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# Characteristics of mechanically ventilated COVID-19 patients in the Al-Ahsa Region of Saudi Arabia: a retrospective study with survival analysis

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**BACKGROUND:** About 5-10% of coronavirus disease 2019 (COVID-19) infected patients require critical care hospitalization and a variety of respiratory support, including invasive mechanical ventilation. Several nationwide studies from Saudi Arabia have identified common comorbidities but none were focused on mechanically ventilated patients in the Al-Ahsa region of Saudi Arabia.

**OBJECTIVES:** Identify characteristics and risk factors for mortality in mechanically ventilated COVID-19 patients.

**DESIGN:** Retrospective chart review

**SETTING:** Two general hospitals in the Al-Ahsa region of Saudi Arabia

**PATIENTS AND METHODS:** We included mechanically ventilated COVID-19 patients (>18 years old) admitted between 1 May and 30 November 2020, in two major general hospitals in the Al-Ahsa region, Saudi Arabia. Descriptive statistics were used to characterize patients. A multivariable Cox proportional hazards (CPH) model was used exploratively to identify hazard ratios (HR) of predictors of mortality.

**MAIN OUTCOME MEASURES:** Patient characteristics, mortality rate, extubation rate, the need for re-intubation and clinical complications during hospitalization.

**SAMPLE SIZE AND CHARACTERISTICS:** 154 mechanically ventilated COVID-19 patients with median (interquartile range) age of 60 (22) years; 65.6% male.

**RESULTS:** Common comorbidities were diabetes (72.2%), hypertension (67%), cardiovascular disease (14.9%) and chronic kidney disease (CKD) (14.3%). In the multivariable CPH model, age >60 years old (HR=1.83, 95% CI 1.2-2.7, *P*=.002), CKD (1.61, 95% CI 0.9-2.6, *P*=.062), insulin use (HR=0.65, 95% CI 0.35-.08, *P*<.001), and use of loop diuretics (HR=0.51, 95% CI 0.4, *P*=.037) were major predictors of mortality.

**CONCLUSION:** Common diseases in mechanically ventilated COVID-19 patients from the Al-Ahsa region were diabetes, hypertension, other cardiovascular diseases, and CKD in this exploratory analysis.

**LIMITATIONS:** Retrospective, weak CPH model performance.

**CONFLICTS OF INTEREST:** None.

In just two and a half months since the first clusters of pneumonia cases were reported in Wuhan, China, the World Health Organization (WHO) announced the newly discovered coronavirus disease 2019 (COVID-19) as a global pandemic.[1] The causative agent, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belongs to a large group of viruses called coronaviruses, commonly found in animals and humans. It can cause mild symptoms like rhinorrhea, headache, fever, cough, and sore throat that last for several days in immunocompetent people and can progress to symptoms of lower respiratory infections like acute bronchitis or pneumonia.[2] The most prevalent symptoms of this viral infection are fever, cough, and dyspnea, with a typical incubation period of 5 days and an illness duration of more than 8 days.[3,4] Males are more at risk than females and one-third of patients having comorbidities such as hypertension, cardiovascular diseases, and diabetes.[5]

It is estimated that 20% of hospitalized patients require admission to an intensive care unit (ICU), with a case fatality rate (CFR) of over 13%.[4] Common complications from the infection include acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury, disseminated intravascular coagulation (DIC) and sepsis. Additionally, in-hospital death is greater in elderly patients, males, and patients with co-morbidities.[6] Several studies from different countries have identified independent risk factors as being associated with higher mortality, like age and male sex.[7] However, the rank of comorbidities, which harbor the highest risk for being intubation and death, have varied among critically ill patients (hypertension,[8] heart failure, body mass index greater than 40, diabetes,[9-11] coronary artery disease, cerebrovascular disease,[12] smoking, chronic obstructive pulmonary disease,[13] and simultaneous occurrence of three or more comorbidities).[14] Several nationwide studies from Saudi Arabia have identified common comorbidities in intensive care patients (hypertension, diabetes, ischemic heart disease).[15,16]

In this study, we examined the clinical characteristics of COVID-19 mechanically ventilated patients admitted to two major hospitals in the Al-Ahsa region. We used survival analysis exploratively to investigate predictors of mortality. The findings of this study may be useful to local practitioners who require such information in this population.

## METHODS

This was a retrospective study conducted via medical record review. Patients were included if they were 18 years of age or older, had a COVID-19 diagnosis confirmed with SARS CoV-2 by real time reverse transcriptase polymerase chain reaction, and were admitted to King Fahad Hospital Hofuf (KFH) and Prince Saud Bin Jalawi Hospital (PSBJH) between 1 May 2020, and 30 November 2020. Only COVID-19 patients admitted to the ICU or inpatient ward with a mechanical ventilator were included. The list of critical cases was obtained from medical records. We excluded patients who died or recovered before being connected to a mechanical ventilator during their hospital stay as well as those who had incomplete files. This study was approved by both King Faisal University (IRB# 2020-05-10) and King Fahad Hospital Hofuf (IRB# H-05-H5-065) Institutional Review Board Human Subjects Protection Programs.

Demographic characteristics and other clinical variables such as comorbid conditions, medication used during hospitalization, symptoms at presentation, COVID-19 regimen used and clinical complications were collected from the electronic and non-electronic medical records and managed using Research Electronic Data Capture (REDCap) software.[17] The patient list was obtained from the medical records staff. There was no formal sample size calculation. We screened all patient charts at our disposal using convenience sampling.[18] The primary outcome was to identify the characteristics of patients that required mechanical ventilation in the Al-Ahsa region. We report the mortality rate, extubation rate, need for re-intubation and clinical complications during hospitalization. We also explored predictors of mortality.

