



## Outcomes of acute coronary syndromes in coronavirus disease 2019

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Sirs:

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a fast spreading disease with high morbidity and mortality [1]. COVID-19 can contribute to severe myocardial injury,

ultimately culminating in acute coronary syndromes (ACS) [2]. Clinical features and outcomes of patients with SARS-CoV-2 associated ACS have not been elucidated, yet.

In a multicenter study, COVID-19 positive patients diagnosed with angiographically confirmed ACS between February 19 and April 9 2020 at 17 sites in Italy, Spain, and

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**Table 1** Characteristics of ACS Patients

	COVID-19 positive N=45	COVID-19 negative N=76	P value
<b>Demographics</b>			
Male sex—no./total no. (%)	37/45 (82.2)	59/76 (77.6)	0.55
Age (years)	69.7 ± 11.1 (N=45)	65.8 ± 10.7 (N=76)	0.06
BMI (kg/m <sup>2</sup> )	26.5 ± 3.2 (N=44)	27.7 ± 4.9 (N=74)	0.11
<b>ACS type</b>			
STE-ACS	27/45 (60.0)	43/76 (56.6)	0.71
NSTE-ACS	18/45 (40.0)	33/76 (43.4)	0.71
<b>Symptoms on admission—no./total no. (%)</b>			
Chest pain	34/45 (75.6)	54/71 (76.1)	0.95
Dyspnea	23/45 (51.1)	14/71 (19.7)	<0.001
<b>Cardiac biomarkers—median (IQR)</b>			
Troponin maximum—factor increase in ULN <sup>a</sup>	97.36 (33.44–411.78) N=43	139.46 (17.16–410.14) N=76	0.79
Creatine kinase maximum—factor increase in ULN	6.55 (1.39–20.96) N=27	4.16 (0.94–10.48) N=76	0.14
BNP maximum—factor increase in ULN <sup>b</sup>	2.56 (0.92–22.26) N=20	4.03 (1.62–11.05) N=72	0.80
<b>Inflammatory markers—median (IQR)</b>			
CRP maximum (mg/l)	15.20 (7.95–60.68) N=36	26.00 (6.80–62.00) N=75	0.59
WBC maximum (10 <sup>3</sup> /μl)	11.94 (9.44–16.58) N=44	11.16 (8.42–15.56) N=75	0.15
<b>Vital signs—mean ± SD</b>			
Heart rate on admission (beats/min)	82.4 ± 16.0 (N=37)	79.5 ± 15.7 (N=76)	0.37
Systolic blood pressure on admission (mmHg)	131.6 ± 26.6 (N=45)	134.0 ± 27.4 (N=76)	0.64
Diastolic blood pressure on admission (mmHg)	78.1 ± 16.1 (N=45)	77.9 ± 14.6 (N=76)	0.94
LVEF (%)	42.5 ± 11.4 (N=43)	44.7 ± 13.1 (N=53)	0.40
<b>ECG on admission</b>			
Sinus rhythm—no./total no. (%)	41/45 (91.1)	70/74 (94.6)	0.48
QTc (ms)	430.2 ± 28.0 (N=31)	435.9 ± 34.5 (N=74)	0.42
<b>Cardiovascular risk factors/comorbidities—no./total no. (%)</b>			
Arterial hypertension	36/45 (80.0)	39/76 (51.3)	0.002
Diabetes mellitus	12/44 (27.3)	19/76 (25.0)	0.78
Hypercholesterolemia	19/45 (42.2)	42/76 (55.3)	0.17
Cancer	2/45 (4.4)	6/76 (7.9)	0.71*
Cerebrovascular disease	3/45 (6.7)	7/76 (9.2)	0.74*
COPD/asthma	2/45 (4.4)	7/76 (9.2)	0.48*
Coronary artery disease	13/45 (28.9)	22/76 (28.9)	1.0
Renal disease	5/45 (11.1)	10/76 (13.2)	0.74
<b>Medication on admission—no./total no. (%)</b>			
ACE inhibitor	15/45 (33.3)	15/71 (21.1)	0.14
AT antagonist	7/45 (15.6)	20/71 (28.2)	0.12
Beta-blocker	16/45 (35.6)	18/71 (25.4)	0.24
Calcium-channel antagonist	8/45 (17.8)	13/71 (18.3)	0.94
Statin	16/45 (35.6)	29/71 (40.8)	0.70*
Coumarin	1/45 (2.2)	4/71 (5.6)	0.64
Direct oral anticoagulant	1/45 (2.2)	1/71 (1.4)	1.0*
<b>COVID-19 specific therapy—no./total no. (%)</b>			
Hydroxychloroquine	24/45 (53.3)		
Remdesivir	1/45 (2.2)		
Lopinavir/Ritonavir	12/45 (26.7)		
Baricitinib	1/45 (2.2)		
Tocilizumab	3/45 (6.7)		

