Original Article

Predictors of severity in COVID-19

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Abstract

Background: In the context of home monitoring of severe acute respiratory syndrome coronavirus-2 disease (COVID-19) patients, it is imperative to evaluate the accuracy of finger pulse oximetry oxygen saturation (SpO_2) in the assessment of hypoxia.

Methods: Retrospective data analysis was performed on (n = 132) hospitalised COVID-19 patients with various levels of severity, in whom SpO_2, haematological, biochemical and arterial blood gas (ABG) parameters were measured within 48 h after admission. Discrepancy between SpO_2 and arterial blood oxygen saturation SaO_2 was compared between mild, moderate and severe COVID-19 to assess the accuracy of finger pulse oximetry.

Results: We found that total white blood cell count, neutrophil %, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, ferritin, C-reactive protein and lactate dehydrogenase (LDH) were significantly increased in severe COVID-19, while lymphocyte % was significantly less when compared to mild and moderate cases. Multivariable analysis suggested that red cell distribution width (RDW) and LDH together account for significant variance in the severity of disease. The SpO_2 and SaO_2 were significantly less in the severe group. The difference between SpO_2 and SaO_2 has a clinically meaningful albeit statistically nonsignificant trend with the discrepancy greater in severe COVID-19 cases when compared to mild and moderate cases.

Conclusions: Finger pulse oximetry has the potential to underestimate the severity of hypoxia in severe COVID-19 and this has implications in the decision to start oxygen therapy. RDW and LDH constitute the best parsimonious set of variables to predict severity.

Keywords: Arterial blood gas analysis, COVID-19, finger pulse oximetry, hypoxia

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INTRODUCTION

The sheer scale of the severe acute respiratory syndrome coronavirus-2 disease (COVID-19) pandemic has caught the health-care system off guard in every country, especially straining meagre health resources in a country like India.[1-4]

Several studies[5-8] have identified the early alteration in haematological parameters in the disease and the utility of clinical laboratory parameters in stratification of severity of disease, i.e., differentiation of mild, moderate cases and severe cases. Fall in lymphocyte count has been widely documented in COVID-19, with the level of lymphocyte count related to the severity of disease.[5-7] In addition, the rise of the neutrophil count, neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte

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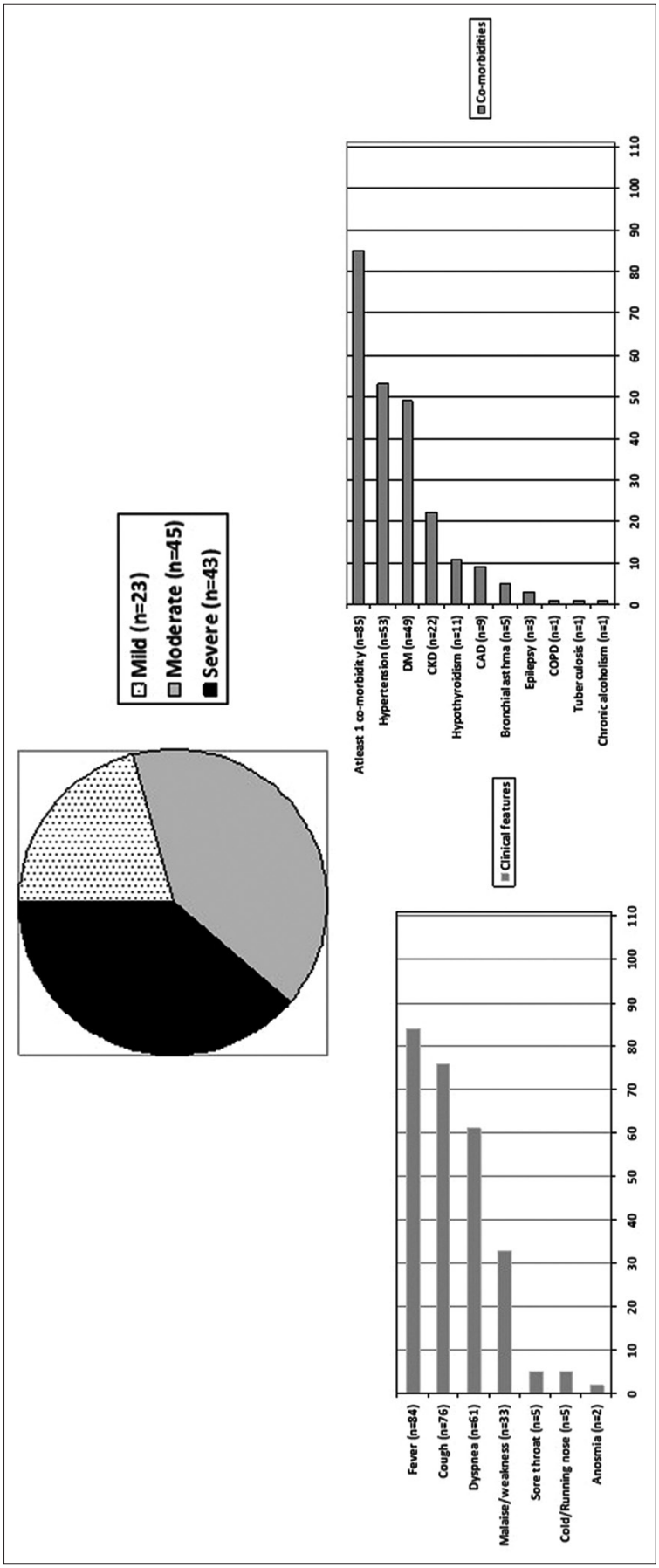

