European Review for Medical and Pharmacological Sciences 2023; 27: 3208-3217

COVID-19 pandemic on coronary artery and cerebrovascular diseases in Southern Spain: interrupted time series analysis

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Abstract. – OBJECTIVE: Healthcare systems have been put under intense pressure by the COVID-19 pandemic, although some studies have shown a decline in hospital admissions for cardiovascular and cerebrovascular diseases during the first and second wave of the pandemic. In addition, studies analyzing gender and procedural differences are scarce. The present study aimed to determine the impact of the pandemic on hospital admissions for acute myocardial infarction (AMI) and cerebrovascular disease (CVD) in Andalusia (Spain) and analyzed differences by gender and by percutaneous coronary interventions performed.

PATIENTS AND METHODS: An interrupted time series analysis of AMI and CVD hospital admissions in Andalusia (Spain) was carried out to measure the impact of the COVID-19 outbreak. AMI and CVD cases admitted daily in public hospitals of Andalusia between January 2018 and December 2020 were included.

RESULTS: During the pandemic, significant reductions in AMI [-19%; 95% confidence interval (CI): (-29%, -9%), $p<0.001$] and CVD [-17%; 95% CI: (-26%, -9%); $p<0.01$] in daily hospital admissions were observed. Differences were also produced according to the diagnosis (ST-Elevation Myocardial Infarction, Non-ST-Elevation Myocardial Infarction, other AMI and stroke), with a greater reduction in females for AMI and in males for CVD. Although there were more percutaneous coronary interventions during the pandemic, no significant reductions were observed.

CONCLUSIONS: A decline in AMI and CVD daily hospital admissions during the first and second wave of COVID-19 pandemic was noted. Gender differences were observed, but no clear impact was observed in percutaneous interventions.

Key Words:
Coronavirus Disease 2019, Acute coronary syndromes, Cerebrovascular disease, Gender, Percutaneous coronary interventions.

Introduction

In December 2019, the first case of pneumonia caused by the new coronavirus was detected. Subsequently, the World Health Organization (WHO) declared a global pandemic due to COVID-19, a disease caused by a severe acute respiratory syndrome associated with Coronavirus 2 (SARS-CoV-2)[1,2]. Since then, 571,192,618 people have contracted the disease worldwide, of whom 6,386,255 have died[3]. In Andalusia (Spain), the first confirmed case occurred on 26 February 2020. Since the start of the COVID-19 pandemic, 833,874 Andalusians have been diagnosed with COVID-19, of whom 11,361 have died[4].

Following an increase in the cumulative incidence (CI), a state of emergency was decreed in Spain on 14 March 2020 by Royal Decree

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463/2020, which was extended and modified by other Royal Decrees on several occasions and remained in force until 9 May 2021. During this period, different measures were applied to control the spread of SARS CoV-2. Measures were gradually phased out until the end of the state of emergency[4]. During the COVID-19 pandemic, several factors have influenced the detection of new cases of other diseases. Among these factors were the targeting of health care resources to stop the pandemic and patients' fear of being infected when attending emergency and primary care services[5]. These and other factors have influenced the decrease in the detection of new cases of other diseases, as well as in the treatment of already diagnosed chronic diseases[5-7].

Regarding cerebrovascular and cardiovascular diseases, specifically acute myocardial infarction (AMI), we do not know to what extent they may have been affected in Spain, or, more specifically in Andalusia. However, studies[8,9] have been conducted addressing the impact of the pandemic on the diagnosis of these diseases, such as the one conducted by Clodfelder et al[8] in four hospitals in Colorado (USA), which concluded that during the pandemic period from 19 March 2020 to 11 June 2020, emergency transport services for these diseases were used less frequently[8]. In other two hospitals in Colorado, a decrease in the number of emergency department visits and an increase in telehealth visits was observed[9].

In Andalusia, diseases of the circulatory system are the leading cause of death. Since the beginning of the pandemic, numbers have remained high: so much so that, during the year 2020, they continued to be the leading cause of death[10]. However, since hospital care for these patients may have been affected by the pandemic, an analysis of its potential effect is needed.

