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Original Article

Gender differences in acute coronary syndromes patterns during the COVID-19 outbreak

Umberto Barbero[1], Cinzia Moncalvo[1], Daniela Trabattoni[2], Marco Pavani[1], Gisella Rita Amoroso[1], Pier Paolo Bocchino[3], Alessandra Truffa Giachet[4], Andrea Saglietto[3], Silvia Monticone[5], Gioel Gabrio Secco[6], Gianluca Campo[7,8], Roberto Verardi[3,9], Mario Iannaccone[10], Marcello Galvani[11], Fabrizio Ugo[12], Vincenzo Infantino[13], Luca Olivotti[14], Marco Mennuni[15], Matteo Vercellino[6], Sebastiano Gili[2], Ottavio Zucchetti[7], Gianni Casella[9], Massimo Giammaria[16], Michele De Benedictis[1], Paolo Tolomeo[7], Baldassarre Doronzo[1], Walter Grosso Marra[17], Andrea Rognoni[15], Antonio Montefusco[3], Giuseppe Patti[15], Massimo Mancone[18], Gaetano Maria De Ferrari[3], Fabrizio D'Ascenzo[3]

[1]Ospedale Civile SS. Annunziata, Savigliano, Italy; [2]Department of Cardiovascular Sciences, IRCCS Centro Cardiologico Monzino, University of Milan, Italy; [3]Division of Cardiology, A.O.U Città della Salute e della Scienza di Torino, Turin, Italy; [4]Division of Cardiology, Ospedale "Cardinal Massaia" Asti, Italy; [5]Division of Internal Medicine 4 and Hypertension Unit, Department of Medical Sciences, University of Turin, Torino, Italy; [6]Department of Cardiology, Interventional Cardiology and Cardiac Surgery Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [7]Cardiology Unit, Azienda Ospedaliera Universitaria di Ferrara, Ferrara, Italy; [8]Maria Cecilia Hospital, GVM Care & Research, Cotignola, Ravenna Italy; [9]Department of Cardiology, Maggiore Hospital Carlo Alberto Pizzardi, Bologna, Italy; [10]Division of Cardiology, San Giovanni Bosco Hospital, Turin, Italy; [11]U.O.C. Cardiologia, Dipartimento Cardiovascolare AUSL Romagna, Ospedale Morgagni, Forlì, e Unità di Ricerca Cardiovascolare, Fondazione Cardiologica Sacco, Forlì, Italy; [12]Division of Cardiology, Presidio Ospedaliero Sant'Andrea di Vercelli, Vercelli, Italy; [13]Division of Cardiology, Ospedale di Ciriè, Italy; [14]Division of Cardiology, Ospedale Santa Corona, Pietra Ligure, Italy; [15]Coronary Care Unit and Catheterization laboratory, A.O.U. Maggiore della Carità, Novara, Italy; [16]Department of Cardiology, Maria Vittoria Hospital, Turin, Italy; [17]Division of Cardiology, Ivrea's Hospital, Ivrea, Italy; [18]Department of Cardiovascular, Respiratory, Nephrology, Anesthesiology and Geriatric Sciences, Sapienza University of Rome, Rome, Italy

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Abstract: Background: Mortality from acute coronary syndromes (ACS) is strictly related to early management. As female patients usually experience longer delays before diagnosis and treatment, we assessed whether women were more affected by the dramatic drop in hospital admissions for ACS during the Covid-19 pandemic. Methods: We performed a retrospective analysis of clinical and angiographic characteristics of consecutive patients who were admitted for ACS at 15 hospitals in Northern Italy comparing men and women data. The study period was defined as the time between the first confirmed case of Covid-19 in Italy (February 20, 2020) and March 31, 2020. We compared hospitalization rates between the study period and two control periods: the corresponding period during the previous year (February 20 to March 31, 2019) and the earlier period during the same year (January 1 to February 19, 2020). Incidence rate ratios comparing the study period with each of the control periods were calculated with the use of Poisson regression. Results: Of the 547 patients who were hospitalized for ACS during the study period, only 127 (23%) were females, accounting for a mean of 3.1 admissions per day, while ACS hospitalized males were 420, with a mean of 10.2 admissions per day. There was a significant decrease driven by a similar reduction in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) diagnosis in both sexes compared to the control periods. A trend toward a greater reduction in admitted females was shown in the intra-year control period (46% admission reduction in females vs 37% in males, with females accounting for 26% of ACS, P=0.10) and a significant reduction when compared to the previous year control period (40% admission reduction in females vs 23% in males, with females accounting for 28% of ACS, P=0.03), mainly related to Unstable Angina diagnosis. Conclusion: The Covid-19 pandemic period closed the gap between men and women in ACS, with similar rates of reduction of hospitalized STEMI and NSTEMI and a trend toward greater reduction in UA admission among women. Furthermore, many typical differences between males and females regarding ischemic heart disease presentations and vessel distribution were leveled.