We present continuous data as median with interquartile range (IQR). Categorical data are presented as frequencies and percentages. We used survival analysis by fitting a Kaplan-Meier (KM) model for the mortality outcome. Two KM models were fitted: one when time 0 was the time of admission, and the second when time 0 was initiation of mechanical ventilation. We censored the data at the time of follow up if no event occurred (i.e., patient discharged alive). We plotted survival probability indicating the median time of survival. We then implemented univariable Cox proportional hazards (CPH), a semiparametric model, to identify important and pertinent clinical predictors of mortality. The results of the univariable analysis guided our approach to narrowing down important variables to be included in the multivariable CPH, including the use of clinical importance in our modeling. Starting with a full model, we implemented backward elimination to obtain the best model based on the Akaike information criterion (AIC). Some variables were retained in the final model despite their non-significance due to improving the overall model fit. The proportional hazard assumption was tested using Schoenfeld residuals, with plots and statistical tests of independence between residuals and time. The time-varying effect assumption was tested using the "timereg" package, which uses a resampling method with 500 simulations to test time-varying effects.[19] The package provides two statistical tests for time-varying coefficients (the Kolmogorov-Smirnov test and the Cramér–von Mises criterion). We checked Martingale residuals for the linearity assumption. In case of violation, the variable was transformed into a categorical variable. The variables included in the final model were reported with hazards ratios along with 95% confidence intervals (CI). We quantified the predictive ability of the model using the index of discrimination (C index), the concordance between the predicted and observed survival.[20] This was calculated from Kendall's $\tau$ and Somers' rank correlation (Dxy). C index values close to 1 indicate excellent prediction ability, and values <0.5 indicate the model is not better than chance. To internally validate the model, a bootstrapping bias corrected (overfitting corrected) estimate of the C index was obtained.[21] We emphasize that modeling survival in this cohort was exploratory and not meant to inform clinical practice. All statistical analyses were performed using the R Core Team (2020) software (R Foundation for Statistical Computing, Version 4.0.1, Vienna, Austria). The following R packages were used in our analyses: survival, survminer, ggplot2, timereg, MASS and rms.[22-24]

## RESULTS

Of 1976 patients admitted for COVID-19 in the two hospitals during the study period only 167 patients were identified as critical cases, of which 154 patients were included in our analysis. Twelve were excluded for various reasons (**Figure 1**). The majority (72%) were admitted to KFH, and most were from the Eastern region of Saudi Arabia (77.1%). The median age (IQR) was 60 (22) years old (range, 49 to 71 years). Male patients represented 65.6% of the cohort. Diabetes (72.7%) and hypertension (67%) were the most prevalent comorbidities, followed by other cardiovascular diseases (14.9%) and chronic kidney disease (CKD) (14.3%) (**Table 1**). All patients with diabetes were using insulin, either alone or in combination with other medications. Acetaminophen (74%) and loop diuretics (59.7%) were commonly used. Presenting symptoms and regimen used for COVID-19 management are listed in **Table 1**. Four among 154 cases had hematological diseases, including two with sickle cell disease patients (SCD), one had both SCD and glucose 6 phosphate dehydrogenase deficiency, (G6PD) and one case had only G6PD. Most patients died (n=138, 89.6%) (**Table 2**). Thirteen (8.4%) needed reintubation. Twenty (13%) were fully extubated. The most common complication was ARDS (89%) followed by acute kidney injury (38.3%), sepsis (33.1%) and multiorgan failure (20.8%).

The median survival of the cohort was 13 days (95% CI:11 to 16) and the median survival after mechanical ventilation was 8 days (95% CI: 6 to 9). The 50% probability of survival was at day 13 (**Figure 2A**). From the date of mechanical ventilation the 50% probability of survival was at day 8 (**Figure 2B**). Factors associated with mortality were age greater than 60 years old and chronic kidney disease (**Table 3**). Factors associated with a decrease in mortality were insulin use and loop diuretic use. The model had a corrected C index of 0.59 (weak performance). The KM curves for survival for these variables are plotted in (**Figures 3A, B, C, D**).

