ORIGINAL ARTICLE

Inflammatory Markers as Early Predictors of Disease Severity in COVID-19 Patients Admitted to Intensive Care Units: A Retrospective Observational Analysis

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Abstract

Background: In pandemic situations, it is essential that the limited resources are used judiciously to achieve most benefits. Prediction of the disease severity at the earliest will help in better allocation, thus, positively affecting prognosis and treatment.

Aim and objective: To investigate patient characteristics and specific biomarkers as possible early predictors of disease severity of SARS-COV-2 infection.

Materials and methods: Retrospective single-centric observational study conducted at 70-bedded intensive care unit of tertiary care hospital at Haryana, India. 100 consecutive RT-PCR positive coronavirus disease-2019 (COVID-19) adult patients. Demographics, acute physiology and chronic health evaluation II (Apache-II) score, and Inflammatory markers were compared with respect to oxygenation defect (PaO_2/FiO_2 ratio: <300 or ≥300 mm Hg), need of invasive ventilation, ICU length of stay and 28-day mortality.

Findings: Mean age was significantly more in lower PF ratio group (58.01 ± 15.33 vs 50.97 ± 13.78, $p = 0.023$) whereas sex ratio was comparable among patients in two groups. Significantly, higher APACHE-II score ($p \leq 0.001$) and presence of hypertension (43.54% vs 23.68%; $p = 0{\cdot}045$) in low PF ratio group along with higher C-reactive protein (171.78 ± 124.45 vs 101.52 ± 88.70), IL-6 (173.51 vs 53.18) and ferritin (1677.60 ± 2271.13 vs 643.54 ± 718.68) levels. Procalcitonin, lactate dehydrogenase, and creatine phosphokinase (CPK) levels were not significant.

Interpretation: Age and APACHE II score and among laboratory parameters CRP, ferritin, and IL-6 levels were significantly higher in low PF ratio group, patients requiring invasive ventilation and in mortality group. Use of this triad (CRP, ferritin, and IL-6 levels) at admission may predict the disease severity early in the course. Addition of APACHE-II may further improve the accuracy of the score.

Keywords: APACHE II, Conservative oxygen therapy, COVID-19 ARDS, Hypoxemia, Indian Intensive care unit, Inflammatory biomarker.

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Highlights

- Can demographic and clinical parameters along with inflammatory markers (at admission) be the early predictor triad for disease severity and outcome in coronavirus disease-2019 (COVID-19) patients?
- Retrospective observational study of 100 COVID-19 positive ICU patients suggested that age and acute physiology and chronic health evaluation II (APACHE II) score together with CRP, serum ferritin, and serum Interleukin-6 levels may significantly predict the disease severity with respect to oxygenation defect, ventilator requirement, and mortality.
- Limited assay of just three markers-CRP, S. ferritin and Interleukin-6 levels, together with age and acute physiology and chronic health evaluation II (APACHE-II) score, may help in prediction of disease severity and early prognostication along with best channelization of scant resources.

Introduction

Novel coronavirus disease-2019 (COVID-19) was declared as a public health emergency by the World Health Organization on March 11, 2020, when this pandemic had already affected 114 countries, infecting 118,000 people and taking 4,291 lives.[1] The first case in India was diagnosed on January 30, 2020, at Thrissur district in Kerala with a travel history from Wuhan, China, where this disease originated. Since then, the numbers have been increasing at an alarming rate despite all precautionary measures. Till now, we have 4.27 million confirmed cases in India with reported mortality of around 5,09872.[2] Although most patients have mild symptoms and good prognosis, severe COVID-19 cases may have a fulminant course. SARS-COV-2 viral replication triggers inflammatory response and cellular destruction causing release of cytokines and chemokines (inflammatory mediators) which further leads to exaggerated immune response and its effects causing systemic inflammation leading to multi-organ involvement and, thus, the grave prognosis.[3] Although, around the world, the overall recovery rate from SARS-COV-19 infection is high, recovery rate of patients admitted to ICU is low (around 79–80%) and is further alarming (around 54.4%) for ventilated patients.[4] As the case becomes more critical, patients will have more stormy inflammatory reactions and release of such mediators. Studying

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a set of such biomarkers may help in swift prediction of critical disease severity and hence guide further management. With early detection and segregation of severely ill critical patients, there may be a possibility of better prognosis in severely affected patients with timely aggressive supportive measures. As the disease is new and emerging, there has been a continuous addition to the current meagre knowledge with lots of data coming mainly from China, Europe, and USA. There is still paucity of data on Indian patients. This cluster of patient characteristics may play a pivotal role in determining the disease severity.

