Research Article

ACS Admissions in COVID-19 Outbreak: A Long-way back to Normality

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Abstract

Background: The pandemic spread of the COVID-19 pneumonia caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) lead to severe social containing measures in Italy. We evaluated changes in hospitalization rates for acute coronary syndromes (ACS) during SARS-CoV-2 outbreak compared to both intra-year and inter-year control periods.

Methods: ACS-related hospitalization rates at the Centro Cardiologico Monzino in Milan were retrospectively assessed during SARS-CoV-2 outbreak. The timespan from the first confirmed case of SARS-CoV-2 in Italy and lockdown ending (February 21-May 3, 2020) was the case-period (epidemic peak period). Hospitalization rates of the case-period and two control periods, one preceding (January, 1- February 20, 2020) the epidemic outbreak and the other following the end of lockdown (May 3-June 30, 2020) were analyzed and compared to same inter-year (2019) control periods.

Results: 183 ACS patients were included: 80 in the case-period; and 103 in the two intra-year control periods (33 pre-case period and 70 post-case period, respectively) and compared to same periods of the previous year. ACS-related hospitalization rate was significantly higher in the case period compared to previous year, mainly driven by an increase in ST- and non-ST-elevation MI .

Conclusions: ACS-related hospitalizations dramatically increased after SARS-CoV-2 outbreak onset and consequential restrictive measures, conversely to early pandemic phase observations leading to a significant decrease in emergency room accesses led by citizens' fear of viral infection.

Introduction

The epidemic viral pneumonia (COVID-19) caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), started in Wuhan (China) in December 2019, rapidly spread throughout the globe accounting for 59,2 Mln confirmed cases as of November 9, 2020 [1]. The worldwide spread of SARS-CoV-2 prompted the World Health Organization (WHO) to proclaim the state of pandemic on March 11, 2020. According to the first inclusive report about the disease, SARS-CoV-2 carries an overall high fatality rate, which is estimated to be almost five times as higher in patients with previous cardiovascular disease (10.5%) and nearly three times in patients with known cardiovascular risk factors, i.e. hypertension (5.6%) and diabetes (7.3%) [2].

In Italy, the first confirmed local case of SARS-CoV-2 was reported on February 20, 2020 in Codogno, a small city in Lombardy region. In response to the growing epidemic, the Italian Government adopted progressive measures to contain the outbreak culminating in the institution of a national lockdown on March 9, 2020 [3]. By the time this analysis was conceived, Italy was the first most involved Country in the world for infected patients, actually ranking tenth in number of infected patients (995,463) and sixth in infection-related fatalities (42,330 deaths) [4].

Aim of the present study is to investigate the effect of this pandemic scenario and of national lockdown on the rates of hospital admissions for acute coronary syndromes (ACS) during SARS-CoV-2 outbreak and to compare them to the same periods of the previous year.

Methods

This is an observational, retrospective study conducted in a single center in Milan (Italy). Epidemiological data of consecutive patients admitted for ACS from January 1- February 20, 2020 (pre-epidemic outbreak period); February 21-May 3, 2020 (epidemic peak period, with national lockdown starting from March 9) and May 4-June 30, 2020 (post-lockdown period) were anonymously extracted from hospital's electronic database and checked for accuracy by study investigators. As a control, ACS patients admitted to our institution during the same time-span in 2019 were retrieved. All adult (≥ 18 years old) patients admitted for ACS, for whom the ACS diagnosis was confirmed at hospital discharge, were included in this study. Patients dying before hospital arrival were not considered in the present analysis. Our hospital offered 24/7 pPCI service to all eligible patients presenting with acute STEMI. Data on key time points in STEMI care are recorded in a clinical registry.

The study was conducted in accordance with the Declaration of Helsinki. All included patients gave their informed consent on admission for data collection and future publications in anonymous studies.

