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Global cardiovascular risk, COVID-19 severity and post-COVID-19 syndrome: a clinical study

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Abstract. – OBJECTIVE: Post-COVID-19 is a syndrome defined by signs and symptoms present until 12 weeks after COVID-19, lasting for more than 8 weeks, not explained by an alternative diagnosis. The present study aimed to assess whether the cardiovascular risk (CVR) of patients with COVID-19 correlates with symptoms and changes in respiratory function parameters in post-COVID-19. The association between CVR and the severity of acute disease was also considered.

PATIENTS AND METHODS: Between 21/04/21-01/09/21, we enrolled 1,782 consecutive patients with COVID-19. We divided these subjects into (i) 4 levels, based on the severity of COVID-19 (home care; hospitalized/no oxygen therapy; hospitalized/oxygen therapy; hospitalized/NIV-ICU), (ii) 2 levels, according to CVR calculated with the European Society of Cardiology SCORE tables (low-intermediate risk; high or very high risk). All subjects underwent a 3-month follow-up considering post-COVID-19 symptoms.

RESULTS: In post-COVID-19 patients, high or very-high CVR was associated with (i) increased risk of hospitalization for COVID-19 ($p<0.0001$), (ii) higher prevalence of severe clinical manifestations and ICU admission ($p<0.0001$), (iii) development of post-COVID-19 ($p<0.0001$) and (iv) increased risk of a larger post-COVID-19 burden of disease.

CONCLUSIONS: We found a statistically significant association between CVR, severity of COVID-19, and post-COVID-19 syndrome three months after the end of acute disease.

Key Words:
Post-Acute COVID-19 Syndrome (PACS), Long-COVID, Cardiovascular risk, COVID-19 disease.

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has affected over 765 million people and caused over 6.9 million deaths globally[1]. Based on these data, it is even more evident that the new COVID-19 pandemic has caused such a significant impact and expenditure of resources on the healthcare system that the ability to combat the disease effectively has been compromised and has therefore contributed to further increases in associated mortality rates[2].

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In the context of the pathogenetic mechanisms implicated in the development of COVID-19, the disease, initially considered as an acute respiratory distress syndrome (ARDS), has progressively taken on the configuration of a multi-organ pathological condition, characterized by a cytokines storm, endothelial inflammation and dysfunction, micro- and macro-vascular thrombosis inducing multi-organ damage.

For this reason, understanding the possible risk factors associated with the severity of COVID-19 is therefore of utmost value to clinicians in identifying patients at high risk and requiring priority treatment to prevent progression to the more severe stages of the disease and adverse outcomes to reduce the impact on the healthcare system and reduce mortality rates associated with severe and critical forms of COVID-19[3]. Several studies[4-6] have shown that the presence of cardiovascular and metabolic comorbidities, such as systemic hypertension, diabetes mellitus, obesity, and smoking, are risk factors for increased severity and mortality of COVID-19 infection. In these patients, the pre-existence of cardiovascular disease is significantly associated with unfavorable outcomes in terms of COVID-19 severity and mortality[7].

Recent studies[8] have revealed that some of the pathological changes induced at the organ level by COVID-19 are long-lasting; in line with these findings, a large number of patients who have been infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) continue to experience symptoms after the acute phase of infection, which may evolve over time and persist for months. Such effects are referred to as "Post-Acute Sequelae of SARS-CoV-2 infection", "Long COVID" or "post-COVID-19 syndrome". Outcome studies[7,9] have shown that – two to six months after hospital discharge – the most reported symptoms are represented by fatigue or weakness, cough, resting and exertional dyspnea, arthralgias, chest pain, palpitations and arrhythmias, memory loss, anxiety and depression, concentration difficulties and sleep disturbances. Of note, 14-30% of COVID-19 patients develop clinical sequelae that require medical treatment or hospitalization within four months following the acute phase of the disease[7,10]. Regarding the spectrum of manifestations in post-COVID syndrome, respiratory symptoms appear to be common. A recent meta-analysis[11] of 40 studies involving 11,196 patients indicated that up to 48% of patients with post-COVID syndrome complained of respiratory symptoms. Some scholars[12] have shown the persistence of radiological and pulmonary functional changes after acute infection. Among the main respiratory functional changes, an alteration in gas exchange measured by the diffusing capacity of the lungs for carbon monoxide (DLCO) has been documented up to 12 weeks of follow-up[13,14]. The altered DLCO could be associated with interstitial and vascular damage secondary to acute infection[15,16]. These features may depend on the severity of the disease during acute COVID-19[17,18].

Little is known about the underlying causes of post-COVID-19 syndrome. For a better understanding of the post-COVID-19 syndrome, it is necessary to investigate its incidence, type of association, and risk factors. Studies[19] have shown that most of these patients have comorbidities, such as cardiovascular disease, diabetes mellitus, obesity, cancer, and chronic renal failure. In addition, other risk factors potentially associated with post-COVID-19 were advanced age, female gender, the severe clinical status of acute disease, a high number of comorbidities[20], hospitalization, and the need for oxygen therapy in the acute phase[21].

The goal of this study was to assess whether global CVR correlates with a greater risk of post-COVID-19 and with the incidence of a more serious burden of post-COVID-19 symptoms. We also assessed the association between estimated CVR and severity of the course of acute COVID-19.

