Idiopathic Inflammatory Myopathies in the Post-COVID-19 Era: A Spotlight on Cardiac Impairment

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Abstract

Background

As the COVID-19 pandemic progresses, there have been reports of a syndrome involving multisystem organ damage following the immune response to the virus. However, it remains unclear whether patients with specific autoimmune diseases, such as idiopathic inflammatory myopathies (IIMs), exhibit a predisposition to unique pathological damage and whether their clinical phenotypes are altered by COVID-19.

Methods

This study was a retrospective case—control study that included 62 patients with IIMs who had a prior history of COVID-19 (prior COVID-19, PC) and 52 patients without such a history (no prior COVID-19, NPC). Medical histories, laboratory examinations, and echocardiography data were compared between the two groups. Additionally, we investigated the potential molecular mechanisms underlying the association between COVID-19 and post infection clinical phenotypes in IIMs using publicly available transcriptome databases.

Results

Compared to the NPC group, patients in the PC group exhibited a higher prevalence of cardiopulmonary symptoms, including palpitation and dyspnea, as well as elevated levels of pulmonary and cardiovascular myositis activity assessment visual analog scales (MYOACT)/myositis intention-to-treat activity index (MITAX), cardiac troponin T, and hydroxybutyrate dehydrogenase (HBDH). Echocardiographic analysis revealed larger left atrium (LA) dimensions, interventricular septum (IVS) thickness, and an increased ratio of peak velocity of left ventricular early-diastolic fast filling to the velocity of early diastolic myocardial movement at mitral ring (E/e') in the PC group compared to the NPC group. Transcriptional data analysis based on public databases revealed that various mechanisms, including collagen matrix proliferation, regulation of the calcium ion pathway, oxidative stress, cell proliferation, and inflammatory molecules, collectively contribute to the pathogenesis of IIMs and COVID-19 infection.

Conclusion

Patients with IIMs exhibit more pronounced myocardial damage and impaired cardiac diastolic function following COVID-19, thereby offering valuable insights for the clinical management of IIMs patients and potential avenues for further investigation into the long-term consequences of COVID-19.

Introduction

Although the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has diminished, effective control measures have been implemented for coronavirus disease 2019 (COVID-19), leading to a gradual decline in the COVID-19 epidemic. However, as we transition into the post-COVID-19 era, increasing attention is being directed toward post-COVID-19 syndrome. According to a previous report, SARS-CoV-2 infections have been associated with an increased susceptibility to cardiovascular conditions, coagulation and hematological disorders, diabetes, neurological ailments, pulmonary complications, and mortality [1]. The salient point is that post-COVID-19 can induce immune dysregulation, leading to the generation of multiple autoantibodies alongside diverse clinical manifestations [2, 3]. Various autoantibodies, including anti-nuclear antibodies (ANA), lupus anticoagulants, anti-2-glycoprotein 1β, and anti-cardiolipin antibodies, have been identified in COVID-19 patients [2]. A plethora of reports on autoimmune thrombocytopenic purpura, autoimmune hemolytic anemia, inflammatory arthritis, and vasculitis following COVID-19 further substantiate the potential association between COVID-19 and autoimmune diseases [2, 3].

IIMs are a group of systemic autoimmune inflammatory diseases, including dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), anti-synthase antibody syndrome (ASS), and inclusion body myositis (IBMs), mainly involving the proximal muscles of the extremities [4]. Various viral infections, such as coxsackie B, parvovirus, enterovirus, human T-cell-lymphotropic virus (HTLV-1), and human immunodeficiency virus (HIV), have been recognized as significant environmental factors in the development of IIMs [2]. Following COVID-19 infection, patients frequently experience symptoms such as myalgia, myasthenia, and elevated creatine kinase levels, and even new-onset IIMs have been reported [3]. However, it remains unclear whether COVID-19 has altered the clinical manifestations of IIMs. Our study aims to comprehensively summarize the clinical features, laboratory findings, and imaging data of IIMs patients with a history of COVID-19 while exploring the potential mechanisms underlying post-COVID-19 IIMs.

Methods

Research design and subjects

In this retrospective case–control study conducted at a single center, we included 333 patients with IIMs who were admitted to West China Hospital between January 2022 and May 2023. The outbreak of COVID-19 in China occurred widely in early 2023. To eliminate the potential influence of seasonal and climatic factors on the disease, we excluded 144 IIM patients hospitalized between June and December 2022. Additionally, we excluded 10 patients with suspected IIMs diagnosis, 15 patients with missing data, 30 individuals with other connective tissue diseases (CTD), 11 patients with malignant tumors, 3 individuals with neurogenic myopathy, 1 patient with tuberculosis, and 8 patients in the acute phase of COVID-19 infection. Subsequently, the remaining patients were divided into two groups based on their year of hospitalization visit. Among the total cohort of 52 IIM patients hospitalized in 2022, no prior

history of COVID-19 was reported (nonprior COVID-19, NPC). Furthermore, to obtain a group that had experienced a previous episode of COVID-19 infection, prior to enrollment, we excluded 7 patients from those hospitalized in 2023 who did not have a history of COVID-19. Thus, a final cohort of 62 IIMs patients with a history of prior COVID-19 (PC) was established. The evaluation and inclusion process for these patients is illustrated in Fig. 1. All participants were aged 18 years or older and met the 2017 EULAR/ACR criteria for the classification of IIMs [5]. The study protocol was approved by the ethics committee of West China Hospital, Sichuan University (No695 in 2020), and complied with the Declaration of Helsinki.

Collection of clinical features

The patients' medical records were retrospectively reviewed. Data missing more than 10% of clinical features were deleted. The data collected included demographic characteristics, such as age, sex/gender, duration of IIMs, clinical symptoms and signs, including fever, cough, expectoration, dyspnea, arthritis, myalgia, myasthenia, and rash, and laboratory features, including routine blood parameters, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, alkaline phosphatase (ALP) level, gamma glutamyltransferase (GGT), creatine kinase (CK) level, lactate dehydrogenase (LDH) level, hydroxybutyrate dehydrogenase (HBDH) level, myoglobin protein (MYO) level, cardiac troponin T (cTnT) level, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, creative kinase isoenzyme MB (CK-MB) level, triglyceride level, cholesterol level, d dimer level, antinuclear antibodies (ANA), anti-Ro52 antibody, myositis specific antibodies, and echocardiographic parameters.

