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# Predictors of Mortality for Patients with Severe COVID-19 Admitted to the Intensive Care Unit

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## Abstract

*Background:* Severe Covid-19 infection resulted in high death rates globally, however, the predictors of mortality had been varied widely regarding their significance or effects due to different viral mutations, settings, or subjects.

*Aim of Study:* To identify the predictors of mortality in patients with severe Covid-19 who were admitted to the intensive care unit.

*Patients and Methods*: An observational, prospective cohort study was conducted on 231 consecutive COVID-19 patients admitted to ICU, where we compared the data for survivors versus the non-survivors, and our primary end point was death or discharge.

*Results:* Fifty-one patients (22%) were non-survivors, where they had significantly more comorbid conditions, abnormal WBC count, lymphopenia, increased ESR and CRP, impaired renal function, and hyperbilirubinemia; while in multivariant analysis using the Cox regression model, the higher levels of total bilirubin, and low counts of WBCs were independently associated with higher mortality among cases after adjustment of confounders with *p*-value 0.001 and 0.040 respectively.

*Conclusion:* Hyperbilirubinemia due to direct or indirect liver injury in patients with severe Covid-19 in addition to inappropriate response of WBC to the infection constituted the predictors of mortality in our cohort.

***Key Words:*** *Covid-19 – ICU – Mortality.*

## Introduction

**COVID-19** is a multisystemic disease resulting from infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that initially affects the respiratory system in mild or moderate forms, but its severe form can occur in 20% of patients causing respiratory failure, acute respiratory distress syndrome (ARDS), multi-organ damage, and other complications, yet up to 6.5 million died all over the world [1-3]. Many searches looked upon the mortality predictors in this disease spectrum and suggested many personal and clinical predictors such as age, hematological and coagulation biomarkers, immune status, renal, hepatic, and cardiac impairment, and the presence of comorbid conditions [4-13]. Interestingly, the significance of these predictors, their values, and their odds ratio are variables and different, this can be explained by the various mutations that occurred in the virus, the methods, and the subjects used in these searches [14,15]. Nevertheless, the predictors in patients with a severe form of the disease and admitted to the ICU may be varied due to the accumulated effects of infection with a severe form, and being admitted in intensive care, so it is very important to address and understand the clinical characteristics of those patients, which can help in mapping the disease, identify the high-risk population in our area, and guide future health care management.

*Aim of the work:*

To identify predictors of mortality of patients with severe COVID-19 in the ICU.

## Subjects and Methods

An observational, prospective cohort study was conducted on 231 consecutive COVID-19 patients,

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who met the inclusion criteria and were admitted to the ICU of King Fahd Hospital, Medina, KSA at the period from 1st May, till the end of October 2020. In-hospital mortality or discharge was the primary endpoint. The inclusion criteria are all adult patients >18 years old, confirmed SARS-CoV-2 infection by RT-PCR or antigen test **[16]**, initially admitted to our hospital, and accepted to share in the study, while the process of suspicion-to-confirmation of COVID-19 was guided by the Saudi Centers for Disease Control and Prevention guidelines (updated in June 2020) **[17]**. Those patients who were referred from other hospitals or centers and those who refuse to participate in the study orimpossible to obtain their consent form (due to a critical/unconscious state) were excluded. All the medical history data and initial investigations were recorded including CBC (total and differential count), clotting profile, ABG, renal (urea and creatinine), hepatic functions (ALT, AST, PT, albumin, bilirubin, and total protein), cardiac enzymes (CPKmb, troponin), serum electrolytes (sodium and potassium), and inflammatory markers (ESR, CRP). They were followed-up and received the usual protocol of management according tothe local protocols made by the Ministry of Health **[18]**. Finally, we compared the data for survivors versus non-survivors. Ethical approval has been taken (IRB525-July, 2020).

*Data analysis:* Data has been collected and entered into the computer using SPSS (Statistical Package for Social Science) program for statistical analysis, (version 21; Inc., Chicago. IL). Data were extracted from the patients' sheets and entered as numerical or categorical, as appropriate. Two types of statistics have been done: (1) Descriptive statistics: Where quantitative data are shown as mean and SD, while qualitative data are expressed as frequency and percent. (2) Analytical statistics: where the Chi-square test was used to measure the association between qualitative variables. Student *t*-test has been used to compare the mean and SD of 2 sets of quantitative normally distributed data while Mann Whitney test was used when this data is not normally distributed. The Cox regression model has been used to give an adjusted hazard ratio and 95% confidence interval of the effect of the different factors on survival. A *p*-value of below 0.05 was considered statistically significant.

