients recruited in the study were alive. Moreover, they did not experience re-hospitalizations. 45 % (n = 206) of COVID-19 survivors reported at least one long-standing symptom (Table 6). Particularly, unvaccinated patients reported more frequent symptoms such as dyspnea (20.5 % vs 10 %, p = 0.002), psychological symptoms, including anxiety and/or depressive disorder (10 % vs 3.5 %) and chronic rhinosinusitis/cough (6.6 % versus 2.6 %, p = 0.04) as compared to vaccinated ones. Other one-year follow-up findings were reported in Table 7. Among patients who reported cardiovascular symptoms at one-year follow-up, no onset of CVD was detected during the visit.

3.4. Case-control matching analysis

After a 1:1 case-control matching analysis adjusted for baseline characteristics (age, dyslipidemia, diabetes, current smoking, COPD, AF, KD, HF), a total of 72 COVID-19 survivors were included (36 persons per group). Baseline characteristics were comparable with respect to comorbidities (Supplementary Table 3)**.** Vaccinated patients had lower rates of intensive care unit (ICU) admission (0 % vs 16 %, p = 0.01) and fewer severe respiratory complications requiring intubation (2.7 % vs 19.4 %, p = 0.02) or non-invasive ventilation such as high-flow nasal oxygen therapy (0 % vs 11.1 %, p = 0.04) and continuous positive airway pressure (CPAP) (0 % vs 25 %, p= < 0.001) compared to unvaccinated patients (Supplementary Table 4). At 2 months, unvaccinated patients had a higher incidence of myocarditis (16 % vs 2.7 %, p = 0.05). They were also more likely to have a significant pulmonary embolism (0 % vs 8.3 %, p = 0.007) compared to the vaccinated. Persistent ground-glass opacities (38 % vs 0 %, p= <0.001) or consolidations (8 % vs 0 %, p = 0.04) were more common in unvaccinated patients than in vaccinated ones. On clinical examination, unvaccinated individuals had more significant respiratory impairment as evidenced by desaturation (<90 % SpO2) during the 6-min walk test (33 % vs 8.3 %, p = 0.009) and altered spirometry results with at least mild ventilatory deficiency (36 % vs 13.8 %, p = 0.03). See Supplementary Table 5

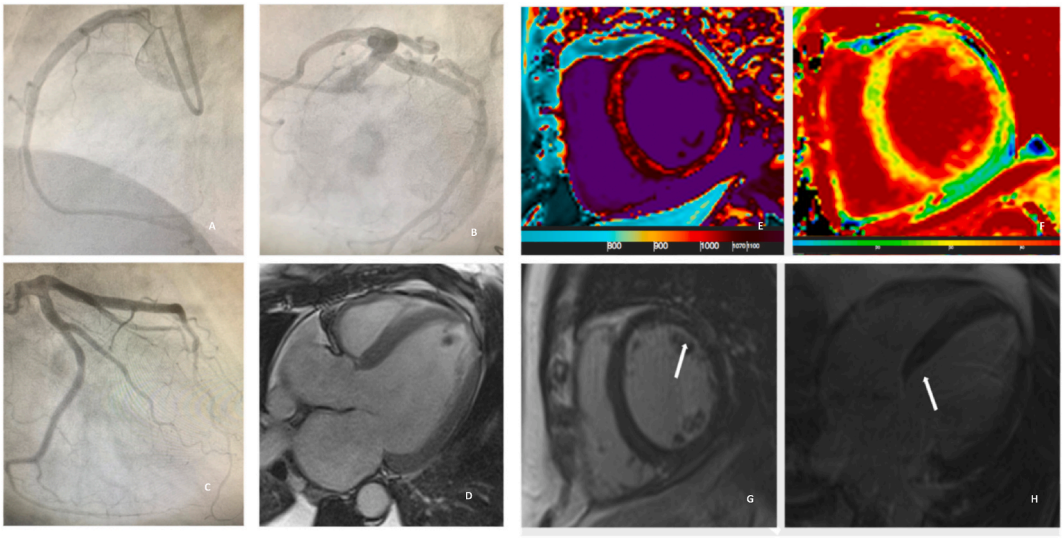


Fig. 2. Example of myocarditis at 2 months follow-up visit. A 60-year-old male patient presented at follow-up visit in NYHA class II and new onset of severe ventricular disfunction. The patient underwent coronary angiography revealing unobstructed coronary arteries (A,B,C) and Cardiac Magnetic Resonance suggestive of acute myocarditis, according to Lake Louis' criteria (D,E,F,G,H).