The autonomous community of Andalusia is located in Southern Spain. According to Eurostat data (2019), it has the highest population of the 19 autonomous communities in Spain, with 8,427,405 inhabitants. Andalusia covers an area of 87,268 km², which is equivalent to 17.3% of the Spanish territory, making it comparable to many European countries both in terms of surface area and internal complexity. Fifty-two public hospitals provide healthcare coverage in the region (6 are considered as regional hospitals, 9 special hospitals, 17 district hospitals and the others are high-resolution hospitals).

The main objective and novelty of this study is therefore to determine the impact of the pandemic on hospital admissions of patients in Andalusia with AMI and cerebrovascular disease, both of which are diseases of the circulatory system.

Patients and Methods

An observational, interrupted time series study was conducted to analyze the impact of the COVID-19 pandemic on hospital admissions of patients with AMI and/or cerebrovascular disease (CVD). The patients included in this study were those seen for AMI and CVD between January 1, 2018, and December 31, 2020, in the first wave (15 March - 15 May) and the second wave (9 October - 11 December) of the COVID-19 pandemic in Andalusia and aged between 20 and 75 years. The criteria adopted to diagnose these pathologies are those included in the International Classification of Diseases 10th revision (ICD-10) (**Supplementary File 1**).

Statistical Analysis

Data on AMI and CVD mortality for 2018, 2019, and 2020 were obtained from the Spanish National Institute of Statistics. We first conducted descriptive analyses for the relevant variables, calculating frequencies and means and standard deviations. Comparisons between the two groups (before and after the first case) for continuous variables were assessed using Mann-Whitney U tests. Categorical data were compared using χ^2 or Kruskal-Wallis tests, as appropriate. The "CausalImpact" package (version 1.2.7) for the R statistical software[11] was used to perform the interrupted time series analysis, with a Bayesian structural time-series model[12]. This package came out in 2015 and allows us to estimate the causal influence of a specific intervention, located within a temporal space. The type of statistical analysis used was the Markov chain Monte Carlo (MCMC)[13]. To develop the statistics, a time series is firstly required, which in the present study, is made up of the observations made on hospital admissions registered in the autonomous community of Andalusia, from 2018 to 2020, both years included. In addition, an event or intervention at a known point in time is required, which in our case is the first positive case of SARS-CoV-2 detected; this event occurred on 26 February 2020. The context produced by the absence of the event that interrupts the series (or the expected data), is known as the "counterfactual" model. This expected trend is vital to compare the impact of

the disrupting event. As a sensitivity analysis, control variables such as wind speed and atmospheric pressure from a meteorological station in Southern Spain (which provided all the necessary data) were selected as covariates. Both control variables showed stationarity (using augmented Dickey-Fuller test). All *p*-values were bilateral and $p<0.05$ was considered statistically significant.

Results

Table I shows that, during the study period, 21,226 patients were admitted to Andalusian hospitals diagnosed with acute myocardial infarction, with a mean age of 60.45 (SD 9.6) years. 24,097 patients were also admitted due to a cerebrovascular disease, with a mean age of 62.04 years. 77.2 % of the patients admitted with AMI were men and 22.8 % were women. 55.8 % were diagnosed with STEMI and 43.1 % had NSTEMI; the remaining 1.1% were patients diagnosed with unspecified AMI and other types of AMI. 3.8% of the total number of patients diagnosed with AMI died in hospital. The differences between before- and during-outbreak admission rates were found for STEMI, NSTEMI and other AMI, showing a pre-pandemic higher percentage. Surprisingly, the percentage of percutaneous interventions was higher during the pandemic ($p=0.02$).

For CVD, 65% of the patients were men and 35% women. Among the cerebrovascular diseases, cerebral infarction was the most frequently diagnosed (64.4%). 9.4 % died in hospital, and this rate rose during the pandemic (10.1 *vs.* 9.1; $p=0.01$).

Impact Analysis for AMI Admissions

Figure 1 shows three graphs showing the decrease in admissions for AMI after the first confirmed case in Andalusia of SARS CoV-2. The downward trend is clearly visible in the lower part of Figure 1.

