Reduction in acute coronary syndromes during coronavirus disease 2019 global pandemic: data from the Marche region of Italy
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Aims During the novel severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019) pandemic, a worldwide reduction in total acute coronary syndrome (ACS) has been reported. In early 2020, Italy became the most affected country and national lockdown was declared early on in March. We described trends in ACS from all the Marche coronary catheterisation laboratories (CCL) during the global pandemic.

Methods Retrospective study of all consecutive patients admitted to the four regional CCL. The coronavirus disease 2019 period (20 February 2020 to 15 April 2020) was compared with the interyear control period (1 January 2020 to 19 February 2020) and to the intrayear control period (20 February 19 to 15 April 19). All patients with an initial diagnosis of ACS were included in the analysis, and further stratified into ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI)/unstable angina.

Results A total of 1239 patients were enrolled. Daily incidence of ACS was 6.1, 6.3 and 4.5 for the interyear control period, the intrayear control period and the case period, respectively. There was no difference in overall STEMI daily incidence while NSTEMI/unstable angina fell from 3.6 and 3.3–1.8 during the case period \( (P = 0.01) \). Incidence rate ratios were significantly lower when the case period was compared with the intrayear control period \( (\text{incidence rate ratios: } 0.49, 95\% \text{ confidence interval } 0.41–0.59, P = 0.001) \) and the interyear control period \( (\text{incidence rate ratios: } 0.67, 95\% \text{ confidence interval } 0.50–0.90, P = 0.008) \).

Conclusion During the global pandemic there was a significant reduction in total ACS and NSTEMI in the Marche region. Unlike previous reports, there was no difference in overall access to CCL for STEMI during the same period.

Keywords: acute coronary syndrome, coronary angiography, coronavirus disease 2019, non-ST-segment elevation myocardial infarction, percutaneous revascularization, ST-segment elevation myocardial infarction, unstable angina

Introduction
The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), also known as coronavirus disease 2019 (COVID-19), was first described in China during late 2019 and rapidly spread to Europe and other countries becoming a worldwide pandemic.

During the first months of 2020 Italy became the most affected country with over 100,000 confirmed active cases at 14 April 2020.

In absence of vaccination and effective treatment for the severe form of acute respiratory distress syndrome, social distancing, quarantine and ‘stay at home’ are the only measures for reducing onward spread of COVID-19. Starting from 10 March 2020, the government in Italy declared national lockdown, reducing economical activities and limiting freedom of movement of people.

Although the clinical manifestations of SARS-CoV2 are dominated by respiratory symptoms, myocardial injury during SARS-CoV2 infection has been reported and some proposed therapy such as lopinavir/ritonavir may favour thrombosis and myocardial infarction (MI). As opposed to such considerations, after the Italian government declared a general lockdown, a significant reduction in hospitalization for acute coronary syndrome (ACS) was observed all over the country. Data from northern Italy as well as from the Italian region Campania reported a significant reduction in both ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI) access to coronary catheterization laboratories (CCL). Likewise, a nationwide Italian registry reported a significant reduction in overall access to CCL for STEMI during the same period.
reduction in hospitalization for acute MI and higher mortality and more major complications for STEMI patients during the global pandemic. Other European and American registries reported a similar reduction in ACS, leading to an increasing awareness of an inappropriate reduction in healthcare seeking for ACS.

We looked for such a phenomenon in the Marche region of Italy, which had areas with a very high prevalence of confirmed COVID-19 cases and areas almost without any confirmed cases. As the Italian healthcare system is divided into regions, we collected data from all regional CCL for a complete overview of all ACS managed invasively.

Methods

Regional and epidemiological subset

The Marche region is located in central Italy, with an extension of about 9500 square kilometres and a population of over 1.5 million people. The ACS network is composed of four CCL that are, from north to south, in the cities of Pesaro, Ancona, Macerata and Ascoli Piceno. As the healthcare system administration is divided into regions, which have a high degree of autonomy, all percutaneous coronary interventions (PCI) for ACS of the region are performed by one of these laboratories, with few exceptions.

On 30 January 2020 the first COVID-19 case was confirmed in Italy. Subsequently, confirmed cases increased each day and the first case in Pesaro city was reported on 20 February 2020. During the COVID-19 outbreak the area of Pesaro city was affected early on, with confirmed cases rising sharply. On 15 April 2020 confirmed cases in the areas of Pesaro, Ancona, Macerata and Ascoli Piceno were 6.3, 3.5, 2.7 and 1.2 for 10,000 inhabitants, respectively.