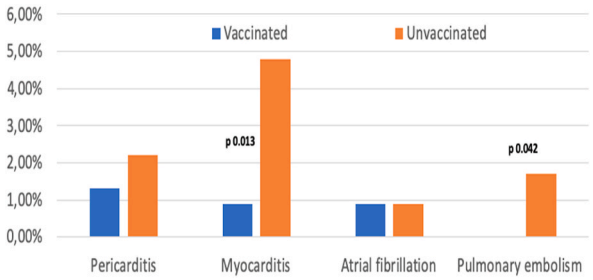
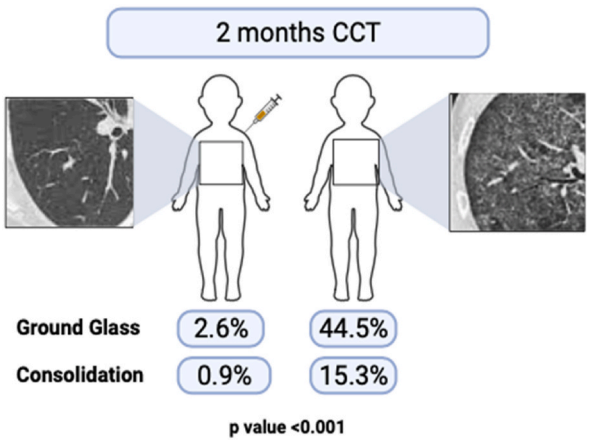


Fig. 3. Incidence of cardiovascular events at 2 months follow-up. Unvaccinated patients experienced more frequent myocarditis and pulmonary embolism.



Figs. 4. 2 months CCT. Persistent ground-glass opacities or consolidations were more frequent in unvaccinated patients as compared to vaccinated ones.

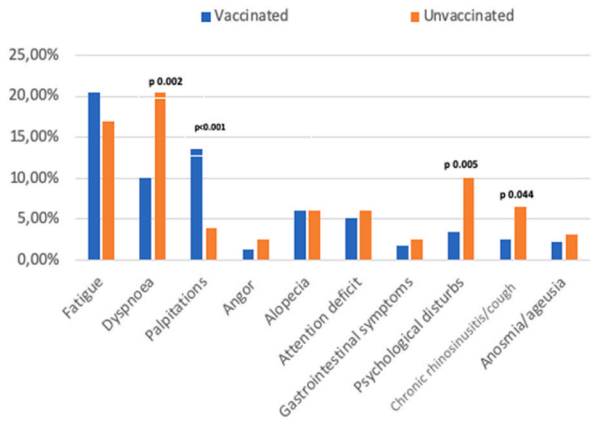


Fig. 5. Long-lasting symptoms at 1 year phone call follow-up. Unvaccinated patients reported more frequent long-lasting symptoms such as dyspnea, psychological symptoms and chronic rhinosinusitis/cough as compared to vaccinated ones.

Table 5
Clinical and radiological short-term outcomes at 2-months follow up – Vaccinated and unvaccinated patients.

	Vaccinated (n = 229)	Unvaccinated (n = 229)	p-value
Pericarditis, n (%)	3 (1.3 %)	5 (2.2 %)	0.459
Myocarditis, n (%)	2 (0.9 %)	11 (4.8 %)	**0.013**
New onset AF, n (%)	2 (0.9 %)	2 (0.9 %)	0.991
Pulmonary embolism, n (%)	0 (0 %)	4 (1.7 %)	**0.042**
Ground Glass at CCT, n (%)	6 (2.6 %)	102 (44.5 %)	**<0.001**
Consolidation at CCT, n (%)	2 (0.9 %)	35 (15.3 %)	**<0.001**
Pleural effusion at CCT, n (%)	5 (2.2 %)	7 (3,1 %)	0.379
Desaturation during 6MWT, n (%)	8 (3.5 %)	21 (9.2 %)	**0.005**
At least mild ventilatory deficiency at spirometry, n (%)	20 (8.7 %)	33 (14,4 %)	**0.043**

Abbreviations- AF: Atrial Fibrillation; CCT: Chest Computed Tomography; LVEF: Left Ventricular Ejection Fraction; 6MWT: 6 min walking test.

Table 6
Symptoms at one year telephone follow-up- Overall data.

	Patients (n = 458)
Fatigue, n (%)	86 (18,8 %)
Dyspnea, n (%)	70 (15.3 %)
Palpitations, n (%)	40 (8.7 %)
Angor, n (%)	9 (2 %)
Alopecia, n (%)	28 (6.1 %)
Attention deficit, n (%)	26 (5.7 %)
Gastrointestinal symptoms, n (%)	10 (2.2 %)
Psychological disturbs, n (%)	31 (6.8 %)
Chronic rhinosinusitis/cough, n (%)	21 (4,6 %)
Anosmia/ageusia, n (%)	12 (2.6 %)

for further details. One year after COVID-19, unvaccinated patients reported more symptoms of dyspnea (30.5 % vs 2.7 %, p = 0.002), psychological symptoms including anxiety and/or depressive disorders (25 % vs 5.5 %, p = 0.02) and chronic rhinosinusitis/cough (27.7 % vs 8.3 %, p = 0.03) than vaccinated patients. Other one-year follow-up results are reported in Supplementary Table 6.