Pre-pandemic daily AMI admissions ranged from 5 to 39, with a median daily admission of 20. During the COVID-19 pandemic, the range of daily admissions varied from 0 to 32, with a median daily admission of 18. With no pandemic, one would expect a mean daily admission of 21.53 [95% CI: (19.46, 23.72)]. The effect of the COVID-19 pandemic was a decrease of 4.01 admissions per day [95% CI: (-6.20, -1.94)]. In relative terms, AMI admissions showed a decrease of 16% [95% CI: (-29%, -9%)]. The causal effect of the pandemic on AMI admissions is considered statistically significant ($p<0.01$).

When analyzed by gender, the reduction of hospital admissions during the outbreak was significantly higher in women [-20.67% (-34.78%, -5.70%) *vs.* -17.64% (-28.07%, -7.10%); $p<0.001$].

Regarding STEMI, the median daily hospital admissions observed was 11, although during the pandemic, the median was 9. According to the predictive model, if there had been no

Table I. General characteristics of the study population. Figures before and during the COVID-19 pandemic.

Variable			COVID-19 outbreak				
Acute Myocardial Infarction (N=21,226)			**Before (15,791)**		**During (5,435)**		***p*-value**
Variable	**n**	**%**	**N**	**%**	**n**	**%**	
Men†	16,381	77.2	12,194	77.2	4,187	77.0	0.77
Women	4,840	22.8	3593	22.8	1,247	23.0	
Mortality in Public Hospitals	810	3.8	615	3.9	195	3.6	0.30
Percutaneous coronary intervention	890	4.1	633	4.0	257	4.7	**0.02**
STEMI	11,849	55.8	8,883	56.3	2,966	54.6	**0.03**
NSTEMI	9,154	43.1	6,874	43.5	2,280	42.0	**0.04**
Other AMI	223	1.1	34	0.2	189	3.4	**<0.01**
Cerebrovascular Disease (N=24,097)			**Before (17,905)**		**During (6,192)**		***p*-value**
Variable	**n**	**%**	**n**	**%**	**n**	**%**	
Men†	15,662	65	11,649	65.1	4,013	64.8	0.73
Women†	8,430	35	6,253	34.9	2,177	35.2	
Mortality in Public Hospitals	2,258	9.4	1,630	9.1	628	10.1	**0.01**
Cerebral stroke	15,529	64.4	11,511	64.3	4,018	64.9	0.39
Other CVD	8,568	35.6	6,394	35.7	2,174	35.1	

ST Elevation Myocardial Infarction (STEMI), Non-ST Elevation Myocardial Infarction (NSTEMI), Acute Myocardial Infarction (AMI), Cerebrovascular Disease (CVD). †Gender of 5 subjects not known.

