Original Article

DOI: 10.7860/JCDR/2021/47148.14811

Pathology Section

Comparison of Clinical, Haematological, Biochemical Findings and Significance of Co-morbidities amongst COVID-19 Positive Survivors and Non Survivors

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ABSTRACT

Introduction: Coronavirus Disease 2019 was first isolated in 1960. Middle East Respiratory Syndrome virus (MERS) and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) also belongs to Corona viridae family. Human Coronavirus causes fever, cough, fatigue, respiratory infection and abdominal symptoms. This virus has a strong affinity to human respiratory receptors and transmits rapidly. Since, the virus has spread around the world and has acquired features of emergency, World Health Organisation (WHO) declared it as a pandemic in March 2020.

Aim: To study the clinical, haematological, biochemical findings and significance of co-morbidities amongst COVID-19 positive survivors and non survivors.

Materials and Methods: A retrospective cohort study was done at Chattrapati Shivaji Subharti Hospital (CSSH), Meerut, Uttar Pradesh, a level 3 COVID-19 Hospital from mid-June 2020 to end of August 2020 including 140 COVID-19 positive patients selected randomly. Patients were categorised into asymptomatic and symptomatic. Symptomatic were further divided into survivors and non survivors. Haematological and biochemical parameters were analysed amongst survivors and non survivors, with calculation of significant p-value (<0.01).

Results: Out of total 140 patients, 37/140 patients (26%) were asymptomatic and 103/140 (74%) symptomatic. Amongst symptomatic, survivors were 78/140 (56%) and non survivors were 25/140 (18%) of total positive patients. Out of 37/140 (26%) asymptomatic patients, majority were in the age group 21-30 years 14/140 (10%) with female preponderance 10/140 (7.1%). Out of 78/140 (56%) survivors, majority were in 51 to 60 years age group, with male predominance17/140 (12.1%). Amongst 25/140 (18%) non survivors most common affected age group was 51 to 60 years 10/140 (7.1%). Most common symptoms in survivors was cough (51/78 patients; 65.4%) and fever (35/78 patients; 44.9%). In Non survivors, pneumonia was seen in 100% (25/25) patients. Out of 23/25 (92%) patients presented with fever, 19/25 (76%) had breathlessness, 16/25 (64%) had myalgia, 9/25 (36%) had cough, 5/25 (20%) presented with vomiting or pain in abdomen. Amongst non survivors, Total Leucocyte Count (TLC), Absolute Neutrophil Count (ANC), Neutrophil Lymphocyte Ratio (NLR), urea, serum creatinine, serum bilirubin, Aspartate Amino Transferase (AST) and Alanine Amino Transferase (ALT) were significantly raised as compared to survivors (p<0.01); meanwhile platelet count and Platelet Lymphocyte Ratio (PLR) in non survivors was significantly lower than survivors (p<0.01). Most common co-morbidity was diabetes in 12/25 (48%) and hypertension in 6/25 (24%) among non survivors.

Conclusion: COVID-19 infection more likely affects older men with co-morbidities like diabetes mellitus and hypertension and can rapidly progress to pneumonia, Acute Respiratory Distress Syndrome (ARDS) and septic shock. Certain haematological and biological parameters have been found to be in concordance with increased mortality which can be reduced by early identification of these parameters.

Keywords: Co-morbidity, Coronavirus, Neutrophil lymphocyte ratio, Neutrophilia, Platelet lymphocyte ratio

INTRODUCTION

Coronavirus Infection-2019 (COVID-19) dates back to 1960 when it was first isolated and named and was thought to spread between animals and humans. There are seven known Coronaviruses that can infect humans, four of these cause common cold and other symptoms like fever and throat infection [1]. In 2002 and 2003 more than 8000 people were infected in Asia with Severe Acute Respiratory Syndrome (SARS). It caught attention because it resulted in a mortality of 9.6% [2-5].

Further similar symptoms were observed in patients suffering from MERS virus, the disease which broke in Middle East, Africa and other regions in 2012. Mortality was huge 34.4% although only 2000 cases were diagnosed [6-8].

The novel virus was named in 2019 SARS-CoV-2 by WHO and is the 3rd fatal Coronavirus. Since, December 2019 an increasing number of pneumonia cases were reported to WHO Country Office, Wuhan, Hubei, China [9-14].

