



## Cohort Study

## In-hospital mortality in SARS-CoV-2 stratified by sex differences: A retrospective cross-sectional cohort study

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## ARTICLE INFO

## Keywords:

Gender  
COVID-19  
In-hospital mortality  
Sex  
SARS-CoV-2

## ABSTRACT

**Background:** The aim of this study was to determine in-hospital mortality in patients presenting with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) and to evaluate for any differences in outcome according to sex differences.

**Methods:** Patients with SRS-CoV-2 infection were recruited into this retrospective cohort study between February 26 and September 8, 2020 and stratified according to the sex differences.

**Results:** In total of 3360 patients (mean age  $44 \pm 17$  years) were included, of whom 2221 (66%) were male. The average length of hospitalization was 13 days (range: 2–31 days). During hospitalization and follow-up 176 patients (5.24%) died. In-hospital mortality rates were significantly different according to gender ( $p < 0.001$ ). Specifically, male gender was associated with significantly greater mortality when compared to female gender with results significant at an alpha of 0.05, LL = 28.67, df = 1,  $p = 0.001$ , suggesting that gender could reliably determine mortality rates. The coefficient for the males was significant,  $B = 1.02$ ,  $SE = 0.21$ ,  $HR = 2.78$ ,  $p < 0.001$ , indicating that an observation in the male category will have a hazard 2.78 times greater than that in the female category. Multivariate logistic regression confirmed male patients admitted with SARS-CoV-2 had higher cumulative all-cause in-hospital mortality (6.8% vs. 2.3%; adjusted odds ratio (aOR), 2.80; 95% (CI): [1.61–5.03];  $p < 0.001$ ).

**Conclusions:** Male gender was an independent predictor of in-hospital mortality in this study. The mortality rate among male SARS-CoV-2 patients was 2.8 times higher when compared with females.

### 1. Background

In-hospital mortality in patients affected with SARS-CoV-2

reportedly ranges from 17% to 77% [1–3]. Recent data from 38 countries suggests that mortality may be up to 1.7 times higher males than in females [4]. The prevalence of SARS-CoV-2 infection was also

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<https://doi.org/10.1016/j.amsu.2022.104026>

Received 7 May 2022; Received in revised form 15 June 2022; Accepted 16 June 2022

Available online 20 June 2022

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reportedly higher in males compared with females [5,6]. Previous studies in patients admitted with MERS and SARS-CoV have also reported a higher mortality amongst males [7,8], who appear to be more susceptible to infection than females [9]. One contributory factor may be smoking history which is more prevalent amongst males [10]. The lower incidence of SARS-CoV-2 in females may also be related to oestrogen-related protection and X-linked gene-related immune responses [11,12]. The aim of this study was to determine in-hospital mortality in patients presenting with acute respiratory syndrome corona virus 2 (SARS-CoV-2) and to evaluate for any differences in outcome according to sex differences.

## 2. Methods

All patients aged 18 and older diagnosed with SRS-CoV- between February 26 and September 8, 2020 were included both Kuwaitis and non-Kuwaitis into this retrospective cross-sectional cohort study. All data were abstracted from electronic medical records of two tertiary care hospitals in Kuwait: Jaber Al-Ahmed Hospital and Al-Adan General Hospital [13,14]. A positive RT-R swab from the nasopharynx confirmed SRS-oV-2 infection. All patients were treated with a standard universal protocol according to The Ministry of Health, Kuwait. The research was retrospectively registered, the standing committee for health coordination and medical research at the Ministry of Health in Kuwait approved the study protocol and accepted the request for waiver of the consent (Registered as MOH/108-1422). This study is registered with Research Registry UIN: researchregistry8002 (<https://www.researchregistry.com/register-now#home/registrationdetails/62a6e4071a43e3001eceeef/>).

The primary endpoint was in-hospital mortality due to COVID-19, as specified by ID 10 code U07.1. The collected data comprised socioeconomic factors, co-morbidities, clinical presentation, on admission test results, and ICU and hospital admission duration. For data entry, an electronic case-record form (CRF) was employed. This work has been reported in line with the STROCSS criteria [15].

