# Clinical Characteristics and outcome analysis of SARS-CoV-2 patients admitted to different Critical Care Units in Nepal

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### ABSTRACT

**Background:** The clinical presentation, biochemical characteristics, and outcomes of patients infected with SARS-CoV-2 can vary in different populations. The purpose of the study is to assess the clinical presentation and identify predictors of mortality among patients with severe acute respiratory distress syndrome admitted to different critical care units in Nepal.

**Methods:** An observational study was conducted among the confirmed SARS-CoV-2 patients admitted to different critical care units in seven provinces of Nepal. Retrospective data was collected for the period of three months (April 14, 2021 to July 15, 2021) in relation to the peak of the second wave of COVID-19 pandemic in Nepal. Clinical, biochemical and mortality data were collected from the admitted patients of different critical care units. Univariate logistic regression analysis was done among the selected variables at 5% significance. Final predictor variables were identified after multiple regression analysis.

**Results:** Out of total of 646 patients admitted to critical care units of different provinces of Nepal, there was a male predominance 420 (65%). A total of 232(35.91%) patients were non-survivors with the majority of mortality occurring in patients > 50 years of age. Cough (72.3%), shortness of breath (70.9%) and fever (56%) were the most common presenting clinical features. Increasing age, presence of comorbidity, critical COVID-19 cases, respiratory rate, temperature, serum urea and alanine aminotransferase were identified as predictors of mortality after multiple regression analysis.

**Conclusions:** Approximately 36 % of the confirmed SARS-CoV-2 patient admitted to critical care units did not survive. There was a male preponderance with most casualties occurring in patients more than 50 years of age. Cough, shortness of breath and fever were the most common presenting features. After multiple regression analysis of the identified clinical and biochemical factors, age, presence of comorbidity, respiratory rate, temperature, severity grade as per the World Health Organization classification, serum urea and alanine aminotransferase were identified as the predictors of mortality.

Keywords: Corona virus disease; critical care; outcome; severe acute respiratory syndrome; mortality.

### INTRODUCTION

On March 11, 2020, the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic due to the constantly increasing number of cases outside China.<sup>1</sup> The first case of SARs CoV-2 was detected in Nepal in January from a Nepali student traveling from Wuhan

with signs and symptoms of corona virus infection and confirmed by real-time polymerase chain reaction (RT-PCR). <sup>2</sup> Upon analyzing from April 20 to June 20, 2021 the death rate rose from approximately three thousand to eleven thousand with case fatality rising from 1.08 to 1.43 as per the World Health Organization (WHO) office in Nepal which relies on the data provided by the Ministry of Health and Population (MoHP). <sup>3,4</sup> Patients

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<sup>1</sup>National Academy of Medical Sciences, National Trauma Center, Kathmandu, Nepal, <sup>2</sup>National Academy of Medical Sciences, Bir Hospital, <sup>3</sup>Pokhara Academy of Health Sciences, Pokhara, <sup>4</sup>Bheri Hospital, Nepalgunj, <sup>5</sup>Karnali Academy of Health Sciences, Jumla, <sup>6</sup>Dadeldhura Hospital, Dadeldhura, <sup>7</sup>Koshi Hospital, Biratnagar, <sup>8</sup>Provincial Hospital, Janakpurdham, <sup>9</sup>Nepal Health Research Council, Kathmandu with SARS-CoV-2 infection can develop coronavirus disease 2019 (COVID-19), which has resulted in high rates of hospitalization with overwhelming intensive care unit (ICU) admission.

Understanding predictive factors in COVID-19 is crucial for clinical decision making by better identifying those patients at higher risk of mortality, timely intervention to reduce the risk of death, optimize resource allocation and improve outcome. Studies relating to the assessment of factors related to mortality and survival of patients admitted to the intensive care units are found mostly in literature from the developed countries. During the surge of the second wave of the COVID-19 pandemic, preparedness for critical care services were either poorly developed or were in the process of formation with most struggling with the infrastructure, trained manpower and oxygen supplies due to the overwhelming surge of cases.<sup>5,6</sup> It is yet to be seen what population, biochemical and clinical characteristics predictors will be the best fit in our context to help prognosticate the COVID-19 mortality. Moreover, the true predictors of morality in Nepali population is difficult to generalize with a single-center study or from studies done in other populations. Knowledge of the baseline characteristics and outcomes of critically ill patients is crucial for health and government officials engaged in planning efforts to address local outbreaks. The aim of the study was to find out the clinical characteristics and outcome of patients with laboratory-confirmed COVID-19 admitted to different selected critical care units in Nepal.