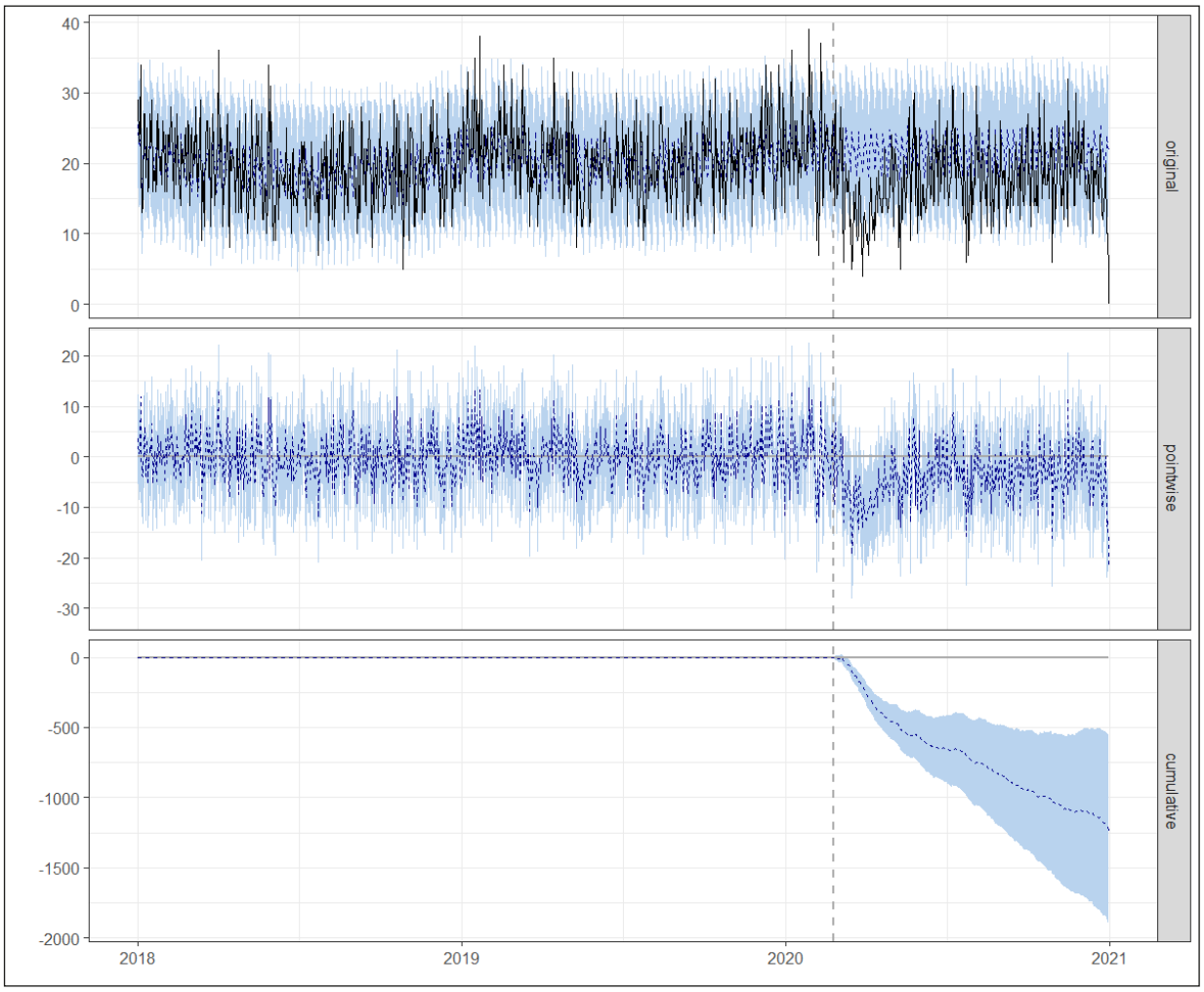

Figure 1. Original and predicted number of daily admissions for AMI between January 2018 and December 2020 in public hospitals in Andalusia. Figure 1 shows an interrupted time series for AMI with three graphs: The graph labelled "original" shows the stationary pattern of AMI admissions and the expected values after the turning point. These values are shown by a dotted line. The "pointwise" graph shows the difference between observed and expected values. Finally, the "cumulative" graph shows the trend after the turning point.

pandemic, the mean number of admissions would have been 11.76 [95% CI: (10.48, 13.09)]. The effect of the pandemic was equivalent to a decrease in daily hospital admissions of 2.20 [95% CI: (-3.52, -0.92)]. In relative terms, the statistically significative decrease was 19% [95% CI: (-30%, -8%)]. Specifically, there was a high reduction in hospital admissions of women [-21.75% (-42.27%, -0.80) *vs.* -17.78% (-29.46%, -5.40%); $p<0.001$].

For people diagnosed with NSTEMI, the median daily hospital admissions prior to the pandemic were 8, while, during the pandemic, the median daily admissions were 7. If the effect of the pandemic is removed, the predictive model yields a mean daily admission of 9.44 [95% CI: (8.16, 10.50)]. In this case, the pandemic effect is equivalent to a decrease in daily admissions of 2.09 [95% CI: (-3.15, -0.82)]. In relative terms, NSTEMI admissions decreased during the outbreak by 21% [95% CI: (-34%, -9%)]. For women, there were greater differences in the reduction of NSTEMI hospital admissions [-25.93% (-46.29%, -3.97%) *vs.* -19.88 (-33.47%, -5.25%); $p<0.001$].

Regarding percutaneous coronary interventions, although it may look as though the intervention exerted a negative effect on the response variable when considering the intervention period as a whole, this effect was not statistically significant ($p=0.22$).

