RESEARCH LETTER

Myocarditis after COVID-19 pneumonia: incidence and risk factors

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Introduction Although the clinical course of SARS--CoV-2 infection is predominantly manifested as respiratory involvement, it is already widely known that COVID-19 affects multiple organ systems, including the cardiovascular system.[1-5] Cardiac manifestations of COVID-19 vary widely from mild to severe arrhythmias, heart failure with left, right, or biventricular dysfunction, acute coronary syndrome, thrombotic disease (causing venous and arterial thromboembolism), to myocarditis and pericarditis.[4,6-10] True incidence of myocarditis caused by COVID-19 is difficult to assess due to ambiguous definitions and lack of systemic prospective data in this field. The diagnosis of myocarditis (also in mildly symptomatic patients) can be based on the cardiac magnetic resonance (CMR) criteria. Routine CMR as a screening tool for myocarditis for all the patients who have recovered from COVID-19 is often inaccessible, for example, due to its cost. Therefore, it is crucial to distinguish the features that would allow the physicians to identify the group requiring extended diagnostics of myocarditis.

The aim of this study was to assess the incidence of infection-related myocarditis and attempt to identify the risk factors for heart involvement in a short period after hospitalization for moderate to severe pneumonia caused by SARS-CoV-2.

Patients and methods This was a prospective observational cohort study conducted in a group of consecutive patients 1 month after discharge from a hospital after moderate to severe COVID-19 pneumonia. The study was performed in the outpatient clinic of the National Tuberculosis and Lung Diseases Research Institute (NTBLDRI) in Warsaw, Poland, and covered the period from September to November 2020.

All patients underwent standard clinical assessment, laboratory tests, radiological chest examination (including high-resolution computed tomography [HRCT]), and electrocardiography during hospitalization. Shortly after discharge (7–30 days, following 2 negative polymerase chain reaction tests for SARS-CoV-2) all patients underwent pulmonary function tests (PFTs) (including spirometry, body plethysmography, and lung transfer factor for carbon monoxide [TL_{CO}]) and CMR.

The methodology of PFT and CMR is described in Supplementary material (section *Methods*).

The updated Lake Louise criteria were used for the diagnosis of myocarditis on CMR.[11]

Ethics The patients provided written informed consent to participate in the study. The study was also approved by NTBLDRI Ethics Committee (KB 80/2020, KB 97/2020).

Statistical analysis Descriptive data are presented as medians and interquartile ranges (IQRs) as indicated. Group comparisons were made with the Mann–Whitney test with continuity correction. The incidence and its ratios are presented as numbers of patients in groups and percentages. The χ^2 test was used to check the differences in the frequency of observations. Logistic regression analysis was used to predict myocarditis based on the presence of the examined potential risk factors. The model that was well-fitted (Hosmer–Lemeshow test), and showed the best accuracy (area under the receiver operating characteristics [ROC] curve) was chosen. A P value below 0.05 was considered significant. All statistical analyses were performed using Statistica package version 9.1 (StatSoft Inc., Tulsa, Oklahoma, United States) and MedCalc statistical

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software version 20.2 (MedCalc Software Ltd, Ostend, Belgium)

Results A total of 75 consecutive patients at a median (IQR) age of 59 (46–66) years were included. Of those, 46 (61%) were men, 28 (37%) were ever smokers, and their median lung involvement was 50% (IQR, 30%–60%). Detailed characteristics are given in Supplementary material (section *Results, Table S1*). None of the patients had previously been diagnosed with chronic lung disease, however, 33% were diagnosed with heart-related comorbidity. All patients exhibited resting oxygen saturation above 90% at the beginning of the walk test (none of them needed oxygen supplementation).

CMR revealed signs of active myocarditis in 32 patients (43%), pericarditis in 27 patients (36%), and 26 participants were free of any heart involvement.

The patients with the signs of myocarditis had significantly different functional parameters as assessed with CMR, except for right ventricular ejection fraction, more frequently were men and ever smokers, and more frequently had reduced TL_{CO} (**TABLE 1**).

Several models including the factors easily accessible in clinical practice were estimated to evaluate an association with myocarditis as outcome. The final model with satisfactory accuracy included: sex, smoking status, lung function disturbances, and degree of lung involvement in the acute phase of COVID-19. Multivariable analysis indicated that male sex (odds ratio [OR], 4.22; 95% CI, 1.16–15.32; $P = 0.03$), low TL_{CO} (OR, 6.17; 95% CI, 1.4–27.0; $P = 0.02$), and ever smoking (OR, 4.29; 95% CI, 1.25–14.67; $P = 0.02$) were the factors associated with myocarditis (Supplementary material, section *Results, Figure S1*). The lung involvement was inversely associated (OR, 0.96; 95% CI, 0.93–0.99; $P = 0.01$) with myocarditis. This model correctly classified 80% of cases and was predictive in over 84% (area under the ROC curve).