#### **METHODS**

An observational study was conducted in different critical care facilities in 7 provinces of Nepal. The data was collected retrospectively from the hospital records for three months (April 14, 2021 to July 15, 2021) when the caseload was surging during the second wave of the COVID-19 pandemic in Nepal. Critical care facility here means any facility where there is the provision of respiratory support of any kind (invasive or noninvasive), with or without other organ support systems and run by a specialist or a group of specialists with some form of critical care training. It is difficult to ensure optimal number of patient to nurse ratio during the surge of the pandemic. The sites were selected based on the availability of critical care facilities either existing or in the developmental phase, retrieved from authentic sources of the Government of Nepal. They were also chosen based on the maximum number of critical care cases available during the second wave of the pandemic where maximum mortality had occurred. The facilities were Koshi Zonal Hospital, Biratnagar (Province 1), Janakpur Provincial Hospital,

Janakpur (Madhesh Province), National Trauma Center, Kathmandu (Bagmati Province), Pokhara Academy of Health Sciences, Pokhara (Gandaki Province), Bheri Zonal Hospital, Nepalgunj (Lumbini Province), Karnali Academy of Health Sciences, Karnali (Karnali Province), Dadeldhura Hospital, Dadeldhura (Sudurpachim Province).

The inclusion criteria included confirmed cases with SARSCoV-2 made by a positive RT-PCR assay of nasal or pharyngeal swabs or aspirates of the lower respiratory tract as defined by the WHO, aged more than 16 years and admitted to designated critical care units were included in the study. Cases who received care in a designated critical care facility and were later referred to another facility, left against the medical advice, discharged on request, cases who did not want to continue ongoing care and resuscitation in the critical care facility, pregnant patients , and patients receiving ongoing care till the stipulated data collection date were excluded from the study.

Data were collected from the hospital record by the assigned data collector in coordination with the site coordinator with a prespecified proforma. The collected data included information on age, gender, comorbidity, severity grade as per the World Health Organization (WHO),<sup>7</sup> modalities of oxygen therapy, number of days in critical care facility, biochemical parameters (arterial blood gas, total count, differential count, urea, creatinine, sodium, potassium, liver function tests). Any discrepancies in data collection were finalized with the site coordinator who will be an expert in intensive care services. The anonymity of the patients was maintained during different stages of data collection and analysis. Direct identifiers and indirect identifiers were deleted as required.

Continuous variables are presented as median and interguartile range (IQR) with 95% confidence interval (CI). Categorical variables are expressed as the number of patients (percentage) with 95% Cl. Percentages of available data for the overall population are based on the total number of patients included in the study, distribution of available data over the age subgroups are based on the available data for that variable, and the other percentages are calculated using the number of available data for that subgroup. Logistic regression analysis was performed for the variables depending upon the type of variable used at 5 % significance. Multiple regression analysis was performed for variables with significant association with mortality. In multiple logistic regression analysis, stepwise logistic regression analysis was used to identify the predictor variable using AIC (Alkaline Information Criteria).

Ethical approval was taken by the site coordinator of the respective site from the Institutional Review Board (IRB) or the hospital administration wherever applicable, as per the guidelines of the Nepal Health Research Council and the regulations of the local sites. Cumulative ethical approval was taken from the Nepal Health Research Council.

## RESULTS

Table 1. Number of survivors and non-survivors according to the different provincial site.			
Study Site	Survivors N (%)	Non-survivors N (%)	Total N
Bheri Zonal Hospital	25 (36.76)	43 (63.23)	68
Dadeldhura Regional Hospital	138 (88.89)	19 (11.11)	157
Janakpur Provincial Hospital	9 (32.14)	19 (67.85)	28
Karnali Academy of Health Sciences	32 (72.72)	12 (27.27)	44
Koshi Hospital	76 (71.69)	30 (28.30)	106
National Trauma Center	14 (25.92)	40 (74.07)	54
Pokhara Academy of Health Sciences	120 (63.49)	69 (36.50)	189
Total	414 (64.08)	232 (35.91)	646

Table 1. shows that approximately 36% of the total patients admitted to critical care units of different hospitals located in different provinces of Nepal were non-survivors.