4. Discussion

This monocentric observational study aimed to evaluate the impact of vaccinal status on short and long-term sequelae in COVID-19 survivors using a multidisciplinary approach. It is becoming increasingly important to address the long-term health effects experienced by COVID-19 survivors. Persistent signs and symptoms beyond the acute phase of the infection have emerged as a major public health concern [12–14]. Both clinicians and researchers are interested in understanding the impact of vaccination status on these long-term effects to better guide healthcare policies and practices [15]. Follow-up studies on COVID-19 survivors have primarily focused on pulmonary short-term consequences, with small sample sizes and heterogeneous protocols [16–18]. This is the first follow-up study on

Table 7
Clinical outcomes at one year call phone follow-up- Vaccinated and unvaccinated patients.

	Vaccinated (n = 229)	Unvaccinated (n = 229)	p-value
Fatigue, n (%)	47 (20.5 %)	39 (17 %)	0.338
Dyspnea, n (%)	23 (10 %)	47 (20.5 %)	**0.002**
Palpitations, n (%)	31 (13.5 %)	9 (3.9 %)	**<0.001**
Angor, n (%)	3 (1.3 %)	6 (2.6 %)	0.309
Alopecia, n (%)	14 (6.1 %)	14 (6.1 %)	1
Attention deficit, n (%)	12 (5.2 %)	14 (6.1 %)	0.695
Gastrointestinal symptoms, n (%)	4 (1.7 %)	6 (2.6 %)	0.523
Psychological disturbs, n (%)	8 (3.5 %)	23 (10 %)	**0.005**
Chronic rhinosinusitis/cough, n (%)	6 (2.6 %)	15 (6.6 %)	**0.044**
Anosmia/ageusia, n (%)	5 (2.2 %)	7 (3.1 %)	0.559

COVID-19 survivors with a multidisciplinary assessment and adequate sample size.

The main findings of this follow-up study could be summarized as follows: a) unvaccinated patients had a more severe in-hospital course, including admission to the intensive care unit and oxygen support requirement; b) at two months follow-up, unvaccinated patients experienced more frequent myocarditis, pulmonary embolism and persistent respiratory CCT and functional abnormalities; c) at 1-year follow-up, persistent dyspnea, chronic rhinosinusitis/cough and psychological disturbs were more commonly reported in unvaccinated patients.

The widespread availability of SARS-CoV2 vaccination has provided a crucial opportunity to control the COVID-19 pandemic on both national and global scales. From groundbreaking trials [19,20] and post-marketing data [21–23], mRNA vaccines are highly effective in reducing mortality rates and burden on the healthcare systems. Previous other retrospective studies have demonstrated that vaccination could limit disease progression and pulmonary deterioration among hospitalized COVID-19 patients [24]. Our results are in line with these previous findings**,** showcasing the immense potential of vaccination in attenuating the severity of the disease and improving the in-hospital course of vaccinated patients. Specifically, patients who received mRNA vaccines had lower ICU admissions and were less likely to require invasive or non-invasive oxygen support. However, our analysis did not reveal any significant difference in the in-hospital major adverse cardiac and cerebrovascular events (MACCEs) among vaccinated and unvaccinated patients. Previous studies had demonstrated a significant prevalence of myocardial involvement in unvaccinated patients due to the SARS-CoV2-induced cytokine storm [2,25,26]. The mild severity of illness in vaccinated patients and the exclusion from the follow-up program of the patients who experienced acute cardiovascular events and subsequent death could explain the underestimation of myocardial involvement rates.

During our follow-up visit with COVID-19 survivors after two months, we found that it is important to carefully investigate respiratory functions, especially in patients who have not received the vaccine. These patients are more likely to have long-term parenchymal abnormalities, including ground glass patterns and consolidations, and functional ones. Our study is consistent with previous observational studies and meta-analyses [27–31], which have shown that the severity of illness is correlated with persisting severe functional and parenchymal lung impairment. The pathophysiologic mechanisms underlying these findings are microvascular damage with interstitial thickening, loss of alveolar spaces, and muscle impairment related to systemic inflammation, intensive ventilation, sedation, and prolonged bed rest [31,32].

Moreover, unvaccinated patients have a higher risk of late pulmonary embolism (PE) and acute myocarditis (AM). Several case reports and a few small observational studies have shown that the risk of PE persists for up to 62 days after infection due to a persisting hypercoagulability state caused by SARS-CoV2 [33,34]. Indeed, the virus persistence due to extracellular vesicles (EVs) promotes a coagulative cascade, which explains the potential residual thrombotic risk in COVID-19 survivors [32]. Additionally, AM has been recognized as a relatively rare post-COVID-19 sequela within one year from the index infection, especially in younger patients and those with pre-existing cardiovascular diseases [35]. However, available data on the risk of AM during the follow-up period are debated. Some authors have supposed that the risk of AM is higher in patients admitted to the ICU, where they may have received higher doses of immunomodulatory drugs, affecting their immunosuppression and the cytocidal effect of the virus on the cardiac muscle [36,37].

