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Clinical features and biochemical parameters influencing mortality in COVID-19 patients — Retrospective study from Telangana, India

Sumayya Zainab Sabeena[1], Archana Pathy[2], Hajra Luqman[1], NN Sreedevi[1], Siraj Ahmed Khan[1], Madhulatha K[1], M Vijaya Bhaskar[1], KSS Sai Baba[1], Padmaja Durga[2] & M Noorjahan[1]*

[1]Deptartment of Biochemistry; [2]Department of Anaesthesiology and Critical Care, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad-500 082, Telengana, India

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The coronavirus disease COVID-19 caused by SARS-CoV-2 was a worldwide public health emergency which affected millions of people including frontline healthcare workers too. We evaluated the clinical features and biochemical investigations in COVID-19 affected healthcare workers (HCW) admitted to NIMS Intensive care unit (ICU) including survivors and non-survivors to identify risk factors for mortality. We did a retrospective study of 78 HCW with RTPCR confirmed COVID-19 infection admitted in ICU between July and November, 2020. Subjects were grouped into survivors and non-survivors. Clinical features and biochemical investigations were compared. Survival analysis was performed to analyze the risk factors of mortality. Out of the 78 patients admitted to ICU, the majority were males (64%). Non-survivor patients were older with a median age of 64 years. There were significantly higher proportion of females (59%) in non-survivors. COVID-19 non-survivors had significantly more incidence of cardiovascular disease and also higher blood levels of AST, CPK, CRP, D-dimer, IL-6, LDH, urea, NTproBNP and procalcitonin. Hazard's ratios showed that the mortality risk was significantly higher and survival was significantly lower in patients more than 60 years in age, females and those having IL-6 >40.06 pg/mL, LDH >461U/L, NTproBNP >1188 pg/mL, procalcitonin >0.5 pg/mL, urea >67 mg/dL, creatinine >1.3 mg/dL, D-dimer >573 ng/mL, ferritin >1488 ng/mL, andCPK >191U/L. Our study identified that the mortality risk was significantly higher and survival was significantly lower in patients older age group, females and those having higher IL-6, LDH, NTproBNP, procalcitonin, urea, creatinine, D-dimer, ferritin and CPK. Determination of specific clinical and biochemical features as above would help in better understanding of the pathophysiology, prognosis and appropriate intervention for potential outcomes.

Keywords: Comorbidity, Healthcare workers, SARS-CoV-2

*Correspondence:
Phone: +91 9440207335; +91 9490517966 (Mob.)
E-Mail: noorjahannims@gmail.com

Health-care workers (HCWs) are at the frontline of response to COVID-19 especially those working in hospital non-emergency wards and nurses being the most commonly infected and subsequently exposing patients and others[1]. The situation is especially difficult in developing countries where health and social systems are weak. It was reported that many HCWs suffered from covid and announced that many died of COVID-19[2-4]. Determining specific clinical and biochemical features associated with COVID-19 will lead to development of screening and treatment protocols. We compared those features in those who survived against those who couldn't survive.

The duration from onset of symptoms to death is around two weeks[2]. On the other hand, a number of COVID-19 patients could be suffering from hypertension, coronary artery disease and diabetes. Therefore, study of the background co-morbidities is important in understanding COVID-19. SARS-CoV-2 causes hyperinflammatory response sometimes leading to death of patients. The clinical features vary from no symptoms to fast progression, like respiratory failure or even death. The virus can involve the liver, spleen, cardiovascular, stomach etc.[5] leading to hospitalization, ICU care and sometimes intubation[3].

Earlier Shahid *et al*.[6] have demonstrated elevated blood concentrations of cytokines in ICU patients. Here, we used the hazard's ratio and survival analysis to analyze the risk factors for proper clinical care. Further, we have investigated comorbidities such as hypertension, CKD and diabetes.

Methodology

A retrospective study of 78 healthcare worker patients with PCR confirmed COVID-19 infection admitted in the Intensive care unit of Nizam's Institute of Medical Sciences, Hyderabad between July and November, 2020. Depending on the outcome, the subjects were grouped into two categories: those who survived and those who succumbed. Patients with positive real time polymerase chain reaction (RT-PCR) or radiological findings consistent with COVID-19 were included in the study. Clinical features and laboratory values were collected from case records.