This study aimed to investigate set of patient characteristics (age, sex, presenting symptoms and comorbidities), acute physiological and chronic health evaluation (APACHE-II) score; and specific biomarkers [C-reactive protein (CRP), Creatinine kinase (CK), Procalcitonin, Lactate dehydrogenase (LDH), Ferritin, Interleukin-6 (IL-6)] as possible early predictors of severity of SARS-COV-2 infection in COVID. Real-time polymerase chain reaction (RT-PCR) positive patients admitted to intensive care unit (ICU) and to further co-relate with the need of mechanical ventilation, length of hospital stays, and mortality.

Materials and Methods

This retrospective observational study was conducted at a tertiary care institute in Haryana, India, between March 2020 and September 2020 after taking Institutional Ethical Committee approval for consent waiver. It included 100 consecutive RT-PCR assay confirmed COVID-19 infected patients aged >18 years admitted to 20-bedded dedicated COVID ICU. Being an emerging infectious disease, with retrospective data collection and no novel treatment methods adopted, need for patient consent was waived off by the institutional ethical committee.

Data were collected retrospectively from the patient electronic medical records and were limited largely to demography, clinical, and laboratory parameters at the time of admission along with outcome measure at 28 days of admission. Interventions performed were based on independent decision of the physician in charge. We obtained the following data for each patient: age, gender, presenting clinical symptoms, underlying comorbid diseases (type and number), APACHE-II score, and initial laboratory findings including complete blood count with differential count, organ function involvement—Liver function test [alanine aminotransferase (ALT), aspartate aminotransferase (AST), Albumin], Kidney function test (S. creatinine), and specific set of biomarkers—CRP, LDH, procalcitonin, IL-6 and ferritin], and analyzed with respect to severity of oxygenation defect (partial pressure of oxygen in blood (PaO_2)) and fraction of oxygen in inspired air (FiO_2) ratio <300 or ≥300 mm Hg, need of invasive ventilation, ICU length of stay (LOS), and final outcome on day 28. Further, we compared these variables between intubated and nonintubated patients.

The statistical software SPSS version 24.0 was used in the analysis. For comparison of mean values between two groups, students unpaired *t*-test was used whereas median was used for nonnormally distributed data. Pearson Chi-square test and Pearson correlation tests were used for categorical and scalar data, respectively. Nonparametric tests (Chi-square test and Mann-Whitney test) were used where data were not distributed normally. Logistic regression test was performed wherever applicable. *p*-value less than 0.05 was considered as significant at 95% confidence level whereas value less than 0.01 was considered highly significant.

