Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Covid-19 diagnosis and mortality in patients with non-ST-elevation myocardial infarction admitted in Italy during the national outbreak

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ARTICLE INFO

Keywords:
Non-ST elevation myocardial infarction
Acute coronary syndromes
Percutaneous coronary intervention
National outbreak
Covid-19

ABSTRACT

Introduction: We sought to assess the clinical impact of Covid-19 infection on mortality in patients with Non-ST elevation myocardial infarction (NSTEMI) admitted during the national outbreak in Italy.
Methods: We analysed a nationwide, comprehensive, and universal administrative database of consecutive NSTEMI patients admitted during lockdown for Covid-19 infection (March,11st - May 3rd, 2020) and the equivalent periods of the previous 5 years in Italy. The observed rate of 30-day and 6-month all-cause mortality of NSTEMI patients with and without Covid-19 infection during the lockdown was compared with the expected rate of death according to the trend of the previous 5 years.
Results: During the period of observation, 48.447 NSTEMI hospitalizations occurred in Italy. Among these, 4981 NSTEMI patients were admitted during the 2020 outbreak: 173 (3.5%) with and 4808 (96.5%) without a Covid-19 diagnosis. According to the 5-year trend, the 2020 expected rate of 30-day and 6-month all-cause mortality was 6.5% and 12.2%, while the observed incidence of death was 8.3% ($p = 0.001$) and 13.6% ($p = 0.041$), respectively. Excluding NSTEMI patients with a Covid-19 diagnosis, the 6-month mortality rate resulted in accordance with the prior 5-year trend. After multiple corrections, the presence of Covid-19 diagnosis resulted one of the independent predictors of all-cause mortality at 30 days [adjusted odds ratio (OR) 4.3; 95% confidence intervals (CI) 2.90–6.23; $p < 0.0001$] and 6 months (adjusted OR 3.5; 95% CI: 2.43–5.03; $p < 0.0001$).
Conclusions: During the 2020 national outbreak in Italy, a concomitant diagnosis of Covid-19 in NSTEMI was associated with a significantly higher rate of mortality.

1. Introduction

The coronavirus disease 2019 (Covid-19) infection has caused millions of deaths worldwide with a substantial impact on healthcare system and organization. Italy, that accounts about 59 million inhabitants, was the first European nation to be affected by Covid-19, with around 19 million confirmed total cases and >170.000 deaths to date [1,2]. The pandemic has mainly affected the North of Italy, where, especially in the first half of 2020, most confirmed cases of Covid-19 and related fatal events occurred [1,2].

Italy was the first western country to ratify a nationwide lockdown for Covid-19 [3], officially starting from March 11st and ending, after two addition decrees prolonging the national outbreak, on May 3rd 2020, restricting the movement of the population except for necessity, work, and health circumstances [4,5]. The national lockdown was the period with the widest spread of Covid-19 and the highest rate of mortality related to the infection, during which only health emergencies were admitted to hospitals in Italy [6].

Several studies have reported that hospitals admissions for acute myocardial infarction (MI), particularly for ST-elevation myocardial infarction, have been significantly reduced during the Covid-19 pandemic, with a concomitant increase in early mortality rate [7–10],

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https://doi.org/10.1016/j.ijcard.2022.11.008
Received 22 September 2022; Received in revised form 26 October 2022; Accepted 2 November 2022
Available online 7 November 2022

without clear explanation of this phenomenon.

We aimed at analysing the clinical impact of Covid-19 infection on mortality in patients with Non-ST-elevation myocardial infarction (NSTEMI) admitted during the national outbreak and in the equivalent periods of the previous 5 years in Italy using a nationwide, comprehensive, and universal administrative database.

2. Methods

2.1. Study design

This was a retrospective cohort study that enrolled consecutive patients admitted to all public and private hospitals in Italy for a NSTEMI event during the national outbreak for Covid-19 (March, 11st -May 3rd, 2020) and the equivalent periods of the 5 previous years. We compared baseline characteristics, hospitalization rates and 30-day and 6-month all-cause mortality between NSTEMI patients admitted during the national outbreak for Covid-19 in 2020 and the prior 5-year equivalent periods. The Italian National Registry of Hospital Discharge Records (HDR), provided by the Italian Ministry of Health (MoH), and other administrative databases available through a collaboration with the Italian National Program for Outcome Evaluation (PNE-AGENAS) were used as sources of data.

