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Original Research Article

Assessment of clinical, biochemical and radiological profile of SARS COVID-19 patients in a tertiary healthcare hospital and subsequent prediction of prognostic indicators

Shreya Jayaram*, Raghavendra Rao

Kasturba Medical, Kasturba Medical College, Manipal, Karnataka, India

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***Correspondence:**
Dr. Shreya Jayaram,
E-mail: shreyaj125@gmail.com

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ABSTRACT

Background: To describe the clinical characteristics and outcomes of SARS COVID-19 patients in Karnataka state, India and to evaluate risk factors and laboratory abnormalities leading to adverse outcomes. Radiological chest x-ray features of patients were studied and further elaborated upon.
Methods: A hospital-based, single centre observational prospective study was conducted which included 144 adults with confirmed cases of SARI as per the accepted definition admitted to Kasturba hospital, Manipal in a one-month time frame period who tested positive for the coronavirus. Symptoms taken into consideration were cough, sore throat, breathlessness, and fatigue commonly seen co-morbidities were diabetes, hypertension, IHD and chronic kidney disease. Laboratory variables taken were haemoglobin, CRP, urea, creatinine, NT-Pro BNP and LDH. Final outcome measured was the need for mechanical ventilation which correlates to disease severity. Multivariate logistic regression analysis was done for NLR ratio. Also evaluated was the abnormal radiological appearance of affected patients on chest X-ray describing baseline status and distribution of infiltrates.
Results: Median age of patients was 58 years, 69.4% males (100) and the remaining 30.6% females (44). The mean symptom duration before hospitalization was 3.5 days with a maximum of 30 days and minimum of 1 day. Breathlessness (52.8%) was most commonly seen symptom with almost half (50%) patients having pre-existing hypertension as a co-morbid condition. 46.5% patients had pre-existing diabetes. Abnormal lab values of parameters studied was shown to have a positive association with disease severity. Chi square statistics for decreased haemoglobin was 18.5363, urea-44.6823, creatinine-33.4771, NT PRO BNP-39.812, LDH- 81.3515, with $p<0.00001$ in all cases. An elevated NLR ratio was found in most patients requiring mechanical ventilation with a significant $p<0.05$. The 59.7% patients had bilateral lung involvement on CXR with 38.9% showing basal infiltration.
Conclusions: Early detection of laboratory abnormalities in haemoglobin, urea, creatinine, NT pro BNP, LDH and NLR ratio were found to be efficacious in forecasting need for mechanical ventilation in COVID-19 patients and can help better predict patient outcomes to avoid delays in management and care.

Keywords: Mechanical ventilation, Breathlessness, Hypertension, NLR, Haemoglobin, Urea, Creatinine, NT pro BNP, LDH

INTRODUCTION

Towards the end months of 2019 and continuing on to 2020, the world witnessed the rise of COVID-19 (SARS-CoV-2 infection) which soon assumed the status of a fast-spreading pandemic as declared by the WHO on March 11th 2020. The Novel Coronavirus also known as COVID 19 with its rapidly growing death rate and confirmed cases worldwide, became a global pandemic and major hit to our healthcare systems. The world was hit out of sudden and healthcare professionals were quick to respond in the hope of curbing its spread.

First detected and told to have emerged from the city of Wuhan in the Hubei province of China, this "pneumonia of unknown source" caused by an enveloped beta coronavirus caught healthcare professionals across nations by complete surprise.

It is the third in the line of coronaviruses that have emerged among the human population in the last two decades. The other two are the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak in 2002-03 and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012-13.[1]

The first case in India was detected on the 30th of January 2020 in the Kerala state. Subsequently the spread throughout the subcontinent has been rapid with almost 6.55M cases in India alone as of October 4th 2020. Although likely to have been started as a zoonotic transmission in the large sea food market of Wuhan, human-to- human transmission via droplets and contact with fomites has since been established to be the modus operandi of the virus spread. [2]

The clinical profile of those affected has been varied with a wide spectrum of symptoms and many atypical cases as well.

While most people with COVID-19 infection develop mild or uncomplicated illness, approximately 14% develop severe disease that requires hospitalization and oxygen support, and 5% require admission to an intensive care unit.[3]

SARI defined as a severe acute respiratory illness has a similar presentation, case definition, specimen type and testing platform to COVID-19. Hence, screening and surveillance of patients admitted with SARI for Coronavirus becomes a very important aspect both from a treatment and prognostic point of view. The study and interpretation of critical variables in a SARI patient's profile, clinical presentation, history and initial biochemical testing can reveal factors that determine the likelihood of a COVID-19 infection.

