Impact of COVID-19 infection on short-term outcome in patients referred to stress myocardial perfusion imaging

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Abstract

Purpose

We assessed the impact of COVID-19 infection on cardiovascular events in patients with suspected or known coronary artery disease (CAD) referred to stress myocardial perfusion single-photon emission computed tomography (MPS).

Methods

A total of 950 consecutive patients with suspected or known CAD were submitted by referring physicians to stress MPS for assessment of myocardial ischemia between January 2018 and June 2019. All patients underwent stress-optional rest MPS. Perfusion defects were quantitated as % of LV myocardium and expressed as total perfusion defect (TPD), representing the defect extent and severity. A TPD $\geq 5\%$ was considered abnormal.

Results

During a mean follow-up of 27 months (range 4–38) 31 events occurred. Moreover, 55 (6%) patients had a COVID-19 infection. The median time from index MPS to COVID-19 infection was 16 months (range 6–24). At Cox multivariable analysis, abnormal MPS and COVID-19 infection resulted as independent predictors of events. There were no significant differences in annualized event rate in COVID-19 patients with or without abnormal MPS ($p = 0.56$). Differently, in patients without COVID-19 the presence of abnormal MPS was associated with higher event rate ($p < .001$). Patients with infection compared to those without had a higher event rate in the presence of both normal and abnormal TPD.

Conclusion

In patients with suspected and known CAD the presence of COVID-19 infection during a short-term follow-up was associated with a higher rate of cardiovascular events.

Introduction

The recent outbreak of Coronavirus disease 2019 (COVID-19) has been rapidly spreading on a global scale [1] and it has resulted in considerable morbidity and mortality worldwide. COVID-19 is accompanied by a cluster of flu-like symptoms and life-threatening severe illnesses including acute respiratory distress syndrome, acute kidney injury, myocarditis, and organ failure [2]. The data derived from initial reports and more recent case series has consistently shown a high incidence of cardiac injury, heart failure, circulatory shock and arrhythmias [3]. Therefore, increasing attention is being directed to the relationships between COVID-19 infection and the cardiovascular system regarding two key aspects: 1) the role of

cardiovascular disease as a risk factor for COVID-19 infection and as related unfavorable prognostic element; and cardiovascular complications of COVID-19 infection. Cardiovascular symptoms occur frequently in COVID-19 patients because of systemic inflammatory responses and immune system dysfunction due to disease development. It has been reported that myocardial injury can occur with COVID-19 infection due to a 'cytokine storm' that is stimulated via an imbalanced response and can cause respiratory dysfunction, hypoxemia, shock, or hypotension [4, 5]. The prevalence of COVID-19 in patients with cardiovascular diseases (CVD) is difficult to estimate due to varying degrees of national surveillance and data collection around the world [6]. Approximately 12% of COVID-19 patients have been found to have sustained acute heart injuries [7]. Moreover, in a review study approximately 5–25% of hospitalized COVID-19 cases had elevations in cardiac Troponin, a biomarker of myocardial injury [8]. Patients with acute myocardial injury are older, with a higher prevalence of pre-existing CVD and more likely to require intensive care unit admission [9]. Patients with coronary artery disease (CAD) and COVID-19 have higher rates of comorbidities, inpatient mortality and need for renal replacement therapy compared to their non-CAD counterparts. However, CAD was not associated with mortality after adjusting for other covariates, suggesting that other factors may play a predominant role in the increased mortality and poor outcomes in these patients [10]. Evaluating the presence of these chronic conditions is fundamental to mitigate COVID-19 complications and mortality. In a meta-analysis involving 13 studies in patients with COVID-19, cardiac injury was associated with mortality, need for intensive care and severity of disease [11]. However, the effect of COVID-19 infection on the progression and outcome of CVD is still unclear. The aim of the retrospective study was to evaluate the impact of COVID-19 infection on cardiovascular events in patients with suspected or known CAD referred to stress myocardial perfusion single-photon emission computed tomography (MPS).