2.2. Study population

All HDR of patients aged 18 to 100 years, resident in Italy, admitted during the study period and reporting diagnosis of NSTEMI were selected. For the purposes of this study NSTEMI patients were defined as patients reporting the ICD 9 CM codes 410.7 or 410.9 in primary diagnosis or the same codes in secondary diagnosis with any concomitant AMI complication within the primary diagnosis (ICD-9-CM codes 411, 413, 414, 426, 427, 428, 423.0, 429.5, 429.6, 429.71, 429.79, 429.81, 518.4, 518.81, 780.01, 780.2, 785.51, 799.1, 997.02 and 998.2) (*Outcomes evaluation National program [PNE]* Ed. 2020; available at https://pne.agenas.it/) [11].

Patients discharged to home within 2 days from admission (probable false NSTEMI cases) were excluded. Furthermore, to avoid the inclusion of multiple admissions due to the same event, duplicate records and records concerning both transfers of patients to another hospital and patients with a previous AMI admission within 30 days from the index admission were excluded [12].

According to the Italian Ministry of Health official documents for the Covid-19 cases identification released between March and October 2020, NSTEMI patients with a concomitant definite or suspected diagnosis of Covid-19 were defined as NSTEMI cases with at least one of the following ICD 9 CM codes: 078.89 Other specified diseases due to viruses (MoH first guidelines - 20th of March 2020); 043 Covid-19 disease, 480.4 Covid-19 Pneumonia, 518.9 Covid-19 Acute respiratory distress syndrome (ARDS), 519.7 Covid-19 Other respiratory infections (MoH Decree - 28th of October 2020); 079.82 SARS-associated coronavirus, 480.3 Pneumonia due to SARS-associated coronavirus (ICD-9-CM codes for SARS); codes identifying exposure, isolation, anamnesis, observation ('V01.85', 'V01.79', 'V71.83','V07.0′, 'V71.84′, 'V07.00′, 'V12.04′, 'V01.82′) or pneumonia in other infectious diseases (484.8) [13].

Data on patient risk factors and comorbidities, according to the ICD9-CM codes reported in Suppl Table 1, were retrieved either from the index admission or the previous 5-year hospitalizations. We also assessed the rate of coronary angiography or percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) performed within the first 2 and 30 days from hospital admission, respectively.

In order to evaluate the impact of Covid-19 infection on NSTEMI mortality in different areas of the country, Italy was divided in three macro-regions: Northern (Lombardia, Piemonte, Valle d'Aosta, Veneto, Friuli Venezia-Giulia, Trentino Alto-Adige, Liguria and Emilia-Romagna; accounting for a total of 13.480.648 inhabitants in 2020), Central (Lazio, Toscana, Umbria and Marche; 5.719.084 inhabitants) and Southern (Abruzzo, Molise, Puglia, Basilicata, Campania, Calabria, Sicilia and Sardegna; 9.850.364 inhabitants).

Table 1
Baseline characteristics of the enlisted population by year.

