

Gender Differences in the Presentation and Outcomes of Hospitalized Patients With COVID-19

Carloalberto Biolè, MD¹, Matteo Bianco, MD¹, Iván J Núñez-Gil, MD, PhD², Enrico Cerrato, MD, PhD^{1,3*}, Amanda Spirito, MD¹, Sergio Raposeiras Roubin, MD, PhD⁴, María C Viana-Llamas, MD⁵, Adelina Gonzalez, MD⁶, Alex F Castro-Mejía, MD⁷, Charbel Maroun Eid, MD⁸, Cristina Fernández-Pérez, MD⁹, Aitor Uribarri, MD¹⁰, Emilio Alfonso-Rodríguez, MD¹¹, Fabrizio Ugo, MD¹², Federico Guerra, MD¹³, Gisela Feltes, MD¹⁴, Ibrahim Akin, MD¹⁵, Inmaculada Fernández-Rozas, MD¹⁶, Natividad Blasco-Angulo, MD¹⁷, Jia Huang, MD¹⁸, Marcos García Aguado, MD¹⁹, Martino Pepe, MD²⁰, Rodolfo Romero, MD²¹, Víctor Manuel Becerra-Muñoz, MD²², Vicente Estrada, MD², Carlos Macaya, MD, PhD²

¹Division of Cardiology, San Luigi Gonzaga University Hospital, Orbassano (Turin), Italy; ²Hospital Clínico San Carlos, Madrid, Spain; ³Interventional Cardiology Unit, San Luigi Gonzaga University Hospital, Orbassano, and Rivoli Infermi Hospital, Rivoli (Turin), Italy; ⁴University Hospital Álvaro Cunqueiro, Vigo, Spain; ⁵Hospital Universitario Guadalajara, Guadalajara, Spain; ⁶Hospital Universitario Infanta Sofía, San Sebastian de los Reyes, Madrid, Spain; ⁷Hospital General del norte de Guayaquil IESS, Los Ceibos, Ecuador; ⁸Hospital La Paz, Madrid, Spain; ⁹Hospital Santiago de Compostela, Santiago de Compostela, Spain; ¹⁰Hospital Clínico Universitario de Valladolid, Valladolid, Spain; ¹¹Instituto de Cardiología y Cirugía Cardiovascular, Havana, Cuba; ¹²Sant'Andrea Hospital, Vercelli, Italy; ¹³Cardiology and Arrhythmology Clinic, Ospedali Riuniti "Umberto I - Lancisi - Salesi", Ancona, Italy; ¹⁴Hospital Nuestra Señora de América, Madrid, Spain; ¹⁵First Department of Medicine, University Heidelberg, Mannheim, Germany, German Center for Cardiovascular Research, Heidelberg-Mannheim, Mannheim, Germany; ¹⁶Hospital Severo Ochoa, Leganés, Spain; ¹⁷Instituto de Investigación Sanitaria, Incliva, Universidad de Valencia, Valencia, Spain; ¹⁸The Second People's Hospital of Shenzhen, Shenzhen, China; ¹⁹Hospital Puerta de Hierro, Majadahonda, Spain; ²⁰Azienda Ospedaliero-Universitaria Consorziata Policlinico di Bari, Bari, Italy; ²¹Hospital Universitario Getafe, Madrid, Spain; ²²Unidad de Gestión Clínica Área del Corazón, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Universitario Virgen de la Victoria, Universidad de Málaga (UMA), Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Málaga, Spain.

Gender-related differences in COVID-19 clinical presentation, disease progression, and mortality have not been adequately explored. We analyzed the clinical profile, presentation, treatments, and outcomes of patients according to gender in the HOPE-COVID-19 International Registry. Among 2,798 enrolled patients, 1,111 were women (39.7%). Male patients had a higher prevalence of cardiovascular risk factors and more comorbidities at baseline. After propensity score matching, 876 men and 876 women were selected. Male patients more often reported fever, whereas female patients more often reported vomiting, diarrhea, and hyposmia/anosmia.