The Italian government declared restriction and quarantine of affected areas of northern Italy on 21 February 2020. As cases kept rising, on 10 March 2020, a national lockdown was declared: nonessential activities, including restaurants and schools, were closed and people were forced home (stay at home) unless for primary needs and essential works.

Study population

The current retrospective study enrolled all consecutive patients admitted to one of the four regional CCL during specific time periods (see below). All patients with an initial diagnosis of ACS were included in the analysis, and further stratified into STEMI and NSTEMI/unstable angina according to European guidelines. Data were collected regarding age, sex, type of revascularization performed (PCI vs. coronary artery bypass graft [CABG] vs. no revascularization) and enrolling centre. Patients admitted for elective treatment of coronary artery disease, stable or chronic angina, or staged treatment of former ACS were excluded.

The study was carried out according to institutional standards, national legal requirements and the Declaration of Helsinki. At the time of admission, all patients agreed to the treatment of personal data. Being an observational study on urgent procedures performed during the pandemic, approval of the ethics committee was not sought, nor written informed consent requested. The current article was designed, conducted and reported according to the STROBE initiative.

Study periods and outcome

For the current study, we considered the following time intervals:

1. Case period: from 20 February 2020 (date of the first reported case in the Marche region) to 15 April 2020 (end of enrolment).
2. Interyear control period: from 1 January 2020 to 19 February 2020.

The main outcome of analyses was to compare the rates of ACS during case and control periods. A sensitivity analysis was performed considering as a time cut-off the date of Italian national lockdown (10 March 2020) instead of the date of the first reported case. In this case, the interyear control period (from 1 January 2020 to 9 March 2020) and the intrayear control period changed accordingly (from 10 March 2019 to 15 April 2019). Secondary outcomes included rates of STEMI, NSTEMI/unstable angina, percutaneous revascularization, CABG and stratification according to the enrolling centre.

Statistical analysis

Categorical variables were described as absolute or relative prevalence and assessed by Chi-square analysis (when the expected frequency was $\geq 5$) or Fisher’s exact value (when the expected frequency was $<5$), as appropriate. The Kolmogorov–Smirnov test was used to assess normality of continuous variables. Normally distributed variables were described as mean and SD. Nonnormally distributed variables were described as median and first quartile to third quartile. Incidence rate was calculated by dividing the total number of events by the number of days in each time period (55 for the case period, 49 for the interyear control period, 104 for the intrayear control period). A general linear model using Poisson regression was used to calculate the incidence rate ratios (IRR) comparing the case period with each of the control periods for both the main and the sensitivity analysis. SPSS 25.0 (SPSS Inc., Chicago, Illinois, USA) and R (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. Values of $P$ less than 0.05 were considered statistically significant.
0.05 (two-tailed) were considered as statistically significant.

**Results**

A total of 1239 patients were seen from 1 January to 15 April for both 2019 and 2020, of which 333 in the interyear control period (from 20 February 2019 to 15 April 2019), 321 from the intrayear control period (from 1 January 2020 to 19 February 2020) and 247 from the COVID period (20 February 2020 to 15 April 2020). Figure 1 shows the cumulative number of ACS cases during the time, stratified according to year and type of ACS. General characteristics of the population are shown in Table 1. The incidence of ACS was 6.1/day, 6.3/day and 4.5/day for the interyear control period, the intrayear control period and the case period, respectively.

STEMI incidence varied from 2.5/day to 3.0/day to 2.7/day, with no significant difference between the two groups (Fig. 2). On the other hand, NSTEMI/unstable angina fell from 3.6/day and 3.3/day in the intrayear control and interyear control periods to 1.8/day during the case period (P = 0.01). The NSTEMI/unstable angina rate in the case period was significantly lower than the intrayear control period [IRR: 0.49, 95% confidence interval (CI) 0.41–0.59, P < 0.001] and the interyear control period (IRR: 0.67, 95% CI 0.50–0.90, P = 0.008, Fig. 3).

The sensitivity analysis confirmed the decreased incidence of NSTEMI/unstable angina in the postlockdown period when compared with both the intrayear control period (IRR: 0.63, 95% CI 0.44–0.89, P = 0.01) and the prelockdown control period (IRR: 0.58, 95% CI 0.48–0.70, P < 0.001, Fig. 3). There was no interaction between the incidence rate ratio of NSTEMI/unstable angina and the different catheterization labs, neither in the main analysis nor in the sensitivity analysis (all P for interaction >0.05).