Myositis Disease Activity Assessment

Disease activity scores were performed by two experienced rheumatologists based on medical records. Disease activity for IIMs was measured using myositis activity assessment visual analog scales (MYOACT) and the myositis intention-to-treat activity index (MITAX), which was established by the International Myositis Assessment and Clinical Studies (IMACS) group. Detailed scoring methods can be found in our previous article [6].

Analysis of Differentially Expressed Genes

We retrieved the COVID-19 patient dataset (GEO accession ID: GSE151879), which used the high-throughput sequencing Illumina NextSeq 500 platform to detect RNA sequences, from which we sorted out the information of myocardial tissue samples from 3 COVID-19 patients and 3 normal people[7]. The DM patient dataset (GEO accession ID: GSE143323), including muscle samples from 39 DM patients and 20 healthy controls, was extracted from RNA sequences using the high-throughput sequencing Illumina HiSeq 3000 platform[8]. Using R software (2) the "DESeq2" and the "edgeR" package, COVID-19 dataset (GSE151879) and DM dataset (GSE143323), to |Log2 Fold Change| > 0.585 and | adj.P.Val. A value of | < 0.05 was used as the implementation standard to find the differentially expressed genes (DEGs) of the two datasets, and the "Venn" package in R software (4.2.1) was used to screen out the common DEGs

that were differentially expressed and upregulated or downregulated in the two datasets at the same time. Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis were performed on DEGs using the enrichment database to reveal the functions of DEGs. The "clusterProfiler" package in R software (4.2.1) was used to screen the common DEGs of potential biological functions and physiological pathways. GO terms included three parts: biological process (BP), cellular component (CC) and molecular function (MF). A P value < 0.05 and q-value < 0.25 were used as standardized indexes.

Statistical analysis

SigmaPlot 12.5 and/or GraphPad Prism 8.0.2 software were used for data analysis. Continuous variables are presented as the mean ± standard deviation (M ± SD) or median (Q25, Q75) depending on whether they fit the normal distribution. Categorical variables are described statistically using percentages. When the normality (Shapiro–Wilk) test was passed, an independent-samples T test and one-way ANOVA were conducted for two-group or multiple comparisons, respectively; otherwise, the Mann–Whitney U test was conducted for comparison. Chi-square tests were used to compare categorical variables. All tests were bilateral, and P < 0.05 was considered statistically significant.

Results

Baseline demographic

The baseline characteristics of the patients are presented in Table 1. As observed, the general baseline characteristics, including age, sex, BMI, and duration of IIMs, were comparable between both groups (Table 1). The proportion of patients with a first diagnosis of IIMs was 33 (63.46%) and 42 (67.74%) in the NPC and PC groups, respectively, showing no significant difference (p > 0.05). In the PC group, the time elapsed from prior COVID-19 infection ranged from 3 weeks to 5 months (data not shown), with an average duration of 2.48 ± 1.19 months. There were no statistically significant differences in comorbidity prevalence between the two groups (P > 0.05). Both groups included patients with various subtypes of IIMs; however, a trend toward a higher proportion of ASS subtypes was noted in the PS group (p = 0.068), while a lower proportion of DM subtypes was observed (p = 0.053).

Table 1
Baseline characteristics of IIMs patients

Characteristic	No prior COVID-19 (NPC, n = 52)	Prior COVID-19 (PC, n = 62)	*P*
Female sex, n(%)	43(82.69)	45(72.58)	*0.290*
BMI (kg/m^2)§	22.86(19.78,25.86)	22.22(20.32,24.46)	0.576
Age (years)	50.65(44.88,57.10)	51.85(45.05,57.03)	0.567
Newly diagnose, n(%)	33(63.46)	42(67.74)	*0.667*
Disease duration (months)	6.0(3.0,24.0)	9.5(2.0,24.0)	*0.936*
Time since prior COVID-19 (months)#	-	2.48 ± 1.19	-
Comorbidities			
Hypertension, n(%)	4(7.69)	10(16.13)	*0.280*
Diabetes, n(%)	10(19.23)	10(16.13)	*0.852*
Coronary artery disease, n(%)	3(5.77)	2(3.23)	*0.840*
Hyperlipidaemia, n(%)	14(26.92)	15(24.19)	*0.907*
COPD, n(%)	0	2(3.23)	-
Interstitial lung disease, n(%)	28(53.84)	40(64.52)	*0.280*
Chronic kidney disease, n(%)	0	2(3.23)	-
Chronic liver disease, n(%)	0	4(6.45)	-
Anemia, n(%)	7(13.46)	6(9.68)	*0.736*
Arrhythmia, n/total(%)	8/23(34.78)	14/26(53.85)	*0.293*
Malignant arrhythmia, n/total(%)	0/23(0)	1/26(3.85)	-
Sinus tachycardia, n/total(%)	5/23(21.7)	10/26(38.46)	-
Other types, n/total(%)	4/23(17.4)	4/26(15.38)	-
Subtypes of IIMs, n(%)			
ASS	2 (3.85)	10 (16.13)	*0.068*
DM	37(71.15)	32 (50.00)	*0.053*
IMNM	9 (17.31)	10 (16.13)	*0.933*
PM	0 (0)	2 (3.23)	-