Discussion The diagnosis of myocarditis is still difficult, as it can be clinically "silent" at the early stage of heart impairment and cause nonspecific symptoms. However, the first discernible symptoms can be related to malignant arrhythmias, progressive heart failure, or even sudden cardiac death.[12]

The age-standardized incidence of myocarditis in the general population is estimated at about 40 per 100 000.[13] The actual frequency as well as risk factors for COVID-19–mediated myocarditis are poorly recognized. Epidemiological data on the incidence of myocarditis in COVID-19 patients varies, although a higher percentage than in the general population can be expected.[14] In our study, 43% of the consecutive patients shortly after COVID-19 pneumonia requiring hospitalization presented with radiological signs of myocarditis. However, at the time of the CMR examination, they had no evident acute clinical symptoms suggesting myocarditis. In a study conducted in the German cohort recently recovered from COVID-19,[14] CMR revealed ongoing myocardial inflammation in 60% of patients, out of which only 33% required hospitalization during the acute phase of the disease. In another prospective study conducted in the United Kingdom,[15] 19% prevalence was reported at a median of 141 days (IQR, 110–162) after the initial symptoms of COVID-19. Post–COVID-19 myocarditis can even develop in healthy, well-trained athletes, where the criteria on CMR have been met in 2.3% to 19% of individuals (Supplementary material, *Reference List 2*).[S16-S18]

In our group, all the patients had suffered from pneumonia requiring hospitalization, but during the CMR examination only a few of them reported symptoms such as cough, shortness of breath, or other nonspecific symptoms (such as chest discomfort) that could also be caused by myocarditis. It is known that myocarditis can occur even after resolution of the respiratory tract infection.[12,S19] We found no relationships between the presence of symptoms and the presence of myocarditis.

We can rule out a potential effect of COVID-19 vaccinations on myocarditis[S20], because we analyzed a group of patients who had not yet been vaccinated (the study was conducted prior to the widespread access to vaccination).

In our study, the significant risk factor for myocarditis was male sex. This factor also predominates in other reports on COVID-19–related myocarditis.[14,S21,S22] To date, the findings from a study on experimental autoimmune myocarditis (EAM)[S23] have indicated sex-specific alterations at the inflammatory stage of EAM, with a pro-inflammatory phenotype in men and an anti-inflammatory phenotype in women.

In another cohort study[S24] of Spanish COVID-19 survivors, performed at least 6 months after the disease, female sex and tobacco consumption were risk factors for symptomatic long COVID. However, the patients were not examined for myocarditis.

Another risk factor for myocarditis in the studied group was the fact of ever smoking. There are no studies with a design that enables a comparative approach to this phenomenon. In the previously mentioned prospective study from Germany,[14] no differences were found regarding myocarditis prevalence in smokers and nonsmokers.

There are few studies that provide parallel information on PFTs and features of myocarditis on CMR, and they differ in methodology and group selection. We did not find a significant impact of myocarditis on the 6-minute walking distance test, although such an association was observed in another study.[5] This may be due to clinically asymptomatic myocarditis, where significant structural and hemodynamic disturbances have not yet occurred. TL_{CO} disturbances are the most sensitive indicator of alveolar-capillary barrier pathology, which may be an expression of both lung and heart diseases, and had been reported in

TABLE 1 Study group characteristics according to the results of cardiac magnetic resonance examination