After the acute phase of COVID-19, patients may experience long-term symptoms known as “long COVID-19″ or “post-acute COVID-19 syndrome” [3,38]. However, the impact of vaccination on post-COVID-19 syndrome is still uncertain, as per current literature [39–44]. At a one-year follow-up, people who were recalled reported persisting unexplained symptoms such as fatigue, dyspnea, and palpitation. Our analysis shows that dyspnea, rhinosinusitis, and psychological complaints were reported less frequently in the unvaccinated group as compared to the vaccinated one. Previous observational studies and meta-analyses indicate that vaccines lower the risk of long-term COVID-19 [38–40]. Dyspnea is a common long COVID-19 symptom, and anatomical or functional test abnormalities cannot explain it. Its incidence is higher among unvaccinated patients than vaccinated ones [45]. Inflammatory cell infiltration, oedema, and hyaline membrane formation can cause pulmonary interstitium and parenchyma changes. This can lead to a gradual loss of lung function, which can profoundly affect daily quality of life for people [46]. Finally, unvaccinated COVID-19 survivors may experience persisting psychological impairments due to prolonged isolation during longer hospital stays, greater fear of the unknown consequences of the disease, and the social stigma associated with being an early COVID-19 sufferer [47,48]. Therefore, it is essential to implement a psychological support program for COVID-19 survivors, particularly for unvaccinated patients with moderate

to severe clinical manifestations.

5. Limitations

This study has several important limitations. Firstly, the study was conducted at a single center, which may limit its generalizability to other settings. Secondly, the population enrolled does not reflect all COVID-19 survivors but only those who agreed to participate in the follow-up program. Also, the enrolled population was heterogeneous, with the unvaccinated group having been recruited mainly during the first wave of the pandemic. This means that the subsequent emergence of SARS-CoV-2 variants may have influenced the clinical presentation, onset, and severity of the disease.

Additionally, unvaccinated patients primarily presented with moderate to severe respiratory symptoms, whereas vaccinated patients presented with symptoms unrelated to SARS-CoV-2 infection but incidentally tested positive for SARS-CoV-2 in nasopharyngeal swabs. Thirdly, the vaccination program in Italy prioritized healthcare workers and older patients, which may have introduced sex and age bias. Finally, symptoms were self-reported by telephone, which may have introduced subjectivity and influenced the results.

6. Conclusion

Our results show a low prevalence of cardiovascular involvement in COVID-19 survivors at short-term follow-up. Despite frequent reported persistence of non-specific symptoms, there is no correspondence between cardiovascular symptoms and onset of cardiovascular disease at one-year follow-up.

Unvaccinated patients have more frequent cardiopulmonary sequelae at short term follow-up and symptoms one year later the infection, in addition to having a more severe in-hospital course.

In conclusion, COVID-19 vaccination improves not only in-hospital course but also short-term clinical and radiological outcomes and may reduce Long COVID-19 prevalence up to a year after the initial infection.

CRediT authorship contribution statement

Lucia Ilaria Birtolo: Writing – original draft. **Gianluca Di Pietro:** Writing – original draft. **Antonella Ciuffreda:** Writing – original draft. **Riccardo Improta:** Writing – review & editing. **Sara Monosilio:** Writing – review & editing. **Silvia Prosperi:** Writing – review & editing. **Sara Cimino:** Writing – review & editing, Formal analysis. **Nicola Galea:** Writing – review & editing. **Paolo Severino:** Writing – review & editing. **Gioacchino Galardo:** Writing – review & editing. **Maria Chiara Colaiacomo:** Writing – review & editing. **Patrizia Pasculli:** Writing – review & editing. **Angelo Petroianni:** Writing – review & editing. **Paolo Palange:** Writing – review & editing. **Claudio Maria Mastroianni:** Writing – review & editing. **Laura de Vito:** Writing – review & editing. **Carlo Catalano:** Writing – review & editing. **Francesco Pugliese:** Writing – review & editing. **Maria Rosa Ciardi:** Writing – review & editing. **Paola Celli:** Writing – review & editing. **Roberto Badagliacca:** Writing – review & editing. **Francesco Fedele:** Writing – review & editing. **Carmine Dario Vizza:** Writing – review & editing. **Viviana Maestrini:** Writing – review & editing. **Massimo Mancone:** Writing – review & editing, Writing – original draft, Conceptualization.

Data and code availability statement

Data included in article/supplementary material is referenced in the article.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40409.

References

[1] WHO WHO coronavirus (COVID-19) dashboard, Available online: https://covid19.who.int, 31 August 2022. (Accessed 1 September 2022).

[2] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention, JAMA 323 (13) (2020) 1239–1242.