Characteristic	No prior COVID-19 (NPC, n = 52)	Prior COVID-19 (PC, n = 62)	*P*
Unclassified IIM	4 (7.69)	8(12.90)	*0.551*
Disease activity evaluation			
MTOACT constitutional (score)	6(6, 7)	7(6, 8)	*0.093*
MYOACT cutaneous (score)	6(0, 7)	5(0, 7)	*0.101*
MYOACT skeletal (score)	0(0, 0)	0(0, 2.8)	*0.666*
MYOACT gastrointestinal (score)	0(0, 0)	0(0, 5)	*0.231*
MYOACT pulmonary (score)	5(0, 6)	7(5.8, 7.3)	*0.001***
MYOACT cardiovascular (score)	2(0, 6)	6(0, 7)	*0.002***
MYOACT muscle (score)	4(0, 7)	6(0, 7.3)	*0.200*
MITAX constitutional (score)	3(3, 3)	3(3, 3)	*0.967*
MITAX cutaneous (score)	3(0, 3)	3(0, 3)	*0.271*
MITAX skeletal (score)	0(0, 0)	0(0, 1)	*0.832*
MITAX gastrointestinal (score)	0(0, 0)	0(0, 3)	*0.249*
MITAX pulmonary (score)	3(0, 9)	6(3, 9)	*0.006**
MITAX cardiovascular (score)	1(0, 9)	9(0, 9)	*0.013**
MITAX muscle (score)	1(0, 3)	1(0, 9)	*0.458*
MYOACT global (score)	0.3(0.2, 0.4)	0.4(0.3, 0.5)	*0.001***
MITAX global (score)	0.25 ± 0.1	0.33 ± 0.1	*0.005**
Clinical manifestation, n/total (%)			
Fever	12(23.08)	20(20.97)	*0.380*
Loss of weight	17(32.69)	22(35.48)	*0.909*
Fatigue	40(76.92)	54 (87.10)	*0.435*
Thoracalgia	0 (0)	8(12.90)	-
Palpitation	3(5.77)	13(20.97)	*0.040**
Shortness of breath/ dyspnea	26(50.00)	45(72.58)	*0.022**
Rash	37(71.15)	30(48.39)	*0.023**
Myasthenia	22(42.31)	29(46.77)	*0.773*

Characteristic	No prior COVID-19 (NPC, n = 52)	Prior COVID-19 (PC, n = 62)	*P*
Myodynia	17(32.69)	15(30.65)	*0.426*
Arthritis / arthralgia	18(34.6)	20(24.19)	*0.320*
Dysphagia	9(17.31)	16(25.81)	*0.387*
Cough	24(46.15)	40(64.52)	*0.075*
Expectoration	24(46.15)	36(58.06)	*0.280*
Heart rate, beats per minute	88.50(80.00, 105.30)	89.00(80.00, 101.00)	*0.693*
Respiratory rate, breathes per minute	20(20, 20)	20(20, 21)	*0.055*

Data are presented as the mean±SD, median, and range, n (%) or n/N (%)

*Indicates statistical difference between two groups, *P<0.05, **P<0.005.

§ The bode-mass index(BMI) is the weight in kilograms divided by the square of the height in meters.

The time of COVID-19-related symptoms improving and throat swab results turning negative to the time of admission.

Abbreviations:

COPD, chronic obstructive pulmonary disease; ASS, anti-synthase antibody syndrome; DM, dermatomyositis; IMNM, immune-mediated necrotizing myopathy; PM, polymyositis; immune-mediated necrotizing myopathy; MYOACT, myositis disease activity assessment visual analog scales; MITAX, myositis intention to treat activity index.

Effects of COVID-19 on the clinical characteristics of IIMs

We analyzed the clinical symptoms of patients with IIMs and observed that the PC group exhibited a higher prevalence of cardiopulmonary symptoms than the NPC group (Table 1). These symptoms included palpitation (20.97% vs. 5.77%, p = 0.04), shortness of breath/dyspnea (12.9% vs. 5.77%, p = 0.022), cough (64.52% vs. 46.15%, p = 0.075), and respiratory rate (20 (20, 21) vs. 20 (20, 20), p = 0.055). The incidence of rash in the PC group was lower than that in the NPC group (48.39% vs. 71.15%, p = 0.023). No significant difference was found in heart rate between the two groups. Furthermore, disease activity was assessed in both groups as well (Table 1). Compared to the NPC group, patients in the PC group demonstrated higher MYOACT/MITAX global scores (0.3 (0.2, 0.4) vs. 0.4 (0.3, 0.5), p = 0.001; 0.25 ± 0.1 vs. 0.33 ± 0.1, p = 0.005), pulmonary involvement scores (5 (0, 6) vs. 7 (5.8, 7.3), p = 0.001; 3 (0, 9) vs. 6 (3, 9), p = 0.006), and cardiovascular involvement scores (5 (0, 6) vs. 7 (5.8, 7.3), p = 0.001; 1 (0, 9) vs. 9

(0, 9), p = 0.013). These findings suggest a greater presence of cardiopulmonary symptoms and increased cardiopulmonary disease activity among IIMs patients with a history of COVID-19.

Subsequently, we conducted an analysis of the laboratory characteristics of the two patient groups, as presented in Table 2. Notably, there were no significant disparities observed in the positive rates of myositis-specific antibody, ANA, and anti-Ro52 antibody between the two groups. However, it is worth mentioning that troponin T and HBDH levels were significantly elevated in the PC group compared to the NPC group (51.45 (16.28, 209.18) vs. 17.50 (9.40, 70.68), p = 0.019; 278.50 (186.75, 487.50) vs. 224.0 (172.50, 290.25), p = 0.036). Additionally, ALP and GGT levels were significantly higher in the PC group than in the NPC group. Although platelet counts fell within normal ranges for both groups, patients with a history of COVID-19 exhibited lower platelet levels than those without such a history (192.59 ± 63.69 vs. 222.23 ± 76.07, p = 0.026). Conversely, CK levels, LDH levels, blood creatinine levels, triglyceride levels, cholesterol levels, CRP levels, ESR levels, hemoglobin levels, white blood cell counts, lymphocyte counts, and neutrophil counts showed no statistically significant differences between these two groups (Table 2). These findings suggest that patients with idiopathic inflammatory myopathies who have previously contracted COVID-19 display altered clinical symptoms and laboratory test results, particularly pertaining to cardiac and pulmonary characteristics.

