Clinical and Laboratory Predictors of Mortality in COVID-19 Infection: A Retrospective Observational Study in a Tertiary Care Hospital of Eastern India

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Abstract

Introduction
COVID-19 is associated with huge morbidity and mortality in India. Identification of factors associated with mortality would make a difference in the management of COVID-19 infection-related illness.

Objective
To assess clinical & laboratory parameters associated with adverse outcomes among 984 patients with COVID-19 infection admitted to a tertiary care hospital in eastern India.

Materials and methods
All patients with real-time polymerase chain reaction (RTPCR) or rapid antigen positive for COVID-19 admitted at our All India Institute of Medical Sciences (AIIMS) Patna between 1st July to 30th Aug 2020 were included for analysis. Statistical analysis was performed using Stata, version 10 (Stata Corp, College Station, USA). Four subgroup regression models have been analyzed to predict the odds of death.

Results
A total of 984 COVID-19 cases admitted to our hospital during the given period were analyzed. Out of 984 cases, 762 (77.44%) were males and 222 (22.56%) females. The overall case-fatality rate among admitted cases was 254 (25.81%) [males (26.64%) and females (22.96%)]. The final logistic regression model showed that patients presenting with severe COVID-19 disease (adjusted odds ratio [aOR]: 17.81), cough (aOR: 3.83), dyspnea (aOR:2.35), age 60-75 (aOR:1.47), age >75 years (aOR:3.97), presence of chronic kidney disease (CKD) (aOR:2.95), were found to be significantly associated with a high risk of mortality after controlling for the confounders (p<0.05). Among lab variable, total leukocyte count (TLC) (>10,000/mm3) (aOR: 1.74), neutrophil-lymphocyte ratio (NLR) (>3.3) (aOR:2.37), serum albumin (<3.4 g/dl) (aOR : 2.3), blood urea (>43 gm/dl) (aOR:3.72), ferritin (>522) (aOR:2.39), and D-dimer (>0.5) (aOR:5.58) were significantly associated with higher mortality (p<0.05)

Conclusion
Age 60 years plus, presence of CKD, and severe covid infection carried the highest risk of mortality. Lab markers such as raised TLC, ferritin, D-dimer, and low albumin were associated with worse outcomes in our subset of COVID-19-related illness.

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characteristics and risk factors that can potentially distinguish between high and low risk of mortality in an Indian population will lead to improved risk assessment and better clinical management. This study has been conducted with the aim to identify factors associated with a higher risk of mortality in COVID-19 patients needing admission and determine the case fatality rate of our institute which would help in early intervention and aggressive treatment.

**Materials And Methods**

This was a single-center, retrospective, medical record-based observational study involving all COVID-19 patients requiring admission at a tertiary care hospital All India Institute of Medical Sciences, Patna, India. After the approval of the ethics committee, records of all patients admitted to the institute between 1st July 2020 to 30th August 2020 were evaluated.

**Data collection**

Two post-graduate residents collected data in a predesigned proforma from patient records present in the medical record department which was reviewed and cross-checked for validation by two faculty members from pulmonary medicine and the department of community medicine. Retrieved data include demographic information, exposure history, clinical symptoms, comorbidities, and laboratory test results, details of treatment provided, length of hospitalization, complications, and outcome. The severity of covid infection was defined according to guidelines issued by the Ministry of Health and Family Welfare, Government of India (MoHFW) [5]. All patients admitted to our institute are investigated and treated as per the COVID-19 treatment protocol of our institute. A baseline battery of investigations was performed and based upon clinical characteristics and severity, patients are triaged. If fulfilling the admission criteria, severely ill patients are shifted to our intensive care units else they are shifted to various treatment wards. The following investigations are routinely done on admission. Hematological: complete blood counts, blood sugar levels, liver function test, kidney function test, prothrombin time, international normalized ratio (INR), D-dimer, and inflammatory markers like C-reactive protein (CRP), pro-calcitonin, and serum ferritin. Viral markers for hepatitis B and C and HIV are also noted. Chest X-ray, ECG, arterial blood gases, and glycosylated hemoglobin whenever indicated are ordered.

**Definitions of mild, moderate, and severe COVID-19 [5]**

Mild: No evidence of breathlessness or hypoxia (normal saturation).

Moderate: Breathlessness and/or hypoxia (saturation 90-94% on room air), respiratory rate of 24 or more, and no features of severe disease.

Severe: Any of the following: severe respiratory distress, oxygen saturation < 90% on room air, respiratory rate > 30, or shock or evidence of life-threatening organ dysfunction.