## Results

Table (1) shows that 231 patients were included in this study, nearly half of the subjects aged 41-60-year-old (47.6%), while those aged 18-40 constituted the minority (14.8%); regarding gender, 133 were males (57.6%), and 98 were females (42.4%); the table also shows that 51 patients (22%) were non-survivors, where more than half of them are males (56.9%), have an average age of 57.98 years old, and with nearly half of them aging from 41-60 years old (45.1%); however, there were no statisticallysignificant differences between survivors and non-survivors regarding age or gender ($p>0.05$). The follow-up period of patients was ranging from 7-49 days with mean ± SD of 18.53±8.14 days. Regarding the medical history of patients, the non-survivors had significantly more comorbid conditions (74.51%) compared to survivors (32.78%), on the contrary, the history of contact with confirmed positive cases of COVID-19 was significantly more in survivors (47.78%) versus non-survivors (21.57%). No significance has been found between the two groups regarding the history of GIT symptoms ($p<0.05$) (Table 2). Regarding the blood picture and the inflammatory markers, Table (3) shows that means ±SD of WBC, ESR 1st hour, and CRP were significantly higher in non-survivors compared to survivors (11.89±5.52 versus 9.04±4.74, 88.79±39.63 versus 66.78±39.63, and 158.25±64.61 versus 83.37±70.96 respectively); while the mean ± SD of the Hb level, lymphocytic count, and d-dimer levels were significantly lower in non-survivors compared to survivors (11.31 ±2.79 versus 12.41 ± 2.61, 12.43± 13.33 versus 21.19± 16.49, and 22.5±55.5 versus 46.3±90.6 respectively) Regarding liver profiles, Table (4) shows that the mean ± SD of the serum bilirubin was significantly elevated in non-survivors versus the survivors (3.08±0.3 versus 1.69±0.3 respectively), while ALT, AST, PT, s. albumin, and total protein were insignificantly ($p<0.05$) higher in non-survivors versus survivors. The mean+SD of urea and creatinine were significantly higher in non-survivors compared to the survivors (1.83 ±1.73 versus 1.37± 1.01, and 77.89±54.94 versus respectively), however, there were no significant differences between the two groups regarding the electrolytes (Na and K), although they were slightly higher in the non-survivors group. Finallyin multivariant analysis using the Cox regression model in Table (5) we found that, higher levels of Total bilirubin, and low counts of WBCs were independently associated with higher mortality among cases after adjustment of confounders (age, gender, Lymphocytes, history of contact, Hb, creatinine, CRP, presence of co-morbidities, D-dimer, Urea, and ESR) with *p*-value 0.001 and 0.040 respectively.

Table (1): Demographic data of participants distributed by their survival.

| Variables | Survivors (n=180) | % | Non-survivors (n=51) | % | Total (n=231) | % | *p*-value |
|---|---|---|---|---|---|---|---|
| Age (Mean ± SD) | 55.35±14.99 | | 57.98±20.58 | | 55.92±16.35 | | 0.482 |
| 18- 40 | 26 | 14.4 | 8 | 15.7 | 34 | 14.8 | 0.201 |
| 41-60 | 87 | 48.3 | 23 | 45.1 | 110 | 47.6 | |
| >6o | 67 | 37.3 | 20 | 39.2 | 87 | 37.6 | |
| Males | 104 | 57.8 | 29 | 56.9 | 133 | 57.6 | 0.438 |
| Females | 76 | 42.2 | 22 | 43.1 | 98 | 42.4 | |

Table (2): Medical history for survivors and non-survivors.

| Variables | Survivors (n=180) | % | Non-survivors (n=51) | % | *p*-value |
|---|---|---|---|---|---|
| +ve history of contact with confirmed COVID-19 cases | 86 | 47.78 | 11 | 21.57 | <0.001* |
| +ve history of Comorbid conditions | 59 | 32.78 | 38 | 74.51 | <0.001* |
| +ve history of GIT symptoms | 4 | 2.20 | 6 | 11.76 | 0.621 |

* Significant *p*-value <0.05.

Table (3): Hematological and inflammatory markers among survivors and non-survivors.

| Variables | Survivors (n=180) Mean ± SD | Non-survivors (n=51) Mean ± SD | *p*-value |
|---|---|---|---|
| WBC count | 9.04±4.74 | 11.89±5.52 | <0.001* |
| Neutrophils % | 67.99±20.65 | 80.04±14.37 | 0.331 |
| Lymphocytes% | 21.19±16.49 | 12.43±13.33 | 0.009* |
| Monocytes% | 8.56±5.12 | 5.95±2.73 | 0.221 |
| Eosinophil% | 1.69±0.76 | 1.19±0.93 | 0.140 |
| Hb | 12.41±2.61 | 11.31±2.79 | 0.007* |
| Platelets count | 313.33±162.40 | 284.84±130.63 | 0.112 |
| LDH | 349.94±254.69 | 425.86±362.19 | 0.081 |
| ESR 1st hour | 66.78±39.63 | 88.79±39.63 | 0.001* |
| CRP | 83.37±70.96 | 158.25±64.61 | 0.001* |
| D-dimer | 46.30±90.60 | 22.50±55.50 | 0.010* |

* Significant *p*-value <0.05.