Table 2
Laboratory findings of IIMs patients on admission to the hospital

Characteristic	No prior COVID-19 (NPC, n = 52)	Prior COVID-19 (PC, n = 62)	*p*
Myositis specific antibodies			
MSA, negative, n (%)	8(15.38)	14(22.58)	*0.465*
MDA5, positive, n (%)	22(42.31)	20(32.26)	*0.361*
ARS, positive, n (%)	5(9.62)	12(19.35)	*0.234*
Mi2/SAE, positive, n (%)	2(3.85)	2(3.23)	*0.740*
NXP2, positive, n (%)	3(5.77)	3(4.84)	*0.842*
TIF1γ, positive, n (%)	5(9.62)	2(3.23)	*0.306*
SRP/HMGCR, positive, n (%)	8(15.38)	7(11.29)	*0.714*
ANA, positive, n/total (%)	21/50(42.00)	31/60(51.67)	*0.413*
+~++, n/total (%)	14/50 (28.00)	22/60 (36.67)	-
≥ 3+, n/total (%)	7/50 (14.00)	9/60 (15.00)	-
Anti-Ro52, positive, n/total (%)	15/49(30.61)	29/59(49.15)	*0.079*
MYO(ng/ml)	40.15(21.11, 226.28)	113.99(23.45, 912.93)	*0.114*
CK-MB, (ng/ml)	2.10(1.17, 9.00)	7.12(1.23, 126.95)	*0.090*
cTnT (ng/L)	17.50(9.40, 70.68)	51.45(16.28, 209.18)	*0.019**
NT-proBNP(ng/L)	83.00(43.50, 141.75)	148.00(58.00,304.00)	*0.110*
CK(IU/L)	81.50(35.00, 521.25)	225.50(41.50, 2240.00)	*0.174*
LDH, (IU/L)	313.50(231.75, 397.50)	392.00(242.00, 635.50)	*0.072*
HBDH, (IU/L)	224.0(172.50, 290.25)	278.50(186.75, 487.50)	*0.036**
ALT (U/L)	34.50(21.25, 97.75)	56.50(24.50, 129.75)	*0.171*
AST (U/L)	37.00(20.00, 93.25)	49.00(23.75, 118.25)	*0.261*
ALP (U/L)	64.00(51.00, 82.75)	77.50(58.75, 97.25)	*0.012**
GGT (U/L)	27.00(17.00, 70.25)	61.50(23.00, 144.75)	*0.028**
Creatinine (umol/L)	54.00(42.00, 59.75)	54.00(45.75, 64.50)	*0.635*
Triglyceride (mmol/L)	1.95(1.32, 2.73)	1.961.56, 2.67)	*0.528*

Characteristic	No prior COVID-19 (NPC, n = 52)	Prior COVID-19 (PC, n = 62)	*p*
Myositis specific antibodies			
Cholesterol (mmol/L)	4.91(4.07, 5.81)	4.93(4.08, 5.78)	*0.811*
D dimer	0.91(0.27, 1.62)	0.61(0.36, 1.39)	*0.772*
White blood cell count ($\times 10^9$/L)	6.61(4.41, 8.90)	7.42(5.14, 10.27)	*0.071*
Neutrophils count ($\times 10^9$/L)	4.86(2.89, 6.48)	5.29(3.61, 7.68)	*0.118*
Lymphocyte count ($\times 10^9$/L)	1.01(0.74, 1.70)	1.25(0.84, 1.68)	*0.406*
Platelet count ($\times 10^9$ /L)	222.23 ± 76.07	192.59 ± 63.69	*0.026**
Hemoglobin (mg/L)	123.14 ± 16.52	126.13 ± 20.36	*0.396*
CRP (mg/L)	4.60(2.03, 12.65)	5.53(3.13, 13.9)	*0.279*
ESR (mm/h)	43.00(20.00, 61.00)	31.00(9.75, 52.52)	*0.212*

Data are presented as the mean±SD, median, and range, n (%) or n/N (%).

*Indicates statistical difference between two groups, *P<0.05.

Abbreviations:

MAS, myositis specific antibody; MDA5, antimelanoma differentiation associated gene 5 antibody; ARS, anti-aminoacyl transfer RNA synthetase antibody; NXP2, antinuclear matrix protein 2 antibody; Mi2, anti-helicase protein antibody; SAE, anti-small ubiquitin-like modifier activating enzyme; TIF1γ, anti-transcription intermediary factor 1 γ; HMGCR, anti-3-hydroxy-3-methyglutaryl coenzyme A reductase; SRP, anti-signal recognition particle; ANA, antinuclear antibody; Ro52, anti-cytoplasmic ribonucleoprotein of 52 kDa; MYO, myoglobin; CK-MB, creatinine kinase MB; cTnT, cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CK, creatine kinase; LDH, lactate dehydrogenase; HBDH, hydroxybutyrate dehydrogenase; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyltransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate;

Echocardiographic parameters exhibited alterations in IIMs patients with a history of COVID-19

To further investigate the impact of COVID-19 on cardiac function in patients with idiopathic inflammatory myopathies (IIMs), we analyzed echocardiography parameters, including measures of cardiac structure and function (Table 3). Due to missing echocardiography data, there were 48 and 54 patients in the no prior COVID-19 (NPC) and prior COVID-19 (PC) groups, respectively. Cardiac structural

parameters revealed that the left atrium (LA) was larger in the PC group than in the NPC group (33.00 (29.00, 36.00) vs. 30 (28.00, 33.00), p = 0.021), as was the interventricular septum ((10.00 (9.00, 12.00) vs. 9.00 (8.00, 10.00), p = 0.019, IVS). The velocity of early diastolic myocardial movement at the mitral ring (e') was lower in the PC group than in the NPC group (6.00 (5.00, 8.00) vs. 7.80 (6.00, 10.00), p = 0.012), while the peak velocity ratio of left ventricular early-diastolic fast filling (E)/e' was higher in the PC group than in the NPC group (10.00 (8.50, 13.50) vs. 10.00 (8.00, 12.00), p = 0.028). No significant differences were observed for other echocardiographic parameters examined. The characteristics associated with cardiac damage in all patients with IIMs are summarized in Fig. 2.

