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International Journal of Cardiology 332 (2021) 227–234

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Impact of COVID-19 pandemic and infection on in hospital survival for patients presenting with acute coronary syndromes: A multicenter registry☆

Fabrizio D'Ascenzo [a], Ovidio De Filippo [a,*], Andrea Borin [a], Lucia Barbieri [b], Marianna Adamo [c], Nuccia Morici [d], Alessandra Truffa Giachet [e], Mario Iannaccone [f], Gabriele Crimi [g], Luca Gaido [h], Pier Paolo Bocchino [a], Carlo Andrea Pivato [i], Gianluca Campo [j], Daniela Trabattoni [k], Alaide Chieffo [l], Nicola Gaibazzi [m], Filippo Angelini [a], Andrea Rubboli [n], Andrea Rognoni [o], Giuseppe Musumeci [p], Fabrizio Ugo [q], Sebastiano Gili [k], Bernardo Cortese [r,t], Paolo Vadalà [s], Veronica Dusi [a], Guglielmo Gallone [a], Giuseppe Patti [o], Gaetano Maria de Ferrari [a]

[a] Division of Cardiology, Cardiovascular and Thoracic Department, Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[b] Division of Cardiology, ASST Santi Paolo e Carlo, 20142 Milan, Italy
[c] Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Cardiac Catheterization Laboratory and Cardiology, ASST Spedali Civili di Brescia, University of Brescia, Brescia, Italy
[d] Intensive Cardiac Care Unit and De Gasperis Cardio Center, ASST Grande Ospedale Metropolitano Niguarda, Italy
[e] Division of Cardiology, Ospedale "Cardinal Massaia" Asti, Italy
[f] Department of Cardiology, Ospedale San G Bosco, Torino, Italy
[g] Cardiovascular Disease Unit, Istituto di Ricerca e Cura a Carattere Scientifico Ospedale Policlinico San Martino, IRCCS Italian Cardiology Network, Genova, Italy
[h] Division of Cardiology, Ospedale Maria Vittoria, Torino, Italy
[i] Humanitas Clinical and Research Center IRCCS - Rozzano, Milan, Italy.; Department of Biomedical Sciences - Pieve Emanuele, Humanitas University, Milano, Italy.
[j] Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Cona, Italy
[k] Invasive Cardiology Unit 3, Centro Cardiologico Monzino, IRCCS, Via Parea, 4 - 20138 Milan, Italy
[l] Interventional Cardiology Unit, San Raffaele Scientific Institute, Milan, Italy
[m] Cardiology Department, Parma University Hospital, Parma, Italy
[n] Division of Cardiology, S Maria delle Croci Hospital, Ravenna, Italy
[o] Coronary Care Unit and Catheterization Laboratory, A.O.U. Maggiore della Carità, Novara, Italy
[p] Cardiology Department, Azienda Ospedaliera Ordine Mauriziano di Torino, Torino, Italy
[q] Division of Cardiology, Presidio Ospedaliero Sant'Andrea di Vercelli, Vercelli, Italy
[r] San Carlo Clinic, Milan, Italy
[s] Division of Cardiology, Ospedale Michele e Pietro Ferrero, Verduno, Italy
[t] Fondazione Ricerca e Innovazione Cardiovascolare, Milan, Italy

ARTICLE INFO

Article history:
Received 21 December 2020
Received in revised form 4 March 2021
Accepted 22 March 2021
Available online 29 March 2021

Keywords:
COVID-19
Acute coronary syndromes
Cardiovascular outcomes

ABSTRACT

Introduction: The impact of Covid-19 on the survival of patients presenting with acute coronary syndrome (ACS) remains to be defined.
Methods: Consecutive patients presenting with ACS at 18 Centers in Northern-Italy during the Covid-19 outbreak were included. In-hospital all-cause death was the primary outcome. In-hospital cardiovascular death along with mechanical and electrical complications were the secondary ones. A case period (February 20, 2020-May 3, 2020) was compared vs. same-year (January 1–February 19, 2020) and previous-year control periods (February 20–May 3, 2019). ACS patients with Covid-19 were further compared with those without.
Results: Among 779 ACS patients admitted during the case period, 67 (8.6%) tested positive for Covid-19. In-hospital all-cause mortality was significantly higher during the case period compared to the control periods (6.4% vs. 3.5% vs. 4.4% respectively; p 0.026), but similar after excluding patients with COVID-19 (4.5% vs. 3.5% vs. 4.4%; p 0.73). Cardiovascular mortality was similar between the study groups. After multivariable adjustment, admission for ACS during the COVID-19 outbreak had no impact on in-hospital mortality. In the case period, patients with concomitant ACS and Covid-19 experienced significantly higher in-hospital mortality (25% vs. 5%,

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: A.O.U. Città della Salute e della Scienza di Torino, Corso Bramante 88, 10125 Turin, Italy.
E-mail address: odefilippo@cittadellasalute.it (O. De Filippo).

https://doi.org/10.1016/j.ijcard.2021.03.063

$p < 0.001$) compared to patients without. Moreover, higher rates of cardiovascular death, cardiogenic shock and sustained ventricular tachycardia were found in Covid-19 patients.
Conclusion: ACS patients presenting during the Covid-19 pandemic experienced increased all-cause mortality, driven by Covid-19 positive status due to higher rates of cardiogenic shock and sustained ventricular tachycardia. No differences in cardiovascular mortality compared to non-pandemic scenarios were reported.