Keywords: Gender, acute coronary syndromes, COVID-19

Introduction

In the Western world, acute coronary syndrome (ACS) and myocardial infarction (MI) mortality has substantially decreased during the last decades [1]. During the Covid-19 pandemic and the associated lockdown period, the pattern of hospital admissions for conditions other than Covid-19 has been deeply influenced, with a tragic 40% average reduction in MI admissions [2-5]. The pandemic may have reduced the possibility of screening for atypical or short-term symptoms, this behavior potentially leading to an increase in cardiovascular mortality and late complications, especially for women for whom late admission and longer time from symptoms onset were already more frequent before the pandemic [6, 7].

The aim of the present study was to analyze differences between men and women hospitalized for ACS during the lockdown in order to provide results that could help in projecting more focused preventive and therapeutic actions in the next months.

Material and methods

We conducted a multicenter, observational, retrospective analysis of clinical and angiographic characteristics of consecutive patients who were admitted for ACS at 15 hospitals in Northern Italy.

All the hospitals were hubs of local networks for treatment involving primary percutaneous coronary intervention (PCI). The study period was defined as the time between the first confirmed case of Covid-19 in Italy (February 20, 2020) and March 31, 2020.

We compared hospitalization rates between the study period and two control periods: the corresponding period during the previous year (February 20 to March 31, 2019) and an earlier period during the same year (January 1 to February 19, 2020). The primary outcome was the overall rate of hospital admissions for ACS in men and women. Epidemiological data were anonymously extracted from each hospital's electronic database and checked for accuracy by study investigators. Inclusion criteria were: adult patients (≥ 18 years old); ACS admission, with diagnosis confirmed at hospital discharge. Exclusion criteria: patients died before hospital arrival.

Ethic statement: 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.

Statistical analysis

Categorical variables are presented as absolute numbers, percentages, and risk ratio (RR) with 95% confidence interval (95% CI), and compared by the chi-square test. Continuous variables are presented as mean and standard deviation (SD) and compared by the Student's t-test. Incidence rates (IR) for the primary outcome (ACS-related hospitalizations) were calculated by dividing the number of cumulative events by the number of days for each time period. Incidence-rate ratios (IRR) comparing the case period to each of the control periods were calculated using Poisson regression to model the number of ACS-related hospitalizations per day. Statistical analysis was performed using SPSS 24 (IBM Corporation, Armonk, NY, USA) and R Studio version 3.3.0.

Results

A total of 2202 ACS patients were included in the study (547 during the study period, 899 during the intra-year control period, and 756 during the inter-year control period).

From February 20, 2020, to March 31, 2020, a total of 127 hospital admissions for ACS in female patients were observed, accounting for a mean of 3.1 admissions/day, while ACS hospitalized males were 420, with a mean of 10.2 admissions/day. Compared to the intra-year and the inter-year control periods, case-period females experienced less ST-segment elevation myocardial infarction (STEMI) (IRR 0.66; 95% CI 0.47-0.91 and IRR 0.63; 95% CI 0.44-0.87, respectively) and non-ST-segment elevation myocardial infarction (NSTEMI) (IRR 0.57; 95% CI 0.39-0.81 and IRR 0.51; 95% CI 0.35-0.73, respectively) but no difference regarding unstable angina (UA) (IRR 1.23; 95% CI 0.78-1.42 and IRR 0.64; 95% CI 0.37-1.21, respectively) (**Table 1**). Similarly, compared to the intra-year and the inter-year control periods, case-period male patients faced

Table 1. Incidence rates and incidence-rate ratios of admissions for ACS in females and in males during the study period (February 20 - March 31, 2020) as compared with intra-year (January 1 - February 19, 2020) and inter-year (February 20 - March 31, 2019) control periods

