

# Risk factors for mortality among patients with SARS-CoV-2 infection: A longitudinal observational study

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## Abstract

Recent literature suggests that approximately 5%–18% of patients diagnosed with severe acute respiratory syndrome coronavirus 2 may progress rapidly to a severe form of the illness and subsequent death. We examined the relationship between sociodemographic, clinical, and laboratory findings with mortality among patients. In this study, 112 patients were evaluated from February to May 2020 and 80 patients met the inclusion criteria. Tocilizumab was administered, followed by methylprednisolone to patients with pneumonia severity index score  $\leq 130$  and computerized tomography scan changes. Demographic data and clinical outcomes were collected. Laboratory biomarkers were monitored during hospitalization. Statistical analyses were performed with significance  $p \leq .05$ . A total of 80 patients: 45 males (56.25%) and 35 females (43.75%) met the study inclusion criteria. A total of 7 patients (8.75%) were deceased. An increase in mortality outcome was statistically significantly associated with higher average levels of interleukin-6 (IL-6) with  $p$  value (.050), and D-dimer with  $p$  value (.024). Bivariate logistics regression demonstrated a significant increased odds for mortality for patients with bacterial lung infections (odds ratio [OR]: 10.83; 95% confidence interval [CI]: 2.05–57.40;  $p = .005$ ) and multiorgan damage (OR: 103.50; 95% CI: 9.92–1079.55;  $p = .001$ ). Multivariate logistics regression showed a statistically significant association for multiorgan damage (adjusted odds ratio [AOR]: 94.17; 95% CI: 7.39–1200.78;  $p = .001$ ). We identified three main predictors for high mortality. These include IL-6, D-dimer, and multiorgan damage. The latter was the highest potential risk for in-hospital deaths. This warrants aggressive health measures for early recognition of the problem and initiation of treatment to reverse injuries.

## KEYWORDS

clinical outcomes, COVID-19, mortality, multiorgan damage, SARS-CoV-2

## 1 | INTRODUCTION

In February 2020, a novel beta coronavirus infection referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has demonstrated rapid dissemination in the United States.<sup>1</sup> As a respiratory illness, SARS-CoV-2 pathogen acts by binding the angiotensin-converting enzyme 2 (ACE2) receptor found on Types I and II alveolar epithelial cells.<sup>1,2</sup> Subsequently, multiorgan damage is considered a potential sequela of the illness due to the wide expression of the ACE2 receptors in multiple organs, including cardiac and renal tissues.<sup>3</sup> Moreover, SARS-CoV-2 has a broad-spectrum of clinical symptoms and signs such as asymptomatic presentation, mild upper respiratory tract infection, severe viral pneumonia, respiratory failure, and death.<sup>4,5</sup> Recent literature suggests that approximately 5%–18% of SARS-CoV-2-positive patients may progress to severe cases that ultimately require mechanical ventilation, resulting in a case fatality rate of less than 5%.<sup>5</sup>

Current data indicates that individuals of all age groups are susceptible to SARS-CoV-2 infections.<sup>6</sup> Furthermore, mortality in patients with SARS-CoV-2 is typically associated with older age, male sex, a higher score in the scale used for assessing the severity of organ failure known as sequential organ failure assessment (SOFA) score, elevation in D-dimer levels, and severe pneumonia.<sup>4,6–9</sup> As of late August 2020, the mortality rate of SARS-CoV-2 is 3.42% worldwide, 3.10% in the United States, 2.00% in Texas, and 2.06% in El Paso, Texas, the location of our study.<sup>10</sup> Therefore, in this longitudinal observational study, we intended to evaluate the relationship of the sociodemographic, clinical, and laboratory findings with our primary outcome of mortality in patients with SARS-CoV-2 infection.

