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Frequency and prognosis of CVD and myocardial injury in patients presenting with suspected COVID-19 – The CoV-COR registry

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ABSTRACT

Background: The COVID-19 pandemic led to an alteration of algorithms in emergency medicine, which may influence the management of patients with similar symptoms but underlying cardiovascular diseases. We evaluated key differential diagnoses to acute COVID-19 infection and the prevalence and the prognosis of myocardial injury in patients presenting for suspected COIVD-19 infection.

Methods: This prospective observational study includes patients presenting with symptoms suggestive of COVID-19 infection during the pandemic. In patients without COVID-19, leading diagnoses was classified according to ICD-10. Myocardial injury was defined as elevated high-sensitivity Troponin I with at least one value above the 99th percentile upper reference limit and its prevalence together with 90-days mortality rate was compared in patients with vs without COVID-infection.

Results: From 497 included patients (age 62.9 ± 17.2 years, 56 % male), 314 (63 %) were tested positive on COVID-19 based on PCR-testing, while another cause of symptom was detected in 183 patients (37 %). Cardiovascular diseases were the most frequent differential diagnoses (40 % of patients without COVID-19), followed by bacterial infection (24 %) and malignancies (16 %). Myocardial injury was present in 91 patients (COVID-19 positive: n = 34, COVID-19 negative: n = 57). 90-day mortality rate was higher in patients with myocardial injury (13.4 vs 4.6 %, p = 0.009).

Conclusion: Cardiovascular diseases represent the most frequent differential diagnoses in patients presenting to a tertiary care emergency department with symptoms suggestive of an acute infection. Screening for cardiovascular disease is crucial in the initial evaluation of symptomatic patients during the COVID pandemic to identify patients at increased risk.

Trial Registration: Clinicaltrials.gov Identifier: NCT04327479.

1. Introduction

Coronavirus disease 2019 (COVID-19) has severely affected the global health system. Due to highly variable clinical presentations, diagnostic algorithms and initial risk evaluation of patients with suspected COVID-19 remains a crucial part of clinical work. It has been proposed that more than 60 % of all patients hospitalized for COVID-19 have prevalent cardiovascular disease or increased cardiovascular risk burden, and increased mortality is found in patients with various forms of cardiovascular disease, with a case fatality rate of 10.5 % [1–4]. In addition, severe cardiovascular complications from COVID-19 are common and include heart failure, myocardial infarction, thromboembolism, and cardiovascular death [5,6]. Complications can furthermore arise as a result from cardiovascular stress induced by the severe systemic inflammation in COVID-19 in the form of a cytokine storm leading to multi-organ damage and coagulation abnormalities [4,6,7]. Given the broad consequences for the cardiovascular system, early detection of myocardial injury is essential. Myocardial injury, defined as elevated cardiac troponin levels, is frequently found in patients with COVID-19 in the acute phase as well as after recovery, and is linked with increased

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mortality [8–12].

Arguably, the pandemic has further major implication on health care systems worldwide and negatively affect standards of care for patients with cardiovascular diseases [13]. For ST-elevation myocardial infarction, delays in seeking medical care increased treatment delay times and increased complication and mortality rates were reported [14–16]. In addition to acute myocardial infarction, other cardiovascular entities show significant overlap in clinical presentation such as dyspnea as a potential COVID-19 infection. However, the precise prevalence of cardiovascular diseases as leading cause of symptoms in patients being evaluated for potential COVID-19 infection as well as the prevalence of myocardial injury in patient with and without COVID-19 infection has not been evaluated in detail. In this prospective observational single-center registry, we evaluated the prevalence of myocardial injury in patients evaluated for suspected COIVD-19 infection during the pandemic at the emergency department of a tertiary care healthcare center and defined key differential diagnoses to acute COVID-19 infection in this population.

2. Methods

2.1. Study sample

The present analysis is based on the cohort of the CoV-COR registry, which was designed to assess cardiovascular risk factors and cardiovascular diseases in patients with suspected COVID-19 infection, presenting to the University Hospital Essen. Consecutive patients, presenting to the Center of Emergency Medicine at the University Hospital Essen with symptoms suggestive of COVID-19 infection between April 2020 and March 2021 were included (n = 570). Presence or absence of COVID-19 infection was evaluated by PCR on a deep nasopharyngeal swab sample. Initially, all patients were treated by an interdisciplinary team of physicians in the emergency room. If hospital admission was considered necessary according to treating physician's discretion, COVID-positive patients were transferred to specialized COVID wards, whereas COVID-negative patients were transferred to respective specialty unit, based on the leading diagnosis. All patients underwent a standardized questioner, received a transthoracic echocardiography (TTE) exam, a 12-channel electrocardiogram, and standardized laboratory work-up. For the present analysis, all patients with available troponin levels evaluated at hospital admission were included (n = 497). The study was carried out considering the ethical guidelines of the Declaration of Helsinki and received the corresponding vote through the local ethic committee (20–9213-BO). All patients provided written informed consent. The study has been registered prior to inclusion of the first patient (NCT04327479).