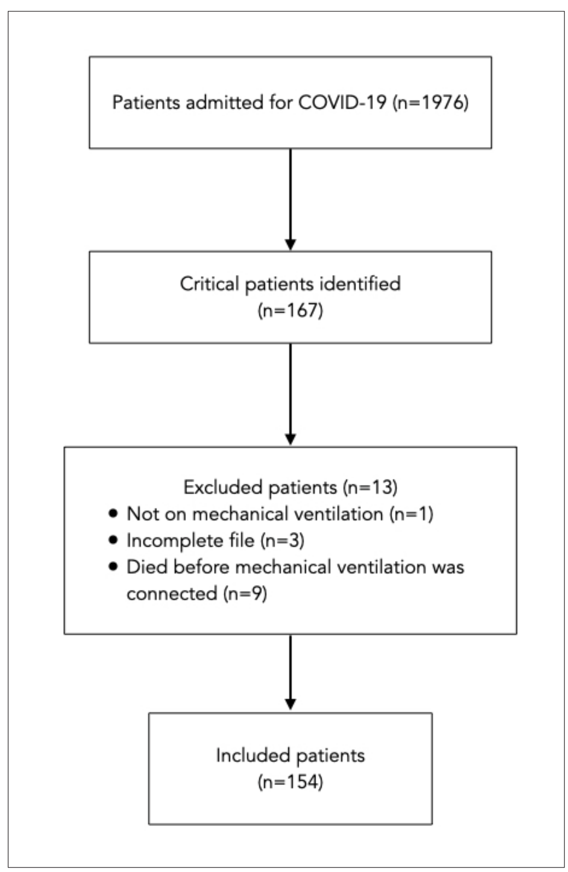


**Figure 1.** Patient selection flowchart.

**Table 1.** Baseline characteristics of mechanically ventilated COVID-19 patients (n=154).

| | |
|---|---|
| King Fahad Hospital Hofuf | 111 (72.07) |
| Prince Saudi Bin Jalawi Hospital | 43 (27.9) |
| Age (years) (median, IQR, range) | 60 (22), 49-71 |
| Female | 53 (34.4) |
| Ethnicity | |
| Middle eastern | 120 (77.1) |
| South/Southeast or Central Asian | 32 (20.7) |
| African | 2 (1.3) |
| Weight (kg) (median, IQR, range) | 79 (23.5), 41-168 |
| Comorbidities | |
| Diabetes | 112 (72.7) |
| Hypertension | 95 (61.7) |
| Established cardiovascular disease[a] | 23 (14.9) |
| Chronic kidney disease | 22 (14.3) |
| Asthma | 9 (5.8) |
| Atrial fibrillation | 8 (5.2) |
| Chronic obstructive pulmonary disease | 4 (2.6) |
| Cancer | 3 (1.9) |
| Sickle cell disease | 3 (1.9) |
| Stroke | 2 (1.3) |
| Dyslipidemia | 2 (1.3) |
| Glucose-6-phosphate-dehydrogenase deficiency | 2 (1.3) |
| Venous thromboembolism | 1 (0.6) |
| Autoimmune disease | 1 (0.6) |
| Medications | |
| Acetaminophen | 114 (74.0) |
| Insulin | 112 (72.7) |
| Loop diuretics | 92 (59.7) |
| Calcium channel blocker | 61 (39.6) |
| Statin | 44 (28.6) |
| Aspirin | 41 (26.6) |
| Beta-blocker | 27 (17.5) |
| Angiotensin converting enzyme inhibitor | 12 (7.8) |
| Thiazide diuretics | 6 (3.9) |

**Table 1 (cont.)**. Baseline characteristics of mechanically ventilated COVID-19 patients (n=154).

| | |
|---|---|
| Angiotensin Receptor Blocker | 5 (3.2) |
| Non-steroidal anti-inflammatory drug | 2 (1.3) |
| Symptoms at presentation | |
| Dyspnea | 122 (79.2) |
| Fever | 97 (63.0) |
| Cough | 93 (60.4) |
| Diarrhea | 6 (3.9) |
| COVID-19 regimen | |
| Dexamethasone | 109 (70.8) |
| Favipiravir | 100 (64.9) |
| Azithromycin alone | 77 (50.0) |
| Tocilizumab | 77 (50.0) |
| Lopinavir/ritonavir | 60 (39.0) |
| Hydroxychloroquine/ azithromycin | 29 (18.8) |
| Hydroxychloroquine alone | 17 (11.0) |

Data are n (%) unless noted otherwise. a Established cardiovascular disease: a documented history of stable angina, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery, or myocardial infarction (MI). Heart failure and cerebrovascular disease included transient ischemic attack (TIA) or stroke.

## DISCUSSION

The aim of our study was to understand the characteristics of mechanically ventilated COVID-19 patients who were admitted to two of the tertiary care hospitals in Saudi Arabia's Al-Ahsa region. The study included mechanically ventilated COVID-19 patients with a median age of 60 years old. Advanced age is a known risk factor for critical illness in COVID-19 patients.[25-28] Our study cohort were both advanced-aged and critically ill, which mandated invasive mechanical ventilation, and hence the higher overall mortality rate in our cohort. The study by Khan and Alruthia et al[29] from Saudi Arabia found that mechanical ventilated patients have five times the risk of death compared to non-mechanically ventilated patients. The Khan and Alruthia study was conducted using the Health Electronic Surveillance Network (HESN) database from the Saudi Ministry of Health (MoH) for COVID-19 patients. The majority of the patients in their study were from Madina (68.8%); only 82 patients (5.8%) of the patients were from Al-Ahsa. Their results were comparable to our cohort. The survival probability

**Table 2.** Clinical outcomes and complications (n=154).

| | |
|---|---|
| Clinical outcomes | |
| Death | 138 (89.6) |
| Fully extubated | 20 (13) |
| Need for re-intubation | 13 (8.4) |
| Discharge alive | 16 (10.4) |
| Clinical complications | |
| Acute respiratory distress syndrome | 137 (89.0) |
| Acute kidney injury | 59 (38.3) |
| Sepsis | 51 (33.1) |
| Multi-organ failure | 32 (20.8) |
| Pulmonary embolism | 4 (2.6) |
| Cardiac injury | 4 (2.6) |
| Disseminated intravascular coagulation | 2 (1.3) |
| Stroke | 2 (1.3) |

Data are n (%).