Results

A total of 100 SARS-COV-19 RT-PCR positive patients admitted to ICU were studied. Demographics including age and sex were compared between low PF ratio (PaO_2/FiO_2 <300 mm Hg) group and high PF ratio group (PaO_2/FiO_2 ≥300 mm Hg). Sex ratio was comparable between two groups whereas age was found significantly higher in low PF ratio group (58.016 ± 15.326 vs 50.974 ± 13.781; $p = 0.023$) (Table 1). Clinically presenting symptoms, comorbidities, and APACHE II score at 24 hours were studied. With respect to presenting symptoms, 77% had fever, 41% had cough, 37% shortness of breath, 26% had sore throat, 9% neurological symptoms, 7% gastrointestinal symptoms, and 2% had genitourinary symptoms. Only shortness of breath was found to be highly significant in low PF ratio group (50% vs 15.78%; $p = 0.001$) (Table 2). Among comorbidities, presence of hypertension was found to be significant (43.54% vs 23.68%; $p = 0{\cdot}045$) in low PF ratio group whereas presence of asthma (1.47% vs 2.85%), CAD (9.67% vs 10.52%), CKD (8.06% vs 5.26%), DM (40.32% vs 23.68%), thyroid (3.22% vs 7.89%), and cancer (3.22% vs 0%) were found to be insignificant. There was no correlation found between comorbidities and ventilator or ICU days. As compared to high PF ratio group, in low PF ratio group, higher APACHE II score (14.90 ± 8.03 vs 7.74 ± 5.70; $p \leq 0.001$), low serum albumin (3.40 ± 0.49 vs 3.63 ± 0.47; $p = 0.021$) though within normal range, longer ICU LOS (11.01 ± 1.41 vs 6.86 ± 1.11; $p = 0.001$), high CRP (171.78 ± 124.45 vs 101.52 ± 88.70; $p = 0.004$), and high ferritin (1677.60 ± 2271.13 vs 643.54 ± 718.68; $p = 0.010$) were significant whereas CK ($p = 0.492$), procalcitonin ($p = 0.564$), LDH ($p = 0.189$), and IL-6 ($p = 0.071$) levels were found insignificant (Fig. 1). On subgroup analysis, APACHE-II was non-normally distributed with significantly higher median APACHE-II score (21 vs 10; $p \leq 0.001$) in mortality group (Fig. 2). Mortality group also showed significantly higher ICU LOS (20.36 ± 9.24 vs 13.69 ± 10.02; $p = 0.022$), high CRP (231.18 ± 134.09 vs 132.24 ± 109.30; $p = 0.005$), ferritin (2804.50 vs 1057.30; $p = 0.003$), IL-6 (414.26 vs 84.68; $p \leq 0.001$) levels. In low PF ratio subgroup analysis, ventilated patients had shown significant results with respect to high APACHE II ($p \leq 0.001$), low albumin ($p = 0.017$), longer ICU LOS ($p \leq 0.001$), high CRP ($p = 0.002$), ferritin ($p = 0.018$), IL-6 ($p = 0.003$) levels. On overall correlation, ventilator days were correlated highly significantly with ICU LOS (Pearson correlation 0.828; $p \leq 0.001$), and mortality (Pearson correlation 0.875; $p \leq 0.001$). ICU LOS also correlated highly significantly with raised CRP (Pearson correlation 0.875; $p \leq 0.001$) and ferritin (Pearson correlation 0.282; $p \leq 0.007$) levels.

Table 1: Showing age, and APACHE II scores at admission

Parameter	*Group*	*N*	*Mean*	*SD*	*Std error of mean*	*p value*
Age	<300	62	58.016	15.326		0.023
	≥300	38	50.974	13.781		
APACHE-II	<300	62	14.90	8.03	1.02	<0.001
	≥300	38	7.74	5.70	0.92	

Table 2: Comparison of sex and presenting complaints between low PF ratio (<300) and high PF ratio (≥300 groups)

		P/F ratio (n)				
		<300	*≥300*	*Total (N)*	*Pearson Chi-square*	*p value*
Sex	Male	50	29	79	0.266	0.606
	Female	12	9	21		
Fever	No	14	9	23	0.016	0.899
	Yes	48	29	77		
Cough	No	39	20	59	1.028	0.311
	Yes	23	18	41		
Sorethroat	No	46	28	74	0.003	0.955
	Yes	16	10	26		
SOB	No	31	32	63	11.829	0.001
	Yes	31	6	37		
Gl symptom	No	56	37	93	1.797	0.18
	Yes	6	1	7		
GU symptom	No	61	37	98	0.125	0.724
	Yes	1	1	2		
Neuro	No	55	36	91	1.045	0.307
	Yes	7	2	9		
Symptoms	0	1	3	4	5.518	0.238
	1	11	9	20		
	2	30	20	50		
	3	20	6	26		

