International Journal of Advanced Research in Medicine

Dr. Yadvendra Singh
Junior Resident, Department of Respiratory Medicine, SRMS IMS, Bareilly, Uttar Pradesh, India

Dr. Lalit Singh
Professor & Head, Department of Respiratory Medicine, SRMS IMS, Bareilly, Uttar Pradesh, India

Dr. Rajeev Tandon
Associate Professor, Department of Respiratory Medicine, SRMS IMS, Bareilly, Uttar Pradesh, India

Dr. Pradeep Nirala
Assistant Professor, Department of Respiratory Medicine, SRMS IMS, Bareilly, Uttar Pradesh, India

Comparative study of the vital parameters and biomarkers in predicting the outcome of patients in Covid ICU

Dr. Yadvendra Singh, Dr. Lalit Singh, Dr. Rajeev Tandon and Dr. Pradeep Nirala

Abstract
The aim of our study was to evaluate the role of vital parameters and biomarkers in predicting the outcome of patients in Covid ICU.
Material and Methods: In our study among 186 Covid-19 cases admitted in ICU we compared the vital parameters and levels of biomarkers on the day of admission and last day of hospitalisation among those who Expired (Group A) and the survivors (Group B).
Results: The median values of vital parameters were significantly raised on the day of admission in comparison to last day of hospitalisation. Vital parameters worsened among those who expired (Group A) and improved in the survivors (Group B). The levels of biomarkers increased with the duration of hospitalisation among those who expired (Group A) and declined among the survivors (Group B).
Conclusion: The worsening of vital parameters and raised levels of biomarkers is associated with poor outcome and higher mortality.

Keywords: coronavirus diseases, intensive care unit, vital parameters, heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, oxygen saturation, biomarkers, procalcitonin, c-reactive protein, d-dimer, ferritin, lactate dehydrogenase, interleukin-6, mortality

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the zoonotic agent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Human infection began in the late December 2019 in Wuhan, Hubei province, central China and then spread across the globe [1, 2]. Due to the rapid increase in the number of COVID-19 cases and worldwide spread, it was declared as a public health emergency of International Concern on January 30, 2020 by the WHO, and furthered labeled as a pandemic on March 11, 2020 [3, 4]. The clinical presentation of COVID-19 ranges from mild to critically ill. While majority of patients have a mild influenza-like illness and may be asymptomatic, a minority of patients are experiencing severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure, and even death [5] As soon as patients progress to the severity or critical stage, the risk for poor outcomes increases significantly [6]. It is estimated that around 10–15% of mild COVID-19 patients advance to severe, and 15–20% of severe cases progress to become critical, who need treatment in intensive care units (ICU).7 As the number of COVID-19 cases are increasing globally and treatment in ICU has become a major challenge, early identification of severe forms of COVID-19 is crucial for the timely triaging of patients [8]. Severe or critical COVID-19 is strongly linked with mortality [9] and the high mortality rate amongst these cases is linked with SARS-CoV-2 infection-induced hyperinflammation of the innate and adaptive immune systems and the resulting cytokine storm, a cytokine release syndrome (CRS)-like syndrome in severe or critical COVID-19 cases [10-12]. Earlier studies have reported that inflammatory parameters are closely linked to COVID-19 severity and mortality [13-15].

Background: In the ongoing pandemic of covid-19, there has been a lot of debate regarding the role of inflammatory markers in covid-19 patients, especially those who were critically ill. So to support the clinical management it was important to study the trend of inflammatory markers (PCT, CRP, D-dimer, Ferritin, LDH, IL-6) among hospitalised

Corresponding Author:
Dr. Yadvendra Singh
Junior Resident, Department of Respiratory Medicine, SRMS IMS, Bareilly, Uttar Pradesh, India

patients in ICU. The purpose of our study is to see their trend among those who expired and those who survived, which in turn will retrospectively help us to modify our treatment plan.

Aims
1. To compare the vital parameters (Heart Rate, Systolic blood pressure, Diastolic blood pressure, Respiratory rate, and Oxygen saturation) on the day of admission and last day of hospitalisation.
2. To compare the levels of biomarkers (Procalcitonin, C-Reactive Protein, D-dimer, Ferritin, Lactate dehydrogenase and Interleukin-6) on the day of admission and last day of hospitalisation.
3. To compare the vital parameters and levels of biomarkers between patients those who Expired (Group A) and the survivors (Group B).
4. To study the outcome of patients admitted in Covid ICU.

Study design: Prospective observational study
Material and Methods: This study was conducted among 186 confirmed COVID-19 patients admitted in Covid-ICU

of a Level-3 Covid Hospital over a period of 1 yr. In our study, patient population were divided in to two groups, Group A of those who expired and Group B of the survivors. Based on review of case files data, basic demographic data like Age, Sex, and the vital parameters such as Heart Rate (HR), Systolic BP (SBP), Diastolic BP (DBP), Respiratory Rate (RR), Oxygen Saturation (SpO2) on the day of admission and last day of hospitalisation were collected for patients in Group A (Expired) and Group B (Survived). The mean for each parameter was calculated and compared among the two groups and based on which p value was calculated for each parameter undertaken in clinical evaluation. Blood reports of investigations assessing the levels of biomarkers like Procalcitonin (PCT), C-Reactive Protein (CRP), D-dimer, Ferritin, Lactate dehydrogenase (LDH) and Interleukin-6 (IL-6) sent on first day and last day of hospitalisation in covid ICU were collected for Group A (Expired) and Group B (Survived) and master chart was prepared. Further mean value for each inflammatory marker was calculated and compared among both groups. Finally p value was calculated using statistical analysis among both arms for each inflammatory marker and their significance analysed.

