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Research Article

Effect of Systemic Illness and Comorbidities in the Prognosis of Severe Acute Respiratory Illness Patients: An Observational Study

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ABSTRACT

Background: Globally critically ill COVID-19 (Coronavirus disease-19) patients have stretched critical care services. This study was undertaken to find factors implicated in mortality amongst COVID positive and negative patients presenting with severe acute respiratory illness (SARI) and factors having the probability of indicating COVID positivity.
Methods: The demographic parameters, comorbid illness, clinical parameters and laboratory values of 327 patients were retrospectively analyzed to find the risk factors for mortality in COVID positive and negative patients and factors predicting COVID positivity amongst SARI patients.
Results: 58% of SARI patients tested positive by RTPCR. Most common comorbidities were diabetes and hypertension, 35.2% and 33% respectively. Duration of swelling and low haemoglobin were significantly associated with mortality in COVID positive group (p=0.01, 0.005). Acidosis and tachycardia (p=0.003, 0.034) were associated with mortality amongst COVID negative. Creatinine, Sequential Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) were higher in non-survivors of both groups (p<0.001). Age, history of contact or from containment zone, cough, pain abdomen and P/F ratio were significant predictors of COVID positivity (1.020(1.006–1.035); 3.889(1.316–11.495); 2.908(1.182–7.152); 2.147(1.149–4.012); 0.997(0.994-1.000) respectively) by multivariable regression analysis.
Conclusion: A long duration of swelling and low haemoglobin (<12 g%) were responsible for COVID positive mortality while pain abdomen, raised levels of AST, tachycardia and acidosis were associated with mortality in COVID negative. Deranged creatinine, higher SOFA and qSOFA were associated with mortality in both groups. Age, contact history, residence in containment zone, cough, pain abdomen and poor P/F ratio are predictive factors for COVID positivity.

The outbreak of the COVID-19 pandemic continues to engulf the globe even more than a year since commencement.1 The rapid influx of cases at a single point in time may burden healthcare resources of developed, developing and underdeveloped nations as well.2, 3 Outreach to health care resources and

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their optimal utilization may be of concern at such times.3 Patients may thus present in a deteriorated state of health without even a Reverse Transcrptase Polymerase Chain Reaction (RTPCR) report. These would then need efficient triaging. Data on this is sparse.

To address these lacunae of knowledge, this study was undertaken to primarily find reasons of high mortality amongst COVID positive and negative patients presenting with SARI.4 Our secondary objective was to find factors that can predict COVID positivity amongst SARI patients.

Methods

This retrospective study was carried in the COVID Suspect ICU of our tertiary care hospital after obtaining clearance from the ethical committee (Letter No. IEC /Project/20202-08/CC-40). All patients above 12 years of age, presenting with SARI and requiring ICU admission were included in our study between 1.04.2020 to 31.07.2020. All below 12 years were excluded. The imperative of informed consent was waived off by the ethics committee given the retrospective nature of the study. All demographic parameters, contact history, smoking history, symptoms at presentation along with their duration, comorbidities like hypertension, diabetes, coronary, pulmonary, liver and renal diseases were collected at presentation along with whether from the containment zone. Laboratory parameters (haemoglobin, total leucocyte count with differentials, platelets, urea, creatinine, liver enzymes, sodium, potassium, clotting parameters, blood gas parameters like pH, partial pressures of carbon dioxide and oxygen and bicarbonate) at presentation were also noted. Heart rate, temperature, mean arterial pressure and respiratory rate were noted at presentation along with the institution of vasopressors. These data were recorded from the patient files retrospectively. No subsequent follow up of the factors were done. A total of 327 patients with SARI) including both RT-PCR confirmed COVID-19 patients as well as negative patients were included in our analysis. SARI was defined as having a history of fever or measured temperature ≥38 C° and cough; onset within the last ~10 days; and requiring hospitalization.5 Severe cases of pneumonia were those having symptoms such as (1) Shortness of breath, RR ≥ 30 times/min, (2) Oxygen saturation (Resting-state) ≤ 93%, (3) PaO2/FiO2 ≤ 300 mmHg, requiring admission in ICU.

Continuous variables were presented as mean (± SD) if normally distributed or median (IQR: Q1, Q3) when not normally distributed. Categorical variables were presented as frequency (n) along with percentage (%). Patients were categorized into COVID positive and negative groups and further as survivors and non-survivors in each of these groups. Continuous data with normal distribution was evaluated using an unpaired t-test while the Mann Whitney U test was used to compare the skewed data set. Categorical data were evaluated using the $\chi 2$ test. Basic demographic characteristics were represented using a bar diagram and pie chart. The logistic regression (univariate and multivariate) was applied to identify significant factors alone (univariate) and the optimum combination of significant factors (multivariate) in terms of odds ratio and 95% Confidence Interval (CI) as a causal effect relationship for the development of COVID. SPSS statistical software version 24.0 was used for analysis. The factors were analyzed by the above methods to determine outcomes like mortality and COVID positivity in each group.