2.2. Risk factor and clinical assessment

Risk factors and clinical diagnoses were collected using standardized case report forms and questionnaires on admission. Clinical characteristics, laboratory values and all information regarding the intra-hospital course was retrieved from the digital hospital information system. Systolic and diastolic blood pressures were assessed from admission records. Hypertension was defined as systolic pressure > 140 mmHg or diastolic blood pressure of > 90 mmHg or currently being on antihypertensive medication. The body mass index (BMI) was calculated as body weight divided by the square of height, as documented on admission. Hemoglobin levels, white blood cell count, creatinine, and C-reactive protein levels were evaluated using standardized enzymatic measures and recorded from blood samples drawn on hospital admission. Diabetes was defined based on fasting glucose levels, HbA1c levels, and medication. Standardized questionnaires evaluated the patient's symptoms, previous cardiovascular (e.g. coronary artery disease, atrial fibrillation, heart failure, peripheral arterial disease, cerebrovascular disease) and non-cardiovascular medical history (e.g. chronic

Table 1
Baseline characteristics for the overall cohort as well as stratified by presence and absence of COVID-19 infection.

	Overall (n = 497)	COVID-19 (n = 314)	No COVID-19 (n = 183)	p-value
Age, mean (SD), years	62.9 ± 17.2	61.5 ± 16.7	65.5 ± 17.9	0.01
Male sex, n (%)	279 (56.1)	178 (56.7)	101 (55.2)	0.8
Cardiovascular risk factors				
Body mass index, mean (SD), kg/m^2	27.3 ± 5.8	28.3 ± 6.3	26.1 ± 4.7	0.001
Systolic blood pressure, mean (SD), mmHg	126.6 ± 20.5	127.7 ± 20.9	124.6 ± 19.7	0.11
Diastolic blood pressure, mean (SD), mmHg	73.1 ± 14.6	73.5 ± 13.2	72.3 ± 16.9	0.5
Hypertension, n (%)	352 (70.8)	208 (66.2)	144 (78.7)	0.004
Antihypertensive therapy, n (%)	325 (65.4)	190 (60.5)	135 (73.8)	0.003
Dyslipidemia, n (%)	182 (36.6)	89 (28.3)	93 (50.8)	<0.001
Lipid lowering therapy, n (%)	167 (33.6)	84 (26.8)	83 (45.4)	<0.001
Smoking, n (%)				
Current	24 (4.8)	10 (3.2)	14 (7.7)	0.03
Former	46 (9.3)	19 (6.1)	27 (14.8)	0.002
Diabetes, n (%)	52 (10.5)	43 (13.7)	9 (4.9)	0.002
Prior cardiovascular disease				
Coronary artery disease, n (%)				
Prior PCI	60 (12.1)	22 (7.0)	38 (20.8)	<0.001
Prior ACB	27 (5.4)	13 (4.1)	14 (7.7)	0.10
Atrial fibrillation, n (%)	72 (14.5)	31 (9.9)	41 (22.4)	<0.001
Heart failure, n (%)	80 (16.1)	15 (4.8)	65 (35.5)	<0.001
Peripheral arterial disease, n (%)	27 (5.4)	8 (2.6)	19 (10.4)	<0.001
Cerebrovascular disease, n (%)	7 (1.4)	1 (0.3)	6 (3.3)	0.01
Other cardiovascular disease, n (%)	20 (4.0)	9 (2.9)	11 (6.0)	0.1
Prior comorbidity				
Chronic obstructive pulmonary disease, n (%)	46 (9.3)	23 (7.3)	23 (12.6)	0.06
Asthma, n (%)	19 (3.8)	16 (5.1)	3 (1.6)	0.06
Malignancy, n (%)	66 (13.3)	29 (9.2)	37 (20.2)	<0.001
Laboratory parameters				
Hemoglobin levels, mean (SD), g/dl	11.7 ± 2.3	11.9 ± 2.3	11.3 ± 2.3	0.004
White blood cell count, mean (SD), /ml	7.3 ± 3.3	6.8 ± 3.1	8.2 ± 3.5	<0.001
Creatinine, mg/dl	0.90 (0.72; 1.24)	0.84 (0.69; 1.06)	1.03 (0.80; 1.50)	<0.001
C-reactive protein, median (IQR), mg/dl	3.3 (0.9; 7.5)	4.0 (1.1; 8.0)	2.2 (0.4; 6.9)	0.07
Interleukin 6, median (IQR), pg/ml	20.3 (8.3; 54.3)	19.3 (8.5; 51.2)	22.2 (6.7; 67.6)	0.34
Procalcitonin, median (IQR; 90th percentile), ng/ml	0.01 (0.01; 0.01)	0.01 (0.01; 0.01; 0.01)	0.01 (0.01; 0.01; 602.0)	0.001
Patient's symptoms				
Fever, n (%)	152 (30.6)	110 (35.0)	42 (23.0)	0.005
Shortness of breath, n (%)	139 (28.0)	70 (22.3)	69 (37.7)	0.0003
Cough, n (%)	130 (26.2)	103 (32.8)	27 (14.8)	<0.0001
Other leading symptoms, n (%)	63 (12.7)	26 (8.3)	37 (20.2)	0.0002

ACB – aortocoronary bypass, IQR – interquartile range, PCI – percutaneous coronary intervention, SD – standard deviation.