## 2 | METHODS

### 2.1 | Study design

PubMed, Google Scholar, and Medline were used for database collection and literature review on SARS-CoV-2 disease and mortality from February to August 2020. SARS-CoV-2-positive patients from four different hospitals in El Paso, Texas, were included within this longitudinal observational study from the 1st of February to the 31st of May 2020. A total of 112 patients with positive SARS-CoV-2 PCR were screened. Our inclusion criteria were patients with positive SARS-CoV-2 PCR, more than 18 years old, O<sub>2</sub> supplement of more than 3 L, and pneumonia severity index (PSI) score  $\leq 130$  with computerized tomography (CT) scan changes. Exclusion criteria were negative SARS-CoV-2 PCR, mechanically ventilated patients, end-stage comorbid conditions such as cardiomyopathy, cardiac arrhythmia, cancer, septic shock, end-stage renal disease, O<sub>2</sub> supplement of less than 3 L, and PSI score more than 130.

### 2.2 | Procedures

Recruited patients were given tocilizumab (TCZ) 4 mg/kg/day q12hr within the first 24 h of their hospitalization, followed by

methylprednisolone 60 mg q8hr for 72 h. Other medications such as ceftriaxone and azithromycin were added empirically to the treatment plan if patients had any rise in procalcitonin with leukocytosis suggesting secondary bacterial infections. Demographic data, medical history, and clinical outcomes were collected from all patients included in this study. Labs were monitored on admission, Days 3 and 6 for interleukin-6 (IL-6), C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), D-dimer, procalcitonin, complete blood count, complete metabolic panel, and blood and urine cultures if fever occurred. All patients had chest X-rays, or CT scans upon admission and subsequent imaging studies as needed. The duration of hospital stay was monitored for each patient.

### 2.3 | Statistical analysis

Data were retrieved from electronic health records and computed using Excel 365 version. The Excel-computed data were imported into statistical software, Stata/IC 16.0, for data analysis. Descriptive statistics were presented in frequency and percentages. Shapiro–Wilk normality test for continuous variables showed that the distribution of data was nonnormal; therefore, median (interquartile range [IQR]) were used as values for the summary statistics. The Mann–Whitney *U* test was used for associating selected continuous independent variables with mortality outcomes. Bivariate logistic regression analysis was performed to determine the risk association for categorical variables (using odds ratios, [ORs]). All ORs were reported with their 95% confidence interval [CI] and corresponding *p* values. Multivariate analysis was also done to adjust for the effect of confounders. An observation is said to be statistically significant if *p* value is less than or equal to .05 ( $p \leq .05$ ).

## 3 | RESULTS

A total of 112 patients were evaluated of which 80 positive patients (45 males, 56.25%; 35 females, 43.75%) met the study criteria. Table 1 summarized the general sociodemographic characteristics, medical history, and clinical presentations of patients with SARS-CoV-2 treated with TCZ. Most of the patients were within the ages 30–64 years (39, 48.75%) and  $\geq 65$  years (37, 46.25%), with a median (IQR) age of 63 (51, 72) years. The least were those less than 30 years (4, 5.0%). Patients with Hispanic ethnicity were the majority in the study (44, 57.14%), followed by White/Hispanic (25, 32.47%), which can be mainly attributed to the fact that the population of El Paso is predominately Hispanic. Comorbidities observed most among the patients were Hypertension (47, 65.28%), Type II diabetes mellitus (37, 51.39%), and hyperlipidemia (18, 25%). Other comorbidities presenting was (31, 43.05%), with the total number of presenting comorbidities on admission noted to be  $\leq 2$  symptoms on presentation in (46, 63.89%) of our patients, and those with 3 or more comorbidities (26, 36.11%), with a median of 2 comorbidities (1–3). The most common presenting symptom was shortness of breath