Definitions

Demographics, clinical and main angiographic characteristics were retrospectively retrieved. We defined "presentation symptom" as the leading symptom urging patients to contact the Emergency Care System or to refer to Emergency Department (ED); such piece of information was retrieved from Emergency Department admission records. Known coronary artery disease (CAD) was defined as the prior history of myocardial infarction, percutaneous or surgical coronary revascularization.

ACS included ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina (UA) and myocardial infarction with nonobstructive coronary arteries (MINOCA), all defined according to the current European Society of Cardiology guidelines definitions [5,6].

Symptom-onset-to-first-medical contact time is defined as the time from patient-reported chest discomfort onset to the time of first medical contact. Door-to-balloon time is defined as the time from Accident and Emergency Department arrival to successful wire crossing time during pPCI.

Study periods and outcomes

The "case period" (i.e. the epidemic peak period) was set as the time span immediately after detection of the first local case of COVID-19 in Codogno (Lodi, Lombardy; February 20, 2020) to May 3, 2020 last day of national lockdown. To perform analyses and comparison, we defined three similar control periods. The first is the "intra-year" control period (January 1- February 20, 2020 and May 4-June 30, 2020). The second is an "inter-year" control period (from January 1 to February 20, 2019; February 21-May 3, 2019 and May 4-June 30, 2019). The outcome of analyses was to compare ACS-related hospitalizations rate during case and control time periods.

Statistical analysis

Categorical variables were reported as number, percentage and compared by means of Pearson's Chi square test (or by Fisher exact test as appropriate). Continuous variables were reported as medians with interquartile ranges and were compared by means of non-parametric Mann Whitney test.

ACS hospital admission incidence was described as cases per day; incidence rate ratio was computed by means of Poisson regression analysis and reported with respective non-adjusted 95% confidence intervals. Statistical significance was set at an alpha-error < 0.05. All analyses were performed with SPSS 21 (IBM Corporation, Armonk, NY, USA) and Jamovi version 1.2.27.0 (gamlj extension).

Results

A total of 183 ACS patients were hospitalized during the study period, compared to 99 ACS pts in the same time-span in 2019. In the 2020 study period, 33 patients were treated during the pre-epidemic outbreak period, 80 patients during the epidemic peak period and 70 during the post-lockdown period, which corresponds to 0.63, 1.11 and 1.20 pts/day, respectively; in 2019, the same ratios were 0.54, 0.61 and 0.47, respectively. The incidence ratio observed during epidemic peak in 2020 was significantly higher compared to the 2019 corresponding period (incidence rate ratio 1.51, 95% CI 1.05 – 2.20, P=0.028), but not different compared to same year pre-epidemic outbreak and post-lockdown periods (**Supplementary Table 1**). More in detail, during 2020 the number of ACS cases dropped during the first 3 weeks of epidemic peak period (-61%) and grew markedly thereafter, with a trend persisting throughout the whole post-lockdown period, defining a peculiar J-shaped curve (**Figure 1**).

	Incidence rate ratio	95% confidence interval	P value
Inter-year comparisons			
Pre-epidemic outbreak 2020 vs. 2019	1.19	0.750 - 1.88	0.47
Epidemic peak (case period) 2020 vs. 2019	1.51	1.05 - 2.20	**0.028**
Post-lockdown 2020 vs. 2019	1.52	0.986 - 2.41	0.065
Intra-year comparisons (2020)			
Epidemic peak (case period) vs. pre-epidemic outbreak	1.32	0.891 - 2.01	0.18
Epidemic peak (case period) vs. postlockdown	0.898	0.650 - 1.24	0.51

Supplementary Table 1: Incidence rate ratios for 2019 and 2020 study periods.