Table 3
Echocardiographic characteristics of IIMs patients

Characteristic	No prior COVID-19 (NPC, n = 48)	Prior COVID-19 (PC, n = 54)	*p*
LV, mm	45.00(44.00, 47.50)	46.00(42.00, 48.00)	*0.558*
LA, mm	30(28.00, 33.00)	33.00(29.00, 36.00)	*0.021**
RV, mm	21.00(19.00, 22.00)	20.00(19.00, 22.00)	*0.544*
RA, mm	31.36 ± 4.06	32.48 ± 4.42	*0.314*
IVS, mm	9.00(8.00, 10.00)	10.00(9.00, 12.00)	*0.019**
LVPW, mm	8.00(8.00, 9.00)	9.00(8.00, 10.00)	*0.129*
AAO, mm	30.37 ± 3.74	31.34 ± 3.96	*0.206*
MPA, mm	21.00(20.00, 23.00)	22.00(20.00, 23.00)	*0.784*
E, m/s	0.70(0.60, 0.80)	0.70(0.60, 0.80)	*0.374*
A, m/s	0.75 ± 0.23	0.80 ± 0.19	*0.232*
AV, m/s	1.31 ± 0.20	1.37 ± 0.27	*0.211*
PV, m/s	0.90(0.80, 1.00)	0.90(0.80, 1.05)	*0.502*
e', cm/s	7.80(6.00, 10.00)	6.00(5.00, 8.00)	*0.012**
a', cm/s	8.00(7.00, 9.00)	8.00(7.00, 10.00)	*0.565*
E/ e'	10.00(8.00, 12.00)	10.00(8.50, 13.50)	*0.028**
EDD, mm	45.00(43.50, 47.00)	46.00(42.00, 48.00)	*0.458*
ESD, mm	29.00(26.00, 31.00)	29.00(26.00, 31.50)	*0.407*
EDV, ml	90.00(84.00, 102.00)	98.00(78.50, 111.50)	*0.218*
ESV, ml	31.00(25.50, 36.00)	32.00(26.00, 42.50)	*0.155*
SV, ml	62.45 ± 10.31	62.51 ± 12.49	*0.979*
EF, %	67.00(61.00, 72.00)	65.00(61.00, 69.00)	*0.184*
FS, %	37.18 ± 4.50	35.74 ± 4.67	*0.140*

Data are presented as the mean±SD, median, and range.

*Indicates statistical difference between two groups, *P<0.05.

Abbreviations:

LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium; IVS, interventricular septum; LVPW, left-ventricular posterior wall; AAO, ascending aorta. MPA, main pulmonary artery; E, peak velocity of left ventricular early-diastolic fast filling; A, peak velocity of left ventricular late-diastolic filling; AV, aortic valve; PV, pulmonary valve; e', velocity of early diastolic myocardial movement at mitral ring; a', velocity of late diastolic myocardial movement at mitral ring; EDD, end-diastolic dimension; ESD, end-systolic dimension; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume per minute; EF, ejection fraction; FS, fraction shortening;

To ascertain the potential association between the extent of cardiac impairment in individuals with post-COVID-19 IIMs and the duration elapsed since their COVID-19 infection. Patients with a history of COVID-19 from IIMs were categorized based on the time elapsed since their prior infection, and no statistically significant differences in clinical features were observed among all groups (Supplementary Table 1, Table 2).

The putative mechanism underlying COVID-19-induced cardiac damage in patients with IIMs

To investigate the potential mechanism of cardiac injury in patients with IIMs and a history of COVID-19, we employed RNA-seq technology coupled with bioinformatics analysis to elucidate disparities in gene expression profiles between dermatomyositis (DM) patients and COVID-19 patients. Upon examining the number of differentially expressed genes (DEGs) between DM patients and COVID-19 patients, we identified 7189 DEGs in DM patients (Fig. 3A), comprising 5654 upregulated genes (depicted as red dots) and 1679 downregulated genes (depicted as blue dots). Conversely, COVID-19 patients exhibited 3080 DEGs (Fig. 3A), including 1278 upregulated genes (red dots) and 1802 downregulated genes (blue dots). A comparison of DEGs between DM patients and COVID-19 patients revealed an overlap of 720 genes (Fig. 3C). To explore the underlying mechanisms and pathways associated with these DEGs within our datasets, functional enrichment analyses using Gene Ontology terms and Kyoto Encyclopedia of Genes and Genomes were performed. The results demonstrated that biological processes and enriched pathways related to collagen matrix proliferation, calcium ion pathway regulation, oxidative stress response, cell proliferation, and cell inflammatory molecules were significantly enriched among these targets (Fig. 3D).

Discussion

With an enhanced understanding of COVID-19, numerous survivors of early SARS-CoV-2 infection continue to experience prolonged recovery periods lasting weeks or even months after the acute phase of symptoms, referred to as post-acute sequelae of SARS-CoV-2 infection (PASC) [9]. Healthcare professionals are increasingly acknowledging the significance of COVID-19 recovery. A mounting body of research has focused on elucidating the association between COVID-19 and rheumatoid immune diseases [2, 3]. From autoantibody production to the onset of autoimmune disease, there is a growing body of evidence linking COVID-19 with the development of autoimmune phenomena [2, 3]. Through

analysis of clinical characteristics in patients with IIMs, our study identified notable alterations in IIMs patients with a history of COVID-19, particularly concerning indicators related to cardiac damage.

Case reports have documented the emergence of IIMs following the COVID-19 pandemic [3, 10, 11]. Several studies have identified notable similarities between COVID-19 and anti-MDA5 dermatomyositis in terms of clinical features and pathogenesis, including comparable pulmonary interstitial lesions, cytokine storms, and response to immunosuppressive therapy. These findings suggest that COVID-19 may serve as an environmental risk factor for the onset of IIMs [12]. However, it remains unclear whether patients with IIMs after COVID-19 differ from those with traditional IIMs. While muscle damage, such as myalgia, myasthenia gravis, and elevated CK levels, is common in individuals with SARS-CoV-2 infection [13], our study found that cardiac damage is more prominent among patients with a history of SARS-CoV-2 infection who also have IIMs. This conclusion was supported by increases in cTnT and HBDH levels as well as scores reflecting cardiac disease activity. Notably, there were no significant differences in muscle injury disease activity scores or CK levels between the two groups studied here; this partly reflects a lack of difference in muscle damage between these groups, while changes in cTnT levels largely reflect myocardial damage instead. Although echocardiographic parameters were normal overall for both groups studied here (PC vs NPC), PC group parameters were worse than those observed for NPC group members. Such subclinical cardiology changes may represent early stages of heart reconstruction that will eventually manifest clinically as heart disease; thus, they cannot be ignored. Taken together, these results indicate that SARS-CoV-2 has the potential to alter long-term trajectories associated with cardiac suffering among individuals affected by IIMs.