Rates of PCI were similar between the three groups (73.9 vs. 70.0 vs. 76.5%; P = 0.186) and consistent even in the STEMI (91.1 vs. 94.8 vs. 96.7%; P = 0.175) and...
NSTEMI/unstable angina subgroups (53.8 vs. 53.6 vs. 54.9%; \( P = 0.303 \)).

Similarly, rates of CABG were similar between the three groups (5.0 vs. 8.0 vs. 7.6%; \( P = 0.438 \)) and consistent after stratification into STEMI (1.3 vs. 0.9 vs. 0.0%; \( P = 0.598 \)) and NSTEMI/unstable angina groups (10.7 vs. 16.3 vs. 16.0%; \( P = 0.186 \)).

Discussion

Overall, on 10 May 2020 we found nine studies reporting population trends in rates for ACS associated with the COVID-19 outbreak. All studies included a ‘COVID period’ referred to as the time with the observed reduction in ACS during the pandemic. To compare the reduction in ACS, all but one of the studies considered a ‘reference period’ before the global pandemic (previous months of the same year or same months of previous year). Figure 4 summarizes available studies with the inclusion of the data from the Marche region and Fig. 5 aggregates daily ACS and STEMI incidences from such studies.

The issue of reduction in healthcare seeking for ACS during the global pandemic was first proposed in a research letter from Hong Kong by Tam et al.,\(^{12}\) underlying a prolonged time to first medical contact in seven STEMI patients. A subsequent study from the same authors confirmed such a phenomenon in a larger cohort of 64 patients who presented with ACS during the ‘COVID period’ and demonstrated in this group of patients more in-hospital deaths, cardiogenic shocks, sustained ventricular tachycardia/ventricular fibrillation (VT/VF) and use of mechanical circulatory support.\(^{13}\) Accordingly a nationwide Italian registry from 54 hospitals across the country reported a significant reduction in

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**Fig. 2**

Incidence of acute coronary syndrome during the case period, the intrayear control period and interyear control period.

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**Fig. 3**

<table>
<thead>
<tr>
<th></th>
<th>IRR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case vs. interyear period</td>
<td>0.674</td>
<td>0.502</td>
<td>0.903</td>
</tr>
<tr>
<td>Case vs. intrayear period</td>
<td>0.494</td>
<td>0.414</td>
<td>0.590</td>
</tr>
</tbody>
</table>

Forrest plot comparing the incidence rate ratios for non-ST-segment elevation myocardial infarction/unstable angina between the case period and control periods (panel a). Forrest plot comparing the incidence rate ratios for non-ST-segment elevation myocardial infarction/unstable angina using the national lockdown as the cut-off date (panel b).
hospitalization for ACS during the pandemic with higher mortality and more major complications for STEMI patients.\textsuperscript{13} Reports from Spain,\textsuperscript{5} France,\textsuperscript{7} Austria\textsuperscript{8} and USA\textsuperscript{6} indicated a significant reduction in access to CCL for both STEMI and NSTEMI during the ‘COVID period’. Two independent groups from northern Italy\textsuperscript{3} and the Italian region of Campania\textsuperscript{9} confirmed these data on Italian territory.

The global reduction in ACS led to great concerns among cardiologists. This trend has been documented all over the world with two possible explanations proposed. First a reduction in the overall incidence of ACS may be the consequence of national lockdown, that led in a reduction in excessive alcohol and food intake, global air pollution and physical activity. Moreover, the reduction in nonurgent surgery and the absence of occupational stress may

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**Fig. 4**

1. Spain
   - Centers: 73 PCI center
   - COVID period: 16 Mar 2020 - 31 Mar 2020
   - High volume of confirmed COVID19 in the area: heterogeneous
   - Findings: 48% reduction in PCI, 40% reduction in STEMI

2. France
   - Centers: 12 PCI center in western France
   - COVID period: March 2020
   - High volume of confirmed COVID19 in the area: no
   - Findings: 25% RR in STEMI

3. Italy, Northern Area
   - Centers: 15 PCI center in Northern Italy
   - COVID period: 26 Feb 2020 - 31 Mar 2020
   - High volume of confirmed COVID19 in the area: yes
   - Findings: IRR of ACS 0.74 (0.68-0.82) STEMI 0.77 (0.69-0.81)

4. Austria
   - Centers: 17 out of 19 regional PCI
   - COVID period: March 2020
   - Findings: 38% ACS reduction over time from first to last week of March

5. Italy, Marche Region
   - Centers: 4 out of 4 regional PCI center
   - COVID period: 27 Feb 2020 - 26 Mar 2020
   - High volume of confirmed COVID19 in the area: no
   - Findings: IRR of ACS 0.74 (0.66-0.82) STEMI 0.58 (0.53-0.64) NSTEMI 0.74 (0.65-0.83)