Patients and Methods

We conducted a prospective, observational study using the "Post-acute COVID-19 Day Hospital Unit registry – Fondazione Policlinico Universitario Agostino Gemelli IRCCS di Roma, Italy", a prospective single-center observational registry including outpatients with previous COVID-19 who underwent a thorough medical evaluation in the post-acute phase of the disease through a comprehensive clinical and multidisciplinary assessment. Special attention was paid to the COVID-19-related history: each patient was asked to describe past and present symptoms and signs of COVID-19 and the treatment received for the disease[22].

The study was performed in accordance with the Declaration of Helsinki and was approved by

the ethics committee of the University Cattolica del Sacro Cuore in Rome (protocol ID number: 003220/20). All the patients gave their written consent to participate.

All subjects evaluated during the period from 21/04/2020 to 01/09/2021 with a previous COVID-19, aged 18 years or older, were consecutively enrolled and offered a clinical and instrumental follow-up at three months after the end of the acute illness by an outpatient service for post-acute patients established on 21/04/2020 at the Agostino Gemelli IRCCS University Polyclinic Foundation in Rome, Italy.

Exclusion criteria were: (i) age < 18 years, (ii) subjects lost at the follow-up. Patients who did not survive to the acute COVID-19 were not considered. At enrollment, a test for molecular detection of SARS-CoV-2 nucleic acid by Real Time-Reverse Polymerase Chain Reaction (RT-PCR) was performed in all patients. Only subjects with negative test results were included. Patients were offered a comprehensive, interdisciplinary medical evaluation with a thorough history and physical examination. Data on demographic, clinical, biochemical, instrumental, and COVID-19 characteristics were collected in an electronic database and managed using REDCap (Vanderbilt University, TN, USA) electronic data capture tools to minimize missing inputs and allow real-time data validation and quality control.

For this study, we considered the following variables: age, sex, cardiovascular risk factors (age, sex, total cholesterol, HDL, LDL, triglycerides, cigarette smoking, systemic hypertension, dyslipidemia), the clinical severity of the previous COVID-19 and the clinical symptoms of the post-COVID-19 syndrome (fever, asthenia and fatigue, cough, diarrhea, headache, anosmia, dysgeusia, conjunctival hyperemia, blurred vision or visual disturbances, syncope, dizziness, arthralgias and arthritis, skin, and mucous membrane lesions, sicca syndrome, Raynaud's phenomenon, myalgias, chest pain, sore throat, expectoration, rhinitis, inappetence, dyspnea, cough).

Post-COVID-19 dyspnea severity was summarized in a 4-level categorical variable (no dyspnea, mild exertional dyspnea, moderate exertional dyspnea, resting dyspnea); post-COVID-19 cough severity was summarized in a 3-level categorical variable (no cough, dry cough, productive cough).

The global cardiovascular risk was calculated by adopting the categories and scores (Systematic COronary Risk Evaluation 2, SCORE2 and Systematic COronary Risk Evaluation 2 Older Persons, SCORE2-OP) proposed by the European Society of Cardiology (ESC) 2021 Guidelines[23], subdividing the patients into a 2-level categorical variable:

1) Low or moderate risk: estimated cardiovascular risk <5% at ten years according to SCORE2 and SCORE-OP and without the conditions described below.
2) High risk [estimated cardiovascular risk 5-10% at ten years according to SCORE2 and SCORE-OP; moderate renal failure with estimated Glomerular Filtration Rate (eGFR) 30-44 mL/min/1.73 m^2 and ACR < 30 or eGFR 45-59 mL/min/1.73 m^2 and Albumin-to-Creatinine Ratio (ACR) 30-300 or eGFR ≥60 mL/min/1. 73 m^2 and ACR >300; familial hypercholesterolemia; diabetes mellitus (DM) patients without Atherosclerotic Cardiovascular Disease (ASCVD) or severe Target Organ Damage (TOD) and who do not meet moderate risk criteria] or very-high risk (estimated cardiovascular risk >10% at ten years according to SCORE2 and SCORE-OP; severe chronic renal failure with eGFR<30 mL/min/1.73 m^2 or eGFR 30-44 mL/min/1.73 mL/min/1.73 m^2 and ACR >30; DM with ASCVD or TOD or eGFR <45 mL/min/1.73 m^2 regardless of the presence of albuminuria or eGFR 45-59 mL/min/1.73 m^2 and microalbuminuria – ACR 30-300 mg/g – or proteinuria ACR >300 mg/g; presence of microvascular disease in at least three different sites, microalbuminuria plus retinopathy plus neuropathy; ASCVD documented clinically or on imaging).
3) We summarized the clinical severity of previous COVID-19 in a four-level categorical variable: (i) "home care" group, comprising home patients, (ii) "hospital, no oxygen" group, obtained by considering hospitalized patients who did not require oxygen therapy, (iii) "hospital, oxygen" group, which considered hospitalized patients who required oxygen supplementation but did not require high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), mechanical ventilation (VAM) or extracorporeal membrane oxygenation (ECMO), (iv) the "hospital, NIV or ICU" group, which consisted of patients undergoing HFNC, NIV, VAM, ECMO admitted to intensive care (ICU) or in the sub-intensive care units.

We also synthesized the clinical severity of COVID-19 into a dichotomous variable, considering non-hospitalized patients (category i of the categorical variable) and hospitalized patients (categories ii-iv of the categorical variable).

Statistical Analysis

Data were collected in an Excel file, then transformed into SPSS 13.0 (Chicago, IL, USA) files for statistical analysis, and processed anonymously.

