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ORIGINAL ARTICLE

Cardiovascular sequelae in symptomatic SARS-CoV-2 infection survivors

Short title: Cardiovascular consequences of COVID-19

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Abstract

Background: SARS-CoV-2 infection may lead to myocardial and endothelial damage. The present study sought to characterize the cardiovascular sequel in a large group of consecutive patients admitted for out-patient cardiovascular follow-up after a symptomatic COVID-19 infection.

Methods: The aims of this study were as follows: to evaluate the presence of post-covid cardiovascular symptoms in an unselected population of outpatients referred to a post-COVID outpatient cardiology clinic and to characterize the long-term abnormalities associated with a more severe COVID-19 infection clinical course. A total of 914 patients were included in this single-center, observational, cross-sectional study, of which 163 were hospitalized and 149

required mechanical ventilation for COVID-19 pneumonia. Patients were analyzed at follow-up according to the care setting during the initial presentation.

Results: The median time to follow-up was 126 days. At that time, only 3.5% of patients reported no persistent dyspnea, chest pain, or fatigue on exertion. In a follow-up echocardiographic assessment, patients who required hospitalization showed slight alterations in the pulmonary acceleration time and the tricuspid regurgitation pressure gradient, as well as reduced exercise tolerance during treadmill exercise testing when compared to patients with a benign clinical course. 24-hour Holter EKG monitoring or 24-hour blood pressure monitoring did not identify significant differences between the analyzed subgroups.

Conclusions: The current study reports on an association between COVID-19 severity and the presence of cardiovascular alterations at follow-up. A simple diagnostic protocol, comprising an exercise treadmill test and transthoracic echocardiography is useful in identifying patients who may benefit from regular, structured cardiovascular medical care.

Keywords: myocardial damage, endothelial damage, COVID-19, long-COVID-19, PACS

Background

Severe cases of viral pneumonia, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may lead to myocardial injury in patients with and without previously known cardiovascular disease and is associated with higher mortality. In this regard, hypertension, diabetes, and pulmonary disease have been named as leading co-morbidities driving mortality in COVID-19 [1–4]. The direct mechanisms of myocardial injury have not been fully elucidated yet. However, as characterized in literature hereto, in the acute phase, SARS-CoV-2 displays an affinity for the angiotensin converting enzyme-2 (ACE2) receptor located on the surface of myocytes which acts as the entryway for direct viral access to the cell [5]. A second possible mechanism of acute cell injury is linked to the increased expression of cytokines during COVID-19 infection leading to pericyte injury, endothelial dysfunction causing microvascular dysfunction, plaque instability generating myocardial infarction, and finally the development of myocardial fibrosis [6, 7]. The mechanisms perpetuating cardiovascular sequelae in post-acute COVID-19 patients include cell injury, downregulation of ACE2, and inflammation affecting the structural integrity of the

myocardium, pericardium, and conduction system [8]. There is relevant heterogeneity reported regarding the frequency of cardiovascular complications following COVID-19, with reports most commonly identifying the development of myocarditis, arrhythmias, and heart failure [9], however, cardiac involvement seems to be correlated with COVID-19 severity [10]. Substrate-wise, evidence of myocardial fibrosis or active myocarditis was reported in cardiac magnetic resonance imaging (CMR) in up to 78% of patients and signs of inflammation in 60% of patients recovering from COVID-19, with recovering patients characterized by lower ejection fraction of the left ventricle (LVEF) and higher left ventricle (LV) volume compared with risk factor-matched controls [11]. The term “long-COVID-19” or “PACS” — post-acute COVID syndrome has been coined to describe the late multi-organ complications and accompanying persistent symptoms present after the acute phase of infection [7, 12].

The aims of this study were as follows: 1) to evaluate the presence of post-covid cardiovascular symptoms in an unselected population of outpatients referred to a post-COVID out-patient clinic, 2) to characterize the long-term abnormalities associated with a more severe COVID-19 clinical course.

Methods

This was a single-center, observational, cross-sectional study of consecutive 914 post-COVID-19 patients evaluated between 2020-2022 at an outpatient cardiology clinic of a tertiary hospital. Patients were analyzed at follow-up according to the care setting during the initial presentation, which included either out-patient treatment (no hospitalization due to COVID-19 deemed necessary, comprising the benign clinical course subgroup), hospitalization without need for ventilation support or hospitalization requiring ventilation support (both comprising the severe clinical course subgroup). Information on the presence of persistent cardiovascular symptoms was gathered using a dedicated questionnaire. Additional studies: transthoracic echocardiography (TTE), treadmill exercise walking test (ExT), 24-hour Holter EKG monitoring, 24-hour ambulatory blood pressure monitoring (ABPM), chest imaging studies, laboratory blood panels were performed. Elements of the proposed work-up are also included in the European Society of Cardiology position paper regarding long-COVID-19 and the cardiovascular system [12].