Females (n=577)	Study period (Feb 20 - Mar 31, 2020)	Intra-year control period (Jan 1 - Feb 19, 2020)	Inter-year control period (Feb 19 - March 31, 2019)	Males (n=1625)	Study period (Feb 20 - Mar 31, 2020)	Intra-year control period (Jan 1 - Feb 19, 2020)	Inter-year control period (Feb 19 - March 31, 2019)
Overall				Overall			
No. of events per day	3.1	4.7	5.3	No. of events per day	10.2	13.2	13.6
IRR (95% CI)		0.65 (0.53-0.81)	0.58 (0.47-0.72)	IRR (95% CI)		0.77 (0.68-0.87)	0.76 (0.68-0.85)
P value		<0.001	<0.001	*P* value		<0.001	<0.001
STEMI				STEMI			
No. of events per day	1.4	2.1	2.2	No. of events per day	4.6	5.7	5.7
IRR (95% CI)		0.66 (0.47-0.91)	0.63 (0.45-0.87)	IRR (95% CI)		0.81 (0.67-0.98)	0.79 (0.67-0.93)
NSTEMI				NSTEMI			
No. of events per day	1.1	1.9	2.1	No. of events per day	3.1	5.2	5.6
IRR (95% CI)		0.57 (0.39-0.81)	0.51 (0.35-0.73)	IRR (95% CI)		0.61 (0.49-0.75)	0.72 (0.59-0.86)
Unstable angina				Unstable angina			
No. of events per day	0.6	0.7	1.0	No. of events per day	2.4	2.4	2.4
IRR (95% CI)		1.23 (0.78-1.42)	0.64 (0.37-1.21)	IRR (95% CI)		1.04 (0.80-1.36)	0.79 (0.61-1.01)

less STEMI (IRR: 0.81; 95% CI 0.67-0.98 and IRR: 0.79; 95% CI 0.67-0.93, respectively) and NSTEMI (IRR: 0.81; 95% CI 0.67-0.98 and IRR: 0.79; 95% CI 0.67-0.93, respectively) but no difference in UA rates (IRR: 1.04; 95% CI 0.80-1.36 and IRR: 0.79; 95% CI 0.61-1.01, respectively).

Table 2 shows the demographic and clinical data of the enrolled patients divided by sex for each of the investigated periods. Females accounted for 577 (26.2%) of all the included patients. 127 patients (23%) were female in the case period, with a trend toward reduction compared to the intra-year control period (237 women, 26%, P=0.07) and a significant reduction when compared to the inter-year control period (28%, P=0.03). Mean female age was 73 ± 11 years old, while mean male age was 67 ± 11 years old (P<0.001). Females were older than males in all the study periods. Angina was the leading admission symptom for both sexes in all the three explored periods, whereas dyspnea was more frequent in females than in males during the study period (19.7% vs 10.7%, P=0.008). Atypical presentation occurred more frequently in females than in males in the intra-year control period (9.3% vs 4.7%, P=0.01). The largest percentage of patients (n=903, 43.5%) was admitted with STEMI, which also was the diagnosis with a greater percentage reduction in women than men in bot periods (**Figure 1**) despite no absolute statistical difference (P=0.39). One-vessel disease was the most common angiographic finding (41.0%) and no significant differences were noted between sexes except for a more frequent involvement of the left main in males than females during the case period (10.5% vs 4.7%, P=0.049).

Discussion

From this observational cohort of patients presenting with ACS during the Covid-19 pandemic in Italy, some main observations must be highlighted: the number of patients admitted to our hospital because of ACS dramatically reduced during the lockdown, this trend affecting both men and women and all kind of ACS; women with ACS were older than men; atypical symptoms (especially dyspnea) increased among women during the pandemic but, conversely, many typically gender-related differences attenuated.

ACS events are well known to increase mortality and morbidity: they can lead to heart muscle damage which in turn may evolve into heart failure, induce arrhythmic events and even lead to sudden cardiac death [8]. To reduce such complications, efforts have been made on increasing people knowledge of cardiac symptoms and on the importance of shortening delay times, since a clear association between longer intervals from symptoms onset to treatment and a worse prognosis has been found [9, 10].

Indeed, many international studies showed longer delays in women presenting with ACS and also that they are usually older with a greater burden of co-morbidities [11-13] and less likely than men to receive guideline-mandated therapies at every level of risk [11].

De Rosa et al. recently described a greater STEMI rate decline for women than men (41.2% vs 17.8%), while NSTEMI showed a similar rate between the two sexes (66.7% vs 65.4%) and UA rate was not reported [2]. In our study the only statistically significant difference among sexes is between the study period the inter-year control period, driven by the fact that UA trended higher in men than women and by a lower reduction in percentage of STEMI among men. This diversity may be explained by the different time frames analyzed (1 week vs 6 weeks) between the two studies.

