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Original Research Article

Comparative Study of Bun/Albumin Ratio (BAR) with D Dimer/Albumin Ratio (DAR), A Better Prognostic Indicator for Outcomes of Hospitalized COVID-19 Patients

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Abstract

Introduction: On December 31, 2019, China reported cases of pneumonia of unknown etiology in the city of Wuhan, Hubei Province of China. With further investigations, the Chinese health authorities, on 7th January 2020 reported the agent as the novel Coronavirus, 2019-nCOV. Initially, Wuhan and later the entire Hubei province was brought under stringent lockdown.

Materials and Methods: This retrospective record analysis study involving laboratory investigations was carried out in a single center in the months of June and July 2022. The ethical clearance for this single-centre study was obtained from the Institutional Ethics Committee (IEC). This study included 112 patients, of ages more than or equal to 18 years, who were confirmed cases of COVID-19 with at least one reverse transcriptase polymerase chain reaction test positive and admitted for inpatient treatment for a minimum of 8 days or longer in the wards or ICU between May 2020 to March 2022.

Results: A total of 112 patients who had a positive RT PCR test were identified and included in the study after excluding patients who had sought discharge against medical advice, who had been referred to other hospitals and patients with a history of chronic renal failure. The mean age of patients included was 60.25 $\pm$ 15.66. Among these patients 76 (67.9%) were male and 36 (32.1%) were female. Of the 112 patients, 47 patients (42%) survived of which 21(32.3%) were male, 15(31.9%) were female and 65 patients (58%) did not survive, of which 44(67.7%) were male and 21(32.3%) were female.

Conclusion: Through this study, we can see that all the parameters considered ie. Serum Albumin, Serum Blood urea nitrogen (BUN), D dimer, BUN/Albumin ratio (BAR) and D dimer/Albumin ratio (DAR) are very solid indicators of predicting the outcome of admitted COVID-19 patients.

Keywords: Bun Albumin Ratio, High Dependant Unit.

Introduction

On December 31, 2019, China reported cases of pneumonia of unknown etiology in the city of Wuhan, Hubei Province of China. [1] With further investigations, the Chinese health authorities, on 7th January 2020 reported the agent as the novel Corona

virus, 2019-nCOV. [2] Initially Wuhan and later the entire Hubei province was brought under stringent lockdown. Though the virus was initially limited to China, as it was highly contagious compared to the already known strains, it started spreading all around the world. [3] Later, the WHO officially named the virus as COVID-19 virus and the disease caused by it as COVID-19.[4] According to the preliminary information, there was no significant evidence of human to human transmission.[1] Currently it has been accepted that the possible modes of transmission are droplet, contact, airborne, faeco oral, fomites, blood borne, animal to human and mother to child. [5] On 11th March,2020, WHO declared the COVID-19 outbreak as a pandemic as the cases outside China had increased by 13 times and the number of countries with COVID cases had increased 3 times. [6] On 30th January 2020, the first COVID case was reported from Kerala, India and the patient had a travel history to Wuhan City, China. [7] As on 17th October 2022, India reported 26,834 active cases, 4,40,75,149 discharges and 5,28,905 deaths. [8] The symptoms of COVID-19 include fever or chills, cough, shortness of breath or breathing difficulties, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, vomiting, diarrhea. [9] Though most infected people will develop mild to moderate illness and recover without hospitalization, the case fatality rate varies 2%-30% worldwide. [10] There is no proven anti-viral drug as yet to combat this virus, which makes timely diagnosis and assessment of severity of COVID-19 patients to determine the best possible management by the health care providers all the more important. Thus there is a need for accessible biomarkers that can easily and quickly predict the outcome of COVID-19 patients in the emergency department. In this study we have proposed using lab parameters like blood urea nitrogen (BUN), Albumin and D dimer which are easy and quick to analyze not just in big tertiary care centers but also in remote areas and are also cost effective. Here, in this study we aim to analyze and compare the predictive power of BUN to Albumin ratio (BAR) and D dimer to Albumin ratio (DAR) in determining the outcome of hospitalized COVID-19 patients.

Potential benefits

This study aims at analyzing the mild cases admitted in wards which later becomes severe, to predict severity and mortality-predictive value of BUN/Albumin ratio and D dimer/albumin ratio. The estimation of BUN, Albumin and D dimer is cheaper, not requiring technologically advanced laboratory set-up, that can be used even in the peripheral health centers. Early analysis of patient details who may require HDU CARE at admission or during hospital stay at a later date and to predict prognosis may alert in future to predict mortality. It is important for a physician to plan the course and place of treatment when the resources are limited. There has been no study published on this topic to the best of our knowledge.