Currently, existing research suggests that cardiovascular symptoms are the predominant manifestation of PASC [9]. However, limited research has investigated the potential association between COVID-19 and myocardial damage in individuals with IIMs. Previous studies have indicated that the concurrent presence of myositis and inflammatory cardiac disease in COVID-19 patients is characterized by a younger age group and fewer respiratory symptoms [13, 14]. In individuals with newly diagnosed ASS following SARS-CoV-2 infection, clinical manifestations solely involve myocardial and skeletal muscle involvement [10]. Consistent with prior investigations, our study demonstrates an increased susceptibility to myocardial injury among patients with post-COVID-19 IIMs compared to those without COVID-19 IIMs; this association remains independent of the time elapsed since COVID-19 infection. To further investigate the potential mechanisms of myocardial injury in post-COVID-19 IIMs, we employed transcriptomics and bioinformatics analysis. The enrichment analysis of DEGs revealed collagen matrix proliferation, regulation of calcium ion pathways, oxidative stress, cell proliferation, and inflammatory molecules as key factors contributing to cardiac damage in IIMs patients infected with SARS-CoV-2. Our bioinformatics analysis results are consistent with the hypothesized mechanisms underlying COVID-19-associated heart injury. Persistence of the virus in cardiac tissue triggers inflammation leading to myocardial fibrosis; alternatively, viral-induced changes in host proteins can cross-react via molecular mimicry mechanisms [9]. A study investigating postmortem examinations of COVID-19 fatalities reported widespread muscle and myocardial damage despite low or negative viral loads in tissues, suggesting a possible role for immune-mediated muscle injury [15]. In conclusion, cardiac injury following SARS-CoV-2 infection is likely

multifactorial; therefore, a comprehensive understanding of these mechanisms is crucial for improving diagnosis and treatment processes. Further clinical and basic research efforts are urgently needed to explore this area.

Furthermore, our study revealed a higher level of bile duct enzymes in patients with IIMs who had a history of COVID-19 than in those without. These findings are consistent with previous research [16]. Given the increased expression of ACE2 in the biliary epithelium, it becomes susceptible to SARS-CoV-2 infection, leading to chronic liver disease and providing insights into the potential molecular mechanism underlying biliary tract damage caused by COVID-19 [17]. Roth et al. characterized liver biopsies from three individuals experiencing cholestasis after recovering from COVID-19 and concluded that post-COVID-19 cholangiopathy represents a distinct form of liver injury [17]. Therefore, clinicians encountering unexplained cases of cholestasis should consider the possibility of post-COVID-19 cholangiopathy.

Although platelet count levels in both groups fell within the normal range, it was observed that patients with IIMs and a history of COVID-19 exhibited significantly lower average platelet levels than those without. It is widely acknowledged that severe COVID-19 induces hypercoagulation, leading to thrombocytopenia. Martins-Goncalves investigated platelet function in post-COVID-19 recovery patients and discovered persistent platelet activation and hyperactivity when compared to healthy controls [18]. An 18-month follow-up study on peripheral blood clotting status among individuals recovering from COVID-19 revealed an enduring procoagulant state associated with persistent symptoms [19]. These findings collectively suggest that abnormal coagulation plays a crucial role in postSARS-CoV-2 systemic damage.

Our study examined the clinical characteristics of specific patients with IIMs who had a history of COVID-19 while also accounting for confounding seasonal factors and investigating potential underlying mechanisms of the disease. This analysis provides valuable insights into the association between COVID-19 and IIMs. However, our study has certain limitations. First, it is a retrospective study conducted at a single center with a small sample size and short follow-up period (average time after infection: 2.48 months). Therefore, there is a need for large-scale multicenter cohort studies with long-term follow-up to validate our findings. Second, more comprehensive measures, such as cardiac troponin I levels and cardiac MRI, are required to accurately assess cardiac damage in these patients. Last, due to the evident impact of COVID-19 on both the heart and lungs, it remains challenging to determine whether heart damage in IIMs patients is primarily caused by lung damage. Further investigations are warranted to elucidate the relationship between COVID-19 and cardiac involvement in individuals with IIMs.

Conclusion

The clinical manifestations of patients with IIMs following COVID-19 exhibit notable alterations, particularly in terms of cardiac impairment. Our findings serve as a crucial reminder for clinicians to remain vigilant regarding the enduring cardiovascular consequences associated with IIMs subsequent to COVID-19.

Declarations

Ethics approval

The study was approved by the ethical committee of West China Hospital of Sichuan University (No. 695 in 2020). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study did not involve animal studies, and no ethical approval was needed.

Consent for publication

All patients and controls provided written informed consent.

Availability of data

The data supporting the conclusions of this article are included within the article and its additional file.

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

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Authors' contributions

LZA, TCY, and LYB conceived and designed the study. LZA, LY and TCY guided the study. CL, LYH, WYL, ZY, YT, WJ, LXP, ZJ, HDY and WT collected the clinical samples. CL, LYH, WYL and YT analyzed the data. CL, LYH wrote the main text of the manuscript. All authors drafted and revised the manuscript. All authors drafted and revised the manuscript. Lu Cheng and Yanhong Li contributed equally to this work.