The delays in seeking medical advice among women have previously been ascribed to sex differences related to social, environmental and community factors in the way men and women experience cardiac symptoms, to the common misjudgment that heart disease is a 'man's disease' and to the suggestion that women prioritize their role as the family primary caregiver above their own health needs [8, 14]. An older study found that 'not wanting to trouble anyone' was a factor associated with prolonged delay in women, but not in men [7] and this factor indeed seems to be absent in more gender-equal countries [10]. During the Covid-19 outbreak, however, the reduction in MI hospital admissions was consistent between men and women, while we also saw a significant increase in women presenting with dyspnea, thus allegedly inducing diagnostic and treatment delays. What really transpires from our data however, is quite a flattening of

Table 2. Characteristics of patients admitted for ACS during the case period (February 20 - March 31, 2020) as compared with intra-year (January 1 - February 19, 2020) and inter-year control periods (February 20 - March 31, 2019) divided by sex

Characteristics	Case period (Feb 20 - Mar 31, 2020)			Intra-year control period (Jan 1 - Feb 19, 2020)			Inter-year control period (Feb 20 - Mar 31, 2019)		
	Male (n=420)	Female (n=127)	*P*-value	Male (n=662)	Female (n=237)	*P*-value	Male (n=543)	Female (n=213)	*P*-value
Age-yr	66.7 ± 11.9	72.7 ± 11.9	*0.000*	67.7 ± 12.1	72.3 ± 11.2	*0.000*	67.4 ± 11.6	72.6 ± 11.9	*0.000*
Age ≥ 65 yo	244 (58.1%)	90 (70.9%)	*0.010*	400 (60.4%)	184 (77.6%)	*0.000*	303 (55.8%)	159 (74.6%)	*0.000*
Known CAD	95 (22.6%)	17 (13.4%)	*0.024*	152 (23.0%)	38 (16.0%)	*0.025*	47 (8.7%)	41 (19.2%)	*0.000*
COPD	39 (9.3%)	8 (6.3%)	0.292	62 (9.4%)	21 (8.9%)	0.818	126 (23.2%)	26 (12.2%)	*0.001*
Residence-City	151 (36.0%)	46 (36.2%)	0.956	241 (36.4%)	87 (36.7%)	0.934	194 (35.7%)	82 (38.5%)	0.477
Presentation Symptom									
Angina	313 (74.5%)	86 (67.7%)	0.130	458 (69.2%)	155 (65.4%)	0.283	386 (71.1%)	153 (71.8%)	0.839
Dyspnea	45 (10.7%)	25 (19.7%)	*0.008*	91 (13.7%)	38 (16.0%)	0.389	53 (9.8%)	26 (12.2%)	0.323
Atypical chest pain	22 (5.2%)	8 (6.3%)	0.645	31 (4.7%)	22 (9.3%)	*0.010*	38 (7.0%)	24 (11.3%)	0.054
Major arrythmia or CA	12 (2.9%)	2 (1.6%)	0.423	22 (3.3%)	2 (0.8%)	*0.042*	20 (3.7%)	3 (1.4%)	0.101
ACS type									
STEMI	190 (45.2%)	58 (45.7%)	0.932	284 (42.9%)	107 (45.1%)	0.549	228 (42.0%)	90 (42.3%)	0.947
NSTEMI	129 (30.7%)	44 (34.6%)	0.404	260 (30.3%)	94 (39.7%)	0.917	221 (40.7%)	84 (39.4%)	0.750
UA	101 (24.0%)	25 (19.7%)	0.306	118 (17.8%)	36 (15.2%)	0.356	94 (17.3%)	39 (18.3%)	0.746
Angiographic findings									
Left main disease	44 (10.5%)	6 (4.7%)	*0.049*	59 (8.9%)	22 (9.3%)	0.864	48 (8.8%)	22 (10.3%)	0.525
1-vessel disease	181 (43.1%)	65 (51.2%)	0.108	278 (42.0%)	95 (40.1%)	0.609	193 (35.5%)	91 (42.7%)	0.067
2-vessel disease	116 (27.6%)	29 (22.8%)	0.284	190 (28.7%)	59 (24.9%)	0.261	163 (30.0%)	49 (23.0%)	0.053
3-vessel disease	84 (20.0%)	20 (15.7%)	0.285	132 (19.9%)	37 (15.6%)	0.143	127 (23.4%)	40 (18.8%)	0.169
MINOCA	8 (1.9%)	9 (7.1%)	*0.003*	14 (2.1%)	22 (9.3%)	*0.000*	24 (4.4%)	25 (11.7%)	*0.000*

ACS: acute cardiovascular syndrome; CA: cardiac arrest; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; MINOCA: myocardial infarction with non-obstructive coronary arteries; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; UA: unstable angina. CA was defined as ventricular fibrillation, pulseless electrical activity, asystole. Major arrythmia was defined as sustained ventricular tachycardia or life-threatening atrioventricular block leading to urgent coronary angiography.