The parameters studied were complete blood picture (Beckman coulter unicel DXI800), liver and kidney function tests, CPK, LDH, ferritin (Roche Cobas 6000 chemistry autoanalyser), NTproBNP (Advia centaur XPT chemiluminescence analyser), Interleukin-6 (IL-6), Procalcitonin (Beckman coulter DXI 600 chemiluminescence analyser), CRP (Latex agglutination) and D-dimer (Instrumentation Laboratory, ACL TOP 500) levels in blood. Statistical analysis was done by MedCalc® Statistical Software version 20.015 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021)

Statistical analysis

The quantitative data were presented as mean ± standard deviation, median and range or as frequency and percent. Association of variables was tested by Chi-square test and means were compared by independent sample test or Mann-whitney test. Survival analysis was done using Kaplan-Meier survival curves. P <0.05 was considered as significant. ROC curves were used to establish the cutoff values between the two groups. This study was approved by the Institutional Ethics Committee (EC/NIMS/2707/2021).

Results and Discussion

A total of 78 patients diagnosed with COVID-19 who were admitted in ICU from 1st July to 30th November 2020 were included in the study. Depending on their outcome they were divided into two groups, survivor and non-survivor groups. Out of the 78 patients admitted to ICU, the majority were males (64%). Baseline clinical parameters and comorbidities of patients are summarized in Table 1. The median age of the survivor group patients admitted to the ICU was 52 years (IQR 46–60). Non-survivor patients were older with a median age of 64 years (IQR 58.5–75, p =0.002). There were significantly higher percentages of females (59%) in non-survivors than in survivors. COVID-19 non-survivor group had higher incidence of comorbidities. Hypertension was the most common co-morbid condition (60.7%), followed by diabetes (57.1%) and coronary artery disease (35.7%). Number of patients with cardiovascular disease in non-survivors were significant. Median ICU stay was 6 (2-15) days in survivors and 7 (2-25) days in non-survivors.

Statistically significant difference was observed in the blood levels of parameters like albumin, AST, CPK, CRP, D-dimer, IL-6, LDH, urea, NTproBNP and procalcitonin but not for ALT, ALP, creatinine, ferritin, lymphocytes, neutrophils, N/L ratio, platelets, total bilirubin, total protein as shown in Tables 2 & 3. We obtained cutoff values of the variables by ROC analysis between non-survivor and survivor groups. Based on these cut-off values survival analysis was done and hazards ratios were obtained (Table 4 & Fig. 1). From the hazard's ratios, it can be concluded that the mortality risk is significantly higher and survival is significantly lower in patients more than 60 years in age, females and those having IL-6 >40.06 pg/mL, LDH >461U/L, NTproBNP >1188 pg/mL, procalcitonin >0.5 pg/mL, urea >67 mg/dL, creatinine >1.3 mg/dL, D-dimer >573 ng/mL, ferritin >1488 ng/mL, CPK >191U/L. Though the risk is higher in patients having albumin <3.5 g/dL, Hemoglobin <10 g/dL and N/L ratio >10.88, it is statistically not significant.

Health care workers are at the front line of the COVID-19 outbreak response and as such are exposed to different hazards that put them at risk. A significant number of them suffered from COVID-19. We evaluated 78 HCWs infected with COVID-19 disease and who were admitted to ICU out of which 50 survived and 28 succumbed. We evaluated the available clinical information and characteristics, as well as the risk factors involved in mortality.