The study was approved by the local institutional ethics committee.

Dedicated questionnaire

During the first follow-up visit to the outpatient clinic, all patients were asked to fill out a simple yes/no questionnaire regarding symptoms present during the initial COVID-19 infection and symptoms present at follow-up, which included: dyspnea, chest pain, and fatigue on exertion.

Transthoracic echocardiography

Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [13]. All examinations were performed by a physician certified in echocardiography using the Affinity system (Philips).

Data on: left ventricular ejection fraction (LVEF), left atrium area (LAA), right atrium area (RAA), intraventricular septum thickness (IVS), tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitation pressure gradient (TRPG), pulmonary acceleration time (AcT) were collected.

ABPM

ABPM (Oxford Oscar 2) was performed at follow-up in all patients. Data on: average systolic blood pressure (SBP avg), average diastolic blood pressure (DBP avg) were collected and analyzed.

24-hour Holter EKG monitoring

24-hour Holter EKG monitoring (Oxford 300-4L) was performed at follow-up in all patients. Data on: minimum heart rate (HR min), maximum heart rate (HR max), average heart rate (HR avg), number of supraventricular ectopic beats (SVEB), number of ventricular ectopic beats (VEB), presence of atrial fibrillation (AF) were collected and analyzed.

Treadmill exercise walking test

A treadmill exercise walking test (GE Healthcare T2100) was performed at follow-up.

Data on: metabolic equivalents (METs) were recorded and analyzed.

Imaging studies

Patients underwent chest computed tomography (CT) scans (Siemens SOMATOM Definition AS) for the diagnosis and evaluation of the severity of pulmonary lesions caused by SARS-CoV-2 during the initial presentation. Lesions were also assessed using either chest CT or X-ray during follow-up. The choice of lung imaging modality at follow-up was left to the discretion of the treating physician.

Laboratory analysis

COVID-19 was diagnosed when acute respiratory symptoms or an exacerbation of chronic respiratory symptoms were present and one of the following: SARS-CoV-2 target genes were detected using a reverse-transcriptase polymerase chain reaction (RT-PCR) assay (CovGenX) from biological material collected using nasopharyngeal swabs or with a positive immunochromatographic lateral flow test detecting the target nucleocapsid protein of SARS-CoV-2 from nasopharyngeal swabs (Abbott, IL, U.S.A.).
Data on concentrations of: D-dimer (DD), troponin I (TnI), N-terminal pro–B-type natriuretic peptide (NT-proBNP), serum creatinine (sCrea), estimated glomerular filtration rate (eGFR) and hemoglobin (Hgb) were collected.

Plasma concentrations of troponin I were measured using a high-sensitivity automated sandwich electrochemiluminescence immunoassay (Abbott Alinity I) with the upper limit of normal values < 0.0342 µg/L.

D-dimer concentrations were quantitatively measured using an automated enzyme-linked fluorescent assay (Versen) with the upper limit of normal values 0.50 µg FEU/mL.

Data storing

A dedicated database for storing patient data was used.

Statistical analysis

Data are expressed as parameter or median followed by interquartile range. The Shapiro-Wilk test was used to identify continuous variables with a skewed distribution which were then compared using the Mann-Whitney U test. Categorical data were compared using the Chi^2 test. For all performed tests P-values of < 0.05 were considered significant. All tests were

two-tailed. To explore the sequelae associated with a more severe clinical course, multivariable logistic regression models were used.
Analyses were performed using the STATISTICA 13 data analysis software system (TIBCO Software Inc., CA, USA) and the MedCalc software system (MedCalc Software Ltd, Ostend, Belgium).

Results

Medical records of 914 patients were analyzed: 751 (82.1%) patients received at-home treatment while 163 (17.8%) patients were treated in hospital, of which 149 (16.3% of the entire population) were treated in hospital and required mechanical ventilation for COVID-19 pneumonia. The median time from the initial presentation to the follow-up was 126 days.
The flow of patients is presented in Figure 1.