Table (4): Liver profiles, renal function, and electrolytes levels among survivors and non-survivors.

| Variables | Survivors (n=180) Mean ± SD | Non-survivors (n=51) Mean ± SD | *p*-value |
|---|---|---|---|
| ALT | 47.14±11.3 | 69.09±20.2 | 0.232 |
| AST | 55.47±8.4 | 81.75±12.8 | 0.087 |
| S. bilirubin | 1.69±0.3 | 3.08±0.3 | 0.006* |
| S. albumin | 3.28±0.9 | 3.05±0.99 | 0.068 |
| PT | 13.1±2.6 | 13.48±1.2 | 0.210 |
| Total protein | 6.59±1.1 | 6.28±2.8 | 0.058 |
| Creatinine | 1.37±1.01 | 1.83±1.73 | 0.047* |
| Urea | 30.97±26.44 | 77.89±54.94 | 0.010* |
| Na | 137.88±7.19 | 139.02±6.43 | 0.140 |
| K | 4.15±0.63 | 4.27±0.54 | 0.097 |

* Significant *p*-value <0.05.

Table (5): Predictors of mortality among studied patients.

| Variables | HR* | 95% CI | *p*-value |
|---|---|---|---|
| Total bilirubin | 1.196 | 1.074-1.332 | 0.001 |
| WBCs | 0.943 | 0.892-0.997 | 0.040 |

* Hazard Ration (HR) has been adjusted for age, gender, Lymphocytes, history of contact, Hb, creatinine, CRP, presence of co-morbidities, D-dimer, Urea, and ESR.

## Discussion

This study included 231 patients initially admitted to the ICU with confirmed severe infection with COVID-19, where we followed them until the endpoint, which is death or discharge, and finally we compared these 2 outcomes. Fifty-one patients (22.17%) constituted the non-survivors, this is comparable to another study in Saudi Arabia where out of 352 patients isolated in ICU, 89 (25.3%) died **[19]**; but less than a Serbian Cohort Study which reported 28.4% mortality rate **[20]**; however still our mortality high compared to another large study in Saudi Arabia that reported overall fatality rate 3.1 % where the in-hospital mortality rate was 9.7% out of 7484 confirmed Covid-19 cases **[21]**. So, this high mortality rate in our study can be attributed to the severity of the-cases and the increased burden of ICU admission, which is reported by Olayan et al., who reported that the intensive care unit (ICU) was approximately seven times higher odds of mortality compare with those who were not admitted (OR = 6.48, 95% CI 2.52-16.63, $p<0.001$) **[22]** Regarding gender and age, most of our non-survivors were males (56.9%), had more average age (58.15), and the majority aged 41-60 (45.1%), however, there were no statistical differences from the survivors; this is going with this large study in KSA where the rate of in-hospital mortalitywas significantly higher among male and older patients **[21]**; another local study by Rawabi et al., who reported That the mean age of non-survivors was 69.66± 14.68 years, and 142 (63.4%) of the cases were male **[23]**; moreover the older age and male gender as predictors of mortality were reported in a large study which screened 516 study all over the world **[24]**. The high mortality rate in men may be explained by a report confirming that men have higher ACE2 levels than women, and therefore, ACE2 helps the virus to infect healthy cells **[25]**. Interestingly in our study, it showed that the survivors have more significantly contacted with positive confirmed cases of Covid-19 than non-survivors with an odds ratio of 3.32, but we do not know for how long this contact or how much the infectious load they get, but this is may carry the possibility that they get a low dose of infection and or had time to overcome the virus; this observation also was reported in another study where we found our medical students who had more contact with positive cases had a higher incidence of infection than non-medical students who had less contact with positive cases **[26]**. Our study also that the non-survivors had significantly more comorbid conditions with an odds ratio of 5.99, and this is going with all the studies which documented that the presence of comorbid conditions is a predictor of mortality using different univariant and multivariant analysis **[19-24,26-28]**. Regarding CBC in our study, total WBC count, lymphopenia, and low hemoglobin were significantly more in non-survivors using univariant analysis; these changes were also observed in some local **[21,22]** and international studies **[20,28]**. These can be explained as the decreased Hb level would affect the oxygen-carrying capacity and hence hypoxia was more in non-survivors, while the increased WBC may be an indicator for the inflammatory response or marker for complications such as secondary infection or septicemia which added more risks in the non-survivor group, however still lymphopenia is important significant mortality risk, as The SARS-CoV-2 virus incites an immune response causing CD4+T cell-dependent activation of B lymphocytes to cause increased antibody production, and CD+8 T cells also play a significant role in clearing the virus, so those with decreased count will suffer more **[29,36]**. The inflammatory markers, ESR and CRP, were significant predictors of mortality in our cohort, which go with many other studies **[20-24,27-30]**, not only in predicting mortality but also have been linked to the disease severity and progression. Other significant predictors of mortality in our study using the univariant analysis are the increased levels of urea and creatinine in our patients; these also have been reported in many studies as predictors of mortality; either acute renal injury due to Covid-19 or more deteriorating function in already patient with chronic renal failure, this will result inunfavorable outcome partially due to persistent low-grade inflammation and dysregulated immune response **[20,38]**. Surprisingly in our study, we found a significant decrease in D-dimer in the non-survivor group, which is not predicted in many other studies that reported the increased level to be a predictor of severity and mortality **[19-23,27-28]**; although it is difficult to explain this, it is a fact we must search for. Regarding the liver profile in our study, we found a significantly higher level of bilirubin in the non-survivors, insignificant increased ALT, AST, and PT, and insignificant decreased serum albumin and total protein; these go with other many searches