Results

We retrospectively analyzed 327 patients (Figure 1). 56.3% were males and 43.7% were females (figure 2A). Maximum patients fell in the 50–70-year age group (Figure 2B). Diabetes and hypertension were the most common comorbidities followed by Chronic Obstructive Pulmonary Disease (COPD), Coronary Artery Disease (CAD), Renal and Liver diseases respectively (Figure 2C). Most patients required mechanical ventilation at presentation (53.2%- 106 COVID positive and 68 COVID negative) followed by a non-rebreathing mask (32.7%) (figure 2D). 40% of patients had succumbed during the hospital stay (Figure 2E).

We compared presenting variables between survivors and non-survivors within each group of COVID positive and negative patients. There was no significant difference between the age and sex distribution of survivors and non-survivors in the two groups. There was no cut off age above which there is significant mortality in the COVID positive group of patients (AUC 0.532, p 0.33). Shortness of breath (SOB), fever, cough, pain abdomen, altered sensorium, swelling and chest pain at presentation to suspect ICU were evaluated with mortality. Only SOB and cough had statistical significance ($\chi 2$ 4.143, p 0.04 for both) within COVID positive patients. However, patients presenting with pain abdomen had significant mortality in the COVID negative group ($\chi 2$ 5.645, p 0.02). In the COVID positive group, the median time from onset of symptoms to presentation in ICU was shorter and statistically significant for SOB and cough amongst those who succumbed and similarly for fever in the COVID negative group. However, the median duration of 7 days for onset of generalized swelling to presentation in non-survivors was significantly long when compared to survivors in COVID positive patients (Z= -2.518, p 0.01).

Chi-square test to evaluate presenting comorbidities (DM, HTN, Renal disease, Liver disease, COPD and CAD) between the two groups was not significant. The median number of comorbidities for each individual at presentation bore no statistical significance amongst groups (Table 1).

Among blood counts (Hemoglobin, Total Leucocyte count-TLC, Platelet counts and Neutrophil to lymphocyte ratio-NLR), only low levels of haemoglobin had statistical significance between survivors and non-

survivors amongst COVID positive patients (95% CI= -1.9, -0.3; p 0.005). To further validate this, we used a cut off haemoglobin < 10 g/dL and found that mortality was significant in this group of patients (Table 1).

Among biochemical parameters, high creatinine was associated with mortality in both groups (Table 1). Sodium and potassium values were statistically significant amongst COVID positive and negative groups respectively but they may not be of clinical significance (Table 1). Apart from this, raised levels of AST (Aspartate Aminotransferase) were associated with mortality in the negative group (Table 1).

Median SOFA and qSOFA scores at presentation were significantly higher in non-survivors in both groups. Non-survivors in both groups also had low median GCS scores (Table 1). Institution of vasopressors at presentation was also strongly associated with mortality among both these groups (Table 1). Categorization of GCS also showed a significant variation within each group (Table 1).

The presenting vitals (Respiratory rate-RR, Heart rate-HR and Mean Arterial Pressure- MAP) were evaluated using a t-test. Mean values of MAP were lower among non survivors in both the groups (95% CI= -11.803, -1.937; p 0.002 and 95% CI= -12.944, -2.246; p 0.006 respectively for positive and negative groups). Tachycardia was significantly associated with mortality in the COVID negative group (95% CI= 0.659, 16.499; p 0.034) but not in the COVID positive group of patients. Tachypnea on presentation showed no significance in any of the groups.

None of the ABG parameters (Table 1) showed any significant relation with mortality in the COVID positive group. However, a low pH and a decreased level of bicarbonate (HCO3) were significantly related to mortality in the COVID negative group of patients (Z= -2.936, p 0.003 and Z= -2.061, p 0.04 respectively).

Age, history of contact or from containment zone, SOB, cough, pain abdomen and P/F ratio were identified as significant predictors for identifying COVID in those presenting with features suggestive of SARI on univariate logistic regression (ULR). (Table 1). All these except SOB showed significance when put in the multivariable logistic regression model (Table 2). Thus, the presence of these factors in our cohort was more suggestive of COVID positivity in a patient of SARI.

ROC curves were used to get a cut off of 53 years above which there is more chance for a patient with SARI to be COVID positive (Table 3, Figure 4). ROC curves also were used to demonstrate a cut off of 12g/dL for haemoglobin values below which there was increased mortality in COVID positive patients (Table 3, Figure 3).