Impact Analysis for CVD Admissions

Figure 2 shows three graphs indicating the decrease in admissions for CVD after the confir-

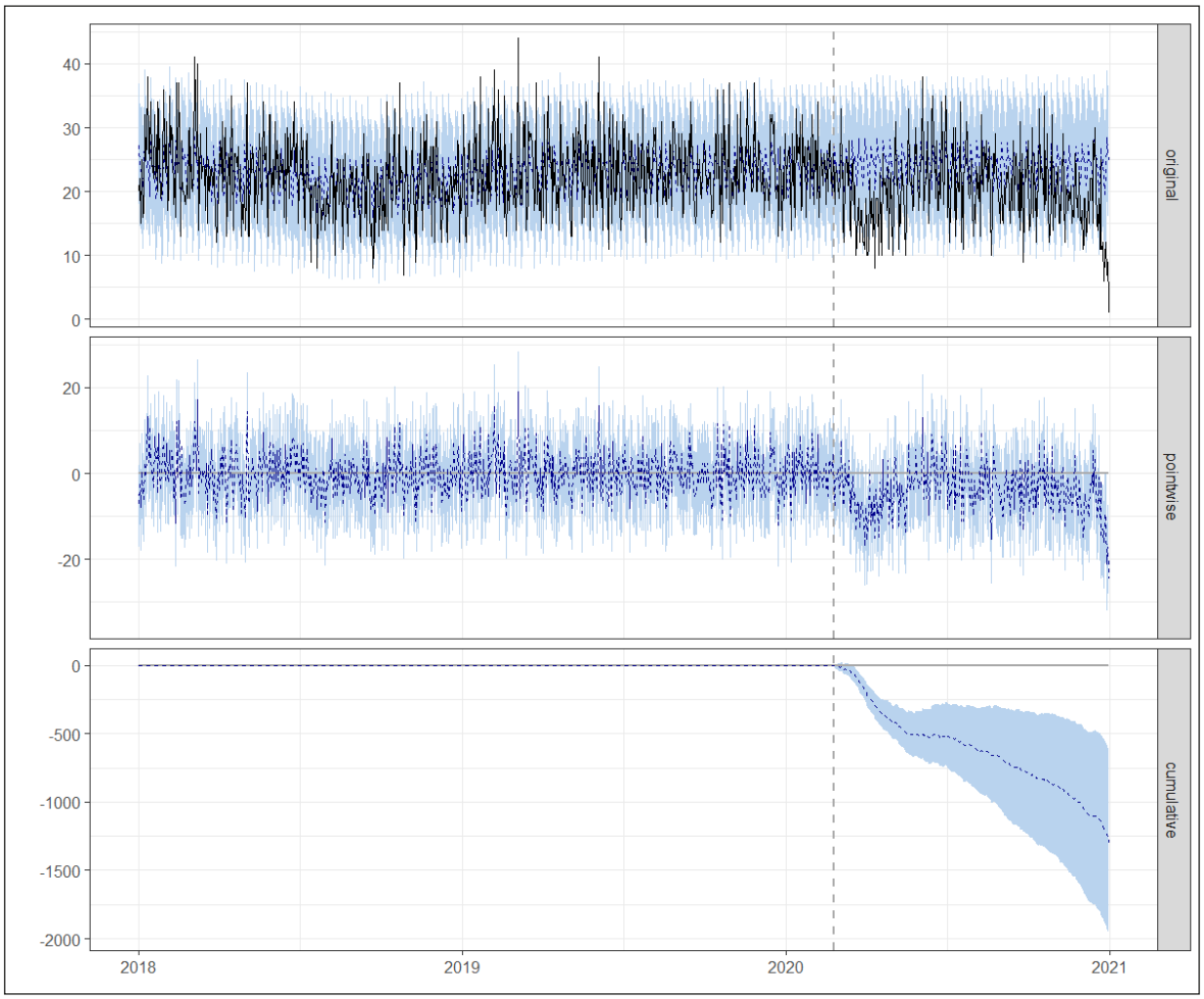

Figure 2. Original and predicted number of daily admissions for CVD between January 2018 and December 2020 in public hospitals in Andalusia. Figure 2 shows an interrupted time series for CVD with three graphs: the graph labelled "original" shows the stationary pattern of CVD admissions and the expected values after the turning point. These values are shown by a dotted line. The "pointwise" graph shows the difference between observed and expected values. Finally, the "cumulative" graph shows the trend after the turning point.

mation of the first case following SARS CoV-2. The downward trend is visible in the lower area.