Imaging studies were performed in 674 (74%) out of 914 patients, the choice of modality was left to the discretion of the treating physician. Any signs of parenchymal involvement were noted in 142 (21.1%) patients, of which all had lesions covering less than 50% of the lungs.

Patients who experienced a more complicated clinical course were characterized by a higher number of co-morbidities on follow-up (Table 1).

Symptoms-wise, the most common post-COVID-19 symptom was fatigue on exertion (872 pts, 95.4%), followed by dyspnea which was reported by 701 (77%) patients; 100 of whom subjectively identified COVID-19 infection as the leading cause of this symptom, and chest pain (440 pts, 48.1%). Out of all dyspneic patients, differences were found for BMI, number of SVEB, average SBP and DBP, measured LVEF in TTE, but not for the severity of the initial presentation. No other significant differences between analyzed factors in the aforementioned subgroups were found.

It was found that patients treated ambulatorily when compared with hospitalized patients differed on follow-up by: age, BMI, number of SVEB, average SBP, measured LVEF, LAA, RAA, IVS, TRPG, AcT in TTE, METs achieved during ExT, concentrations of DD, Hgb, and sCrea. However, the alternations in these parameters were usually not severe. However, in 9 patients (1%, one whom was hospitalized) significantly reduced LV ejection fractions (EF < 30%) were found at follow-up. Full results are presented in Table 2. Multiple logistic

regression revealed that a severe clinical course was associated with features of pulmonary hypertension (PH, Table 3).

Finally, analyses for hospitalized patients showed that mechanically ventilated patients vs non-mechanically ventilated hospitalized patients differed on follow-up only by total exercise capacity during the treadmill exercise walking test expressed in METs (6.5 vs. 10 METs), and Hgb levels (15 g% vs. 14 g%) (Table 4).

Discussion

The key findings emerging from our cross-sectional study are that irrespective of the clinical severity of presentation of the acute COVID-19 episode, fatigue on exertion, persistent dyspnea, and chest pain are frequently reported by patients after a median of 4 months of follow-up. In the present study, only 3.5% of the studied population had none of the aforementioned symptoms. Wang *et al.* reported on the presence of at least one persistent symptom in 76% of all COVID-19 survivors, with fatigue occurring most commonly [14]; other reports show that even in mild infections persistent shortness of breath or dyspnea on exertion may be present in up to 20% and 56% of patients, respectively [15].

Secondly, it was found that the cardiovascular consequences of both benign and severe COVID-19 infection at later (four month), follow-up are common, but not severe and may be diagnosed with TTE and ExT. Moreover, the degree of quantifiable cardiovascular alterations differs between patients with a benign vs severe clinical course: after a median time of four months post-COVID, in TTE assessment, patients who required hospitalization had larger LAA and RAA, lower LVEF, as well as moderately higher TRPG and moderately reduced AcT values when compared to ambulatorily treated patients. The former alternations did not meet the criteria for PH, nor did they exceed the respective reference ranges. Lastly, patients with a severer clinical course more often reported the presence of co-morbidities at follow-up. These observations may be considered consistent with others, who report on a substantial burden of cardiovascular diseases covering both non-ischemic and ischemic entities, evident even among those patients who did not require hospitalization in a nationwide cohort of over 100000 individuals [16]. Reports identify cardiac abnormalities, often severe, in half of all COVID-19 patients undergoing echocardiography in the acute phase [17]. The actual prevalence of PH in acute COVID-19 patients is reported at around 10% and is associated with worse in-hospital outcomes [18]. Other authors have reported on the presence of both features of PH as well as RV impairment, the latter characterized by reduced TAPSE in non-critically

ill COVID-19 patients during the initial episode, with systolic LV dysfunction being less common [18].

In the current study, it was noted that only a reduction in AcT and higher TRPG values between subgroups, which may reflect the sustained lung injury, is presumably more advanced in more severe cases. No differences RV systolic function assessed with TAPSE were found. Of note, all alterations although statistically significant were in the reference range of values for the respective parameter.

Another major observation is that in this large population of post-COVID patients, exercise limitations were more prominent in patients who required mechanical ventilation due to COVID-19 pneumonia. This subpopulation of patients was also characterized by higher hemoglobin levels on follow-up, a plausible pathophysiological explanation for this may be persistent hypoxia.

