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SHORT COMMUNICATION

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Impact of gender on patients hospitalized for SARS-COV-2 infection: A prospective observational study

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Abstract

Biological sex could affect the natural history of severe acute respiratory syndrome coronavirus 2 infection. We enrolled all COVID-19 patients admitted to two COVID-19 hospitals in Milan in a prospective observational study. The primary outcome was death during the study period and the secondary outcome was critical disease at hospital admission. The association(s) between clinically relevant, noncollinear variables, and the primary outcome was assessed with uni- and multivariable Logistic regression models. A total of 520 patients were hospitalized of whom 349 (67%) were males with a median age 61 (interquartile range: 50–72). A higher proportion of males presented critically ill when compared to females (30.1% vs. 18.7%, $p < .046$). Death occurred in 86 (24.6%) males and 27 (15.8%) females ($p = .024$). In multivariable analysis age (per 10 years more) (adjusted odds ratio [AOR]: 1.83 [95% confidence interval {CI}: 1.42–2.35], $p < .0001$), obesity (AOR: 2.17 [95% CI: 1.10–4.31], $p = .026$), critical disease at hospital admission (AOR 6.34 [95% CI: 3.50–11.48], $p < .0001$) were independently associated to higher odds of death whereas gender was not. In conclusion, a higher proportion of males presented critically ill at hospital admission. Age, critical disease at hospital admission, obesity, anemia, D-dimer, estimated glomerular filtration rate, lactate dehydrogenase, and creatine kinase predicted death in hospitalized COVID-19 patients.

KEYWORDS
COVID-19, disease severity, female, mortality, outcomes

1 | INTRODUCTION

Since the beginning of the COVID-19 pandemic it appeared clearly from the first Chinese reports that a higher proportion of males required hospital admission when compared to females.[1] A similar pattern was also observed in Italy in a significantly older population when compared to the Chinese one.[2–4] In addition, according to the Italian official reports, males accounted for the majority of COVID-19 related death in all age categories except for those aged above 90 years of age.[5] Sero-epidemiological studies conducted in the general population showed how gender does not seem to provide a different susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, whereas different demographic, cultural and behavioral factors appeared to be the main determinants of SARS-CoV-2 infection.[6–8] Consequently, it could be speculated that gender could affect the natural history of SARS-CoV-2 infection by means of a higher likelihood to progress to severe disease requiring hospitalization in males.

We aimed to assess the impact of gender on disease severity at hospital admission and mortality of COVID-19 hospitalized patients during the first wave of the Italian epidemic.

2 | MATERIALS AND METHODS

This prospective cohort study enrolled COVID-19 patients admitted to two COVID-19 dedicated hospitals in Milan, Italy (Luigi Sacco and Fatebenefratelli Hospitals). The clinical characteristics of all the COVID-19 patients hospitalized between February 21 and May 31, 2020 were recorded upon admission and the observation was censored as of July 31, 2020. A case of COVID-19 was defined according the presence of a positive nasopharyngeal swab for SARS-CoV-2 and the disease severity at hospital admission was categorized according to the World Health Organization criteria into mild/moderate/severe/critical.[9]

The primary outcome was death during the study period and the secondary outcome was critical disease at hospital admission, the life status of the patients discharged before the censoring date was ascertained by means of telephone calls made by two physicians.

The descriptive statistics include proportions for categorical variable, and median values and interquartile range (IQR) for continuous variables. The baseline demographic and clinic-epidemiological characteristics of females and males were compared using χ^2 or Fisher's exact test where necessary for categorical variables and Wilcoxon's rank-sum test for continuous variables.

Kaplan–Meier curves were built to assess the time dependent probability of death in males and females and further stratified by disease severity at hospital admission (critical vs. noncritical disease).

The association(s) between clinically relevant, noncollinear variables and the primary and secondary outcome was assessed by means of uni- and multivariable Logistic regression models. The multivariable analysis was made by introducing into the model the variables that found to be significantly associated with outcome in the univariate analysis, as well as potential confounders.