Laboratory tests in men presented alterations consistent with a more severe COVID-19 infection (eg, significantly higher C-reactive protein, troponin, transaminases, lymphocytopenia, thrombocytopenia, and ferritin). Systemic inflammatory response syndrome, bilateral pneumonia, respiratory insufficiency, and renal failure were significantly more frequent in men. Men more often required pronation, corticosteroids, and tocilizumab administration. A significantly higher 30-day mortality was observed in men vs women (23.4% vs 19.2%; $P = .039$). Trial Numbers: NCT04334291/EUPAS34399. *Journal of Hospital Medicine* 2021;16:349-352. © 2021 Society of Hospital Medicine.

There is growing evidence that gender may be associated with COVID-19 infection, presentation, and prognosis.¹⁻⁴ Most published evidence, however, has focused on individual aspects, such as specific symptoms or prognoses. We sought to provide a comprehensive analysis of gender and COVID-19 infection from admission to 30 days after discharge in a large, multinational cohort.

METHODS

The registry HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19, NCT04334291) is an international

investigator-initiated study.⁵ The study was approved by the ethics committee of the promoting center and was appraised and accepted by the institutional review board or local committee of each participating hospital. It was designed as an ambispective cohort study. Patients are eligible for enrollment when discharged (whether dead or alive) after an in-hospital admission with a positive COVID-19 test or if their attending physician considered them highly likely to have presented with SARS-CoV-2 infection. All decisions and clinical procedures were performed by the attending physician team independently of this study, following the local regular practice and protocols. The information presented here corresponds to the HOPE-COVID-19 Registry, with a cutoff date of April 18, 2020.

Study methods and definitions are available in Appendix 1 and Appendix 2, respectively, and detailed in a previous paper⁵ and online on the web page of the study.⁶

Enrolled patients were divided into two groups according to their gender, then propensity score matching (PSM) analysis was performed (1:1 nearest neighbor matching,

*Corresponding Author: Enrico Cerrato, MD, Email: enrico.cerrato@gmail.com; Telephone: +390119026802; Twitter: @enrico_cerrato.

Drs Biolè, Bianco, and Cerrato contributed equally to this article.

Published online first May 19, 2021.

Find additional supporting information in the online version of this article.

Received: September 22, 2020; Revised: January 17, 2021; Accepted: January 18, 2021

© 2021 Society of Hospital Medicine DOI 10.12788/jhm.3594

TABLE. In-Hospital Management and COVID-19 Outcomes of 876 Men and 876 Women Matched on Baseline Medical Conditions

	Overall, % (n = 1,752)	Women, % (n = 876)	Men, % (n = 876)	P value
Oxygen therapy	65.6 (1,125/1,716)	62.6 (535/855)	68.5 (590/861)	.009
High-flow nasal cannula	16 (271/1,696)	15.8 (133/844)	16.2 (138/852)	.805
Noninvasive mechanical ventilation	11.6 (196/1,692)	11.4 (96/844)	11.8 (100/848)	.788
Invasive mechanical ventilation	6.2 (104/1,685)	5.5 (46/839)	6.9 (58/846)	.242
Pronation	8.2 (139/1,689)	6.5 (55/845)	10 (84/844)	.010
Circulation support/ECMO	2.6 (45/1,705)	2.4 (20/850)	2.9 (25/855)	.462
Corticosteroids use	20.2 (346/1,712)	18 (154/857)	22.5 (192/855)	.021
Chloroquine/HCQ use	85.2 (1,468/1,724)	85.3 (735/862)	85 (733/862)	.892
Antivirals	65.3 (1,124/1,720)	65.2 (561/861)	65.5 (563/859)	.867
Interferon	17.2 (293/1,703)	15.9 (135/851)	18.5 (158/852)	.143
Tocilizumab	6.6 (112/1,703)	5.2 (44/854)	8 (68/849)	.017
Antibiotics	74.3 (1,230/1,656)	71.5 (587/821)	77 (643/835)	.010
ACE/ARB	15.3 (254/1,661)	14.9 (123/823)	15.6 (131/838)	.697
Anticoagulation in hospital	34.9 (611/1,752)	35.7 (313/876)	34 (298/876)	.903
Respiratory insufficiency	45.2 (781/1,728)	41.9 (361/862)	48.5 (420/866)	.006
Upper respiratory tract infection	14.1 (239/1,701)	13.8 (117/848)	14.3 (122/853)	.764
Bilateral pneumonia	65.2 (1,142)	62 (543)	68.4 (599)	.05
Sepsis	12.2 (209/1,719)	11.9 (102/860)	12.5 (107/859)	.705
SIRS	17.9 (306/1,709)	15.6 (133/851)	20.2 (173/858)	.014
Clinically relevant bleeding	1.9 (32/1,703)	1.4 (12/850)	2.3 (20/853)	.156
Embolic event	1.5 (25/1,706)	1.8 (15/852)	1.2 (10/854)	.311
Skin rash	3.6 (22/612)	4.5 (14/312)	2.7 (8/300)	.227
Heart failure	6 (103/1,720)	5.9 (51/863)	6.1 (52/857)	.890
Renal failure	14.8 (256/1,725)	11.6 (100/860)	18 (156/865)	≤.001
Death at 30 days	20.8 (365/1,752)	19.2 (168/876)	23.4 (205/876)	.039