## 3. Statistical analysis

Descriptive statistics were used to summarise clinical data. Categorical variables were presented as frequencies and percentages, and the Pearson's  $\chi^2$  test used to analyse them. Continuous variables were summarized as mean and standard deviation. Multivariate logistic regression was performed to identify the impact of gender on all-cause mortality. Input variables included gender, age, neutrophils, platelet count, and hemoglobin were used to adjust the odds ratios (ORs) for in-hospital all-cause mortality outcome. A Cox proportional hazards model was utilised to see if gender had a major impact on the risk of mortality. The significance threshold was set at  $p < 0.05$ . R statistical packages [16] and SPSS version 27 (SPSS, Chicago, IL, US) were used to perform statistical analyses.

## 4. Results

A total of 3360 study participants were included. The mean age was  $44 \pm 17$  years, and 2221 (66%) of the patients were males. The median length of hospital stay was 13 (range 2–31) days. In this cohort 176 patients (5.24%) died with significantly higher mortality in males ( $p < 0.001$ ) (Table 1).

When compared to females, males had significantly higher hemoglobin ( $132$  vs  $177$  g/L;  $p < 0.001$ ), white blood cell ( $8.1$  vs  $7.3$   $10^9$ /L;  $p < 0.001$ ) and neutrophil ( $57$  vs  $54$ /mCL;  $p < 0.001$ ) counts, prothrombin ( $15.6$  vs  $14.6$  s;  $p = 0.016$ ) and activated partial thromboplastin ( $37.8$  vs  $35.4$  s;  $p = 0.047$ ) times, as well as international normalized ratio ( $1.2$  vs  $1.1$   $10^9$ /L;  $p = 0.016$ ) (Table 2).

Mortality was higher in individuals with lower hemoglobin (124, 22.4%) when compared to individuals with higher hemoglobin (52,

**Table 1**

Demographics and clinical characteristics of the cohort stratified by gender among patients admitted with SARS-CoV 2.

Characteristic	All	Female	Male	p-value	N
	N =	n =	n =		
	3360	1139	2221		
Age, Mean $\pm$ SD, years	$44 \pm 17$	$43 \pm 19$	$44 \pm 16$	0.093	3360
ICU admission, median (IQR), days	0 (0–4)	0(0–2)	0(0–4)	<0.001	3360
Length of hospital stay, median (IQR), days	13 (2–31)	14 (2–29)	13 (2–32)	0.002	2900
ICU to discharge, median (IQR), days	9 (0–39)	6(0–23)	10 (0–39)	0.008	416
Admission to ICU, median (IQR), days	$1.5 \pm 2.9$	$1.4 \pm 2.1$	$1.5 \pm 3.0$	0.684	257
Mortality, n (%)	176 (5.2%)	26 (2.3%)	150 (6.8%)	<0.001	3360

SD, standard deviation; ICU, intensive care unit; IQR, interquartile range. Percentages might not add up to 100% due to rounding off.

**Table 2**

Laboratory investigations stratified by gender.

Characteristic, mean $\pm$ SD	All N =	Female n =	Male n =	p-value	N
	3360	1139	2221		
Hemoglobin, g/L	127 (21.7)	117(15.1)	132(22.8)	<0.001	3360
WBC count, $10^9$ /L	7.85 (4.74)	7.34(3.76)	8.12 (5.15)	<0.001	3345
Neutrophils,/mCL	56.0 (15.1)	54.2(14.4)	56.9 (15.4)	<0.001	3344
Platelets, $10^9$ /L	305(120)	306(110)	304(125)	0.69	3345
Prothrombin time, sec	15.3 (5.98)	14.6(4.56)	15.6 (6.49)	0.016	851
INR	1.14 (0.49)	1.09(0.37)	1.17 (0.54)	0.016	851
aPTT, sec	37.1 (16.6)	35.4(14.0)	37.8 (17.6)	0.047	799

SD, standard deviation; WBC, white blood cell count; INR, international normalized ratio; APTT, activated partial thromboplastin time.