Figure 1: Characteristics of study patients
DM = Diabetes mellitus; CKD = chronic kidney disease; CAD = Coronary artery disease; COPD = Chronic obstructive pulmonary disease

ratio (PLR), red cell distribution width (RDW) and a fall in haemoglobin, haematocrit and oeosinophil count have found to occur early in the disease and also correlated with the severity of disease.[5] Studies have also reported an increase in inflammatory cytokines which are far more expensive to measure.[5,8] Due to increased caseload and consequent saturation of health care facilities, home monitoring of mild-to-moderate cases with finger pulse oximetry oxygen saturation (SpO_2) has been recommended. Several questions have been raised on the accuracy of finger pulse oximetry for that purpose, as it has a critical role in the decision to institute potentially life-saving oxygen therapy.[9] The present study is an exploratory study based on the metrics routinely measured in hospitalised COVID-19 patients with the purpose of evaluating their prognostic potential and the explore the issues in the use of finger pulse oximetry for clinical decision-making. The current study has two-fold objectives: (i) to further explore and determine the utility of early measured clinical, haematological, biochemical and arterial blood gas (ABG) parameters in the ability to predict the eventual severity of COVID-19 during the hospital stay; and (ii) to determine the discrepancy between SpO_2 and ABG arterial oxygen saturation (SaO_2) in COVID-19 patients of varying degrees of severity.

MATERIAL AND METHODS

The data from (n = 200) consecutive patients hospitalised between October 2020 to February 2021 were included in the study. The data were anonymised before the statistical analysis. The study was approved by Institutional Ethics Committee (EC/AIMSR/1527/2021/08/003 Dt 3-11-2021).

The data collected included clinical features, haematological, biochemical and ABG analysis parameters assessed/measured within the first 48 h after the admission. Also collected was their eventual clinical outcome in terms of maximal severity during the hospital stay and discharge/death. Severity assessment was made according to the criteria in the clinical management protocol for COVID-19, version 4, issued on 27th June 2020, by the Ministry of Health and Family Welfare, Government of India.[10] Of the 200 cases, only the ones with complete data were selected for further analysis, which resulted in the final cohort size of 132 patients (n = 132, females = 38) (Figure 1).

The haematological parameters were measured using Mindray BC-5300 5-part coulter. C-reactive protein (CRP) was estimated using immunoturbidometric method, while lactate dehydrogenase (LDH) and ferritin were estimated with chemiluminescence immune assay. ABG analysis was performed using Radiometer® ABL800 BASIC blood gas analyser (Radiometer Copenhagen).