[3] V. Maestrini, L.I. Birtolo, M. Francone, G. Galardo, N. Galea, P. Severino, F. Alessandri, M.C. Colaiacomo, G. Cundari, C. Chimenti, C. Lavalle, M. Ciardi, P. Palange, A. Deales, G. d'Ettorre, C.M. Mastroianni, C. Catalano, F. Ruberto, F. Pugliese, G. d'Amati, F. Fedele, M. Mancone, I. Policlinico Umberto, COVID-19 Group, Cardiac involvement in consecutive unselected hospitalized COVID-19 population: in-hospital evaluation and one-year follow-up, Int. J. Cardiol. 339 (2021 Sep 15) 235–242, https://doi.org/10.1016/j.ijcard.2021.06.056. Epub 2021 Jul 3. PMID: 34224766; PMCID: PMC8253670.

[4] J.B. Soriano, S. Murthy, J.C. Marshall, P. Relan, J.V. Diaz, WHO clinical case definition working group on post-COVID-19 condition. A clinical case definition of post-COVID-19 condition by a delphi consensus, Lancet Infect. Dis. 22 (4) (2022 Apr) e102–e107, https://doi.org/10.1016/S1473-3099(21)00703-9. Epub 2021 Dec 21. PMID: 34951953; PMCID: PMC8691845.

[5] G. Mazzaglia, Long COVID syndrome: lesson learned and future implications, J. Clin. Med. 12 (10) (2023 May 13) 3450.

[6] R.M. Lang, L.P. Badano, V. Mor-Avi, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J. Am. Soc. Echocardiogr. 28 (1) (2015 Jan) 1–39.e14.

[7] S.F. Nagueh, O.A. Smiseth, C.P. Appleton, et al., Recommendations for the evaluation of Left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging, Eur Heart J Cardiovasc Imaging 17 (12) (2016 Dec) 1321–1360.

[8] ATS Statement: guidelines for the six-minute walk test, Am. J. Respir. Crit. Care Med. 166 (2002) 111–117.

[9] A. Chetta, A. Zanini, G. Pisi, M. Aiello, P. Tzani, M. Neri, D. Olivieri, Reference values for the 6-min walk test in healthy subjects 20-50 years old, Respir. Med. 100 (9) (2006) 1573–1578.

[10] C. Casanova, B.R. Celli, P. Barria, et al., The 6-min walk distance in healthy subjects: reference standards from seven countries, Eur. Respir. J. 37 (1) (2011) 150–156.

[11] CDC, People with certain medical conditions, in: Cent. Dis. Control Prev, 2022. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

[12] S. Lopez-Leon, T. Wegman-Ostrosky, C. Perelman, et al., More than 50 long-term effects of COVID-19: a systematic review and meta- analysis, Sci. Rep. 11 (1) (2021) 16144.

[13] D. Groff, A. Sun, A.E. Ssentongo, et al., Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review, JAMA Netw. Open 4 (10) (2021) e2128568.

[14] T. Nasserie, M. Hittle, S.N. Goodman, Assessment of the frequency and variety of persistent symptoms among patients with COVID- 19: a systematic review, JAMA Netw. Open 4 (5) (2021) e2111417.

[15] I.C.H. Lam, C.K.H. Wong, R. Zhang, C.S.L. Chui, F.T.T. Lai, X. Li, E.W.Y. Chan, H. Luo, Q. Zhang, K.K.C. Man, B.M.Y. Cheung, S.C.W. Tang, C.S. Lau, E.Y.F. Wan, I.C.K. Wong, Long-term post-acute sequelae of COVID-19 infection: a retrospective, multi-database cohort study in Hong Kong and the UK, EClinicalMedicine 60 (2023 Jun) 102000, https://doi.org/10.1016/j.eclinm.2023.102000. Epub 2023 May 11. PMID: 37197226; PMCID: PMC10173760.

[16] O.F. Ahmed, F.H. Kakamad, B.J. Hama Amin, B.A. Abdullah, M.N. Hassan, R.Q. Salih, S.H. Mohammed, S. Othman, G.S. Ahmed, A.M. Salih, Post COVID-19 pulmonary complications; a single center experience, Ann Med Surg (Lond). 72 (2021 Dec) 103052, https://doi.org/10.1016/j.amsu.2021.103052. Epub 2021 Nov 10. PMID: 34777798; PMCID: PMC8578026.

[17] C. Huang, L. Huang, Y. Wang, et al., 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study, Lancet 397 (10270) (2021) 220–232.

[18] X. Han, Y. Fan, O. Alwalid, et al., Six-month follow-up chest CT findings after severe COVID-19 pneumonia, Radiology 299 (1) (2021) E177–E186.

[19] F.P. Polack, S.J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J.L. Perez, Marc G. Pérez, E.D. Moreira, C. Zerbini, R. Bailey, K.A. Swanson, S. Roychoudhury, K. Koury, P. Li, W.V. Kalina, D. Cooper, R.W. Frenck Jr., L.L. Hammitt, Ö. Türeci, H. Nell, A. Schaefer, S. Ünal, D.B. Tresnan, S. Mather, P. R. Dormitzer, U. Şahin, K.U. Jansen, W.C. Gruber, C4591001 clinical trial group. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine, N. Engl. J. Med. 383 (27) (2020 Dec 31) 2603–2615, https://doi.org/10.1056/NEJMoa2034577. Epub 2020 Dec 10. PMID: 33301246; PMCID: PMC7745181.