The obvious barriers connected with further diagnostic testing of large populations of post-COVID patients mandates the need for more feasible diagnostic protocols. The present assessment, in an unselected consecutive follow-up of largely symptomatic post-COVID-19 patients with fatigue on excertion, studies influencing further clinical decisions were TTE and ExT. ABPM and Holter EKG monitoring was performed, as well as basic laboratory blood analyses, and it was found that the results of these tests, although differing between the analyzed subgroups, did not modify patient management. Some authors have tested concentrations of biomarkers collected during the initial presentation as a benchmark for further follow-up: in one study increased levels of troponin T prognosticated cardiovascular complications during the index hospitalization, but not during a one-year follow-up period [19]. Current findings are similar: no statistically significant differences were found at four-month follow-up between the overall low troponin T concentrations in patients with benign vs severe clinical course [19].

Based on the present findings and on data from meta-analyses regarding the beneficial influence of structured rehabilitation on patient functional outcomes post-COVID-19, it can be proposed that these tests may be used to pinpoint candidates for rehabilitation programs and systematic echocardiographic follow-up [20].

Several study limitations should be acknowledged. Firstly, there was a lack of data on exercise capacity and LV and RV function before the COVID-19 infection, while data on comorbidities was based on a patient survey only. Patients were analyzed according to hospitalization status and nearly all hospitalized patients received mechanical ventilation, which underlines that only the highest risk patients were admitted to the hospital. Secondly,

data was lacking regarding COVID-19 vaccinations and their impact on the course of the infection. Lastly, available data limited distinguishing cause from effect in the obtained results.

Conclusions

This cohort study reports on a ubiquitous presence of persistent cardiovascular symptoms at follow-up in COVID-19 patients irrespective of the severity of clinical presentation of the acute episode. There were slight alterations found in parameters of right ventricular function and atrial sizes between patients with a benign vs severe clinical course. In patients with fatigue on exertion, a simple diagnostic protocol, comprising treadmill exercise testing and transthoracic echocardiography is useful in identifying patients who may benefit from regular, structured medical care. All the more so, particular attention should be paid to cardiovascular protection during COVID-19 infection, further, it is important to continuously acknowledge the benefits of vaccination for the prevention of commonly occurring, post-covid cardiovascular sequelae.

Conflict of interests: None.

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Table 1. Characteristics of the study group. Data are presented as number followed by percentage. Data gathered at follow-up. Chi^2 test was used for comparison; P-values are presented in the fourth column. Statistically significant results shown in bold. A benign clinical course was defined as ambulatory treatment of Sars-Cov-2, while a severe clinical course was diagnosed in patients requiring in-hospital management

	Benign clinical course (n = 751)	**Severe clinical course (n = 163)**	**P-value**
Male/Female	463/288	70/96	–
Age	54 (44–65)	**53 (43–63)**	**63 (52–70)**
BMI (kg/m^2)	27.55 (24.7–30.9)	**27.18 (24.2–30.4)**	**29.32 (26.5–32.3)**
Neoplasm (n, %)	24 (3.2%)	7 (4.3%)	0.49
Paroxysmal AF (n, %)	32 (4.3%)	11 (6.75%)	0.17
Other AF (n,%)	12 (1.6%)	4 (2.45%)	0.45
Heart failure (n,%)	**58 (7.72%)**	**22 (13.5%)**	**0.02**
Coronary artery disease (n, %)	**32 (4.26%)**	**9 (5.52%)**	**< 0.001**
Hyperlipidemia (n, %)	**153 (20.4%)**	**50 (30.7%)**	**0.003**
Diabetes mellitus (type 1 or type 2) (n, %)	**59 (7.9%)**	**31 (19%)**	**< 0.001**
COPD (n, %)	**7 (0.9%)**	**5 (3.1%)**	**< 0.001**
Asthma (n, %)	58 (7.7%)	7 (4.3%)	0.012
Hypertensive medication (n, %)	**284 (38%)**	**100 (61.5%)**	**< 0.001**
Anticoagulation/antiplatlet agent (n, %)	**46 (6.1%)**	**27 (16.5%)**	**< 0.001**
Statin (n, %)	**124 (16.5%)**	**47 (29%)**	**< 0.001**

AF — atrial fibrillation; ASA — acetylsalicylic acid; BMI — body mass index; COPD — chronic obstructive pulmonary disease; n — number

Table 2. COVID-19 patients with a benign vs severe clinical course. Data gathered on follow-up. Data are presented as median followed by interquartile range. Statistically significant results shown in bold

NT-proBNP (pg/mL)	131.4)	74 (40.5–127.5)	75.75 (41.3–167.4)	0.43
eGFR (ml/min/1.73m^2)	93.52 (80.2–103.6)	94.7 (81.3–104.6)	89.11 (77.6–98.6)	0.42