Statistical analysis

Scalable continuous variables are summarised as mean ± standard deviation; nominal variables are summarised as percentages. For univariate analysis, mild, moderate and severe categories were compared using one-way analysis of variance (ANOVA). Multivariable analysis was performed using multinomial logistic regression, to determine the sparse set of laboratory parameters that can predict the severity of COVID-19. Fisher's exact test was used to evaluate the association between comorbidities and severity of COVID-19. The difference/discrepancy between SpO_2 and SaO_2 was compared between mild, moderate and severe using one-way analysis of variance (ANOVA). Statistical analysis was done using IBM SPSS Statistics, Version 25.0, (Armonk, NY)

RESULTS

The mean age of the study population was 47.6 ± 16.5 years. The most common symptoms were fever (75%), cough (66%) and dyspnoea (53%). Consistent with previously published literature,[10,11] the upper respiratory tract symptoms such as running nose (6.8%) and sore throat (4.5%) were relatively infrequent. Only two patients in the cohort complained of an altered sense of smell. Patient characteristics and clinical features are shown in Table 1; comorbidities are shown in Table 2. The haematological, biochemical and arterial blood analysis parameters and the results of univariate analysis (one-way ANOVA) are shown in Table 3. Total white blood cell count, neutrophil %, NLR, PLR, CRP, ferritin and LDH were significantly higher in the severe group when compared to mild and moderate groups, whereas the lymphocyte % was lesser in the severe group. Multinomial logistic regression revealed that RDW and LDH in combination were the best sparsest set of predictors for severe (RDW odds ratio [OR] = 0.617, $P < 0.001$; LDH OR = 1.018, $P < 0.001$) and moderate (RDW OR = 0.765, $P = 0.003$; LDH: OR = 1.011, $P = 0.005$) categories with respect to the mild group. Risk of severity increases as the LDH values increase and the RDW decreases.

Table 1: Demographics and clinical features

Measure	Mild (*n*=44)	Moderate (*n*=45)	Severe (*n*=43)
Age (years)*	47.6±16.5	55.4 (15.3)	56.6 (13.7)
Sex†			
Females	12	15	11
Males	32	30	32
Fever‡	31 (70.5)	36 (80)	32 (74.4)
Cough	20 (45.5)	34 (75.6)	33 (76.7)
Shortness of breath	13 (29.5)	27 (60)	30 (69.8)
Cold	5 (11.4)	1 (2.2)	3 (7)
Sore throat	3 (6.8)	0	3 (7)
Weakness	18 (40.9)	13 (28.9)	12 (27.9)
Anosmia	2 (4.5)	0	0
Dysgeusia	0	0	0

*Data are presented as mean±standard deviation
†Data are presented as numbers
‡Data are presented as No. (%)

Table 2: Comorbidities

Measure	Mild (*n*=44) No. (%)	Moderate (*n*=45) No. (%)	Severe (*n*=43) No. (%)
Hypertension	13 (29.5)	26 (57.8)	20 (46.5)
Diabetes mellitus	8 (18.2)	23 (51.1)	23 (53.5)
Hypothyroidism	5 (11.4)	3 (6.7)	6 (14)
Chronic kidney disease	0	6 (13.3)	16 (37.2)
Coronary artery disease	4 (9.1)	6 (13.3)	2 (4.7)
Bronchial asthma	1 (2.3)	3 (6.7)	1 (2.3)
Tuberculosis	0	0	1 (2.3)
COPD	0	0	1 (2.3)
Epilepsy	0	1 (2.2)	2 (4.7)
Alcoholism	0	1 (2.2)	0

COPD=Chronic obstructive pulmonary disease

Blood gas parameters from ABG revealed that partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), $paCO_2$, bicarbonate, SaO_2 and SpO_2 decreased with an increase in severity. The coefficient of variation (CV) = (100 × standard deviation/mean) of SaO_2 is higher for the severe category (22.3%) when compared to mild (6.9%) and moderate (7.3%), while the CV for SpO_2 was 4.6% for the severe category, 3% for moderate and 1.5% for mild.