**TABLE 1** General sociodemographic characteristics, medical history, and clinical presentations of SARS-CoV-2 patients

Characteristics	Frequency (n = 80)	Percentage (%)	Characteristics	Frequency (n = 80)	Percentage (%)
Age			Fever (n = 76)		
<30 <sup>R</sup>	4	5.0	Yes	53	73.61
30-64	39	48.75	No	19	26.39
≥65	37	46.25	Cough (n = 72)		
Median values (IQR)	63 (51, 72)		Yes	49	68.06
Sex			No	23	31.94
Male	45	56.96	Shortness of breath (n = 72)		
Female	35	43.04	Yes	62	86.11
Race/ethnicity (n = 77)			No	10	13.89
Hispanic	44	57.14	Other symptoms (n = 72)		
White/Hispanic	25	32.47	Yes	42	58.33
White/Non-Hispanic	3	3.90	No	30	41.67
White/none listed	2	2.60	Total number of symptoms (n = 72)		
White	1	1.30	≤2	20	27.78
Black/Non-Hispanic	1	1.30	3 or more	52	72.22
Caucasian	1	1.30	Median values (IQR)	3 (2 - 5)	
Type 2 diabetes mellitus (n = 72)			Bacterial lung coinfection		
Yes	37	51.39	Yes	12	15.00
No	35	48.61	No	68	85.00
Hypertension (n = 72)			Multiorgan damage		
Yes	47	65.28	Yes	10	12.50
No	25	34.72	No	70	87.50
Hyperlipidaemia (n = 72)			Travel history (n = 70)		
Yes	18	25.00	Yes	11	15.71
No	54	75.00	No	59	84.29
Other comorbidities (n = 72)			Contact history (n = 70)		
Yes	31	43.05	Yes	34	48.57
No	41	56.94	No	36	51.43
Total number of comorbidities (n = 72)					
≤2	46	63.89			
3 or more	26	36.11			
Median values (IQR)	2 (1-3)				

Abbreviations: n, number of patients; %, percentage of patients; IQR, interquartile range; R, reference; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(62, 86.11%), followed by fever (53, 73.61%), cough (49, 68.06%), and other associated symptoms (42, 58.33%), with a median (IQR) number of symptoms 3 (2-5). A limited number of patients had lung bacterial coinfection (12, 15%) and multiorgan damage (10, 12.50%). Multiorgan damage was identified as the development of potentially reversible physiologic derangement involving two or more organ systems not involved in the primary admission disease.<sup>11</sup> Recent travel history was reported in 11 patients (15.71%), and 34 patients had positive contact history (48.43%). The primary clinical outcome was mortality among SARS-CoV-2 patients, as summarized in Table 2. A total of 7 patients (8.7%) were deceased during the study

period. The duration of hospital stays ranged from 5 to 10 days for all patients.

Using the Mann-Whitney *U* test, we noted statistically significant results between average IL-6 and mortality and D-dimer level with mortality. An increase in mortality outcome was noted among those with higher average levels of IL-6 with *p* value (.050). A similar finding was observed with D-dimer, as the higher the average D-dimer, the significant correlated increase in the risk of mortality with *p* value (.024). However, no statistically significant relationship with mortality was observed among CRP, procalcitonin, ferritin, and LDH levels in our study population, as illustrated in Table 3.

**TABLE 2** Mortality outcomes among SARS-CoV-2 patients treated

Clinical outcomes	Frequency (n = 80)	Percentage (%)
Mortality		
Yes	7	8.75
No	73	91.25

Abbreviations: n, number of patients; %, percentage of patients; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

From the bivariate logistics regression model (Table 4), there were statistically significant associations between bacterial lung infections, multiorgan damage, and mortality. Those with a bacterial lung infection were 10.83 times more likely to die from SARS-CoV-2 than those with no bacterial lung infection (OR: 10.83; 95% CI: 2.05–57.40;  $p = .050$ ). Also, those with multiorgan damage were 103.50 times more likely to die from SARS-CoV-2 than those with no multiorgan damage (OR: 103.50; 95% CI: 9.92–1079.55;  $p = .001$ ; Table 5).

After adjusting for possible confounders, the multivariate logistics regression model was only statistically significant for multiorgan damage, although with a slightly lower odds (adjusted odds ratio [AOR]: 94.17; 95% CI: 7.39–1200.78;  $p = .001$ ). Bacterial lung infection was no longer statistically significant, meaning that bacterial lung infection can be considered a confounding determinant of mortality as they became nonsignificant at the multivariate analysis level (AOR: 9.10; 95% CI: 0.71–111.27;  $p = .090$ ). To conclude, patients with positive SARS-CoV-2 and multiorgan damage are 94.17 times more likely to die than those without organ damage.