Novel Coronavirus causes fever, cough, fatigue, respiratory infection and abdominal symptoms [15]. Coronavirus are enveloped nonsegmented Ribonucleic Acid (RNA) viruses belonging to the family of Coronaviridae. Epidemiological studies done on novel coronavirus revealed that most of the patients suffering from ARDS had visited a local seafood market in Wuhan [16,17]. The gene sequence of the virus obtained was similar to that obtained in bats [18]. This virus has a strong affinity to human respiratory receptors and thus a potential threat to public health globally [19]. The transmission is rapid, initially it was thought to be transmitted from animals but by January 2020 it was suspected to have human-to-human transmission [20]. Since, the virus has spread around the world and has acquired features of Emergency, WHO declared it as a pandemic in March 2020 [21]. Most patients with novel coronavirus infection are mild to asymptomatic. Those patients with moderate illness experience dyspnea after a week. WHO has reported about 80% of infected people has mild to moderate symptoms, 13.8% have moderate infections and 6.2 % have severe infections [11].

The severity of illness is defined by WHO according to clinical management of severe acute respiratory infection. Critical illness is defined as patients with ARDS or sepsis with acute organ dysfunction.

Severe illness is designated when patients have fever or suspected respiratory infection, plus one of the following, respiratory rate >30 breaths/min, severe respiratory distress or pulse oximeter oxygen saturation <93% on room air [10]. Severely-ill patients progressed rapidly to acute respiratory failure, ARDS, metabolic acidosis, coagulopathy and later on septic shock [22].

Patients who were COVID-19 positive initially may show normal Total Leukocyte Count (TLC) or leukopenia. Lymphopenia has been reported by many studies [23]. Patients admitted in Intensive Care Unit (ICU) show decrease in haemoglobin, high TLC with neutrophilia. Leukocytosis, lymphopenia and thrombocytopenia are associated with greater fatality. In such patients' serum urea, creatinine, bilirubin, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT) were also raised [24].

Patients who had co-morbidities like diabetes mellitus type 2, hypertension, thyroid disorders, liver diseases were found to be more susceptible to the viral infection and were likely to have bad prognosis [24]. As the data regarding this virus is still inadequate, hence the present study was conducted with the following objectives:

1. To compare the clinical findings amongst COVID-19 positive survivors and non survivors.
2. To compare the haematological findings amongst COVID-19 positive survivors and non survivors.
3. To compare the biochemical findings amongst COVID-19 positive survivors and non survivors.
4. To study the significance of co-morbidities amongst COVID-19 positive survivors and non survivors.

MATERIALS AND METHODS

This retrospective cohort Study was conducted at Chatrapati Shivaji Subharti Hospital (CSSH), Meerut, Uttar Pradesh which is a level 3 COVID hospital. Study was done in the month of October and data was collected from 18 June to 30th August, after taking Ethical Committee approval (SMC/UECM/2021/230/146). In this study, convenience sampling technique was adopted i.e., all the COVID-19 positive patients were included during the study period. During the study period 179 patients were found COVID-19 positive, out of which 39 failed to provide the consent. Remaining 140 COVID-19 positive patients who were admitted with suspected symptoms of novel coronavirus like fever, cough and respiratory problems and asymptomatic health worker were included. Patients were divided into asymptomatic and symptomatic patients. Symptomatic patients were further divided into survivors and non survivors. Asymptomatic patients were not categorised further. For the virus detection nasal swabs were taken and were tested by Qiagen rotor gene Q5 plex HRM.

Real Time Polymerase Chain Reaction (RT PCR) for SARS-Co-2 RNA was done. Complete Blood Count (CBC) was done by 5 part haematology analyser Horiba XL -80. Kidney Function Test (KFT) and Liver Function Test (LFT) was performed by Siemens Dimension RxLMax-2.

STATISTICAL ANALYSIS

Demographic, clinical and laboratory findings from patients medical record data were collected. All statistical analysis was performed by using SPSS software (23.0) version. Comparison of mean score of various haematological and biochemical parameters of survivors and non survivors was done by double sample mean test/Z score at 1% level of significance. The p-value less than 0.01 was considered significant.

RESULTS

Out of 140 patients, asymptomatic patients were 37 (26%) of total COVID positive patients. Asymptomatic patients were discharged and no further follow-up was done. Amongst asymptomatic patients, most {14/140 (10%)} were in the age group 21-30 with female preponderance accounting for 7.1% of total patients.