0.82%;  $p < 0.001$ ). Individuals with a hemoglobin level less than 100 g/L had a greater cumulative all-cause in-hospital mortality than those with hemoglobin levels higher than 100 g/L (22.4% vs. 0.8%;  $R$ , 0.29; 95% CI: [0.18–0.46];  $p < 0.001$ ). In-hospital mortality was associated with a higher neutrophil count [aOR, 1.17; 95% CI:(1.14–1.20,  $p < 0.001$ ) and a lower platelet count [aOR, 1.00; 95% I:(1.00–1.00,  $p = 0.005$ ). With respect to all-cause cumulative in-hospital mortality, age had no significant impact among the groups (aOR, 1.00; 95% CI [0.98–1.02];  $p < 0.960$ ) (Table 3). Male gender had a large impact on cumulative all-cause in-hospital mortality (6.8% vs. 2.3%) [ $R$ , 2.80; 95% CI: [1.61, 5.03];  $p < 0.001$ ] (Table 3).

Kaplan-Meier survival probability plots were used for the analysis based on gender. Each plot depicts the survival probabilities of various groups over time. Male sex was related to increased mortality (Kaplan-Meier survival probability plot). The model's results were significant and could not be explained by an alpha of 0.05,  $LL = 28.67$ ,  $df = 1$ ,  $p = 0.001$ , showing that gender could appropriately estimate the risk of mortality. The coefficient for male gender was significant,  $B = 1.02$ ,  $SE = 0.21$ ,  $HR = 2.78$ ,  $p < 0.001$ , indicating that male gender was associated with risk of mortality 2.78 times greater than female gender at any given point in time. Gender was observed to be important in predicting in-hospital mortality among SRS-oV-2 patients in this study [Fig. 1].

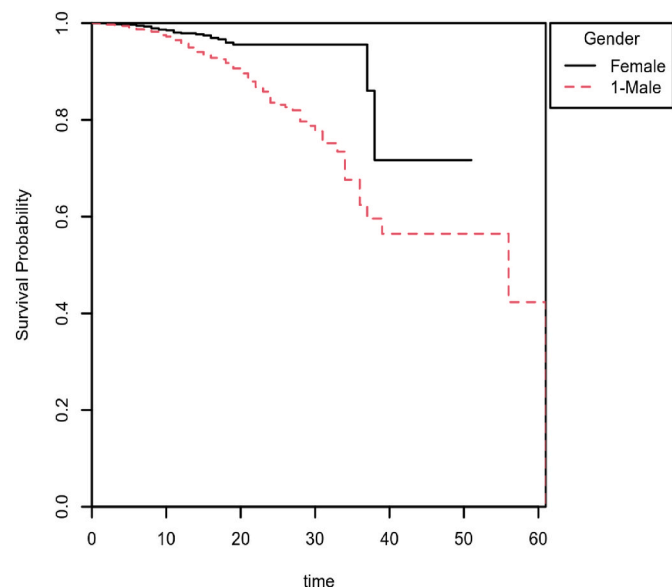
## 5. Discussion

The main finding of our study is that male gender is an independent

**Table 3**  
Predictors of in-hospital mortality by univariate and multivariate logistic regression.

In-hospital mortality		Alive	Dead	Univariate OR (95% CI, p-value)	Multivariate logistic regression aOR (95% CI, p-value)
Gender, n (%)	Female	1113 (97.7)	26 (2.3)	-	-
	Male	2071 (93.2)	150 (6.8)	3.10 (2.07–4.83, p < 0.001)	2.80(1.61–5.03, p < 0.001)
Age, years	Mean ± SD	43 ± 17	57 ± 12	1.05 (1.04–1.06, p < 0.001)	1.00(0.98–1.02, p = 0.960)
Neutrophils, %	Mean ± SD	55 ± 13.6	87 ± 8	1.23 (1.20–1.26, p < 0.001)	1.17(1.14–1.20, p < 0.001)
Platelets, 10 <sup>9</sup> /L	Mean ± SD	288 ± 103	217 ± 151	0.99 (0.99–0.99, p < 0.001)	1.00(1.00–1.00, p = 0.005)
Hemoglobin, g/L	HB ≤ 100	430 (77.6)	124 (22.4)	-	-
	HB > 100	6325 (99.2)	52 (0.8)	0.03 (0.02–0.04, p < 0.001)	0.29(0.18–0.46, p < 0.001)

Number in data frame = 6931, Number in model = 3344, Missing = 3587, AIC = 554.1, C-statistic = 0.976, H&L = Chi-sq(8) 2.97 (p = 0.936). OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; Multivariable analyses were conducted using logistic regression models utilizing the simultaneous method. The models were adjusted for gender, age, neutrophils, hemoglobin, and platelet.