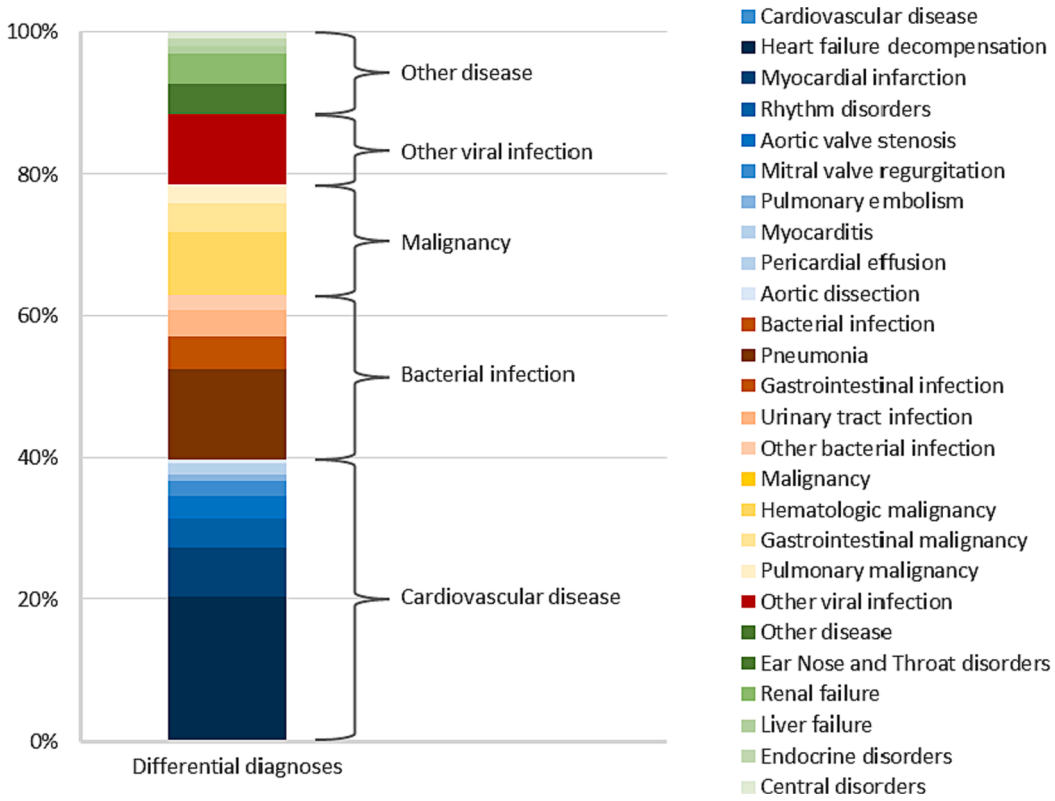

Fig. 1. Primary diagnoses in COVID-19 negative patients Primary diagnoses in COVID-19 negative patients, representing key differential diagnoses in patients with symptoms suggestive of COVID-19 infection.

obstructive pulmonary disease, asthma, malignance), and medication.

2.3. Endpoint definition

The primary endpoint of the CoV-COR registry was myocardial injury, defined as elevated cTn with at least one value above the 99th percentile upper reference limit (URL). A high-sensitive troponin I assay (Siemens Atellica, Erlangen, Germany) was used in all patients. Initial troponin was determined as part of the study protocol, while serial troponin evaluation was applied according to the discretion of treating physicians. As exploratory secondary endpoint, 90-day survival was evaluated. The survival status was assessed via standardized phone interviews.

2.4. Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) if normally distributed and as median (interquartile range) if non-normally distributed. Categorical variables were reported as frequency and percent. Baseline characteristics were stratified by subgroups with and without confirmed COVID-19 infection by PCR testing as well as in subgroups with and without myocardial injury. Differences were compared using a two-sided *T*-test or Mann-Whitney *U* test for continuous variables and Fisher's Exact test for categorical variables. Univariate and multivariable logistic regression analysis was performed to determine the association of clinical characteristics with the presence of myocardial injury. Multivariable adjustment sets included all variables also tested in univariate analysis. Further, we stratified by patients with and without COVID-19 infection. Given the limited number of patients with myocardial injury in subgroup analysis, the multivariable model was limited to the 4 tested variables in this subgroup analysis. Lastly, survival rates were compared between patients with and without myocardial injury in exploratory analysis, using Fisher's Exact test. Logistic regression analysis to evaluate the association of myocardial injury with 90-days mortality was performed in unadjusted and COVID-19 infection adjusted models. All analyses were performed using SAS software (Version 9.4, SAS Institute Inc.). A p-value of < 0.05 indicated statistical significance.