Amongst asymptomatic patients' CBC, LFT, KFT were within normal range. However, 3 males between 21-30 years of age had elevated HbA1c which was a chance finding and they were further investigated for diabetes mellitus.

Survivors were 78/140 (56%) of total positive patients. Survivors were mostly in the 51 to 60 years age group, with males being more affected 17/140 (12.1%).

Non survivors were 25/140 (18%) of total positive patients. Out of these mostly were males in age group of 51 to 60 years 7/140 (5%) followed by males in 31-40 years 4/140 (2.8%). Between 41-70 years age three females 3/140 (2.1%) were non survivors in each age group [Table/Fig-1].

Age range (years)	Asymptomatic=37 (n=26%)		Symptomatic=103 (n=74%)			
			Survivors=78 (n=56%)		Non survivors=25 (n=18%)	
	Male=19	Female=18	Male=49	Female=29	Male=14	Female=11
0-10	5	0	1	0	0	0
11-20	0	0	0	5	0	0
21-30	4	10	5	5	0	1
31-40	2	3	7	1	4	0
41-50	2	0	7	3	1	3
51-60	3	5	17	9	7	3
61-70	2	0	8	4	0	3
71-80	1	0	4	2	2	1

[Table/Fig-1]: Distribution of cases according to age, sex, survivors and non survivors.

Fever, cough, breathlessness, myalgia, vomiting or pain in abdomen was the predominant symptoms amongst survivors. Cough was seen in 65.4%, fever in 44.9%, breathlessness in 25.6%, myalgia in 19.2%, vomiting in 8.9% and pneumonia was seen in only 3.8% patients. In these patients, diabetes was present in 5.1%, Chronic Obstructive Pulmonary Disease (COPD), hypertension and thyroid dysfunction each was seen in 1.2% patients [Table/Fig-2]. Amongst the non survivors, COVID-19 pneumonia was seen in 100% patients, 92% patients presented with fever, 76% had breathlessness, 64% had myalgia, 36% had cough, 20% presented with vomiting or pain in abdomen [Table/Fig-2].

Variables	Survivors n=78 (56%)	Non survivors n=25 (18%)
Clinical features		
Fever	35 (44.9%)	23 (92%)
Cough	51 (65.4%)	9 (36%)
Breathlessness	20 (25.6%)	19 (76%)
Pneumonia	3 (3.8%)	25 (100%)
Myalgia/generalised body weakness	15 (19.2%)	16 (64%)
Vomiting/pain abdomen	7 (8.9%)	5 (20%)
Co-morbid condition		
Hypertension	1 (1.2%)	6 (24%)
Diabetes	4 (5.1%)	12 (48%)
Chronic obstructive pulmonary disease	1 (1.2%)	2 (8%)
Cerebrovascular disease	-	2 (8%)
Renal disease	-	4 (16%)
Liver disease	-	3 (12%)
Cardiomyopathy	-	2 (8%)
Thyroid dysfunction	1 (1.2%)	4 (16%)

[Table/Fig-2]: Clinical features and co-morbid conditions amongst survivors and non survivors.

In non survivors, most patients were diabetics 48% and hypertension was seen in 24%. Renal disease or thyroid dysfunction each was present in 16% patients and liver disease was found in 12%.

Cardiovascular disease, COPD or cerebrovascular disease was present in 2 patients (8%) each [Table/Fig-2].

Amongst non survivors haemoglobin was low, mean being 10.32 g/dL. Mean TLC was found to be raised (13.49×10^9/L) with mean ANC being 9.92×10^9/L. Mean Absolute Lymphocyte Count (ALC) was however within normal range. Mean Platelets value was reduced but Red Cell Distribution Width (RDW-CV) was within normal range. NLR and PLR are indicators of systematic inflammatory response. Mean NLR was raised while mean PLR was within normal limits. Mean serum urea and creatinine were increased being 98.76 mg/dL and 1.70 mg/dL, respectively. Mean total protein was approximately within normal range being 6.3 g/dL, however mean albumin was slightly reduced. Mean Serum bilirubin was slightly increased 1.8 mg/dL and AST and ALT mean values were raised being 111.4 mmol/L and 190.4 mmol/L, respectively. Serum alkaline phosphatase was however within normal range [Table/Fig-3].