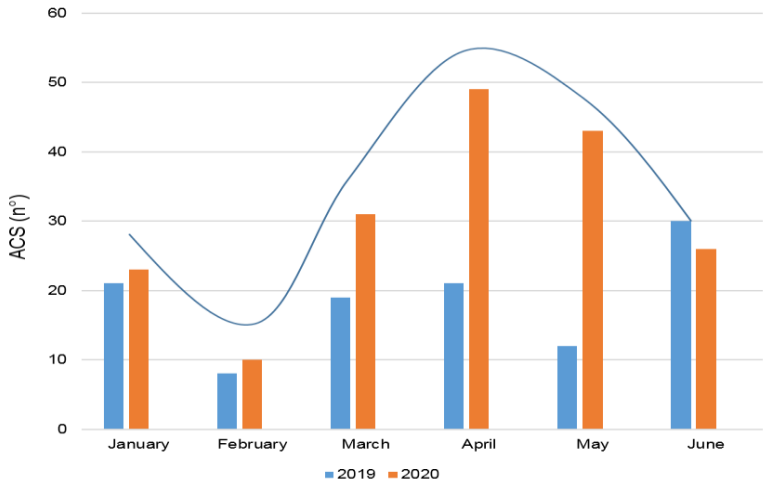

Figure 1: Temporal trends of hospital admission rates for acute coronary syndromes in 2019 and in 2020.

Inter-year comparison

Patients hospitalized during the pre-epidemic outbreak period did not show relevant clinical differences compared to those hospitalized during the same time-span in 2019 (**Table 1**). During the epidemic peak period, a higher prevalence of hypertension and chronic kidney disease, lower platelet counts with higher C-reactive protein levels and a lower ejection fraction at discharge were observed compared to patients from previous year. Similar differences were consistently reported during the post-lockdown period compared to previous year.

	A. Pre-epidemic outbreak (Jan - Feb 20th)			B. Epidemic peak (Feb 21st - May 3rd)			C. Post-lockdown (May 4th - Jun 30th)		
	2019	**2020**	**P value**	**2019**	**2020**	**P value**	**2019**	**2020**	**P value**
	N=28	**N=33**		**N=44**	**N=81**		**N=27**	**N=69**	
Age (years, median;interquartile –range)	63.5 (58.5 - 77.5)	66.0 (61.0 - 73.0)	0.76	63.0 (55.0 - 74.0)	69.0 (59.0 - 80.0)	0.066	65.0 (56.0 - 81.0)	64.0 (57.0 - 78.0)	0.94
Female sex (n, %)	1 (3.6)	6 (18.2)	0.11	13 (29.5)	22 (27.2)	0.78	6 (22.2)	13 (18.8)	0.71
Smoke			0.32			0.23			**0.005**
Current (n, %)	1 (3.6)	5 (15.2)		3 (6.8)	12 (14.8)		3 (11.1)	15 (36.6)	
Former (n,%)	3 (10.7)	3 (9.1)		3 (6.8)	2 (2.5)		1 (3.7)	7 (17.1)	
Diabetes (n, %)	1 (3.6)	1 (3.0)	1	2 (4.5)	13 (16.1)	0.083	2 (7.4)	10 (31.2)	**0.028**
Dyslipidemia (n,%)	5 (17.9)	11 (33.3)	0.25	7 (15.9)	24 (29.6)	0.09	4 (14.8)	21 (30.4)	0.12
Hypertension (n,%)	7 (25.0)	9 (27.3)	0.84	10 (22.7)	37 (45.7)	**0.011**	5 (18.5)	31 (70.5)	< **0.001**
Previous PCI (n,%)	5 (17.9)	5 (15.2)	1	6 (13.6)	21 (25.9)	0.11	4 (14.8)	8 (21.6)	0.54
Previous CABG (n, %)	4 (14.3)	0	**0.042**	3 (6.8)	2 (2.5)	0.24	0	4 (11.8)	0.12
CKD (n,%)	8 (28.6)	10 (30.3)	0.88	8 (21.6)	34 (42.0)	**0.032**	0	10 (32.3)	**0.001**
ACS type			0.18			0.059			0.95
STEMI (n,%)	18 (64.3)	14 (42.4)		23 (52.3)	39 (48.1)		14 (51.9)	37 (54.4)	
NSTEM (n,%)	6 (21.4)	14 (42.4)		17 (38.6)	21 (25.9)		11 (40.7)	27 (39.7)	
UA(n,%)	4 (14.3)	5 (15.2)		4 (9.1)	21 (25.9)		2 (7.4)	4 (5.9)	
MINOCA (n,%)	0	0	-	0	2 (6.5)	0.53	0	1 (6.3)	
EF at discharge (%, median;interquartile –range)	54.0 (44.5 - 56.0)	55.0 (49.0 - 61.0)	0.21	56.0 (53.0 - 62.0)	54.0 (42.0 - 57.0)	**0.014**	59.0 (49.0 - 62.0)	52.0 (42.5 - 56.0)	**0.032**