The range of daily admissions for CVD during the pre-pandemic period was between 7 and 44, with a median of 22 admissions per day. During the pandemic, hospital admissions ranged from 1 to 38, with a median daily admission of 20. If the impact of the pandemic were not considered, the expected mean daily admissions would be 24.15 [95% CI: (22.07, 26.36)]. The effect of the pandemic on CVD admissions translates into a decrease of 4.18 [95% CI: (-6.39, -2.10)]. In relative terms, CVD admissions decreased by 17% [95% CI: (-26%, -9%)]; $p<0.01$. There was a greater reduction in hospital admission rates for men than for women [-18.18% (-27.81%, -8.42%) *vs.* -15.14% (-28.10%, -1.83%); $p<0.001$].

Specifically, the median daily hospital admissions associated with cerebral stroke for the pre-pandemic period were 15. According to the Bayesian model, without the pandemic effect, the mean should be 11.76 [95% CI: (14.07, 16.84)]. The pandemic effect has led to a decrease in daily admissions of 2.50 [95% CI: (-3.89, -1.12)] or an equivalent of 19% [95% CI: (-25%, -7%)], and this effect was statistically significant ($p<0.01$). Significantly higher percentages were found in men than in women [-16.79% (-27.26%, -6.63%) *vs.* -14.93% (-31.18%, 1.02%); $p<0.001$].

Discussion

These results highlight the existence of a statistically significant decrease in hospital visits by patients with AMI and CVD after the COVID-19 outbreak in Andalusia (Spain). A similar decrease was found for patients with STEMI and NSTEMI and in cerebral infarction.

The significant decrease in the trend of hospital admissions for AMI, STEMI and NSTEMI is comparable with that detected in other international time series of cardiovascular diseases in European and Asian countries[14-18]. The decrease in the number of admissions for cerebrovascular diseases (CVD and STROKE) is also in line with other studies[19-26]. However, the previous works only considered the first wave of the pandemic, while the present study has studied a broader time period, including the first and second waves. Also, in contrast to published international time series based on patient discharge databases[19] or private insurance databases[22], the present study is based on data from the Andalusian public system on hospital admissions; the benefit of having a public registration system for admissions is that there is less possibility of omissions than in the cases described above.

Although the causes of the decline in hospital admissions vary, the authors highlight two in particular. The first is generated by the patients' reluctance to use the health services for fear of contracting COVID-19. Some studies[19,22] relate this phenomenon specifically to patients with cerebrovascular disease, namely stroke, stroke-related illness and stroke-related death. The second cause could be related to the social isolation of individuals caused by the lockdown measures. This could result in patients with unnoticed AMI and CVD suffering events[19,24].

Although there is a degree of controversy, there is evidence that, during COVID pandemic, the time taken between calling for help and receiving it was significantly longer, with patients receiving either delayed or late treatment[27,28]. In addition, several studies[21-23] show that the decrease in hospital admissions does not correlate with waiting times for treatment and the percentage of patients treated for CVD. If we consider this aspect for the cardiovascular diseases analyzed in this study, there are several works that link patients' fear of contracting COVID-19 with a decrease in patient admissions[14-16]. Specifically, some articles describe a fall in the treatment of patients with STEMI[14] and in the length of hospital stay of patients with STEMI[16]. The present work presents statistically significant results, showing a decrease in hospital admissions of patients not only with STEMI, but also with NSTEMI and other cardiovascular diseases. The reduction in the different types of cardiovascular disease reinforces the hypothesis of a decrease in the number of hospital admissions due to the pandemic. In non-vascular pathologies, such as schizophrenia, a decrease in hospital admissions has also been observed since the beginning of the pandemic[29].

On the other hand, most studies[30,31] that analyze the decline in hospital admissions make no gender distinction. To the best of our knowledge, the study by Barbero et al[30] is one of the few papers that looks specifically into this area. These authors observed a reduction in hospitalized STEMI and NSTEMI patients, with a greater reduction in women, specifically in cases of unstable angina. Our findings are along the same lines, with significantly greater reductions in women in all AMI cases (STEMI, NSTEMI and other AMI). Several authors[30,31] have argued that the reduction may be due to cultural, social, and environmental differences between women and men. In addition, it has been suggested that the symptoms considered to be associated with AMI are specific to men and not to women, so there may be further under-reporting[30-31]. In fact, to support the above arguments, the reduction was significantly greater in men for the other pathology studied in this work (cerebrovascular disease). On the other hand, no differences were found for percutaneous interventions: although it was not significant, a higher percentage of these interventions was observed during the pandemic. To our knowledge, this important finding has not been considered by any other study. In fact, most studies[32] report a greater reduction for percutaneous interventions during the pandemic.