As per our hospital KMC Manipal's COVID-19 protocol-SARI (Severe acute respiratory Infection) is defined as a patient with acute respiratory infection-with fever ≥ 100.4°F and-cough and-onset within the last 10 days and-requiring hospitalization.

Patients fitting this definition criterion were tested for COVID-19 and included in our study. SARS COVID-19 testing is done by the ICMR approved gold standard method RT-PCR using throat and naso-pharyngeal swab specimens from patients. Lower respiratory specimens like sputum or endotracheal aspirate can be used for patients admitted in the SARI ICU with a more severe respiratory disease.

The principal objective of this case series is to analyse and describe the epidemiological and clinical profile of COVID-19 positive SARI cases during a four-week period of August 1 2020 to September 1, 2020 in the tertiary healthcare set up of Kasturba hospital, Manipal, Karnataka, India.

METHODS

Study population

This was a hospital based, single centre observational prospective study conducted which included 144 adult confirmed cases of SARI as per accepted definition admitted to Kasturba hospital during a one-month period of August 2020 to September 2020. RT-PCR testing was done to confirm COVID-19 positive patients.

Presenting complaints of the patients was noted along with co-morbid conditions and laboratory values for haemoglobin, neutrophil/ lymphocyte ratio, CRP, urea, creatinine, NT pro BNP, LDH.

Graphs and charts were generated to show most common features and abnormalities seen in the patient's part of this study. Descriptive and inferential statistics were used.

Chest x-ray features was studied based on baseline chest X-ray if normal or abnormal and also distribution of lung infiltrates if peripheral/ basal or both in either single or both lungs.

Statistical analysis and interpretation

SPSS software was used for statistical analysis. Pearson's chi-square test was used to investigate the association and risk analysis of abnormal laboratory parameters in the COVID-19 positive patients with requirement of mechanical ventilation. The probability value $p \leq 0.05$ was considered as significant. We also used multivariate logistic regression analysis and plotted an ROC curve to check for relation between an elevated NLR ratio and severity of disease. Graphs were made for most commonly seen symptoms, co-morbid conditions and chest X-ray patterns with abnormalities.

RESULTS

A total of 144 adult patients diagnosed with SARI with median age 58 were selected for this study. The maximum age recorded was 98 and minimum was 18. 69.4% patients were male. Mean symptom duration was 3.5 days with a standard deviation of 3.4, maximum being 30 days and minimum 1 day.

Major presenting symptoms taken into consideration were fever (40%), cough (34%), sore-throat (2.8%), Breathlessness (52.8%) and fatigue (14.6%). Majority of the SARI patients complained of difficulty breathing for a

few days after which they visited the hospital and were included under this study.

Atypical symptoms like vomiting, diarrhoea and loss of taste/smell was seen in 4.6%, 3.2% and 2.8% of patients respectively.

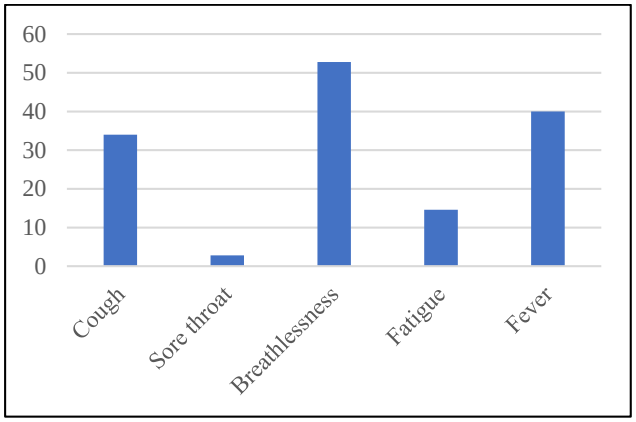

Figure 1: Symptoms associated with COVID-19 illness.

Almost half (50%) patients had pre-existing hypertension as a co-morbid condition. 46.5% patients had pre-existing diabetes, 11.8% had ischemic heart disease and 18.8% had chronic kidney disease.

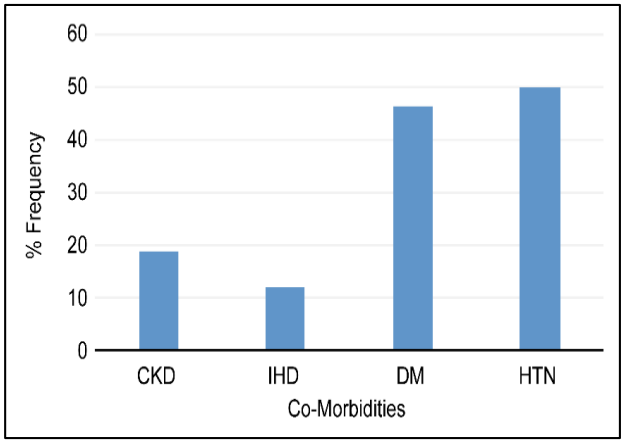

Figure 2: Co-morbidities associated with COVID-19 illness.