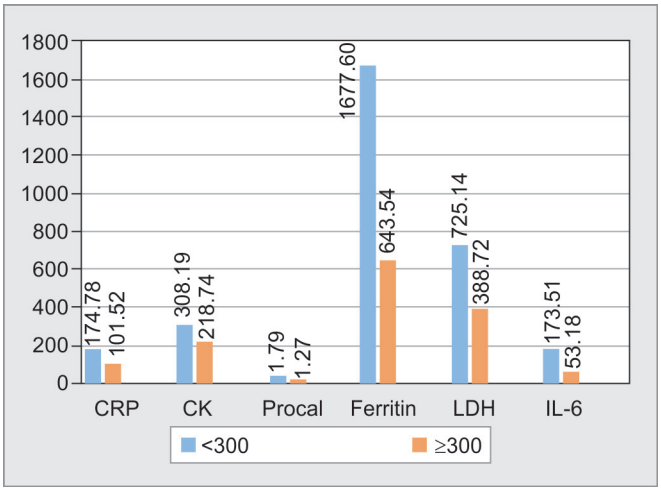

Fig. 1: Comparison between at admission levels of different inflammatory markers among low PF ratio (<300) and high PF ratio (≥300 groups)

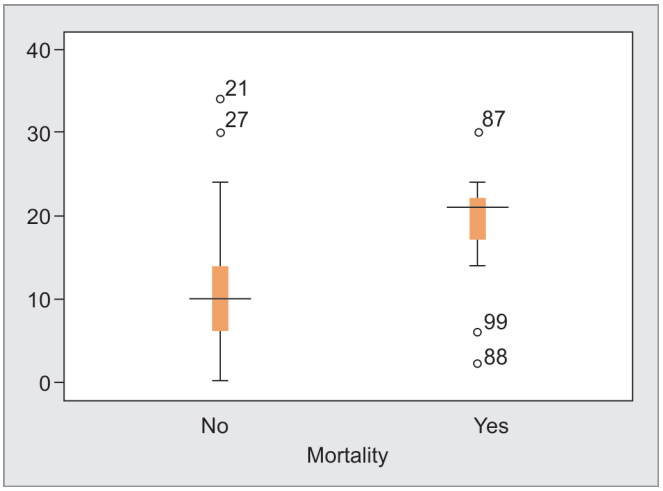

Fig. 2: APACHE-II score stem-and-leaf plot for mortality and nonmortality group

Logistic regression was performed but was not found to be the appropriate model due to fewer entries of some variables. When performed with APACHE II, CRP and ferritin as independent variables taking PF ratio as dependent variable, APACHE-II score was highly significant (OR: 0.875; 95% CI: 0.8082–0.956; $p = 0.003$) while on taking mortality as dependent variable, APACHE-II score (OR: 1.132; 95% CI: 1.026–1.248; $p = 0.013$) and ferritin (OR: 1; 95% CI: 1–1.001; $p = 0.015$) were significant. On adding IL-6, and other independent variables, none was found significant. On Spearman's correlation analysis of nonmortality group, APACHE II score positively correlated with ICU days (Correlation coef. = 0.0453; $p = 0.01$), whereas in mortality group, APACHE II score was negatively correlated with ICU days (Correlation coef. = −0.319).

Discussion

Ever-changing coronavirus strain has been presenting vividly in all parts of the world. It is imperative to know its presentation and effects in Indian population to be able to deal with it in a better way and to aid in exploration of interventions. SARS-CoV-2 uses Angiotensin converting enzyme receptor (ACE-2 receptor) for penetration into cells.[5] Once inside human body, it effects various organ systems causing blend of signs and symptoms, respiratory system being the

most common target. Involvement of lungs involves intermingling of multiple complex mechanisms. Inflammatory response thus triggered, induces cytokine and chemokine production and, hence, the host immune system dysregulation.[3,6,7] Understanding the prime factors associated with worsening of disease may result in early prediction of severity and, thus, guide the therapy and work in moving toward decline in severity curve. We studied the demographics, clinical parameters, as well as set of inflammatory markers in hundred patients admitted to COVID ICU. Older age was found to adversely affect the severity. This may be due to progressive deterioration in immunity/defence response with age.[8] Studies from China suggested higher severity between 50 and 59 years of age whereas Republic of Korea showed bimodal peak.[9,10] There was no gender disparity found with respect to severity of disease though disease-inflicted males were twice as many as females.[11] Though our study was consistent with Wang et al., the results from several studies are inconclusive.[12] Review article postulated hormonal and genetic modulation as the reason for gender disparity in numerous studies but larger studies with vivid ethnicity are required before any reasonable conclusion be given.