**Fig. 1.** Kaplan-Meier survival plot of Mortality grouped by Gender Cox Proportional Hazards Regression Coefficients for Gender.

predictor of in-hospital mortality in patients diagnosed with SARS-CoV-2. Specifically, mortality in males with SARS-CoV-2 was 2.8 times higher than in females. Moreover, average length of ICU stay was longer in males. Although older in age, especially middle age and above, had higher mortality, this did not reach statistical significance. A higher neutrophil count and a lower platelet count had a significant impact on in-hospital mortality. The mortality rate was also seen higher in those with lower hemoglobin levels, which has been reported previously [17].

Reasons for these findings most probably relate to severity of infection and the extent of immune response that could be associated with increase in mortality.

One reason for higher mortality observed in males could be the higher prevalence of ACE-2 in the lungs [18]. Oestrogen-related protection in females may suppress SARS-CoV-2, thereby leading to lower mortality [19,20]. The male to female ratio observed in our study was higher than that in prior studies (1.5:1) [21,22]. The significance of gender is equally important as other risk factors in SARS-CoV-2 infection [23]. Several studies have reported higher mortality from SARS-CoV-2 in males. For example, in 144,279 patients in England and Wales significantly higher mortality was observed in males [24]. Similar findings were reported in Europe and Wuhan [25,26]. In addition, a study from Italy reported lower mortality in hospitalized females, but similar mortality among males and females in critically ill SARS-CoV-2 patients [27]. while more critically ill male patients were seen in a study conducted in Europe [28].

Delays in admission have also contributed to an increased rate of mortality in male patients in the setting of SARS-CoV-2 [29]. Younger males and elderly females were the most vulnerable in terms of mortality [30]. In a systematic review and meta-analysis, it was evident that both alcohol consumption and smoking increase mortality in males and females [31].

Our study does have some limitations. First, the study is retrospective limiting causal inference while unmeasured confounding factors, such as clinical co-morbidities and medications, could have affected the outcomes. As this study mainly focused on the sex differences and related in-hospital mortality, we didn't do any adjustment for comorbidities. Our study was focused towards only in-hospital mortality and hence the available clinical variables were limited.

**6. Conclusions**

This study demonstrated that gender is an independent predictor of in-hospital mortality in SARS-CoV-2 patients with males 2.8 times more likely to die than females. Despite males having a shorter overall hospitalization than females, males spent a greater proportion of time in intensive care unit. More prospective studies are required to better understand sex-related morbidity and mortality.

**Provenance and peer review**

Not commissioned, externally peer reviewed.

**Funding statement**

No funding available for this study.

**Conflict of interest disclosure**

No conflict of interest exists for any author on this manuscript.

**Ethics approval statement**

This study was approved by the ethics committee and Ministry of Health Kuwait.

**Patient consent statement**

Patient consented was not mandated for this retrospective observational study. Permission to reproduce material from other sources: No material from other sources is included in this study.

**Clinical trial registration**

This study was not a clinical trial.

## Ethical Approval

Ethics Committee Approval 1081422

## Consent

The standing committee for health coordination and medical research at the Ministry of Health in Kuwait approved the study protocol and accepted the request for waiver of the consent (Institutional the requirement of informed \1081422).

## Author contribution

MAJ participated in analysis and manuscript preparation. RR participated in data analysis and manuscript preparation. AAS and JP did the statistical analysis as well as manuscript review. All authors had access to data and take responsibility for the integrity of data and the accuracy of data analysis. All authors have read and approved the manuscript.

## Registration of Research Studies

1. Name of the registry: Not a registry
2. Unique Identifying number or registration ID: Not applicable
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): Not applicable

## Guarantor

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## Data availability

The data are not publicly available due to privacy or ethical restrictions.

## Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ICU	Intensive Care Unit
RT-PCR	Reverse Transcription Polymerase Chain Reaction
CI	Confidence Interval
aOR	Adjusted Odds Ratio
CRF	Case Record Form

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2022.104026>.

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