We considered as continuous variables: age, blood gas analysis results (partial pressure of oxygen, PaO_2, partial pressure of carbon dioxide, pCO_2, PaO_2/FiO_2 ratio, and oxygen saturation, SpO_2) and all the spirometric data (forced ventilatory capacity, FVC, and FVC%, forced expiratory volume in one second, FEV1 and FEV1%, FEV1/FVC%, mean forced expiratory flow between 25% and 75% of the FVC, MMEF25-75, total lung capacity, TLC and TLC%, DLCO, and DLCO%).

All continuous variables were tested for normality using the Kolmogorov-Smirnov test: normal-distribution variables were presented as mean and standard deviation (SD) and compared with the *t*-test (two variables) or one-way analysis of variance (ANOVA, multilevel variables); non-normal-distribution variables were presented as a median and interquartile range [IQR] and were compared with the non-parametric Mann-Whitney U-test (two variables) and the Kruskal Wallis H-test (multilevel variables). ANOVA was also used to study linear trends between factor levels with polynomial analysis.

The following variables were collected as binary variables: cigarette smoking, systemic arterial hypertension, dyslipidemia, fever, asthenia or fatigue, cough, diarrhea, headache, anosmia, dysgeusia, conjunctival hyperemia, blurred vision, syncope, dizziness, arthralgia/arthritis, skin and mucosal lesions, sicca syndrome, Raynaud's phenomenon, myalgia, dyspnea on exertion, pain, and presence of cough.

We synthesized the post-COVID-19 symptoms, when expressed as binary variables, in a single categorical variable to express the number of post-COVID-19 manifestations. We also collected: 2-levels CVR (low or intermediate risk; high or very high risk), 4-level clinical severity of previous COVID-19, 2-level clinical severity of previous COVID-19. Last, we prepared a categorical variable containing both the clinical severity of previous COVID-19 (4-levels) and, in each level, we classified the patient at "low or intermediate risk" or at "high or very-high risk", thus obtaining an 8-levels categorical variable. Categorical or dichotomous variables were presented as absolute numbers and percentages and compared with the Chi-square test, odds ratios (OR) were calculated from 2×2 tables.

To clarify the relationship between post-COVID-19, CVR and clinical severity of COVID-19 we adopted a logistic regression model considering post-COVID-19 as dependent variable, CVR and clinical severity of COVID-19 as independent variables. Age, sex and single cardiovascular diseases or risk factors were not included in the model to reduce multicollinearity, since these factors were already considered in the SCORE definition.

We considered all differences to be significant at a level of $p<0.05$ in a two-tailed test. Statistical analysis was performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA) software for Windows systems.

Results

We enrolled a total of 1,782 consecutive patients. We summarized the baseline characteristics of the sample in Table I.

In patients with previous COVID-19, we observed that a high or very-high CVR was significantly associated with an increased risk of hospitalization for COVID-19, as shown in Panel A of Table II and Figure 1 (OR: 1.387; 95% CI: 1.150-1.673; $p<0.0001$, Chi-square test).

At the same time, we observed that high or very-high CVR, compared to low-moderate CVR, was associated with an increased prevalence of severe clinical manifestations of previous COVID-19 and hospitalization in the ICU when clinical severity is stratified at four levels, as shown in Panel B of Table II ($p<0.0001$, Chi-square test).

At three months, patients with a high or very-high CVR, compared to low-moderate CVR, were more likely to develop a post-COVID-syndrome with at least one symptom, as shown in Panel C of Table II (OR: 1.507; 95% CI: 1.228-1.849; $p<0.0001$, Chi-square test).

Of the symptoms observed at the 3-month follow-up visit of patients with previous COVID-19, we observed a significant relationship between CVR and the number of post-COVID-19 mani-

Table I. Baseline characteristics of the sample.

Age (± SD), years	55.0 ± 14.6
Male Sex (n, %)	917 (51.5%)
Clinical Severity (4 levels)	
1. Home Care (n, %)	1. 839 (47.1%)
2. Hospital. No Oxygen (n, %)	2. 123 (6.90%)
3. Hospital, Oxygen (n, %)	3. 454 (25.5%)
4. Hospital, NIV or ICU (n, %)	4. 366 (20.5%)
Clinical Severity (2 levels)	
1. Home Care (n, %)	1. 839 (47.1%)
2. Hospitalized (n, %)	2. 943 (52.9%)
Cardiovascular Risk (2 levels)	
1. Low-Moderate risk (n, %)	1. 722 (38.4%)
2. High risk or Very- High risk (n, %)	2. 1060 (61.5%)
Persistent post-COVID-19 symptoms at three months	
Fever (n, %)	33 (1.8%)
Asthenia or fatigue (n, %)	1019 (57.2%)
Cough (n, %)	
• No cough (n, %)	• 815 (45.7%)
• Dry cough (n, %)	• 173 (9.7%)
• Productive cough (n, %)	• 17 (0.9%)
Diarrhea (n, %)	147 (8.2%)
Headache (n, %)	322 (18.0%)
Anosmia (n, %)	243 (13.6%)
Dysgeusia (n, %)	214 (12.0%)
Conjunctival hyperemia (n, %)	117 (6.5%)
Blurred or reduced vision (n, %)	296 (16.6%)
Syncope (n, %)	13 (0.7%)
Vertigo (n, %)	181 (10.1%)
Arthritis or arthralgias (n, %)	541 (30.3%)
Skin or mucosal lesions (n, %)	115 (6.5%)
Sicca syndrome (n, %)	179 (10.0%)
Raynaud's phenomenon (n, %)	18 (1.0%)
Myalgias (n, %)	507 (28.4%)
Dyspnea (n, %)	
• No dyspnea (n, %)	• 1226 (68.8%)
• Resting dyspnea (n, %)	• 431 (24.2%)
• Mild effort dyspnea (n, %)	• 116 (6.5%)
• Moderate effort dyspnea (n, %)	• 9 (0.5%)
Dyspnea (n, %)	
• No dyspnea (n, %)	• 1226 (63.1%)
• Any Dyspnea (n, %)	• 556 (31.2%)
Chest pain (n, %)	343 (19.2%)
Sore throat (n, %)	88 (4.9%)
Expectoration (n, %)	105 (5.9%)
Rhinitis (n, %)	118 (6.6%)
Lack of appetite (n, %)	106 (5.9%)
Spirometric Parameters at three months	
FVC (± SD)	3.77-1.00
FVC% [IQR], %	0.95 [0.18]
FEV1 [IQR]	2.97 [1.11]
FEV1% [IQR], %	0.96 [0.18]
FEV1/FVC% (± SD)	0.83 (0.10)
MMEF 25-75 (± SD)	1.01 (± 0.31)
TLC (± SD)	5.81 (± 1.94)
TLC% [IQR]	0.96 [0.17]
DLCO (± SD)	22.9 (± 6.66)
DLCO% [IQR], %	0.86 [0.20]
Blood gas analysis results at post-COVID control at three months	
PaO_2 (± SD), mmHg	95.8 ± 11.9
pCO_2 (± SD), mmHg	39.2 ± 4.12
PaO_2/FiO_2 ratio (± SD), mmHg/%	430.6 ± 47.3
SpO_2 (± SD), %	96.7 ± 5.6