Review of Literature

We did a thorough search for articles on major platforms for compiling the work done till now on the various parameters that we have chosen to predict outcomes in COVID-19 patients.

Albumin, a blood protein, negative acute phase reactant used to assess malnutrition is decreased in pneumonia, acute coronary syndrome, pancreatitis and geriatric patients with mortality. [11] Studies have also shown decreased albumin levels in COVID-19 patients with mortality. [11] Violi et al. took a sample size of 319 COVID-19 patients, of which 64 had died, to study the impact of Serum Albumin on the survival of COVID-19 patients. They reported that Serum Albumin values have an independent association with mortality in COVID-19 patients, irrespective of the

adjustment for various other parameters and that it was significantly lower among the non survivors compared to the survivors. [11] They also reported getting an odd's ratio of 2.48 in predicting mortality among COVID-19 patients when the cut off was taken as <3.2 g/dL. [11] A meta-analysis conducted by Aziz et al which included [11] studies, demonstrates the relationship of mortality in COVID-19 patients with low Albumin. [12] Huang et al. had a sample size of 299 COVID-19 patients of whom 106 patients had hypoalbuminemia and they reported that hypoalbuminemia can be an independent predictor of mortality in COVID-19 patients. [13]

Blood urea nitrogen (BUN) levels are used to evaluate kidney function, hypovolemia and high BUN levels are seen in pneumonia, chronic obstructive pulmonary disease, pancreatitis, acute myocardial infarction, heart failure, sepsis and geriatric patients with mortality. [14] Studies have shown a higher BUN level in COVID-19 patients is associated with mortality. Küçükceran et al. have reported that they obtained an odds ratio of 7.048 in predicting mortality among COVID-19 patients by taking BUN values of >16.05mg/dL as cut off and have reported that BUN can be an independent indicator. Cheng et al. have also reported similarly and they obtained an AUC value of 0.88 to predict mortality among COVID-19 patients. [15] Ok et al. reported that BUN values can predict severity of COVID-19 with an AUC value of 0.790. [16] Arihan O et al. have reported that high levels of BUN have a solid correlation with mortality among severely ill patients. [17]

Studies have found the severity and mortality-predictive power of BUN/albumin ratio (BAR) in geriatric and pneumonia patients to be higher than those of BUN and albumin. [18] Studies have shown BAR value to be higher in COVID 19 patients with mortality. [19] Küçükceran et al. have reported that BAR can be considered a better indicator for predicting mortality in COVID-19 patients than BUN or albumin levels alone. [19] They achieved an odd's ratio of 10.45 while considering a cut off of 3.9mg/g for BAR. [19] Singh et al. have reported that hypoalbuminemia can be a better predictor of mortality of COVID patients than BAR or BUN, though BAR comes out as a reliable indicator too with an AUC value of 0.695 and odd's ratio of 3.75, with a cut off of 6.23mg/g. [20] Dundar et al. have reported that BUN values with a cut off > 23 mg/dL, albumin values with a cut off < 3.5 g/dL, and BAR values with a cut off > 6.25 mg/g among elderly patients in the Emergency Department have a greater risk of mortality. [18] Gao et al. have reported that old age can be a risk factor for severity and outcome of COVID-19 patients. [21] Gemcioglu wt al. have also reported that BAR can be an independent predictor of severity of COVID-19 patients. [22] Ryu et al. have reported that BAR can be considered to predict mortality among patients of aspiration pneumonia and they obtained an AUC value of 0.70 with an odd's ratio of 3.40 with a cut off of 7.0mg/g. [23] Feng et al. have reported low survival among patients with hospital acquired pneumonia who had an elevated BAR with a cut off of 0.165mg/g. [24] Huang et al. have reported that high BAR can be an independent predictor of critical illness in COVID patients, with an AUC value of 0.821 and a cut off of 3.7887mg/g. [25]

D dimer levels are used to assess coagulopathy in patients. Studies have shown the elevation of D dimer levels in COVID-19 patients with mortality. [26] Yao et al. have reported that the D dimer levels were significantly higher among the non survivors than the survivors. They obtained an AUC value of 0.85 and reported a cut off value of > 2.14 mg/L for predicting the mortality among COVID-19 patients. [26] Zhou et al., who took a sample size of 191 patients of which 54 died, have reported that they achieved an

odd's ratio of 20.04 while taking >1 µg/mL as the cut off for D dimer, to predict the mortality of COVID-19 patients. [27] Zhang et al., on studying a sample size of 343 patients with COVID-19 reported that D dimer can predict mortality among COVID-19 patients, after obtaining an AUC value of 0.89. [28] Elevated D dimer levels are seen in a state of hypercoagulation. [29] COVID-19 has been reported to cause hypercoagulation, which in turn causes increased risk of formation of microthrombi and thus organ failure following inflammation. [30]