1. Introduction

The Covid-19 pandemic started in Wuhan in December 2019 and rapidly spread throughout the Globe infecting more than 40 million people across 217 countries/areas or territories as of October 20, 2020 (1,2). The first Italian confirmed case of Covid-19 was reported on February 20, 2020 in a small city in the region of Lombardy (Codogno, Lodi); thereafter, the rapid diffusion of the infection across the Country urged the Italian government to reorganize the Health Care System and the access to hospitals and health care facilities and to impose a national lockdown, which lasted from March 8, 2020 until May 3, 2020 (3).

Based on a pathophysiological background, SARS-CoV-2 outbreak was supposed to raise the incidence of acute coronary syndromes (ACS) due to the cardiovascular implications of virus-related systemic inflammatory status (4,5). In accordance, a remarkable proportion of patients suffering from Covid-19 experienced a certain degree of myocardial injury exacerbating their clinical course and worsening their prognosis (6). However, previous report showed that Covid-19 pandemic and Governments' harsh measures to contain the contagion were associated with a reduction of hospital admission rates for ACS and percutaneous coronary intervention (PCI) procedures (7–9). In parallel, it was observed an increased incidence of out-of-hospital cardiac arrests and a remarkable delay of emergency system activation for ST segment-elevation myocardial infarction (STEMI) (10–12). There is a paucity of data regarding clinical features and in-hospital outcomes of patients who had been treated for ACS in such pandemic scenario. Whether time dilations from symptoms onset to medical treatment, along with healthcare systems reorganization to cope with the demanding need for hospitalizations impacted on patients' prognosis had been investigated by previous studies with conflicting results (7,12). Furthermore, up to one third of patients suffering from Covid-19 admitted for ACS received a final diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) (13,14). The aim of the present analysis, due to second outbreak of Covid-19 in Europe, was to investigate changes in the clinical presentation and treatment features of ACS patients throughout the lockdown period in Italy and their implication on in-hospital deaths and AMI-related mechanical or electrical complications.

2. Methods

The "COVID-19 ACS registry" is a multicenter retrospective observational registry involving 18 Centers in Northern Italy (see Supplementary appendix for participating centers). We included all consecutive adult (≥18 years) patients who were admitted for ACS in a period ranging from January 1, 2020 until May 3, 2020, and from February 20, 2019 until May 3, 2019. All hospitals were hub centers of local network for primary percutaneous coronary intervention (PCI).

The study was conducted in accordance with the Declaration of Helsinki and with the International Conference of Harmonization Good Clinical Practices. All patients gave their informed consent on admission for de-identified data collection and future publication in anonymous fashion.

2.1. Data collection and definitions

Demographic, clinical and angiographic data were extracted in an anonymous fashion and collected on pre-specified electronic databases. Reduced kidney function was defined as an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 according to Modification of Diet in Renal Disease (MDRD equation), presentation symptom as the leading symptom urging patients to seek medical attention, known coronary artery disease (CAD) as previous myocardial infarction or percutaneous or surgical coronary revascularization, ACS, hereby including ST-segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), unstable angina (UA) and myocardial infarction with non-obstructive coronary arteries (MINOCA) according to the definition of European Society of Cardiology (15,16). These data were retrospectively retrieved from patients' medical history records and hospital discharge letters. The Division of Cardiology of A.O.U. Città della Salute e della Scienza (Turin, Italy) was the leading study center gathering all the data of interest in an anonymous electronic database. A physician at each center took responsibility to check for the accuracy and completeness of the data. Missing data were not imputed and not considered in the analyses. Proportion of missing data for each collected variable is reported in the Supplementary appendix and was mostly modest.

2.2. Study periods and outcomes

For the purpose of the present analysis, we compared outcomes between three different time periods, namely "case period" vs. "same-year control period" vs. "previous-year control period". The "case period" was defined as the time span between the day when the first local case of Covid-19 was detected in Codogno (Lodi, Lombardy; February 20, 2020) to the end of the lockdown period in Italy (May 3, 2020). Two different control periods were set, namely a "previous-year" control period (from February 20 to May 3, 2019) and a "same-year" control period (from January 1 to February 19, 2020).