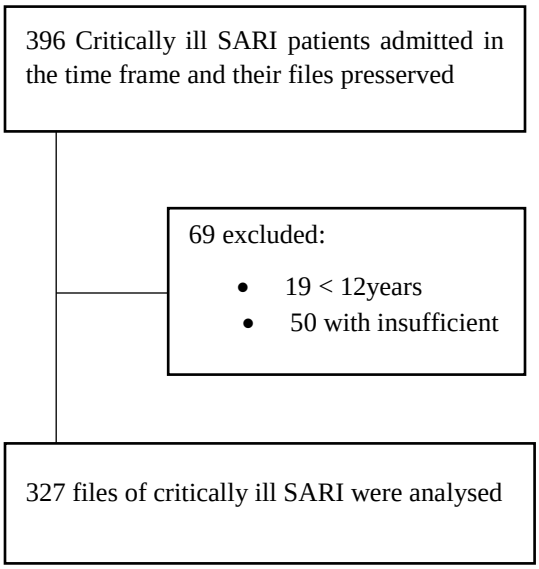

Figure 1- Flow Diagram of the study

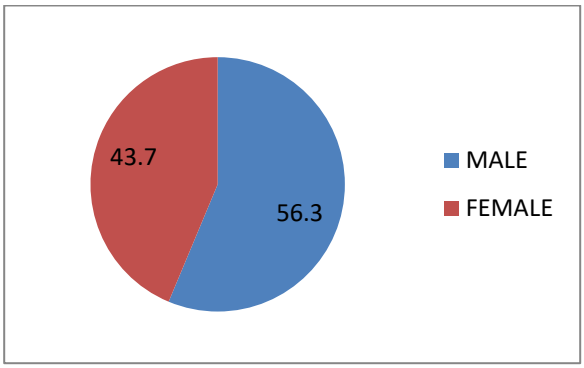

Figure 2A- Percentage of male and female presenting to Suspect ICU

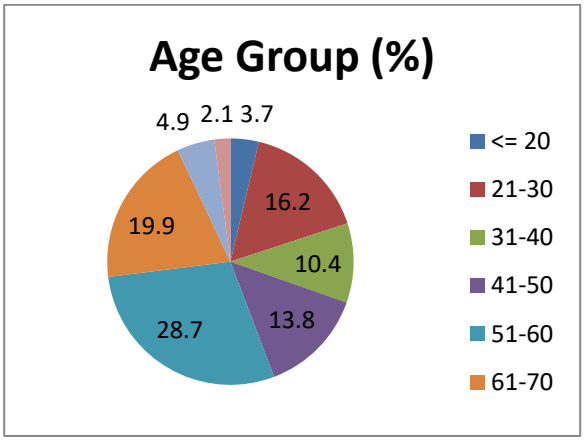

Figure 2B- Percentage in various age groups presenting to Suspect ICU

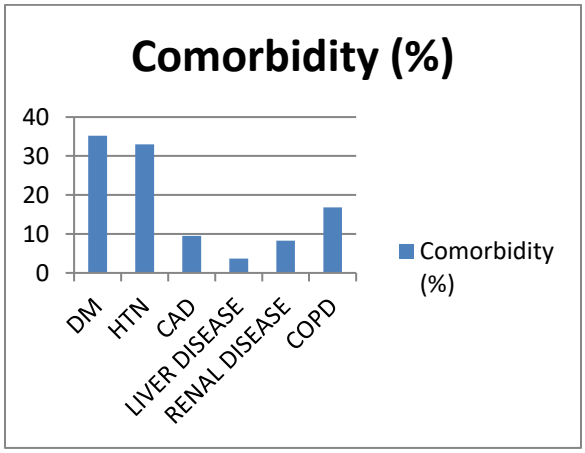

Figure 2C- Comorbidity (%) of various patients presenting to Suspect ICU

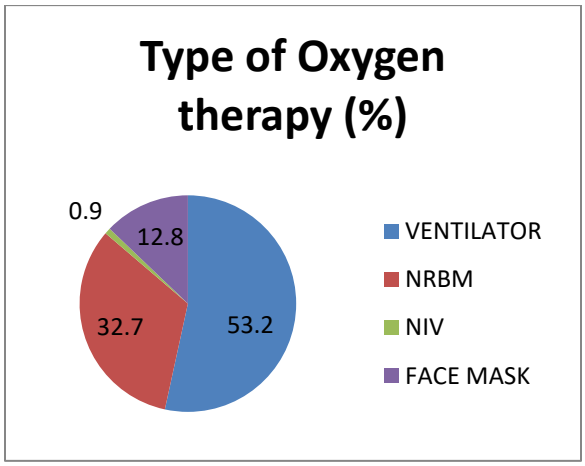

Figure 2D- Type of oxygen therapy received on arrival to Suspect ICU

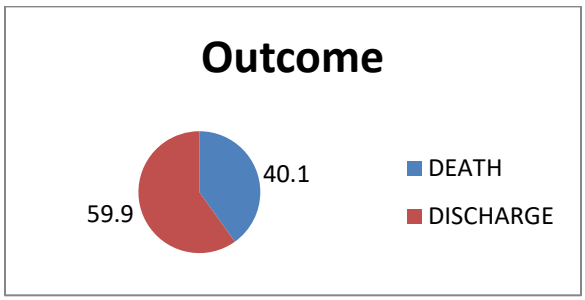

Figure 2E- Number & Percentages of death and discharges from Suspect ICU

Figure 2- Various demographic data (pie chart)

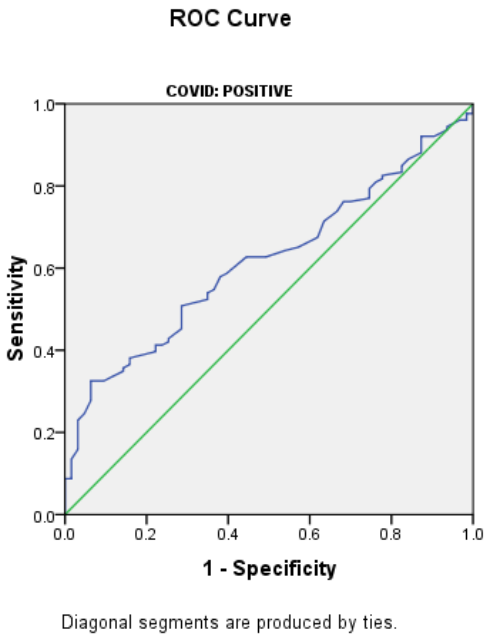

Figure 3- ROC curve of hemoglobin values in COVID positive group (Table IV- Hemoglobin).