Table 1 — Demographic variables and co-morbidities in the Non-Survivor and Survivor groups

Demographic variables and comorbidities		Non-Survivors (N=28) (%)	Survivors (N=50) (%)	P value
Age (Years)	≤60	32.14	82	<0.0001
	>60	67.9	18	
Gender	M	29.5	70.5	0.0268
	F	59	41	
HTN	Yes	60.7	39.5	0.08
	No	39.3	60.4	
DM	Yes	57.14	33.33	0.42
	No	42.9	66.66	
COPD	Yes	3.6	16.3	0.5
	No	89.3	83.7	
CKD	Yes	14.8	16.2	0.87
	No	85.2	83.7	
CAD	Yes	35.7	4.6	0.0009
	No	64.3	95.3	
Days Of Symptoms	≤6days	75	55.8	0.1
	>6days	25	44.2	
ICU Stay	≤7days	53.6	52	0.89
	>7days	46.4	48	

[CAD, Coronary artery disease; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; DM, Diabetes mellitus; HTN, Hypertension]

Table 2 — Laboratory parameters in Non-survivor and Survivor groups

	Non-Survivors				Survivors				
	Mean	Median	SD	25 - 75 P	Mean	Median	SD	25 - 75 P	P-Value
AGE (yr)	63.6	64	13.7	58.5-75	52.6	52	12.51	46-60	0.0002
ALB (g/dL)	3.16	3.3	0.55	2.95-3.5	3.51	3.5	0.49	3.2-3.8	0.0068
ALP (IU/L)	102	87.5	56.8	63.5-125	76.5	73	23.7	59-84	0.0837
ALT (IU/L)	249	34.5	867	21-74	41.4	32	27.7	24-52	0.6096
AST (IU/L)	398	50	1678	35-95.5	37.92	30	23.7	22-48	0.001
CPK (IU/L)	2771	278	10935	122-549	200	99	300	51-211	0.0006
CREAT (mg/dL)	1.87	1.04	2.03	0.77-2.25	1.08	0.92	0.78	0.80-1.04	0.1435
Lymphocytes (%)	7.5	6.5	3.72	5-10	10.44	10	6.74	5.25-12	0.1147
Neutrophils (%)	85.7	86.5	5.89	80.5-90.5	82.95	84	7.58	80-88	0.2077
N/L Ratio	14.49	13.49	7.24	8.5-18.6	11.7	8.5	7.63	6.73-16.39	0.1127
NTproBNP (pg/mL)	15271	7973	14376	2165-30000	712	313	1504	103.9-580.5	<0.0001
PLT ($\times 10^3/\mu L$)	24.696	2.3	102.81	1.725-3.725	2.469	2.3	0.9179	1.8-2.725	0.8747
TBIL (mg/dL)	0.686	0.6	0.4866	0.4-0.900	1.514	0.5	4.86	0.4-0.6	0.1928
TP (g/dL)	6.046	6.25	0.73	5.75-6.45	6.313	6.5	0.9721	5.9-6.9	0.0659
Urea (mg/dL)	69.4	58	45.5	37.3-81.5	45.9	41	23.1	30-56	0.0119

[ALB, Albumin; ALP, Alkaline phosphatase; ALT, Alanine transaminase; AST, Aspartate transaminase; CPK, Creatine phosphokinase; CREAT, Creatinine; N/L_ratio, Neutrophil/lymphocyte ratio; PLT, Platelets; TBIL, Total bilirubin; TP, Total protein]

Table 3 — Inflammatory markers in Non-survivor and Survivor groups

	Non-Survivors				Survivors				
Inflammatory Marker	Mean	Median	SD	25 - 75 P	Mean	Median	SD	25 - 75 P	P-Value
CRP (mg/L)	32.7	24	14.9	24-48	21.1	18	16.9	6.0-24.0	0.0045
D-dimer (ng/mL)	5372	1864	9765	538-5546	1214	249	4077	161-604	0.0001
Ferritin (ng/mL)	1233	900	884	575-1882	914	687	793	278-1316	0.1064
IL-6 (pg/mL)	240	85.4	397	47.5-170	154.8	28.4	365.7	5.37-79.88	0.0059
LDH (U/L)	890	698	775	477-941	352	328	127	251-415	<0.0001
PCT (pg/mL)	5.987	0.677	12.064	0.386-8.68	1.524	0.315	6.851	0.129-0.617	0.0031

[CRP, C-reactive protein; IL-6, Interleukin-6; LDH, Lactate dehydrogenase; PCT, Procalcitonin]