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ECMO, extracorporeal membrane oxygenation; HCQ, hydroxychloroquine; SIRS, systemic inflammatory response syndrome.

caliper = 0.01, without replacement and maximizing execution performance). Our primary end point was all-cause mortality at 30 days. Other clinically relevant events were recorded as secondary end points: invasive mechanical ventilation, noninvasive mechanical ventilation, pronation, respiratory insufficiency, heart failure, renal failure, upper respiratory tract involvement, pneumonia, sepsis, systemic inflammatory response syndrome, clinically relevant bleeding, hemoptysis, and embolic events. Events were allocated based on HOPE-COVID-19 registry definitions, following local researchers’ criteria. Abnormal blood test values

were classified according to the reference values of local laboratories (Appendix 2).

Statistical analysis methods are outlined in Appendix 1.

RESULTS

Of the 2,798 patients consecutively enrolled in the HOPE registry, 1,111 were women (39.7%) and 1,687 were men (60.3%). Of the 2,375 (84.9%) patients who had a nasopharyngeal swab positive for COVID-19, 962 were women and 1,413 were men. Among the 2,798 patients initially included in the analysis, 876 gender-balanced pairs were selected after PSM.

Baseline Characteristics and Clinical Presentation

The baseline characteristics and clinical presentation of the overall population included in the study are summarized in Appendix Table 1. In the raw population, men had a significantly higher prevalence of conventional cardiovascular risk factors, such as diabetes, dyslipidemia, and smoking history, as well as a history of lung and cardiovascular diseases. On presentation, the most common symptoms for all patients were fever, cough, and dyspnea. Fever was more common in men, whereas vomiting, diarrhea, and upper airway symptoms (eg, sore throat, hyposmia/anosmia, dysgeusia) were more common in women.

Most patients had increased values of acute phase reactants. C-reactive protein (CRP) was elevated in 90.2% and D-dimer in 64.2% of patients, both significantly more often in men. Lymphocytopenia was present in 75.4% of patients, more commonly among men. Bilateral pneumonia occurred in 69.2% of the population, more frequently in men.

After PSM analysis (Appendix Table 2), a higher prevalence of hyposmia/anosmia and gastrointestinal symptoms in women was confirmed, as well as a higher prevalence of fever in men. Laboratory tests in men still presented alterations consistent with a more severe COVID-19 infection (significantly higher CRP, troponin, transaminases, lymphocytopenia, thrombocytopenia, and ferritin). There was no significant difference in the time between onset of symptoms and hospital admission by gender (6.2 ± 7.1 days in women vs 5.9 ± 7.6 days in men; $P = .472$).

The main findings after PSM analysis are summarized in Appendix Figure 1 and Appendix Figure 2.

In-Hospital Management and Outcomes

The supportive and pharmacologic treatments of study patients and their outcomes are summarized in Appendix Table 3. During the in-hospital stay, men required oxygen supplementation more frequently than women. Noninvasive mechanical ventilation, invasive mechanical ventilation, and pronation were more commonly used in men. Chloroquine/hydroxychloroquine, antivirals, and antibiotics were the medications most widely used in our population (84.5%, 65.8%, and 74.4% of patients, respectively), without significant differences between male and female patients, with the exception of antibiotics, which were used more often in men (76.6% vs 71.1%). Immunomodulators (corticosteroids, tocilizumab, and interferon) were used more often in male patients.