Table 1: Select lab parameters with statistical values.

Parameters	Total patients with available records of parameter	Median	SD
Haemoglobin	142	11.591	3.4018
CRP	140	117.78	95.859
Urea	136	72.03	58.721
Creatinine	137	2.5612	1.74436
LDH	135	662.21	235.735
NT-pro-BNP	86	7103.95	326.764

Cross tabs for final outcome (patient status and need for mechanical ventilation) in association with laboratory parameters was done to determine significant associations between presence of deranged tested lab values and an adverse end result (mechanical ventilation requirement).

A chi-square test of independence was performed to examine the relation between abnormal lab values and need for mechanical ventilation which is used as a marker for severe disease in the study. Only the lab parameters with significant value at $p<0.05$ were included in the study with results: CRP-chi-square statistic is 18.5363. The $p<0.000001$, urea-chi-square statistic is 44.6823. The $p<0.00001$. Creatinine-chi-square statistic is 33.4771. The $p<0.00001$. NTPRO BNP-chi-square statistic is 39.812. The $p<0.00001$. LDH-chi-square statistic is 81.3515. The $p<0.00001$.

Table 2: Significance of abnormal select laboratory values with need for mechanical ventilation.

Variables		Mechanical ventilation	
		No	**Yes**
Haemoglobin, (n=142)			
Normal	Count	32	13
	%		28.8
Abnormal	Count	21	76
	%		78.3
CRP, (n=140)			
Normal	Count	18	10
	%		35.7
Abnormal	Count	25	87
	%		77.65
Urea, (n=136)			
Normal	Count	30	14
	%		31.8
Abnormal	Count	11	81
	%		88
Creatinine, (n=137)			
Normal	Count	24	11
	%		31.42
Abnormal	Count	17	85
	%		83.33
NT pro-BNP, (n=86)			
Normal	Count	20	3
	%		13.04
Abnormal	Count	9	54
	%		85.7
LDH, (n=135)			
Normal	Count	51	5
	%		8.92
Abnormal	Count	10	69
	%		87.3

From results, 78.3% patients with a low hemoglobin level during testing on presentation required mechanical ventilation eventually as part of treatment. 77.65% with elevated CRP, 88% with elevated urea, 83.3% with elevated creatinine, 85.7% with high NT PRO BNP and

87.3% with increased LDH values were put under mechanical ventilation. Compared to patients with normal baseline values of the selected parameters, a significant number with abnormal values had severe disease. Percentage of normal lab value patients needing mechanical ventilation were- 28.8% (Hemoglobin), 35.7% (CRP), 31.8 (Urea), 31.42 (Creatinine), 13.04% (NT PRO BNP), and 9.92% (LDH).

Pro-calcitonin status was also recorded and revealed a total of 81 patients out of the 144 taken were positive for this parameter (56.3%).

Another variable studied was the N/L ratio. Neutrophil/Lymphocyte ratio abnormality was recorded with significant value being taken as more than 3.5. Multivariate logistic regression analysis was carried out to see if a higher NLR was associated with a higher risk of need for mechanical ventilation.

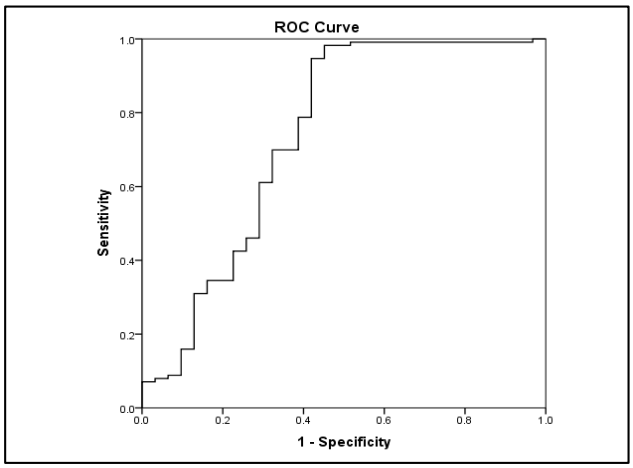

Figure 3: ROC curve for NLR.

Table 3: NLR ratio statistics.