Table 4 — Hazard's ratios of Variables

Variable	Cut-off	Hazard's ratio (95% CI)
Age in years	>60	6.9015 (3.0090-15.8293)
Albumin (g/dL)	<3.5	0.5193(0.2407-1.1202)
Gender	M & F	2.7825(1.0843-7.1409)
HB (g/dL)	<10	0.4685(0.1838-1.1940)
IL-6 (pg/mL)	>40.06	3.8528(1.6140-9.1972)
LDH (U/L)	>461	12.4920(5.5376-28.1803)
NL ratio	>10.88	2.4202(0.9880-5.9284)
NTproBNP(pg/mL)	>1188	24.6359(8.6161-70.4413)
PCT (pg/mL)	>0.5	2.6914(1.1995-6.0387)
Urea (mg/dL)	>67	5.8301(2.2508-15.1014)
Creatinine (mg/dL)	>1.3	3.4351(1.2292-9.5992)
D-dimer (ng/mL)	>573	5.3464(2.4451-11.6906)
Ferritin (ng/mL)	>1488	2.4839(1.0527-5.8608)
CPK (IU/L)	>191	4.0517(1.7914-9.1638)

[CPK, Creatine phosphokinase; HB, Hemoglobin; IL-6, Interleukin-6; LDH, Lactate dehydrogenase; N/L ratio, Neutrophil/ lymphocyte ratio; PCT, Procalcitonin]

We found that elderly have high risk which could be due to comorbidities which is in agreement with earlier reports[6,7]. Though males were more in number, higher percentage of females succumbed to death. Patients with comorbidities have been shown to have a greater risk of mortality with COVID-19, similar to other studies[6]. In this study, 51.3% of the infected healthcare workers had hypertension, 46% had DM, 17.9% CKD, 16.7% COPD and 14% had CAD. Presence of CAD has shown significant difference between the two groups (p=0.0009) similar to other studies[6]. Increased NTproBNP in non-survivor group supports the data.

Median ICU stay was 6 (2-15) days in survivors, after that they were shifted to general ward or discharged. In non-survivors' median ICU stay was 7 (2-25) days and after that they succumbed to death.

Though lymphocytosisis significant marker for the fast progression of the condition, we did not find significant difference between the two groups. Also, poor nutrition can lead to hypoalbuminemia affecting host immunity[8]. Some of the malnourished patients may deteriorate fast resulting in respiratory distress or death[9]. Our data also showed significant decrease of albumin in non-survivor group. Also, the mortality was higher in cardiac, hypertensive and diabetes patients[6,7] similar to our results. Among the routine parameters' neutrophils, lymphocytes and their ratio (NL ratio), platelets, ALT, ALP, creatinine, total bilirubin, total proteins did not differ significantly between survivors and non-survivors whereas

