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Medicine

A RETROSPECTIVE ANALYSIS OF THE CLINICAL SEVERITY AND LABORATORY INVESTIGATIONS OF COVID INFECTED HEALTH CARE WORKERS AND THEIR FAMILY MEMBERS.

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ABSTRACT

BACKGROUND AND METHODOLOGY- The healthcare professionals are at a higher risk of covid 19 infection. The multitude of investigations burdens the laboratory services and often the results do not correlate with disease progression .We planned to identify the laboratory parameters for early recognition , intervention and prognostication of covid 19.

AIMS AND OBJECTIVES- The results were categorised according to clinical severity of the disease. The data was analysed using SPSS vs 25. Using logistic regression , we aimed to find out which demographic variables and blood tests can accurately diagnose the severity of infection and also predict the disease outcome.

RESULTS- Severe hypoalbuminemia is associated with severe covid infection. Age > 60, Neutrophil- lymphocyte ratio above 3 and C- reactive protein more than 6mg/l were strong predictors of adverse outcome.

CONCLUSION- These blood tests will decrease the tendency of over investigating without compromising the disease related information.

KEYWORDS : covid, laboratory markers, India, healthcare workers

INTRODUCTION-

The covid 19 infection is associated with changes in serum levels of many blood based molecules. There have been studies to prove their utility in recognizing the severity of the disease. [1] This has helped in early estimation of course of disease and interventions before clinical deterioration. The association of investigations with cytokine storm or major thrombotic events has been a point of debate.[2] Symptoms of covid 19 infection, laboratory and radiology (High resolution CT chest) interplay to decide the severity of infection. High CT severity index and low cycle threshold in reverse transcriptase PCR report were considered to be poor prognostic signs. Emergency physicians are at a unique disadvantage that we never had the luxury of knowing the test results of specific investigations as patients stay for a very short time with us. This has changed during covid times as laboratories are processing the samples faster .We analysed the various laboratory investigations in covid positive cases and identified the investigations with the highest likelihood ratios to predict the outcome of disease within 6 hours of presentation to ED. The patients were divided into three categories of mild, moderate and severe disease based on the Indian council of Medical Research recommendations [3] (Table 1). We also identified the parameters which correlated positively with an adverse clinical outcome..

Statistical analysis-

The data was analyzed using SPSS software version 25. Descriptive statistics and frequencies were cross-tabulated. Continuous predictor variables were dichotomized as 0 for values within normal range, and 1 for values outside the normal range. The relationship between clinical outcome (discharge/death) or Severity (mild/moderate/severe) and the dichotomized predictor variables was assessed by Univariate analysis using pearson's chi-square test/Fisher's exact test and multivariate analysis using logistic regression. Three levels in the Severity of covid-19 (mild/moderate/severe) was converted as a binary variable by aggregating moderate and severe categories and was compared against mild category, due to sample size issues. Stepwise method was used to implement binary logistic regression that performed an automatic selection of most important variables for the prediction of clinical outcome or severity. The overall accuracy of the resulting models was estimated based on their ability to correctly predict clinical outcome/severity.

RESULTS-

1060 healthcare workers or their immediate family members were admitted through emergency to our hospital covid facility in 2020. The survival rate was 94.15% as a whole. A cohort of 112 patients were included in the present study as they had reported within 24 hours of symptoms onset and were investigated early. This also shows that only 10.47% of HCWs were looking for inpatient treatment and the rest 90% were either not very sick or they preferred self treatment at home in the initial phase of covid infection. Men were affected 1.5 times more than women. The patients who died were older by at least 20 years to the survivors. Severe covid infection was associated with higher mortality in 78% of nonsurvivors.Table 2 depicts the baseline characteristics of patients.