## 4 | DISCUSSION

A total of 7 patients (8.7%) of our study population (total of 80) were deceased during our study period. All our patients have had hypoxemia with higher oxygen requirement more than 3 L and PSI

score  $\leq 130$  and significant radiological changes. The majority of our patients have shown elevation in levels of CRP, ferritin, LDH, and D-dimer on initial presentation. After examining the association between all independent variables and mortality outcomes, we noted that mortality rates were higher among those patients with higher D-dimer and higher levels of IL-6 throughout their hospitalization period. Nevertheless, the sequential use of TCZ and methylprednisolone within 72 h of admission and its effect on the cytokine release syndrome as used in our study protocol was examined in our previous study by Antony et al.<sup>12</sup> Moreover, in this study we discovered that the occurrence of multiorgan damage in the presence of SARS-CoV-2 infection accounted for the highest risk of mortality as compared to all other examined variables. Nevertheless, the coexistence of bacterial lung infection was a confounding factor in the presence of multiorgan failure.

On the molecular level, SARS-CoV-2 is considered more closely related to the SARS-CoV than the Middle East respiratory syndrome-related coronavirus in its sequence identity.<sup>13</sup> Moreover, SARS-CoV-2 shares the same cellular receptor as SARS-CoV which is the ACE2 receptor<sup>14</sup> that commonly found in alveolar epithelial Type II cells of lung tissues<sup>15</sup> and also seen in other extrapulmonary tissues such as the cardiac endothelium, kidneys, and intestines,<sup>16,17</sup> which might play a key role in the multiorgan damage in SARS-CoV-2 infection.

In a prospective cohort study conducted by Rong-Hui et al.<sup>18</sup> to examine mortality predictors, the presence of a secondary bacterial infection led to higher concentrations of CRP and procalcitonin.<sup>18</sup> Their study noted that deceased patients had higher levels of inflammatory biomarkers than those who survived the SARS-CoV-2 infection, which might go in favor of possible increased risk of mortality with a secondary bacterial infection. Moreover, another study found that 81.7% of patients who died with SARS-CoV-2 disease were associated with bacterial infections.<sup>19</sup> Also, Martins-Filho et al.<sup>20</sup> found that sepsis was associated with a 2.5-fold increase in death risk among these patients.<sup>20</sup> Our study examined the relationship between superimposed bacterial

**TABLE 3** Laboratory biomarkers and mortality (n = 80; Mann–Whitney U test)

Lab biomarkers	Mortality		Z test	p Value
	Yes, median (IQR)	No, median (IQR)		
Average interleukin-6 (IL-6)	1028.75 (488.05–1682)	523 (326.4–677)	1.95	.050*
Average C-reactive protein (CRP)	6.4 (5.42–15.25)	3.4 (1.75–7.56)	1.31	.190
Average procalcitonin	0.145 (0.13–0.34)	0.45 (0.3–0.55)	1.67	.095
Average ferritin	794 (351.95–1013.5)	512 (324.25–842.25)	1.26	.209
Average lactate dehydrogenase (LDH)	398.5 (323.5–565.5)	364.5 (259–439.25)	1.46	.145
Average D-dimer	3.91 (1.95–7.86)	1.2 (0.81–1.5)	2.26	.024*

Note: IL-6, normal 0.0–12.2 (pg/ml); CRP, normal less than 8.0 (mg/L); procalcitonin, normal 0.10–0.49 (ng/ml); ferritin, normal 12–300 for males, 12–150 for females (ng/ml); LDH, normal 109–245 (U/L); D-Dimer, normal <0.5 (mcg/ml)

Abbreviation: IQR, interquartile range.

\*Statistically significant ( $p \leq .05$ ).