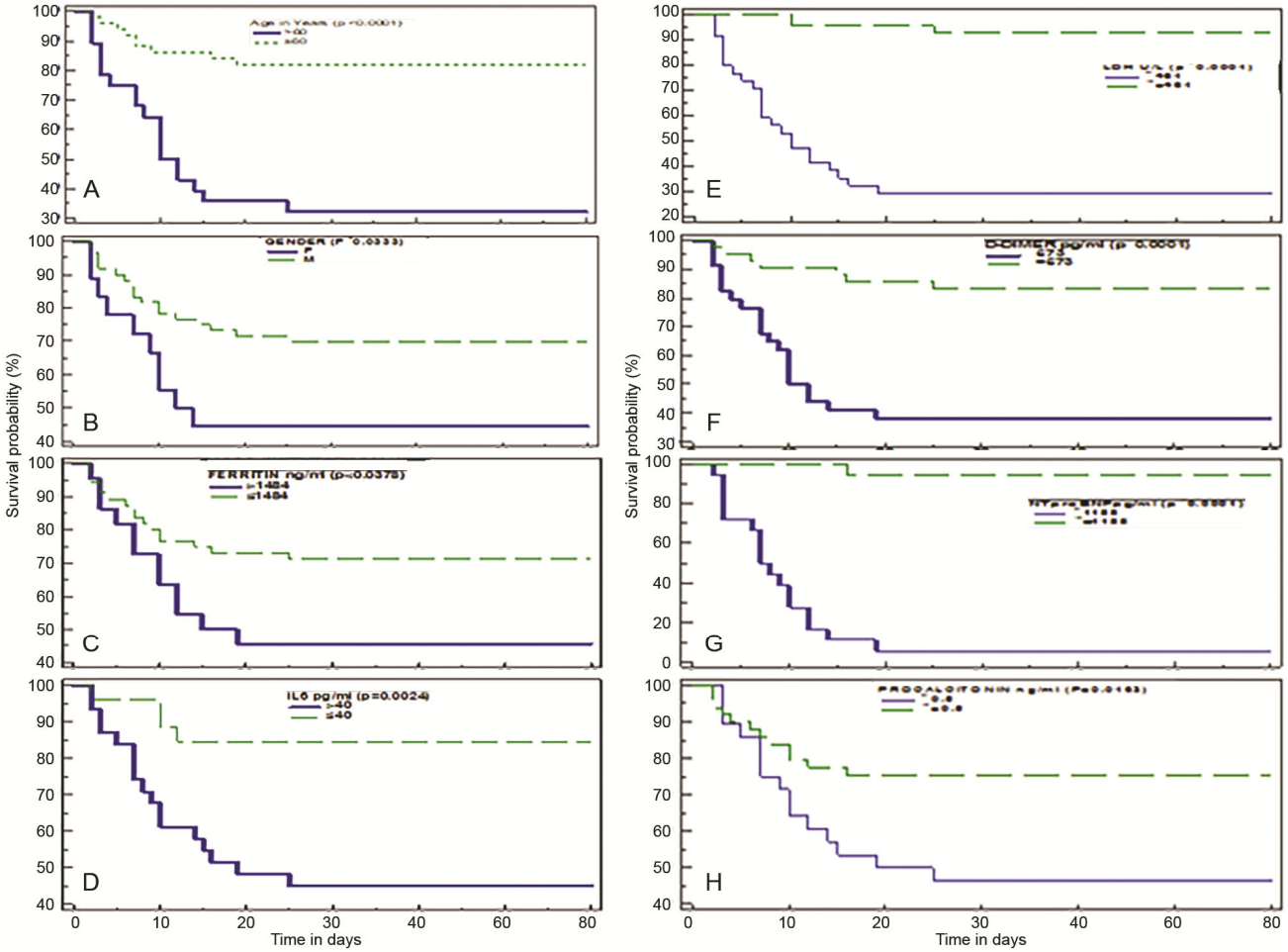

Fig. 1 — Kaplan Meier curves based on risk factors in COVID-19. Survival probability in ICU patients based on (A) Age; (B) Gender; (C) Ferritin; and (D) Interleukin-6 (IL-6); (E) LDH; (F) D-dimer; (G) NT- proBNP; and (H) Procalcitonin

albumin, AST, CPK, urea have shown significant difference.

The hyperinflammatory state initiated the virus is mainly responsible for the mortality of the patients[8]. In our findings inflammatory markers CRP, IL-6, LDH and procalcitonin have shown significant differences between the non-survivor and survivor groups; whereas ferritin level did not show any significant difference, though it was increased among non-survivors.

Significant increase in various parameters hazards ratio showed that involvement of multiple organs in non-survivor patients. From the hazard's ratios, it can be concluded that the mortality risk is significantly higher and survival is significantly lower in patients older age group, females and those having higher IL-6, LDH, NTproBNP, procalcitonin, urea, creatinine, D-dimer, ferritin and CPK.

Conclusion

With the above results it is clear that the clinical features and laboratory parameters viz. age, gender and levels of IL-6, CRP, LDH, NTproBNP, procalcitonin, urea, creatinine, D-dimer, ferritin and CPK influence mortality in COVID-19. However, futher research with larger sample size would clarify these issues and better understanding of the patho-physiology, prognosis and appropriate intervention for significant outcomes.

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