3. Results

Overall, 497 patients (mean age 62.9 ± 17.2 years, 56 % male) were included in our analysis. Of those, 314 (63 %) were tested positive on COVID-19 infection based on PCR-testing, while another disease as cause of symptom was detected in 183 patients (37 %). Fever was the most frequent leading symptom (reported in 31 % of patients), followed by shortness of breath (28 %), and cough (26 %). Stratifying by presence and absence of COVID-19 infection, COVID-19 positive patients were more frequently complaining about fever (35 vs 23 %, $p = 0.005$) or cough (33 vs 15 %, $p < 0.0001$) as leading symptom, while shortness of breath was more frequently reported in COVID-19 negative patients (22 vs 38 %, $p = 0.0003$, for COVID-19 positive vs negative patients, respectively). 70 % of the patients had prior diagnosis of arterial hypertension, 18 % had coronary artery disease, 16 % had heart failure, and 10 % had chronic obstructive pulmonary disease. Detailed patient characteristics are depicted in Table 1. Stratifying according to COVID-19 infection, we found higher frequency of most cardiovascular risk factors and higher frequency of preexisting cardiovascular diseases, chronic obstructive pulmonary disease as well as malignancies in the group of patients with symptoms suggestive of COVID-infection but negative PCR-test. COVID-positive patients had slightly higher hemoglobin levels, lower white blood cell count, lower creatinine levels, but higher C-reactive protein levels.

Fig. 1 depicts the leading diagnoses for COVID-19 negative patients. Cardiovascular diseases were the most frequent differential diagnoses (present in 40 % of patients without COVID-19 infection), while

Table 2
Baseline characteristics for the overall cohort as well as stratified by presence and absence of myocardial injury.

	Myocardial injury (n = 91)	No myocardial injury (n = 405)	p-value
Age, mean (SD), years	68.7 ± 15.9	61.6 ± 17.2	<0.001
Male sex, n (%)	55 (60.4)	224 (55.2)	0.04
COVID-19 positive	34 (37.4)	280 (69.0)	<0.001
Cardiovascular risk factors			
Body mass index, mean (SD), kg/m^2	26.0 ± 4.1	27.7 ± 6.1	0.01
Systolic blood pressure, mean (SD), mmHg	126.8 ± 20.3	126.5 ± 20.6	0.9
Diastolic blood pressure, mean (SD), mmHg	72.4 ± 15.1	73.2 ± 14.6	0.6
Hypertsion, n (%)	81 (89.0)	271 (66.8)	<0.001
Antihypertensive therapy, n (%)	78 (85.7)	247 (60.8)	<0.001
Dyslipidemia, n (%)	52 (57.1)	130 (32.0)	<0.001
Lipid lowering therapy, n (%)	49 (53.9)	118 (29.1)	<0.001
Smoking, n (%)	5	19	
Current	(5.5)14	(4.7)32	0.79
Former	(15.4)	(7.9)	0.043
Diabetes, n (%)	11 (12.1)	41 (10.1)	0.5
Prior cardiovascular disease			
Coronary artery disease, n (%)	28	32	
Prior PCI	(30.8)10	(7.9)17	<0.001
Prior ACB	(11.0)	(4.2)	0.02
Atrial fibrillation, n (%)	22 (24.2)	50 (12.3)	0.008
Heart failure, n (%)	39 (42.9)	41 (10.1)	<0.001
Peripheral arterial disease, n (%)	11 (12.1)	16 (3.9)	0.004
Cerebrovascular disease, n (%)	2 (2.2)	5 (1.2)	0.6
Other cardiovascular disease, n (%)	10 (11.0)	10 (2.5)	0.001
Prior comorbidity			
Chronic obstructive pulmonary disease, n (%)	10 (11.0)	36 (8.9)	0.5
Asthma, n (%)	3 (3.3)	16 (3.9)	1.0
Malignancy, n (%)	11 (12.1)	55 (13.6)	0.9
Laboratory parameters			
Hemoglobin levels, mean (SD), g/dl	10.8 ± 2.4	11.9 ± 2.2	<0.001
White blood cell count, mean (SD), /ml	8.5 ± 2.9	7.1 ± 3.4	<0.001
Creatinine, median (IQR), mg/dl	1.22 (0.89; 1.73)	0.86 (0.71; 1.10)	<0.001
C-reactive protein, mean (SD), mg/dl	3.1 (1.1; 11.4)	3.3 (0.9; 7.1)	1.0
Patient's symptoms			
Fever, n (%)	20 (22.0)	132 (32.6)	0.06
Shortness of breath, n (%)	32 (35.2)	107 (26.4)	0.10
Cough, n (%)	11 (12.9)	119 (29.4)	<0.001
Other leading symptoms, n (%)	12 (13.2)	51 (12.6)	0.9

ACB – aortocoronary bypass, IQR – interquartile range, PCI – percutaneous coronary intervention, SD – standard deviation.

bacterial infection was present in 24 %, malignancy in 16 %, and other viral infections in 10 %. 13 patients were diagnosed with non-ST-elevation myocardial infarction.