Presence of one or more comorbidities is associated with the severe form of disease ($P < 0.001$). Both diabetes mellitus ($P = 0.001$) and hypertension were found to be associated with the severe form of COVID-19 ($P = 0.017$). The difference between ABG oxygen saturation and pulse-oximetry oxygen saturation appeared to be greater in severe cases when compared to mild and moderate cases, though the difference was not statistically significant at the 5% level, as shown in Table 4.

DISCUSSION

The present study was conducted to determine the relationship between the severity of hospitalised COVID-19 patients and the various clinical, haematological, biochemical and ABG parameters assessed/measured within the first 48 h after the admission into the hospital for which the data from 132 patients were analysed. We found that NLR and PLR were significantly increased in severe cases when compared to mild and moderate cases. This increase can be explained by high neutrophil % and relatively low lymphocyte % in severe cases. NLR has been found to be correlated with severity in a number of other studies.[12-17] The rise in the neutrophil count is related to increased levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-12, interferon-gamma and monocyte chemoattractant protein 1 reported by several studies.[17,18] Fall in lymphocyte count is thought to be due to lymphocyte sequestration, increased cytokines and viral targeting of lymphocytes.[19,20] As the increase in levels of cytokines correlates well with lung damage, the association between severity of COVID-19 and NLR, which is a consequence of 'cytokine storm', can be used to infer severity in patients.

High levels of CRP, ferritin and LDH were found to be associated with the severity of disease in the present study and several others.[21-23] CRP and ferritin are acute-phase proteins synthesised and released by the liver in response to inflammation and this synthesis increases in response to the large plethora of cytokines produced in the disease. LDH is a ubiquitously found intracellular enzyme and is released from the cells in response to tissue damage. High levels of LDH can potentially indicate greater tissue damage and severity of disease. Therefore, both the CRP, ferritin and LDH are useful indicators of the severity of COVID-19 by virtue of their dependence on the levels of cytokines and the extent of tissue damage, respectively. Biochemical investigations are helpful in gauging the extent of tissue damage and the consequent systemic inflammatory response and therefore provide pathophysiologically plausible metrics to predict the severity and impending worsening of the clinical state of the patient.

Different types of blood gas abnormalities and acid-base disorders have been reported in COVID-19 patients.[24,25] We report a fall in PaO_2 with severe disease indicating impaired gas exchange in the lungs even within 48 h of admission. Fall in PaO_2 was accompanied by a fall in $PaCO_2$ and we interpret this finding to be the consequence of hyperventilation induced by hypoxia. However, the possible respiratory alkalosis is not accompanied by a fall in pH as both the groups did not differ in the pH that was in the normal range. This discrepancy between low $PaCO_2$ and normal pH can be explained by the changes in lactate and