Characteristics	Myocarditis		*P* value
	No (n = 43)	Yes (n = 32)	
CMR findings shortly after the acute phase of COVID-19 (7–30 days)			
LVEF, %	61 (58–67)	59.5 (53.5–63.75)	0.04
LVEDV, ml	139.8 (108.6–163.3)	158.8 (148.8–179)	0.003
LVEDVi, ml/m^2	68.1 (56.1–79.3)	77.2 (72.7–84)	0.005
LVESV, ml/m^2	49.2 (39.9–70)	67.85 (57.1–71.2)	0.003
LVESVi, ml/m^2	24.8 (21.6–31.4)	31.6 (27.1–36)	<0.001
RVEF, %	60 (55–65)	58 (51–62)	0.09
RVEDV, ml	145.2 (110.2–171.3)	174.9 (151.1–188.2)	0.005
RVEDVi, ml/m^2	70.4 (56.3–84)	84.15 (72.5–92.1)	0.005
RVESV, ml/m^2	57.2 (43.5–75.8)	76 (60.1–89.6)	0.003
RVESVi, ml/m^2	27.6 (22.6–36.2)	36.05 (29.1–41)	0.003
LGE, any pattern	17 (39.5)	32 (100)	<0.001
LGE, nonischemic pattern	16 (37.2)	32 (100)	<0.001
LGE, ischemic pattern	1 (2.3)	2 (6.3)	0.39
Acute pericarditis	14 (32.6)	9 (28.1)	0.63
Edema	5 (11.1)	32 (100)	<0.001
Demographic and clinical data			
Male sex	20 (46.5)	26 (81.3)	0.002
Age, y	59 (46–67)	56 (47–65)	0.90
BMI, kg/m^2	28.91 (25.4–33.3)	27.57 (25.5–30.6)	0.19
Ever smokers	10 (23.3)	18 (56.3)	0.004
Heart-related comorbid disease	18 (41.9)	7 (21.9)	0.07
The acute phase of COVID-19 (during hospitalization)			
Lung involvement on HRCT, %	50 (30–60)	40 (25–60)	0.08
CRP, mg/l	74 (46–177)	72 (40–147)	0.32
NT-proBNP, pg/ml	131 (56–328)	127 (51.2–263)	0.63
IL-6, pg/ml	32.25 (13.8–66.3)	51.45 (24–89.1)	0.15
WBC, $\times 10^9$/l	6.1 (4.4–9)	5.6 (4.5–6.4)	0.27
CK-MB, IU/l	113 (59–180)	110 (63–160)	0.94
Symptoms after the acute phase of COVID-19 (7–30 days)			
Cough (persistent)	21 (48.8)	15 (46.9)	0.87
Dyspnea (persistent)	3 (7)	1 (3.1)	0.46
Low exercise tolerance	22 (51.2)	18 (56.3)	0.66
Any symptoms	33 (76.7)	24 (75)	0.86
Lung function shortly after the acute phase of COVID-19 (7–30 days)			
FEV1/FVC, Z-score	0.29 (–0.26 to 0.96)	–0.02 (–0.67 to 0.61)	0.13
Airway obstruction	2 (4.7)	2 (6.3)	0.76
TLC, Z-score	–0.32 (–1.21 to 0.65)	–0.63 (–1.03 to 0.24)	0.59
TLC, %pred	96.23 (85.02–107.91)	92.09 (87.39–102.9)	0.51
TLC < LLN, %	7 (16.7)	4 (12.5)	0.62
FVC, Z-score	–0.36 (–1.18 to 0.4)	–0.19 (–0.84 to 0.44)	0.60
FVC, %pred	95.1 (82.55–106.53)	97.4 (87.1–106.05)	0.63
FVC < LLN, %	8 (18.6)	4 (12.5)	0.48
FEV1, Z-score	–0.33 (–0.81 to 0.4)	–0.52 (–0.79 to 0.67)	0.75
FEV1, %pred	95.33 (86.32–105.74)	93.04 (86.88–108.53)	0.79
TL_{co}, Z-score	–0.92 (–1.42 to –0.07)	–1.61 (–2.35 to –0.07)	0.09
TL_{co}, %pred	85.74 (80.03–98.92)	76.35 (67.3–98.91)	0.06
TL_{co} < LLN, %	8 (18.6)	15 (46.9)	0.009
6MWD, m	544.5 (480–613)	580.5 (465–654)	0.46

Data are shown as number (percentage) of patients or median (interquartile range).

Abbreviations: 6MWD, 6-minute walking distance; BSA, body surface area; CK-MB, creatine kinase-myoglobin binding; CMR, cardiac magnetic resonance; CRP, C-reactive protein; FEV1, forced expiratory volume at 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IL-6, interleukin 6; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index (calculated by LVEDV/BSA); LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index (calculated by LVESV/BSA); NT-proBNP, N-terminal pro–B-type natriuretic peptide; RVEDV, right ventricular end-diastolic volume; RVEDVi, right ventricular end-diastolic volume index (calculated by RVEDV/BSA); RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVESVi, right ventricular end-systolic volume index (calculated by RVESV/BSA); TLC, total lung capacity; TL_{co}, lung transfer factor for carbon monoxide; WBC, white blood cell count

post-COVID patients as the most common finding in terms of lung function abnormalities.[5,S25,S26] Since the extent of underlying lung disease does not sufficiently explain the impairment of TL_{CO}, circulatory causes must be considered. Our prospective analysis, conducted in a group of consecutive COVID-19 patients, indicates that myocarditis may be associated with the reduction of TL_{CO}.

Interestingly, models including other factors, such as preexisting cardiovascular comorbidity or symptoms appearing after COVID-19 had less statistical power (worse goodness of fit for the logistic regression model when assessed in the Hosmer–Lemeshow test).

Based on simple indicators, such as sex, smoking status, and PFT, it is possible to preselect the group in which CMR may be the best available modality to assess and quantify myocardial inflammation in the setting of long COVID.

All patients with abnormalities on CMR were immediately referred to a cardiologist for further care, and we have not received any feedback about severe or unfavorable further course of the heart disease as a consequence of myocarditis.

Limitations of the study The analysis did not cover mildly symptomatic patients in the first acute phase of COVID-19 who were not hospitalized. We were able to determine the prevalence, not incidence of myocarditis, because we do not know if the patients we observed were previously healthy. The conclusion regarding risk factors for myocarditis may be limited due to the relatively small size of the group. The Lake Louise criteria we used had not been validated as a screening tool for low-to-intermediate risk patients.[11] We also did not analyze pediatric patients.

Conclusions Myocarditis was detected in 43% of consecutive patients who experienced COVID-19 pneumonia. This finding was not associated with initial lung involvement on HRCT, the presence of clinical symptoms, and abnormalities in available laboratory tests. However, we were able to identify the risk factors for the presence of myocarditis features on CMR in the studied group. Based on that, we conclude that male sex and ever smoking, together with low TL_{CO} after COVID-19 may help to identify patients who should undergo heart examination.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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