The analysis on the primary outcome (death) was repeated after restricting only to males and females.

All of the statistical analyses were made using SAS software, version 9.4, and differences with p values of less than .05 were considered statistical significant.

3 | RESULTS

A total of 520 patients were hospitalized of whom 349 (67%) were males with a median age 61 (IQR: 50–72) (Table 1). No significant difference between males and females were observed regarding age, chronic conditions and influenza vaccination. Males presented more frequently with fever and less frequently complaining gastrointestinal symptoms when compared to females (67.6% vs. 51.5% [$p = .001$] and 11.2% versus 19.3% [$p = .015$], respectively).

A higher proportion of males presented with a critical disease at hospital admission when compared to females (30.1% vs. 18.7%, $p < .046$). In multivariable analysis male gender did not result independently associated to critical disease at hospital admission. Time from symptoms onset to hospital admission (adjusted odds ratio [AOR]: 1.01 [95% confidence interval {CI}: 1.01–1.08], $p = .010$), C-reactive protein levels ≥50 mg/L (AOR: 3.75 [95% CI: 2.18–6.46], $p < .0001$) and lactate dehydrogenase (LDH) ≥245 IU/L (AOR: 6.74 [95% CI: 2.44–18.59], $p < .001$) were independently associated to higher odds of critical presentation, whereas influenza vaccination in the 2019–2020 season was associated to a lower odds of critical presentation (AOR: 0.47 [95% CI: 0.24–0.94], $p = .032$).

During the time of observation death occurred in 86 (24.6%) males and 27 (15.8%) females ($p = .024$) (Figure S1A). A trend toward a higher survival probability in critically ill females when compared to males was observed ($p = .094$) (Figure S1B). In multivariable analysis male gender did not resulted independently associated to death (Table 2). Age (per 10 years more) (AOR: 1.83 [95% CI: 1.42–2.35], $p < .0001$), obesity (AOR: 2.17 [95% CI: 1.10–4.31], $p = .026$), critical disease at hospital admission (AOR: 6.34 [95% CI: 3.50–11.48], $p < .0001$), LDH ≥245 IU/L (AOR: 3.30 [95% CI: 1.12–9.71], $p = .034$), anemia (AOR: 2.13 [95% CI: 1.21–3.76], $p = .009$), estimated glomerular filtration rate (eGFR) less than 60 ml/min (AOR: 2.79 [95% CI: 1.49–5.22], $p = .001$) and creatine kinase (CK) more than 185 IU/L (AOR: 2.22 [95% CI: 1.26–3.90], $p = .006$) were independently associated to higher odds of death. Influenza vaccination and time from symptoms onset did not result independently associated with death.

After restricting the analysis only to males (Table S1), age (per 10 years more) (AOR: 1.63 [95% CI: 1.23–2.16], $p = .001$), obesity (AOR: 2.12 [95% CI: 1.01–4.47], $p = .048$), critical disease at hospital admission (AOR: 5.63 [95% CI: 2.90–10.93], $p < .0001$), anemia (AOR: 1.92 [95% CI: 1.01–3.65], $p = .045$), eGFR less than 60 ml/min (AOR: 2.51 (95% CI: 1.22–5.14), $p = .012$) and CK more than 185 IU/L (AOR: 2.45 [95% CI: 1.30–4.65], $p = .006$) were independently associated to higher odds of death.

When the same analysis was repeated only on females (Table S2), age (per 10 years more) (AOR: 2.39 (95% CI: 1.45–3.94], $p = .001$] and critical disease at hospital admission (AOR: 6.42 [95% CI: 1.96–21.03], $p < .002$) were independently associated to higher odds of death.