	2015 (*N* = 8660)	2016 (*N* = 8822)	2017 (*N* = 8796)	2018 (*N* = 8536)	2019 (*N* = 8652)	2020 (*N* = 4981)	P value*
Gender (F). n (%)	3217 (37.1)	3155 (35.8)	3141 (35.8)	3052 (35.8)	3043 (35.2)	1635 (32.8)	0.046
Age (years). mean ± SD	72.3 ± 13.1	72.2 ± 12.9	72.3 ± 12.7	72.1 ± 12.7	72.1 ± 12.8	71.3 ± 12.7	0.005
Hypertension. n (%)	2376 (27.4)	2431 (27.6)	2260 (27.6)	2031 (23.8)	2069 (23.9)	1072 (21.5)	0.271
Diabetes. n (%)	1543 (17.8)	1518 (17.2)	1475 (17.2)	1313 (15.4)	1405 (16.2)	724 (14.5)	0.360
Heart failure. n (%)	1108 (12.8)	1112 (12.6)	1027 (12.6)	986 (11.6)	1015 (11.7)	508 (10.2)	0.137
Cerebrovascular disease. n (%)	959 (11.1)	939 (10.6)	908 (10.6)	844 (9.9)	801 (9.3)	394 (7.9)	0.069
Vascular disease. n (%)	624 (7.2)	693 (7.9)	651 (7.9)	590 (6.9)	599 (6.9)	284 (5.7)	0.023
Chronic coronary syndromes. n (%)	2055 (23.7)	2056 (23.3)	1970 (23.3)	1855 (21.7)	1901 [22]	1059 (21.3)	0.844
Arrhythmias. n (%)	1085 (12.5)	1032 (11.7)	1036 (11.7)	962 (11.3)	978 (11.3)	562 (11.3)	0.493
Anemia. n (%)	534 (6.2)	570 (6.5)	512 (6.5)	543 (6.4)	525 (6.1)	281 (5.6)	0.345
Blood clotting defects. n (%)	18 (0.2)	22 (0.2)	23 (0.2)	17 (0.2)	15 (0.2)	8 (0.2)	0.792
Other hematological diseases. n (%)	59 (0.7)	53 (0.6)	59 (0.6)	50 (0.6)	59 (0.7)	22 (0.4)	0.180
Cardiomyopathy. n (%)	182 (2.1)	196 (2.2)	165 (2.2)	163 (1.9)	151 (1.7)	91 (1.8)	0.533
Rheumatic heart disease. n (%)	141 (1.6)	140 (1.6)	121 (1.6)	121 (1.4)	115 (1.3)	67 (1.3)	0.634
Endocarditis and acute myocarditis. n (%)	8 (0.1)	12 (0.1)	13 (0.1)	11 (0.1)	10 (0.1)	9 (0.2)	0.575
Other chronic heart conditions. n (%)	210 (2.4)	256 (2.9)	224 (2.9)	228 (2.7)	256 (3)	123 (2.5)	0.139
Chronic kidney disease. n (%)	822 (9.5)	852 (9.7)	826 (9.7)	800 (9.4)	786 (9.1)	428 (8.6)	0.402
Other chronic disease (liver. Pancreas. intestine). n (%)	187 (2.2)	182 (2.1)	183 (2.1)	152 (1.8)	163 (1.9)	78 (1.6)	0.487
Obesity. n (%)	218 (2.5)	209 (2.4)	189 (2.4)	181 (2.1)	179 (2.1)	109 (2.2)	0.312
Chronic obstructive pulmonary disease. n (%)	748 (8.6)	638 (7.2)	646 (7.2)	585 (6.9)	549 (6.3)	265 (5.3)	0.303
Malignant neoplasms. n (%)	788 (9.1)	788 (8.9)	795 (8.9)	833 (9.8)	766 (8.9)	423 (8.5)	0.191
Previous AMI	1813 (20.9)	1786 (20.2)	1685 (20.2)	1598 (18.7)	1664 (19.2)	960 (19.3)	0.162
Previous vascular surgery. n (%)	594 (6.9)	617 (7)	584 (7)	557 (6.5)	593 (6.9)	302 (6.1)	0.246
Previous cerebral revascularization. n (%)	160 (1.8)	147 (1.7)	140 (1.7)	138 (1.6)	121 (1.4)	60 (1.2)	0.547
Previous CABG	711 (8.2)	734 (8.3)	688 (8.3)	643 (7.5)	631 (7.3)	331 (6.6)	0.425
Other previous cardiac surgery than CABG. n (%)	184 (2.1)	218 (2.5)	208 (2.5)	203 (2.4)	224 (2.6)	130 (2.6)	0.935
Previous PCI	1627 (18.8)	1686 (19.1)	1694 (19.1)	1654 (19.4)	1748 (20.2)	1092 (21.9)	0.044

Abbreviations: CABG: coronary artery bypass grafting; MI: myocardial infarction; PCI: percutaneous coronary intervention.

* The p values refer to the comparison between the observed and expected rates of comorbidities in the 2020 study period.

The 30-day and 6-month all-cause mortality represented the main adverse outcomes.

2.3. Statistical analysis

Prevalence of risk factors and comorbidities were presented as counts and percentages; age was expressed as the mean ± standard deviation.

The number of expected NSTEMI events and the rates of the comorbidities and outcomes in 2020 national outbreak was estimated by a linear regression model using the number of NSTEMI events and the rates of the comorbidities and outcomes in the prior 5-year equivalent periods as predictors. The number of the actual and the expected events in the 2020 study period was compared by the Poisson test. The observed and expected rates of both comorbidities and outcomes were compared using the log-normal distribution property of the rate ratio (H0: observed rate / expected rate = 1).

The normal distribution of continuous parameters was tested with the Kolmogorov-Smirnov test. Variables with a skewed distribution were compared with the use of Wilcoxon rank sum tests. *t*-Test, Chi-square or Fisher exact tests were used to compare frequencies among Covid-19 and non- Covid-19 patients in the 2020 NSTEMI cohort, as appropriate.

