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Decrease and Delay in Hospitalization for Acute Coronary Syndromes During the 2020 SARS-CoV-2 Pandemic

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ABSTRACT

The diffusion of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) forced the Italian population to restrictive measures that modified patients' responses to non-SARS-CoV-2 medical conditions. We evaluated all patients with acute coronary syndromes admitted in 3 high-volume hospitals during the first month of SARS-CoV-2 Italian-outbreak and compared them with patients with ACS admitted during the same period 1 year before. Hospitalization for ACS

RÉSUMÉ

La propagation du coronavirus 2 du syndrome respiratoire aigu sévère (SRAS-CoV-2) a obligé la population italienne à prendre des mesures contraignantes qui ont modifié la réaction des patients face aux affections médicales non liées au SRAS-CoV-2. Nous avons évalué tous les patients atteints de syndromes coronariens aigus (SCA) admis dans 3 hôpitaux à fort volume d'activité au cours du premier mois de l'épidémie italienne de SRAS-CoV-2 et les avons comparés aux

After the first outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in late December 2019, in the Chinese city of Wuhan, Italy soon became the center of a fast-growing epidemic in late February to March 2020: more severe in some areas of northern and central Italy.[1] After the first confirmed case reported on February 20, 2020, in Codogno, a small town near Milan, the rapid diffusion of the infection prompted the Italian government to proclaim a national lockdown on March 9, 2020, forcing the entire population to severe restrictive isolation measures. These measures, certainly helpful in reducing the diffusion of SARS-CoV-2 infection, significantly modified patients' responses to non-SARS-CoV-2 medical conditions, including acute coronary syndrome (ACS).[2] Because ACS is a life-threatening condition, with outcomes strictly dependent on prompt recognition and treatment, under- or misdiagnosis and late or missed treatment might be deleterious. In the current study, we report data from high-volume hospitals from 3 variably affected regions—Piedmont, Marche, and Tuscany—to evaluate changes in rate of hospitalization for ACS during the first month of the SARS-CoV-2 Italian outbreak.

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See page 1155 for disclosure information.

Methods

This is a multicentre, observational, retrospective study involving 3 high-volume centres distributed in northern and central Italy. Epidemiologic data of consecutive patients with ACS admitted in March 2019, and March 2020 were anonymously extracted and entered into a dedicated database. Data

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decreased from 162 patients in 2019 to 84 patients in 2020. In 2020, both door-to-balloon and symptoms-to-percutaneous coronary intervention were longer, and admission levels of high-sensitive cardiac troponin I were higher. They had a lower discharged residual left-ventricular function and an increased predicted late cardiovascular mortality based on their Global Registry of Acute Coronary Events (GRACE) scores.

patients atteints de SCA admis au cours de la même période un an auparavant. L'hospitalisation pour un SCA a été réduite de 162 patients en 2019 à 84 patients en 2020. En 2020, le délai porte cardio-ballon et le délai symptômes-intervention coronarienne percutanée étaient plus longs, et les niveaux de troponine I cardiaque de haute sensibilité mesurés à l'admission étaient plus élevés. Les patients avaient une fonction ventriculaire gauche résiduelle altérée et une mortalité cardiovasculaire tardive plus élevée que prévu d'après leur score comparé au registre mondial des syndromes coronariens aigus (GRACE).

collections included procedural results and in-hospital outcomes.

The "case period" was set in the month of March because it was when the severe social containing measures were adopted. The rate of ACS-related hospitalization during March 2020 was compared with the rate in the control period (March 2019). Subanalyses comprised the rate of ACS type (ST-elevation myocardial infarction [STEMI], non−ST-elevation myocardial infarction [NSTEMI] and STEMI with a time-to-reperfusion delay >24 hours), the delay between admission to percutaneous coronary intervention (PCI) and symptoms to PCI. Risk of NSTEMI was stratified using the **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) score. Time to reperfusion, basal admission, and peak high-sensitivity troponin level, as well as left-ventricular ejection fraction (LVEF) at discharge and in hospital mortality were also collected and compared. Patients signed informed consents for data collection, and the study was conducted according to the Declaration of Helsinki.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation, whereas categorical variables were presented as numbers and percentages. Distributions of continuous variables were examined for skewness and were logarithmically transformed as appropriate. Continuous variables with normal distribution were compared using the unpaired Student's *t*-test. Nonparametric continuous variables were compared using the U Mann-Whitney test. Categorical variables were compared using the χ^2 test. Incidence rate (IR) for ACS related hospitalization was calculated by dividing the number of cumulative events by the number of days for both time periods. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 26 (IBM Corporation, Armonk, NY).

Results

Patient characteristics are shown in Table 1. A total of 246 ACS-patients were included in the study (162 patients with ACS admitted in March 2019, and 84 patients with ACS admitted in March 2020). During the case period, a total of 84 hospital admissions for ACS were observed, accounting for an IR of 2.7 admissions per day vs an IR of 5.2 admissions per day observed in the control period (odds ratio [OR], 0.52; 95% confidence interval [CI], 0.39-0.67; $P < 0.001$). Of the 84 patients with ACS in 2020, 26 were positive for COVID-19; of these, 5 patients were already hospitalized for interstitial pneumonia, whereas—in the remaining 21 cases—the diagnosis of COVID-19 infection was an incidental finding from the routine COVID reverse transcription polymerase chain reaction (RT-PCR) assay of a nasal swab performed immediately at admission before cardiac catheterization.