Methods

Patients

A total of 950 consecutive patients with suspected or known CAD were submitted by referring physicians to stress MPS for assessment of myocardial ischemia between January 2018 and June 2019. Patients' clinical history was collected, and cardiac risk factors were assessed before testing. A patient was considered to have known CAD at the time of the MPS based on a provided history of previously diagnosed atherosclerotic coronary disease, history of myocardial infarction (chest pain or equivalent symptom complex, positive cardiac biomarkers, or typical electrocardiographic changes), history of percutaneous coronary intervention, or history of coronary artery bypass grafting. The Ethics Committee of our institution approved the study, and all patients gave informed consent (Protocol Number 110/17).

Study protocol

All patients underwent stress-optional rest MPS by CZT-SPECT systems (D-SPECT, Spectrum Dynamics, Caesarea, Israel) by 99m-Tc sestamibi physical exercise or dipyridamole stress test, according to the recommendations of the European Association of Nuclear Medicine [12, 13]. In all patients, beta-blocking

medications and calcium antagonists were withheld for 48 hours and long-acting nitrates for 12 hours before testing. For patient undergoing exercise test, symptom-limited treadmill standardized protocols were performed, with monitoring of heart rate and rhythm, blood pressure, and ECG. Test endpoints were achievement of 85% maximal predicted heart rate, horizontal or down-sloping ST-segment depression > 2 mm, ST-segment elevation > 1 mm, moderate to severe angina, systolic blood pressure decrease > 20 mm Hg, blood pressure $> 230/120$ mmHg, dizziness, or clinically important cardiac arrhythmia. For dipyridamole stress test, patients were instructed not to consume products containing caffeine for 24 hours before the test. Dipyridamole was infused at dose of 0.142 mg/kg per min intravenous over 4 minutes. A dose of 100 mg of aminophylline was administered intravenously in the event of chest pain or other symptoms, or after significant ST depression. At peak exercise, or 4 minutes after completion of dipyridamole infusion, a bolus of 370 MBq of ^{99m}Tc -sestamibi was injected intravenously. For both types of stress, heart rate, blood pressure, and 12-lead ECG data were recorded at rest, at the end of each stress stage, at peak stress and in the delay phases at rest. Maximal degree of ST-segment changes at 80 ms after the J-point of the ECG was measured and assessed as horizontal, down-sloping, or up-sloping. Horizontal or downsloping ST-segment depression ≥ 0.1 mV, persisting for at least 0.06 to 0.08 seconds after the J-point in one or more ECG lead, were considered diagnostic for ischemia, whereas upsloping ST depressions ≥ 1.0 mm were considered nondiagnostic. All ST depression < 1.0 mm additional from baseline was defined as negative. Recordings were obtained using 9 pixilated CZT crystal detector columns mounted vertically spanning a 90° geometry. Each of the columns consists of 1,024 ($16 \cdot 9 \cdot 64$) 5-mm thick CZT crystal elements ($2.46 \cdot 9 \cdot 2.46$ mm). Square hole tungsten collimators are fitted to each of the detectors, which are shorter than conventional low-energy, high-resolution collimators, yielding significantly better geometric speed [14]. Data were acquired focusing on the heart by the detectors rotating in synchrony and saved in list mode. Images were obtained with the patient in a semi recumbent position. A 10-s pre-scan acquisition was performed to identify the location of the heart and to set the angle limits of scanning for each detector (region of interest-centric scanning). Using the myocardial count rate from the pre-scan acquisition, the time per projection was set to target the recording of 1000 myocardial kcounts; the duration of the scans was less than 10 minutes for stress and 4 minutes for rest. Summed and gated projections were reconstructed with an iterative maximum likelihood expectation maximization algorithm using 7 and 4 iterations, respectively [15]. An automated software program (e-soft 2.5, QGS/QPS, Cedars-Sinai Medical Center, Los Angeles, CA) was used to calculate left ventricular (LV) volumes, ejection fraction, wall motion, wall thickening, and the scores incorporating both the extent and severity of perfusion defects, using standardized segmentation of 17 myocardial regions [16, 17]. The total perfusion defect (TPD) of the stress images was also generated, representing the defect extent and severity and expressed as a percentage of the LV myocardium. A TPD $\geq 5\%$ was considered abnormal [18].