There haven't been many studies on DAR as yet. Studies have shown the severity and mortality predictive power of D dimer/Albumin ratio (DAR) in COVID-19 patients [31] although there aren't many of them. Küçükceran et al. have reported DAR is a good predictor of mortality risk among COVID-19 patients with an AUC 0.773 and an odd's ratio 7.898 with the cut off as >56.36. [32]

Aims and Objectives

- To study the utility of BUN, serum albumin, D dimer, BUN/Albumin ratio (BAR), D dimer/Albumin ratio (DAR) for prediction of severity among patients having COVID-19 infection.
- To compare BUN/Albumin ratio (BAR) and D dimer/Albumin ratio (DAR) for prediction of outcomes of hospitalized COVID-19 patients.

Materials and Methods

This retrospective record analysis study involving laboratory investigations was carried out in a single center in the months of June and July 2022. The ethical clearance for this single center study was obtained from the Institutional Ethics Committee (IEC).This study included 112 patients, of ages more than or equal to 18 years, who were confirmed cases of COVID-19 with at least one reverse transcriptase polymerase chain reaction test positive and admitted for inpatient treatment for a minimum of 8 days or longer in the wards or ICU between May 2020 to March 2022. Patients who had sought discharge against medical advice, who had been referred to other hospitals and patients with a history of chronic renal failure were excluded. The patients were categorized as survivors and non survivors based on whether the patient was discharged or had in hospital mortality. They were also categorized as mild, moderate and severe based on the guidelines issued by the Ministry of Health and Family Welfare, Government of India.[32] Mild patients are those with upper respiratory tract symptoms and/or fever without shortness of breath or hypoxia. Moderate patients are those having respiratory rate $\geq$ 24/min, breathlessness and/or spO_2 90% - $\leq$93% on room air. Severe patients are those with respiratory rate >30/min, breathlessness and/or spO_2 <90% on room air.

Collection of Data

The following data of the patients were recorded from the medical records using the hospital information management system program: Serum BUN, Serum Albumin, Serum D dimer. These analytes were measured on Ortho Clinical Diagnostics VITROS5600 autoanalyser in the Clinical Biochemistry Section of the Diagnostic Laboratory of the Institute. Colorimetric analysis was used to determine the above mentioned lab parameters. Serum Albumin was recorded using Bromocresol Green (BCG) method, Serum BUN was recorded using Urease method, Serum D dimer was recorded using Immunoturbidimetry method. In addition patient complaints (fever, cough, shortness of breath), comorbidities and hospital outcome (discharge or in-hospital exitus) were also recorded.

Statistical Analysis

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on

continuous measurements are presented on Mean SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, **Assumptions:** 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent The one-way analysis of variance (ANOVA) is employed to determine whether there are any statistically significant differences between the means of three or more independent (unrelated) groups. The one-way ANOVA compares the means between the groups you are interested in and determines whether any of those means are statistically significantly different from each other. Specifically, it tests the null hypothesis:

$$H_0: \mu_1 = \mu_2 = \mu_3 = \cdots = \mu_k$$

Where μ = group mean and k = number of groups. If, however, the one-way ANOVA returns a statistically significant result, we accept the alternative hypothesis (H_A), which is that there are at least two group means that are statistically significantly different from each other.

Assumptions for ANOVA test:

1. The dependent variable is normally distributed in each group that is being compared in the one-way ANOVA
2. There is homogeneity of variances. This means that the population variances in each group are equal.
3. Independence of observations.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven`s test for homogeneity of variance has been performed to assess the homogeneity of variance. A t-test is a statistical test that is used to compare the means of two groups. It is often used in hypothesis testing to determine whether a process or treatment actually has an effect on the population of interest, or whether two groups are different from one another with the null hypothesis (H_0) is that the true difference between these group means is zero and the alternate hypothesis (H_a) is that the true difference is different from zero. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

Statistical software

The Statistical software namely SPSS 22.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