AcT — pulmonary acceleration time; BMI — body mass index; DBP avg. — average diastolic blood pressure; EF — left ventricular ejection fraction; eGFR — estimated glomerular filtration rate; Hgb — blood hemoglobin; HR avg. — average heart rate; IVS —

intraventricular septum; LAA — left atrium area; METs — metabolic equivalents; n — number; NT-proBNP — N-terminal pro–B-type natriuretic peptide; RAA — right atrium area; TAPSE — tricuspid annular plane systolic excursion; TnI — Troponin I; TRPG — tricuspid regurgitation pressure gradient; SBP avg. — average systolic blood pressure; sCrea — serum creatinine; SVEB — supraventricular ectopic beat; VEB — ventricular ectopic beat

Table 3. Cardiovascular sequelae of the severe clinical course of COVID-19 infection. Log-reg analysis. Data are presented as odds ratio followed by 95% confidence interval and P-value. Statistically significant results shown in bold

Sequelae	**Median, 95% CI, P-value**
AcT (ms)	**1.02 (1.01–1.03); 0.002**
TRPG (mmHg)	**0.94 (0.90–0.98); 0.01**
RAA (cm^2)	1.04 (0.93–1.15); 0.53
D-dimer (ng/mL)	1.007 (0.96–1.05); 0.19
eGFR (mL/min/1.73m^2)	1.01 (0.1–1.02); 0.11
Hgb (g/dL)	0.98 (0.94–1.006); 0.71

AcT — pulmonary acceleration time; CI — confidence interval; eGFR — estimated glomerular filtration rate; Hgb — hemoglobin; LAA — left atrium area; RAA — right atrium area; TRPG — tricuspid regurgitation pressure gradient

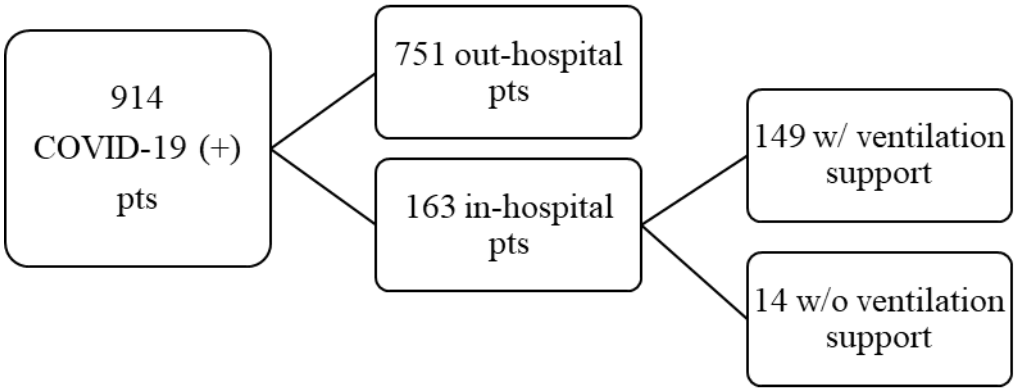
Table 4. Comparison for ventilation support vs no ventilation support. Data gathered on follow-up. Data are presented as median followed by interquartile range. Statistically significant results shown in bold

	Ventilation support, n = 149	**No ventilation support, n = 14**	**P–value**
METs	**6.45 (4.9–9.3)**	**9.7 (7.0–10.3)**	**0.01**
Hgb (g/dL)	**15.15 (14.1–16.3)**	**14.05 (13.05–15.1)**	**0.01**

BMI (kg/m^2)	29.32 (26–32.2)	29.30 (26.5–32.3)	0.28
HR avg (beats/min)	74 (70–78)	29.30 (67–79)	0.63
SVEB (n)	22 (4–62)	23 (9–94)	0.84
VEB (n)	13 (1–35)	4 (1–50)	0.33
SBP (mmHg)	124 (114–130)	127 (121–139)	0.67
DBP (mmHg)	72 (67–79)	75 (67–83)	0.79
EF (%)	65 (60–65)	60 (60–65)	0.94
LAA (cm^2)	17.5 (16–26)	19 (16–21.5)	0.56
RAA (cm^2)	16 (14–18.5)	16 (14–18)	0.15
IVS (cm)	1 (0.9–1.1)	1 (1.0–1.1)	0.34
TAPSE (cm/s)	2.5 (2.0–2.7)	2.4 (2.2–2.7)	0.92
TRPG (mmHg)	24 (20–28)	24 (20–28)	0.2
AcT (ms)	121 (119–150)	123 (110–145)	0.81
D–dimer (ng/mL)	0.345 (0.240–0.435)	0.425 (0.290–0.611)	0.27
TnI (ug/L)	0.01 (0.006–0.01)	0.01 (0.01–0.01)	0.85
NT–proBNP (pg/ml)	66.15 (42.1–233.5)	76.5 (41.4–170)	0.93
eGFR (ml/min/1.73m^2)	87.55 (77.5–108.3)	89.41 (77.6–98.6)	0.84
sCrea (mg/dL)	0.88 (0.74–0.93)	0.83 (0.7–0.99)	0.3