Last but not least, in the present study, data on mortality from AMI and CVD were consulted, in order to find out whether the decrease in hospital admissions of these patients was really caused by any of the factors mentioned above or by the fact that the incidence of these diseases decreased during that period. The data obtained by the Spanish National Statistics Institute (INE) show that total mortality did not vary significantly between 2019 and 2020. These data are in agreement with those offered in other studies[14,21], in which pathologies such as stroke and heart failure are assessed. In fact, data regarding the place of death for AMI and CVD provided by the INE[11] show an

increase in mortality at home in 2020 for the two pathologies studied, compared to 2019, as well as a decrease in hospital mortality in 2020 for these pathologies, compared to 2019[33]. Therefore, such data suggests that the decrease in hospital admissions was not due to a decrease in mortality.

Limitations

Finally, several limitations must be considered in the present work. Firstly, although the data provided belong to a public system, in which all hospital admissions to Andalusian public hospitals are registered, and which the majority of the population attends, we must also take into account the fact that patients attending private hospitals have not been included. Secondly, our data did not include the onset time of these pathologies; therefore, the time which elapsed from symptom onset to hospital admission was not analyzed in detail. Thirdly, our research only included cases admitted to hospital and not those who were treated at home and did not require hospital admission. However, the mortality analysis, although obtained at a national level and not specifically for the Andalusian autonomous community, allows us to conclude that these data are not overestimated. Despite this, the interrupted time series approach used in our study provides clear evidence of the impact of the COVID-19 pandemic on cardiovascular and cerebrovascular pathology. Finally, COVID-19 is still present in society and more waves have occurred in later periods. However, due to the relaxation of restrictions and the perception that the disease, although more contagious, is becoming less virulent, the reduction in hospital admissions may now be less notable.

Conclusions

The COVID-19 pandemic led to a statistically significant reduction in hospital admissions due to AMI and CVD in general, and particularly for STEMI, NSTEMI and stroke in the Andalusian population. Our analysis of a large national database has shown that the reduction in hospital admissions was greater for AMI than for CVD, specifically in NSTEMI cases. Moreover, the analysis by gender showed that there was a greater reduction in women for cardiovascular diseases, while for cerebrovascular diseases the reductions were greater for men. No differences were observed for percutaneous procedures performed. The results show the need to implement measures to ensure the follow-up of these pathologies in cases of high hospital frequentation.

Funding

This work has been partialy supported by a research grant from the University of Ferrara, (Fondo per l'Incentivazione alla Ricerca Dipartimentale –FIRD– 2022, Prof. Roberto Manfredini). This research also received specific grants from the Instituto de Salud Carlos III "PI19/01405", co-funded by the European Union.

Conflict of Interest

The Authors declare they have no potential conflict of interest.

Ethics Approval

The study was approved by the Cordoba Provincial Research Ethics Committee (ref. 4513).

Availability of Data

The data presented in this study are available on request from the corresponding author.

Authors' Contribution

All the authors (FJRC, JEJH, JFAD, RMMD, JLRC, RM, MARB, PJLS) have made intellectual contributions to the manuscript. FJRC, JEJH and PJLS contributed to the conception and design, and was involved in drafting the manuscript. JFAD and JLRC have contributed to the conception and design, and have been involved in drafting the manuscript, revising it critically for intellectual content. RMMD, RM and MARB have been involved in revising the document critically. Each author has accepted individual responsibility for their own contributions and committed to addressing any queries related to the accuracy or integrity of the work, even those that do not directly pertain to their involvement. Any such issues will be investigated, resolved, and documented in the literature as appropriate. All authors have thoroughly reviewed and endorsed the final manuscript.

Informed Consent

In accordance with Spanish legislation, when using secondary data, informed consent is not required. In any case, the Helsinki guidelines were complied.

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