Observations and Results

A total of 112 patients who had a positive RT PCR test were identified and included in the study after excluding patients who had sought discharge against medical advice, who had been referred to other hospitals and patients with a history of chronic renal failure. The mean age of patients included was 60.25 $\pm$ 15.66. Among these patients 76 (67.9%) were male and 36 (32.1%) were female. Of the 112 patients, 47 patients (42%) survived of which 21(32.3%) were male, 15(31.9%) were female and 65 patients (58%) did not survive, of which 44(67.7%) were male and 21(32.3%) were female. When grouped according to severity on admission 55 patients (49.1%) were mild, out of which 30(63.8%) patients survived and 25(38.5%) patients did not, 27 patients (24.1%) were moderate, out of which 8(17%) patients survived and 19(29.2%) patients did not and 30 patients (26.8%) were severe, out of which 9(19.1%) patients survived and 21(32.3%) patients did not. On considering the co-morbidities it was found that 67 patients were known cases of Diabetes Mellitus of which 23(48.9%) survived and 44(67.7%) did not. 60 patients had

hypertension of which 18(38.3%) survived and 42(64.6%) did not. 48 patients (42.9%) had other co morbidities like cardiovascular disease, cerebrovascular disease, hypothyroidism, pulmonary disease. On analyzing the lab parameters recorded the mean Albumin g/dL, D dimer µg/dL FEU, Blood Urea Nitrogen BUN mg/dL, Serum Creatinine mg/dL, BUN Albumin Ratio mg/g(BAR), D- dimer Albumin ratio µg /g(DAR) were found to be 2.71±0.47, 423.93±385.69, 26.48±15.88, 1.71±0.74, 9.77±7.31, 151.24±139.52 respectively. The average number of days the patients were admitted was found to be 11.78±5.72. No establishing differences were found in the age, co-morbidities, gender or the complaints of patients between the survivors and non survivors group.

Table 1 shows the detailed features of the patients.

The mean Albumin g/dL value was found to be significantly lower in the non-survivor group compared to the survivor group (non-survivor 2.96±0.38; survivor 3.23±0.40). The mean D dimer µg/dL FEU was found to be significantly higher in the non-survivor group compared to the survivor group (non-survivor 607.25±407.32; survivor 170.40±122.36). The mean blood urea nitrogen (BUN) mg/dL was found to be higher in the non-survivor group compared to the survivor group (non-survivor 28.02±16.17; survivor 24.34±15.38).

The mean BUN Albumin Ratio (BAR) mg/g was found to be higher in the non-survivor group compared to the survivor group (non-survivor 10.12±7.07; survivor 9.29±7.67). The mean D dimer Albumin Ratio (DAR) µg /g was found to be significantly higher in the non-survivor group compared to the survivor group (non-survivor 212.06±148.24; survivor 67.13±62.80).

Table 2 shows the comparison of clinical variables according to outcome of patients studied Table 3 shows the Comparison of clinical/study variables according to SEVERITY of patients studied

Table 1: Features of the participants

Patient Characteristics		Normal range
No. of patients (n)	112	
Age- mean±SD	60.25±15.66	
Gender- n (%)		
Male Female	76 (67.9%) 36 (32.1%)	
Diabetes Mellitus	67(59.8%)	
Hypertension	60(53.6%)	
Other Comorbidities - cardiovascular disease, cerebrovascular disease, hypothyroidism, pulmonary disease)	48(42.9%)	
Laboratory Investigations		
Blood Urea Nitrogen BUN mg/dL mean±SD	26.48±15.88	6-23 mg/dL
Albumin g/dL mean±SD	2.71±0.47	3.5-5.2 g/dL
D dimer µg/dL FEU or mg/L mean±SD	423.93±385.69	<0.5 µg/mL FEU
Serum Creatinine mg/dL mean±SD	1.71±0.74	0.45-1.10 mg/dL
BUN Albumin Ratio mg/g(BAR) mean±SD	9.77±7.31	
D- dimer Albumin ratio µg /g(DAR) mean±SD	151.24±139.52	
Outcome		
Survivors, N (%)	Mild Moderate Severe	30(63.8%) 8(17%) 9(19.1%)

Non-Survivors, N (%)	Mild Moderate Severe	25(38.5%) 19(29.2%) 21(32.3%)
Severity on admission (based on respiratory rate and SpO_2)		
Mild- n (%)	55(49.1%)	
Moderate- n (%)	27(24.1%)	
Severe- n (%)	30(26.8%)	
Length of stay in hospital (days)	11.78	

Table 2: comparison of clinical variables according to outcome of patients studied