Table 2. Clinical Characteristics of COVID-19 patient.			
Number (%), Mean $\pm$ Standard deviation, minimum, maximum]	Non-Survivor (%)	Survivor (%)	
	149	271	
	81	145	
51.95 ± 15.17 (18, 93)			
	7 (14.3)	42 (85.7)	
	41 (32.3)	86 (67.7)	
	, ,	96 (71.6)	
	, ,	79 (55.2)	
	80 (41.5)	113 (58.5)	
Yes: 247 (38.2)	99 (41.1)	148 (59.9)	
No: 399 (61.76)	119 (32.9)	243(67.1)	
	Number (%), Mean ± Standard deviation, minimum, maximum] 51.95 ± 15.17 (18, 93) Yes: 247 (38.2)	Number (%), Mean ± Standard deviation, minimum, maximum]       Non-Survivor (%)         149       149         51.95 ± 15.17 (18, 93)       7 (14.3)         7 (14.3)       41 (32.3)         38 (28.4)       64 (44.8)         80 (41.5)       99 (41.1)	

Table 2. Clinical Characteristics of COVID-19 patient.			
Clinical Characteristics	Number (%), Mean $\pm$ Standard deviation, minimum, maximum]	Non-Survivor (%)	Survivor (%)
Severity at the time of critical care unit admissions	Critical:139 (21.5) Severe: 446 (69) Not categorized clearly: 61 (9.4)#	74 (53.2) 116 (25.6) 40 (65.6)	65 (46.8) 330 (74.4) 21 (34.4)
Clinical presentation*	Cough: 467 (72.3) Shortness of breath: 458 (70.9) Fever: 362 (56.0) Fatigue: 242 (37.5) Myalgia: 228 (35.3) Headache: 175 (27.1) Sore throat: 133 (20.6) Asymptomatic: 130 (20.11) Anorexia: 108 (16.7) Arthralgia: 94 (14.6) Anosmia: 63 (9.8) Nasal Congestion: 44 (6.8) Ageusia: 42 (6.5) Diarrhea: 37 (5.7) Chest pain: 3 (0.5) Abdominal pain: 1 (0.2)		
Number of days in critical care units	7.19 $\pm$ 5.072 (1, 30)		
Number of days in from hospital admission to discharge or expiry	$8.13 \pm 5.917$ (1, 36)		

<sup>\*</sup>Possibility of overlap of clinical features for the same patient; <sup>#</sup>Lack of clarity in classification as per the World Health Organization guidelines(7)

Majority (65%) of the patients were male with most presenting with cough (72.3%), shortness of breath (71%) and fever (56%) (Table 2).

Table 3. Oxygen therapy at the time of critical care unit admissions.			
Oxygen therapy	Number (%)		
Oxygen mask with reservoir bag	242 (37.5)		
Simple facemask	116 (18.0 %)		
Nasal prong	90 (13.9 %)		
Non-invasive ventilation <ul> <li>Continuous Positive</li> <li>Airway Pressure (CPAP)</li> <li>High flow nasal cannula (HFNC)</li> </ul>	( )		
Invasive ventilation	30 (4.64)		
Not mentioned clearly	25 (3.86)		

Table 3. displays that most of the patients (37.5%) used an oxygen mask with reservoir bag at the time of critical care unit admission, followed by a simple mask (18%).

Table 4. Bivariat biochemical variat		of different clinical,
Variable	Estimate	Odds Ratio (95% CI)
Age (years)	0.02	1.02[1.01,1.03] *
Gender • Male • Female	0.008 reference	1.01[0.72,1.41)
Comorbidity • Yes • No	0.28 reference	1.33[1.02,1.86] *
COVID-19 Severity <ul> <li>Severe</li> <li>Critical</li> </ul>	-1.16 reference	0.31[0.21,0.46] *
рН	-2.79	0.06[0.01,0.66]
Systolic (mm Hg)	-0.007	0.99[0.98,1.00]
Diastolic (mm Hg)	-0.006	0.99[0.98,1.01]
Respiratory rate (breaths/min)	0.04	1.04[1.02,1.07] *
Temperature (Fahrenheit)	0.27	1.32[1.14,1.53] *

Table 4. Bivariat	e Analysis	of different clinical,			
biochemical variab	biochemical variables.				
Variable	Estimate	Odds Ratio (95% CI)			
Neutrophil (% total leucocyte count) (cells/cmm <sup>3</sup> )	0.01	1.02[1.01,1.03]			
Lymphocyte (% total leucocyte count) (cells/ cmm <sup>3</sup> )	-0.01	0.99[0.97,1.00]			
Urea (mg/dl)	0.026	1.03[1.02,1.04] *			
Creatinine (mg/dl)	0.47	1.60[1.11,2.32] *			
Sodium (mmol/L)	0.05	1.06[1.01,1.11] *			
Potassium (mmol/L)	0.39	1.49[0.95,2.33]			
Total bilirubin (mg/dl)	0.47	1.61[1.02,2.58] *			
Direct bilirubin (mg/dl)	2.22	9.22[2.9,29.36] *			
AST (Aspartate Aminotransferase) (IU/L)	0.017	1.02[1.01,1.03] *			
ALT (Alanine Aminotransferase) (IU/L)	0.023	1.02[1.01,1.04] *			
Total Protein (g/L)	0.33	1.39[1.02,1.91] *			
Albumin (g/L)	0.79	2.22[1.32,3.72] *			