Table 2 depicts the differences in baseline characteristics, stratifying by presence and absence of myocardial injury. Patients with myocardial injury were older, more frequently male, had higher frequency of most cardiovascular risk factors as well as higher frequency of pre-existing cardiovascular diseases including coronary artery disease, atrial fibrillation, heart failure, and peripheral arterial disease. Likewise, hemoglobin levels were lower, white blood cell count was higher, and creatinine levels were higher in patients with myocardial injury.

Myocardial injury was present in 91 patients (18.3 %). Prevalence of myocardial injury was lower in COVID-19 positive patients (n = 34, 10.8 %) as compared to patients with negative PCR for COVID-19 infection (n = 57, 31.2 %, p < 0.001). Table 3 shows the univariate and multivariable regression analysis for the association of cardiovascular risk factors, cardiovascular diseases, hemoglobin, white blood cell count, and creatinine with myocardial injury. Except for male sex, smoking status, and diabetes, all parameters associated with presence of myocardial injury in univariate analysis. In multivariable models, prior diagnosis of heart failure, hemoglobin levels, and white blood cell count remained independently associated with myocardial injury. Subgroup analyses for the association of risk factors with myocardial injury in patients with and without COVID-19 infection are depicted in Fig. 2.

Table 3
Univariate and multivariable logistic regression analysis for the association of clinical characteristics with the presence of myocardial injury.

	Univariate		Multivariable	
	Beta-estimate (95 % CI)	p-value	Beta-estimate (95 % CI)	p-value
Age	1.58 (1.22–2.05)	<0.001	1.06 (0.76–1.48)	0.74
Male sex	1.24 (0.78–1.97)	0.36	1.12 (0.65-0.1.95)	0.68
COVID-19 positive	0.27 (0.17–0.43)	<0.001	0.45 (0.25–0.81)	0.007
Hypertension	4.04 (2.03–8.03)	<0.001	2.01 (0.87–4.64)	0.10
Dyslipidemia	2.83 (1.78–4.51)	<0.001	0.86 (0.45–1.62)	0.64
Smoking	1.72 (0.95–3.11)	0.07	0.87 (0.43–1.77)	0.71
Diabetes	1.22 (0.60–2.49)	0.58	1.36 (0.58–3.18)	0.48
CAD	4.56 (2.69–7.74)	<0.001	1.92 (0.96–3.82)	0.064
Other ASCVD	3.27 (1.52–7.07)	0.003	1.25 (0.50–3.15)	0.64
Atrial fibrillation	2.27 (1.29–3.99)	0.004	0.97 (0.47–1.99)	0.93
Heart failure	6.68 (3.94–11.30)	<0.001	2.93 (1.49–5.77)	0.002
Hemoglobin	0.61 (0.48–0.77)	<0.001	0.69 (0.52–0.91)	0.008
White blood cell count	1.46 (1.18–1.82)	<0.001	1.25 (0.96–1.49)	0.09
Creatinine	1.34 (1.10–1.63)	0.004	1.20 (0.96–1.49)	0.11

Beta estimates per 1 standard deviation increase for continuous variables.
ASCVD – atherosclerotic cardiovascular disease, CAD – coronary artery disease, CI – confidence interval.

90-days follow-up was available in a subset of 482 patients (97.0 %). Of those, 28 patients (5.8 %) died. Mortality rate was higher in patients with myocardial injury (13.4 vs 4.6 % in patients with vs without myocardial injury, respectively; p = 0.009). Mortality rates were slightly higher in COVID-19 negative as compared to covid-19 positive patients (8.5 vs 4.3 % in patients with vs without acute COVID-19 infection, p = 0.083). Comparable differences in mortality rate in patients with and without myocardial injury were observed when stratifying by presence or absence of COVID-19 infection, however, without reaching statistical significance due to the low number of observations in each group (COVID-19 negative: 13.2 vs 7.3 %, p = 0.25; COVID-19 positive: 16.7 vs 3.4 %, p = 0.10). In univariate regression analysis, presence of myocardial injury was associated with a 3.2-fold increased probability for death within 90 days (Odds ratio [95 % confidence interval]: 3.23 [1.40–7.49], p = 0.006). Adjusting for presence of COVID-19 infection slightly attenuated the effect sizes (2.44 [0.97–6.10], p = 0.058).

4. Discussion

The present study evaluated the clinical presentation and prevalence of myocardial injury in patients presenting with symptoms suggestive of COVID-19 infection to a tertiary healthcare center during the pandemic. The main findings are: (i) cardiovascular diseases and high cardiovascular risk burden are frequent in this cohort; (ii) cardiovascular diseases were the most frequent differential diagnoses in this cohort; and (iii) myocardial injury is frequently present independent of the COVID-19 status and is associated with an increased 90-days mortality. Our results acknowledge the critical role of cardiovascular diseases, leading to the increased morbidity and mortality during the COVID pandemic.