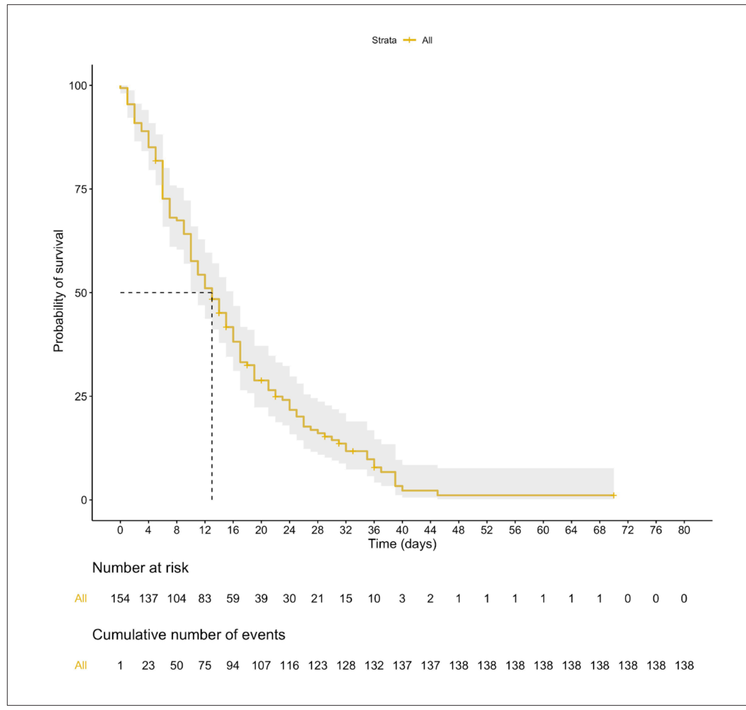


**Figure 2A.** Survival probability date of admission (dashed line is median time; shadowed areas are confidence intervals).

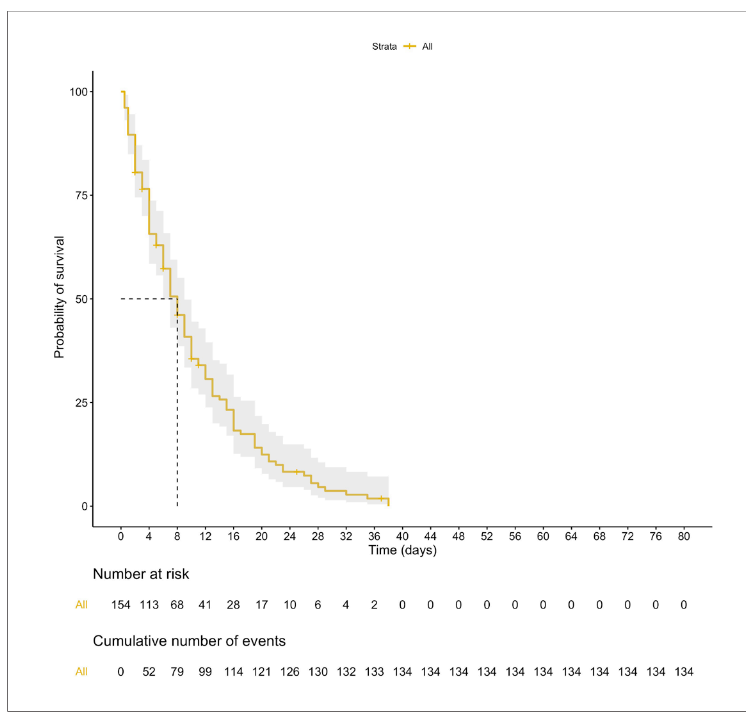


**Figure 2B.** Survival probability from date of starting mechanical ventilation (dashed line is median time; shadowed areas are confidence intervals).

of the patients in the Khan et al study was estimated to be less than 50% after day 10 of admission. Although not emphasized in the report, the overall mortality in mechanically ventilated patients was greater than 80% at the end of the follow up. Another nationwide study by Almutair et al conducted in 20 tertiary hospitals in Saudi Arabia examined critically ill COVID-19 patients admitted to the intensive care units. As in our study, diabetes (52.4%) and hypertension (46%) were the most common comorbidities. In line with our findings, the mortality rate among the recipients of mechanical ventilation was high at 82.7%.[15] A large study by Alhumaid et al[30] reported clinical features and prognostic factors of 1014 COVID-19 patients from six hospitals in Al-Ahsa between 1 March 2020 and 30 July 2020, a 2-month overlap with our study and found the same common comorbidities as in our study. However, Alhumaid et al did not report mortality rates among patients on mechanical ventilation.

A study from Mexico reported high mortality at 73.7% among the mechanically ventilated COVID-19 population.[31] On the other hand, a Spanish study reported a better survival probability in mechanically ventilated COVID-19 patients (>50% after 180 days of follow up).[32] The meta-analysis of 69 studies by Lim et al reported a CFR of 45% (95% CI: 39 to 52%) among mechanically ventilated COVID-19.[33] The difference

**Table 3.** Multivariable Cox proportional hazards model and survival analysis.

| Variable | Hazard ratio (95% CI), *P* value | Median survival in days (95% CI), *P* value |
|---|---|---|
| Age >60 | 1.83 (1.239 - 2.706), *P*=.002 | 7 (5-9) vs 9 (7-13), *P*=.034 |
| Chronic kidney disease | 1.61 (0.977- 2.638), *P*=.062 | 7 (4-11) vs 8 (6-10), *P*=.099 |
| Insulin use | 0.65 (0.439- 0.975), *P*=.037 | 8 (7-10) vs 7 (5-9), *P*=.24 |
| Loop diuretics use | 0.51 (0.348- 0.766), *P*<.001 | 9 (7-12) vs 6 (4-10), *P*=.035 |

