Original Research

Association and Correlation of Laboratory Investigation Values and Disease Outcome among COVID-19 Patients in a Tertiary Care Medical College in India

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Background- COVID-19 and post-COVID sequel are a persistent challenge in India. We as tertiary care institute, managed much of the COVID-19 cases. We have studied associations between COVID-19 disease outcomes and common lab investigation values to ascertain their association by analyzing 467 RTPCR confirmed COVID-19 cases.

Methods- Records of 467 RTPCR confirmed COVID-19 admitted in ICU were analyzed. Descriptive data about routine investigation taking all admitted patients as a single cohort were analyzed. Further, patients were divided into 2 groups, those requiring ventilatory support and those not requiring ventilatory support, independent sample t-test was applied to ascertain differences in mean values of investigation in these groups. Pts were also divided according to the severity in chest X-ray films by using RALES score as criteria. A hierarchical regression analysis study was done and model was developed.

Results- The descriptive data of investigation values mean median mode and CI was calculated for all admitted patients as single cohort. Among cohort of patients requiring ventilatory support vs not requiring ventilatory support, an independent t-sample test indicated significant differences of mean values (2-tailed p-value < 0.05) among these groups, differences in pulse, SpO2, total leucocyte count, neutrophil%, lymphocyte%, neutrophil to lymphocyte ratio (NLR), serum sodium (S.Na), serum potassium (S.K), serum urea, serum creatinine, serum ferritin, serum lactate dehydrogenase (S LDH), d-dimer, C reactive protein (CRP), serum glutamic oxaloacetic transaminase (SGOT), chest X-ray radiographic assessment of lung edema (RALE) score. Among the cohort divided on chest X-ray severity on RALES score, we applied hierarchical regression analysis, further 5 tests values were found to pedict adverse RALES outcome more closely, those were SpO2, CRP, LDH, ferritin, RBS on admission with p-values and beta coefficient significant.

Conclusion- There is significant association with specific laboratory investigations and adverse disease outcome on COVI19 pneumonia.

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Introduction

COVID-19 has pandemic has been a persistent threat to the worldwide population till very recently. As a tertiary care teaching medical college in central india treated COVID-19 cases, including many referral cases. We conducted a retrospective observational study among the cases admitted in the COVID-19 ICU unit in our hospital to ascertain the association between laboratory investigations values that are most closely associated with adverse disease outcomes

Main outcome variables were, admission to ICU, severity indicators like the adverse outcome of death vs discharge, a requirement of invasive or non-invasive ventilation during the course of treatment, chest X-ray severity score as severity indicator (RALES score). Factors analyzed for these outcomes were all routine laboratory & point of care investigations relevant to COVID-19 and vitals. Analysis of means, descriptive values, independent sample t-tests & Linear regression analysis were done to identify laboratory and point of care investigations associated with adverse outcomes.

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Few studies had conducted t-tests comparisons and hierarchial regression model analysis to ascertain the strongest association with laboratory investigation and point of care investigation values with severe disease and adverse disease outcomes. [1]

Objectives

To ascertain the association & correlation of laboratory investigation values & disease outcomes among the COVID-19 intensive care unit (ICU) unit.

Material & Methods

Study design

This is a retrospective observational study with data retrieved from Medical records of patients admitted with reverse transcription polymerase chain reaction (RTPCR)-positive COVID-19 in the intensive care unit of our institute.

Setting

From the medical record section of our institute, records of 467 eligible patients admitted in the COVID-19 dedicated ICU in our institute from June 2020 to January are analyzed for the study.

Participants and Eligibility Criteria

All RTPCR-confirmed COVID-19 cases admitted in ICU of our hospital, age 15 years onward

Participants

A total of 467 COVID-19 RT-PCR-positive cases were admitted in COVID-19 ICU unit (June 2020 to January 2021)

Variables

Data were retrieved from the medical record section, following information was noted (i) Demographic parameters (age,sex) of the patients; (ii) presenting symptoms and duration of symptoms; (iii) available investigations (complete blood count, liver and kidney function tests, electrolytes, inflammatory markers, chest X-ray, etc.), (v) Outcome,(vi) Disease course and ventilatory requirement status

Outcome Variables

Main outcome measures were admission to the ICU, severity indicators like the adverse outcome of death vs discharge, the requirement of invasive or non-invasive ventilation during the course of treatment, and chest X-ray severity score as severity indicator (RALES score). Factors analyzed for these outcomes were all routine laboratory & point of care investigations relevant to COVID-19 & vitals. Analysis of means, descriptive values, independent sample t-tests & linear regression analysis were done to identify laboratory and point of care investigations associated with adverse outcome