Parameters and normal range	Non survivors			Survivors			p-value
	Mean	Median	SD	Mean	Median	SD	
Haemoglobin (12-16)g/dL	10.32	10.4	1.65	11.9	12.0	1.72	0.0874
Total leucocyte count (4.0-10)×10^9/L	13.49	13.0	5.85	8.88	7.7	4.25	0.0002*
Absolute neutrophil count (1.50-7.00)×10^9/L	9.92	9.0	5.32	5.95	4.5	4.21	0.0031*
Absolute lymphocyte count (1.00-4.00)×10^9/L	1.85	1.5	1.13	2.24	1.8	1.20	0.0421
Neutrophil lymphocyte ratio (0.43-2.75)	6.3	5.2	4.0	3.7	2.0	4.0	0.0003*
Platelet count (150-400)×10^9/L	130	108	85.9	234.5	229.0	125.9	0.0001*
Platelet lymphocyte ratio (36.63-149.13)	135.6	70	262.7	157.1	90.0	160.0	0.0001*
RDW-CV (12.0-18.0) %	15.5	14.5	3.2	13.82	12.9	1.89	0.0311
Serum urea (17.1-49.2) mg/dL	98.76	93	50.8	31.45	26.0	16.3	0.0001*
Serum creatinine (0.7-1.3) mg/dL	1.70	1.5	0.91	0.83	0.74	0.31	0.0004*
Serum bilirubin (0.2-1.0) mg/dL	1.8	0.6	4.4	0.49	0.30	0.49	0.0005*
Total protein (6.4-8.2) g/dL	6.3	6.6	0.74	6.7	6.7	0.71	0.1322
Albumin (3.4-5.0) g/dL	3.15	3.1	0.39	3.6	3.5	0.72	0.1052
AST (15-37) U/L	111.4	42	178.9	40.8	30.0	40.3	0.0001*
ALT (16-63) U/L	190.4	48	488	36.25	27.0	19.9	0.0001*
Alkaline phosphate (46-116) U/L	87.7	90	30.04	72.9	74.0	17.1	0.0042*

[Table/Fig-3]: Haematological and biochemical parameters amongst 103 symptomatic survivors and non survivors with p-value (Z-test).
*p-value indicates difference in parameters between survivors and non survivors of COVID-19 patients. p<0.01 was considered statistically significant; RDW-CV: Red cell distribution width; AST: Aspartate amino transferase; ALT: Alanine amino transferase

Amongst survivors who were moderately-ill, mean value of haemoglobin was slightly low and mean value of NLR was slightly raised. Mean value of rest of the parameters was within normal range. In non survivors, TLC, ANC, NLR, serum urea, creatinine, serum billirubin, AST and ALT were significantly raised as compared to survivors (p<0.01); meanwhile, platelet count and PLR amongst non survivors was significantly lower than survivors (p<0.01) [Table/Fig-3].

Out of 25 non survivors, NLR was increased in 22 patients and PLR was increased in 3 patients. 8/25 patients among non survivors were in <50 years of age and NLR was in range of 0.77-6.5. Rest of 17 non survivors was >50 years and NLR range was 0.86-19.3 and 15 showed NLR value >3.1 [Table/Fig-4].

DISCUSSION

SARS-CoV-2 is a very contagious virus which has taken the form of a pandemic world over with clustering of cases, but its mortality is less severe than SARS CoV and MERS-CoV [1,25-29]. Many experts believe that therefore COVID-19 will co-exist with humans for a long time [1,25]. SARS in 2003 caused 8,098 confirmed cases with 774 deaths, resulting in a mortality of 9.6% in 37 countries [5,8]. Outbreak of MERS in 2012 caused 2,494 confirmed cases and deaths 858 resulting in mortality of 34.4% in 27 countries [7,8].

In the early stages, even COVID-19 showed a high mortality (15%) in Wuhan from December 2019 to January 2020. Patients were critical, having respiratory distress and required Intensive Care Unit (ICU) monitoring and treatment [1,30]. Higher mortality was seen in patients of older age group associated with development of ARDS [31].