Table 3: Haematological, biochemical and arterial blood gas analysis parameters

Measure	Mild (*n*=44)	Moderate (*n*=45)	Severe (*n*=43)	*P*-value
Total WBC count (×10^3 cells/mm^3)	6.9 (3.0)	7.5 (3.7)	10.4 (5.2)	<0.001
Neutrophil (%)	67.3 (14.0)	76.3 (12.0)	86.1 (6.7)	<0.001
Lymphocyte (%)	24.5 (13.0)	16.6 (10.5)	9.0 (5.7)	<0.001
NLR ratio	5.4 (7.1)	8.6 (10.2)	17.8 (20.2)	<0.001
RDW-CV (%)	13.2 (1.4)	13.6 (1.6)	13.9 (1.5)	0.103
RBC count (×10^6 cells/mm^3)	4.7 (0.6)	4.6 (0.9)	4.4 (0.8)	0.401
Haemoglobin (g/dL)	13.3 (2.2)	12.7 (2.0)	12.3 (2.2)	0.114
Haematocrit (%)	39.3 (5.2)	38.0 (6.0)	37.1 (6.3)	0.223
Platelet count (×10^3 cells/mm^3)	248.6 (118.5)	245.7 (93.0)	227.1 (86.9)	0.574
PLR ratio	16.0 (16.6)	27.6 (37.3)	39.1 (31.0)	0.002
MPV (fL)	8.9 (1.1)	8.69 (0.7)	8.85 (0.9)	0.485
PDW-CV (%)	16.2 (0.5)	16.2 (0.3)	16.4 (0.4)	0.158
Plateletcrit (%)	0.2 (0.1)	0.2 (0.1)	0.2 (0.8)	0.698
CRP (mg/L)	50.7 (59.3)	67.7 (43.2)	111.5 (60.5)	0.001
LDH (IU/L)	251.5 (73.1)	335.6 (128.9)	491.2 (177.5)	<0.001
Ferritin (ng/mL)	264.5 (240.2)	470.0 (439.7)	715.73 (613.6)	0.002
pH	7.43 (0.0)	7.44 (0.0)	7.43 (0.1)	0.431
$PaCO_2$ (mmHg)	35.3 (8.8)	32.4 (5.8)	29.9 (5.3)	0.003
PaO_2 (mmHg)	78.6 (21.7)	81.9 (27.1)	68.4 (21.8)	0.034
Lactate (mEq/L)	1.6 (0.6)	1.7 (0.7)	2.0 (0.9)	0.061
Bicarbonate (mEq/L)	22.6 (3.7)	21.9 (3.4)	20.3 (3.1)	0.014
SaO_2 (%)	92.8 (6.4)	93.7 (6.8)	84.8 (18.9)	0.016
SpO_2 (%)	97.7 (1.5)	96.5 (2.9)	94.7 (4.4)	0.009

WBC=White blood cell; NLR=Neutrophil-to-lymphocyte; RDW-CV=Red cell distribution width - coefficient of variation; RBC=Red blood cell; PLR=Platelet–lymphocyte ratio; MPV=Mean platelet volume; PDW-CV=Platelet distribution width - coefficient of variation; CRP=C-reactive protein; LDH=Lactate dehydrogenase; SpO_2=Pulse oximetry oxygen saturation; SaO_2=Arterial oxygen saturation

Table 4: Comparison of oxygen discrepancy in mild, moderate and severe cases

SpO_2–SaO_2 (severe)	SpO_2–SaO_2 (moderate)	SpO_2–SaO_2 (mild)	*P*-value
9.2 (20.3)	2.9 (7.0)	4.6 (6.3)	0.08

SpO_2=Pulse oximetry oxygen saturation; SaO_2=Arterial oxygen saturation

bicarbonate levels. Lactate levels appear to have a higher trend in severe cases (P = 0.061). Bicarbonate levels are significantly lower in severe cases. The pattern of rising lactate and low bicarbonate levels suggests the presence of metabolic acidosis in addition to respiratory alkalosis discussed above. This combined presence of respiratory alkalosis with metabolic acidosis can account for the normal pH found in severe cases. These facts indicate the occurrence of complex acid-base disorder in severe COVID-19 cases even early after hospital admission.

We also found a greater discrepancy in the oxygen saturation in severe cases when the ABG and finger pulse oximetry methods were compared. It is known from the published literature that pulse oximetry measured saturation can be different from the ABG measured saturation by 4% in when the true SaO_2 is above 80%, with pulse-oximetry values relatively higher.[9] This finding is important as it impacts the decision to start supplemental oxygen in severe COVID-19 cases. It is also interpreted to mean that pulse oximetry underestimates the severity of hypoxia in Severe COVID-19 with implications for the institution of oxygen therapy.

In contrast to the previous studies,[26-29] the present study did not find any significant differences in platelet indices between mild, moderate and severe cases. Our data suggest that RDW and LDH in combination have the best prognostic potential.

The data from the present study support the utility of NLR ratio, PLR ratio, CRP, ferritin and LDH in the assessment of the severity of COVID-19. RDW and LDH are the minimal set of useful predictors for severity. We have found ABG patterns consistent with the complex acid-base disorder, i.e., respiratory alkalosis with metabolic acidosis that tends to worsen with the severity of disease. Furthermore, finger pulse oximetry was found to underestimate the severity of hypoxia in severe COVID-19 with profound implications for the decision to start oxygen therapy.

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Conflicts of interest
There are no conflicts of interest.

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