4 | DISCUSSION

In our study we observed a male to female ratio of hospitalized COVID-19 patients of 2:1 which is in line with previous reports which suggested a different gender susceptibility in the requirement of hospital care despite a similar between genders infection risk.[10,11] Moreover, we observed that males more frequently presented with a critical disease. This finding is in line with a recent meta-analysis by Peckham et al of reported global cases showing a higher odds of intensive care requirement for males (OR = 2.84; 95% CI = 2.06, 3.92).[12] Nevertheless, in our multivariable model male gender did not resulted independently associated to death and other correlated factors were identified such as influenza vaccination and time from symptoms onset to hospital care. The potential association between influenza vaccination and SARS-CoV-2 infection[13] and COVID-19 severity is intriguing and it has been supported by epidemiological[14] and echological studies.[15] In particular, in line with our observation

TABLE 1 Characteristics of the study population at hospital admission

Characteristics	Total (*n* = 520)	Female: 171 (33%)	Male: 349 (67%)	*p* Value
Age in years, median (IQR)	61 [50, 72]	61 [49, 73]	61 [50, 71]	.722
Chronic conditions				
Respiratory diseases, *n* (%)	78 (15.0)	29 (17.0)	49 (14.0)	.433
Cardiovascular diseases, *n* (%)	254 (48.8)	79 (46.2)	175 (50.1)	.403
Diabetes, *n* (%)	61 (11.7)	16 (9.4)	45 (12.9)	.310
Kidney diseases, *n* (%)	42 (8.1)	11 (6.4)	31 (8.9)	.394
Oncological diseases, *n* (%)	50 (9.6)	20 (11.7)	30 (8.6)	.270
Immune system disorders, *n* (%)	39 (7.5)	16 (9.4)	23 (6.6)	.289
Liver diseases, *n* (%)	11 (2.1)	2 (1.2)	9 (2.6)	.517
Obesity, *n* (%)	92 (17.7)	23 (13.5)	69 (19.8)	.087
Influenza vaccination (%)				
YES	109 (21.0)	36 (21.1)	73 (20.9)	.427
NO	319 (61.3)	110 (64.3)	209 (59.9)	
nn	92 (17.7)	25 (14.6)	67 (19.2)	
Median time from onset of illness (IQR), days	8 (4, 11)	8 (4, 11)	8 (4, 10)	.829
Symptoms, *n* (%)				
Cough (%)	271 (52.1)	91 (53.2)	180 (51.6)	.779
Dyspnea (%)	225 (43.3)	67 (39.2)	158 (45.3)	.221
Sore throat (%)	26 (5.0)	11 (6.4)	15 (4.3)	.292
Artrhralgia/Myalgia (%)	29 (5.6)	6 (3.5)	23 (6.6)	.221
Headache (%)	25 (4.8)	8 (4.7)	17 (4.9)	.999
Asthenia (%)	62 (11.9)	17 (9.9)	45 (12.9)	.388
Vomiting and/or diarrhea (%)	72 (13.8)	33 (19.3)	39 (11.2)	*.015*
Fever (>37.3°C) (%)	324 (62.3)	88 (51.5)	236 (67.6)	*.001*
Disease severity, *n* (%)				
Mild	40 (7.7)	14 (8.2)	26 (7.4)	*.046*
Moderate	226 (43.5)	80 (46.8)	146 (41.8)	
Severe	117 (22.5)	45 (26.3)	72 (20.6)	
Critically	137 (26.3)	32 (18.7)	105 (30.1)	
Laboratory parameters				
White blood cell count × 10^9/L, median (IQR)	6.4 (4.8, 9.1)	6.3 (4.6, 8.8)	6.5 (4.9, 9.2)	.384
Anemia[a] (%)	241 (46.3)	68 (39.8)	173 (49.6)	*.040*
Platelets × 10^9/L, median (IQR)	199 (152, 256)	210 (161, 282)	194 (149, 244)	*.021*
Prothrombin (INR), median (IQR)	1.21 (1.13, 1.31)	1.18 (1.09, 1.26)	1.23 (1.13, 1.33)	*<.001*
D-dimer (μg/L), median (IQR)	835 (455, 1772)	805 (478, 1342)	849 (452, 2056)	.179
PaO_2 (mmHg), median (IQR)	70.0 (59.8, 82.3)	74.0 (60.5, 92.0)	69.0 (59.0, 80.0)	*.032*
C-reactive protein (mg/L), median (IQR)	60.0 (23.2, 143.5)	53.4 (18.8, 113.9)	70.1 (25.2, 150.0)	.053
Creatinine (mg/dl), median (IQR)	0.93 (0.74, 1.15)	0.72 (0.61, 0.87)	1.02 (0.86, 1.21)	*<.001*
eGFR (MDRD), median (IQR)	83.8 (65.9, 101.7)	88.9 (71.9, 110.4)	80.9 (64.9, 99.3)	*.006*

