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LETTER TO THE EDITORS

Outcomes of acute coronary syndromes in coronavirus disease 2019

Victoria L. Cammann[1] · Konrad A. Szawan[1] · Fabrizio D'Ascenzo[2] · Sebastiano Gili[3] · Sara Dreiding[1] · Michael Würdinger[1] · Robert Manka[1] · Barbara E. Stähli[1] · Erik W. Holy[1] · Patrick Siegrist[1] · Philipp Jakob[1] · Philippe Meyer[4] · Mario Iannaccone[5] · Emanuela Di Simone[5] · Gioel Gabrio Secco[6] · Matteo Saccocci[7] · Luca Bettari[8] · Alfonso Ielasi[9] · Maurizio Tespili[9] · Giorgio Quadri[10] · Ferdinando Varbella[10] · Sergio Raposeiras-Roubin[11] · Emad Abu-Assi[11] · Massimo Mancone[12] · Gennaro Sardella[12] · Fabio Infusino[12] · Francesco Fedele[12] · Giuseppe Patti[13] · Marco Mennuni[14] · Andrea Rognoni[14] · Mario Bollati[15] · Luca Olivotti[16] · Stefano Cordone[17] · Stefano Carugo[18] · Lucia Barbieri[18] · Luca Gaido[19] · Massimo Giammaria[19] · Alfonso Gambino[20] · Maurizio D'Amico[20] · Alessandro Galluzzo[5] · Fabrizio Ugo[5] · Daniela Trabattoni[3] · Ovidio De Filippo[2] · Gaetano Maria De Ferrari[2] · Carmine Vecchione[21] · Rodolfo Citro[21] · Jelena R. Ghadri[1] · Christian Templin[1]

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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

Victoria L. Cammann, Konrad A. Szawan, Jelena R. Ghadri and Christian Templin contributed equally to this work.

✉ Christian Templin
Christian.Templin@usz.ch

1 Andreas Grüntzig Heart Catheterization Laboratories and Acute Cardiac Care, University Heart Center, Department of Cardiology, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland

2 Division of Cardiology, Department of Medical Sciences, AOU Città Della Salute E Della Scienza, University of Turin, Turin, Italy

3 Centro Cardiologico Monzino, IRCCS, Milan, Italy

4 Service de Cardiologie, Hôpitaux Universitaires de Genève, Geneva, Switzerland

5 Department of Cardiology, San Giovanni Bosco Hospital, Turin, Italy

6 Interventional Cardiology and Cardiac Surgery Unit, Azienda Ospedaliera SS Antonio E Biagio E Cesare Arrigo, Alessandria, Italy

7 Cardiac Surgery Unit, Cardiovascular Department - Poliambulanza Foundation Hospital, Brescia, Italy

8 Interventional Cardiology Unit, Cardiovascular Department - Poliambulanza Foundation Hospital, Brescia, Italy

9 Clinical and Interventional Cardiology Unit, Sant'Ambrogio Cardio-Thoracic Center, Milan, Italy

10 Cardiology Unit, Rivoli Hospital, Turin, Italy

11 Cardiology Department, University Hospital Alvaro Cunqueiro, Vigo, Spain

12 Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

13 University of Eastern Piedmont, Interventional Cardiology, Maggiore Della Carità Hospital of Novara, Novara, Italy

14 Interventional Cardiology, Maggiore Della Carità Hospital of Novara, Novara, Italy

15 Cardiology Division, Ospedale Maggiore, Lodi, Italy

16 Department of Cardiology, Ospedale Santa Corona, Pietra Ligure, Savona, Italy

17 Department of Cardiology, Ospedale San Paolo, Savona, Italy

18 Division of Cardiology, ASST Santi Paolo E Carlo, Milan, Italy

19 Division of Cardiology, Maria Vittoria Hospital, Turin, Italy

20 Interventional Cardiology, S. Croce Hospital of Moncalieri, Turin, Italy

21 Heart Department, University Hospital "San Giovanni Di Dio E Ruggi D'Aragona", Salerno, Italy

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Table 1 Characteristics of ACS Patients

	COVID-19 positive $N=45$	COVID-19 negative $N=76$	*P* value
Demographics			
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^2)	26.5 ± 3.2 ($N=44$)	27.7 ± 4.9 ($N=74$)	0.11
ACS type			
STE-ACS	27/45 (60.0)	43/76 (56.6)	0.71
NSTE-ACS	18/45 (40.0)	33/76 (43.4)	0.71
Symptoms on admission—no./total no. (%)			
Chest pain	34/45 (75.6)	54/71 (76.1)	0.95
Dyspnea	23/45 (51.1)	14/71 (19.7)	< 0.001
Cardiac biomarkers—median (IQR)			
Troponin maximum—factor increase in ULN"	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[$]	2.56 (0.92–22.26) $N=20$	4.03 (1.62–11.05) $N=72$	0.80
Inflammatory markers—median (IQR)			
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^- 3/µl)	11.94 (9.44–16.58) $N=44$	11.16 (8.42–15.56) $N=75$	0.15
Vital signs—mean ± SD			
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
ECG on admission			
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
Cardiovascular risk factors/comorbidities—no./total no. (%)			
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
Medication on admission—no./total no. (%)			
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*
COVID-19 specific therapy—no./total no. (%)			
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)°	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

"Including upper limits of troponin T, high-sensitivity troponin T and troponin I

$Including upper limits of brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide

°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 (NSTE)-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%) NSTE-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 NSTE-ACS showed numerically higher mortality rates compared to COVID-19 negative NSTE-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 ($45.3\pm10.3\%$ vs. $34.3\pm9.5\%$; $P=0.003$) 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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