RALES Score

RALES score has been found to be closely associated with clinical outcomes in ARDS.5 This is scoring for quantification of the involvement of lung in the parenchymain pneumonia as seen in chest X-ray films. The suitability of RALES score in ARDS has been determined by many previous studies. [6-9]

Use of the RALES score in the assessment of COVID-19 severity has also been doneby other works as by Saluja et al. 2020

"To quantify the extent of infection, a severity score was calculated by adapting and simplifying the radiographic assessment of lung edema (RALE) score proposed by Warren et al.[10] A score of 0-4 was assigned to each lung depending on the extent of involvement by consolidation or GGO" (Saluja et al., 2020)

RALES score ranges from 0 to 48. We tested the applicability of the RALES score in this scenario, severity cut point as RALE score>/= 24 was analyzed by risk estimation for adverse outcome death. The association was significant with Pearson Chi-square factor 9.98 odds Ratio 2.105 (1.319-3.358) CI 95% *p-value* < 0.002) significant.

Therefore, we adopted RALES>24 as a marker for criticality.

RALES score is calculated, after dividing each radiograph into 4 quadrants and giving each quadrent a consolidation score ranging from 0-4 to quantify extent of alveolar opacities, a density score based on percentage of opacification, ranging from 1–3 (1=hazy, 2=moderate, 3=dense) . The final RALES score is calculated as product of consolidation score and density score for each quadrant and summing all four.[2]

Statistical Methods

We use SPSS 23 package for analysis. For analysis of proportion Pearsons Chi-square test was used with an estimation of risk by Odds ratio estimate and fisher exact test for calculating 2-sided *p-values*.

Comparison of means, odds ratio estimation, descriptive values analysis, independent sample t-tests & linear regression analysis were done.

Table 1: Charasteristics of Cohort of Discharges vs Death patients

Variables	*Freq.*	*Discharged Cohort*		*Death Cohort*		
Investigation	n	Mean	Mode	n	Mean	Mode
Pulse	359	89	90	104	98	90
Resp. Rate	359	20	18	105	23	20
SpO2	359	87.8%	88%	105	74	60
Hemoglobin	330	12.92 gm%	13g m%	101	12.7	13
Total Leucocyte Count	329	9049 /µL	8000 /µL	101	14834	8440
Neautrophil Percentage	330	74.48%	80%	101	85%	90%
Lymphocyte Percentage	330	18%	8%	101	9.46%	7%
Platelets	330	272640 /µL	170000 /µL	101	232260 /µL	66000 /µL
RBS	307	151	101	98	215	189
S. Na	329	136	138	105	137	136
S. K+	328	4.54	4.4	105	4.81	4
S. Urea	328	37	20	105	78	32
S. Creat	320	0.89	1	100	1.56	1
S.CRP	311	6650 µg/dl	< 500 µg/dl	97	12828 µg/dl	< 500/µg/dl
S.Ferritin	281	352	101	84	797	115
d-dimer	281	1417 U	1000 U	81	3455	10000
LDH	318	346	233	94	650	311
T.Bil	308	0.68	0.60	102	1.01	1
SGOT/AST	307	51	55	102	78	36
SGPT/ALT	310	52	30	102	55	30
ALBUMIN	310	3.74	3.70	102	3.31	4
HBA1C	88	7.89	7.14	46	8.1	7
CXR RALES SCORE	356	19	18	107	28	28
ESR	228	33	28	61	35	18

Results

Descriptives

In the cohort of 467 cases, the mean age was 54 (Age range 15–92 years) years. There was 297 (63%) male and 170 (37%) females. Among 467 cases, cases Cured and discharged were 359 & fatality of 108 was reported, which we consider on the high side. This may be because ours is a tertiary referral center and only caters to refferal services for other regional hospitals. Similar mortality rates have been reported in few previous papers3, and upto 38% overall mortality rate has been reported in other studies4 (Ciardullo et al. 2021).

Charateristics of patients investigations according to cohort of death vs discharged cases

The results are depicted in Table 1

Comparison of means

Cases were divided in to groups requiring ventilator support vs not requiring ventilator support. Investigation reports values were compared and an independent sample t-test was applied to ascertain significance. Relevent *p-value* quoted after applying Levene's Test for Equality of Variances, is shown in Table 2

Ventilatory support Vs Not requiring Ventilatory Support

Table 2 shows comparison of means between 2 groups requiring ventilatory support vs not requiring ventilatory support.