6. Italy, Campania Region
   - Centers: 20 out of 21 regional PCI center
   - COVID period: 27 Feb 2020 - 26 Mar 2020
   - High volume of confirmed COVID19 in the area: no
   - Findings: IRR of ACS 0.74 (0.66-0.82) STEMI 0.77 (0.66-0.91) NSTEMI 0.68 (0.60-0.77)

Worldwide reports of trends in acute coronary syndrome incidence during global pandemic. See text for references. CI, confidence interval; IRR, incidence rate reduction; RR, relative risk.

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**Fig. 5**

Comparative cumulative daily incidence of acute coronary syndrome and ST-segment elevation myocardial infarction during global pandemic versus control period from worldwide reports. When interyear and intrayear control periods were both available, only the intrayear period was considered. Study numbers are referred to Fig. 4 report.
further reduce ACS incidence. The second and more troublesome explanation for such a phenomenon may be the reduction in healthcare seeking, with many patients having ACS symptoms and not coming to medical attention. Tam et al.\textsuperscript{13} reported a significant prolongation of time to first medical contact in STEMI patients during the global pandemic with more patients reaching medical attention outside the revascularization window. Concerns about virus exposure is the first and most obvious mechanism, but many factors must be taken into account: hospital overcrowding, public information campaigns, resources availability and local socio-psychological factors.

As the magnitude of the reduction in ACS is reported to be between 25 and 50% of total ACS, it is hardly explained by a reduction in incidence alone and avoidance of healthcare seeking is very likely, especially considering that the observed negative trend is in contrast with the general positive trend in CCL workload in Italy.\textsuperscript{14}

In our study we confirm the numeric reduction in ACS and NSTEMI/unstable angina coming to medical attention during the global pandemic. Unlike other reports, we have not observed a reduction in access to CCL for STEMI cases. The exact reason for this finding is not clear. In the USA loss of employment may lead to loss of health insurance and reduce accessibility to the healthcare system. This is not the case in Italy which has a full public healthcare system. As suggested above, many factors may concur in modulating patient choice in avoiding healthcare services and this phenomenon may somehow be less pronounced in the Marche region. As Italy was affected early on by the global pandemic, a reduction in healthcare seeking was not suspected by health authorities and no specific public information campaign was performed, and not in the Marche region either. Previous studies reported in NSTEMI/unstable angina more atypical symptoms and a prolonged time to medical attention compared with STEMI.\textsuperscript{15,16} In the Marche region, people may therefore have reduced healthcare seeking only in those cases of less typical symptoms and may have preserved the will of medical advice when typical chest pain was present.

On the other hand, the observed fall in NSTEMI/unstable angina is in line with previous reports and is still of concern.

Considering these data, in our experience it is likely that national lockdown and its consequences have not reduced per se the total ACS incidence. Public concern in the local epidemiological subset may be the leading cause of such a phenomenon. This mechanism is further suggested by the reports of a reduction in other critical illnesses such as acute gastrointestinal bleeding\textsuperscript{17} or acute surgery,\textsuperscript{18} or even in other cardiovascular incidents such as arrhythmic emergencies.\textsuperscript{19} For this reason, a worldwide campaign of correct public information and local policy for promoting appropriate healthcare seeking is pivotal to avoid excess mortality from critical illness.

Limitations
In this study, we did not consider total hospital admission for ACS but only access to CCL. As there were no changes during the global pandemic in the regional hub-and-spoke care system and in the management of ACS patients, we can consider the number of CCL accessed as proportional to total ACS. Second, we did not include clinical endpoints such as cardiovascular mortality, VT/VF or need for mechanical circulatory support as this was not our primary endpoint. Third, the absence of clinical information, such as risk factors, ischemic time, ejection fraction and such precludes any clinical comparison between the different periods. Fourth, although a subgroup analysis according to the four different CCLs would have been very interesting in comparing areas with high and low COVID-19 incidence, our sample size was unfortunately underpowered to detect any significant difference.

Conclusion
The global pandemic led to a worldwide reduction in access to CCL for ACS. In the Marche region of Italy there was a significant reduction in CCL access for total ACS and NSTEMI. Unlike other reports, there was no difference in STEMI during the COVID-19 period. Avoidance of an inappropriate reduction in healthcare seeking for critical illness is of greater importance to prevent excess mortality.

Conflicts of interest
There are no conflicts of interest.

References