Severity	Outcome		Total (n=112)	P value
	Survivors (n=47)	Non survivors (n=65)		
Mild	30(63.8%)	25(38.5%)	55(49.1%)	Mild
Moderate	8(17%)	19(29.2%)	27(24.1%)	Moderate
Severe	9(19.1%)	21(32.3%)	30(26.8%)	Severe
Age in years	55.21±16.24	63.89±14.40	60.25±15.73	Age in years
Spo2%	93.94±5.47	90.40±7.98	91.88±7.23	Spo2%
RR	22.98±6.30	26.80±6.59	25.20±6.71	RR
No. of days of admission	10.57±3.97	12.65±6.6	11.78±5.72	No. of days of admission
DM	23(48.9%)	44(67.7%)	44(67.7%)	DM
HTN	18(38.3%)	44(67.7%)	44(67.7%)	HTN
Serum Creatinine (mg/dl)	1.21±0.39	2.08±0.72	1.71±0.74	Serum Creatinine (mg/dl)
BUN mg/dL	24.34±15.38	28.02±16.17	26.48±15.88	BUN mg/dL
Albumin(mg/dl)	3.23±0.40	2.96±0.38	2.71±0.47	Albumin(mg/dl)
D dimer µg/dL FEU	170.40±122.36	607.25±407.32	423.93±385.69	D dimer µg/dL FEU
DAR µg/g	67.13±62.80	212.06±148.24	151.24±139.52	DAR µg/g
BAR mg/g	9.29±7.67	10.12±7.07	9.77±7.31	BAR mg/g

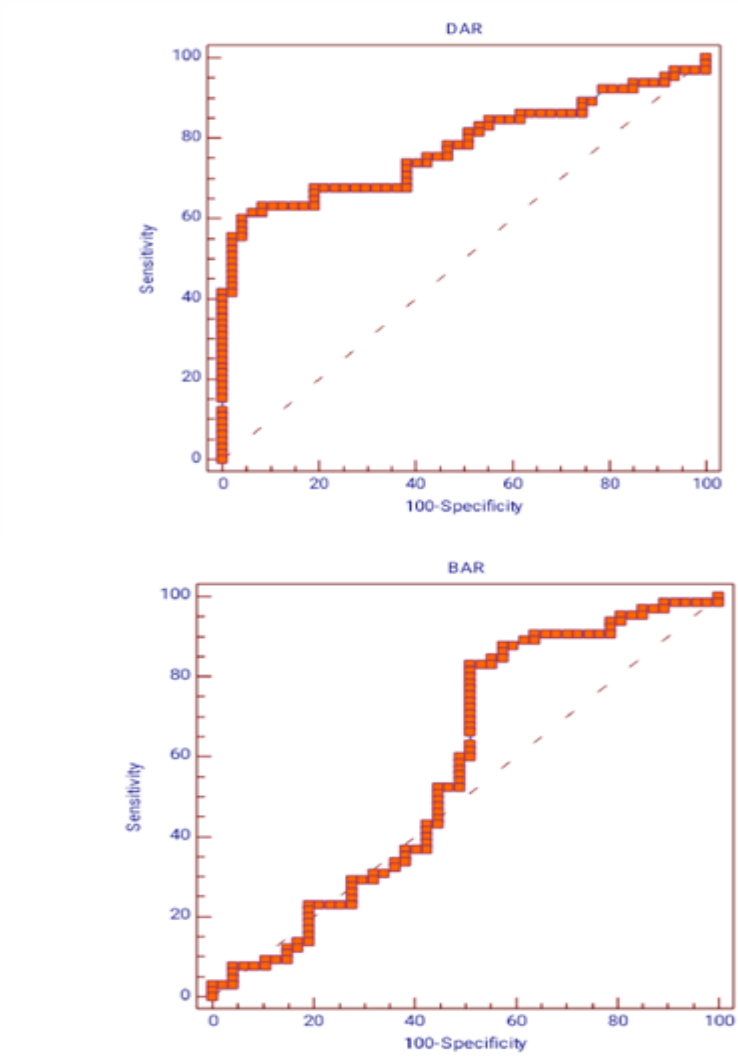
Table 3: Comparison of clinical/study variables according to SEVERITY of patients studied