After PSM (Table), men more frequently received immunomodulators (corticosteroids and tocilizumab), antibiotics, and pronation. No differences in invasive and noninvasive mechanical ventilation were observed.

Thirty-day outcome data were available for all patients included in the analysis. During the in-hospital stay, 48% of patients developed respiratory insufficiency, 18.8% systemic inflammatory response syndrome (SIRS), and 13.2% overt sepsis. Respiratory insufficiency and SIRS were more common in male patients. Mortality at 30 days in the raw population was 21.4%, and men died more often than women (23.5% vs 18.2%; $P = .001$).

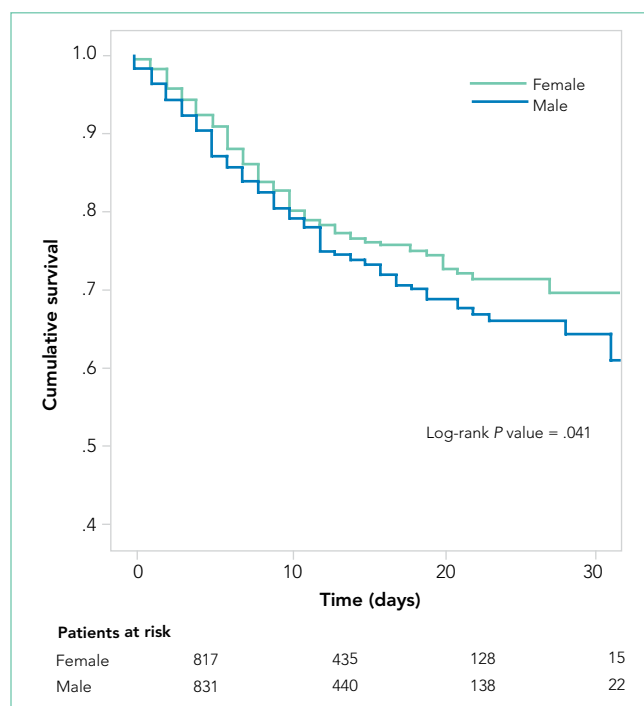


FIG. Kaplan-Meier Survival Analysis After Propensity Score Matching

The PSM analysis continued to show a higher 30-day mortality rate among men (Figure), as well as greater need for oxygen, pronation, and use of immunomodulators and antibiotics (Table).

DISCUSSION

The results of our study confirm that among patients with COVID-19, men have a poorer prognosis than women. Because of the design of the study, it is not possible to determine if men are more prone to SARS-CoV-2 infection in our population; however, given the prevalence of men in our unselected, all-comers population, we can assume that men are either infected more often and/or more frequently symptomatic.

After PSM analysis, the 30-day all-cause mortality remained higher among men than women. The poorer prognosis of male patients is attributable not only to a higher burden of cardiovascular risk factors, but may also be related to unmodifiable biological factors, such as sex differences in angiotensin-converting enzyme 2 expression.^{7,8} The worse prognosis observed in our study confirms the higher incidence of death in male patients that was observed in previous studies.⁹ Liu et al questioned the role of gender as an independent prognostic factor in COVID-19¹⁰; however, that study included fewer patients, who were also younger and had less severe disease.

The clinical presentation of COVID-19 also differed by gender in our study. Gastrointestinal symptoms and hyposmia/anosmia were more common in women, whereas fever was more common in men. The prevalence of olfactory and gustatory dysfunction in women has already been described,^{11,12} and these symptoms have been linked with milder disease.¹³ It is possible that women presenting to the hospital had milder

forms of COVID-19, or that there were systematic differences in how men and women sought medical care. The results of our study emphasize the need for a high level of suspicion for COVID-19 infection in women, even in the presence of mild mucosal or gastrointestinal symptoms and/or relatively minor laboratory abnormalities.

Laboratory values indicative of more severe COVID-19 infection in men could suggest a higher inflammatory response to the infection. Men also received more immunomodulators and antibiotics in this study. A recent paper from Scully et al¹⁴ pointed out the different immune response to viruses observed in men that could partially explain the higher level of inflammation markers and the more severe disease observed in men.