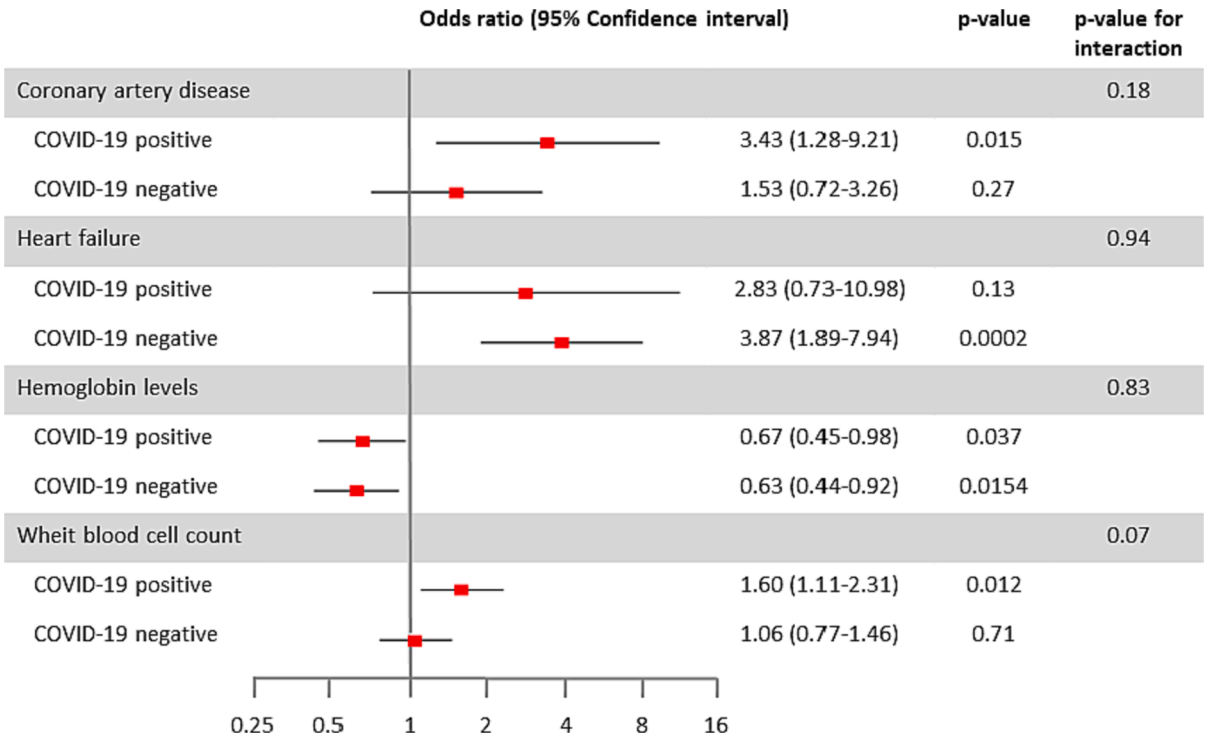

Fig. 2. Different conditions and myocardial injury in patients with and without COVID-19 infection Association of coronary artery disease, heart failure, hemoglobin levels, and white blood cell count with myocardial injury in subgroups of patients with and without COVID-19 infection.

The obtained data on the prognostic implications of myocardial injury are in line with recent, predominantly retrospective observations from different collectives. Early evidence on myocardial injury in COVID-19 was derived from 416 Wuhan patients in early 2020 (9). With 19.7 % of patients showing myocardial injury, the authors determined increased in-hospital mortality, with worse laboratory inflammatory parameters, more pronounced radiographic findings, and increased rates of mechanical ventilation [9]. Comparable data were recapitulated in different studies [8,10,17–19], including a study with 2,736 patients from New York City [17]. Here, an association of myocardial injury and pre-existing cardiovascular disease including coronary artery disease, atrial fibrillation arterial hypertension and heart failure was found as confirmed in the present study. Correspondingly, the *Task Force for the management of COVID-19 of the European Society of Cardiology* emphasizes the high prognostic value and comment on the level of troponin elevation. Mild elevations, defined as up to three times the upper normal limit, are common in patients with pre-existing cardiovascular disease and COVID 19-related myocardial injury, while elevations above three times the upper normal limit may indicate presence of acute cardiac disease, myocarditis, or presence of shock [20]. It must be noted here that only patients with confirmed COVID-19 infection were included to the aforementioned analyses with uncertain relevance for patients with suggestive symptoms, but yet uncertain diagnosis as commonly seen as first medical contact. While myocardial injury in patients with symptoms suggestive of COVID-19 indicates acute myocardial stress during COVID-19-associated systemic inflammation, it also shows a strong association to cardiovascular risk factors and cardiovascular disease. Univariate and multivariable logistic regression analysis determined an association between myocardial injury and presence of cardiovascular risk factors, including arterial hypertension, dyslipidemia, and smoking. In parallel, myocardial injury was associated with manifest cardiovascular disease including coronary artery disease, heart failure, and atrial fibrillation. Additionally, we show data on peripheral artery disease, which has not been included in the majority of previous studies, demonstrating a robust association with a 3.1-fold higher rate of peripheral artery disease in patients with suspected COVID-19 and myocardial injury. This signal was recapitulated in all patients with suggestive symptoms irrespective of COVID-19 test results. Recently, Brücker et al evaluated the prognosis of patients with acute COVID-19 infection, treated on an intensive care unit. In this retrospective analysis of consecutive patients, the authors differentiated between COVID-19 infection as primary cause of the ICU admission or being a comorbidity [21]. Likewise, myocardial injury in COVID-19 patients may be caused by various underlying circumstances. These include leading cardiovascular disease with COVID-19 infection as comorbidity, COVID-19 associated myocarditis, tachycardia, myocardial strain secondary to COVID-19-induced pulmonary embolism, myocardial infarction, or pulmonary hypertension or oxygen deficiency in severe course, or oxygen. Depending on the underlying cause, not only the applied treatment but also the prognosis of patients may vary. Further data is needed, evaluating the influence of the origin of myocardial injury as a potential marker of patient's prognosis in the setting of acute infection.