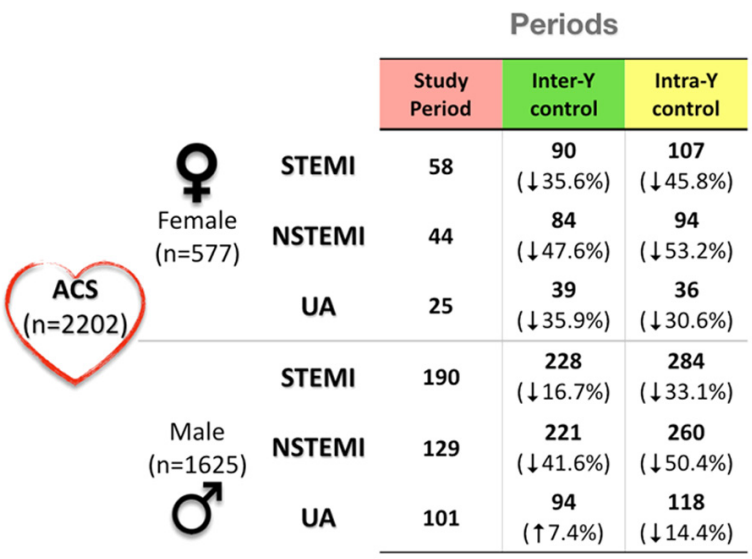

Figure 1. (GRAPHICAL ABSTRACT): Numbers and percentages of ACS (divided in STEMI, NSTEMI and unstable angina) compared between study periods and between genders. ACS: acute cardiovascular syndrome; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; UA: unstable angina.

the differences traditionally observed between men and women in ACS registries: the number of MINOCA among women in our registry was far distant from the nearly 60% of symptomatic women previously reported [15]. Furthermore, disease distribution into the coronary vessel does not show any particular difference apart for a more common left main involvement in men.

In the landmark 2010 Institute of Medicine (IOM) publication "Women's Health Research Progress, Pitfalls, and Promise" [16] women's health was defined by two aspects: on one side the abovementioned gender-related differences; on the other, sex differences due to biological factors. But instead of being simply "protected" by estrogens as traditionally thought, a gender-specific analysis from the INTERHEART study [17] found that several risk factors including diabetes mellitus (DM) are more potent in women than men, and many studies expanded these results [18-20].

Given all that, the fact women experienced their first myocardial infarction at an older age may appear counterintuitive, but is largely- and simply-explained by the higher risk factor levels in younger men compared to women. The women enrolled in our registry were significantly older than men but this difference was again lower than usually reported [9, 13, 17], and this fact might be explained by the greater lethality of Covid-19 in older patients and the fear of that may have prevented the older and atypically-symptomatic women to report their discomfort.

Finally, since coronary plaques show different pathophysiologic features between sexes [15] with women having a higher prevalence of plaque erosion and men more commonly plaque rupture [21], female patients present with fewer STEMI and more MINOCA. In our registry the percentage of women with MINOCA is much lower than usual, but still this diagnosis is strongly sex-related and consistent throughout the study periods. It is reasonable that these low numbers of MINOCA may be related to a further decrease of medical admissions of such patients, who usually have atypical symptoms.

In conclusion, the pandemic period reduced the gap between men and women in ACS: the extraordinary reduction in admission rates observed during the Covid-19 pandemic in Italy seems to have strongly affected women as men, with similar rates of reduction of hospitalized STEMI and NSTEMI and a trend toward greater reduction in UA admission among women. Indeed, the typical differences between males and females regarding ischemic heart disease presentations were flattened and clinical presentation and distribution of the atherosclerotic burden were overall similar between sexes.

Limits

The study results must be interpreted in the context of some limitations. First, this was an observational study; however, despite its limitations, the observational nature of this study could help extend our results to real-life patients. Moreover, this was a retrospective

study, thus carrying all concerning limitations. Furthermore, data collection during the intense months of the lockdown was challenging and some data may be missed despite every effort was made to avoid it; however, because of that, some potentially relevant variables were not registered. Finally, how these epidemiological changes and ACS under referral would affect cardiovascular morbidity and mortality in the next years has to be investigated with focused longer follow-up.

Disclosure of conflict of interest

None.

Address correspondence to: Umberto Barbero, Cardiology Department, "SS. Annunziata" Hospital, Savigliano (CN), Italy. Tel: +390172719046; E-mail: umberto.barbero@unito.it

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