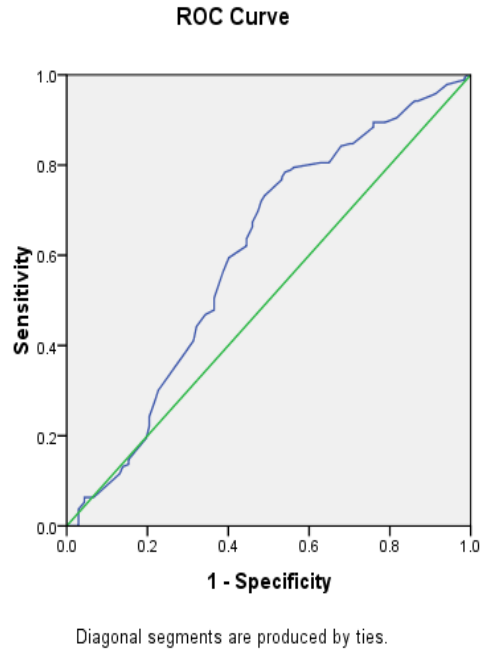

Figure 4- ROC curve of age in COVID suspect group

Table 1- Comparison of variables between COVID positive and negative groups & death and discharge in each group

Variables	COVID POSITIVE (N= 190)	Z/Mean diff	p value	COVID NEGATIVE (N= 137)	Z/Mean diff	p value	COVID POSITIV	COVID NEGATIVE	Z/Mean diff	p va

	Death (n=127)	**Discharge (n=63)**	**(CI)/χ 2value**		**Death (n=69)**	**Discharge (n=68)**	**(CI)/χ 2value**		**E (N= 190)**	**(N= 137)**	**(CI)/χ 2value (between COVID positive and negative)**	**lue**
Age**	53.49 (± 14.25)	50.55 (± 17.18)	-2.944 (-7.602 to 1.714)	0.214	45.9 (± 18.46)	46.4 (± 18.21)	0.499 (-5.698 to 6.695)	0.874	52.5 (± 15.28)	46.2 (± 18.27)	6.386 (2.726 to 10.046)	0.001
<53*									77 (40.5%)	82 (59.9%)	11.904	0.001
>= 53*									113 (59.5%)	55 (40.1%)		
Sex*												
Male	72 (64.9%)	39 (35.1%)	0.471	0.493	36 (49.3%)	37 (50.7%)	0.069	0.793	111 (58.4%)	73 (53.3%)	0.853	0.356
Female	55 (69.6%)	24 (30.4%)			33 (51.6%)	36 (49.3%)			79 (41.6%)	64 (46.7%)		
Symptoms*												
SOB	119 (93.7%)	63 (100%)	4.143	0.042	61 (88.4%)	61 (89.7%)	0.059	0.807	182 (95.8%)	122 (89.1%)	5.528	0.019
Fever	83 (65.4%)	48 (76.2%)	2.310	0.129	46 (66.7%)	36 (52.9%)	2.685	0.101	131 (68.9)	82 (59.9%)	2.899	0.089
Cough	119 (93.7%)	63 (100%)	4.143	0.042	59 (85.5%)	60 (88.2%)	0.223	0.637	182 (95.8%)	119 (86.9%)	8.670	0.003
Pain Abd	16 (12.6%)	7 (11.1%)	0.088	0.767	22 (31.9%)	10 (14.7%)	5.645	0.018	23 (12.1%)	32 (23.4%)	7.204	0.007
Alt Sens	6 (9.5%)	10 (7.9%)	0.149	0.700	12 (17.4%)	5 (7.4%)	3.175	0.075	16 (8.4%)	17 (12.4%)	1.395	0.238
Swelling	9 (7.1%)	3 (4.8%)	0.385	0.535	2 (2.9%)	3 (4.4%)	0.208	0.649	12 (6.3%)	5 (3.7%)	1.117	0.291
Chest Pain	5 (3.9%)	5 (7.9%)	1.351	0.245	7 (10.1%)	3 (4.4%)	1.664	0.197	10 (5.3%)	10 (7.3%)	0.575	0.448
Comorbidities*												
DM	51 (40.2%)	24 (38.1%)	0.075	0.784	23 (33.3%)	17 (25%)	1.150	0.283	75 (39.5%)	40 (29.2%)	3.687	0.055
HTN			0.262				0.179				0.032	
CAD			0.446				0.001				0.143	