\*Statistically significant at 5%

We included all the variables that were significant at 5% level of significance to identify the most significant variables for prediction of mortality. From the bivariate analysis, age, comorbidity, severity, respiratory rate, temperature, Urea, and ALT were significantly associated variables with COVID-19 mortality and were taken for final model (Table 4).

Table 5. Variables after multiple regression analysis.			
Variable	Estimate	Odds ratio (Confidence Interval)	p-value
Age	0.25	1.27(1.03,1.58)	0.02
Comorbidity Yes	-2.88	0.06(0.01,3.93)	0.18
Severity with	-8.19	0.02(0.01,0.09)	0.005
Severe COVID-19			
Respiratory rate	0.76	2.15(1.10,4.22)	0.025
Temperature	-1.34	0.26(0.06,1.18)	0.07
Urea	0.10	1.12(0.99,1.25)	0.06
ALT (Alanine Aminotransferase)	-0.06	0.93(0.87,0.99)	0.04

From multiple regression analysis, age, severe grade of COVID-19, respiratory rate, urea and ALT were found to be predictors of COVID-19 mortality.

## DISCUSSION

Identification of mortality predictors help clinicians and policymakers to stratify patient at-risk early and make prompt clinical decisions. Mortality predictors can differ with populations characteristics, level of facility, resources and treatment modalities. Increasing age is identified as a significant predictor of mortality in our study [OR: 1.27, 95% CI: 1.03-1.58]. Studies done in a well-equipped center in Nepal has also reported a high rate of mortality among patients > 60 years of age in mechanical ventilator.<sup>8</sup> Similarly, infectious disease hospital in Nepal also shows more than 72 % of cases who lost their lives were of age > 65 years.<sup>9</sup> Age stratification shows that age group more than 60 years and 51-60 years had a high rate of mortality compared with other age groups. (Table 4) It is possible that critical care management differed in facilities of different provinces. Increasing age has been identified as a significant predictor of mortality in COVID-19 cases in studies done in cohorts of patients in different centers of different countries.<sup>10</sup> There is ample evidence in a pooled metaanalysis of 36 studies that age >60 is associated with mortality.<sup>11</sup> Predictive modeling done in multicenter of united states hospital with hospitalized COVID-19 patients also identifies age >65 years significant marker for mortality.<sup>12</sup> Studies done in Indian centers also report high mortality among patients above 60 years of age.<sup>13</sup> High rate of mortality even in the age group below 60 years might be related to lack of care, issues of oxygen supplies during the rapid surge of cases during the second wave of the COVID-19 pandemic.

Our study identifies the presence of comorbidity as one of the significant predictors of mortality, however, did not elaborate on the type of disease present. (Table 2) Cases with severe grade COVID-19 were more likely to survive than critical grade COVID-19. A pooled metanalysis of observational studies also identifies the presence of comorbidity [RR: 3.84; 95% CI: 1.81-8.16] particularly chronic kidney disease [RR: 8.37; 95% CI: 3.94-17.8], respiratory, cardiovascular and cerebrovascular diseases, are associated with greater mortality.<sup>11</sup> Studies done in 260 hospitals across the United Kingdom identify the presence of comorbidity as one of the eight variables at the time of initial assessment that determines the mortality with validation of model with 0.79 accuracy.<sup>14</sup> A study i one of the infectious disease hospitals in Nepal, shows that the presence of two or more comorbidities was associated with 64% mortality, with diabetes, hypertension and chronic obstructive pulmonary disease

being the commonest ones.<sup>9</sup> Presence of comorbidity is also well fitted in Dutch model studies <sup>15</sup> and in studies conducted across 54 countries of Africa.<sup>16</sup> Studies in the United States reveal coronary artery disease as one of the significant predictors of mortality. <sup>17</sup> Presence of diabetes and hypertension has been shown to be a strong factor related to non-survivors in studies done in a well-equipped center of Nepal. <sup>8</sup>