**Statistical analysis**

All statistical analysis was performed using Stata, version 10 (Stata Corp, College Station, USA). Shapiro-Wilk test was used to assess the normality of continuous variables, especially the lab parameters. For non-normally distributed data, non-parametric tests such as Mann-Whitney and Wilcoxon Rank test were used to compare the equality of distribution of continuous variables, which were presented as median with interquartile range, otherwise, presented as mean with 95% confidence intervals. The Student's t-test was used to compare the mean between two groups (survived and dead) for normally distributed continuous variables.

The biserial correlation coefficient was used to measure the degree of association between the outcome variable and continuous variables with a significance level of 0.05.

Categorical variables were presented as a proportion with 95% confidence intervals. The Chi-square test was performed to test the independence of attributes. Fisher’s Exact test was used whenever cell frequencies were less than five.

Crude odds ratios were computed for measuring the effect of each categorical covariates with outcome variables, i.e., death or survived. Logistic regression models were performed to predict mortality of COVID-19 taking all the significant covariates as independent variables.

In this study, four models were used to predict death using demographic variables like age and gender, signs and symptoms, severity of disease, comorbidities, and lab variables of COVID-19 cases after checking for the co-linearity of independent variables. Hosmer-Lemeshow test statistic was used to assess the goodness of fit for each model. Deviance test statistic was used to measure the discrepancy between the reduced model and the full model.
Results

Table 1 presents the demographic and clinical features of the total of 984 COVID-19 cases admitted to our hospital during the study period. Out of 984 cases, 762 (77.44%) were males and 222 (22.56%) females. The overall case-fatality rate among admitted cases was 254 (25.81%) \( [\text{males (26.64%) and females (22.96%)}] \). Differences in case-fatality rates due to gender was not found to be significant (crude odds ratio \( [95\% \text{ CI}] = 1.21 \) \([0.856 - 1.73]\), \( p=0.272\)).

| Variables | Dead (n=254) | Survived (n=730) | Unadjusted OR (95% CI) | Test Statistic | p-value |
|-----------|-------------|------------------|------------------------|----------------|---------|
| Male      | 203 (79.99) | 559 (76.57)      | 1.22 (0.856 – 1.73)    | Z=1.10         | 0.272   |
| Age (Years) Mean (SD) | | | | | |
| 0 – 15    | 3 (1.18)   | 14 (1.91)        | 0.61 (0.174 – 2.14)    | 0.77           | 0.442   |
| 16 – 30   | 6 (2.36)   | 100 (13.69)      | 0.15 (0.06 – 0.35)     | 4.41           | 0.0001  |
| 31 – 45   | 31 (12.20) | 165 (22.60)      | 0.46 (0.314 – 0.72)    | 3.52           | 0.0001  |
| 46 – 60   | 80 (31.49) | 283 (36.02)      | 0.816 (0.60 – 1.10)    | 1.30           | 0.192   |
| 61 – 75   | 99 (38.97) | 165 (22.60)      | 2.19 (1.61 – 2.97)     | 5.01           | 0.0001  |
| 75+       | 35 (13.77) | 23(3.15)         | 4.91 (2.84 -8.49)      | 5.07           | 0.0001  |

| Severity  | | | | | |
| Mild      | 35 (13.77) | 439 (60.13)      | 0.61 (0.43 – 0.854)    | -12.73         | 0.00001 |
| Moderate  | 53 (20.86) | 221 (30.27)      | 0.61 (0.43 – 0.854)    | -2.86          | 0.004   |
| Severe    | 166 (65.35) | 70 (9.58)        | 17.84 (12.44 – 25.41)  | 15.80          | 0.0001  |
| Admission in ICU | 230 (90.55) | 70 (9.58) | 90.35 (55.50 – 147.09) | 18.11 | 0.0001 |
| Mean Duration of Hospital Stay | 7.88 (6.11) | 10.60 (6.71) | 0.90 (0.87 – 0.93) | -6.17 | 0.0001 |
| Oxygen Required | 222 (87.40) | 302 (41.36) | 9.83 (6.59 – 14.65) | 11.23 | 0.0001 |
| Non-invasive Ventilation (NIV) | 94 (37.0) | 19 (2.60) | 21.98 (13.04 – 37.05) | 11.60 | 0.0001 |
| Invasive Ventilator | 73 (28.74) | 3 (0.04) | 97.73 (30.44 – 313.65) | 7.70 | 0.0001 |

**TABLE 1: Demographic distribution of COVID-19 cases in relation to mortality**

NIV: non-invasive ventilation

The age of patients who succumbed to this disease was significantly higher at 58.66±14.82 years compared to those who survived 47.97±16.16 years \( (p=0.0001) \). Six dummy variables of 0-15 yrs, 16-30 yrs, 31-45 yrs, 46-60 yrs, 61-75 yrs, and 75+ were created for age groupings, and an increasing trend of fatality was observed as the age advances, with the highest risk of death among cases more than 75 years of age followed by age group 60-75 years.