(Continues)

Characteristics	Total (*n* = 520)	Female: 171 (33%)	Male: 349 (67%)	*p* Value
Lactate dehydrogenase (U/L), median (IQR)	330 (255, 453)	301 (232, 402)	340 (260, 476)	*.002*
Creatine kinase (U/L), median (IQR)	107 (57, 224)	64 (43, 123)	134 (73, 262)	*<.001*
Alanine aminotransferase (U/L), median (IQR)	32 (20, 57)	27 (17, 45)	36 (23, 63)	*<.001*

Note: Italics are for p values <.05.

Abbreviations: CK, creatine kinase; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD, modification of diet in renal disease; n, number; nn, not available.

[a]Anemia defined as a hemoglobin value of less than 12.5 g/dl for females and less than 14 g/dl for males.

in a study by Fink et al.[14] conducted in Brazil a recent inactivated trivalent influenza vaccine shot was associated with a 7% lower odds of needing intensive care treatment and 17% lower odds of requiring invasive respiratory support. This observation seems not to be explained in our cohort by a healthier status of vaccinated subjects which were older than unvaccinated (median years 73 [IQR: 61–79] vs. 57.06 [IQR: 47–68], $p < .001$) and more frequently presenting at least one comorbidity (88.1% vs. 61.1%, $p < .001$). In addition, in our cohort we observed no between gender differences in influenza vaccine coverage and no between gender difference in the proportion of obesity as comorbidity. Nevertheless, our findings which are observational in nature should be look with caution considering the potential presence of unmeasured confounders not taken into account into the analysis.

In addition to the hospitalization risk, global data indicate also a higher COVID-19 case fatality rates for males when compared to females with a pooled odds of death of 1.39 (95% CI = 1.31, 1.47).[11] In particular, most countries with available data indicate a male to female case fatality ratio higher than 1, ranging up to 3.5 in some cases.[16] The differences observed in the between gender case fatality rate in different countries are mainly driven by the different socio-demographic characteristics of these countries. In particular, as mentioned above for Italy males accounted for a higher proportion of COVID-19 death until the age of 80 when the demographic

TABLE 2 Univariable and multivariable model of factors associated to death in COVID-19 patients requiring hospitalization

	OR	OR lower bound (95%)	OR upper bound (95%)	*p* Value	AOR	AOR lower bound (95%)	AOR upper bound (95%)	*p* Value
Male versus female	1.74	1.08	2.81	*0.023*	1.31	0.70	2.43	.394
Age (per 10 years more)	1.75	1.48	2.06	*<0.0001*	1.83	1.42	2.35	*<.0001*
Obesity	1.94	1.14	3.32	*0.015*	2.17	1.10	4.31	*.026*
Cardiovascular diseases	2.64	1.70	4.10	*<0.0001*	0.85	0.45	1.62	.631
Oncological diseases	1.46	0.76	2.81	0.260	–	–	–	–
Flu vaccination for 2019–2020 season	1.54	0.91	2.61	0.111	–	–	–	–
Time from symptoms onset (per 1 day more)	1.00	0.97	1.03	0.973	–	–	–	–
Critical disease at hospital admission	5.38	3.44	8.42	*<0.0001*	6.34	3.50	11.48	*<.0001*
Fever yes versus not	1.19	0.78	1.84	0.431	–	–	–	–
Anemia[a]	2.47	1.61	3.81	*<0.0001*	2.13	1.21	3.76	*.009*
INR >1.3	1.64	1.04	2.59	*0.034*	0.96	0.53	1.72	.888
D-dimer ≥500 μg/L	3.61	1.91	6.83	*<0.0001*	2.31	1.03	5.18	*.042*
CRP ≥50 mg/L	2.88	1.81	4.58	*<0.0001*	0.94	0.51	1.74	.846
eGFR (MDRD) <60 ml/min	4.71	2.95	7.53	*<0.0001*	2.79	1.49	5.22	*.001*
LDH >245 IU/L	7.46	2.96	18.81	*<0.0001*	3.30	1.12	9.71	*.031*
CK >185 IU/L	2.64	1.70	4.08	*<0.0001*	2.22	1.26	3.90	*.006*