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CKD, chronic kidney disease; EF, ejection fraction; MINOCA, myocardial infarction in non-obstructive coronary artery disease NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction

Table 1: Clinical features of patients admitted for acute coronary syndromes during the case-period study (epidemic peak period), the pre-epidemic outbreak period and the post-lockdown period in 2020 and in corresponding periods in 2019.

As reported in **Table 2**, longer times from symptoms onset to ED admission were observed during epidemic peak period compared to the same time period in 2019; as reported in **Figure 2,** however, during the 2020 epidemic peak period, admission times varied over a wider range compared to other periods, with several STEMI patients presenting very late from symptoms onset. Door-to-balloon times were similar during the case period in 2019 and 2020, whereas they proved significantly shorter during the 2020 post-lockdown period compared to previous year. Hospital stay was significantly shorter throughout the three phases in 2020.

	A. Pre-epidemic outbreak (Jan - Feb 20th)			**B. Epidemic peak (Feb 21st - May 3rd)**			**C. Post-lockdown (May 4th - Jun 30th)**		
	2019 N=28	**2020 N=33**	**P value**	**2019 N=44**	**2020 N=81**	**P value**	**2019 N=27**	**2020 N=69**	**P value**
Total hospital stay (days)	7.5 (4.5 - 12.5)	5.0 (3.0 - 7.0)	**0.008**	6.0 (4.0 - 9.5)	3.0 (2.0 - 7.0)	**0.001**	8.0 (6.0 - 10.0)	6.0 (4.0 - 8.0)	**0.031**
Time from symptoms to presentation (hours)	4.0 (3.2 -4.275	4.0 (2.0 - 5.25)	0.8	2.5 (2.0 - 3.25)	5.0 (2.5 - 12.0)	**0.03**	4.0 (2.0 - 6.0)	3.0 (2.0 - 5.0)	0.99
Time from ED to cath-lab (hours)	0.3 (0.2 - 0.4)	0.3 (0.3 - 0.4)	0.8	0.25 (0.20 - 0.40)	0.2 (0.2 - 0.3)	0.72	0.30 (0.30 - 0.40)	0.2 (0.2 - 0.3)	**<0.001**

ED, emergency deparment

Table 2: Time from symptoms onset to hospital admission, door-to-balloon time and total length of hospital stay in 2019 and 2020.

Crude overall mortality was higher in patients hospitalized during epidemic period in 2020 compared to the same time-span in 2019, even if this difference did not prove statistically significant (**Table 3**). Similar results were observed regarding the incidence of shock and the need for mechanical support.