Cases were categorized as mild, moderate, and severe based on the clinical features and presentation at the time of admission. Out of 984 cases, 476 (48.37%) were mild, 274 (27.84%) were moderate, and 136 (13.82%) were severe. Risk of mortality was found to be significantly higher \( (\text{crude odds ratio } = 17.84 [12.44 - 25.41]; p=0.0001) \) among severe cases as compared to mild and moderate cases.

Among 300 ICU admitted patients, 113 (37.66%) were managed with non-invasive ventilation (NIV). Risk of death among them was significantly higher \( (\text{crude odds ratio } = 21.98 [13.04 - 37.05]; p<0.0001) \). Almost one-fourth (25.33%) of ICU patients required invasive ventilation and these had a significant risk of dying \( (\text{crude odds ratio } = 97.73 [50.44 - 313.65]; p<0.0001) \).

We performed a binary logistic regression model taking death as a dependent variable and all covariates, which were found significant in bivariate analyses as independent variables as presented in Table 2. All the predictors as presented in Table 1 (Model 1) were found to be significantly associated with a high risk of...
mortality after controlling for the confounders.

| Covariates       | Adjusted Odds Ratio with 95% CI | Z-statistic | P-value |
|------------------|---------------------------------|-------------|---------|
| Age 60-75 years  | 1.57 (0.89 – 2.74)              | 1.87        | 0.071   |
| Age 75+ Years    | 3.42 (1.18 – 9.93)              | 2.26        | 0.024   |
| Severe Cases     | 14.82 (7.85 – 27.97)            | 8.32        | 0.0001  |
| Moderate Cases   | 2.55 (1.35 – 4.80)              | 2.90        | 0.004   |
| ICU              | 44.94 (25.65 – 78.74)           | 13.30       | 0.0001  |
| NIV              | 3.36 (1.69 – 6.69)              | 3.47        | 0.001   |
| Constant         | 0.010 (0.0055 – 0.0194)         | -14.32      | 0.0001  |

**TABLE 2: model-1: logistic regression model to predict mortality of COVID-19 with clinical conditions and demographic variables**

NIV: non-invasive ventilation

The details of clinical symptoms and comorbidities are summarized in Table 3 and Figures 1, 2. The most common symptoms were fever (73.98%), cough (69.41%), and shortness of breath (50.3%).

| Variables          | Death (n=254) | Survived (n=730) | Total (n=984) | Test Statistic              | p-value |
|--------------------|---------------|------------------|---------------|-----------------------------|---------|
| Cough              | 177 (69.68)   | 22 (3.01)        | 199 (20.22)   | Chi-square at 1d.f. = 22.78 | 0.0001  |
| Shortness of Breath| 185 (72.83)   | 310 (42.46)      | 495 (50.30)   | Chi-square at 1d.f. = 69.52 | 0.0001  |
| Fever >98.5        | 169 (66.53)   | 559 (76.57)      | 728 (73.98)   | Chi-square at 1d.f. = 9.87  | 0.002   |
| Weakness           | 17 (6.69)     | 22 (3.01)        | 39 (3.96)     | Chi-square at 1d.f. = 6.70  | 0.068   |
| Sore Throat        | 6 (2.36)      | 49 (6.71)        | 55 (5.58)     | Chi-square at 1d.f. = 6.75  | 0.009   |
| Diarrhea           | 1 (0.3)       | 7 (0.9)          | 8 (0.8)       | Chi-square at 1d.f. = 0.746 | 0.388   |
| Diabetic Mellitus  | 121 (47.63)   | 209 (28.63)      | 330 (33.53)   | Chi-square at 1d.f. = 30.54 | 0.0001  |
| Hypertension       | 122 (48.03)   | 184 (25.20)      | 306 (31.09)   | Chi-square at 1d.f. = 45.64 | 0.0001  |
| CKD                | 31 (12.20)    | 22 (3.01)        | 53 (5.38)     | Chi-square at 1d.f. = 31.23 | 0.0001  |
| CAD                | 21 (8.26)     | 36 (4.93)        | 57 (5.79)     | Chi-square at 1d.f. = 3.84  | 0.050   |
| Asthma             | 16 (6.29)     | 21 (2.87)        | 37 (3.76)     | Chi-square at 1d.f. = 6.099 | 0.014   |
| Hypothyroid        | 26 (10.23)    | 67 (9.17)        | 93 (9.48)     | Chi-square at 1d.f. = 0.2465| 0.620   |
| Malignancy         | 8 (3.14)      | 10 (1.36)        | 18 (1.82)     | Chi-square at 1d.f. = 3.324 | 0.068   |