Our study shows (Table 3) low albumin levels , high D dimers, high CRP, lymphopenia and raised NLR ratios as statistically highly significant parameters for a severe covid infection. Those patients who died showed statistically significant low albumin, lymphopenia, raised NLR ratio, high CRP, high ESR, high D dimers and high LDH. the parameters overlapped between severe infection and mortality . D-dimer though associated with mortality in univariate analysis, was not found to be a significant predictor of mortality with multivariate analysis and it offered no added value over that offered by NLR,Age,CRP and Albumin Thus the useful variables for prediction of death were Age, NLR and CRP. The accuracy of prediction was 90.4% . The accuracy to predict survival was 98.5% for patients less than 60 years of age and NLR between 1-3 and CRP less than 6. The accuracy however, decreased to 53.3% for ages more than 60 , NLR less than 1 and more than 3 and CRP more than 6. Combined with all other variables when analysed within reference limit values , the accuracy was 97%.

Similarly, serum albumin levels were found to be statistically the most significant parameter to predict disease severity. The accuracy was 100% for albumin levels outside the reference

limits. If combined with other parameters , an accuracy of 85.5% was achieved.

DISCUSSION-

The recognition of covid during the mildly symptomatic and asymptomatic phase and predicting the course of disease is helpful in early interventions and prevention of morbidity.

Shortness of breath in a classic case is seen after 1 week of onset of symptoms. The rise in LDH enzyme is an indirect indicator of lung injury and is seen prior to symptomatic deterioration. Similarly, rise in inflammatory markers like CRP occur before clinical picture evolves. This means that early estimation of laboratory parameters can save many patients from progressing to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, coagulation disorders, and multiorgan failure.

Atieh Pourbagheri-Sigarood et al [1] had reviewed the diagnostic value of laboratory and biochemical findings in 2988 patients in whom 484 (16.1%) had severe covid 19 infection.. Decreased lymphocyte percentage on differential count accompanied by mild thrombocytopenia had diagnostic and prognostic value.Given that most COVID19 fatalities experienced greater lymphopenia, it is reasonable to assume that the lymphocyte count is a rapid and commonly available laboratory parameter that can predict disease severity in COVID19 . The lymphocyte counts lower than 0.8×109/L may be associated with COVID-19 severity, and the number of neutrophils higher than 3.5×109/L may reflect a poor clinical outcome.

Yang et al [4] reported that the elevated neutrophil-to-lymphocyte ratio (NLR) may predict COVID-19 prognosis . The results of a meta-analysis of six studies demonstrated that an increased NLR level may suggest a poor prognosis in patients with SARS-CoV-2 infection [5] Also, the results of a recent study revealed that the incidence of critical illness in COVID-19 patients aged more than 50 was 9.1% (1/11) for patients having NLR < 3.13, while it was 50% (7/14) for those with NLR ≥ 3.13. [6]

The findings of a study by Brody H Foy et al [7] suggest that an elevated red cell distribution width(RDW) measured at admission and increasing RDW during hospitalization were associated with significantly higher mortality risk for patients with SARS-CoV-2 infection and RDW may be helpful for patient risk stratification.

It was previously established that inflammation-related parameters are highly elevated in acute phases. COVID-19 makes no exception to this rule, whereby the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin are increased in the sera of these patients, albeit with different values.CRP was significantly elevated in the progression group compared to the improvement stabilization group (38.9 vs 10.6 mg/l, P = 0.024) [8]. It is worth mentioning that while the diagnostic value of CRP is superior to procalcitonin The elevated D-dimers further support the occurrence of coagulopathy is an important indicator of disease progression. 0.4 μg/mL as a cut-off level for D-dimers to predict poor prognosis was suggested in a study by Bashash D etal [9].Covid virus is also known to be hepatotropic . Increased levels of alanine aminotransferase , aspartate aminotransferase , and total bilirubin and decreased levels of albumin are among the most common abnormal laboratory findings in COVID-19 patients.Liu et al. also reported that albumin was significantly lower in a progression group than an improvement/stabilization group (36.62 vs 41.27 g/l, P = 0.006). [7]

The results of multiple lines of evidence have indicated that measuring the biochemical parameters not only retains a specific diagnostic significance in this infection but their abnormalities may also correlate with unfavorable outcomes.