Note: Italics are for p values <.05.

Abbreviations: AOR, adjusted odds ratio; CK, creatine kinase; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; MDRD, modification of diet in renal disease; OR, odds ratio.

[a]Anemia defined as a hemoglobin value of less than 12.5 g/dl for females and less than 14 g/dl for males.

prevalence of females aged above 90 years inverts the COVID-19 death trend.[5] This male gender predisposition to a more severe disease is reflected by the high percentage of death occurred in our study in males when compared to females (24.6% vs. 15.8%). Nevertheless, in the multivariable model of factors associated to risk of death other expected factors showed an independent association with death. Among these advanced age, obesity and critical disease at hospital admission are well known factors associated to an increase risk of death.[3,10] In particular, advanced age and critical disease at hospital admission were retained as independently associated with higher risk of death in the restricted subanalysis both by males and females, whereas obesity resulted independently associated to a higher odds of death only from males in the restricted analysis. Moreover, several intermediate effect modifiers such as estimated glomerular filtration rate, anemia, elevated D-dimer, LDH, and CK levels were also independently associated with risk of death suggesting that several other parameters apart from gender should be taken into account at hospital admission to better estimate the prognosis of COVID-19 patients. These findings are in line with previous report suggesting a higher inflammation in males when compared to females with SARS-CoV-2 infection partially explaining the observed worse outcomes in males.[17,18]

Our study accounts for several limitations. First, the study was conducted in a daily evolving scenario with multiple pharmacological intervention often in compassionate use. Nevertheless, no significant differences in pharmacological interventions were observed between males and females. Second, the setting and the characteristics of patients were that of the "first wave" of the Italian pandemic and thus not completely generalizable to that of the current "second pandemic wave." In the end, the data for influenza vaccination were not retrievable for 17.7% of patients and consequently a chance finding related to bias, such as the presence of unmeasured confounders, could not be definitely excluded. Nevertheless, the models were run also without influenza as a variable and the output was overall comparable with that reported in the present manuscript (data not shown).

In conclusion, a higher proportion of males presented critically ill at hospital admission after SARS-CoV-2 infection. Nevertheless, in our multivariable model male gender did not resulted independently associated to death and other correlated factors were identified such as age, critical disease at hospital admission, obesity, anemia, D-dimer, eGFR, LDH and CK. In addition, influenza vaccination in the 2019–2020 season resulted associated to a lower odds of critical presentation at hospital admission. Although preliminary, our observation of an association between influenza vaccination and COVID-19 severity at hospital admission warrant further investigation in observational studies assessing COVID-19 outcomes.

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CONFLICT OF INTERESTS

Andrea Giacomelli has received consultancy fees from Mylan and nonfinancial educational support from Gilead.

AUTHOR CONTRIBUTIONS

All authors were involved in writing this manuscript, approved the final version as submitted, and have agreed to be accountable for all aspects of it.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by our local IRB (Comitato Etico Interaziendale Area 1).

CONSENT TO PARTICIPATE

All patients signed a written informed consent.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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