In-hospital all-cause mortality was the primary outcome. In-hospital cardiovascular mortality, AMI-related mechanical (free-wall, septal or papillary muscle rupture, left ventricular aneurysm) and arrhythmic complications (ventricular fibrillation/sustained ventricular tachycardia, pulseless electrical activity, complete atrioventricular block, need for mechanical circulatory support, ventricular thrombosis, bleeding events, acute kidney injury (AKI), stroke, cardiogenic, haemorrhagic or septic shock, pulmonary embolism, need for ventilation and left ventricular ejection fraction (LVEF) at discharge were the secondary outcomes. AKI was defined according to Kidney Disease improving Global outcomes (KDIGO) guidelines (17) Bleeding events were appraised according to Bleeding Academic Research Consortium (BARC) definitions (18). Status of shock and its leading aetiology relied on treating physicians' diagnosis.

2.3. Statistical analysis

Continuous variables were reported as mean (± standard deviation) or median (interquartile range), as appropriate, while discrete variables were presented as absolute numbers (percentage). To detect significant differences in baseline features between the study periods, we used one-way analysis of variance (ANOVA) for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables and chi-square test for categorical variables, accordingly. In order to investigate the association between in-hospital outcomes and the analysed time periods, multivariate logistic regression analyses

were performed adjusting for possible confounding variables (all those with $p < 0.10$ at univariate analysis). Similar analyses were performed comparing the baseline characteristics and outcomes of patients with vs. without Covid-19 during the case period. A sensitivity analysis was also performed to compare characteristics and outcomes of patients presenting with vs. without STEMI during the case period. Significant *p*-value was set at 0.05. Statistical analysis was performed using SPSS 24 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Overall population

779 patients were admitted for ACS during the case period, 748 patients in the previous-year control period and 620 patients in the same-year control period. During the case period, 110 patients were admitted between 20/02/2020 and 29/02/2020, 305 in March and 364 between 01/04/2020 and 03/05/2020. The baseline characteristics of patients presenting with ACS in the case period compared to control periods are listed in Table 1. STEMI was the most frequent presentation in all the study periods. Patients complained less frequently of angina and more often of dyspnea on admission during the case period compared to the same- and previous-year control periods (angina 75% vs. 83.6% vs. 83.3%, respectively; dyspnea 15% vs. 9.1% vs 6.4%, respectively; $p < 0.001$).

In all the three study periods, PCI was performed in more than 90% of the cases (Table S1). Similar rates of critical stenosis of the unprotected left main coronary artery and of chronic total occlusion were reported. Furthermore, residual critical stenosis after index PCI were non-significantly less frequent in the case period as compared to the control periods (50.6% vs. 54.9% vs. 57.5%, respectively; p 0.087) resulting in fewer rates of staged planned revascularization after discharge (8.9% vs. 14.2% vs. 10.7%, respectively; p 0.031).

84 (6.4%) patients died from all causes during the case period as compared to 25 (3.5%) and 27 (4.4%) in the previous-year and same-year control periods respectively (p 0.026) (Table 2, Fig. 1A). No significant differences were found regarding cardiovascular death and mechanical or arrhythmic complications while a significantly higher incidence of shock was observed in the case period (7.1% vs. 3.7% vs. 6.4%, p 0.041) (Table 2), driven by the difference in cardiogenic shock (6.3% vs 3.3% vs 5.6%, p 0.024). Furthermore patients of the case period showed higher rates of AKI (10.6% vs. 6.4% vs. 7.1%, respectively; p 0.015), lower EF at discharge (49 ± 10% vs. 51 ± 10% vs. 50 ± 10%, respectively; $p < 0.001$) and shorter coronary unit stays (2.9 ± 4 vs 3.6 ± 5.1 3 ± 3.8). After excluding patients with Covid-19, rates of in-hospital all-cause death did not differ between the study groups, with 27 (4.5%) patients

Table 1
Clinical characteristics of patients admitted to hospital for ACS in the case period as compared to the previous-year and the same-year control periods.