Backward elimination selection process methodology to select the best predictors for mortality (started from full model). Median survival calculated from a Kaplan-Meier model. Log rank test for *P* value. Time (0) mechanical ventilation day. Corrected C index: 0.59

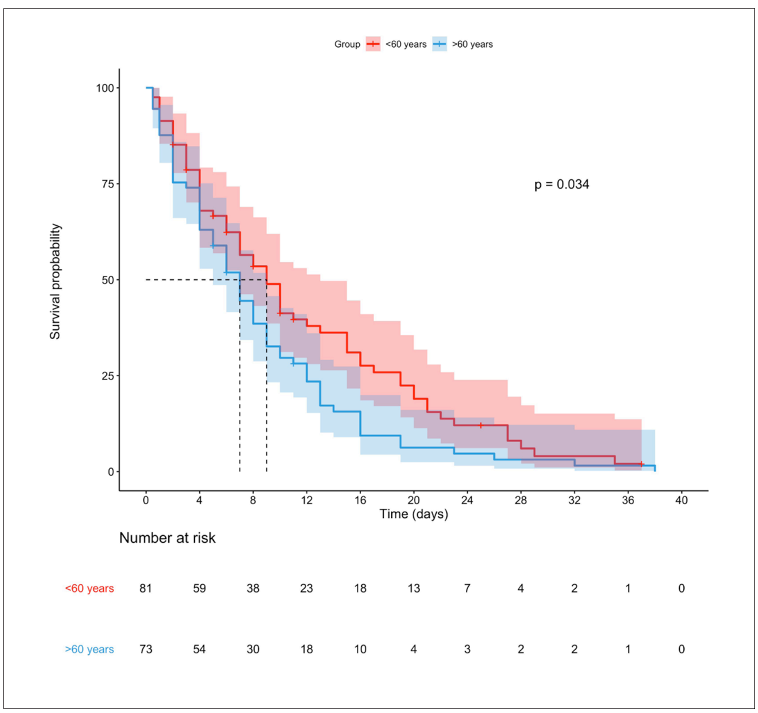


**Figure 3A** . Survival probability by age group (dashed line is median time; shadowed areas are 95% confidence intervals).

in CFRs reported in the literature might be related to quality of care, setting and/or regional differences. The discussion on how to improve mechanically ventilated outcomes has already started in Saudi Arabia. The National Approach to Standardize and Improve Mechanical Ventilation (NASAM) project was initiated in 2019 with a goal to improve patient care by applying evidence-based practices.[34] Although the project did not include mechanically ventilated COVID-19 patients prior to the pandemic, improvement of mechanical ventilation was the goal of this project. A 2-year study (2016 to 2018) by Ismaeil et al from Saudi Arabian hospitals reported an overall mortality of 37% among adults who were mechanically ventilated,[35] which is lower than in studies of COVID-19 patients in Saudi Arabia.[15]

The impact of chronic diseases on COVID-19 prognosis is well established.[36,37] Conditions such as heart disease, diabetes, cancer, chronic renal disease, and obesity raise the risk of COVID-19-related severe illness.[38] Consistent with earlier findings, common comorbid conditions in our mechanically ventilated cohort were diabetes (72.7%), hypertension (61.7%), cardiac disease (14.9%) and CKD (14.3%). This indicates that conditions such as diabetes and hypertension are common risk factors in COVID-19 patients undergoing mechanical ventilation.[39,40] Our exploratory analysis confirms advanced age and CKD as independent risk factors for death.

As we limited our analysis to mechanical ventilation, we found a few findings similar to findings from the study by Alhumaid et al.[30] For example, the use of favipiravir was high in our cohort (64.9%) vs their report of 54.6% in the ICU setting. We report higher use of tocilizumab (50% vs 29.7%) dexamethasone (50% vs 34.8%) and lopinavir/ritonavir (39% vs 16.1%). Lastly, the exploratory analysis revealed unexpected findings. Insulin use was a predictor of lower mortality in our multivariable model. This finding does not agree with that in the published literature. The meta-analysis by Yang et al[41] found that insulin use was associated with a two-fold increase in the risk of mortality (odds ratio=2.10; 95% CI: 1.51-2.93). In addition to the wide confidence interval in the multivariable CPH model for this factor (HR=0.65, 95% CI 0.439- 0.975, *P*=.037) the KM model did not reveal any significance in survival (**Figure 3C**) in our cohort (*P*=.24). This would cast doubt on the variable being a significant predictor. The addition of more important variables in the ICU settings such as oxygenation level, severity scores and hemoglobin A1c may render this variable unimportant.[42] This incidental finding may be the result of not adjusting for important confounders. The use of explanatory modeling that can establish causal effects may be better than using prediction modeling in this case.[43] On the other hand, a mouse study showed that insulin therapy is associated with downregulation of ACE2 receptors.[44] Whether this effect can result in clinical benefits for COVID-19 patients is unknown. The use of loop diuretics as a predictor of low mortality was interesting as well. Mechanistically and in addition to its diuretic effects, furosemide may have an effect on dyspnea due to its effect on the release of pro-inflammatory cytokines (interleukin-9, IL-8 and tumor necrosis factor.[45] The role of furosemide as a potential COVID-19 treatment is being investigated.[46] Our study also reported a high hazard ratio for patients having CKDs who must undergo mechanical ventilation. This confirms earlier findings which reported a high ICU admission and mortality rate among renally ill UK COVID-19 patients, indicating that CKD is a risk factor for in-hospital mortality in COVID-19 patients.[47]