Variables	Value	Df
Pearson chi-square	64.745[a]	1
Linear-by-linear association	64.295	1
N of valid cases	144	

Multivariate logistic regression analysis showed that NLR was an independent risk factor for severe COVID-10 with an AUC-0.738, standard error of 0.062 (95% CI:0.617-0.859).

Sensitivity of 0.982 and specificity of 0.452. Calculated p value was significant at $p<0.05$

Chest X-ray findings were divided as per unilateral/bilateral involvement as well as type of chest infiltrates when found in lungs affected by COVID.

Radiological profiling was done and revealed most patients had an abnormal baseline chest X-ray. Percentage values of distribution of abnormalities seen documented and showed that most commonly seen pattern of lung involvement basal infiltrates (38.9%), followed by combination of basal and peripheral (34%) and finally only peripheral (23.6%). Chest X-ray findings were also divided as per unilateral/bilateral involvement in the abnormal X-rays.

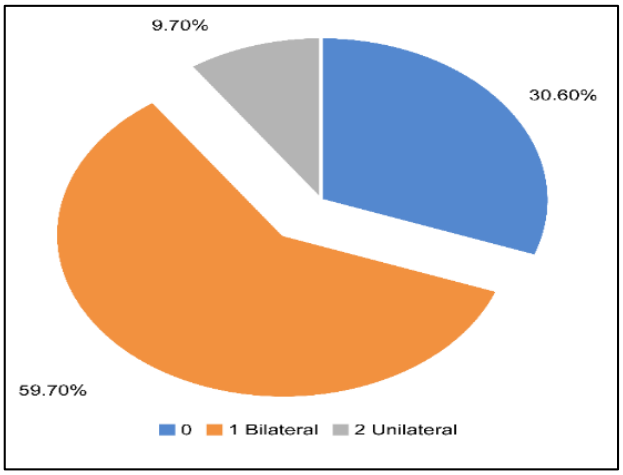

Figure 4: Lung Involvement unilateral/ bilateral/ none.

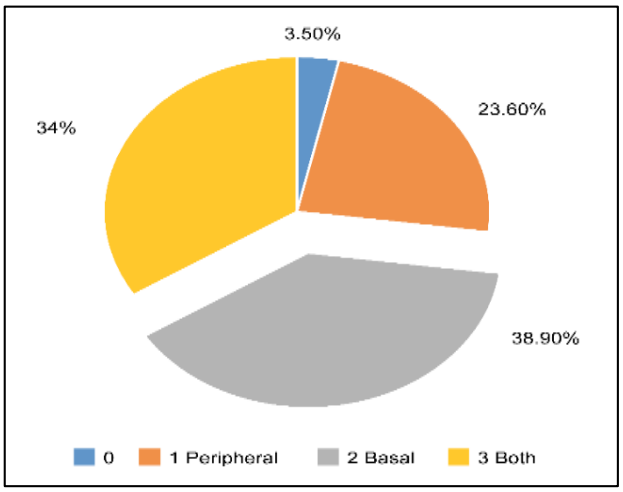

Figure 5: Lung infiltrates pattern seen on chest X-ray.

DISCUSSION

This study was started during the mid stage of disease outbreak in the region. Transmission of SARS CoV and the similarly related MERS-CoV, and influenza is by respiratory droplets and direct contact.[4,5] As SARS-COVID can be detected in the gastrointestinal tract, saliva, and urine, potential transmission via these routes needs to be investigated further.[6]

Infection prevention and control implications include the need for hand hygiene and personal protective equipment to minimize self-contamination and to protect against inoculation of mucosal surfaces and the respiratory tract,

and enhanced surface cleaning and disinfection in healthcare settings.[7]

The COVID pandemic started from Wuhan, China as an epidemic and the disease spread was rapidly noted all over the world. The pandemic resulted in rapid rise in number of cases all over the country leading to enormous burden on health care system. Determining high risk factors in such patients might help in triaging and better management of patients with scarce resources.[8,9]

The median age of the patients in this study was 58 years 69.4% of the total number (144) were males which is a finding similar to an earlier study like one done by Wang et al.[4] The higher incidence in male patients found in previous studies can possibly be explained by more exposure by the male counterparts of the family for foray outside homes and partly by the higher concentration of angiotensin-converting enzyme-2 in males than in women.[10] ACE-2 is expressed ubiquitously in multiple organ systems, enabling SARS-CoV-2 binding into the cell membranes and its subsequent entry. Since ACE-2 is an X-linked gene, further exploration is required for in depth analysis of the sex related differences.[1]

It is of prime importance to identify the high-risk strata of the society which includes older age group and people with co-morbidities. Early detection and contact tracing of positive individuals and awareness of these symptoms in the society should help reduce this delay and possibly have a dramatic favorable effect on the outcome of the disease.[1]

Symptom assessment revealed breathlessness was the most common complaint given by patients of COVID infection (52.8%) followed by fever (40%).