**TABLE 3: Comparison of clinical symptoms and comorbidities in relation to COVID-19 mortality**

CKD: chronic kidney disease; CAD: coronary artery disease
The most common comorbidities reported were diabetes mellitus 330 (33.53%) cases followed by hypertension in 306 (31.09%), hypothyroidism 93 (9.45%), coronary artery disease (CAD) 57 (5.79%), chronic kidney diseases (CKD) 53 (5.38%), asthma 37 (3.76%) and different cancers 18 (1.83%).

Bivariate analyses were performed to assess the effect of signs and symptoms, and comorbidities on mortality in the COVID-19 cases. The odds of mortality were 3.63 times more among cases having symptoms of shortness of breath than those cases without it (crude odds ratio = 3.63, 95% CI [2.65 - 4.96], p=0.0001).

Regarding the effect of co-morbidities
- Diabetes mellitus cases had higher odds of death (crude OR = 2.267, 95% CI [1.69 - 3.04], p=0.0001) compared to those without it.
- Cases with a history of hypertension were found to have a higher risk of death (crude OR = 2.737, 95% CI
[2.03 - 3.68], p=0.0001) compared to those without any history of hypertension.

- Chronic kidney disease was also contributory to a higher risk of death (crude OR = 4.47, 95% CI [2.54 - 7.88], p=0.0001) compared to those without renal problems.

- Cardiovascular diseases were found to be associated with odds of death among COVID-19 cases but statistically not significant (crude OR = 1.737, 95% CI [0.994 - 3.03], p=0.052)

- Asthmatic patients were found to be at a higher risk of death compared to those without it (crude OR = 2.269, 95% CI [1.165 - 4.421], p=0.016).

- Co-existing malignancy with COVID-19 was found to be associated with a high risk of death (crude OR = 2.34, 95% CI: 0.913 - 5.99, p=0.072).

Binary logistic regression analysis was performed to model the risk of death among COVID-19 cases in the presence of various factors which were found to be significant in bivariate analysis. This was considered as Model 2 - taking signs and symptoms, and comorbidities as independent variables having p-values less than 0.10 in bivariate analysis. The result of the logistic regression model is presented in Table 4 (Model 2). All the predictors as presented in Table 4 were found to have a significant association with mortality after controlling for the confounders.

| Covariates       | Adjusted Odds Ratio with 95% CI | Z-statistic | P-value |
|------------------|---------------------------------|-------------|---------|
| Shortness of Breath | 3.72 (2.66 – 5.19)             | 7.73        | 0.0001  |
| Weakness         | 3.29 (1.59 – 6.79)             | 3.23        | 0.001   |
| Diabetes Mellitus | 1.51 (1.08 – 2.10)             | 2.42        | 0.016   |
| Hypertension     | 2.20 (1.57 - 3.08)             | 4.59        | 0.0001  |
| CKD              | 3.08 (1.66 – 5.735)            | 3.56        | 0.001   |
| Malignancy       | 5.15 (1.84 – 14.41)            | 3.12        | 0.002   |

**TABLE 4: Model 2 - logistic regression model to predict mortality in COVID-19 with signs and symptoms, and comorbidities**

CKD: chronic kidney disease

Based on the outcomes of Model 1 and Model 2, a final model (Model 3) was created to predict the risk of death taking all the demographic, clinical, signs and symptoms and comorbidity factors that were found significant in the bivariate analysis. Initially, all the covariates were included in the model, and the step-wise approach was used to drop the variables found insignificant in subsequent iterations. Collinear variables like admission in ICU, use of NIV were dropped from the model because of high association with severity status. The final model included the predictor variables for mortality as presented in Table 5.
### TABLE 5: Model 3 - logistic regression model to predict mortality of COVID-19 with demographic, clinical, signs and symptoms, and comorbidities