In the present study, patients with symptoms suggestive of COVID-19 without yet confirmed diagnosis by PCR test was included, thus leading to a mixed collective with 63 % COVID-19 positive patients. As a result, the examined collective resembled the clinical real world scenario of patients initially presenting in emergency care facilities. The clinical spectrum of symptoms was comparable, however with fever and cough predominantly found in patients that tested positive for COVID-19, while shortness of breath was increasingly found in patients that tested negative. Importantly, cardiovascular disease was identified as the underlying cause for symptoms suggestive of COVID-19 in 40 % of COVID-19 negative patients, underlining the clinical similarities of both disease entities. In line with existing literature, the comparable prevalence of myocardial injury as well as 90-day mortality in irrespective of COVID-19 infection underlines the need for early screening for cardiovascular diseases in all patients presenting with symptoms suggestive of COVID-19 infection to detect patients with impaired prognosis [22]. Interestingly, we observed a higher frequency of myocardial injury in COVID-19 negative vs positive patients, which stresses the need for the screening for cardiovascular causes in patients presenting with symptoms suggesting a COVID infection, even during a pandemic. Likewise, a

relevant proportion of COVID-19 positive patients were diagnosed with a myocardial injury, calling for a structured cardiovascular evaluation in patients with systemic viral infection.

4.1. Limitations

The present study has certain limitations. At first, the single center design only including patients presenting to a tertiary care center may have led to an underrepresentation of mild COVID-19 in the collective. Secondly, differences in baseline characteristics in patients with and without positive COVID-19 tests may be associated with a potential risk for bias. Finally, serial troponin measurements were conducted by the discretion of the treating physician, thereby potentially introducing heterogeneities in the available dataset.

5. Conclusion

Cardiovascular diseases not only adversely affect morbidity and mortality in COVID-19 infection but also represent the most frequent differential diagnosis in patients presenting with symptoms suggestive of an acute infection but tested negative for COVID-infection. Myocardial injury predicts the short-term mortality, irrespective of the COVID-19 infection. Our results suggest that screening for cardiovascular disease is crucial in the initial evaluation of symptomatic patients during the COVID pandemic to identify patients at increased risk.

6. Funding Source

No funding received, no conflicts of interest to declare.

7. Ethical Approval statement

The study was carried out considering the ethical guidelines of the Declaration of Helsinki and received the corresponding vote through the local ethic committee (20-9213-BO). All patients provided written informed consent. The study has been registered prior to inclusion of the first patient (NCT04327479).

8. Author's contribution

Amir A. Mahabadi: Study design, Conceptualization, Methodology, Data analysis, Writing of the manuscript, Raluca Mincu: Data collection, Review of the manuscript, Iryna Dykun: Data analysis, Methodology, Review of the manuscript, Lars Michel: Data collection, Review of the manuscript, Alexander Küng: Data collection, Review of the manuscript, Oliver Witzke: Data collection, Resources, Review of the manuscript, Clemens Kill: Data collection, Resources, Review of the manuscript, Jan Buer: Data collection, Resources, Review of the manuscript, Tienush Rassaf: Study design, Resources, Supervision, Review of the manuscript, Matthias Totzeck: Study design, Conceptualization, Writing of the manuscript.