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Not applicable

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Figures

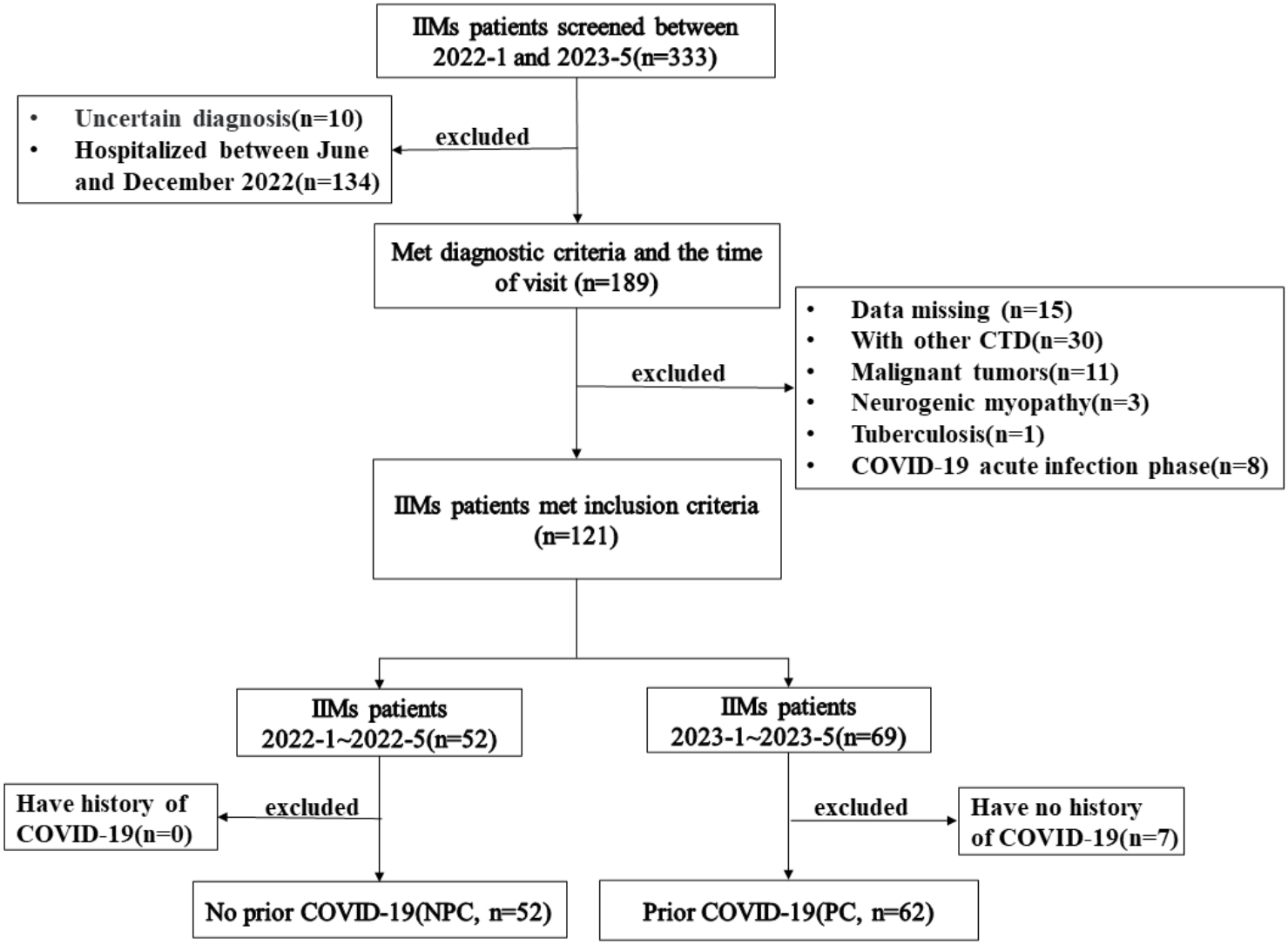

Figure 1

Flow chart of the clinical study participants.

IIMs, idiopathic inflammatory myopathies; CTD: connective tissue disease; COVID-19, coronavirus disease 2019.