CKD: chronic kidney disease

Laboratory parameters were also analyzed and a comparison was made between these values in COVID-19 patients who survived versus those who succumbed. Shapiro-Wilk test revealed none of the variables to be normally distributed (p<0.05), hence, a non-parametric test was applied to test the equality of median using the Mann-Whitney test (Table 6).

| Covariates        | Adjusted Odds Ratio with 95% CI | Z-statistic | P-value |
|-------------------|---------------------------------|-------------|---------|
| Age 60-75 years   | 1.56 (1.05 – 2.34)              | 2.19        | 0.029   |
| Age 75+ Years     | 3.97 (1.94 – 8.15)              | 3.77        | 0.0001  |
| Severe Cases      | 29.43 (17.35 – 49.93)           | 12.54       | 0.0001  |
| Moderate Cases    | 1.96 (1.20 – 3.19)              | 2.71        | 0.007   |
| Cough             | 3.19 (1.97 – 5.16)              | 4.73        | 0.0001  |
| Shortness of Breath | 2.13 (1.43 – 3.15)           | 3.75        | 0.0001  |
| CKD               | 3.23 (1.56 – 6.67)              | 3.16        | 0.002   |

| Variables          | Death (n=254) Median (IQR) | Survived (n=754) Median (IQR) | Mann-Whitney Test Statistic (Z) | p-value |
|--------------------|-----------------------------|--------------------------------|---------------------------------|---------|
| Hb (gm/dl)         | 11 (9.6 – 12.6)             | 12 (10.8 – 13.2)               | 5.780                           | 0.0001  |
| Total leukocyte Count (mm3) | 12.34 (8.0 – 18)             | 7.67 (6.0 – 10.6)               | 10.48                           | 0.0001  |
| Platelet Count (mm3) | 178.5 (116 – 281)            | 183 (133 -244)                  | 0.236                           | 0.8134  |
| Neutrophil (%)     | 89.8 (81 – 93)              | 75.6 (65.4 – 85.7)              | 12.39                           | 0.0001  |
| Lymphocyte (%)     | 6.7 (4.3 – 13.7)            | 19.8 (11.0 – 28)                | 13.35                           | 0.0001  |
| Eosinophil (%)     | 0.70(0.20 – 1.3) (n=82)     | 0.90 (0.20 – 2.2) (n=489)      | 1.43                            | 0.1527  |
| SGPT (U/L)         | 57.2 (35.8 – 100.3) (n=253) | 54.6 (34 – 96.6) (n=727)       | 0.84                            | 0.4013  |
| SGOT (U/L)         | 60.8 (39.7 – 104.9)         | 46.9 (33.5 – 75.5)             | 5.11                            | 0.0001  |
| ALP (U/L)          | 106 (81 – 144)              | 91.4 (73.7 – 116.6)            | 5.10                            | 0.0001  |
| STB (mg/dl)        | 1 (0.75 – 1.36) (n=248)     | 0.92 (0.71 – 1.13) (n=727)     | 3.16                            | 0.0016  |
| SDB (mg/dl)        | 0.36 (0.27 – 0.525) (n=244) | 0.31 (0.24 – 0.40)             | 4.66                            | 0.0001  |
| Total Protein (g/dl) | 6.45 (5.88 – 7.0)            | 7.2 (6.67 – 7.65)              | 11.23                           | 0.0001  |
| Albumin (g/dl)     | 3.20 (2.88 – 3.57)          | 3.825 (3.45 – 4.13)            | 14.07                           | 0.0001  |
| Globulin (g/dl)    | 3.21 (2.85 – 3.645)         | 3.34 (3.04 – 3.69)             | 3.94                            | 0.0001  |
| Urea (mg/dl)       | 57 (36.3 – 104)             | 28.7 (21.9 – 39.95)            | 13.57                           | 0.0001  |
| Creatinine (mg/dl) | 1.0 (0.74 – 1.765)          | 0.76 (0.62 – 0.91)             | 8.49                            | 0.0001  |
| Sodium (mEq/L)     | 136 (131.7 – 140)           | 136 (133 – 138)                | 1.04                            | 0.2972  |
TABLE 6: Comparison of Laboratory Variables of COVID-19 cases at baseline in relation to mortality

| Variables      | Death (n=254) | Survived (n=730) | Total (n=984) | Chi-square | p-value |
|----------------|---------------|------------------|---------------|------------|---------|
| Hb (g/dl) < 13 | 195 (76.77)   | 513 (75.71)      | 708 (71.95)   | 3.29       | 0.073   |
| 13-16          | 59            | 211              | 270           |            |         |
| Total Count (/mm3) >10 thousand | 156 (61.11) | 208 (28.48) | 364 (36.99) | 91.42 | 0.0001 |
| 4-10 thousand  | 94            | 521              | 615           |            |         |
| Platelet Count (/mm3) <150 | 97 (38.11) | 247 (33.83) | 344 (34.95) | 1.57 | 0.222   |
| Neutrophil (%) >80 | 194 (77.95) | 286 (33.17) | 480 (48.78) | 105.75 | 0.0001 |
| 40-80          | 59            | 444              | 503           |            |         |