Declaration of Competing Interest

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

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References

[1] M. O'Hearn, J. Liu, F. Cudhea, R. Micha, D. Mozaffarian, Coronavirus Disease 2019 Hospitalizations Attributable to Cardiometabolic Conditions in the United States: A Comparative Risk Assessment Analysis, J. Am. Heart Assoc. 10 (5) (2021), e019259.
[2] S.L. Harrison, B.J.R. Buckley, J.M. Rivera-Caravaca, J. Zhang, G.Y.H. Lip, Cardiovascular risk factors, cardiovascular disease, and COVID-19: an umbrella review of systematic reviews, Eur. Heart J. Qual. Care Clin. Outcomes 7 (4) (2021) 330–339.
[3] S. Bae, S.R. Kim, M.-N. Kim, W.J. Shim, S.-M. Park, Impact of cardiovascular disease and risk factors on fatal outcomes in patients with COVID-19 according to age: a systematic review and meta-analysis, Heart 107 (5) (2021) 373–380.
[4] M. Nishiga, D.W. Wang, Y. Han, D.B. Lewis, J.C. Wu, COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives, Nat. Rev. Cardiol. 17 (9) (2020) 543–558.
[5] M.K. Chung, D.A. Zidar, M.R. Bristow, S.J. Cameron, T. Chan, C.V. Harding, et al., COVID-19 and Cardiovascular Disease, Circ. Res. 128 (8) (2021) 1214–1236.
[6] T. Rassaf, M. Totzeck, A.A. Mahabadi, U. Hendgen-Cotta, S. Korste, S. Settelmeier, et al., Ventricular assist device for a coronavirus disease 2019-affected heart, ESC Heart Fail. 8 (1) (2021) 162–166.
[7] Group RC, Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial, Lancet 397 (10285) (2021) 1637–1645.
[8] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, et al., Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19), JAMA Cardiol. 5 (7) (2020) 811–818.
[9] S. Shi, M. Qin, B. Shen, Y. Cai, T. Liu, F. Yang, et al., Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China, JAMA Cardiol. 5 (7) (2020) 802–810.
[10] G. Giustino, L.B. Croft, G.G. Stefanini, R. Bragato, J.J. Silbiger, M. Vicenzi, et al., Characterization of Myocardial Injury in Patients With COVID-19, J. Am. Coll. Cardiol. 76 (18) (2020) 2043–2055.
[11] V.O. Puntmann, M.L. Carerj, I. Wieters, M. Fahim, C. Arendt, J. Hoffmann, et al., Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19), JAMA Cardiol. 5 (11) (2020) 1265–1273.
[12] D.S. Knight, T. Kotecha, Y. Razvi, L. Chacko, J.T. Brown, P.S. Jeetley, et al., COVID-19: Myocardial Injury in Survivors, Circulation 142 (11) (2020) 1120–1122.
[13] H.M. Nef, A. Elsasser, H. Mollmann, M. Abdel-Hadi, T. Bauer, M. Bruck, et al., Impact of the COVID-19 pandemic on cardiovascular mortality and catherization activity during the lockdown in central Germany: an observational study, Clin. Res. Cardiol.: Off. J. German Cardiac Soc. 110 (2) (2021) 292–301.
[14] A. Chieffo, G.G. Stefanini, S. Price, E. Barbato, G. Tarantini, N. Karam, et al., EAPCI Position Statement on Invasive Management of Acute Coronary Syndromes during the COVID-19 pandemic, Eur. Heart J. 41 (19) (2020) 1839–1851.
[15] C.S. Kwok, C.P. Gale, T. Kinnaird, N. Curzen, P. Ludman, E. Kontopantelis, et al., Impact of COVID-19 on percutaneous coronary intervention for ST-elevation myocardial infarction, Heart 106 (23) (2020) 1805–1811.
[16] C.F. Tam, K.S. Cheung, S. Lam, A. Wong, A. Yung, M. Sze, et al., Impact of coronavirus disease 2019 (COVID-19) outbreak on outcome of myocardial infarction in Hong Kong, China, Catheter. Cardiovasc. Interv. 97 (2) (2021) E194–E197.
[17] A. Lala, K.W. Johnson, J.L. Januzzi, A.J. Russak, I. Paranjpe, F. Richter, et al., Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection, J. Am. Coll. Cardiol. 76 (5) (2020) 533–546.
[18] A. Liaqat, R.S. Ali-Khan, M. Asad, Z. Rafique, Evaluation of myocardial injury patterns and ST changes among critical and non-critical patients with coronavirus-19 disease, Sci. Rep. 11 (1) (2021) 4828.
[19] S. Shi, M. Qin, Y. Cai, T. Liu, B. Shen, F. Yang, et al., Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019, Eur. Heart J. 41 (22) (2020) 2070–2079.
[20] Cardiology TTFftmoC-otESo. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1—epidemiology, pathophysiology, and diagnosis. Eur. Heart J. (2021).
[21] W. Brucker, A.A. Mahabadi, A. Huschen, J. Becker, S. Daehnke, S. Mohlenkamp, Clinical characteristics and determinants of mortality in coronavirus disease 2019 (COVID-19) patients on an intensive care unit-a retrospective explorative 1-year all-comers study, J. Thorac. Dis. 14 (5) (2022) 1319–1331.
[22] H.N. Sturkenboom, V.A.E. van Hattem, W. Nieuwland, F.M.A. Paris, M. Magro, R.L. Anthonio, et al., COVID-19-mediated patient delay caused increased total ischaemic time in ST-segment elevation myocardial infarction. Netherlands Heart J.: Monthly J. Netherlands Soc. Cardiol. Netherlands Heart Foundation 2022.