Outcome

Patient follow-up was obtained by use of a questionnaire that was assessed by a phone call to the patients, general practitioners or cardiologists and by review of hospital or physicians' records by individuals blinded to the patient's test results. The follow-up questionnaire included all possible data

linked to COVID-19 infection: time and duration of the infection, symptoms, hospitalization and related course. Moreover, outcome was composite end-point of cardiac death, nonfatal myocardial infarction, or unstable angina requiring coronary revascularization, whichever occurred first. The cause of death was confirmed by review of death certificate, hospital chart, or physician's records. Death was of cardiac origin if the primary cause was defined as acute myocardial infarction, congestive heart failure, valvular heart disease, sudden cardiac death, or cardiac interventional/ surgical procedure related. Myocardial infarction was defined when > 2 of the following 3 criteria was met: chest pain or equivalent symptom complex, positive cardiac biomarkers, or typical electrocardiographic changes [19]. The date of the last examination or consultation was used to determine the length of follow-up.

Statistical analysis

Continuous data are expressed as mean $\pm$ standard deviation and categorical data as percentage. A student two-sample t-test and chi-square test were used to compare the differences in continuous and categorical variables, respectively. A $p < 0.05$ (two-sided) was considered statistically significant. Annualized event rates (AER), expressed as % person-years, were calculated as the cumulative number of events divided by person-time. This latter is an estimate of the actual time-at risk that all persons contribute to the study, i.e., the sum of each individual follow-up period. Because patients shifted from the no COVID-19 to the COVID-19 group during follow-up, unadjusted event free survival functions were estimated using the method proposed by Simon-Makuch [20], a modification of Kaplan-Meier analysis, and compared using the Mantel-Byar test [21]. In this context, COVID-19 is treated as a binary nonreversible time-dependent covariate that starts at 0 (no COVID-19) and may switch to 1 (COVID-19) at some time point. Thus, the study cohorts are continually updated as follows: for the time prior to COVID-19 infection, the patient contributes to the no COVID-19 cohort, but for the time after COVID-19 infection, the patient contributes to the COVID-19 cohort. The start time (t_0) for the no COVID-19 group is the beginning of follow-up (index MPS), while for the COVID group t_0 is the date of COVID-19 infection after index MPS. The impact of COVID on event-free survival was evaluated with the extended Cox regression model. To consider differences in the time from index MPS to COVID-19, COVID-19 was treated as a binary non-reversible time-dependent covariate. Thus, COVID-19 patients were members of the no COVID-19 group until the day of infection. At that point, they were crossed over to the COVID-19 group. This means that patients contribute to the hazard estimate of the no COVID-19 group up to the infection time, when they start to contribute to the hazard estimate of the COVID-19 group. Statistical analysis was performed with Stata 16 software (StataCorp, College Station, Texas USA).

Results

Patient characteristics and outcome

Follow-up data were not available in 73 (8%) of the 950 patients, leaving 877 subjects for the analysis. Over a median follow-up of 27 months (range 4–38) 31 cardiac events occurred (3.5% cumulative event

rate) and 6 patients died for COVID-19 infection. Cardiac events were cardiac death in 9 (29%), nonfatal myocardial infarction in 5 (16%) and revascularization procedures in 17 (55%) patients.

Patient's characteristics and imaging findings according to the occurrence of cardiac events are reported in Table 1. Patients with events showed a higher prevalence of smoking history and known CAD. A higher prevalence of abnormal MPS was also observed in patients with events. During the follow-up, 55 (6%) patients presented a COVID-19 infection and 822 (94%) did not. The median time from index MPS to COVID-19 infection was 16 months (range 6–24). Clinical characteristics and imaging findings according to the occurrence of COVID-19 infection are described in Table 2. As shown, patients with COVID-19 had lower mean age and a higher prevalence of atypical angina as compared to patients without COVID-19. All the others clinical characteristics were comparable between the two groups. Moreover, the prevalence of abnormal MPS was similar in patients with and without COVID-19. The cumulative event rate was 14% in patients with COVID-19 and 2.8% in those without ($p < 0.001$).