Baseline characteristics	Period			
Variables	Case period N = 779	Previous-year control N = 748	Same-year control N = 620	p-value
Age (years old)	68 (66–71)	71 (67–74)	70 (68–73)	0.781
Male sex (n, %)	576 (73.9%)	556 (74.3%)	464 (74.8%)	0.703
Smoking habit (n, %)	257 (33.7%)	205 (27.6%)	185 (30.4%)	**0.002**
Diabetes (n, %)	189 (24.8%)	165 (22.3%)	154 (25.3%)	0.430
Dyslipidemia (n, %)	356 (46.7%)	351 (47.3%)	323 (53.0%)	0.134
Hypertension (n, %)	461 (60.4%)	432 (58.2%)	366 (60.1%)	0.619
Family history of CAD (n, %)	126 (17.1%)	139 (20.4%)	117 (20.6%)	0.179
Known coronary artery disease (n, %)	175 (24.7%)	176 (24.4%)	159 (25.7%)	0.845
Previous MI (n, %)	149 (19.2%)	152 (20.3%)	125 (20.3%)	0.833
Previous PCI (n, %)	172 (22.2%)	162 (21.7%)	140 (22.7%)	0.906
Previous CABG (n, %)	36 (4.7%)	46 (6.2%)	38 (6.2%)	0.391
CKD III-IV stage (n, %)	184 (24.1%)	143 (19.2%)	134 (22.0%)	**0.005**
Peripheral artery disease (n, %)	63 (9.6%)	112 (16.7%)	73 (12.7%)	**0.001**
Previous stroke (n, %)	34 (5.4%)	50 (7.6%)	34 (6.0%)	0.418
Atrial fibrillation (n, %)	82 (10.7%)	91 (12.2%)	77 (12.6%)	0.353
COPD (n, %)	63 (9.5%)	68 (10.1%)	65 (11.2%)	0.602
Neoplastic disease (n, %)				0.279
Previous	51 (6.9%)	60 (8.8%)	59 (10.3%)	
Current	15 (6.9%)	13 (1.9%)	14 (2.4%)	
ACS (n, %)				**<0.001**
STEMI	437 (56.1%)	386 (51.7%)	274 (44.3%)	
NSTEMI	254 (32.7%)	289 (38.7%)	247 (40.0%)	
Unstable Angina	86 (11.1%)	72 (9.6%)	95 (15.4%)	
Leading admission symptom (n, %)				**<0.001**
Angina	562 (75.0%)	569 (83.3%)	485 (83.6%)	
Dyspnea	113 (15.1%)	44 (6.4%)	53 (9.1%)	
Other ischemic equivalent	19 (2.5%)	13 (1.9%)	5 (0.9%)	
Atypical chest pain	19 (2.5%)	16 (2.3%)	9 (1.6%)	
Cardiac arrest	27 (3.6%)	26 (3.8%)	19 (3.3%)	
Other	9 (1.2%)	15 (2.2%)	9 (1.6%)	
Killip 3 at admission (n, %)	87 (11.7%)	68 (9.9%)	64 (11.0%)	0.561
EF at baseline (n, %)				0.288
≥50	347 (57.5%)	327 (55.4%)	309 (61.4%)	
35–50	192 (31.8%)	205 (34.7%)	152 (30.2%)	
<35	64 (10.6%)	58 (9.8%)	42 (8.3%)	
Timing of revascularization (n, %)				0.483
≤12 h	465 (80.7%)	396 (82.5%)	480 (81.4%)	
12-48 h	83 (14.4%)	64 (13.3%)	92 (15.6%)	
>48 h	28 (4.9%)	20 (4.2%)	18 (3.1%)	

Significant values are written in bold.
ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; MI, myocardial infarction; NSTEMI; non ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Table 2
In-hospital outcomes of patients admitted to hospital for ACS in the case period as compared to the previous-year and the intra-year control periods.

In-hospital outcomes	Period			
Variables	Case period N = 779	Previous-year (2019) control N = 748	Same-year control N = 620	p-value
All-cause death (n, %)	49 (6.4%)	25 (3.5%)	27 (4.4%)	**0.026**
Cardiovascular death (n, %)	35 (4.4%)	21 (2.8%)	22 (3.5%)	0.294
Stent thrombosis (n, %)	8 (1.3%)	7 (1.1%)	3 (0.6%)	0.668
Mechanical complications (n, %)	14 (2.0%)	12 (1.8%)	7 (1.1%)	0.894
Free wall rupture	5 (0.7%)	4 (0.6%)	2 (0.3%)	
Ventricular septal rupture	3 (0.4%)	2 (0.3%)	1 (0.2%)	
Papillary muscle rupture	2 (0.3%)	2 (0.3%)	0 (0.0%)	
Ventricular aneurysm	4 (0.6%)	4 (0.6%)	4 (0.7%)	
Arrhythmic complications (n, %)	59 (7.6%)	54 (7.2%)	53 (8.5%)	0.141
Ventricular fibrillation/sustained ventricular tachycardia	38 (4.9%)	35 (4.7%)	42 (6.8%)	
Pulseless electrical activity	21 (2.7%)	18 (2.4%)	11 (1.7%)	
Complete atrio-ventricular block	0 (0.0%)	1 (0.1%)	0 (0.0%)	
Ventricular thrombus (n, %)	11 (1.8%)	14 (2.3%)	8 (1.5%)	0.596
Bleeding (n, %)				**0.006**
BARC 1–2	9 (1.1%)	8 (1.1%)	14 (2.2%)	
BARC 3–5	18 (2.2%)	13 (1.7%)	14 (2.3%)	
Transfusion (n, %)	27 (4.6%)	25 (4.2%)	18 (3.7%)	0.744
AKI (n, %)	66 (10.6%)	39 (6.4%)	38 (7.1%)	**0.015**
Stroke (n, %)	8 (1.3%)	3 (0.5%)	7 (1.2%)	0.242
Pulmonary embolism (n, %)	4 (0.6%)	1 (0.2%)	1 (0.2%)	0.255
Shock (n, %)	55 (7.1%)	28 (3.7%)	40 (6.4%)	**0.041**
Cardiogenic shock	49 (6.3%)	25 (3.3%)	35 (5.6%)	**0.024**
Haemorrhagic shock	2 (0.3%)	3 (0.4%)	1 (0.2%)	0.697
Septic shock	4 (0.5%)	0 (0.0%)	4 (0.6%)	0.108
Need for ventilation (n, %)				0.299
Invasive	29 (4.6%)	16 (2.6%)	22 (4.1%)	
Non-invasive	37 (5.9%)	34 (5.5%)	37 (6.9%)	
Need for in-hospital mechanical support (n, %)	35 (4.5%)	22 (2.9%)	28 (4.4%)	**<0.001**
EF at discharge	49% ± 10%	51% ± 10%	50% ± 10%	**<0.001**
≥50% (n, %)	0 (0.0%)	721 (100.0%)	585 (94.2%)	
35–50% (n, %)	510 (79.7%)	0 (0.0%)	36 (5.8%)	
<35% (n, %)	130 (20.3%)	0 (0.0%)	0 (0.0%)	