Variables	Mild Mod Severe			Total	P value
	Mild	Moderate	Severe		Mild
Serum Creatinine (mg/dl)	1.50±0.70	1.77±0.69	2.04±0.76	Serum Creatinine (mg/dl)	1.50±0.70
BUN mg/dL	19.11±13.1	31.66±13.71	35.31±16.37	BUN mg/dL	19.11±13.1
Albumin (g/dl)	3.21±0.42	2.90±0.46	2.66±0.52	Albumin (g/dl)	3.21±0.42
D dimer µg/mL FEU	1.33±1.16	5.83±2.79	8.15±3.63	D dimer µg/mL FEU	1.33±1.16
D dimer µg/dL FEU	132.60±116	582.85±278.97	815±363.13	D dimer µg/dL FEU	132.60±116
DAR µg/g	44.17±44.03	204.17±101.6	299.91±120.12	DAR µg/g	44.17±44.03
BAR mg/g	6.33±5.46	11.92±6.74	14.15±7.84	BAR mg/g	6.33±5.46

Receiver Operating Curve analysis was performed to determine the predictive power of DAR and BAR in predicting the outcome of COVID 19 patients. Using >195 µg/g as the cut off for D dimer Albumin ratio (DAR), the Area Under Curve (AUC) obtained was 0.779, with sensitivity 60% and specificity 95.74%. Similarly using a cut off value of >4.91 mg/g for BUN Albumin ratio (BAR), the Area Under Curve (AUC) obtained was 0.580, with a sensitivity of 83.09% and specificity of 48.94 %. For further analysing the predictive power of BAR and DAR the Odd's ratio (OR) was calculated at the above mentioned cut off values. DAR had an odd's ratio of 40.0 and BAR had an odd's ratio of 2.25. This implies that DAR has performed significantly better than BAR.

Table 4: ROC curve analysis

Variables	ROC results to predict Mortality				Cut- off	AUROC	SE	P value
	Sensitivity	Specificity	LR+	LR-			Sensitivity	Specificity
DAR µg/g	60.00	95.74	14.10	0.42	>195	DAR µg/g	60.00	95.74
BAR mg/g	83.09	48.94	1.17	0.82	>4.91	BAR mg/g	83.09	48.94



Discussion

This study was conducted by us to predict the outcome of COVID 19 patients by using simple lab parameters such as Serum BUN, Serum Albumin, Serum D dimer, BUN Albumin ratio (BAR) and D dimer Albumin ratio (DAR) and to compare the predictive powers of BAR and DAR. As the COVID 19 pandemic shook the entire world, when it was totally unprepared for a large scale pandemic as this, there were immense difficulties in timely diagnosis, prevention of spread and proper management of the patients. Timely diagnosis and prediction of outcome which included testing equipments, skilled manpower and logistics became of utmost importance in efficient triaging of patients for the best possible patient management at a time when there was a heavy shortage of resources. Especially in a country like India with a huge population of different social strata, a quick, efficient and cost effective method of predicting the outcomes of COVID 19 patients was required. On reading a systematic review by Izcovich et al. who included 207 studies, we found out 49 various prognostic factors for predicting the mortality and severity of COVID 19 patients. [33] Among these, keeping in mind our aim of getting a quick, efficient and cost effective method of predicting the outcomes of COVID 19 patients, we decided to consider lab parameters. Hence, we chose the commonly available parameters like Serum BUN, Serum Albumin, Serum D dimer, BUN Albumin ratio (BAR) and D dimer Albumin ratio (DAR).

Based on our study we did not get a correlation between the various co-morbidities and the outcome of COVID 19 patients. Bajgain et al. have also claimed that though patients having one or more morbidity may have a severe disease, there is no clear association between having these co-morbidities and higher risk of mortality. [34] It could also be because of the small sample size taken.

In our study, Serum Albumin levels were significantly lower in the non-survivor group compared to the survivor group ($p<0.001$). On performing ROC analysis for predicting mortality among COVID 19 patients we obtained an AUC value of 0.553, with a sensitivity of 76.92% and specificity of 40.43%. Violi et al. took a sample size of 319 COVID 19 patients, of which 64 had died, to study the impact of Serum Albumin on the survival of COVID 19 patients. They reported that Serum Albumin values have an independent association with mortality in COVID