Although the study's principal objectives were met, there are several limitations that must be addressed. Due to the retrospective nature of the study, there is a risk of bias as we relied solely on the records accessible at the hospital. Manual collection of data was difficult. The availability of electronic medical record systems would be beneficial for future projects. Mechanical ventilation takes on medical wards and the ICU, but ICU beds may be unavailable. We did not explore whether the site of ventilation had an effect on mortality. Moreover, the impact of vaccination status cannot be explored as vaccination was unavailable during the study period. Exploratory CPH analysis was not informative due to the weak performance of the model. Enhancing the performance of the predictability of the model would require additional variables and a larger sample size. Considering powerful variables such as Acute Physiology and Chronic Health Evaluation II (APACHE-II) or Sequential Organ Failure Assessment score (SOFA) might enhance the predictability of our model.

In conclusion, advanced age and CKDs were independent risk factors for the need of mechanical ventilation in COVID-19 patients. A high prevalence of hypertension and diabetes mellitus were also found among our study population. Further, large-scale collaborative studies involving a number of regions of Saudi Arabia will help in determining the characteristics of COVID-19 patients that need mechanical ventilation, which may effectively help in controlling the infection and its devastating impact in our country.

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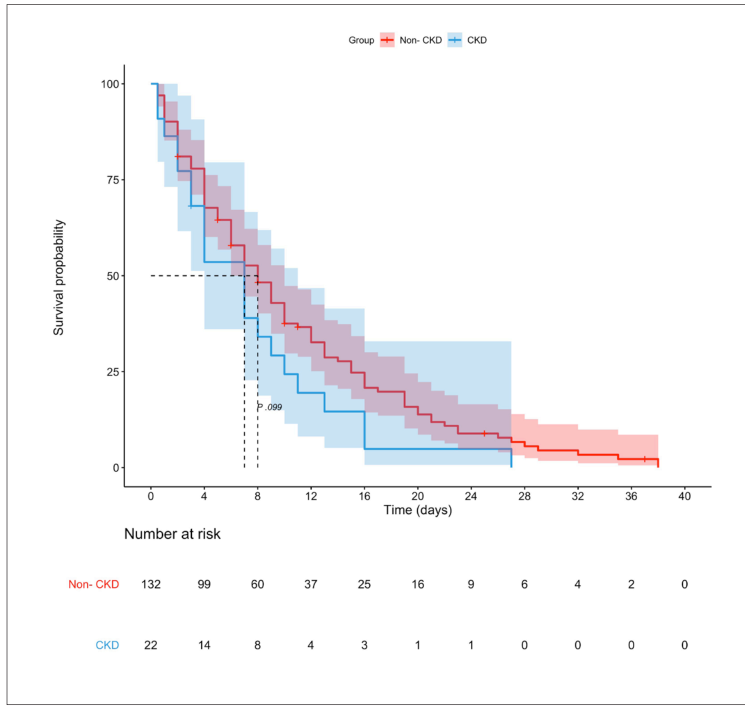


**Figure 3B.** Survival probability by chronic kidney disease (dashed line is median time; shadowed areas are 95% confidence intervals).

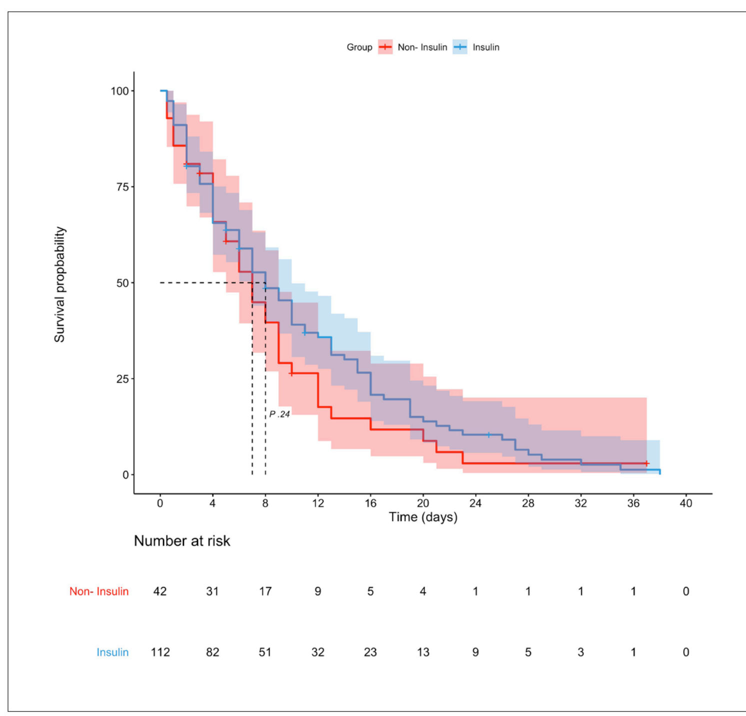


**Figure 3C.** Survival probability by insulin use (dashed line is median time; shadowed areas are 95% confidence intervals).