To provide adjusted outcome data, age, gender, PCI performed ≤48 h from admission, and patients' risk factors and comorbidities were included in the multivariate models as potential confounding factors; stepwise logistic procedures were used to identify independent associations with each of the considered outcomes. Since some chronic comorbidities recorded in the index hospitalization show a paradoxical protective effect [8], the same comorbidities recorded in the previous hospitalizations were also forced into the models.

All assumptions of statistical methods were explicitly checked. Statistical analyses were performed using SAS 9.4 (Cary, NC, USA).

3. Results

During the study period, 48.447 hospitalizations for NSTEMI occurred in Italy. In the almost 8 weeks of the 2020 national outbreak, 4981 NSTEMI patients were admitted at 365 centers in Italy: 173 (3.5%) with and 4808 (96.5%) without a Covid-19 diagnosis. Patients with a Covid-19 infection were older and more frequently had a history of rheumatic heart disease compared to NSTEMI patients without Covid-19 (**Supple** Table 2). Patients with Covid-19 infection less frequently underwent PCI within 48 h from hospital admission (25.4% vs 46.3%; $p < 0.0001$) and coronary angiography not followed by revascularization (19.7% vs 37.9%; $p < 0.0001$), compared to patients without Covid-19. On the other hand, the rate of CABG performed within 30 days from hospital admission was comparable between NSTEMI patients with and without Covid-19 infection (2.9% vs 5.1%; $p = 0.19$). As expected, the length of hospital stay was longer in NSTEMI patients with as compared to those without Covid-19 (9.96 vs 5.30 days; $p < 0.0001$).

Compared to the previous 5 years, the rate of admissions for NSTEMI during the lockdown in 2020 was markedly reduced (from 8660 in 2015 to 4981 in 2020; percentage change −41.7). Considering the 5-year trend, the observed number of STEMI admissions in 2020 was significantly reduced as compared to the expected rate (4981 vs 8633; p < 0.0001) (Fig. 1A). The reduced rate in NSTEMI admissions during the lockdown as compared to the expected rate based on previous 5-year trend was consistent in Northern, Central and Southern Italy (all *p* values <0.0001) (Fig. 1B). Although the absolute number of NSTEMI admissions decreased, the percentage of NSTEMI patients receiving a PCI increased in the study period as compared to the previous 5 years of observation (from 32.5% in 2015 to 45.6% in 2020; percentage change +40.3%). This trend was consistent in North (from 32.7% in 2015 to 42.5% in 2020; percentage change +30.0%), Central (from 33.8% in 2015 to 48.5% in 2020; percentage change +43.5) and South (from 31.4% in 2015 to 46.6% in 2020; percentage change +48.4%) of Italy (Suppl. Fig. 1). In parallel, a significant decrease in the rate of CABG performed within 30 days of admission was observed among NSTEMI patients (from 6.6% in 2015 to 5.0% in 2020; percentage change −24.0), particularly in North and South of Italy (Suppl. Fig. 2).

Table 2
Logistic regression model for 6 months mortality.

	CrudeOR	AdjustedOR	CI 95%	p
Gender (F)	1.6	0.9	0.856–0.967	0.002
Age (years)	1.1	1.1	1.074–1.081	<0.0001
COVID-19	**3.4**	**3.5**	**2.434–5.026**	<0.0001
Other hematological diseases. n (%)	2.1	1.3	0.972–1.773	0.078
Other previous cardiac surgery than CABG. n (%)	1.6	1.3	1.094–1.552	0.003
Previous vascular surgery	2.1	1.3	1.153–1.448	<0.0001
Other chronic heart conditions	2.2	1.2	1.041–1.431	0.014
Anemia	3.3	1.3	1.137–1.386	<0.0001
COPD	2.5	1.2	1.081–1.303	<0.0001
Rheumatic heart disease. n (%)	3.2	1.2	0.963–1.392	0.12
Disorders of lipid metabolism	1.0	0.8	0.712–0.889	<0.0001
Diabetes	2.1	1.3	1.218–1.418	<0.0001
Heart failure	3.5	1.6	1.442–1.692	<0.0001
Cerebrovascular disease	2.4	1.4	1.258–1.492	<0.0001
Vascular disease. n (%)	2.2	1.3	1.167–1.451	<0.0001
Other chronic disease (liver. Pancreas. intestine)	1.7	1.1	0.889–1.292	0.469
Chronic kidney disease	3.3	1.4	1.268–1.524	<0.0001
Obesity	1.2	1.1	0.874–1.278	0.567
Previous PCI	0.7	0.7	0.607–0.717	<0.0001
Previous cerebral revascularization. n (%)	1.2	0.6	0.512–0.808	<0.0001
Malignant neoplasms	2.3	1.7	1.562–1.843	<0.0001
Previous CABG	0.8	0.7	0.643–0.813	<0.0001
PCI ≤48 h	0.2	0.4	0.373–0.437	<0.0001

Abbreviations: CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention.