IQR = interquartile range; SD = standard deviation; FiO_2 = fraction of inspired oxygen; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; MMEF25-75 = mean forced expiratory flow between 25% and 75% of the FVC; PaO_2 = partial pressure of oxygen; pCO_2 = partial pressure of carbon dioxide; TLC=total lung capacity; DLCO = diffusing capacity of the lungs for carbon monoxide.

Table II. Differences between cardiovascular risk, previous COVID-19 and post-COVID-19 manifestations.

	Low-moderate risk	High-very high risk
Panel A: previous COVID-19 hospitalization ($p < 0.0001$, chi-square test)		
Home care (n, %)	414 (51.6%)	389 (48.4%)
Hospitalized (n, %)	425 (43.4%)	554 (56.6%)
Panel B: COVID-19 severity ($p < 0.0001$, chi-square test)		
Home care (n, %)	414 (51.6%)	389 (48.4%)
Hospital, No Oxygen (n, %)	36 (22.6%)	123 (77.4%)
Hospital, Oxygen (n, %)	215 (47.4%)	239 (52.6%)
Hospital, NIV or ICU (n, %)	174 (47.5%)	192 (52.5%)
Panel C: post-COVID-19 ($p < 0.0001$, chi-square test)		
No post-COVID-19 (n, %)	285 (54.3%)	240 (45.7%)
Post-COVID-19 (n, %)	554 (44.1%)	703 (55.9%)
Panel D: number of post-COVID symptoms ($p < 0.0001$, chi-square test)		
• No symptoms (n, %)	• 285 (54.3%)	• 240 (45.7%)
• One symptom (n, %)	• 198 (42.9%)	• 264 (57.1%)
• Two symptoms (n, %)	• 133 (44.5%)	• 166 (55.5%)
• Three symptoms (n, %)	• 94 (43.5%)	• 122 (56.5%)
• Four symptoms (n, %)	• 49 (47.6%)	• 54 (52.4%)
• Five symptoms (n, %)	• 37 (47.4%)	• 41 (52.6%)
• Six symptoms (n, %)	• 24 (43.6%)	• 31 (56.4%)
• Seven symptoms (n, %)	• 9 (33.3%)	• 18 (66.7%)
• Eight symptoms (n, %)	• 7 (87.5%)	• 1 (12.5%)
• Nine symptoms (n, %)	• 3 (33.3%)	• 6 (66.7%)
Panel E: dyspnea at 3 months after COVID-19 ($p < 0.0001$, chi-square test)		
No dyspnea (n, %)	660 (53.8%)	566 (46.2%)
Mild exertional dyspnea (n, %)	138 (32.0%)	293 (68.0%)
Moderate exertional dyspnea (n, %)	39 (33.6%)	77 (66.4%)
Severe exertional dyspnea (n, %)	2 (22.2%)	7 (77.8%)

NIV: non-invasive ventilation; ICU: intensive care unit.