Professor Marc Lipsitch epidemiology Harvard University predicted that 40-70% people of the world would be infected worldwide by COVID-19 virus [1]. While most people with infection are either asymptomatic or have very mild symptoms but approximately 14% to 16% develop moderate illness and require hospitalisation and oxygen support. Around 5% patients are severely or critically ill and thus have to be admitted in ICU or have to be put on ventilator [32,33]. In present study, out of 140 patients who tested positive for COVID-19, 82/140 (58.6%) were males and 58/140 (41.4%) were females, with male:female ratio of 1.4:1. Amongst 37/140 (26%) asymptomatic patients, most were in age group of 21-30 years (10%) with female preponderance (7.1%). They were either health workers or students and so they were quarantined at home according to the latest guidelines of Ministry of Health and Family Welfare (MoHFW). Amongst asymptomatic patients females were also more affected in age group of 51 to 60 years, 5/8 patients. This incidence coincides with the study done by Tiwari N et al., [21]. In their study 20 out of 29 asymptomatic patients were females and out of these eight females were between 21-30 years of age depicting high incidence amongst females in this age group. This change in the gender pattern in the Indian population could be due to some racial or ethnic influence [21].

In present study five asymptomatic patients were between 0 to 10 years of age, similar findings were noted by Tiwari N et al., [21]. This goes in contrast to study done by Li Q et al., in which they have not found any case below 15 years of age [9]. Symptomatic patients showed varied presentation as reported by Zhang JJ et al., [34]. In a study done by Wang Y et al., in majority of the observed patients the outcome was mild or ordinary [35]. Men are seen to be more affected in all age groups amongst symptomatic survivors. This is in accordance to other studies done by Luo SH et al., and Lee N et al., [36,37].

In present study, in the symptomatic survivors females were less affected could be due to reduced susceptibility of females to viral infections, attributed to the protection by X chromosomes which render innate and adaptive immunity to the female [8,21]. Similar findings were observed by Guan WJ et al., Zhang H et al., and Channappanavar R et al., [13,17,19].

Non survivors	Neutrophil lymphocyte ratio	Platelet lymphocyte ratio
1	6.5	25.5
2	4.0	23.4
3	19.3	70
4	6.4	83.0
5	0.86	14.6
6	10.5	133.3
7	0.77	140
8	4.5	1354.2
9	9.3	64.2
10	9.0	38.5
11	6.6	65.1
12	5.1	20.8
13	5.2	102.7
14	2.4	52.5
15	7.6	121.2
16	5.6	81.9
17	3.7	50.5
18	5.2	79.5
19	11.2	50
20	11.5	254
21	3.4	109.6
22	3.1	31.1
23	9.8	300
24	3.7	43.1
25	3.0	83.3

[Table/Fig-4]: Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) amongst non survivors.

Amongst non survivors males were more commonly affected with most common age group being 51-60 years, 7/140 (5%). This was in accordance with study done by Guan WJ et al., and Zhang H et al., [13,17]. In the 71-80 years of age two males and one female succumbed to death, similar to studies by Xu X et al., [20].

In present study, symptomatic survivors presented with cough (65.4%), fever (44.9%), breathlessness (25.6%), myalgia (19.2%) or abdominal pain/vomiting (8.9%). These were common symptoms reported by Zhang JJ et al., [34]. These were the most common symptoms observed in majority of the patients [38].

Non survivors presented with pneumonia in 100% cases, fever (92%), breathlessness (76%), Myalgia (64%), and cough (36%). Similar symptoms in non survivors were reported by Chen N et al., who reported ARDS and shock in terminally ill patients [15].

In this study, out of 25 non survivors co-morbidities like diabetes mellitus type 2 was seen in 12 patients (48%), hypertension in 6 patients (24%), renal disease and thyroid dysfunction in 4 patients each (16%), liver disease in 3 patients (12%) and COPD or cardiomyopathy in two patients (8%), respectively . All these patients rapidly progressed to ARDS and later on septic shock. In three of these patients blood culture/pus culture was positive for Coagulase positive cocci. Similar findings were observed in studies conducted by Wang C et al., [1].

In this study, amongst non survivors haemoglobin was low with a mean of 10.32 gm/dL, TLC was raised in most of these patients and on follow-up of some of the patients it showed a constant rise with neutophilia, which is indicated by mean ANC being 9.92, with lymphocyte count towards lower normal range, which is reflected by mean ALC being 1.85. These findings are in concordance with study done by Tiwari N et al., [21].