Demographic and clinical characteristics of NSTEMI patients admitted during the 2020 lockdown were comparable with those admitted during the equivalent periods in the previous 5 years of observation, except for the mean age, number of females and prior vascular disease that were reduced and those with prior PCI that were significantly increased in the 2020 population (Table 1).

3.1. Mortality trends

According to the 5-year trend, the 2020 expected rate of 30-day all-cause mortality was 6.5%, while the observed incidence of death was 8.3% ($p = 0.001$). Excluding NSTEMI patients with a Covid-19 diagnosis, the observed incidence of 30-day mortality was 7.6% ($p = 0.028$ compared to the expected trend rate) (Fig. 2). Accordingly, the 2020 expected rate of 6-month all-cause mortality was 12.2%, while the observed incidence of death was 13.6% ($p = 0.041$); after excluding NSTEMI patients with Covid-19, the observed incidence of mortality at 6 months was 12.9% ($p = 0.349$ compared to the expected trend rate) (Fig. 3). The difference in the observed rates of 30-day and 6-month mortality among NSTEMI patients admitted during the 2020 lockdown with and without Covid-19 infection was particularly evident in the Northern Italy (Figs. 2 and 3).

After multiple corrections, the presence of Covid-19 diagnosis resulted one of the independent predictors of all-cause mortality at 30 days [adjusted odds ratio (OR) 4.3; 95% confidence intervals (CI) 2.90–6.23; $p < 0.0001$] (**Suppl. Table 3**) and 6 months (adjusted OR 3.5; 95% CI: 2.43–5.03; p < 0.0001) (Table 2).