[20] L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B. S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, T. Zaks, COVE Study Group, Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine, N. Engl. J. Med. 384 (5) (2021 Feb 4) 403–416, https://doi.org/10.1056/NEJMoa2035389. Epub 2020 Dec 30. PMID: 33378609; PMCID: PMC7787219.

[21] M.W. Tenforde, W.H. Self, K. Adams, M. Gaglani, A.A. Ginde, T. McNeal, S. Ghamande, D.J. Douin, H.K. Talbot, J.D. Casey, N.M. Mohr, A. Zepeski, N.I. Shapiro, K.W. Gibbs, D.C. Files, D.N. Hager, A. Shehu, M.E. Prekker, H.L. Erickson, M.C. Exline, M.N. Gong, A. Mohamed, D.J. Henning, J.S. Steingrub, I.D. Peltan, S. M. Brown, E.T. Martin, A.S. Monto, A. Khan, C.L. Hough, L.W. Busse, C.C. Ten Lohuis, A. Duggal, J.G. Wilson, A.J. Gordon, N. Qadir, S.Y. Chang, C. Mallow, C. Rivas, H.M. Babcock, J.H. Kwon, N. Halasa, J.D. Chappell, A.S. Lauring, C.G. Grijalva, T.W. Rice, I.D. Jones, W.B. Stubblefield, A. Baughman, K.N. Womack, J.P. Rhoads, C.J. Lindsell, K.W. Hart, Y. Zhu, S.M. Olson, M. Kobayashi, J.R. Verani, M.M. Patel, Influenza and other viruses in the acutely ill (IVY) network. Association between mRNA vaccination and COVID-19 hospitalization and disease severity, JAMA 326 (20) (2021 Nov 23) 2043–2054, https://doi.org/10.1001/jama.2021.19499. PMID: 34734975; PMCID: PMC8569602.

[22] G. Lorenzoni, P. Rosi, S. De Rosa, V.M. Ranieri, P. Navalesi, D. Gregori, COVID-19 VENETO ICU Network, COVID-19 vaccination status among adults admitted to intensive care units in veneto, Italy, JAMA Netw. Open 5 (5) (2022 May 2) e2213553, https://doi.org/10.1001/jamanetworkopen.2022.13553. PMID: 35608862; PMCID: PMC9131739.

[23] R. Whittaker, A. Bråthen Kristofferson, B. Valcarcel Salamanca, E. Seppälä, K. Golestani, R. Kvåle, S.V. Watle, E.A. Buanes, Length of hospital stay and risk of intensive care admission and in-hospital death among COVID-19 patients in Norway: a register-based cohort study comparing patients fully vaccinated with an mRNA vaccine to unvaccinated patients, Clin. Microbiol. Infect. 28 (6) (2022 Jun) 871–878, https://doi.org/10.1016/j.cmi.2022.01.033. Epub 2022 Feb 25. PMID: 35219807; PMCID: PMC8872711.

[24] N. Busic, T. Lucijanic, B. Barsic, I. Luksic, I. Busic, G. Kurdija, L. Barbic, S. Kunstek, T. Jelic, M. Lucijanic, Vaccination provides protection from respiratory deterioration and death among hospitalized COVID-19 patients: differences between vector and mRNA vaccines, J. Med. Virol. 94 (6) (2022 Jun) 2849–2854.

[25] E. Ammirati, L. Lupi, M. Palazzini, N.S. Hendren, J.L. Grodin, C.V. Cannistraci, M. Schmidt, G. Hekimian, G. Peretto, T. Bochaton, A. Hayek, N. Piriou, S. Leonardi, S. Guida, A. Turco, S. Sala, A. Uribarri, C.M. Van de Heyning, M. Mapelli, J. Campodonico, P. Pedrotti, M.I. Barrionuevo Sánchez, A. Ariza Sole, M. Marini, M.V. Matassini, Vourc'h M, A. Cannatà, D.I. Bromage, D. Briguglia, J. Salamanca, P. Diez-Villanueva, J. Lehtonen, F. Huang, S. Russel, F. Soriano, F. Turrini, M. Cipriani, M. Bramerio, M. Di Pasquale, A. Grosu, M. Senni, D. Farina, P. Agostoni, S. Rizzo, M. De Gaspari, F. Marzo, J.M. Duran, E.D. Adler, C. Giannattasio, C. Basso, T. McDonagh, M. Kerneis, A. Combes, P.G. Camici, J.A. de Lemos, M. Metra, Prevalence, characteristics, and outcomes of COVID-19-associated acute myocarditis, Circulation 145 (15) (2022 Apr 12) 1123–1139, https://doi.org/10.1161/CIRCULATIONAHA.121.056817. Epub 2022 Apr 11. PMID: 35404682; PMCID: PMC8989611.