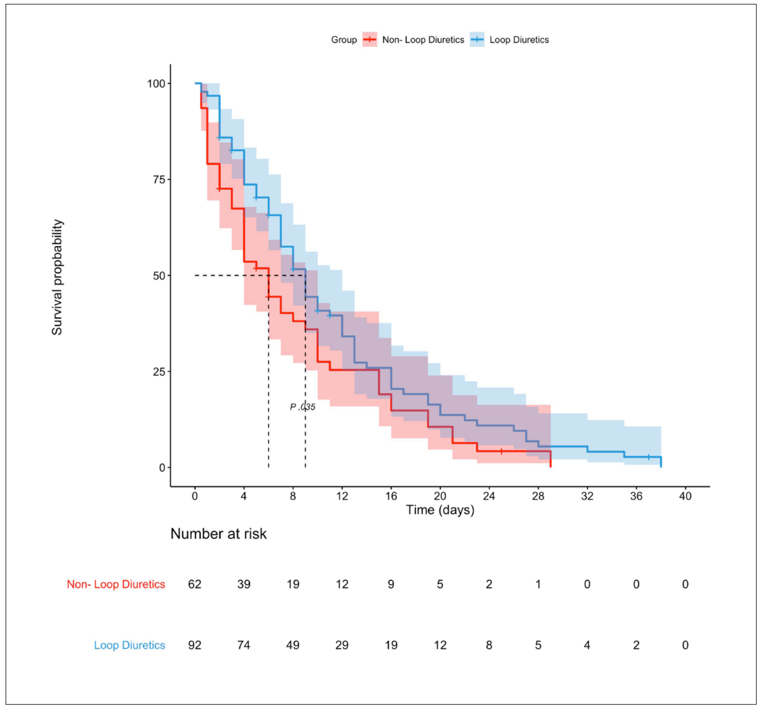


**Figure 3D.** Survival probability by use of loop diuretics (dashed line is median time; shadowed areas are 95% confidence intervals).

## REFERENCES


**1.** World Health Organization. Archived: WHO Timeline - COVID-19. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline. Accessed on 18th October 2021

**2.** Alanagreh LA, Alzoughool F, Atoum M. The human coronavirus disease COVID-19: its origin, characteristics, and insights into potential drugs and its mechanisms. Pathogens. 2020;9(5):331.

**3.** Grant MC, Geoghegan L, Arbyn M, Mohammed Z, McGuinness L, Clarke EL, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): a systematic review and meta-analysis of 148 studies from 9 countries. PloS one. 2020;15(6):e0234765.

**4.** Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.

**5.** Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, Rosser EC, Webb K, Deakin CT. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nature communications. 2020 Dec 9;11(1):1-0.

**6.** Martins-Filho PR, Tavares CS, Santos VS. Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. Eur J Intern Med. 2020;76:97.

**7.** Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.

**8.** Drager LF, Pio-Abreu A, Lopes RD, Bortolotto LA. Is hypertension a real risk factor for poor prognosis in the COVID-19 pandemic?. Curr Hypertens Rep. 2020;22(6):1-6.

**9.** Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369.

**10.** Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020;108:154262.

**11.** Hur K, Price CP, Gray EL, Gulati RK, Maksimoski M, Racette SD, et al. <?covid19?> Factors Associated With Intubation and Prolonged Intubation in Hospitalized Patients With COVID-19. Otolaryngol Head Neck Surg. 2020;163(1):170-8.

**12.** Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, et al. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. Chest. 2020;158(1):97-105.

**13.** Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of COVID-19: A systemic review and meta-analysis. J Med Virol. 2020;92(10):1915-21.

**14.** Kammar-García A, Vidal-Mayo JD, Vera-Zertuche JM, Lazcano-Hernández M, Vera-López O, Segura-Badilla O, et al. Impact of comorbidities in Mexican SARS-CoV-2-positive patients: a retrospective analysis in a national cohort. Rev Invest Clin. 2020;72(3):151-8.

**15.** Al Mutair A, Elhazmi A, Alhumaid S, Ahmad GY, Rabaan AA, Alghdeer MA, Chagla H, Tirupathi R, Sharma A, Dhama K, Alsalman K. Examining the Clinical Prognosis of Critically Ill Patients with COVID-19 Admitted to Intensive Care Units: A Nationwide Saudi Study. Medicina. 2021 Sep;57(9):878.

**16.** Al Sulaiman KA, Aljuhani O, Eljaaly K, Alharbi AA, Al Shabasy AM, Alsaeedi AS, Al Mutairi M, Badreldin HA, Al Harbi SA, Al Haji HA, Al Zumai OI. Clinical features and outcomes of critically ill patients with coronavirus disease 2019 (COVID-19): A multicenter cohort study. International Journal of Infectious Diseases. 2021 Apr 1;105:180-7.