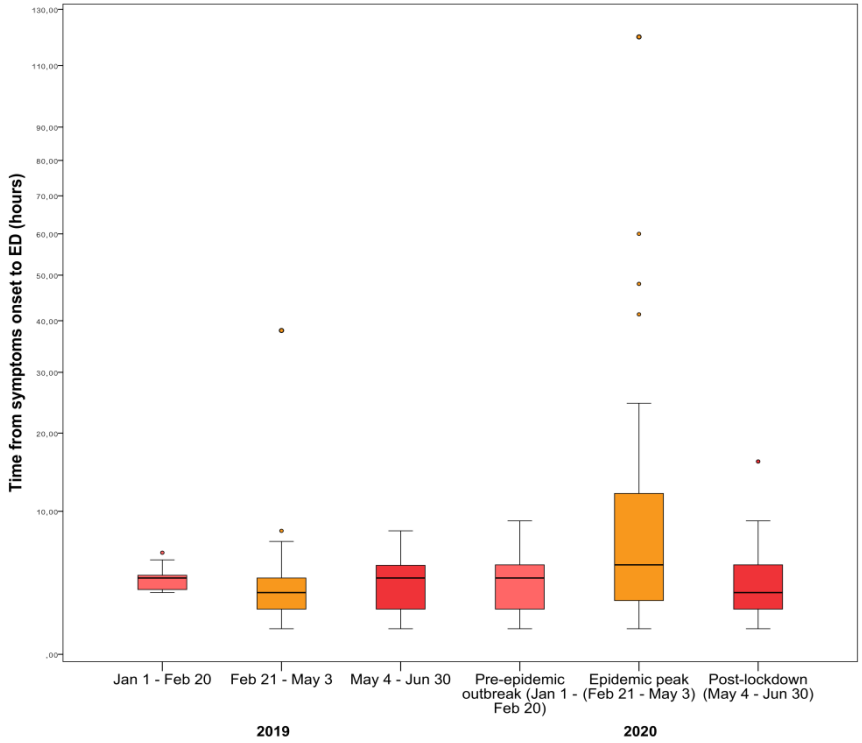

Figure 2: Time from symptoms onset to emergency department admission during the case-period study (epidemic peak period), the pre-epidemic outbreak period and the post-lockdown period in 2019 and 2020.

	A. Pre-epidemic outbreak (Jan - Feb 20th)			B. Epidemic peak (Feb 21st - May 3rd)			C. Post-lockdown (May 4th - Jun 30th)		
	2019 N=28	**2020 N=33**	**P value**	**2019 N=44**	**2020 N=81**	**P value**	**2019 N=27**	**2020 N=69**	**P value**
Death (n,%)	0	0	-	2 (4.5)	9 (11.1)	0.49	1 (3.7)	0	0.28
Cardiovascular death (n,%)	0	0	-	2 (4.5)	7 (8.6)	0.49	0	0	-
Stent thrombosis (n,%)	0	0	-	0	0		0	0	-
Mechanical complications (n,%)	0	0	-	1 (2.3)	1 (2.5)	1	0	1 (1.4)	1
Arrhythmic complications (n,%)	0	0	-	0	0		0	2 (2.9)	1
Ventricular thrombus (n,%)	0	0	-	0	0		0	0	-
Bleedings (n,%)	0	1 (3.0)	1	0	1 (1.2)	1	1 (3.7)	0	0.28
Cardiogenic Shock (n,%	1 (3.6)	0	0.46	1 (2.3)	5 (6.2)	0.33	0	0	-
Ventilation (n,%)	0	0		1 (2.3)	0		0	0	-
Mechanical support (n,%)	1 (3.6)	1 (3.0)	1	2 (4.5)	12 (14.8)	0.14	1 (3.7)	3 (4.3)	1

Intrayear comparisons for 2020 all with P value > 0.05, except for death and cardiovascular death during epidemic peak vs. post-lockdown (P value = 0.015 for both)

Table 3: In-hospital outcomes of patients admitted for acute coronary syndromes during the case-period study (epidemic peak period), the pre-epidemic outbreak period and the post-lockdown period in 2020 and in corresponding periods in 2019.