**TABLE 4** The association of socio-demographic characteristics, medical history, and clinical presentations with SARS-CoV-2 clinical outcomes in term of mortality using the bivariate logistic regression

Variables	Mortality		OR (95% CI)	p Value
	Yes (n = 7) Frequency (%)	No (n = 73) Frequency (%)		
Age				
<30 <sup>R</sup>	0 (0%)	4 (5.48%)	Ref	
30-64	2 (28.57%)	37 (50.69%)	2.52 (0.0–0.0)	.999
≥65	5 (71.43%)	32 (43.84%)	2.89 (0.52–15.93)	.223
Sex				
Male	2 (28.57%)	43 (58.90%)	0.27 (0.05–1.53)	.252
Female	5 (71.43%)	30 (41.10%)		
Hypertension				
Yes	4 (57.14%)	43 (66.15%)	0.68 (0.14–3.32)	.636
No	3 (42.86%)	22 (33.85%)		
Type 2 diabetes				
Yes	4 (57.14%)	33 (50.77%)	1.29 (0.27–6.24)	.749
No	3 (42.86%)	32 (49.23%)		
Hyperlipidaemia				
Yes	1 (14.29%)	17 (26.15%)	0.47 (0.05–4.20)	.500
No	6 (11.11%)	48 (73.85%)		
Total number of comorbidities				
3 or more	1 (14.29%)	25 (38.46%)	0.27 (0.03–02.35)	.234
≤2	6 (85.71%)	40 (61.54%)		
Fever				
Yes	4 (57.14%)	49 (75.38%)	0.44 (0.09–2.16)	.308
No	3 (42.86%)	16 (24.62%)		
Cough				
Yes	4 (57.14%)	45 (69.23%)	0.60 (0.12–2.90)	.518
No	3 (42.86%)	20 (30.77%)		
Shortness of breath				
Yes	7 (100%)	55 (84.62%)	(0.000>1.0E12)	.999
No	0 (0%)	10 (15.38%)		
Total number of symptoms				
3 or more	5 (71.43%)	47 (72.31%)	0.96 (0.17–5.39)	.961
≤2	2 (28.57%)	18 (27.69%)		
Bacterial lung confection				
Yes	4 (57.14%)	8 (10.96%)	10.83 (2.05–57.40)	.005*
No	3 (42.86%)	65 (89.04%)		
Multiorgan damage				
Yes	6 (85.71%)	4 (5.48%)	103.50 (9.92–1079.55)	.001*
No	1 (14.29%)	69 (94.52%)		
Travel history				
Yes	1 (14.29%)	10 (15.87%)	0.88 (0.10–8.151)	.913
No	6 (85.71%)	53 (84.13%)		

(Continues)

TABLE 4 (Continued)

Variables	Mortality		OR (95% CI)	p Value
	Yes (n = 7) Frequency (%)	No (n = 73) Frequency (%)		
Contact history				
Yes	3 (42.86%)	31 (49.21%)	0.77 (0.16–3.75)	.750
No	4 (57.14%)	32 (50.79%)		

Abbreviations: CI, confidence interval; n, number of patients; %, percentage of patients; R, reference; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

\*Statistically significant ( $p \leq .05$ ).

lung infection and mortality; however, our current result did not support the findings of previous literature.

A study published earlier in the *Lancet* has provided further insight into the clinical course and mortality risks for severe SARS-CoV-2 infection among patients in Wuhan.<sup>4</sup> In-hospital mortality was associated with older age, a higher SOFA score, and D-dimer level greater than 1 µg/ml, representing findings known to be associated with severe pneumonia.<sup>4</sup> The rate of in-hospital mortality was noted to be high (28%).<sup>4</sup> Furthermore, several studies have reported that pulmonary embolism and coagulopathy are frequently observed in SARS-CoV-2 patients.<sup>8,21–23</sup> Zhang et al.<sup>8</sup> reported that initial D-dimer level  $\geq 2.0$  µg/ml (equivalent to fourfold increase) was correlated with a higher incidence of mortality, compared to those with D-dimer level of less than 2.0 µg/ml and, therefore, could effectively predict in-hospital mortality in SARS-CoV-2 patients.<sup>8</sup>

In the meta-analysis study conducted by Martins-Filho et al.<sup>20</sup> to assess for mortality risks, dyspnea at the onset of disease, decreased gas exchange, increased IL-6 levels, coagulation abnormalities including increased D-dimer levels and multiorgan damage such as cardiac injury, acute kidney disease, acute respiratory distress syndrome (ARDS), and sepsis were considered important mortality predictors among SARS-CoV-2 positive patients.<sup>20</sup> Their results were relatively similar to our conclusion in regard to significant laboratory markers and multiorgan damage with outcome mortality. Therefore, closer attention must be paid during hospitalization to these factors to minimize the risk of multiorgan damage and possibly reverse it as soon as possible.