Comparing the lab reports of patients who died compared to those who survived the disease, hemoglobin levels were significantly lower (11gm/dl vs 12gm/dl gm%, p=0.001), total leukocyte count on admission significantly raised (12.34/mm3 vs 7.37/mm3, p=0.0001), neutrophil counts significantly higher (89.8% vs 75.6%, p=0.0001), lymphocyte counts significantly lower (6.7% vs 19.8% p=0.0001). Kidney function tests like blood urea (57mg/dl vs 28.7mg/dl) and serum creatinine (1mg/dl vs 0.76mg/dl) were significantly higher (p=0.0001) whereas serum calcium was significantly lower (p=0.0001) among the cases who died (8.29mg/dl vs 8.87mg/dl). Biochemical markers such as CRP, ferritin, D-dimer, and lactate dehydrogenase (LDH) were significantly higher among the cases who died (p=0.0001). Prothrombin time and INR were significantly higher (p=0.0001) among the cases who died.

Lab variables were further categorized as normal and abnormal as categorical variables and compared between survivor and non-survivor (Table 7). Neutrophilia (>80% neutrophil), lymphopenia (<20% lymphocyte), hypoproteinemia (<6.4 gm/dl protein), and hypoalbuminemia (<3.4 gm/dl albumin) were significantly more common in the non-survivors. Similarly, alanine transaminase (ALT), blood urea nitrogen and inflammatory markers like serum ferritin, LDH, and CRP were significantly raised in non-survivors.
| Lymphocyte (%) <20 | 218 (85.82) | 371 (50.82) | 589 (59.85) | 95.72 | 0.0001 |
|---|---|---|---|---|---|
| 20-40 | 36 | 358 | 394 |
| NLR >3.5 | 221 (87.0) | 392 (53.69) | 613 (62.29) | 90.28 | 0.0001 |
| 0.7 – 3.5 | 32 | 337 | 369 |
| Eosinophil (%) <1 | 48 (18.8) | 251 (34.38) | 299 (30.38) | 1.46 | 0.235 |
| 1-6 | 34 | 238 | 272 |
| SGPT >40 | 172 (67.71) | 475 (65.06) | 647 (65.75) | 0.5863 | 0.488 |
| 13 - 40 | 81 | 252 | 333 |
| SGOT >37 | 200 (78.87) | 478 (65.47) | 678 (68.90) | 15.97 | 0.0001 |
| 0-37 | 53 | 251 | 304 |
| ALP >90 | 168 (66.14) | 374 (51.23) | 542 (55.08) | 17.48 | 0.0001 |
| 30-90 | 85 | 356 | 441 |
| STB >1.2 | 81 (31.88) | 141 (19.72) | 222 (22.56) | 18.51 | 0.0001 |
| 0.3 – 1.2 | 167 | 586 | 753 |
| SDB >0.2 | 222 (87.40) | 637 (87.26) | 859 (87.29) | 2.29 | 0.137 |
| 0 – 0.2 | 22 | 92 | 114 |
| Total Protein <6.4 | 118 (46.45) | 110 (15.06) | 228 (23.27) | 105.12 | 0.0001 |
| 6.4 – 8.3 | 135 | 620 | 755 |
| Albumin <3.4 | 163 (64.17) | 150 (20.54) | 313 (31.80) | 166.68 | 0.0001 |
| 3.4 – 4.8 | 90 | 580 | 670 |
| Globulin >3.5 | 79 (31.10) | 274 (37.53) | 353 (35.87) | 3.16 | 0.080 |
| 2 – 3.5 | 173 | 455 | 628 |
| Urea >43 | 168 (66.14) | 142 (19.45) | 310 (31.50) | 188.16 | 0.0001 |
| 13-43 | 86 | 588 | 674 |
| Creatinine >1.3 | 78 (30.70) | 53 (20.86) | 131 (13.31) | 95.70 | 0.0001 |
| 0.7-1.3 | 168 | 586 | 842 |
| Sodium >145 | 27 (10.62) | 7 (0.9) | 34 (3.45) | 52.91 | 0.0001 |
| 135-145 | 226 | 127 | 947 |
| Potassium >5 | 51 (20.07) | 95 (13.01) | 146 (14.83) | 7.53 | 0.008 |
| 3.5-5 | 202 | 634 | 836 |
| Calcium >10 | 4 (1.57) | 29 (3.97) | 33 (3.35) | 3.34 | 0.071 |
| 8.6-10 | 249 | 698 | 947 |
| CRP >5 | 154 (60.62) | 273 (37.39) | 427 (43.33) | 23.73 | 0.0001 |
| 0-5 | 08 | 78 | 86 |
| Ferritin >322 | 157 (61.81) | 257 (35.20) | 414 (42.07) | 58.05 | 0.0001 |
| 24-322 | 31 | 241 | 272 |
| D-Dimer >0.5 | 172 (67.71) | 277 (37.94) | 449 (45.63) | 78.89 | 0.0001 |
| ≤0.5 | 11 | 201 | 212 |
| LDH >460 | 133 (52.36) | 222 (30.41) | 355 (36.07) | 0.0001 | 0.0001 |
| 230-460 | 04 | 49 | 53 |
Logistic regression performed for significant variables found in the univariate analysis showed leukocytosis, high neutrophil-lymphocyte ratio (NLR), low albumin, high ferritin and D-dimer associated higher odds of death (Table 8).