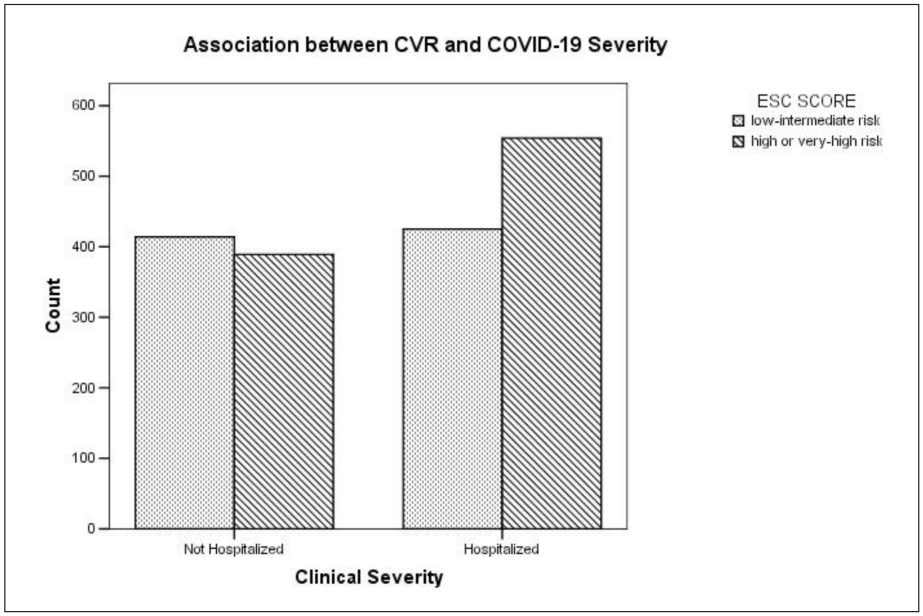

Figure 1. Differences between cardiovascular risk and severity of previous COVID-19 (2 levels), (p<0.0001, chi-square test).

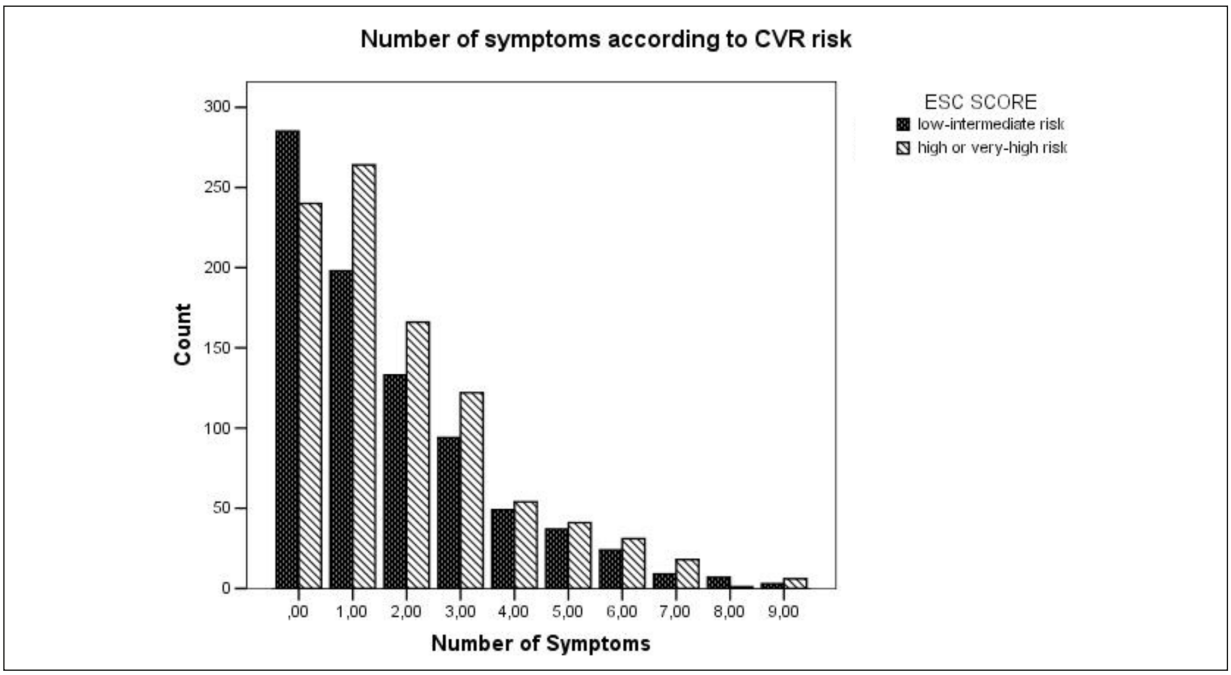

Figure 2. Differences between cardiovascular risk and number of post-COVID-19 symptoms (p<0.0001, chi-square test).

festations: patients with a high or very-high CVR were more likely to have one or more than one post-COVID-syndrome, as shown in Panel D of Table II and Figure 2 (p=0.004, Chi-square test).

Patients with a high or very-high CVR risk had more likely dyspnea at three months, and subjects with higher CVR had a higher prevalence of any form of dyspnea (mild exertion-