Liver Disease	43 (33.9%)	19 (30.2%)	0	0.609	22 (31.9%)	24 (35.3%)	0.667	0.673	62 (32.6%)	46 (33.6%)	0.336	0.858
Renal Disease	14 (11%)	5 (7.9%)	1.272	0.504	6 (8.7%)	6 (8.8%)	2.045	0.979	19 (10%)	12 (8.8%)	0.258	0.705
COPD	4 (3.1%)	2 (3.2%)	0.624	0.993	4 (5.8%)	2 (2.9%)	0.239	0.414	6 (3.2%)	6 (4.4%)	0.001	0.562
	12 (9.4%)	3 (4.8%)		0.259	9 (13%)	4 (5.9%)		0.153	15 (7.9%)	13 (9.9%)		0.611
	24 (18.9%)	9 (14.3%)		0.430	11 (15.9%)	13 (19.1%)		0.625	33 (17.4%)	24 (17.5%)		0.972
Smoker*	17 (13.3%)	4 (6.5%)	1.982	0.159	8 (11.6%)	11 (16.2%)	0.602	0.438	21 (11.1%)	19 (13.9%)	0.588	0.443
Duration of Symptoms#												
SOB	3 [(1),(4)]	4 [(2),(5)]	-2.076	0.038	2 [(1),(4)]	3 [(1),(5.5)]	-1.822	0.068				
Fever	4 [(2),(7)]	4.5 [(3),(7)]	-1.082	0.279	3 [(2),(5)]	4.5 [(2.25),(5.75)]	-2.014	0.044				
Pain Abd	1 [(1),(2.75)]	3 [(2),(6)]	-1.895	0.058	1 [(1),(2.25)]	1 [(1),(5.25)]	-0.633	0.527				
Alt Sens	1 [(1),(2.25)]	1 [(1),(1.25)]	-0.713	0.476	2 [(1),(2.75)]	2 [(1),(4)]	-1.769	0.077				
Cough	3 [(1),(4)]	4 [(2),(5)]	-2.076	0.038	2 [(1),(4)]	1 [(1),(1.5)]	-1.281	0.200				
Swelling	7 [(4.5),(13.5)]	1 [(1),(2)]	-2.518	0.012	2 [(1),(3)]	3 [(1),(5.75)]	-1.732	0.083				
Chest Pain	4 [(2),(5)]	1 [(1),(6)]	-0.437	0.662	2 [(1),(5)]	7 [(5),(20)]	-1.165	0.244				
						5 [(4),(5)]						
No. of comorbidities#	1 [(1),(2)]	1 [(0),(2)]	-1.895	0.058	1 [(1),(2)]	1 [(0),(2)]	-0.944	0.345	2 [(1),(3)]	2 [(1),(3)]	-0.302	0.763
Blood Counts												
Hb (g/dL)#	10.91 (± 2.87)	12.0 (± 1.92)	-1.1 (-1.9 to -0.3)	0.005	10.9 (± 3.6)	10.6 (± 2.6)	0.23 (-0.8 to 1.3)	0.666	11.3 (± 2.6)	10.7 (± 3.1)	0.54 (-0.09 – 1.17)	0.092
Hb (< 10)	45 (35.4%)	11 (17.7%)	6.254	0.012	26 (37.7%)	26 (38.2%)	0.004	0.947				
TLC (*109/L)#	12 [(8.1),(17.1)]	10.6 [(5.9),(16.1)]	-1.082	0.279	13 [(8.5),(20.2)]	10.8 [(8.3),(13.7)]	-1.901	0.057	11.6 [(7.88),(17)]	12 [(8.4),(17.1)]	-0.826	0.409
Lym (*109/L)#	1.33 [(1),(2)]	1.48 [(1),(2)]	-0.688	0.491	1.49 [(0.81),(2)]	1.5 [(1),(2.2)]	-0.534	0.593	1.4 [(1),(2)]	1.5 [(0.9),(2.1)]	-0.115	0.908

Plat (*109/L)#	155 [(98),(241)]	182 [(108),(261)]	-1.382	0.167	145 [(101),(211)]	186 [(104),(262)]	-1.874	0.061	167 [(102),(251)]	153 [(101),(239)]	-0.544	0.586
NL ratio#	5.67 [(3.65),(8.5)]	5.42 [(3.43),(8.17)]	-0.584	0.559	5.4 [(3.75),(10.67)]	5.13 [(3.34),(7.86)]	-0.551	0.582	5.5 [(3.6),(8.35)]	5.3 [(3.5),(10)]	-0.110	0.912
Lab Parameters#												
INR	1.18 [(1.07),(1.34)]	1.12 [(1.02),(1.27)]	-1.238	0.216	1.12 [(1),(1.45)]	1.11 [(0.99),(1.23)]	-0.889	0.374	1.16 [(1.03),(1.31)]	1.12 [(1),(1.29)]	-1.405	0.16
Creat (mg/dL)	1.4 [(0.8),(2.7)]	0.9 [(0.7),(1.3)]	-3.705	<0.001	2.0 [(0.85),(3.2)]	0.9 [(0.5),(2.13)]	-2.953	0.003	1.2 [(0.7),(2.13)]	1.3 [(0.65),(2.95)]	-0.649	0.517
Na (mEq/L)	138 [(134),(143)]	135 [(132),(140)]	-2.480	0.013	138 [(132),(143)]	136 [(132),(140.8)]	-0.944	0.345	137 [(133),(142)]	138 [(132),(142)]	-0.642	0.521
K (mEq/L)	4.5 [(3.9),(5.3)]	4.4 [(4.0),(4.9)]	-1.130	0.258	4.7 [(3.95),(5.4)]	4.2 [(3.63),(4.63)]	-2.969	0.003	4.5 [(3.98),(5.2)]	4.4 [(3.8),(5.1)]	-0.856	0.392
Bil (mg/dL)	0.8 [(0.4),(1.2)]	0.6 [(0.5),(0.85)]	-1.210	0.226	0.9 [(0.45),(2.1)]	0.8 [(0.5),(1.48)]	-0.964	0.335	0.1 [(0.41),(1.2)]	0.8 [(0.5),(1.8)]	-1.798	0.072
AST (U/L)	57 [(40),(92)]	52 [(40),(90)]	-0.360	0.719	76 [(36.5),(108)]	49.5 [(35),(68)]	-2.267	0.023	55 [(40),(90.5)]	56 [(35),(93.5)]	-0.017	0.987
ALT (U/L)	48 [(28),(80)]	51 [(32),(89)]	-0.867	0.386	47 [(31.5),(93)]	43 [(25.8),(74.8)]	-1.430	0.153	50 [(30),(82)]	44 [(29),(80)]	-0.701	0.483
Scores#												
qSOFA	2 [(2),(3)]	1 [(1),(2)]	-5.140	<0.001	2 [(2),(3)]	1.5 [(1),(2)]	-4.653	<0.001	2 [(1),(3)]	2 [(1),(3)]	-1.321	0.186
SOFA	10 [(7),(12)]	6 [(3),(9)]	-5.908	<0.001	11 [(7.5),(14)]	7 [(4.25),(10)]	-4.866	<0.001	9 [(6),(11.25)]	9 [(6),(12)]	-1.203	0.229
GCS	5 [(3),(12)]	15 [(9),(15)]	-5.595	<0.001	5 [(3),(12)]	14 [(3),(15)]	-3.182	0.001	9 [(3),(15)]	7 [(3),(15)]	-0.460	0.646
15	26 (20.5%)	41 (65.1%)	38.968	<0.001	13 (18.8%)	33 (48.5%)	14.154	0.007				
13-14	3 (2.4%)	0			3 (4.3%)	3 (4.4%)						
10-12	19 (15%)	4 (6.3%)			7 (10.1%)	3 (4.4%)						