19 patients, irrespective of the adjustment for various other parameters and that it was significantly lower among the non survivors compared to the survivors They also reported getting an odd's ratio of 2.48 in predicting mortality among COVID-19 patients when the cut off was taken as <3.2 g/dL. [11] A meta-analysis conducted by Aziz et al which included 11 studies, demonstrates the relationship of mortality in COVID-19 patients with low Albumin.[12] Huang et al. had a sample size of 299 COVID-19 patients of whom 106 patients had hypoalbuminemia and they reported that hypoalbuminemia can be an independent predictor of mortality in COVID-19 patients. [13] There can be several reasons for decreased albumin levels in COVID-19 patients with mortality. The levels of albumin are maintained within normal range due to the balance between synthesis and clearance by catabolism, the renal and gastrointestinal system [35] Wada Y et al. have postulated that depletion of the pool of amino acids due to replication and shedding of virus and decrease in levels of the branched chain amino acids which in turn decrease albumin translation as the possible explanations. [36] COVID-19 causes systemic inflammation which increase capillary permeability which in turn causes movement of Albumin into the interstitial space and thus Albumin levels in serum decreases. [37] Albumin has been used for

assessing malnutrition. [38] Malnutrition has been shown to be a risk factor for mortality and rates of malnutrition in the elderly patients are high. [39]

In our study, the serum BUN levels were significantly higher among the non survivors compared to the survivors ($p<0.001$). On performing ROC analysis we obtained an AUC value of 0.617. On considering a cut off value of >16.05mg/dL, we obtained an odd's ratio of 2.94. Küçükceran et al. have reported the same and they obtained an odds ratio of 7.048 in predicting mortality among COVID-19 patients by taking BUN values of >16.05mg/dL as cut off. [14] Cheng et al. have also reported the same and obtained an AUC value of 0.88 to predict mortality among COVID-19 patients. [15] Ok et al. reported that BUN values can predict severity of COVID-19 with an AUC value of 0.790. [16] Arihan O et al. have reported that high levels of BUN have a solid correlation with mortality among severely ill patients. [17] There can be several reasons for elevated BUN values among mortal COVID-19 patients. High BUN values have been reported to be an indicator in predicting the severity of patients of pneumonia. [40] BUN has also been used in the CURB 65 score for pneumonia. [41] Studies have also shown 100% lung damage has been observed among non survivors of COVID-19. [42] The same study has also reported that respiratory failure was the main cause of mortality among 70% of the COVID-19 patients that they considered. Renal injury has also been reported as a risk factor for increased mortality among COVID-19 patients. [43] Minimal changes in the functioning of kidneys have shown large increase in BUN levels. [44] Therefore, lung and kidney injury in COVID-19 patients achieving mortality may be the reasons for elevated BUN values among these patients.

Blood urea nitrogen (BUN)/Albumin ratio (BAR) was also considered as a possible parameter fulfilling our criteria. In our study the BAR values were found to be higher among the non survivors compared to the survivors. We obtained an AUC value of 0.580, with a sensitivity of 83.09% and a specificity of 48.94% for predicting mortality among COVID-19 patients. With a cut off value of >4.91mg/g, we obtained an odd's ratio of 4.32 and thus BAR can be considered as a solid parameter for predicting mortality in COVID-19 patients. We believe BAR is better in predicting mortality among COVID-19 patients than albumin alone (AUC= 0.553) and BUN alone (OR=2.94). Küçükceran et al. have reported that BAR can be considered a better indicator for predicting mortality in COVID-19 patients than BUN or albumin levels alone. [19] They achieved an odd's ratio of 10.45 while considering a cut off of 3.9mg/g for BAR. [19] Singh et al. have reported that hypoalbuminemia can be a better predictor of mortality of COVID patients than BAR or BUN, though BAR comes out as a reliable indicator too with an AUC value of 0.695 and odd's ratio of 3.75, with a cut off of 6.23mg/g. [20] Dundar et al. have reported that BUN values with a cut off > 23 mg/dL, albumin values with a cut off < 3.5 g/dL, and BAR values with a cut off > 6.25 mg/g among elderly patients in the Emergency Department have a greater risk of mortality.[18] Gao et al. have reported that old age can be a risk factor for severity and outcome of COVID-19 patients. [21] Gemcioglu wt al. have also reported that BAR can be an independent predictor of severity of COVID-19 patients. [22] Ryu et al. have reported that BAR can be considered to predict mortality among patients of aspiration pneumonia and they obtained an AUC value of 0.70 with an odd's ratio of 3.40 with a cut off of 7.0mg/g. [23] Feng et al. have reported low survival among patients with hospital acquired pneumonia who had an elevated

BAR with a cut off of 0.165mg/g. [23] Huang et al. have reported that high BAR can be an independent predictor of critical illness in COVID patients, with an AUC

value of 0.821 and a cut off of 3.7887mg/g. [25]