**17.** Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208-08.

**18.** Vassar M, Holzmann M. The retrospective chart review: Important methodological considerations. J Educ Eval Health Prof

2013;10:12.
**19.** Scheike TH, Zhang MJ. Analyzing competing risk data using the R timereg package. J Stat Softw. 2011;38(2).
**20.** Somers RH. A new asymmetric measure of association for ordinal variables. American sociological review. 1962:799-811.
**21.** Regression Modeling Strategies. With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis, second dedition. Springer Nature, 2015. ISBN 978-3-319-19425-7.
**22.** Terry M. Therneau, Patricia M. Grambsch (2000). Modeling Survival Data: Extending the Cox Model. Springer, New York. ISBN 0-387-98784-3.
**23.** Venables WN, Ripley BD (2002). Modern Applied Statistics with S, Fourth edition. Springer, New York. ISBN 0-387-95457-0, https://www.stats.ox.ac.uk/pub/MASS4/.
**24.** Wickham H (2016). ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York. ISBN 978-3-319-24277-4, https://ggplot2.tidyverse.org
**25.** Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323(18):1775–6.
**26.** Fisher D, Heymann D. Q&;A: the novel coronavirus outbreak causing COVID-19. BMC Med 2020;18(1):57.
**27.** Rossella P, Caterina S, David K, Nikki K, Salvatore R. Similarity in case fatality rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. J Infect Dev Ctries 2020;14(02).
**28.** Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med2020;201(11):1380–8.
**29.** Khan AA, AlRuthia Y, Balkhi B, Alghadeer SM, Temsah MH, Althunayyan SM, Alsofayan YM. Survival and estimation of direct medical costs of hospitalized COVID-19 patients in the Kingdom of Saudi Arabia. International journal of environmental research and public health. 2020 Jan;17(20):7458.
**30.** Alhumaid S, Al Mutair A, Al Alawi Z, Al Salman K, Al Dossary N, Omar A, Alismail M, Al Ghazal AM, Jubarah MB, Al Shaikh H, Al Mahdi MM. Clinical features and prognostic factors of intensive and non-intensive 1014 COVID-19 patients: an experience cohort from Alahsa, Saudi Arabia. European Journal of Medical Research. 2021 Dec;26(1):1-3.
**31.** Ñamendys-Silva SA, Gutiérrez-Villaseñor A, Romero-González JP. Hospital mortality in mechanically ventilated COVID-19 patients in Mexico. Intensive Care Med. 2020 ;46(11):2086-8.
**32.** Penuelas O, del Campo-Albendea L, de Aledo AL, Añón JM, Rodríguez-Solís C, Mancebo J, et al. Long-Term Survival of Mechanically Ventilated Patients with Severe COVID-19: An Observational Cohort Study.
**33.** Lim ZJ, Subramaniam A, Ponnapa Reddy M, Blecher G, Kadam U, Afroz A, Billah B, Ashwin S, Kubicki M, Bilotta F, Curtis JR. Case fatality rates for patients with COVID-19 requiring invasive mechanical ventilation. A meta-analysis. American journal of respiratory and critical care medicine. 2021 Jan 1;203(1):54-66.
**34.** Arabi YM, Al Aseri Z, Alaama T, Alqahtani A, Alharthy A, Almotairi A, et al. National approach to standardize and improve mechanical ventilation. Ann Thorac Med. 2019;14(2):101.
**35.** Ismaeil T, Almutairi J, Alshaikh R, Althobaiti Z, Ismaiel Y, Othman F. Survival of mechanically ventilated patients admitted to intensive care units: Results from a tertiary care center between 2016-2018. Saudi medical journal. 2019 Aug;40(8):781.
**36.** Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19. JAMA Netw Open 2020;3(12):e2029058. Erratum in: JAMA Netw Open 2021;1:e2036103 CrossRefexternal icon
**37.** Khan A, Althunayyan S, Alsofayan Y, Alotaibi R, Mubarak A, Arafat M, et al. Risk factors associated with worse outcomes in COVID-19: a retrospective study in Saudi Arabia. East Mediterr Health J. 2020;26(11):1371–1380.
**38.** Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584(7821):430–6.
**39.** Centers for Disease Control and Prevention. People with certain medical conditions. Updated March 29, 2021. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed April 8, 2021.
**40.** Al-Omari A, Alhuqbani WN, Zaidi AR, Al-Subaie MF, AlHindi AM, Abogosh AK, et al Clinical characteristics of non-intensive care unit COVID-19 patients in Saudi Arabia: a descriptive cross-sectional study. J Infect Public Health. 2020 Nov 1;13(11):1639-44.
**41.** Yang Y, Cai Z, Zhang J. Insulin Treatment May Increase Adverse Outcomes in Patients With COVID-19 and Diabetes: A Systematic Review and Meta-Analysis. Front Endocrinol. 2021;12.
**42.** Kow CS, Hasan SS. Insulin Treatment May Not Be Associated with Increased Mortality in Patients with COVID-19 and Concurrent Diabetes. Endocrine Research. 2021 Apr 3;46(2):51-2.
**43.** Sainani KL. Explanatory versus predictive modeling. PM&R. 2014 Sep;6(9):841-4.
**44.** Roca-Ho H, Riera M, Palau V, Pascual J, Soler MJ. Characterization of ACE and ACE2 expression within different organs of the NOD mouse. International journal of molecular sciences. 2017 Mar;18(3):563.
**45.** Yuengsrigul A, Chin TW, Nussbaum E. Decreased cytokine production from human peripheral blood mononuclear cells (pbmcs) by furosemide. 77. Pediatr Res. 1996;39(4):15-.
**46.** Brennecke A, Villar L, Wang Z, Doyle LM, Meek A, Reed M, et al. Is Inhaled Furosemide a Potential Therapeutic for COVID-19?. Am J Med Sci. 2020;360(3):216-21.
**47.** Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20133 UK patients in hospital with COVID-19 using the ISARIC WHO clinical characterization protocol: prospective observational cohort study. BMJ. 2020;369:m1985. https://doi.org/10.1136/bmj.m1985.