Intra-year comparison

Clinical features of patients hospitalized during the three phases are reported in **Table 1** and in **Supplementary Table 2**. Median time from symptoms onset to hospital presentation was not significantly different during the three considered periods. Time from ED admission to cath-lab was significantly lower in the second and third phase compared to the pre-epidemic outbreak period (**Supplementary Table 2**).

Patients hospitalized during epidemic peak period in 2020 showed higher mortality and cardiovascular mortality compared to patients hospitalized after the end of lockdown (11.1% vs. 0%, P=0.015, and 8.6% vs. 0%, P=0.015, respectively; **Table 3**). Gross mortality rate was higher, even if not statistically significant, compared to pre-epidemic outbreak period (11.1% vs. 0%, P=0.11). Shock and need for mechanical support were more frequently observed during the epidemic peak period, but such difference did not prove significant at statistical analysis. A significant between-groups difference in all-cause mortality among STEMI pts was also documented (8.75% during case-period vs 2% in pre-epidemic outbreak and post-lockdown periods, P = 0.030).

Supplementary Table 2.	**(Jan - Feb 20th)**	**(Feb 21st - May 3rd)**	**(May 4th-June 30th)**	**P value**		
	N=33	**N=81**	**N=69**	**A vs. B**	**B vs. C**	**A vs. C**
Age (years)	66.0 (61.0 - 73.0)	69.0 (59.0 - 80.0)	64.0 (57.0 - 78.0)	0.36	0.29	0.90
Female sex (n,%)	6 (18.2)	22 (27.2)	13 (18.8)	0.31	0.23	0.94
Smoke Current (n,%)	5 (15.2)	12 (14.8)	15 (36.6)	0.29	**< 0.001**	**0.036**
Former (n,%)	3 (9.1)	2 (2.5)	7 (17.1)			
Diabetes (n,%)	1 (3.0)	13 (16.1)	10 (31.2)	0.064	0.071	**0.003**
Dyslipidemia (n,%)	11 (33.3)	24 (29.6)	21 (30.4)	0.70	0.91	0.77
Hypertension (n,%)	9 (27.3)	37 (45.7)	31 (70.5)	0.069	**0.008**	**< 0.001**
Previous PCI (n,%)	5 (15.2)	21 (25.9)	8 (21.6)	0.21	0.61	0.49
Previous CABG (n,%)	0	2 (2.5)	4 (11.8)	1.0	0.062	0.11
CKD (n,%)	10 (30.3)	34 (42.0)	10 (32.3)	0.25	0.39	0.87
EF on admission (%; median;interquartile –range)	54.0 (48-5 - 60.5)	50.0 (38.0 - 56.0)	46.5 (36.0 - 51.75)	0.056	0.22	**0.001**
ACS type				0.18	**0.003**	0.25
STEMI (n,%)	14 (42.4)	39 (48.1)	37 (54.4)			
NSTEMI (n,%)	14 (42.4)	21 (25.9)	27 (39.7)			
UA (n,%)	5 (15.2)	21 (25.9)	4 (5.9)			
MINOCA (n,%)	0	2 (6.5)	1 (6.3)	0.23	1.0	0.15
EF at discharge (%)	55.0 (49.0 - 61.0)	54.0 (42.0 - 57.0)	52.0 (42.5 - 56.0)	0.078	0.47	**0.040**
Total hospital stay (days)	5.0 (3.0 - 7.0)	3.0 (2.0 - 7.0)	6.0 (4.0 - 8.0)	0.079	**0.002**	0.19
Time from symptoms to presentation (hours)	4.0 (2.0 - 5.25)	5.0 (2.5 -12.0)	3.0 (2.0 - 5.0)	0.23	0.067	0.55
Time from ED to cath-lab (hours)	0.3 (0.3 - 0.4)	0.2 (0.2 - 0.3)	0.2 (0.2 - 0.3)	**0.022**	0.29	**0.007**

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CKD, chronic kidney disease; ED, emergency department; EF, ejection fraction; MINOCA, myocardial infarction in non-obstructive coronary artery disease; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction

Supplementary Table 2: Clinical features and in-hospital outcomes of patients admitted for acute coronary syndromes during the case-period study (epidemic peak period), the pre-epidemic outbreak period and the post-lockdown period in 2020.