Table 1- Legend- Severity of disease as according to symptoms and signs

Level of disease	Symptoms and Signs
MILD	Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache. The elderly and immunosuppressed may present with atypical symptoms. Patient with pneumonia and no signs of severe pneumonia
SEVERE	Fever or suspected respiratory infection, plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 <90% on room air new or worsening respiratory symptoms within one week of known clinical insult. Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of oedema if no risk factor present. Oxygenation (adults): Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cm H2O, or non-ventilated) Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤200 mmHg with PEEP ≥5 cm H2O, or non-ventilated) Severe ARDS: PaO2/FiO2 ≤ 100 mmHg with PEEP ≥5 cm H2O, or non ventilated) When PaO2 is not available, SpO2/FiO2 ≤315 suggests ARDS (including in non ventilated patients)

Table 2- Legend- Parameters and outcome with reference values

Parameters with Hospital reference values, where applicable	Discharged (No. of patients)	Death (No. of patients)
Males	51	14
Females	44	03
Mean Age(M/F) with Range in parenthesis	41.84[23-73]/40.95[24-62]	64.71[50-75]/62.67[57-66]
Severe infection(number)	30	10
M/F with moderate- severe infection	15/15	8/2
Mean days of hospitalization[Range]	9.82[4-24]	11.37[2-43]
Doctor: Others	10:85	1:16
Percentage of Neutrophils in differential count (N=40-80%)	55.92	81.64
Percentage of Lymphocytes in differential count (N=20-40%)	28.02	11.64
NLR (N ≤ 2.5)	3.3	12.31
NLR severity as based on MDCALC Grade 0:1:2:3 (no. of patients)	81:9:4:1	5:4:5:3
Hemoglobin(N=12-15g/dl)	13.27	12.03
RDW-CV(N=11.6-14%)	14.86	15.50
CRP(N=<6mg/l)	12.06	33.46
ESR(N=0-12mm 1 hour)	29.58	55.70
D dimer(N= <250)	193.23	1131.17
LDH(N=125-220)	243.94	501.25
SGOT(N=<35)	28.15	48.31
Albumin (N= 3.5-5.2)	4.70	3.10

Table 3- Legend- Statistical analysis of parameters for estimation of mortality in mild versus severe covid.

Parameters	Discharge (N/Abn)* Number of patients	Death (N/Abn)* Number of patients	Fisher exact sig(2-sided)
Percentage of Neutrophils in differential count	74/11	8/8	**0.002**
Percentage of Lymphocytes in differential count	51/34	3/13	**0.003**
NLR ratio	59/26	2/14	**0.000**
Hb	53/36	6/10	0.087
CRP	53/33	0/15	**0.000**
D dimer	72/16	5/11	**0.000**
ESR	29/48	0/10	**0.013**
LDH	48/43	0/16	**0.000**
SGOT	70/18	7/9	**0.005**
Albumin	81/7	5/11	**0.000**
RDW(Red cell width)	48/41	6/10	0.174

Table 3 - Legend- Statistical comparison of mild and severe covid patients

Parameter	Mild (N/Abn)	Severe (N/Abn)	Pearson chi square
Percentage of Neutrophils in differential count	55/9	27/10	0.069
Percentage of Lymphocytes in differential count	39/25	15/22	**0.017**
NLR ratio	44/20	17/20	**0.011**
Hb	38/30	21/16	0.236
CRP	44/25	9/23	**0.003**
D dimer	54/16	23/11	**0.013**
ESR	18/38	11/20	0.734
LDH	33/37	15/22	0.303
SGOT	52/16	25/11	0.631
Albumin	63/5	23/13	**0.000**
RDW	37/31	17/20	0.593

Footnotes- N is the number of patients with normal values, Abn is number of patients with abnormal values.

CONCLUSION-

Covid infection causes atypical pneumonia as the primary symptom but the occurrence of severe disease, results from immune-mediated hyper-inflammation. Introducing potent biomarkers to timely predict disease outcomes is an essential field of research in a wide range of diseases from simple infections to human malignancies. Our study provides evidence that laboratory medicine may also provide essential assistance to discriminate between severe and non-severe COVID-19 and estimate the percentage of nonsurvivors. The fatality of the disease and crumbling healthcare infrastructure necessitates the identification and application of novel laboratory biomarkers to rapidly and economically predict COVID-19 prognosis.

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