Our study noted that the most potential risk factor for mortality that demands immediate intervention, as discussed earlier, was the multiorgan damage. The presence of extrapulmonary organ failure was widely influencing the rapid progression of the illness and subsequent death. These observed injuries include ARDS, heart failure, renal failure, shock, and multiorgan failure. Therefore, the coexistence of these findings will precipitate higher mortality rates among the SARS-CoV-2-positive population. Full attention to potential organ injuries is a critical element in the management of the illness. Also, earlier recognition of multiorgan damage is a crucial step in introducing preventative interventions and health measures.

This study's main limitation is the type of study design, a longitudinal observational report of 80 patients with no comparison or matched controls. Thus, the presence of a control group is needed to truly assess differences in lab biomarkers and patients' characteristics with mortality outcomes. Second, the study was limited by the non-heterogeneity of our study population, which seems to be predominantly Hispanic patients due to the study's location in El Paso, Texas. There were missing values observed in some variables as retrieved from the patients' records. Moreover, measures of assessing the magnitude of organ damage such as cardiac injury, kidney injury, liver injury biomarkers, and sepsis were challenging to be evaluated in our study due to the presence of multiple censored variables. Last, microorganisms involved in patients with confirmed secondary bacterial infections were not covered in this study due to a lack of sputum culture and blood culture results by the time the data were collected.

TABLE 5 The association of socio-demographic characteristics, medical history, and clinical presentations with SARS-CoV-2 clinical outcomes in term of mortality using the multivariate logistic regression

Variables	Unadjusted OR (95 CI)	p Value	Adjusted OR (95 CI)	p Value
Bacterial lung coinfection				
Yes	10.83 (2.05–57.40)	.005*	9.10 (0.71–117.27)	.090
No				
Multiorgan damage				
Yes	103.50 (9.92–1079.55)	.001*	94.17 (7.39–1200.78)	.001*
No				

Abbreviations: CI, confidence interval; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

\*Statistically significant ( $p \leq .05$ ).



## 5 | CONCLUSION

In conclusion, this study is meant to reinforce current data published in the literature on mortality among SARS-CoV-2 patients, focusing on examining El Paso, Texas's affected population. Therefore, this study is unusual as it reflects a predominantly Hispanic demographic population with different genetics and social backgrounds than the rest of the United States. We explored and highlighted the relationship between sociodemographic data and other clinical outcomes on SARS-CoV-2 positive patients in the city of El Paso. We identified three main predictors for high mortality among the overall population of SARS-CoV-2 pneumonia patients. These predictors include IL-6, D-dimer, and multi-organ damage. The latter was found to have the highest potential risk for in-hospital deaths. This finding warrant implementation of aggressive health measures and treatment strategies to prevent and reverse adverse outcomes. Otherwise, all described predictors may be associated with fatal outcomes in patients with severe SARS-CoV-2 infection. Finally, observational studies, including systematic reviews and meta-analysis, are required to better understand the rapidly increasing mortality rate in different regions in the United States. and worldwide among SARS-CoV-2 patients.

## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

Nouf Almaghlouth conceptualized this study's primary objective, performed the statistical analysis, summarized all data, and wrote the final manuscript. Monique Davis and Michelle Davis computed the data and assisted with writing the draft of the final paper. Felix Anyiam contributed to data interpretation and to review the performed statistical analysis and the final manuscript. Roberto Guevarra contributed to the collection of data and revised this study. Suresh Antony contributed to the study's main design, data acquisition, and the final manuscript review and editing. Suresh Antony and Roberto Guevarra were involved in patient care. Nouf Almaghlouth and Felix Anyiam checked all data.

## DATA AVAILABILITY STATEMENT

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

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