TABLE 8: Logistic regression for Lab variable found significant in multivariate analysis

The final logistic regression model (Model 4) is presented in Table 9, taking variables of Model 3 and lab variable to predict death.
TABLE 9: Model 4 - final regression model to predict mortality of COVID-19 with demographic, clinical signs and symptoms, comorbidities, and lab variables

| Covariates                  | Adjusted Odds Ratio with 95% CI | Z-statistic | P-value |
|-----------------------------|---------------------------------|-------------|---------|
| Clinico-demographic variable|                                 |             |         |
| Age 60-75 years             | 1.47 (1.02 – 2.21)              | 1.99        | 0.032   |
| Age 75+ Years               | 3.97 (2.11 – 9.03)              | 3.97        | 0.0001  |
| Severe disease              | 17.81 (11.14 – 28.47)           | 12.03       | 0.0001  |
| Cough                       | 3.83 (2.33 – 6.30)              | 5.29        | 0.0001  |
| Shortness of Breath         | 2.35 (1.58 – 3.50)              | 4.24        | 0.0001  |
| Chronic kidney disease      | 2.95 (1.40 – 6.21)              | 2.86        | 0.004   |
| Lab variable                |                                 |             |         |
| Total cell count (>10,000/mm3)| 1.74 (1.20- 2.52)             | 2.97        | 0.003   |
| Neutrophil-lymphocyte ratio (>3.3) | 2.37 (1.48- 3.79)     | 3.62        | 0.000   |
| Serum total protein (<8.4 gm/dl) | 2.10 (1.36-3.22)           | 3.40        | 0.001   |
| Serum Albumin (<3.4 g/dl)   | 2.30 (1.51-3.50)              | 3.88        | 0.000   |
| Blood Urea (>43 gm/dl)      | 3.72 (2.57-5.38)              | 6.98        | 0.000   |
| Ferritin (>322)             | 2.39 (1.21- 4.72)              | 2.53        | 0.012   |
| D-dimer (>0.5)              | 5.58 (2.21-14.05)             | 3.65        | 0.000   |

Discussion

This retrospective observational study included analysis of 984 patients hospitalized with COVID-19 infection to identify the clinical and laboratory factors associated with mortality. The overall case-fatality rate (CFR) among the admitted cases was 25.81%. It varies across studies from less than 1 percentage to 18 percentage in Italy [4]. One of the largest cohorts of 5700 patients showed a case fatality of 21% [6]. In another study of 1697 patients, the CFR was 25.7% [7].

Our case-fatality rate was higher compared to some other reports [4,6,7]. This could be due to many socio-cultural-economic factors which play a role. Ours was a tertiary care referral hospital where only the sickest patients not admitted elsewhere were catered to.

Discussing some factors individually

Gender: In these parts of the world, gender discrimination is prevalent. There are some studies that do report that the male gender has a higher risk for mortality [8-9]. Despite catering largely to a patriarchal society, in our study, no sex-based differences in mortality were noted.