Table 1
Clinical characteristics and imaging findings according to cardiac events

	All patients (<i>n</i> = 877)	Event (<i>n</i> = 31)	No Event (<i>n</i> = 844)	<i>p</i> value
Age (years)	64 ± 10	63 ± 9	64 ± 10	0.67
Male gender, <i>n</i> (%)	587 (67)	24 (76)	563 (66)	0.20
Body mass index (kg/m ²)	28 ± 5	28 ± 4	28 ± 5	0.82
Diabetes, <i>n</i> (%)	274 (31)	13 (48)	261 (30)	0.19
Hypertension, <i>n</i> (%)	753 (86)	30 (97)	723 (85)	0.07
Dyslipidemia, <i>n</i> (%)	591 (67)	23 (69)	568 (67)	0.41
Smoking history, <i>n</i> (%)	529 (60)	26 (76)	503 (60)	< 0.01
Family history of CAD, <i>n</i> (%)	482 (55)	21 (64)	461 (55)	0.14
Angina symptom, <i>n</i> (%)	302 (34)	12 (39)	290 (34)	0.61
Known CAD, <i>n</i> (%)	379 (43)	21 (67)	358 (42)	< 0.01
Abnormal MPS, <i>n</i> (%)	288 (33)	18 (61)	270 (32)	< 0.005
Pharmacological stress test, <i>n</i> (%)	484 (55)	20 (61)	464 (55)	0.52
COVID-19, <i>n</i> (%)	55 (6)	8 (24)	47 (5)	< 0.001
Values are expressed as mean value ± standard deviation or as number (percentage)				
CAD coronary artery disease, MPS myocardial perfusion single-photon emission computed tomography				

Table 2
Clinical characteristics and imaging findings according to COVID-19 infection

	All patients (<i>n</i> = 877)	COVID-19 (<i>n</i> = 55)	No COVID-19 (<i>n</i> = 822)	<i>p</i> value
Age (years)	64 ± 10	61 ± 10	64 ± 10	< 0.01
Male gender, <i>n</i> (%)	587 (67)	37 (67)	550 (67)	0.95
Body mass index (kg/m ²)	28 ± 5	29 ± 5	28 ± 5	0.74
Diabetes, <i>n</i> (%)	274 (31)	18 (35)	256 (31)	0.80
Hypertension, <i>n</i> (%)	753 (86)	49 (88)	704 (86)	0.47
Dyslipidemia, <i>n</i> (%)	591 (67)	42 (75)	549 (67)	0.14
Smoking history, <i>n</i> (%)	529 (60)	32 (58)	497 (60)	0.07
Family history of CAD, <i>n</i> (%)	482 (55)	37 (65)	445 (54)	0.06
Angina symptom, <i>n</i> (%)	302 (34)	26 (48)	276 (33)	< 0.05
Known CAD, <i>n</i> (%)	379 (43)	21 (38)	358 (43)	0.43
Abnormal MPS, <i>n</i> (%)	288 (33)	16 (29)	272 (33)	0.54
Values are expressed as mean value ± standard deviation or as number (percentage)				
<i>CAD</i> coronary artery disease, <i>MPS</i> myocardial perfusion single-photon emission computed tomography				

Predictors of events

The results of Cox univariable and multivariable analysis for prediction of cardiac events are reported in Table 3. At multivariable analysis, only abnormal MPS and COVID-19 infection were significant predictors of events. Event free survival was better in patients without than in those with COVID-19 ($p < 0.001$) (Fig. 1). The AER according to COVID-19 infection and MPS are depicted in Fig. 2. Patients with infection compared to those without had a higher event rate in the presence of both normal and abnormal TPD.