6-9	13 (10.2%)	6 (9.5 %)			10 (14.5%)	6 (8.8%)						
<= 6	66 (52%)	12 (19%)			36 (52.2%)	23 (33.8%)						
Vasopressor*	66 (52.4%)	18 (28.6 %)	9.643	0.002	34 (50.7%)	18 (27.3%)	7.694	0.006	84 (44.4%)	52 (39.1%)	0.915	0.339
Vitals†												
RR	27.49 (± 7.334)	27.06 (± 8.405)	0.425 (-1.917 to 2.767)	0.721	27.90 (± 6.196)	28.75 (± 7.644)	-0.851 (-3.201 to 1.498)	0.475	27.35 (± 7.69)	28.32 (± 6.94)	-0.974 (-2.6 – 0.65)	0.240
HR	110.39 (± 21.989)	106.97 (± 19.465)	3.425 (-3.016 to 9.867)	0.296	111.64 (± 21.346)	103.06 (± 25.381)	8.579 (0.659 to 16.499)	0.034	109.26 (± 21.2)	107.38 (± 23.74)	-0.286 (-3.9 – 3.33)	0.453
MAP	82.67 (± 17.878)	89.54 (± 12.205)	-6.870 (-11.803 to -1.937)	0.002	81.46 (± 16.918)	89.06 (± 14.642)	-7.595 (-12.944 to -2.246)	0.006	84.95 (± 16.91)	85.23 (± 16.23)	1.88 (-3.04 – 6.8)	0.876
ABG parameters‡												
pH	7.36 [(7.19),(7.41)]	7.39 [(7.28),(7.43)]	-1.751	0.080	7.29 [(7.2),(7.39)]	7.39 [(7.27),(7.45)]	-2.936	0.003	7.37[(7.23),(7.42)]	7.37[(7.24),(7.43)]	-0.002	0.998
HCO3	21 [(17),(23.6)]	22 [(18),(26)]	-1.707	0.088	21 [(16),(23.3)]	21 [(18.9),(25)]	-2.061	0.039	21 [(17.25),(25)]	21 [(16.3),(25)]	-0.234	0.815
PCO2	38 [(33),(52)]	39 [(32.7),(60)]	-0.146	0.884	37 [(30.5),(53.5)]	39 [(33.25),(47.75)]	-0.646	0.518	38 [(32.9),(53.2)]	38 [(32),(49.3)]	-0.715	0.474
P/F ratio	77 [(61),(102)]	86 [(66),(124)]	-1.715	0.086	88 [(62),(154)]	97 [(72),(162)]	-0.790	0.429	81.78 [(61),(102.6)]	89 [(66),(159)]	-2.456	0.014

* Chi square test: Data represented as n (%), $\chi 2$ (chi square) value, p value (<0.05 is significant)

†T test: Data represented as Mean (± Standard Deviation), Mean difference (Confidence Interval-CI), p value (<0.05 is significant)

‡ Mann Whitney U test: Data represented as Median [IQR- Inter quartile range], Z value, p value (<0.05 is significant)

SOB= Shortness of breath. DM= Diabetes Mellitus. HTN= Hypertension. COPD= Chronic Obstructive Pulmonary Disease. CAD= Coronary Artery Disease. Hb= Hemoglobin. TLC= Total Leucocyte count. Lym= Absolute Lymphocyte count. Plat= Platelet count. NL ratio= Neutrophil to Lymphocyte count ratio. INR= International Normalized ratio. Creat= Creatinine. Na= Sodium. K= Potassium. Bil= Total Bilirubun. AST= Aspartate amino transferase. ALT= Alanine transferase. SOFA= Sequential Oragn Failure Assessment. qSOFA= quick SOFA. GCS= Glasgow Coma Scale. RR= Respiratory rate. HR= Heart rate. MAP= Mean Arterial Pressure. HCO3= Bicarbonate levels. PCO2= Partial pressure of Carbon dioxide. P/F ratio= Partial pressure of oxygen to fractional of inspired air that is oxygen ration.