Through our study we also aimed to detect the most commonly seen co-morbid conditions in patients who tested positive for COVID and in need of admission. CKD, IHD, hypertension and diabetes mellitus history was checked for in all patients to determine which group of the population were most at risk of contracting this infection based on the pre-existing health conditions. Through calculation, DM and HTN were the most prevalent in the patients admitted under our study, results of which have been mentioned in previous text. It is imperative to categorize COVID-19 patients based on their comorbidities, like impaired kidney function, cardiac disease, etc. to minimize the severity risk and poor prognosis.[11]

Literature suggests laboratory markers like that D-dimer, CRP, ferritin, and LDH levels are important indicator of severity of COVID-19 infections and may predict mortality in these patients.[8,12] In our study we have targeted and focused on baseline hemoglobin, urea, creatinine, CRP, NT pro BNP and LDH levels and studied the relation of deranged values of these parameters with respect to disease severity (need for intubation and mechanical ventilation due to respiratory complications). Percentage values as given in result tables indicate that patients with abnormal values are more likely to require intubation. This significantly higher numbers associated with the parameters describe a worse outcome for patients with deranged laboratory values seen during disease.

Matsumoto et al in their study also concluded CRP levels to be significantly associated with severity i.e., CRP levels were significantly correlated with size of lung lesions and severity of COVID disease.[13]

N/L ratio was another lab value studied and recorded in these patients and showed a positive association with the severity of disease and need for mechanical ventilation. Early measurement of this value may hence be useful in predicting outcome in patients and aid in better management to prevent complications.

As per previously done studies, among other haematological parameters, lymphopenia is found to be clearly associated with disease severity; patients who have died from COVID-19 have had significantly lower lymphocyte counts than survivors. In fact, repletion of lymphocytes may be an important factor for recovery. Granulocyte colony stimulating factor (G-CSF) has been found to be elevated in patients which can explain the high NLR finding as described. [14]

Neutrophil to lymphocyte ratio (NLR) is a dominant biomarker of systematic inflammation and is commonly used to predict the outcome of bacterial infections, especially those of patients with pneumonia. Apart from bacterial infections, NLR can also provide valuable information about patients' prognosis in other inflammatory diseases such as cancers, acute coronary syndrome, intracerebral bleeding, polymyositis, and dermatomyositis. It is suggested that in severe cases of COVID-19, the shift of WBCs towards neutrophils rather than lymphocytes occurs, and possibly the calculation of NLR may help the clinician to properly treat patients.[15]

In a previous study, multivariate logistic regression analysis showed that NLR was an independent risk factor for severe COVID-19 (OR=1.264, 95% CI: 1.046-1.526, p=0.015) with an AUC of 0.831 (95% CI: 0.730-0.932), with a sensitivity of 0.828, and a specificity of 0.723. An increased NLR can hence serve as an early warning signal of severe COVID-19.[16] Our study showed similar results with a significant association between an elevated NLR ratio and disease severity measured by need for mechanical ventilation.

Chest X-ray findings showed 38.9% COVID positive patients with basal chest infiltrates in the lungs and 34% with both peripheral and basal lung involvement. This gives us a general idea on the clinical picture to expect in patients diagnosed with COVID-19 and how imaging studies may guide us by means of comparison with

pictures taken at various time frames during the disease after treatment initiation. Imaging analysis also showed that serial X-ray monitoring may suffice to aid us in management to assess disease progression.

CONCLUSION

Thus, this prospective study identified several risk factors for adverse outcomes like mechanical ventilation need and death in adults. COVID-19 infection possess a major risk to the population across the world. It has resulted in heavy burden on our healthcare system. Our study has identified various risk factors and red flag laboratory abnormalities associated with the increased risk for poor prognosis and mortality.

It has been found through this study that early rise in NT-pro BNP, LDH, CRP, N/L ratio in SARI patients with COVID-19 can be taken as indicators to detect disease severity. Early diagnosis and hence early intervention in such cases can improve patient outcomes and decrease overall hospital stay and mortality. The N/L ratio of such patients must hence be closely monitored as it has been shown to be predictive of severe COVID infection. Hence a fall in this ratio can show, help detect a trend towards clinical improvement in patient status.

People should be encouraged to undergo testing as soon as they become symptomatic as the delay is known to lead to poorer prognosis. Appropriate investigations should be carried out soon after hospitalization to assess prognosis so appropriate treatment initiation does not get delayed.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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