Furthermore, presence of hypertensive disorder correlates with severity (27 vs 9%). Association with ACE-2 receptor may be the possible explanation which needs further investigation.[13] Diabetes was present in 36 patients out of which more than twice (25 vs 11) were in low PF ratio group though it was not statistically significant. Review by Yang et al. also suggested that hypertension (17 ± 7%, CI 14–22%) and diabetes (8 ± 6%, CI 6–11%) were the most common comorbid findings in COVID-19 patients.[14] No other comorbidities like respiratory diseases—COPD or asthma, thyroid dysfunction or cancer—have been seen to be significantly affecting the disease severity in Indian population. Moreover, there was no additive impact in presence of two or more comorbidities and no significant impact of any comorbidity on mortality or need of mechanical ventilation. Studies have noticed the negative impact of comorbidities like diabetes mellitus, hypertension, osteoporosis, etc., especially in the third and the most serious phase of the disease, wherein there is systemic hyperinflammation syndrome with its disastrous airflow limitation and cardiac effects.[15]

Fever seems to be the most common symptom in most of the studies with presence even as high as in 91.7% patients.[15] Next common being cough, around 65–82% vs 42% in our study, followed by shortness of breath. Gastrological (2–10%) as well genitourinary symptoms being the last and least presented ones. Our results were in sync with the data from various parts of the world in these terms. In low PF ratio group, shortness of breath was found to be the most significant presenting complaint impacting the need of mechanical ventilation which may be explained by excessive alveolar injury and inflammation. Its association with the inflammatory markers may further be inspected.