[26] A. Aleksova, A.L. Fluca, G. Gagno, A. Pierri, L. Padoan, A. Derin, R. Moretti, E.A. Noveska, E. Azzalini, S. D'Errico, A.P. Beltrami, A. Zumla, G. Ippolito, G. Sinagra, M. Janjusevic, Long-term effect of SARS-CoV-2 infection on cardiovascular outcomes and all-cause mortality, Life Sci. 310 (2022 Dec 1) 121018, https://doi.org/10.1016/j.lfs.2022.121018. Epub 2022 Sep 29. PMID: 36183780; PMCID: PMC9561478.

[27] J.H. Lee, J.J. Yim, J. Park, Pulmonary function and chest computed tomography abnormalities 6-12 months after recovery from COVID-19: a systematic review and meta-analysis, Respir. Res. 23 (1) (2022 Sep 6) 233, https://doi.org/10.1186/s12931-022-02163-x. PMID: 36068582; PMCID: PMC9446643.

[28] E. Strumiliene, I. Zeleckiene, R. Bliudzius, A. Samuilis, T. Zvirblis, B. Zablockiene, A. Strumila, V. Gruslys, L. Malinauskiene, V. Kasiulevicius, L. Jancoriene, Follow-up analysis of pulmonary function, exercise capacity, radiological changes, and quality of life two months after recovery from SARS-CoV-2 pneumonia, Medicina (Kaunas) 57 (6) (2021 Jun 3) 568, https://doi.org/10.3390/medicina57060568. PMID: 34204878; PMCID: PMC8229364.
[29] A. Watanabe, M. So, M. Iwagami, K. Fukunaga, H. Takagi, H. Kabata, T. Kuno, One-year follow-up CT findings in COVID-19 patients: a systematic review and meta-analysis, Respirology 27 (8) (2022 Aug) 605–616, https://doi.org/10.1111/resp.14311. Epub 2022 Jun 12. PMID: 35694728; PMCID: PMC9350074.
[30] M. Bocchino, G. Rea, L. Capitelli, R. Lieto, D. Bruzzese, Chest CT lung abnormalities 1 Year after COVID-19: a systematic review and meta-analysis, Radiology 308 (1) (2023 Jul) e230535, https://doi.org/10.1148/radiol.230535. PMID: 37404150.
[31] P. Laveneziana, L. Sesé, T. Gille, Pathophysiology of pulmonary function anomalies in COVID-19 survivors, Breathe 17 (3) (2021 Sep) 210065, https://doi.org/10.1183/20734735.0065-2021. PMID: 35035546; PMCID: PMC8753644.
[32] M. Vitacca, M. Paneroni, G. Brunetti, A. Carlucci, B. Balbi, A. Spanevello, N. Ambrosino, Characteristics of COVID-19 pneumonia survivors with resting normoxemia and exercise-induced desaturation, Respir. Care 66 (11) (2021 Nov) 1657–1664, https://doi.org/10.4187/respcare.09029. Epub 2021 Aug 24. PMID: 34429351.
[33] A. Mouzarou, M. Ioannou, E. Leonidou, I. Chaziri, Pulmonary embolism in post-CoviD-19 patients, a literature review: red flag for increased awareness? SN Compr Clin Med. 4 (1) (2022) 190, https://doi.org/10.1007/s42399-022-01273-3. Epub 2022 Aug 19. PMID: 35999860; PMCID: PMC9389494.
[34] G.T. Gerotziafas, et al., Persisting endothelial cell activation and hypercoagulability after COVID-19 recovery—the prospective observational ROADMAP-Post COVID-19 study, Hemato 3 (1) (2022) 111–121.
[35] M. Zuin, G. Rigatelli, C. Bilato, A. Porcari, M. Merlo, L. Roncon, G. Sinagra, One-year risk of myocarditis after COVID-19 infection: a systematic review and meta-analysis, Can. J. Cardiol. 39 (6) (2023 Jun) 839–844, https://doi.org/10.1016/j.cjca.2022.12.003. Epub 2022 Dec 12. PMID: 36521730; PMCID: PMC9743686.
[36] K. Karikó, M. Buckstein, H. Ni, D. Weissman, Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA, Immunity 23 (2005) 165–175.
[37] F. Caso, L. Costa, P. Ruscitti, et al., Could SARS-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? Autoimmun. Rev. 19 (2020).
[38] C. Indolfi, F. Barillà, C. Basso, M.M. Ciccone, A. Curcio, P. Gargiulo, S. Nodari, G. Mercuro, M. Mancone, S. Muscoli, R. Pedrinelli, A. Porcari, C. Spaccarotella, F. Romeo, G. Sinagra, P.P. Filardi, Expert consensus document della Società Italiana di Cardiologia (SIC): Sequele cardiovascolari post-acute dell'infezione da SARS-CoV-2 [Italian Society of Cardiology (SIC) Expert consensus document: Post-acute cardiovascular sequelae of SARS-CoV-2 infection], Italian, G. Ital. Cardiol. 23 (7) (2022 Jul) 491–503, https://doi.org/10.1714/3831.38166. PMID: 35771014.