Hierarchical Regression Model

Hence after establishing the applicability of RALES score in this scenario, we developed a risk factor model by hierarchical regression to explain variance in the dependent variable (DI); here RALES score; on the basis of independent variables (IV), taken as laboratory & point of care investigating values (Table 3). ANOVA is a significant *p-value* 0.001 as shown in additional Table 1a. Adjusted R square 0.459, indicating a 45.9% of change is

Table 2: Comparison of means between 2 groups requiring ventilatory support vs not requiring ventilatory support

S.No	Variables	Ventilation Group	Freq.	Mean	*p-value* (2-sigma)	Significance
1	PULSE	Negative	198	90.33	0.036	Significant
		Positive	246	93.20		
2	R/R	Negative	198	20.73	0.087	
		Positive	247	21.55		
3	SPO2	Negative	198	89.12	0.001	Significant
		Positive	247	80.57		
4	HB	Negative	185	12.87	0.799	
		Positive	229	12.81		
5	TLC	Negative	184	8883.61	0.001	Significant
		Positive	229	11669.2 4		
6	NEUTROPHIL	Negative	185	74.24	0.001	Significant
		Positive	229	79.00		
7	LYMPHOCYTE	Negative	185	18.17	0.006	Significant
		Positive	229	14.76		
8	PLATELET	Negative	185	270.75	0.163	
		Positive	229	255.16		
9	ESR	Negative	115	31.88	0.153	
		Positive	160	35.31		
10	RBS	Negative	168	154.57	0.029	Significant
		Positive	220	176.52		
11	Na	Negative	181	135.68	0.003	Significant
		Positive	235	137.47		
12	POTASSIUM	Negative	180	4.43	0.001	Significant
		Positive	235	4.75		
13	UREA	Negative	179	39.22	0.001	Significant
		Positive	236	54.43		
14	CREATININE	Negative	178	.93	0.051	Significant
		Positive	224	1.19		
15	CRP	Negative	171	6609.78	0.01	Significant
		Positive	221	9305.59		
16	S FERRITIN	Negative	150	406.54	0.031	Significant
		Positive	199	505.85		
17	D DIMER	Negative	153	1216.17	0.001	Significant
		Positive	192	2385.45		
18	LDH	Negative	174	331.10	0.001	Significant
		Positive	226	489.67		
19	TOTAL BILIRUBIN	Negative	167	.69	0.066	
		Positive	227	.82		
20	SGOT	Negative	167	50.04	0.004	Significant
		Positive	226	66.03		
21	SGPT	Negative	167	41.47	0.111	
		Positive	226	49.56		
22	ALBUMIN	Negative	168	3.63	0.941	
23	HBA1C	Negative	50	8.47	0.136	

		Positive	79	7.74		
24	CHEST X-ray (RALES SCORE)	Negative	196	19.23	0.011	Significant
		Positive	248	20.75		

Table 3: Hierarchical regression model summary

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	35.464	2.005		17.687	.000
	CRP	3.704E-5	.000	.068	1.401	.162
	S FERRITIN	.001	.000	.085	1.898	.059
	SPO2	-.210	.020	-.530	-10.703	.000
	LDH	.002	.001	.130	2.702	.007
	RBS	.005	.003	.085	1.938	.054

a. Dependent Variable: chest X-ray (RALE SCORE)

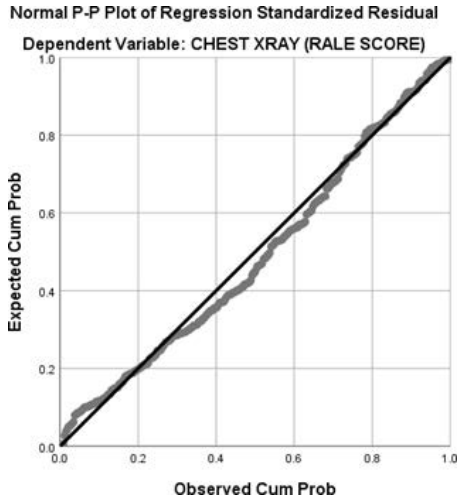

Figure 1: A p-p plot of standarised residual dependent variable RALES Score on expected vs observed values is shown

RALES score is explained by this model and hence on the value ofthese laboratory investigations.