There has been hardly any literature on validity of APACHE II score in COVID patients admitted to ICU. On literature search, we found a study on one hundred fifty-four patients by Zao et al., in which they found that APACHE II score more than 17 predicts mortality in coronavirus disease 2019 with sensitivity of 96.15% and specificity of 86.27%.[16] Mean APACHE II score (23.23 ± 6.05) was much higher in mortality group compared with the mean APACHE II score of 10.87 ± 4.40 in survivors (p <0.001). Even as per our data, APACHE II score holds good in coronavirus-afflicted patients in determining the severity or prognosis. In thirty-two ventilated patients, mean APACHE II score was 17.75 ± 7.62 whereas mean APACHE II score in sixty-eight nonventilated patients was 9.56 ± 6.79 ($p \leq 0.001$). Median APACHE II score in mortality group was 21 (IQR-16.25–22.50) with respect to 10 (IQR-5.75–12.50) in nonmortality group ($p \leq 0.001$). Slight variability is found between our data and data in the above study which could be attributed to ethnic variation in baseline parameters but needs more data before conclusion. Our data also showed statistically significant positive correlation between APACHE II score and ICU LOS in nonmortality group which is self-explanatory as higher APACHE II score depicts sicker patients at ICU admission. In mortality cohort, higher APACHE II score correlated negatively with ICU LOS. This can be explained by the fact that severely ill patients died thereby reducing their ICU LOS. Hence, our data support the use of APACHE II score as an important prognostication tool though, may need larger validation randomized trials involving data from various parts of the world to decide upon the cut-off values before its widespread use. Though albumin was within normal range in both the groups, it was significantly lower in low PF ratio group (3.43 ± 0.52 vs 3.76 ± 0.59, $p = 0.001$) depicting its anabolic role. It was equally significant in ventilated vs nonventilated group, although had no significant effect on mortality. If considered as marker of nourishment, we may infer that malnutrition might exaggerate the disease severity. Talking about the inflammatory markers, there have been a plethora of studies with wide range of results. Markers like CRP, ESR, LDH, procalcitonin, IL-6, ferritin, and D-dimer have been studied in various countries, yet hardly any data from India. This study found out that CRP is significantly raised in low PF ratio group, i.e., severe disease. CRP, an acute phase reactant, is elevated during infection or tissue inflammation due to any cause. Various studies in COVID patients have found conflicting results with statistically insignificant results in few studies though with higher mean values. Our study had uniform results as depicted in meta-analysis with significantly high CRP values in severely ill patients. This may be due to more inflammation and tissue damage in this group. Other inflammatory markers like LDH and PCT were also found to be raised in severely ill patients, more so in mechanically ventilated patients.[17] They have cited secondary bacterial infection or progression of disease as the probable explanation. In our study, both LDH and PCT did not show significant difference among two groups. Also, there was no relation with mortality. This may be due to better protection from secondary infections. Studies have postulated that serum ferritin, surrogate marker of stored iron, may be used as biomarker for COVID-19 disease.[18] Ferritin plays a protective role against infection as hypoferremia hinders pathogen functioning by causing iron deprivation.[19] Meta-analysis found out association of serum ferritin with severity of COVID-19 illness though, only 3 out of 16 retrospective studies included, involved ferritin as a marker.[20] This study revealed significantly high admission levels of ferritin in low PF ratio group. They were grossly elevated in ventilated patients and in mortality group signifying its role as early predictor of severity and mortality.[20] Manson et al. also established that higher admission CRP and ferritin levels correlated with severe disease as well as mortality and accounted hyperinflammation for it.[21] When compared between ICU and non-ICU patients, no significant variation was found in serum IL-6 levels among two groups.[22] Whereas within ICU groups, there are many reports of elevated IL-6 in severe cases as well as in mortality groups.[8,23,24] Our study had consistent results where IL-6 levels were significantly higher in low PF ratio group, wherein more so in ventilated group. Also, nonsurvivors had significantly raised IL-6 levels as compared to survivors ($p = 0.021$). Even the meta-analysis found significant

difference in IL-6 levels among survivors and nonsurvivors [WMD = −4.80 ng/mL, 95% CI = (−5.87, −3.73), p <0.001].[20] This may be attributed to high viral load, its replication, and consequent cytokine storm leading to acute lung injury, multi-organ failure, and even death.[25,26] LOS was significantly affected by PF ratios and was significantly higher in low PF ratio group (16.33 ± 10.94 vs 9.63 ± 6.83; p ≤0.001). Need of mechanical ventilation was also significantly lengthening the ICU stay (21.61 ± 12.43 vs 10.22 ± 6.5; p ≤0.001) as well as mortality. Wang et al. also had the similar findings wherein 97% of ventilated patients died.[12] Increased LOS (19.13 ± 10.08 vs 12.46 ± 9.58, p = 0.013) was directly affecting the mortality in our study which could be due to multiple factors—higher APACHE-II, comorbidities, need of mechanical ventilation, secondary infections, etc.

Retrospective type of the study is one of its limitation as may account for data loss, data collection errors, and lack of uniformity in treatment protocol. Large prospective randomized controlled studies are required. Data attrition was another pitfall as values of each variable for every patient were not available. Moreover, successive values of inflammatory markers at various intervals were not available to study the trend with respect to critical events like intubation/extubation or death/discharge. This study opens ground for further research in this direction which will not only help in better understanding of the disease course but may even positively affect the outcome.

To conclude, advancing age and presence of hypertension play an important role in Indian patients in determining disease severity. Whether to determine the severity of disease or to predict mortality for ICU admitted patients, APACHE-II score works well even in case of COVID-19 affected patients. Lastly, higher the levels of inflammatory markers namely CRP, S. ferritin, and IL-6 at the time of admission, lower are the PF ratio, higher is the requirement for mechanical ventilation, and higher is the mortality in COVID-19 ICU patients.

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