There were no significant differences in patient clinical characteristics or risk factors in the 2 groups. In March 2019, NSTEMI was a more frequent admission diagnosis (57.4% vs 39.3%, $P < 0.01$) and symptom to PCI was significantly shorter (18.8 $\pm$ 20 vs 36.9 $\pm$ 38.4 hours, $P < 0.001$). In the STEMI subgroup, door-to-balloon and symptoms-to-balloons were significantly higher in March 2020 (66 $\pm$ 17 vs 40 $\pm$ 12 minutes, $P < 0.001$ and 5.8 $\pm$ 3.1 hours vs 3.9 $\pm$ 2.2 hours, $P < 0.001$ [Fig. 1]) with a delay from symptoms to wiring for STEMI PCI > 24 hours more frequently in March 2020 (17.8% vs 4.3%, $P < 0.001$). The **G**lobal **R**egistry of **A**cute **C**oronary **E**vents (GRACE) score was significantly higher in 2020 (126 $\pm$ 27 vs 116 $\pm$ 26, $P < 0.001$), and more patients were in the higher European Society of Cardiology (ESC) tertile predictive of higher in-hospital and 6-month mortality (GRACE score above 140: 33.3% vs 18.5, $P < 0.01$, and GRACE score above 118: 59.6 vs 44.4%, $P < 0.05$).

In-hospital clinical outcome is summarized in Table 2. Admission and peak high sensitivity troponin were significantly higher in 2020 (5138 $\pm$ 9408 vs 1142 $\pm$ 4017 ng/L, $P < 0.001$, 13,681 $\pm$ 10,936 vs 9143 $\pm$ 13,825 ng/L, $P < 0.01$ [Fig. 1]). Presence of an LVEF < 40% at discharge was more frequent in March 2020 (42.8% vs 24.7%, $P < 0.01$). No statistical difference in in-hospital mortality was observed between the 2 groups.

Discussion

The SARS-CoV-2 epidemic was associated with a significant decrease in the rate of hospitalization for ACS, a reduction not justified by a possible biological explanation. Viral infections and ACS share the development of a peak during winter as clearly shown by epidemiologic studies and meta-analyses that suggest a significant increase in ACS-STEMI in patients affected by seasonal flu when compared with the remaining population.[3,4] SARS-CoV-2 infection shares many similarities with other coronavirus infections such as SARS-CoV and MERS-CoV, both responsible for increase in acute cardiovascular events rate in infected patients.[5] Patients with SARS-CoV-2 infections also develop general proinflammatory and hypercoagulative status, explaining the frequent in-hospital acute coronary events observed.[2] The opposite phenomenon of a paradoxical reduction observed can

Table 1. Patients clinical characteristics and acute clinical outcome

	Group 2019 162 patients	Group 2020 84 patients	*P* value		Group I 2019 162 patients	Group II 2020 84 patients	*P* value
AGE	69.9 + 32.6	68.3 + 30.9	ns	STEMI	59 (36.4%)	34 (40.5%)	ns
SEX	M:113/F:49	M:62/F:22	ns	STEMI rr > 24 hours	7 (4.3%)	15 (17.8%)	< 0.001
COPD	35 (21.6%)	7 (8.3%)	< 0.01	NSTEMI	93 (57.4%)	33 (39.3%)	< 0.01
HYPERTENSION	108 (66.7%)	65 (77.4%)	ns	Others ACS	3 (1.9%)	2 (2.4%)	< 0.01
DIABETES	48 (29.6%)	31 (36.9%)	ns	Door to balloon (STEMI)	40 ± 12 (minutes)	66 ± 17 (minutes)	< 0.001
SMOKING	85 (52.5%)	34 (40.5%)	ns	Symptoms to PCI (STEMI)	3.9 ± 2.2 (hours)	5.8 ± 3.1 (hours)	< 0.001
DYSLIPIDEMIA	100 (61.7%)	58 (69%)	ns	Symptoms to PCI (NSTEMI)	18.8 ± 20 (hours)	36.9 ± 38.4 (hours)	< 0.001
BMI > 30	36 (22.2%)	23 (27.4%)	ns	hs-cTnI (basal)	1142 ± 4017	5138 ± 9408	< 0.001
KNOWN CAD	41 (25.3%)	31 (36.9%)	ns	hs-cTnI (peak)	9143 ± 13,825	13,681 ± 10,936	< 0.01
AF	18 (11.1%)	6 (7.1%)	ns	LVEF	48.9 + 9.4	45.9 + 12	< 0.05
CKD	21 (13%)	12 (14.3%)	ns	LVEF < 40%	24.7%	42.8%	< 0.01
GRACE SCORE	116 + 26	126 + 27	< 0.01	Death	1.8%	4.7%	ns

Other ACS (Tako-Tsubo syndrome or myocardial infarction with nonobstructive coronary arteries [MINOCA]).