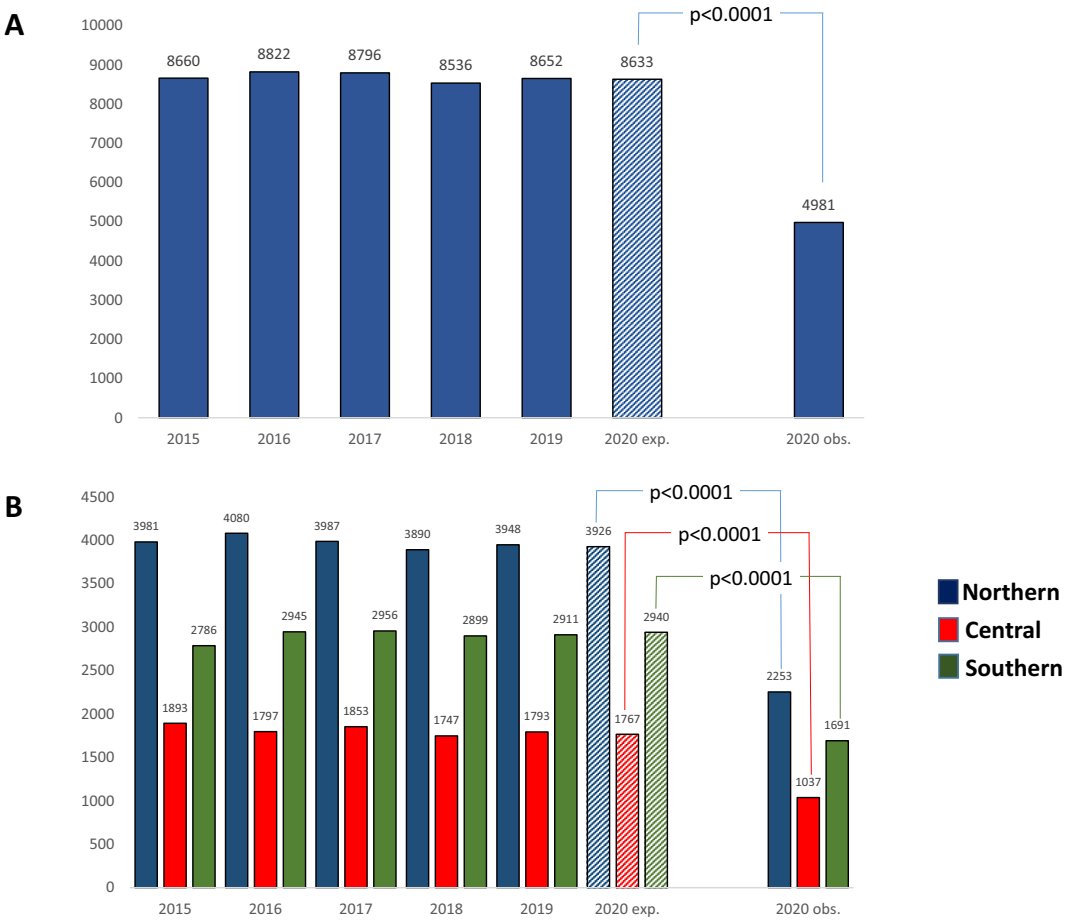

Fig. 1. Expected (exp.) and observed (obs.) incidence of NSTEMI admission during the 2020 national outbreak and over the equivalent periods in the previous 5 years in Italy (panel A) and by geographic regions (panel B).

4. Discussion

This retrospective analysis of nationwide administrative data documented a marked reduction of hospital admissions for NSTEMI during national outbreak for Covid-19 in Italy with a higher-than-expected all-cause death at both 1 and 6 months, compared with the mortality trend for NSTEMI of the same calendar period in the previous 5 years. Notably, when NSTEMI patients with a concomitant Covid-19 diagnosis were excluded from the analysis, the observed 6-month mortality rate resulted in accordance with the prior 5-year trend.

Several studies have already reported a significant decline of hospital admissions for acute MI during Covid-19 outbreak, with percentages ranging from 20 to 40% [7–10,14–20]. A recent study reported a reduction of MI admission of around 20% during the national lockdown in the 2 French provinces with a different medical campaign policy, with a faster normalization of MI incidence was observed in the province in which a large local media campaign was conducted [14]. In another study conducted in 22 centers in France, all located in major cities, a drop of MI as high as 30% was reported [15]. Notably, most studies conducted in Europe did not analyse a nationwide dataset but rather assessed the rate of admissions for MI in a sample of centers, mainly from large cities [7–10,16–20]. This aspect is crucial since in most countries, a migration of populations from the large cities to the countryside areas was observed during lockdown. Therefore, a large and universal assessment of MI cases, especially during lockdown, is essential to catch all variations in MI admissions and related fatal rates.

In our study, the first nationwide assessment of NSTEMI patients during Covid-19 pandemic, the reduction in admissions observed reached 40% as compared to the trends of the previous 5 years. This difference may be due to the greater social restrictions present in Italy at the time of the lockdown compared to other European countries. At the same time as the reduction in admissions for NSTEMI, there was a significant increase in in-hospital mortality. Multiple reasons have been hypotheses to explain this trend [7,8,21,22] such as reduction of air pollution and daily stressful lifestyle, or inefficiencies of the overloaded healthcare system. The main cause of the reduction in the number of hospitalizations for NSTEMI seems to be due to the patients' fear of going to hospital for Covid-19 infection, especially in the lockdown period, where social containment was mandatory in conjunction with the progression of the pandemic and the highest rate of mortality due to Covid-19 infection. On the other hand, the higher rate of in-hospital mortality of acute MI patients admitted during national lockdown is an interesting observation never completely explained. As the proportion of NSTEMI patients referred to PCI was not decreased during that period, unlike the rate of CABG, it could reflect an overall higher proportion of patients being at “high risk” usually referred to surgery, a concomitant time delay in management leading to late reperfusion [18,21], an underuse of revascularization specifically in Covid-19 patients, as documented in our analysis, or a direct Covid-19-related impact on fatality. Our study is the first to suggest a direct correlation between the increased mortality observed in NSTEMI patients during lockdown and Covid-19 infection. In fact, when patients with concomitant Covid-19 infection were excluded from the series, the short- and medium-term fatality rate was in trend with the previous 5 years of observation.