Significant values are written in bold.
AKI, acute kidney injury; BARC, Bleeding Academic Research Consortium. Other abbreviations as in Table 1.

dying in the case period compared to 25 (3.5%) in the previous-year and 27 (4.4%) in the same-year control groups (p 0.73) (Fig. 1B).

At multivariate analysis, being admitted for ACS during the same-year and the previous-year control periods did not impact on in-hospital survival compared to case period (odds ratio [OR] 1.61, 95% confidence interval [CI] 0.74 to 3.5, p 0.227; 0.87, 95% CI 0.41 to 1.87, p 0.723, respectively) (Fig. 2A).

3.2. COVID-19 patients

ACS patients with Covid-19 had less frequent active smoking habit and prior MI, while presented more often with STEMI compared to patients without Covid-19 during the case period. ACS patients with Covid-19 also had higher rates of Killip 3 at admission, increased need of mechanical circulatory support and more frequent complete revascularization during index PCI as compared to patients who tested negative for Covid-19. A final diagnosis of MINOCA was achieved in 8 (12.7%) Covid-19-positive patients compared to 13 (2.4%) Covid-19-negative patients ($p < 0.001$) (Supplementary appendix, Tables S2 and S3).

Rates of all-cause death, cardiovascular death and arrhythmic complications were higher in patients with vs. without Covid-19 (25.4% vs. 4.5%; p < 0.001, 13.4% vs. 3.5%; $p < 0.001$, and 20.9% vs 6.0%, respectively) (Table S4; Fig. S1). Notably, among the arrhythmic complications, both malignant ventricular arrhythmias and pulseless electrical activity were more frequent in patients with vs. without Covid-19 (13.4% vs 4%; p < 0.001 and 7.5% vs 2.1%; p 0.01, respectively). No cases of complete AV block were recorded. Moreover, patients with Covid-19 developed more frequently cardiogenic and septic shock and required more often both invasive and non-invasive ventilation. The independent impact of Covid-19 on all-cause death was confirmed at multivariate regression analysis (OR 4.7, 95% CI 18.-12.1; p < 0.001) (Fig. 2B).

3.3. STEMI patients

437 (56.1%) patients were admitted for STEMI in the case period, 274 (44.3%) in the same-year control period and 386 (51.7%) in the previous-year control period. STEMI patients presented higher rates of reduced kidney function, multivessel revascularization during index PCI and unprotected left main PCI and lower rates of peripheral artery disease and angina complaint in the case period compared to the control periods (Supplementary appendix, Tables S5 and S6). Regarding in-hospital outcomes, rates of all-cause death and cardiovascular death were similar between the aforementioned study periods (9.2% vs. 7.6% vs. 5.1%, respectively; p 0.06, and 6.6% vs. 6.1% vs. 4.9%, respectively; p 0.44) (Supplementary appendix, Table S7).

4. Discussion

Our group firstly reported the negative impact of the Covid-19 pandemic on ACS hospitalizations during national lockdowns in Northern Italy, with several ensuing studies confirming similar patterns across the globe [4]. Despite several reasons were adduced to account for such phenomenon (i.e. reduction of air pollutants (19), it is likely that patients' fear of contagion played a major role. However, whether Covid-19 had an impact on ACS in-hospital outcomes remains a matter of debate. We thus assessed in-hospital outcomes of consecutive patients admitted for ACS at 18 public healthcare facilities representative