Discussion

In the present study we describe a peculiar dynamic of hospital admission rates of ACS during the course of COVID-19 epidemic. Following an initial decline in hospital admission rates in the very first phase of epidemic outbreak and national lockdown, we observed a significant increase in ACS-related admissions, which became evident after the first three weeks of acute pandemic period, i.e. from March 15, 2020 through May 30, 2020. A dramatic reduction in ACS-related hospitalization took place in Italy at the beginning of the epidemic outbreak of SARS-CoV2 and the consequent restrictive social measures adopted by the Government to contain viral diffusion. A previous report showed a significant decrease in ACS-related hospitalization rates across several cardiovascular centers in northern Italy during the early days of the Covid-19 outbreak [7], and other studies described a negative impact of the COVID-19 outbreak on ACS admissions worldwide, in particular with a decline in hospital admission rates for ACS [8,9] and a significant delay in presentation time [10]. Hauguel-Moreau et al have reported a relative reduction of 73% in ACS admissions during the first three weeks after lockdown, when compared to same weeks of 2018-2019 [11]. Recent data suggest moreover that a significant increase in mortality during this period occurred without being fully explained by Covid-19 cases alone [12].

Differently from previous reports, however, we observed a steep increase in ACS hospital admission rates following the very first phase of epidemic outbreak and national lockdown. Several hypothesis could be made regarding such increase in hospital admissions, associated with a decreasing fear of potential SARS-CoV-2 infection through hospital admission [13] and a growing awareness of the fatal risks inherent to a delayed ED admission, divulgated also by a national media information campaign [14]. A potential explanation for such finding could however be found also in the recent meta-analysis by Caldeira et al., which reported a 5-times higher risk of acute myocardial infarction in patients suffering from severe influenza compared to the general population [15]. A similar trend has been additionally confirmed by Hebsur et al. [16], which displayed a superimposition of seasonal incidence of STEMI [17] with WHO Influenza (Flu) data on Italian population from 1998 to 2006 [18]. A biological explanation for such phenomenon could be linked to a viral-induced up-regulation of inflammatory cytokines and systemic inflammation, similarly to what has been observed in COVID-19 patients, which would lead to a pro-coagulant state increasing the likelihood of coronary plaque rupture and ACS. Furthermore, 18 (10%) ACS pts only resulted in positive COVID-19 swab test.

Time from symptoms onset to ED presentation was significantly increased during the case period compared to previous year, highlighting both the diffuse fear related to hospital access during the epidemic peak period as well as the significant stress under which the emergency response system was put during the SARS-CoV-2 pandemic [19,20].

Study limitations

The present study presents some limitations, which should be discussed: first of all, the retrospective, monocentric design does not allow to take in full consideration all potential confounders influencing the reported results. Second, during the epidemic peak period our center acted as cardiovascular hub for a large metropolitan and suburban area usually served by several other hospitals; however, the cardiovascular hub designation was maintained throughout the entire third phase considered in the present study (May 4-June 30, 2020).

Conclusion

To our knowledge this is the first analysis reporting a complete comparative analysis between pandemic period and the pre- and post-pandemic era on the incidence of hospitalizations for ACS, compared to the previous year, showing in conclusion a net increase in the incidence of ACS admissions in a definite sample of the Italian population in association with the acute pandemic outbreak of SARS-CoV2 disease and few weeks thereafter.

Our data strongly support the need to monitor the incidence of ACS during the pandemic, to encourage citizens not to underestimate symptoms of relevant diseases and to be aware that such a viral outbreak changed our life requiring several weeks for a back-to normal clinical activity.

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Conflict of Interest: No potential conflict of interest relevant to this article was reported.

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