Age: We found age as the most important risk factor for mortality in COVID-19 infections. The mean age of deceased patients was 10 years more than those who survived (58.66 years vs 47.97 years). The highest risk of death was noted amongst cases more than 75 years of age, followed by patients in the age group 60-75 years. More than 60% (60.34%) of patients with age more than 75 years died. Advanced age as a risk factor for mortality has been reported by several studies [10-13]. Wu C and colleagues concluded that older age was associated with a greater risk of development of ARDS and death likely owing to less rigorous immune response. [14]

Symptoms: Dyspnea on presentation was found to be significantly associated with mortality. The odds of dying were 3.63 times more among cases having shortness of breath on admission (crude odds ratio = 3.63). Du RH et al [15] have documented the presence of dyspnea, fatigue to be associated with a higher risk of mortality in COVID-19. Our study supported by another Indian study showed the presence of dyspnea significantly increased the risk of mortality [12]. We also noted that patients presenting with generalized weakness had a higher chance of progressing to severe disease. These symptoms may thus warrant more vigilant monitoring. Presence of fever (crude OR = 0.608, p=0.002) and sore throat (crude OR = 0.356, p=0.013) were not found to be associated with higher risk for mortality.
Comorbidities such as diabetes mellitus (DM), hypertension, CKD, and malignancy were seen to be significantly associated with increased risk of mortality. Studies had found that patients with chronic comorbidities were associated with severe COVID-19 infection with higher mortality [16-17]. The worse outcome in diabetes could be due to impaired innate immunity [17] which is the first line of defense against SARS-CoV-2 chronic inflammation or increased coagulation activity among DM patients [18]. It has been shown that diabetes and hypertension treatments with angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II type 1 receptor blockers (ARBs) increase angiotensin-converting enzyme 2 (ACE2) expression which consequently raises the risk of developing severe and fatal complications. Similar to our study, Chilimuri et al [19] also showed higher odds of death in presence of comorbidities such as diabetes, hypertension, chronic obstructive pulmonary disease (COPD), CKD. A meta-analysis by Singh and Misra [20] also observed a significant 1.5 to 3-fold increase in severity of COVID-19 in patients with hypertension or diabetes or cardiovascular disease (CVD) or COPD or CKD and/or cancer. In the final predictive model, after controlling all confounders, diabetes and hypertension were not found as independent risk factors for mortality. Jain et al. [12] also showed diabetes is not an independent risk factor for mortality which is supporting our model.

Among lab variables, total cell count, neutrophil, random blood sugar, blood urea, creatinine was significantly higher, while serum calcium was significantly lower among the cases who died compared to survived cases (p<0.0001). Patients with severe disease had only a mild increase in WBC count while patients who died had a more clinically significant increase in this parameter. Leukocytosis, neutrophilia, and lymphopenia have been a well-proven risk factors for severe disease and worse outcome [21].

Literature suggests that D-dimer, CRP, serum ferritin, and LDH levels are important indicators of the severity of COVID-19 infections and may predict mortality in these patients [19]. This study also found that CRP, ferritin, D-dimer, and LDH were significantly higher among the cases who died (p<0.0001). Increased levels of D-dimer reflect increased coagulation activity which could be attributed to an increase in systemic pro-inflammatory cytokine responses which further contribute to atherosclerosis, plaque rupture. These activities further contribute to local inflammation as well as induction of procoagulant factors and thus predispose patients to ischemia and thrombosis [22-23]. Raised CRP levels, however, reflect the level of inflammation and it may activate complement level and enhance phagocytosis. CRP levels are an important indicator of the severity of COVID-19 infections [24]. Vargas-Vargas and Cortés-Rojo suggested serum ferritin levels as a key mediator suggesting immune dysregulation. Cytokine storm associated with raised serum ferritin levels has been associated with disease severity and adverse outcomes [25].

This study has certain limitations. Firstly, this is a retrospective single-center study which may limit the generalizability of the findings. Recording patient data only at the time of hospital admission could be another limitation of the study.

Conclusions

The overall case-fatality rate among hospitalized COVID-19 patients at our hospital was 25.81%. Age more than 60 years, presence of CKD, and severe COVID-19 infection were the independent risk factors for mortality. Diabetes and hypertension did not independently increase the risk of mortality. The presence of cough or breathlessness was associated with worse outcomes while fever was associated with lower risk. Elevated CRP, ferritin, D-dimer, and LDH were associated with worse outcomes in COVID-19 infection. So, every hospitalized patient should undergo a detailed evaluation for comorbidities, the severity of disease, and these tests at the time of admission.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Institutional Ethics Committee, All India Institute of Medical Sciences, Patna issued approval AIIMS/Pat/IEC/2020/552. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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