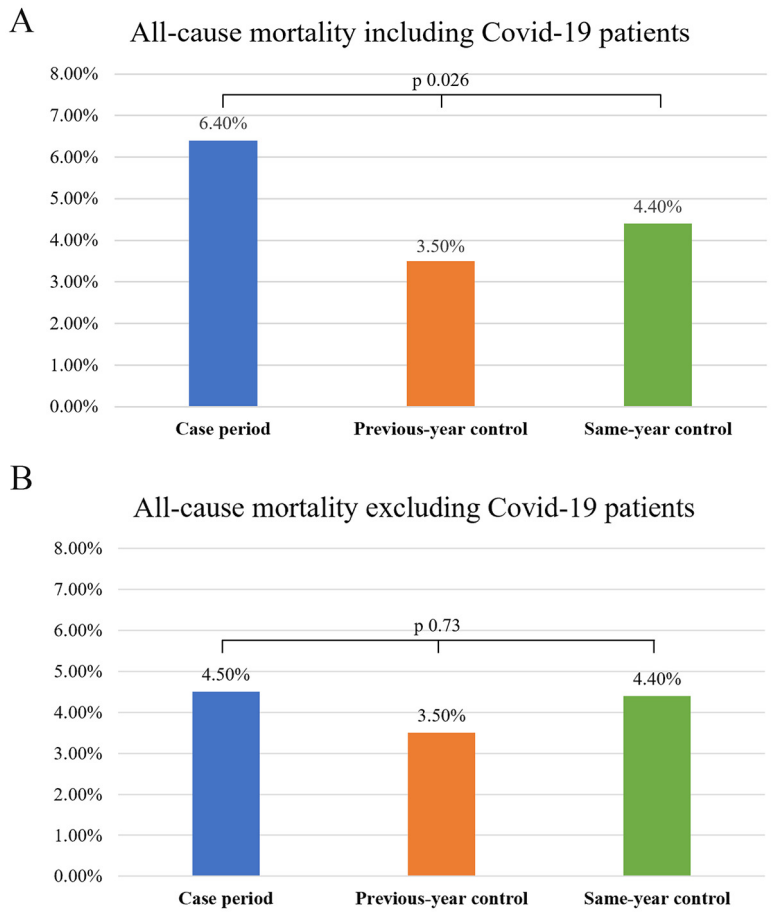

Fig. 1. In-hospital all-cause mortality of patients admitted to hospital for ACS during the case period (*blue*) as compared to the previous-year (*orange*) and same-year (*green*) control periods after inclusion (panel A) or exclusion (panel B) of Covid-19 patients.

of the Northern Italy scenario during the Covid-19 pandemic to provide insights on this issue.

To the best of our knowledge, this is the largest series aiming to systematically describe the impact of the Covid-19 pandemic on the in-hospital outcomes of ACS patients. The main findings of this study can be summarized as follows: being admitted for ACS during the Covid-19 pandemic was not associated with increased in-hospital all-cause mortality compared to the control periods; no difference in cardiovascular mortality, in-hospital electrical and mechanical complications was observed between the case period and the control periods; during the case period, Covid-19 positive patients accounted for approximately 8% of ACS patients; Covid-19 ACS patients more commonly presented with STEMI or MINOCA and showed higher rates of all-cause and cardiovascular mortality, as well as malignant ventricular arrhythmias, pulseless electrical activity, cardiogenic and septic shock and need for acute mechanical circulatory support. Intriguingly, smoking habit was a strong risk factor for in-hospital mortality in the overall population, but a protective factor during the case period. The potential for nicotine to protect against negative Covid-19 evolution has already been suggested as the so-called smoker's paradox, wherein smokers are protected from infection and severe complications of COVID-19 (20). As of now, the data supporting smoker's paradox claims are limited and questionable and we are the first to provide this kind of evidence in the setting of ACS. Advocated biologic mechanisms include an anti-inflammatory effect of nicotine, a blunted immune response in smokers (reducing the risk of a cytokine storm) and increased nitric oxide in the respiratory tract (which may inhibit replication of SARS-CoV-2 and its entry into cells). Further investigation are warranted before drawing any definite conclusion on this matter.

Albeit we observed increased in-hospital all-cause mortality among patients admitted to hospital for ACS during the Covid-19 pandemic compared to the control periods, being admitted for ACS during the case period was not associated with increased mortality at the multivariate analysis. This paramount finding outlines that mechanisms other than the ACS itself are at work accounting for the increased overall mortality risk during the Covid-19 pandemic, as similarly hinted at by the similar cardiovascular mortality rate between the case and control periods. On one hand, it should be acknowledged that patients' avoidance of seeking medical care may have led to an underestimation of the ACS-related adverse events and deaths occurring during the pandemic outbreak, as many of these events may have occurred out-of-hospital without a formal medical evaluation (21). However, our finding is consistent with a previous report from the United Kingdom (8) and suggests that the specific ACS protocols developed at the national and local healthcare system levels translated into effective in-hospital management of ACS during the Covid-19 pandemic. More specifically, very high rates of PCI, comparable to the ones reported in control periods, were noted during the pandemic. This is in contrast with the findings of a recent study from China showing increased utilization of the thrombolysis reperfusion strategy during the Covid-19 pandemic (22). This might be due to the Chinese medical system being the first to face the COVID-19 pandemic with consequent reduced time for investigating, assessing and subsequently instituting adequate protocols therapies.