Limitations

Our study has several limitations. As an observational study of hospitalized patients, it may represent patients with more severe COVID-19. Men and women may have sought hospital care differently. Diagnosis, testing, and treatment were not standardized and may have been influenced by patient gender. Although we attempted to match patients on baseline medical conditions, we may not have completely controlled for differences in preexisting health. Finally, gender data were collected as binary and so did not capture other gender categories.

CONCLUSION

In our multicenter cohort of hospitalized COVID-19 patients, men had a higher burden of risk factors; different clinical presentations, with more fever and less olfactory and gastrointestinal symptoms; and a significantly poorer prognosis than women did at 30 days.

Acknowledgments

The authors thank Cardiovascular Excellence SL for their essential support regarding the database and HOPE web page as well as all HOPE researchers. The authors also thank Michael Andrews for his valuable contribution to the English revision.

Disclosures: The authors have no conflicts to disclose.

Funding: Research reported in this article was supported by a nonconditioned grant from Fundación Interhospitalaria para la Investigación cardiovascular, FIC, Madrid, Spain. This nonprofit institution had no role in the study design; collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

References

- Alkhouli M, Nanjundappa A, Annie F, Bates MC, Bhatt DL. Sex differences in case fatality rate of COVID-19: insights from a multinational registry. *Mayo Clin Proc.* 2020;95(8):1613-1620. <https://doi.org/10.1016/j.mayocp.2020.05.014>
- Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ.* 2020;11(1):29. <https://doi.org/10.1186/s13293-020-00304-9>
- Gausman J, Langer A. Sex and gender disparities in the COVID-19 pandemic. *J Womens Health (Larchmt).* 2020;29(4):465-466. <https://doi.org/10.1089/jwh.2020.8472>
- Walter LA, McGregor AJ. Sex- and gender-specific observations and implications for COVID-19. *West J Emerg Med.* 2020;21(3):507-509. <https://doi.org/10.5811/westjem.2020.4.47536>

- Núñez-Gil IJ, Estrada V, Fernández-Pérez C, et al. Health outcome predictive evaluation for COVID 19 international registry (HOPE COVID-19), rationale and design. *Contemp Clin Trials Commun.* 2020;20:100654. <https://doi.org/10.1016/j.conctc.2020.100654>
- International COVID-19 Clinical Evaluation Registry: HOPE-COVID 19. Accessed February 6, 2021. <https://hopeprojectmd.com/en/>
- Gagliardi MC, Tieri P, Ortona E, Ruggieri A. ACE2 expression and sex disparity in COVID-19. *Cell Death Discov.* 2020;6:37. <https://doi.org/10.1038/s41420-020-0276-1>
- Ciaglia E, Vecchione C, Puca AA. COVID-19 infection and circulating ACE2 levels: protective role in women and children. *Front Pediatr.* 2020;8:206. <https://doi.org/10.3389/fped.2020.00206>
- Peckham H, de Grijter N, Raine C, et al. Sex-bias in COVID-19: a meta-analysis and review of sex differences in disease and immunity. *Research Square.* April 20, 2020. <https://doi.org/10.21203/rs.3.rs-23651/v2>
- Liu J, Zhang L, Chen Y, et al. Association of sex with clinical outcomes in COVID-19 patients: a retrospective analysis of 1190 cases. *Respir Med.* 2020;173:106159. <https://doi.org/10.1016/j.rmed.2020.106159>
- Biadsee A, Biadsee A, Kasseem F, Dagan O, Masarwa S, Ormianer Z. Olfactory and oral manifestations of COVID-19: sex-related symptoms—a potential pathway to early diagnosis. *Otolaryngol Head Neck Surg.* 2020;163(4):722-728. <https://doi.org/10.1177/0194599820934380>
- Costa KVT, Carnáuba ATL, Rocha KW, Andrade KCLD, Ferreira SMS, Menezes PTL. Olfactory and taste disorders in COVID-19: a systematic review. *Braz J Otorhinolaryngol.* 2020;86(6):781-792. <https://doi.org/10.1016/j.bjorl.2020.05.008>
- Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol.* 2020;277(8):2251-2261. <https://doi.org/10.1007/s00405-020-05965-1>
- Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nat Rev Immunol.* 2020;20(7):442-447. <https://doi.org/10.1038/s41577-020-0348-8>