Platelet count was low with a mean of 1.3 lacs/cmm. Some of the patients showed thrombocytosis could be due to the infection. Blood urea was markedly raised with increased creatinine. Patients who had kidney disease showed markedly raised creatinine. Serum Bilirubin was found to be raised in three patients who had liver disease, in these patients AST, ALT and alkaline phosphatase were also elevated. These biochemical results of our study were in accordance with studies done by Yang M et al., Assiri A et al., and Wong RS et al., [39-41]. Protein and albumin in most patients was within normal range. Similar findings have been reported by Leticia S et al., [16].

In non survivors, TLC, ANC, NLR, serum urea, creatinine, billirubin, AST and ALT were significantly raised as compared to survivors ($p<0.01$) which indicates renal and liver function abnormalities which should be taken into attention to provide timely effective treatment to avoid mortality. Platelet count and PLR in non survivors was significantly lower than survivors ($p<0.01$). Similar results were seen in a study done by Wang D et al., [26]. [Table/Fig-5] summaries the present study findings in comparison to previous studies.

NLR is a systemic inflammatory marker showing severity of bacterial infection and is used for assessment of prognosis in patients of pneumonia and tumour [24]. Current study shows that higher NLR value was seen in non survivors than survivors supporting the theory of close association between hyperinflammatory state and COVID-19 pathogenesis. Similar findings were found by Qin C et al., [22].

Amongst symptomatic survivors (78%) most of the haematological and biochemical parameters were within normal range except haemoglobin which was slightly reduced and AST was raised. Studies done by Wang C et al., and Liu J et al., showed similar results [1,24].

Variables	Present study	Guan WJ et al., [13] 2020	Zhang H et al., [17] 2020	Chen N et al., [15] 2020	Tiwari N et al., [21] 2020	Wang D et al., [26] 2020
Gender	Male>Female	Male>Female	Male>Female			
Age group (most commonly affected)	51-60 followed by 41-50 years	41-50 followed by 51 to 60 years	41-50 followed by 51 to 60 years	NA	NA	NA
Common symptom in survivors	Cough	NA	Cough	NA	NA	NA
Common symptom in non survivors	Pneumonia	NA	NA	Pneumonia	NA	NA
CBC profile amongst non survivors as compared to survivors						
Haemoglobin	Decreased	NA	NA	NA	Decreased	Decreased
Total Leucocyte Count	Increased	NA	NA	NA	Increased	Increased
Platelets counts	Low	NA	NA	NA	Low	Low
Biochemical profile amongst non survivors as compared to survivors						
Serum Urea	Significantly Raised	NA	NA	NA	NA	Significantly Raised
Creatinine	Significantly Raised	NA	NA	NA	NA	Significantly Raised
Bilirubin	Significantly Raised	NA	NA	NA	NA	Significantly Raised
Aspartate Amino Transferase	Significantly Raised	NA	NA	NA	NA	Significantly Raised
Alanine Amino Transferase	Significantly Raised	NA	NA	NA	NA	Significantly Raised

[Table/Fig-5]: Comparison of present study finding with previous studies.

Limitation(s)

There are certain limitations of the present study viz., retrospective nature of the study, absence of follow-up of asymptomatic patients. The author recommends further prospective studies with follow-up to further authenticate the findings of the present study.

CONCLUSION(S)

This single centre retrospective study of 140 COVID-19 positive cases from the Indian population shows that there exists an association between haematological, biochemical parameters and co-morbidities with the severity of disease in COVID-19 patients. Old age, male gender and co-morbidities like diabetes mellitus, hypertension, chronic kidney and liver diseases, COPD are associated risk factors with poor outcome. Laboratory parameters associated with increased mortality are leukocytosis, neutrophilia, thrombocytopenia, raised NLR, PLR, urea, creatinine, AST, ALT, bilirubin. With the help of these parameters severe COVID-19 patients can be identified in early stage of disease to provide effective treatment and reduce the mortality.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Oct 12, 2020
- Manual Googling: Jan 23, 2021
- iThenticate Software: Mar 31, 2021 (8%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 10, 2020**
Date of Peer Review: **Dec 18, 2020**
Date of Acceptance: **Feb 26, 2021**
Date of Publishing: **Apr 01, 2021**