[39] E. Azzolini, R. Levi, R. Sarti, C. Pozzi, M. Mollura, A. Mantovani, M. Rescigno, Association between BNT162b2 vaccination and long COVID after infections not requiring hospitalization in health care workers, JAMA 328 (7) (2022 Aug 16) 676–678, https://doi.org/10.1001/jama.2022.11691. PMID: 35796131; PMCID: PMC9250078.
[40] M. Nehme, O. Braillard, J. Salamun, F. Jacquerioz, D.S. Courvoisier, H. Spechbach, I. Guessous, Symptoms after COVID-19 vaccination in patients with post-acute sequelae of SARS-CoV-2, J. Gen. Intern. Med. 37 (6) (2022 May) 1585–1588, https://doi.org/10.1007/s11606-022-07443-2. Epub 2022 Feb 22. PMID: 35194744; PMCID: PMC8863092.
[41] P. Gao, J. Liu, M. Liu, Effect of COVID-19 vaccines on reducing the risk of long COVID in the real World: a systematic review and meta-analysis, Int. J. Environ. Res. Publ. Health 19 (19) (2022 Sep 29) 12422, https://doi.org/10.3390/ijerph191912422. PMID: 36231717; PMCID: PMC9566528.
[42] E. Wynberg, A.X. Han, A. Boyd, H.D.G. van Willigen, A. Verveen, R. Lebbink, K. van der Straten, N. Kootstra, M.J. van Gils, C. Russell, T. Leenstra, M.D. de Jong, G.J. de Bree, M. Prins, RECoVERED Study Group, The effect of SARS-CoV-2 vaccination on post-acute sequelae of COVID-19 (PASC): a prospective cohort study, Vaccine 40 (32) (2022 Jul 30) 4424–4431, https://doi.org/10.1016/j.vaccine.2022.05.090. Epub 2022 Jun 7. PMID: 35725782; PMCID: PMC9170535.
[43] J.P. Wisnivesky, U. Govindarajulu, E. Bagiella, R. Goswami, M. Kale, K.N. Campbell, K. Meliambro, Z. Chen, J.A. Aberg, J.J. Lin, Association of vaccination with the persistence of post-COVID symptoms, J. Gen. Intern. Med. 37 (7) (2022 May) 1748–1753, https://doi.org/10.1007/s11606-022-07465-w. Epub 2022 Mar 9. PMID: 35266128; PMCID: PMC8906626.
[44] C. Fernández-de-Las-Peñas, R. Ortega-Santiago, S. Fuensalida-Novo, J.D. Martín-Guerrero, O.J. Pellicer-Valero, J. Torres-Macho, Differences in long-COVID symptoms between vaccinated and non-vaccinated (BNT162b2 vaccine) hospitalized COVID-19 survivors infected with the Delta variant, Vaccines (Basel) 10 (9) (2022 Sep 6) 1481, https://doi.org/10.3390/vaccines10091481. PMID: 36146560; PMCID: PMC9504977.
[45] K. Cares-Marambio, Y. Montenegro-Jiménez, R. Torres-Castro, R. Vera-Uribe, Y. Torralba, X. Alsina-Restoy, L. Vasconcello-Castillo, J. Vilaró, Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis, Chron. Respir. Dis. 18 (2021 Jan-Dec) 14799731211002240, https://doi.org/10.1177/14799731211002240. PMID: 33729021; PMCID: PMC7975482.
[46] F. Wang, R.M. Kream, G.B. Stefano, Long-term respiratory and neurological sequelae of COVID-19, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 26 (2020 Nov 1) e928996, https://doi.org/10.12659/MSM.928996. PMID: 33177481; PMCID: PMC7643287.
[47] J.P. Rogers, E. Chesney, D. Oliver, T.A. Pollak, P. McGuire, P. Fusar-Poli, M.S. Zandi, G. Lewis, A.S. David, Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic, Lancet Psychiatr. 7 (7) (2020 Jul) 611–627, https://doi.org/10.1016/S2215-0366(20)30203-0. Epub 2020 May 18. PMID: 32437679; PMCID: PMC7234781.
[48] H. Yamamoto, S. Tanaka, D. Kasugai, M. Shimizu, Y. Tsuchikawa, Y. Hori, Y. Fugane, T. Inoue, M. Nagaya, N. Omote, M. Higashi, T. Yamamoto, N. Jingushi, A. Numaguchi, Y. Goto, Y. Nishida, Physical function and mental health trajectories in COVID-19 patients following invasive mechanical ventilation: a prospective observational study, Sci. Rep. 13 (1) (2023 Sep 4) 14529, https://doi.org/10.1038/s41598-023-41684-3. PMID: 37666912; PMCID: PMC10477337.