On hierarchical regression, all independent variables (Lab investigations & pointof care investigation), these five investigations viz: CRP, LDH, SPO2, RBS & S. ferritin; are found to be statistically significantly correlated to RALES score; with significant p-values and beta function & coefficient (additional Table 1b). A p-p plot of the standarised residual dependent variable RALES Score on expected vs observed values is shown in Figure 1. A histogram of frequency vs regression standardised residual showing bell-shaped normal distribution curve is shown on Figure 2.

Results and Discussion

In COVID-19, some laboratory investigation values are consistent with severe disease outcomes. In previous studies. Leucocytosis and lymphopenia has been found to be of prognostic value in COVID-19.[10] In a systemic meta-analysis by Huang and Pranata, lymphopenia was found to be associated with severe coronavirus disease.[11]

CRP was found to be associated with severe COVID-19, and was able to differentiate mild disease to severe disease[12] (Wei Chen, Kenneth I. Zheng, Saiduo Liu *et al.*, 2020) CRP was found to be a promising indicator of poor prognosis[13] by (Bikash R. Sahua, Raj Kishor Kampa, Archana Padhi *et al.*, 2020)

Petrilli et al. further reported that a CRP>200 and SpO2 <88 is the mostimportant cut point in differentiating severe from mild disease.[14]

(A. Berni, D. Malandrino, G. Parenti *et al.*, 2020) In conclusion, S.Na level is inversely correlated with increased IL6 levels and Pao2/Fio2 levels in COVID-19 patients. And hyponatremia can act as a marker for inflammatory response and IL6 levels. [15] Presence of hyponatremia is an indicator for adverse disease outcomes.

S. Ferritin as an acute phase reactant, has been found to be elevated in COVID-19, in sync with CRP levels.[16]

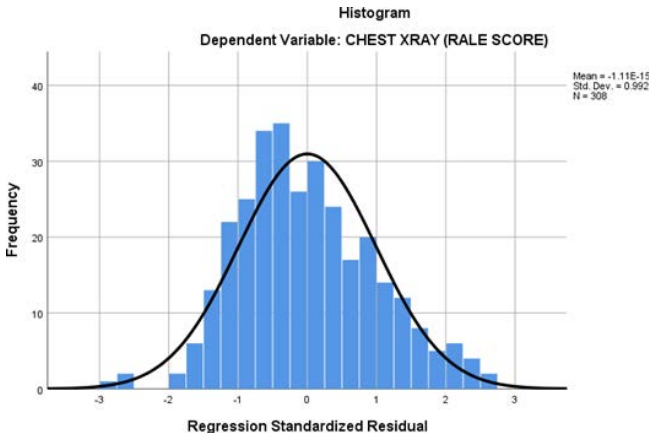

Figure 2: A histogram of frequency vsregression standarised residual showing bell shaped normal distribution curve is shown

COVID-19 disease has been found to be associated with an increased propensity of systemic coagulation. D-dimer levels have been found to be consistently elevated in severe COVID-19 disease.[17]

Comorbidities like diabetes are associated with adverse disease outcomes. RBSvalues at admission and HBA1C values are hence found to be directly associated with adverse disease outcomes [18 19 20]

Conclusion

We found a significant difference in the means of values of laboratory investigations in cohorts who were divided on the basis of Ventilatory requirements during the course of their study. On regression analysis taking RALES score >24 as an independent variable, we developed a model explaining a 45.9% of change is the RALES score. Five common investigations explaining the change in RALES score most accurately were CRP, LDH, SPO2, RBS & S.ferritin, with significant p-values and beta function. Hence we conclude that common routine laboratory investigations can accurately predict the course of the diseaseand adverse disease outcomes in COVID-19.

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None.

Conflicts of Interest

None.

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Additional Data

Table 1(a): ANOVA table for RALES24 Hirarical regression analysis model

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	5362.197	5	1072.439	53.025	.000[b]
	Residual	6108.024	302	20.225		
	Total	11470.221	307			

Dependent Variable: CHEST XRAY (RALE SCORE)
Predictors: (Constant), RBS, S FERRITIN, LDH, CRP, SPO2

Table 1(b): Hierarchial Regression Model Summary

Model	R	R Square	Adjusted R Square	Std. Errorof the Estimate
1	.684[a]	.467	.459	4.497

Predictors: (Constant), RBS, S FERRITIN, LDH, CRP, SpO2