Table 2- Multivariate analysis to identify risk factors in favour of COVID

Variable	UNIVARIATE OR (95% CI)	P value	MULTIVARIATE OR (95% CI)	P value
Age	1.023 (1.009 – 1.037)	0.001	1.020 (1.006 – 1.035)	0.004
Contact/Containment zone	3.280 (1.205 – 8.931)	0.020	3.889 (1.316 – 11.495)	0.014
SOB	2.797 (1.151 – 6.799)	0.023	…	…
Cough	3.441 (1.450 – 8.167)	0.005	2.908 (1.182 – 7.152)	0.020
Pain Abdomen	2.213(1.228 – 3.987)	0.008	2.147(1.149 – 4.012)	0.017
P/F ratio	0.997 (0.994 – 1.000)	0.026	0.997 (0.994 – 1.000)	0.028

Table 3- AUROC for Age and Hemoglobin

Variables	Area	Std Error	95% Confidence Interval		P value
			Lower bound	Upper Bound	
Age§ (years)	0.603	0.033	0.539	0.667	0.001
Hemoglobin‖ (g/dL)	0.617	0.041	0.537	0.697	0.009

§ROC curve within suspect patient group of COVID positive and negative
‖ROC curve within COVID positive group of death and discharge

Discussion

In our study, we found no difference in mortality in COVID group with respect to age. This is in contrast to several studies6-8. This was probably because our cohort only included patients requiring ICU intervention while the above studies encompassed stable COVID patients. Xie et al9 however found age as a risk factor in critically ill patients. The different genetic makeup of our study populations may be responsible for the difference in findings.

Studies have found that male sex is a risk factor for mortality6, 10, 11 in contrast to ours. This is probably due to the critically ill subjects that our study included.

We also found no significance of comorbidity with mortality, a finding in contrast to many studies.6, 8, 10, 12 Hypertension and diabetes were the most common comorbidities in our study. A meta-analysis by Espinosa et al13 showed 17% prevalence of patients with diabetes at ICU admission and 19% prevalence amongst those who succumbed. However, Agarwal N et al8 showed that diabetes was a risk factor for mortality while evaluating SARI patients, but in this study, all patients did not require ICU admission. We don't refute the fact that patients with comorbidities tend to require ICU care when compared to stable hospitalized patients; but amongst critically ill patients, they may bear no significance to mortality as they tend to get equally distributed amongst SARI patients. We also put forth a similar argument to explain why we did not get a significant difference between survivors and non-survivors of the two groups while evaluating smoking and number of comorbidities.

Our study found that none of the presenting symptoms had any relation with mortality amongst COVID positive. This finding is similar to the ones found by Zhou et al.7 Xie et al9 however found breathlessness to be significantly associated with mortality. We attribute it to the genetic difference between the two cohorts. Also, the shorter median duration of symptom onset while presenting to our set-up, may suggest a rapid symptom progression in our cohort as compared to theirs; hence the difference in findings. The time from symptom onset to presentation in our study had no significant bearing on the outcome in the two groups as also is corroborated by the above studies.7,9 Only the duration of generalized body swelling was significantly associated with mortality in COVID positive patients. This could be possible because a progressive swelling signifies kidney involvement, and such patients have high mortality as Angiotensin-Converting Enzyme 2 (ACE2) receptor is 100 times more in the kidney than in the lung. ACE2 is a target for this virus to enter cells.14 Also the hypercoagulable state of COVID-19 can cause acute tubular to cortical necrosis.15 Amongst COVID negative group, pain abdomen was significantly associated with mortality. This is not surprising as abdominal pain increases in-hospital mortality, especially if not evaluated early.16,17 This is also magnified by the fact that this pandemic has caused a delay in the diagnosis of various non-COVID illnesses.

Our study found significantly higher median scores of SOFA and qSOFA amongst non-survivors in both groups. A study by Zou et al18 also found similar results. Their study demonstrated an area under the curve (AUC) of 0.867 (95% CI, 0.808–0.926) with a cut off at 3 for SOFA. Their finding of lower mean GCS amongst non-survivors is also consistent with ours. A study by Liu S et

al19 demonstrated that the performance of qSOFA is acceptable in predicting mortality in COVID but is inferior to SOFA. SOFA, a poor prognostic marker amongst non-COVID patients requiring ICU admission is unrefutable and was also shown in our study.20 SOFA though a good marker for sepsis caused by bacterial infections, even viral infections can cause sepsis-like syndrome.7 Patients on vasopressors also did not do well in both groups. This is not surprising as the use of vasopressors is also a part of SOFA.