4.1. Limitations

There are several limitations of using an administrative health claims

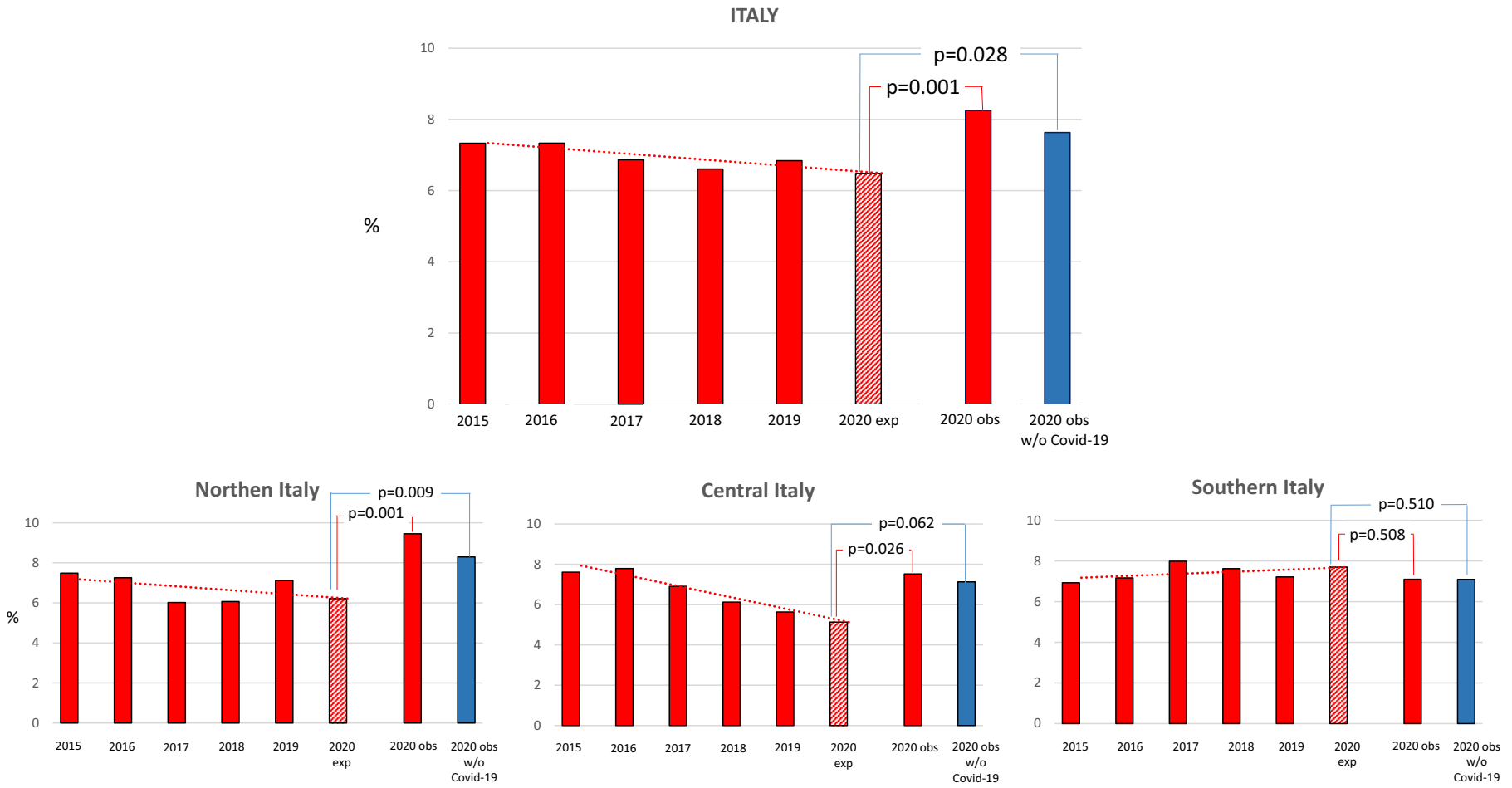

Fig. 2. Expected (exp.) and observed (obs.) mortality rate at 30 days (in the overall NSTEMI population and excluding those with Covid-19 infection) during the 2020 national outbreak and over the equivalent periods in the previous 5 years in Italy and by geographic regions.