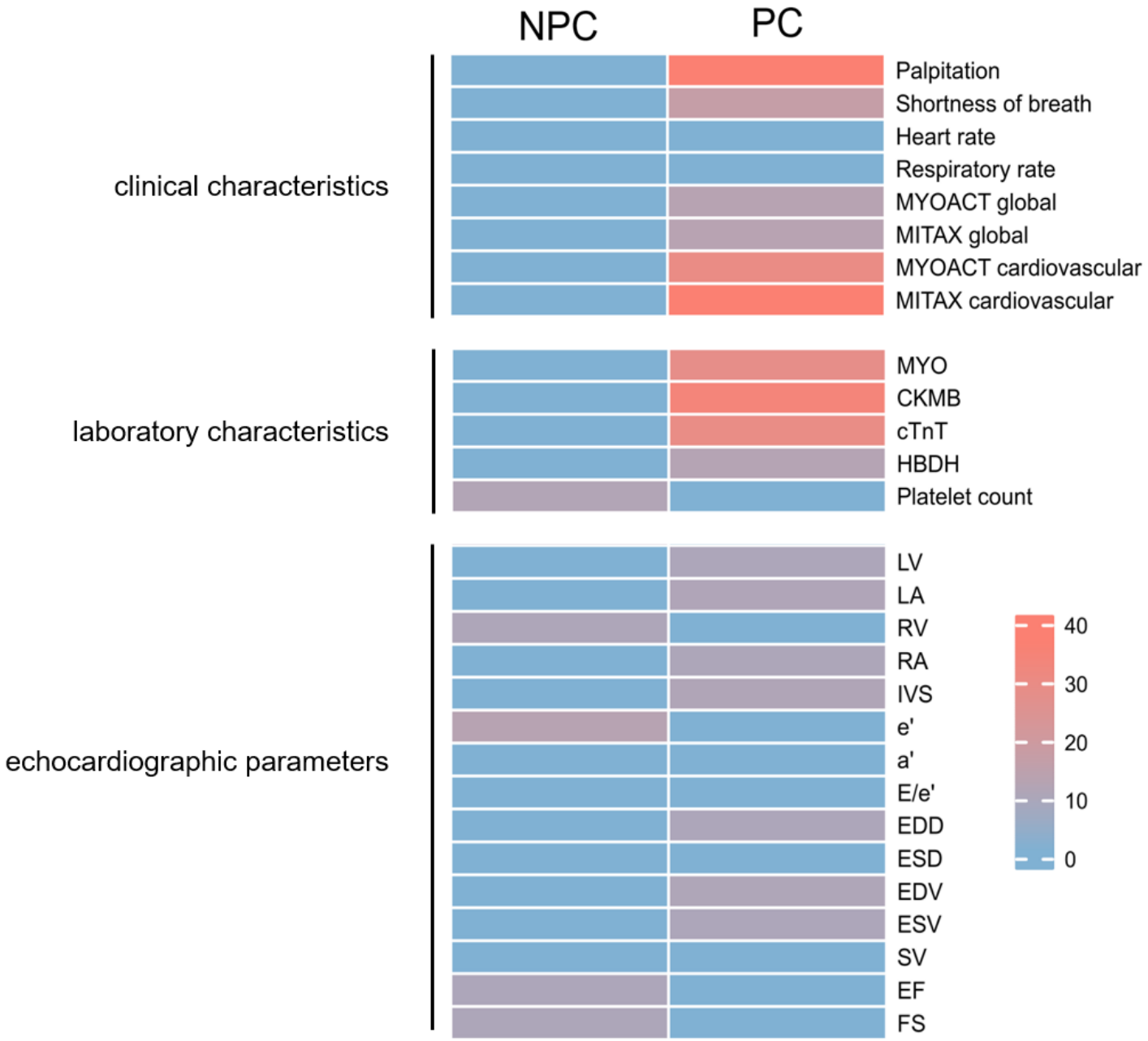

Figure 2

Summary of cardiac injury characteristics in IIMs patients with and without prior COVID-19.

PC, prior COVID-19; NPC, no prior COVID-19; MYOACT, myositis disease activity assessment visual analog scales; MITAX, myositis intention to treat activity index. MYO, myoglobin; CK-MB, creatinine kinase MB; cTnT, cardiac troponin T; HBDH, hydroxybutyrate dehydrogenase; LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium; IVS, interventricular septum; e', velocity of early diastolic myocardial movement at mitral ring; a', velocity of late diastolic myocardial movement at mitral ring; EDD, end-diastolic dimension; ESD, end-systolic dimension; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume per minute; EF, ejection fraction; FS, fraction shortening;

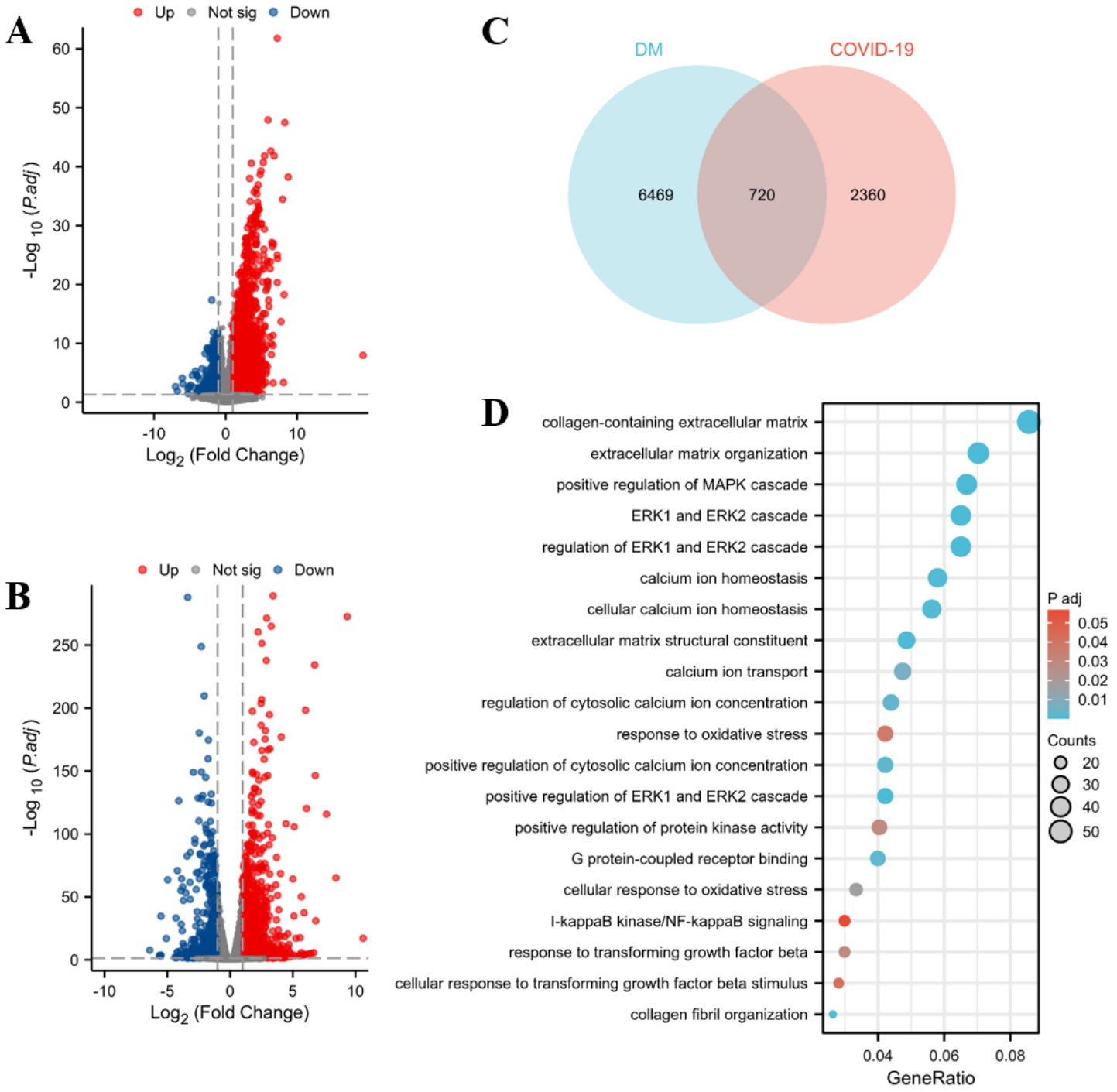

Figure 3

Bioinformatics analysis of the transcriptome of muscle tissues from DM patients and myocardial tissues from COVID-19 patients.

A. DM dataset (GSE143323) differentially expressed genes in the volcanic figure.

B. COVID-19 dataset (GSE151879) differentially expressed genes in the volcanic figure.

C. Venn diagram showing the overlap of differentially expressed genes between COVID-19 and DM.

D. Bubble plot of GO and KEGG functional enrichment analysis results of common DEGs in COVID-19 and DM.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.docx