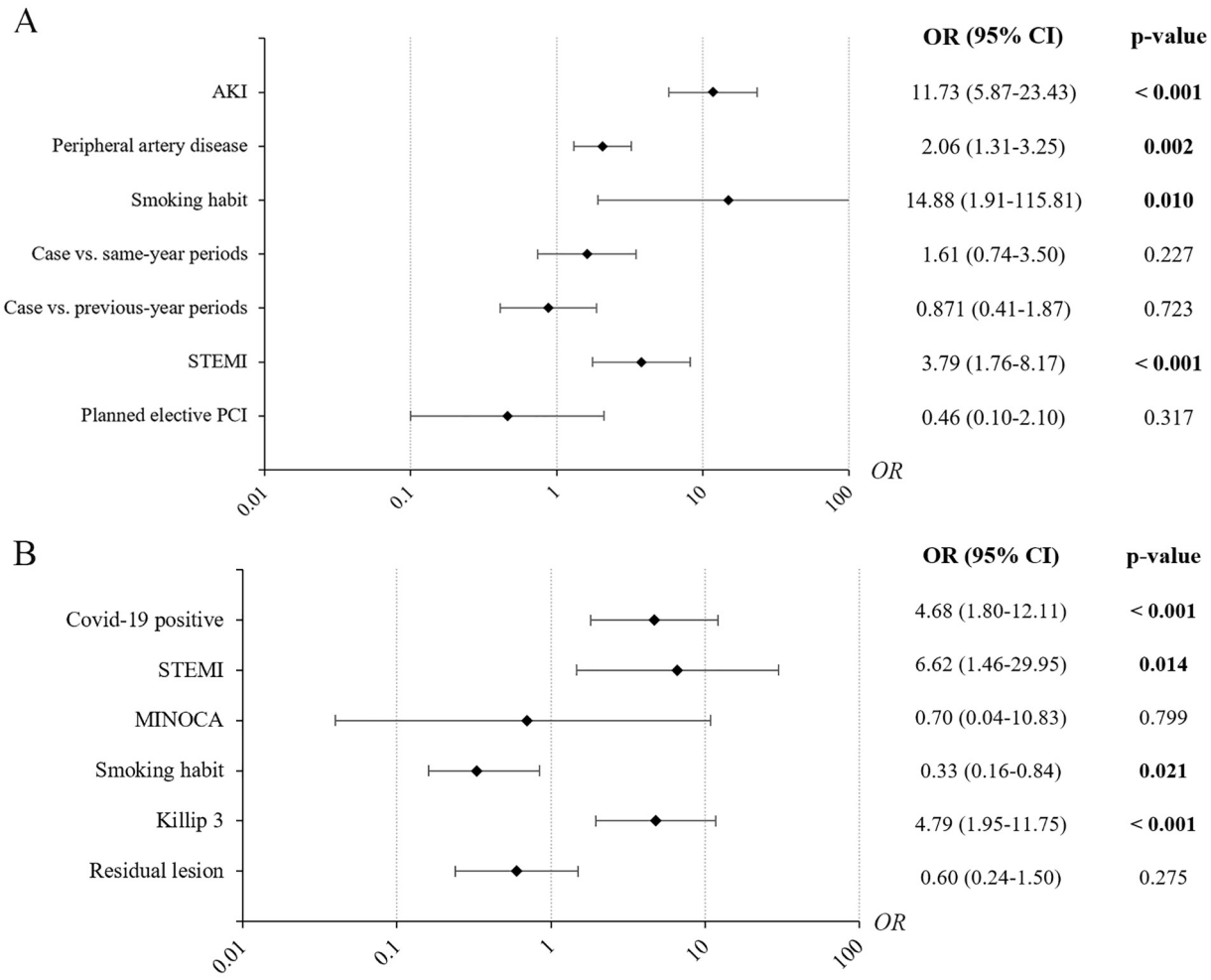

Fig. 2. Multivariate analysis for in-hospital mortality of the study population overall (panel A) and during the case period (panel B). Significant *p*-values are written in bold. AKI, acute kidney injury; CI, confidence interval; MINOCA, myocardial infarction with non-obstructive coronary arteries; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction. Values on the X- axis are in logarithmic scale.

Consistently with a previous report, higher rates of complete revascularization were achieved during the case period (8). While this may reflect the uptake of current evidences regarding the prognostic benefit of complete revascularization in STEMI (23,24), it may also underlie the choice to avoid multiple procedures that may expose health care workers to Covid-19 affected patients or the risk for patients usually scheduled for elective procedures to be put at disadvantage consequently to the halt of non-urgent hospitalizations. In accordance with such hypotheses we observed shorter intensive care unit and hospital stays during the case period.