In Arterial Blood Gas (ABG) parameters (pH, PCO2, P/F ratio, HCO3) we found nothing significantly associated with outcome in critically ill COVID patients, probably due to critically ill subjects in our study groups. A study in Wuhan found that survivors had higher PO2 and lower PCO2 than non-survivors, but they measured ABG only pre- and post-intubation.21 However, a study by Bezuidenhout et al found that survivors had significant alkalemia.22 Their study population was small, and the p-value barely made it to <0.05. They hypothesized that this was due to mineralocorticoid activation and upregulation of the Renin-Angiotensin pathways by the virus. Our median values of pH and bicarbonate were also higher amongst survivors but not of significance. The study by Bezuidenhout et al22 found significantly lower PO2 values amongst non-survivors but we had measured the P/F ratios instead in which we found no significant difference probably because we studied critically ill SARI. Our study also revealed that acidosis amongst non-COVID was associated with mortality. This, however, is a time-tested concept supported by many studies.

We analyzed blood counts and found low levels of haemoglobin had statistical significance between survivors and non-survivors amongst COVID positive patients. To further validate this, we used a cut off haemoglobin <10 g/dL and found that mortality was significant in this group of patients (Table 1). The AUC of 0.617 was also significant and the cut point haemoglobin thus achieved was 12 g/dL, below which there was increased mortality. Our findings are similar to Cen et al23 who found haemoglobin levels below 110 g/L were linked with disease progression in patients with COVID-19; the univariable hazard ratio was 3.91 (95% CI 2.99–5.10). Giacomelli et al24 reported that anaemia (haemoglobin levels below 125 g/L) was more prevalent in Covid-19 non-survivors (66.7%). Haemoglobin is an important determinant to carry oxygen to peripheral tissues. During infection, there is an increased demand for peripheral tissue for oxygen due to the hypermetabolic states. Thus low levels of haemoglobin are associated with mortality. Taneri et al25 further found that low haemoglobin, low red blood cell count, higher ferritin level and red cell distribution width were associated with moderate to severe cases of COVID-19.

In biochemical parameters, high levels of creatinine were associated with mortality in both groups. Yang et al26 in their meta-analysis found the incidence of AKI was 52.9% (95% CI 34.5–71.4%), 0.7% (95% CI − 0.3–1.8%) in non-survivors and survivors respectively. They concluded that the site of impact was renal tubule and it could have been because of the direct impact of hypoxia, hypercoagulability or because of the COVID-19 impact directly. Thus screening of patients for urine analysis, serum creatinine along with proper optimization of fluid volume, and anticoagulant therapy are essential.

We found hyponatremia was associated with mortality in the COVID positive group. The reasons could be diuretic therapy, digestive loss of sodium, decreased intake of sodium or syndrome of inappropriate antidiuretic hormone secretion (SIADH). In some cases, hyponatremia may be the first clinical presentation to appear.27 Hyponatremia could also be considered a negative prognostic factor in patients diagnosed with COVID-19.28 The incidence of hyponatremia was quite common in hospitalized patients with COVID-19 in Hubei, and was associated with a higher risk of severe illness and increased in-hospital mortality29.

Using multivariate analysis, we found an increasing age in critically ill SARI has a higher probability of being labelled as COVID by a factor of 2% for every unit increase in age of presentation. The median age of patients turning out to be COVID was significantly higher than the ones without. This finding we believe can be a factor for efficient triaging. Our finding is corroborated by one study who like us, had studied only on those requiring ICU care.9

Applying multivariate analysis, cough and pain abdomen were significant predictors of the likelihood of COVID positivity amongst critically ill SARI patients. Pain abdomen seems to be protective by a factor of two towards COVID positivity, a finding not found in any study so far. Agarwal et al8 found that cough is a likelihood predictor of COVID positivity amongst SARI patients by a factor of three as was seen in our study as well. Multivariate analysis also showed that being from containment areas increases the chances of being COVID by a factor of four in such patients, a finding corroborated by Tambe et al.6 They hypothesized that a higher population density in these areas may be the reason for such findings. These findings of our study may help the clinician in premeditated treatment in the lines of COVID protocol thus saving crucial time to appropriate medications. Also, every decrease of P/F ratio by a factor of 100, increased the chances of COVID positivity in critically ill SARI patients by 3%. This means that a patient presenting with severe ARDS during peak pandemic without any RTPCR report would have a 12% increased chance of being COVID than not.

However, our study is not without limitations. The first one being the retrospective design and lack of any patient follow up. This did not allow us to associate various symptoms like anasarca with creatinine trends. A study

in that line may be beneficial. Still, our study was based on factors in critically ill SARI patients and such data is sparse. Thus the predictors of mortality in our study and the predictors of COVID positivity would help institutions make better-triaging protocols during the peak of pandemic which may be helpful for future systematic reviews. The knowledge of these factors may guide future research in the form of interventional study designs like the effect of blood transfusion on mortality in COVID-19.

Conclusion

Amongst COVID positive, a long duration of generalized swelling and low haemoglobin (<12 g%) were associated with mortality while pain abdomen, raised levels of AST, tachycardia and acidosis were associated with mortality in COVID negative group. Deranged creatinine, lower MAP, higher SOFA, qSOFA, vasopressor use and lower GCS were associated with mortality in both groups. Our study shows that age, contact history, residence in containment zone, cough, pain abdomen and poor P/F ratio are predictive factors in a patient of SARI towards being COVID.

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