Sex and COVID-19 Mortality

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Spain is one of the countries most affected by the COVID-19 pandemic. Although risk factors for severe disease are published, sex differences have been widely neglected. In this multicentre study, we aimed to identify predictors of inhospital mortality in men and women hospitalised with COVID-19. An observational longitudinal study was conducted in the cohort of patients admitted to four hospitals in Andalusia, Spain, from 1 March 2020 to 15 April 2020. Sociodemographic and clinical data were collected from hospital records. The Kaplan-Meier method was used to estimate 30-day survival and multiple Cox regression models were applied. All analyses were stratified by sex. A total of 968 patients were included (54.8% men, median age 67.0 years). In-hospital mortality reached 19.1% in men and 16.0% in women. Factors independently associated with an increased hazard of death were advanced age, higher CURB-65 score and not receiving azithromycin treatment, in both sexes; active cancer and autoimmune disease, in men; cardiovascular disease and chronic lung disease, in women. Disease outcomes and predictors of death differed between sexes. Inhospital mortality was higher in men, but the long-term effects of COVID-19 merit further research. The sex-differential impact of the pandemic should be addressed in public health policies.

Keywords: COVID-19; SARS-CoV-2; hospital mortality; risk factors; sex

1. Introduction

Since its discovery, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly spread across the globe causing devastating effects. With more than 3.8 million confirmed cases and 80,000 reported deaths as of 30 June 2021, the burden of disease attributable to COVID-19 in Spain is among the highest in the world, not to mention the indirect effects on other diseases. Coronavirus hit hardest in the first wave of the pandemic, characterised by the lack of preparedness from a public health standpoint, the use of drugs with insufficient evidence and, above all, an unprecedented health care collapse.

Several studies have described the clinical spectrum of COVID-19. It ranges from asymptomatic to severe acute respiratory syndrome (SARS) with a variety of complications and, in worst cases, death. Such variability is not random: patients with obesity, chronic conditions or malignancies, those aged > 60 years and immunocompromised hosts, among others, are at higher risk of death. Although many risk factors have been identified, their contribution may not be the same in women and men. Ignoring sex differences in COVID-19 mortality hampers our understanding of infection by SARS-CoV-2 and, indirectly, neglects the importance of gender-based risk factors. For example, previous works have suggested that factors associated with COVID-19 outcomes are different in men and women. However, further research is warranted and several authors have pointed to the need of studies stratified by sex.

Furthermore, geographical singularities must be considered. In the context of the first epidemic wave, disparities among populations were shaped not only by their demography. Social determinants of health —material conditions, psychosocial circumstances and behavioural factors—influenced the risk of infection among the exposed, while health systems (overload and changing protocols for diagnosis, admission and treatment) influenced the risk of death among the infected. As a result, important differences were observed across areas even in the same country. To our knowledge, risk factors for in-hospital mortality have been published so far from four Spanish regions.

Andalusia is the most populated region in Spain (8.4 million inhabitants). Despite not being among the most affected regions in the first wave, it had up to 12,568 confirmed cases as of 10 May 2020, of which 6209 were hospitalised and 1444 died. Besides, limited availability of resources—annual per capita expenditure on health care is the lowest in the country (EUR 1262)—has compromised the healthcare's response to COVID-19. In this multicentre study, our objectives were to describe the baseline characteristics and to analyse the predictors of in-hospital mortality of adult men and women admitted to four Andalusian public hospitals during the first wave of the pandemic.

We described the baseline characteristics, treatments received and main outcomes of patients with COVID-19 admitted to four centres in Andalusia, Spain, in the first wave of the pandemic. We analysed predictors of in-hospital mortality. In both sexes, advanced age, higher CURB-65 score upon admission and not receiving treatment with azithromycin increased the risk of death. Sex-specific risk factors were active cancer and autoimmune disease in men, and cardiovascular disease and chronic lung disease in women.

In this study, men show higher rates of ICU admission and in-hospital mortality. Nevertheless, this may not be the case in middle- and especially low-income countries, where less research is conducted. Another topic that should be addressed in future studies is the long-term impact of the pandemic, as it might be greater on women. Several authors $^{[\underline{1}][\underline{2}]}$ have made a call to address the sex- and gender-specific long-run effects of COVID-19 on population health: healthcare systems are facing the growing demand for care and the mental health fallout $^{[\underline{3}]}$. To this end, governments must allocate resources $^{[\underline{4}]}$ to overcome barriers to health services access and expand social protection.

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