**Table 1** (continued)

	COVID-19 positive N=45	COVID-19 negative N=76	P value
Acute cardiac care treatment—no./total no. (%)			
Catecholamine use	9/37 (24.3)	12/76 (15.8)	0.27
Invasive or non-invasive ventilation	17/45 (37.8)	12/76 (15.8)	0.006
Cardiopulmonary resuscitation	6/37 (16.2)	13/76 (17.1)	0.91
In-hospital death—no./total no. (%)	12/44 (27.3) <sup>o</sup>	6/76 (7.9)	0.004

ACE angiotensin converting enzyme, ACS acute coronary syndrome, AT angiotensin, BMI body mass index, BNP brain natriuretic peptide, COPD chronic obstructive pulmonary disease, COVID-19 coronavirus disease 2019, CRP c-reactive protein, ECG electrocardiogram, IQR interquartile range, LVEF left ventricular ejection fraction, NSTE non-ST-segment elevation, QTc QT time corrected for heart rate, SD standard deviation, STE ST-segment elevation, ULN upper limit of the normal, WBC white blood cell count

<sup>h</sup>Including upper limits of troponin T, high-sensitivity troponin T and troponin I

<sup>s</sup>Including upper limits of brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide

<sup>o</sup>One patient was still hospitalized at time of performing statistical analysis

\*Fisher's exact test

Switzerland were compared to COVID-19 negative ACS patients from the University Hospital Zurich. In addition, patients with ST-segment elevation (STE)-ACS COVID 19 positive vs. COVID-19 negative were compared as well as patients with non-ST-segment elevation (NSTEMI)-ACS COVID-19 positive vs. COVID-19 negative.

Out of 4702 patients with COVID-19, 45 (0.96%) had ACS, of which 27 (60.0%) had STE-ACS and 18 (40.0%) NSTEMI-ACS. Single vessel disease was present in 25 patients (55.6%) of COVID-19 positive ACS and multi vessel disease in 20 patients (44.4%), respectively. All patients received percutaneous coronary intervention.

COVID-19 positive ACS patients were more likely to present with dyspnea (51.1% vs. 19.7%;  $P < 0.001$ ) and arterial hypertension (80.0% vs. 51.3%;  $P = 0.002$ ), while other patients' characteristics were largely comparable to COVID-19 negative ACS patients (Table 1). Of note, in-hospital mortality was more than 3 times higher in COVID-19 positive ACS patients than in COVID-19 negative ACS patients (27.3% vs. 7.9%;  $P = 0.004$ , Table 1). Furthermore, when stratifying patients according to the presence or absence of ST-segment elevation, COVID-19 positive patients with STE-ACS had higher mortality rates compared to COVID-19 negative STE-ACS patients (33.3% vs. 9.3%;  $P = 0.024$ ) and also COVID-19 positive patients with NSTEMI-ACS showed numerically higher mortality rates compared to COVID-19 negative NSTEMI-ACS patients (17.6% vs. 6.1%;  $P = 0.32$ ). Importantly, 9 out of 12 (75%) deceased COVID-19 positive ACS patients had involvement of multiple organ systems in addition to cardiac manifestations, thus indicating a systemic vascular damage. In comparison to recovered COVID-19 positive ACS patients, deceased COVID-19 positive ACS patients had markedly elevated troponin values (factor increase in upper limit of the normal (ULN): 65.00 vs. 323.00;  $P = 0.014$ ) and brain natriuretic peptide

values (factor increase in ULN: 2.00 vs. 113.23;  $P = 0.023$ ) accompanied by severely depressed left ventricular ejection fraction ( $45.3 \pm 10.3\%$  vs.  $34.3 \pm 9.5\%$ ;  $P = 0.003$ ) suggesting incremental SARS-CoV-2 related myocardial injury further aggravating ACS related heart failure.

The relatively low frequency of ACS in COVID-19 may in part explained by the fact that not all COVID-19 positive patients who exhibit ST-segment elevation undergo coronary angiography [3]. The concomitant occurrence of COVID-19 and ACS might be responsible for the increased mortality. Pathophysiological mechanisms underlying COVID-19 related ACS events are unknown but might include acute plaque rupture or erosion facilitated by systemic inflammation, microvascular thrombosis due to hypercoagulability, and/or endothelial dysfunction [4]. The latter is known to play a key role in arterial hypertension and thrombosis and has recently been associated with COVID-19 [5]. In this respect, endotheliitis in COVID-19 might affect various vascular beds thereby increasing the susceptibility for thromboembolic and septic complications or multi-organ-failure [5]. Thus, myocardial ischemia due to ACS might be even aggravated by COVID-19 induced generalized microvascular dysfunction and systemic vascular damage leading to severe heart failure with unfavorable outcomes. Therefore, in addition to a guideline-directed ACS management, therapies to improve endothelial dysfunction might be considered in patients with COVID-19.

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### Compliance with ethical standards

**Conflict of interest** The authors report no conflicts of interest.

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