Of note, among patients presenting with STEMI during the case period, a trend towards a more frequent subacute presentation was noted. This finding may potentially explain the observed lower ejection fraction at discharge in the case period and may herald adverse remodeling and higher rates of chronic heart failure, which portends a negative long-term prognosis. In accordance, in-hospital rates of all-cause death were numerically higher in the STEMI subgroup of patients admitted during the pandemic. In this regard, the recent literature suggests the negative consequences of the pandemic on the incidence of cardiovascular events (7,10). Thus, our findings may reassure on the management and outcomes of ACS patients searching for medical attention. This is also indirectly hinted at by the finding of reduced incidence of angina at presentation in front of an increase in dyspnea, suggesting a patients' focus towards respiratory symptoms during the Covid-19 outbreak.

Among Covid-19 patients, STEMI and MINOCA were more frequent as compared to the previous periods, thus supporting on one hand a potential underlying role of the virus on plaque instability and atherothrombosis and on the other a close relationship between the coronaviruses-related disease and the myocardial injury as outlined by previous findings (25). The action of the virus could indeed be both direct and indirect, mainly linked to the systemic inflammatory response triggering a higher thrombotic burden; (26) this systemic inflammatory milieu, alongside the potential affection of the myocardium itself, may thus explain the rising number of MINOCA during the case period. ACS patients with Covid-19 showed higher all-cause mortality compared to patients without Covid-19. The findings of the present study suggest that this may be related to the infection itself increasing the risk of cardiogenic and septic shock, the need for mechanical circulatory support and arrhythmic complications. Notably, despite the similar prevalence of cardiac arrest at presentation, patients with Covid-19 showed a higher susceptibility to in-hospital arrhythmic complications including not only malignant ventricular arrhythmias (13.4%) but also pulseless electrical activity (7.5%). The increased ventricular arrhythmic risk in Covid-19 patients has already been reported, with as much as 5.9% of patients hospitalized with Covid-19 developing malignant ventricular arrhythmias (27). Covid-19 related arrhythmic risk, due to a combination of several factors including but not limited to systemic inflammation, autonomic imbalance and prolonging QT drug-usage (28), is likely to be further magnified during ACS. The potential

for an increased risk of pulseless electrical activity in Covid-19 patients with ACS is a novel finding of our study and might be related to myocardial stunning in the setting of the cytokines storm/systemic and local inflammation. Thapa et al. recently reported that among 54 Covid-19 patients who had in-hospital cardiac arrest and underwent cardiopulmonary resuscitation, pulseless electrical activity was the most common underlying rhythm (81.5% of the patients) (29). Yet, as opposed to our study, most of these patients were on mechanical ventilation, leading to assume a relevant hypoxic contribution to PEA.

Finally, we observed a significantly higher rate of pulmonary embolism among patients with Covid-19 as compared to patients without Covid-19. Such findings are in line with the previously reported propensity of Covid-19 patients to develop venous thromboembolism due to the prothrombotic state caused by the disease (30). On the other hand, despite the tendency towards a lower LVEF at presentation in patients with Covid-19, the incidence of ventricular thrombus was overall low and similar to that of patients without Covid-19. However, due to the low incidence of thromboembolic events in our cohorts, such findings should be regarded as explorative rather than conclusive.

4.1. Limitations

The results of the present study must be interpreted considering some limitations. First, due the retrospective nature of the study and the logistical limitations occurring during the Covid-19 outbreak in Italy, some baseline clinical and echocardiographic data were missing and could not be retrospectively retrieved. Similarly, some variables potentially associated with the reduction of ACS incidence and in-hospital complications (i.e. air pollutants) were not systematically collected as it was beyond the purpose of the present registry. Moreover, only in-hospital outcomes were assessed as mid- to long-term data were not yet available for the case period population. Therefore, this study may underestimate the relevance of out-of-hospital deaths and ACS-related adverse events, as discussed (21). We recorded a remarkable rate of poor in-hospital outcomes and ventricular arrythmias among patients admitted for ACS during the same-year control period, especially when compared with the previous-year control group. In this context it should be acknowledged that an unknown proportion of patients admitted in the first months of 2020 could have been undiagnosed for COVID-19 due to the early difficulties to recognize and thus to get tested for such disease (31). Finally, the limited sample size of Covid-19 patients limits the inferential power of the present analysis and the results must be interpreted as hypothesis-generating rather than definitive.

5. Conclusions

ACS patients presenting during the Covid-19 pandemic experienced increased all-cause mortality, driven by Covid-19 positive status due to higher rates of cardiogenic shock and sustained ventricular tachycardia. No differences in cardiovascular mortality compared to non-pandemic scenarios were reported.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of Competing Interest

The Authors declare that there is no conflict of interest.

Acknowledgments

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.03.063.

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