Table 3
Univariable and multivariable predictors of cardiac events

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	<i>p</i> value	Hazard ratio (95% CI)	<i>p</i> value
Age	0.994 (0.961–1.028)	0.71		
Male gender	0.590 (0.254–1.368)	0.21		
Body mass index	0.992 (0.926–1.062)	0.81		
Diabetes	1.608 (0.788–3.282)	0.19		
Hypertension	5.070 (0.691–37.179)	0.11		
Dyslipidemia	1.430 (0.639–3.197)	0.38		
Smoking history	3.132 (1.186–8.270)	< .05		
Family history of CAD	1.754 (0.826–3.726)	0.14		
Known CAD	1.812 (0.783–4.190)	0.16		
Abnormal MPS	2.809 (1.376–5.733)	< 0.005	2.201 (1.030–4.704)	< 0.05
COVID-19	15.025 (4.402–25.009)	< 0.001	25.35 (7.802–82.374)	< 0.001
<i>CI</i> /confidence interval, <i>CAD</i> coronary artery disease, <i>MPS</i> myocardial perfusion single-photon emission computed tomography				

There were no significant differences in AER in COVID-19 patients with or without abnormal MPS ($p = 0.56$). On the contrary, in patients without COVID-19 the presence of abnormal MPS was associated with a higher event rate ($p < 0.001$). The event-free survival curves according to COVID-19 and MPS results are reported in Fig. 3. Patients with COVID-19 and abnormal MPS had the worst outcome with a lower event-free survival as compared to patients without COVID-19 with both normal and abnormal MPS ($p < 0.001$). Yet, the event-free survival was similar in patients with COVID-19 and normal MPS and those with COVID-19 and abnormal MPS ($p = 0.48$). There was no difference in event free-survival between patients without COVID 19 and with abnormal MPS and patients with COVID-19 but normal MPS. The best outcome was observed in no COVID-19 patients and normal MPS.

Discussion

The present study demonstrated that patients referred to stress MPS for evaluation of suspected or known CAD, who presented COVID-19 infection during follow-up had a higher incidence of cardiac events compared to patients without subsequent COVID-19 infection. In particular, COVID-19 infection and abnormal MPS were both independent predictors of cardiac events at follow-up.

After its insurgence, COVID infection has spread to more than 200 countries, and mortality of the critical patients has been reported to be as high as 50% [22]. Previous studies demonstrated that patients with COVID-19 infection and other comorbidities were more frequently affected by a severe COVID-19 disease with a higher rate of mortality [23]. Therefore, increasing attention is being directed to analyze the impact of underlying diseases on the prognosis of COVID-19 [24–26]. In particular, cardiac disease represents the most common comorbidity in patients with COVID-19 and it has been demonstrated that CVD can be regarded as a strong risk factor for rapid progression and poor prognosis of COVID-19 [27].

In a retrospective study of 138 patients from the University of Wuhan, patients who met the need for admission to the intensive care unit were significantly older and had underlying comorbidities more frequently, such as hypertension, diabetes mellitus and known CAD [9]. On the other hand, it is plausible that also the presence of COVID-19 infection may contribute to accelerate the cardiovascular disease progression. The basis of myocardial damage from COVID-19 exists direct damage to myocardiocytes, systemic inflammation, myocardial interstitial fibrosis, exaggerated T-cell Helper Type 1 and 2 activation, coronary plaque destabilization and hypoxia [28]. In our study population the presence of COVID-19 infection and abnormal MPS was associated with the worst prognosis in a follow-up of about two years. Patients with normal MPS and without COVID-19 disease showed the best prognosis. Interestingly, there were no significant difference in outcome between patients with COVID-19 and normal or abnormal MPS. The presence of COVID-19 infection in patients with suspected or known CAD is seems to be decisive in defining the risk of cardiac event. It may be possible that the presence of COVID-19 could be responsible of cardiac disease progression and poor outcome independently of others cardiac risk factors and the presence of abnormal perfusion.