As with other studies done in the United Kingdom,<sup>14</sup> Denmark<sup>15</sup> and African nations<sup>16</sup> and studies done in our local context,<sup>8</sup> there is a male preponderance in patients presenting with COVID-19 (Table 2). A similar finding of 3.17 times male preponderance was seen among non-survivors of COVID-19 patients in infectious disease hospital of Nepal. <sup>9</sup> The findings are also similar in studies done at six different centers in three different European nations and in the Chinese population.<sup>12</sup>

Patients who have severe COVID-19 as per the WHO classification<sup>7</sup> have a greater chance of survival than patients with critical COVID in our context. A similar finding was also seen in neighboring India where the population characteristics are comparable which depicts fewer survivors with severe form of COVID-19, however, it is not clear whether the classification was in tandem with the WHO classification.<sup>13</sup> Few cases were unclassified in our study, possibly because of the difficulty in interpretation of clinical findings and complexity in classification of WHO for risk stratification, particularly in newly forming critical care units.

Clinical signs like higher respiratory rate (breaths/min) [OR: 2.15, 95% Cl: 1.10-4.22] and rising temperature (In Fahrenheit) are also found as predictors of mortality in our context (Table 3). Non-survivors have higher temperature and respiratory rates than survivors. Higher temperatures and respiratory rate (p < 0.0001) have been identified as a predictor of mortality.<sup>17</sup> Study performed across 260 hospitals by the International Severe Acute Respiratory and Emerging Infectious Consortium and the World Health Organization using approximate 35,000 patients identifies respiratory rate as a predictor for validation of model with almost 80% accuracy.<sup>14</sup>

Alanine aminotransferase (ALT) and blood urea nitrogen (BUN) have also been identified as markers for mortality in our study. Pooling of 9407 patients in 31 studies in a meta-analysis identifies blood urea level as one of the eight independent predictors among non-survivors with an area under the curve of 0.79.(14) Studies done in Dutch critical care units also [survivor: 27 (17.23 -44.53), non-survivor: 26 (16.12-41)] identifies blood urea nitrogen (U/L) as a marker for predicting mortality. <sup>15</sup> Studies done in Chinese hospitals also identified the rise in ALT by 5.7 U/L as an independent factor for mortality (95% CI, 2.6-8.8, p= 0.0003). The study included 14 studies with 4659 patients.  $^{11}$ 

Most patients presented with cough, shortness of breath and fever in our studies. Headache, myalgia and sore throat were the other prominent symptoms. Hospitalized patients tend to present more with shortness of breath with fever and cough equally among the inpatients and outpatients. <sup>18-20</sup> It seems that most patients who were admitted to the critical care unit and lost their lives happened in the first to the second week of admission to the designated unit. Those who survived had an almost similar stay to those died in the critical care units and both occurred during the first to the second week of admission. Studies report median time for the development of acute respiratory distress syndrome among non-survivors is usually 8-12 days and 10-13 days among survivors. <sup>20</sup>

Our study is limited by the fact that all centers were not well resourced in terms of manpower, and equipment when the patient number surged during the pandemic, hence the level of care might have been hampered and have some bearing on the outcome. The clear demarcation of critical care facility might not have been met in some centers as they were in the process of forming critical care units. Similarly, during the peak of the pandemic, there can be plenty of managerial and administrative issues that influence patient care. All biochemical markers were not interpreted as a few centers did not have the facility and were in process of procuring them. Our study also did not elaborate on the comorbidity and the cause of death as we found a lack of clarity in case definition when making proper clinical diagnosis and labeling the actual cause of death. During data collection at the time of the pandemic, there are also chances of missing data in multiple places. There is a possibility that the laboratory values taken at different centers might vary due to human errors and differences in standard settings of devices. However, the study is multicentric and still provides important insight regarding the population's characteristics, the clinical presentation with mortality statistics, along with an effort to identify predictive markers which can be useful for future studies and decision making.

#### CONCLUSIONS

Approximately 35 % of the confirmed SARS COVID-19 patient admitted to critical care units did not survive. There was a strong male preponderance with most deaths occurring in the age group more than 40 years of age. Cough, shortness of breath and fever were the most common presenting features. After multivariate regression analysis of the identified clinical and biochemical factors, age, presence of comorbidity, respiratory rate, temperature, severity grade as per the

World Health Organization classification, serum urea and alanine aminotransferase were identified as the predictors of mortality.

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### **CONFLICT OF INTEREST**

We declare that we have no conflict of interest.

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