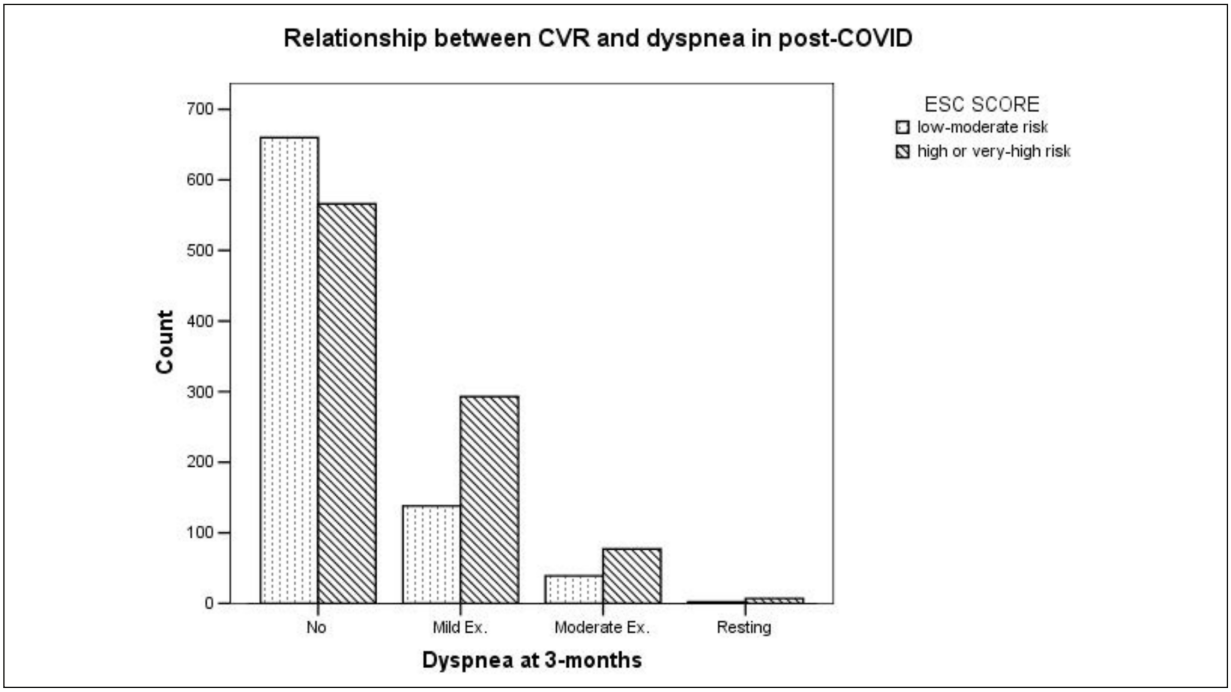

Figure 3. Differences between cardiovascular risk and dyspnea in post-COVID-19 (p<0.0001, chi-square test).

al, moderate exertional and resting dyspnea), as shown in Panel E of Table II and Figure 3 (p<0.001, Chi-square test).

The logistic regression model, considering post-COVID-19 development as the endpoint variable showed that both CVR (OR: 1.210; 95% CI: 1.071-1.369; p=0.002) and previous COVID-19 severity (OR: 1.311; 95% CI: 1.198-1.435; p=0.0001) predicted independently the outcome, as shown in Table III.

When considering the relationship between blood gas analysis data, spirometric data, previous COVID-19 severity and CVR, we observed, at the Kruskal-Wallis H test, that pO_2 (p=0.0001), PaO_2/FiO_2 ratio (p=0.0001), FVC (p=0.008), FVC% (p=0.004), FEV1 (p=0.003), MMEF 25-75 (p=0.043), TLC% (p=0.0001), DLCO (p=0.0001) and DLCO% (p=0.012) had a statistically significant difference of variance between the eight-categories variable. However, we observed that only PaO_2/FiO_2 ratio, DLCO and DLCO% showed a clinically significant difference, as shown in Table IV. Polynomial analysis with ANOVA confirmed a significant linear trend between categories in PaO_2/FiO_2, DLCO and DLCO%, as shown in Figures 4-6.

Discussion

In this study, we aimed to evaluate in a population of patients with previous COVID-19 infection whether CVR correlates with the incidence of symptoms and changes in respiratory function parameters in the context of post-COVID-19 syndrome. We also assessed the association between CVR and acute COVID-19 disease severity in this population.

Literature extensively shows that cardiovascular risk factors such as hypertension, diabetes mellitus, obesity, and previous coronary artery disease unfavorably influence the course of acute COVID-19 disease. A meta-analysis of 21 studies[24] of 77,317 patients hospitalized for COVID-19 showed that cardiovascular risk factors are associated with an increased risk of cardiovascular complications and a higher mortality rate. Consistent with these data, in our population, we observed that – compared to the low-to-moderate

Table III. Logistic regression analysis results.

Variable	p	OR	95% CI	
			Lower	Upper
CVR	0.0001	1.210	1.071	1.369
COVID-19s	0.002	1.311	1.198	1.435

CI = confidence interval; CVR= cardiovascular risk assessed with the ESC SCORE charts (2-levels variable); COVID-19s = previous COVID-19 severity (2-levels variable); OR = odds ratio.

Table IV. Differences in blood gas analysis and spirometric data according to previous COVID-19 severity and cardiovascular risk.

		Home care	Hospitalized, no oxygen	Hospitalized, oxygen	Hospitalized, NIV/ICU
Blood gas analysis					
PaO_2/FiO_2 (median, [IQR]), mmHg/%	L-CVR	450 [72.5]	425 [97]	404 [62.5]	410 [58]
	H-CVR	446 [72.75]	445.5 [63.75]	424 [69]	408 [77.25]
Spirometry					
DLCO (median, [IQR])	L-CVR	23.97 [8.71]	23.31 [10.66]	22.16 [8.49]	19.53 [5.77]
	H-CVR	23.46 [8.02]	22.44 [7.21]	20.81 [7.97]	19.3 [11.36]
DLCO% (median, [IQR])	L-CVR	0.9 [0.18]	0.95 [0.20]	0.83 [0.23]	0.83 [0.21]
	H-CVR	0.88 [0.17]	0.85 [0.16]	0.79 [0.20]	0.77 [0.28]

CVR = cardiovascular risk; L-CVR = low or intermediate cardiovascular risk; H-CVR = high or very-high cardiovascular risk; DLCO = diffusing capacity of the lungs for carbon monoxide; ICU = intensive care unit; IQR = interquartile range; NIV = non-invasive ventilation.