It is well known that Coronaviruses can bind to some metal peptidases such as ACE2, which is present in the epithelial cells of the pulmonary alveoli, epithelial cells of the small intestine, arterial and venous endothelial cells and smooth muscle cells [29]. The variety of expression of ACE2 suggests the correlation between SARS-COVID-2 and extra-pulmonary manifestations, in particular cardiac involvement. COVID-19 through its Spike protein binds strongly to ACE2 receptors and after entering cells, determines a down-regulation of the expression of ACE2, for which the enzyme is no longer able to perform his role. Sars-COVID 2 is therefore able to down regulate the ACE2 pathways at the myocardial and pulmonary level, mediating myocardial inflammation, pulmonary edema and acute respiratory failure [30]. Adult patients affected by CVD, arterial hypertension, diabetes, and/or chronic obstructive pulmonary disease show worse clinical outcome following contraction of the viral illness with fatality rate attaining 10.5% [31]. In addition, the cytokine storm associated to virus infection as an expression of an exaggerated response of the host's immune system, is highly detrimental to the heart. Cardiac complications associated with viral pneumonia include malignant arrhythmias, myocardial infarction, and heart failure [31]. Myocardial damage during COVID-19 can be asymptomatic and therefore can only be evaluated with laboratory markers, or it can be clinically evident. A recent meta-analysis reports how the evolution of COVID-19 disease can exacerbate a pre-existing ventricular dysfunction or predispose to a new cardiomyopathy [32]. Therefore, the presence of underlying cardiovascular comorbidities in patients with COVID-19 is associated with high mortality. However, on the other hand COVID-19 can cause

cardiovascular disorders, including myocardial injury, arrhythmias, acute coronary syndrome and venous thromboembolism. Our preliminary results involved a limited number of patients in a short-term follow-up. Probably an analysis in a larger study population followed for more time could help to better elucidate the relationship between COVID-19 infection and cardiovascular disease and to evaluate the correlation between infection and poor outcome. Moreover, it has been demonstrated that COVID-19 induced an endothelial cell dysfunction by an excessive generation of thrombin and a shutdown of fibrinolysis, which indicate a state of hyper-coagulability [33]. Therefore, investigations on microvascular and endothelial damage can play a fundamental role in explaining the pathophysiological mechanisms, the clinical course and for the development of new treatments, as well as to reduce the number of those who will need intensive care units.

Conclusions

In our series of patients with suspected and known CAD undergoing to stress MPS, the presence of COVID-19 infection was associated with a significantly higher rate of cardiovascular events during a short-term follow-up, independently of others cardiovascular risk factors. COVID-19 and abnormal MPS were both associated with an increased risk of cardiac events in these patients. A possible interaction of COVID-19 infection on cardiovascular system may have a role in a poor outcome in patients with suspected or known CAD.

Declarations

Author contributions R.A, M.P, A.C., and W.A. conceptualized the paper; T.M., V.G., E.Z., C.G.M., E.C., C.N., E.C., R.B., and G.Z. evaluated and reported the imaging findings; V.C. and R.G collected follow-up data; R.A, M.P, A.C., and W.A. drafted the manuscript; and all the authors revised and commented on the paper and approved the final version of the manuscript.

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Ethical approval 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. This article does not contain any studies with animals performed by any of the authors.

Informed approval Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no conflict of interest.

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Figures

Figure 1

Simon and Makuch's modified Kaplan-Meier curves in patients with (red line) and without (blue line) COVID-19 infection (time-dependent covariate). COVID-, patients without infection; COVID+, patients with infection; MPS-, patients with normal MPS (TPD <5%); MPS+, patients with abnormal MPS (TPD ≥5%)

Figure 2

Annualized event rate according to COVID-19 infection and stress MPS findings. COVID-, patients without infection; COVID+, patients with infection; MPS-, patients with normal MPS (TPD <5%); MPS+, patients with abnormal MPS (TPD ≥5%)

Figure 3

Simon and Makuch's modified Kaplan-Meier curves in patients without COVID-19 and normal MPS (blue line), without COVID-19 and abnormal MPS (red line), with COVID-19 and normal MPS (green line) and with COVID-19 and abnormal MPS (yellow line). COVID-, patients without infection; COVID+, patients with infection; MPS-, patients with normal MPS (TPD <5%); MPS+, patients with abnormal MPS (TPD ≥5%)