AF, atrial fibrillation; ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GRACE, Global Registry of Acute Coronary Events; hs-cTnI, high-sensitivity cardiac troponin I (lab range 0-58 ng/L); LVEF, left-ventricular ejection fraction; NSTEMI, non−ST-elevation myocardial infarction; rr, recommended reperfusion; PCI, percutaneous coronary intervention; rr, recommended reperfusion; STEMI, ST-elevation myocardial infarction.

have several possible explanations. First, the fear of risking close contact with infected SARS-CoV-2 patients might have discouraged the access to the emergency department in cases of mild symptoms of chest pain or breathlessness. Second, the insistence on isolation at home may have deterred patients from seeking consultations with their general practitioners or undergoing examinations such as electrocardiography or echocardiography. Mild clinical ACS symptoms, such as dyspnea and chest tightness, associated with increased myocardial enzymes and without clear electrocardiographic changes could have been dismissed as a consequence of widespread viral organ involvement, and the overstress suffered by the National Health Service might have affected the timing of transportation and hospital admission, at least on the most crucial days in mid-March. Unfortunately, underdiagnosis and late or missed treatment might be deleterious for patients with ACS, a life-threatening condition with outcome closely related to prompt recognition and treatment. Untreated ACS might result in both acute and long-term complications such as cardiac rupture; pericardial tamponade; mitral regurgitation; aneurysmal dilatation; and marked reduction in LVEF, resulting in immediate cardiogenic shock and late chronic heart failure. Numbers were too small and follow-up too short to show a survival difference at discharge or in the first month. The higher release of cardiac enzymes, more severe LVEF impairment, and more frequent GRACE scores in the group with predicted higher 6-month mortality suggest high likelihood of worse outcomes at late follow-up. The time delay in the door-to-balloon of 10 extra minutes—probably explained by the need to don personal protective equipment carefully—was sufficient to be statistically significant compared with 2019 but unlikely to cause a clinically relevant worsening in prognosis. In these patients, we have applied the same aggressive approach recommended in the current ESC Guidelines. In Sichuan Provincial People's Hospital, a conservative approach with frequent use of thrombolysis was applied in most ACS-STEMI and NSTEMI syndromes, certainly a suboptimal treatment in the urgent and primary PCI era. It is possible that the creation of dedicated COVID hospitals has led to a dedicated path of treatment, making it difficult to retransfer patients already in COVID areas to hospitals with PCI facilities: a problem not present in any of the 3 hospitals recruiting for this study.[2] The marked reduction of ACS complications observed in the last decades are certainly justified by the widespread diffusion of an emergency network allowing most of our population to early reperfusion therapy. If our findings will be confirmed in large-scale registries, we might expect to face an increase of serious myocardial impairment that will represent a new challenge for the entire cardiology community.

The major limitation of our study is that our series comes from a retrospective evaluation, which is certainly susceptible to selection bias. Moreover, the small sample size and the short-term follow-up did not allow us to draw any conclusions on hard endpoints. The correct antiplatelet/anticoagulant therapy in the prothrombotic state related to COVID infection remains a matter of concern; in our study, the use of glycloprotein IIb/IIIa was low in both groups, whereas cangrelor infusions were used more often in the 2020 group. A larger sample size, including more hospitals and multiple inter-year and intra-year control periods, certainly would have

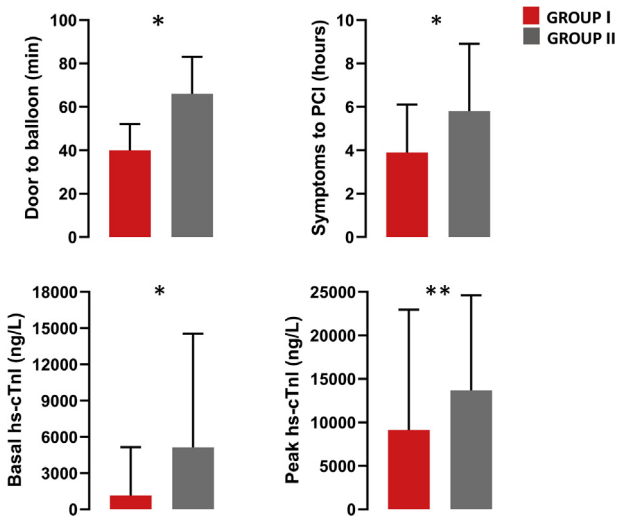

Figure 1. Graph bar shows the difference in door-to-balloon, symptoms-to-percutaneous coronary intervention, basal and peak in high-sensitivity troponin I between the 2 groups. *$P < 0.001$.**$P < 0.01$

improved the statistical power of our findings, but the reduction of hospitalizations for ACS during the first 3 months of the Italian lockdown has been confirmed by our recently published large North Italian registry.[1]

"Stay home" is an important message to contain spreading of the virus, but this message should be tempered by a clear exclusion of chest pain and other medical emergencies that still require rapid in-hospital treatment.

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Disclosures

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