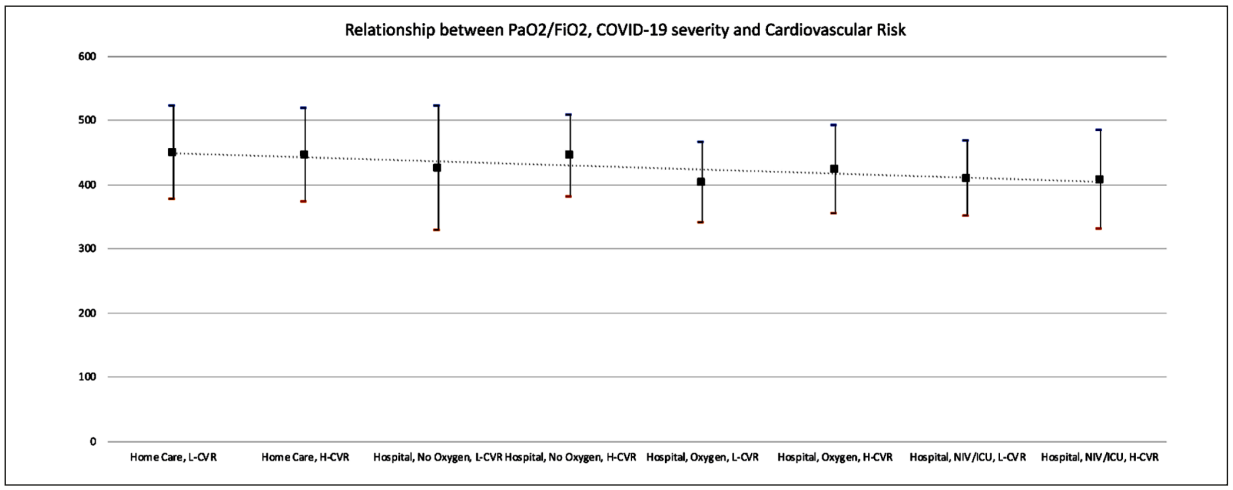

Figure 4. Relationship between PaO_2/FiO_2, previous COVID-19 severity and cardiovascular risk.

CVR – COVID-19 patients at high or very high CVR were more likely to be hospitalized and to develop a severe or critical illness and thus to develop severe respiratory failure requiring invasive or non-invasive ventilation or ECMO and to be admitted to the ICU. Several elderly, critically ill subjects are currently hospitalized for COVID-19 and its complications, such as sepsis[25], in internal medicine departments with subintensive care areas. This result, obtained in a population of subjects who survived acute illness, does not consider mortality.

Regarding post-COVID-19 syndrome, data correlating previous cardiovascular diseases with the development of symptoms referable to the post-COVID-19 syndrome are becoming increasingly convincing in the literature.

In patients with previous COVID-19, cardiovascular comorbidities are associated with an increased risk of post-COVID-19 sequelae, including dyspnea[26]. Furthermore, it is now known that after discharge, patients with previous COVID-19 may present with residual functional respiratory impairment, the most common finding of which is a reduction in DLCO. The severity and duration of the latter impairment correlate with the severity of the acute disease[27]. Impaired DLCO has been reported in 39% of the overall population and 66% of patients with severe disease[28]. To further confirm these observations, a recent cohort

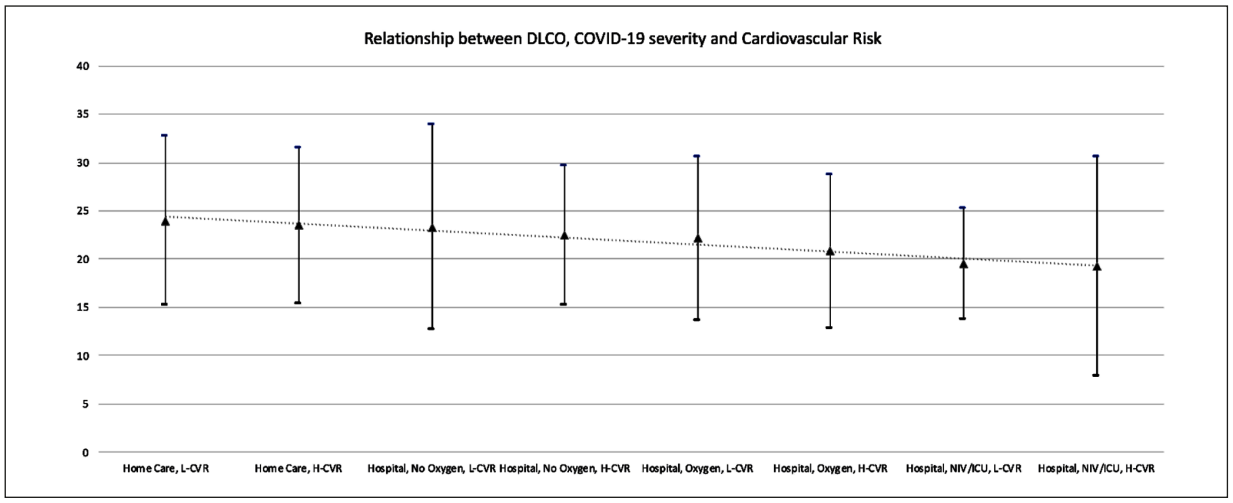

Figure 5. Relationship between DLCO, previous COVID-19 severity and cardiovascular risk.