who documented liver injury during Covid-19 infection **[35-38]**, affecting both catabolic and anabolic activities of the liver. This liver injury has been seen in autopsies, in many reports as hepatomegaly with dark red degenerations, mid lobular focal necrosis with neutrophils, lymphocytes, and monocytes infiltration with portal tract inflammation and steatosis **[36,39-40]**; this may also be evident as there is notable upregulation of ACE receptors due to a compensatory proliferation of the hepatocytes **[41]** and increased levels of monocyte chemoattractant protein 1 (MCP-1) observed in Covid-19 infection which can exacerbate steatohepatitis **[42]**. Finally in our cohort, by multivariant analysis using the Coxregression model, which is more specific in predicting survival, we found that higher levels of Total bilirubin, and low counts of WBCs were independently associated with higher mortality among cases after adjustment of the other confounders, as age, gender, Lymphocytes, history of contact, Hb, creatinine, CRP, presence of co-morbidities, D-dimer, Urea, and ESR. However, moreresearches are needed to find out the cause or nature of this hyperbilirubinemia as either direct or indirect liver injury besides, the studies on the number and functions of the WBC in severe Covid-19 infection.

*Conclusion:*

Hyperbilirubinemia due to direct or indirect liver injury in patients with severe Covid-19 in addition to inappropriate response of WBC to the infection constituted the predictors of mortality in our cohort.

*Conflict of interest:*

We have no conflict of interest to declare.

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# تنبؤات الوفيات للمرضى المصابين بكوفيد من النوع الشديد والذين تم إدخالهم إلى وحدة العناية المركزة

مقدمة : أدت العدوى الشديدة لكوفيد-١٩ إلى ارتفاع معدلات الوفيات على مستوى العالم ومع ذلك فقد اختلفت مؤشرات الوفيات على نطاق واسع فيما يتعلق بأهميتها أو آثارها بسبب الطفرات الفيروسية أو نوعية المرضى أو طريقة البحث.

الهدف من البحث : تحديد مؤشرات الوفيات لدى المرضى المصابين بفيروس كوفيد-١٩ الحاد الذين تم إدخالهم إلى وحدة العناية المركزة.

طريقة البحث : أجريت دراسة جماعية قائمة على الملاحظة على ٢٣١ مريضاً متتالياً مصابين بعدوى شديدة من كوفيد-١٩ تم قبولهم فى وحدة العناية المركزة حيث قمنا بمقارنة البيانات الخاصة بالناجين مقابل غير الناجين وكانت نقطة النهاية الأولية لدينا هى الموت أو الخروج تحسن.

النتائج : ٥١ مريضاً (٢٢٪) كانوا غير ناجين حيث كان لديهم حالات مرضية مصاحبة أكثر بشكل ملحوظ وعدد كريات الدم البيضاء خاصة اللمفاويات غير الطبيعى مع زيادة سرعة الترسيب والبروتين التفاعلى جو اختلال وظائف الكلى وفرط بيليروبين الدم. بينما فى التحليل متعدد المتغيرات باستخدام نموذج انحدار كوكس ارتبطت المستويات الأعلى من إجمالى البيليروبين وانخفاض عدد كرات الدم البيضاء بشكل مستقل مع معدل وفيات أعلى بين الحالات بعد تعديل الإرباك.

الخلاصة : إن فرط بيليروبين الدم الناتج عن إصابة الكبد المباشرة أو غير المباشرة فى المرضى المصابين بفيروس كوفيد الحاد بالإضافة إلى الاستجابة غير المناسبة لكريات الدم البيضاء للعدوى شكل تنبؤات للوفيات فى هؤلاء المرضى.