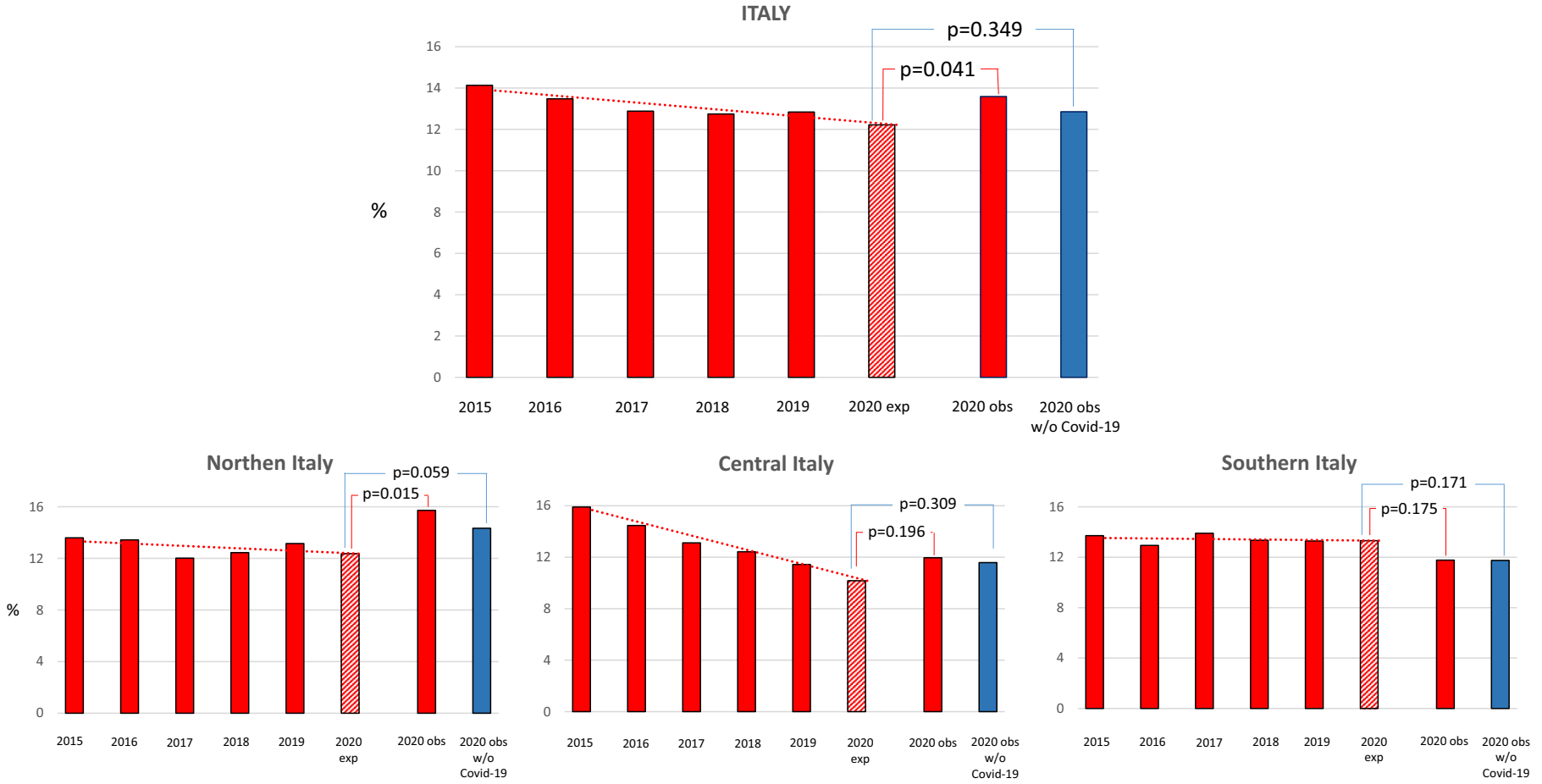

Fig. 3. Expected (exp.) and observed (obs.) mortality rate at 6 months (in the overall NSTEMI population and excluding those with Covid-19 infection) during the 2020 national outbreak and over the equivalent periods in the previous 5 years in Italy and by geographic regions.

database. One is the lack of specific clinical information may have affected the accuracy of the diagnosis, severity and risk stratification of NSTEMI. Indeed, some prognostic data, such as vital signs, instrumental parameters, time to reperfusion and procedural detail were not available. Another limitation is the deficiencies in the ICD-9 CM code descriptions to provide comprehensive data on in-hospital complications and cause of death. In this regard, it was not possible to completely rule out variables associated with Covid-19 infection that may have produced an uncontrolled bias in their association with mortality. Finally, we cannot determine the extent to which misclassification and coding errors may be present.

5. Conclusions

During the 2020 national outbreak in Italy the rate of NSTEMI admissions was markedly reduced, while the number of PCI was consistent with the 5-year expected trend. A concomitant diagnosis of Covid-19 infection significantly increased the mortality rate; indeed, after excluding NSTEMI patients with a diagnosis of Covid-19 the rate of observed 6-month mortality was in trend with previous 5 years.

Further studies are warranted to understand the mechanisms underlying the association between Covid-19 and mortality in the NSTEMI context.

Funding

None.

Author contributions

Conceptualization: De Luca, Seccareccia, Baglio Data curation and Formal analysis: Rosato and D'Errigo Writing - original draft: De Luca Writing - review and editing: all authors.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.11.008.

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