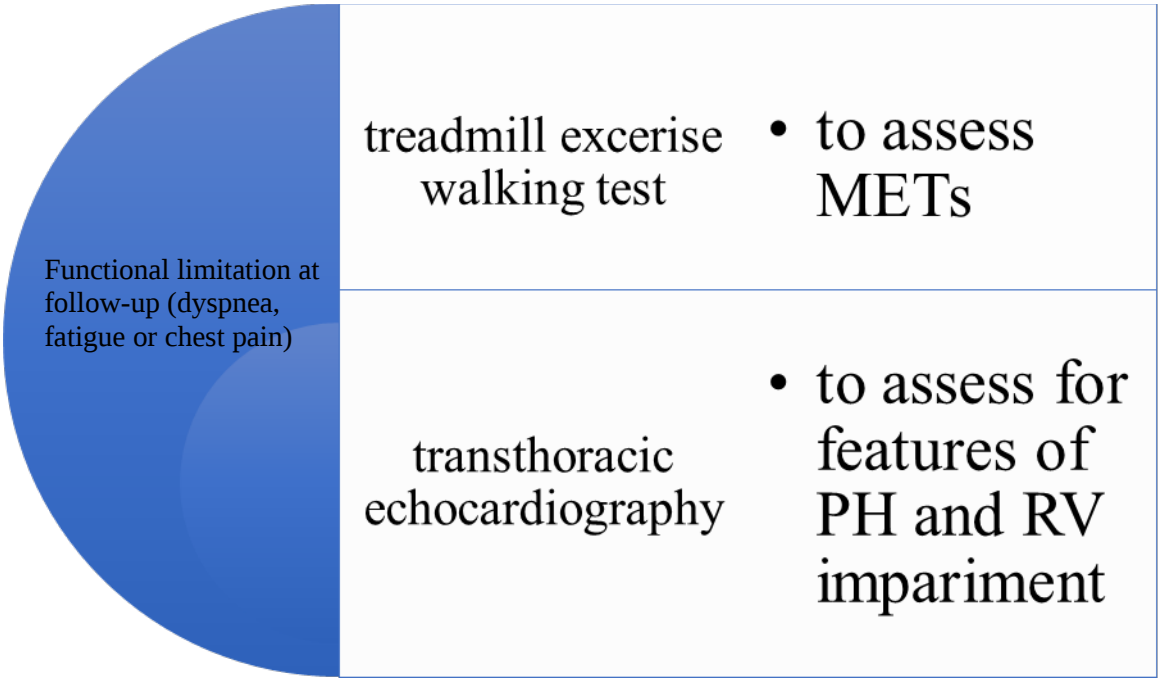
AcT — pulmonary acceleration time; BMI — body mass index; DBP avg. — average diastolic blood pressure; EF — left ventricular ejection fraction,; eGFR — estimated glomerular filtration rate, Hgb — blood hemoglobin; HR avg. — average heart rate; IVS — intraventricular septum; LAA — left atrium area; METs — metabolic equivalents; n — number; NT-proBNP — N-terminal pro–B-type natriuretic peptide; RAA — right atrium area; TAPSE — tricuspid annular plane systolic excursion; TnI — Troponin I; TRPG — tricuspid regurgitation pressure gradient; SBP avg. — average systolic blood pressure, sCrea — serum creatinine; SVEB — supraventricular ectopic beat; VEB — ventricular ectopic beat

Figure 1. Flow of patients in the study



pts — patients; w — with; w/o — without

Figure 2. Proposed diagnostic algorithm for symptomatic patients with persistent dyspnea/chest pain/fatigue on exertion



METs — metabolic equivalents; PH — pulmonary hypertension; RV — right ventricle