In our study, the D dimer values were significantly higher among the non survivors compared to the survivors ($p<0.001$). On performing ROC analysis we obtained an AUC value of 0.763, with a sensitivity of 60.00% and a specificity of 95.74% and a cut off value of >390 µg/dL FEU. There are quite a few studies which report similarly. Zhou et al., who took a sample size of 191 patients of which 54 died, have reported that they achieved an odd's ratio of 20.04 while taking >1 µg/mL as the cut off for D dimer, to predict the mortality of COVID-19 patients. [27] Zhang et al., on studying a sample size of 343 patients with COVID-19 reported that D dimer can predict mortality among COVID-19 patients, after obtaining an AUC value of 0.89. [28] Yao et al. have reported that the D dimer levels were significantly higher among the non survivors than the survivors. They obtained an AUC value of 0.85 and reported a cut off value of > 2.14 mg/L for predicting the mortality among COVID-19 patients. [26] Many reasons are possible for elevated D dimer levels in mortal COVID-19 patients. Elevated D dimer levels are seen in a state of hypercoagulation. [45] COVID-19 has been reported to cause hypercoagulation, which in turn causes increased risk of formation of microthrombi and thus organ failure following inflammation. [46] Hypercoagulation in COVID-19 may be due to thrombosis caused by hypoxia. [47] COVID-19 patients are likely to have co morbidities and undergo invasive procedures which in turn increases the risk of thrombi formation. [28] The prevalence of pulmonary and venous embolism is higher among COVID-19 patients compared to other patients, vascular occlusion along with pulmonary vascular coagulation are frequent autopsy findings among mortal COVID-19 patients and COVID-19 also causes a higher risk of arterial thrombotic events like myocardial infarction, ischemic stroke etc. [48] However infections were reported to be the most common cause of high d dimer levels among adult patients in the emergency department. [49]

We considered D dimer/ Albumin ratio (DAR) as a parameter that could fulfil our criteria. On performing ROC analysis for predicting the outcome of COVID 19 patients, we obtained an AUC value of 0.779, with a sensitivity of 66.15 % and a specificity of 95.74 % and we also achieved an odd's ratio of 23.46 on taking a cut off value of >195 µg/g, and thus DAR seems to be a very good predictor for the outcome of COVID-19 patients. DAR seems to be the best indicator among the parameters we have considered in this study and it also seems to be better than considering D dimer (AUC=0.763) and albumin (AUC=0.553) alone. On comparing DAR with BAR to find a better indicator for predicting the outcomes of COVID-19 patients, DAR (AUC=0.779, OR=23.46) clearly emerged out as a better indicator than BAR (AUC=0.580, OR=4.32). There haven't been many studies on DAR as yet. Küçükceran et al. have reported DAR is a good predictor of mortality risk among COVID-19 patients with an AUC 0.773 and an odd's ratio 7.898 with the cut off as >56.36. [31]

The limitations of this study could be the relatively small sample size taken and that it was a single center study.

Conclusion

Through this study we can see that all the parameters considered ie. Serum Albumin, Serum Blood urea nitrogen (BUN), D dimer, BUN/Albumin ratio (BAR) and D dimer/Albumin ratio (DAR) are very solid indicators of predicting the outcome of admitted COVID-19 patients. When BAR and DAR were compared as to which was a better indicator, DAR turned out to be quite better than BAR. Overall according to our study, DAR has turned out to be the best

parameter for predicting the outcomes of hospitalized COVID-19 patients.

Summary

We carried out a study to find out lab analytes which are easy and quick to analyze not just in big tertiary care centers but also in remote areas and are also cost effective, to predict the outcomes of hospitalized COVID-19 patients and thus considered Serum Albumin, Serum Blood urea nitrogen (BUN), D dimer, BUN/Albumin ratio (BAR) and D dimer/Albumin ratio (DAR). We also wanted to see which one among BAR and DAR was a better predictor. We carried out a single center retrospective case record analysis with 112 patients, of which 65 patients were non survivors and 47 patients were survivors and we collected the required data and performed the necessary calculations.

We can conclude that all the parameters considered can independently play a role in predicting outcome of hospitalized COVID-19 patients. On performing ROC analysis, the AUC for Albumin was 0.553, BUN 0.617, D dimer 0.763, BAR 0.580, DAR 0.779 on comparing BAR with DAR, DAR has emerged as a better predictor. These quickly accessible, easy, efficient and economical parameters can be used for predicting the outcome and thus facilitates efficient triaging of COVID-19 patients in crunch situations where resources are very limited, in all kinds of treatment settings.

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