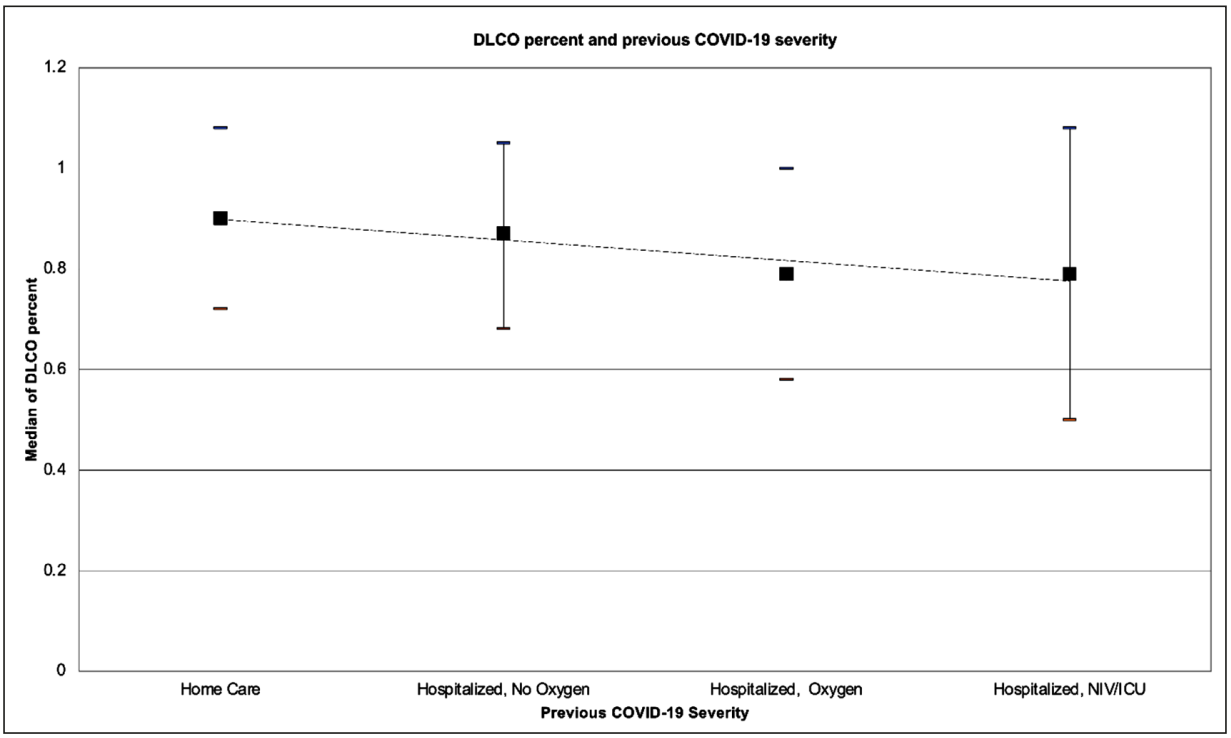

Figure 6. Relationship between DLCO%, previous COVID-19 severity and cardiovascular risk.

study[29], which was the first to investigate the correlation between the severity of acute respiratory failure – as measured by PaO_2/FiO_2 Ratio (P/F) ratio- during hospitalization and residual respiratory impairment after discharge – showed that at follow-up one month after the end of hospitalization, patients with a P/F during hospitalization of less than 200 had a lower DLCO than patients with a higher P/F[30].

Patients with a higher CVR had an increased risk of developing post-COVID-19 syndrome, and we also observed a higher probability of developing more symptomatic post-COVID-19, including fever, asthenia and fatigue, diarrhea, headache, anosmia, dysgeusia, red eyes, impaired or blurred vision, dizziness, arthralgias and arthritis, and chest pain. Notably, patients with a high or very high CVR had a higher prevalence of persistent dyspnea at three months.

Among the spirometric data, we observed that both DLCO and FEV1 were significantly reduced among patients with a higher burden of CVR.

Limitations

We would like to emphasize that our study group consists of a roughly equal proportion of individuals who were not hospitalized (47.1%) and those who were hospitalized (52.9%), but it is important to note that within the hospitalized category, each individual subcategory is smaller compared to the non-hospitalized category. Moreover, in this study, we did not consider the influence of specific SARS-CoV-2 variants and the potential protective effect of vaccines. This aspect should be addressed in dedicated study cohorts designed to investigate these facets of the disease.

Conclusions

The results of our study, conducted in a large prospective sample of patients with previous COVID-19 infection and varying severity of acute illness, demonstrate a statistically significant association between CVR, the severity of COVID-19 acute illness, and post-COVID-19 symptoms.

The results of this study may be of relevance in the management of patients with previous COVID-19 disease to stratify better the potential risk of them developing symptoms and functional alterations typical of the post-COVID-19 syndrome; moreover, the confirmation that individual cardiovascular risk factors and cardiovascular

disease as a whole may influence the course of the acute disease may help the clinician to identify better 'frail' patients deserving of privileged attention in the prevention and management of acute COVID-19 disease.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Informed Consent
Written informed consent was obtained from all participants involved in the study before entry into the study.

Ethics Approval
The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Catholic University of Rome (protocol ID number: 003220/20).

Authors' Contribution
Conceptualization, L.F., V.Z. and L.S.; methodology: L.F., V.Z. and L.S.; software: L.F.; formal analysis: L.F., V.Z. and L.S.; data curation: L.F., V.Z., L.S. M.T. and G.A.C.-P.-A.S.G.; writing—original draft preparation: L.F., V.Z., L.S., S.S., E.G., G.V., S.C., M.D. and C.M.; writing—review and editing: L.F., V.Z., L.S., S.S., E.G., G.V., S.C., M.D., C.M., A.S. and G.M.; supervision: A.G., F.L., A.S. and G.M.; project administration: L.S., A.G., F.L., A.S. and G.M. All authors have read and agreed to the published version of the manuscript.

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Availability of Data and Materials
The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

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