Observations and Results

Table 1: Demographics

S. No	Characteristic	Group A Expired (n = 97)	Group B Survived (n = 89)	P value
1	Mean age	62.96 ± 13.89	57.19 ± 13.15	0.004
2	No. of Male patients	75 (77.32)	70 (78.65)	0.86
3	No. of Female patients	22 (22.68)	19 (21.35)	0.83
4	Mean duration of stay	9.03 ± 4.13	12.58 ± 4.14	<0.001

Table 2: Vital Parameters

S. No	Characteristic	Group A Expired (n = 97)	Group B Survived (n = 89)	P value
1	Mean Heart Rate on first day	99.50 ± 20.51	91.86 ± 16.40	0.005
2	Mean Heart Rate on Last day	108.21 ± 31.29	85.85 ± 13.88	<0.001
3	Mean Systolic BP on first day	131.90 ± 21.09	131.03 ± 20.21	0.77
4	Mean Systolic BP on Last day	100.43 ± 25.53	129.13 ± 13.97	<0.001
5	Mean Diastolic BP on first day	78.82 ± 13.65	79.30 ± 11.46	0.80
6	Mean Diastolic BP on Last day	59.54 ± 14.79	78.13 ± 9.41	<0.001
7	Mean RR on first day	30.75 ± 7.20	26.88 ± 8.41	0.0009
8	Mean RR on Last day	24.33 ± 4.15	21.97 ± 2.83	<0.001
9	Median Spo2 on first day	82 (74,86)	88 (84, 93)	<0.001
10	Median Spo2 on last day	86 (78,93)	97 (95, 98)	<0.0001

Table 3: Biomarkers

S. No	Characteristic	Group A Expired (n = 97)	Group B Survived (n = 89)	P value
1	Mean PCT on first day	0.73 (0.24,2)	0.19 (0.12,0.36)	<0.001
2	Mean PCT on last day	1.9 (0.56,7.6)	0.12 (012,0.2)	<0.001
3	Mean CRP on first day	17.57 ± 13.12	12.88 ± 11.67	0.01
4	Mean CRP on last day	18.21 ± 12.85	6.62 ± 8.75	<0.001
5	Median D-Dimer on first day	2440 (1210,8160)	1160 (722,660)	<0.001
6	Median D-Dimer on last day	4270 (1970,9580)	828 (528,1570)	<0.001
7	Median Ferritin on first day	717 (387.8,1247)	438 (187,801.3)	0.0003
8	Median Ferritin on last day	896 (439,1312.4)	396 (184,586)	<0.001
9	Mean LDH on first day	646 ± 314.83	447.21 ± 187.1	<0.001
10	Median LDH on last day	626 (429,800)	348 (250,519)	<0.001
11	Median IL-6 on first day	65.86 (31.13,180)	32 (15.55,61)	<0.001
12	Median IL-6 on last day	109.9 (41.2, 465.17)	18.48 (8, 49)	<0.001

Discussion
Out of the 200 patient admitted in Covid ICU, 14 patient went LAMA and were excluded from the study. The study population comprised of 186 confirmed Covid-19 cases,

among which those expired (Group A) were 97, and those who survived (Group B) were 89.
The mean Age of expired patients was 62.96 ± 13.89 yrs, and that of survivors was 57.19 ± 13.15 yrs and the

difference was statistically significant (p value = 0.004). This showed that the elderly population (> 60 yrs age) had higher susceptibility and mortality to covid-19 infection. This finding was similar to that of the study conducted by Kayina CA *et al*. [16] in 2020 among 235 adult patients, where mean age of patients was 50.7±15.1 yrs. Also it was similar to that of the study conducted by Chen N *et al*. [17] in 2020 among 99 patients, where the mean age was 55·5 years (SD 13·1).

Among those expired in Group A, Males were 75 (77.32 %) and females were 22 (22.68 %), with male: female ratio of 3.4: 1.0; whereas among those survived in Group B, Males were 70 (78.65 %) and females were 19 (21.35 %), with male: female ratio of 3.6: 1.0. In both groups, Males were predominantly involved. This finding was similar to that of the study conducted by Kayina CA *et al*. [16] in 2020 among 235 adult patients, where 160 of 235 patients (68.1 %) per

cent were males and 75 of 235 (31.9%) were females. Also it was similar to that of the study conducted by Chen N *et al*. [17] in 2020 among 99 patients, where they found that 67 of 99 patients (67.6%) were males and 32 of 99 patients (32.4%) were females.

Further the mean duration of hospitalisation among those expired was 9.03 ± 4.13 days whereas among those survived was 12.58 ± 4.14 days, and the difference was statistically significant (p value < 0.001). This finding was similar to that of study conducted by Serafim RB *et al*. [18] in 2020 among 69093 patient admitted in ICU where they found that the median ICU length of stay was 9 days (95%CI 6.5-11.2 days). Also these findings were similar to that of the study conducted by Larsson E *et al*. [19] in 2021 among 198 patients admitted in ICU, where the mean duration of stay was 12 days (IQR, 6-18 days).
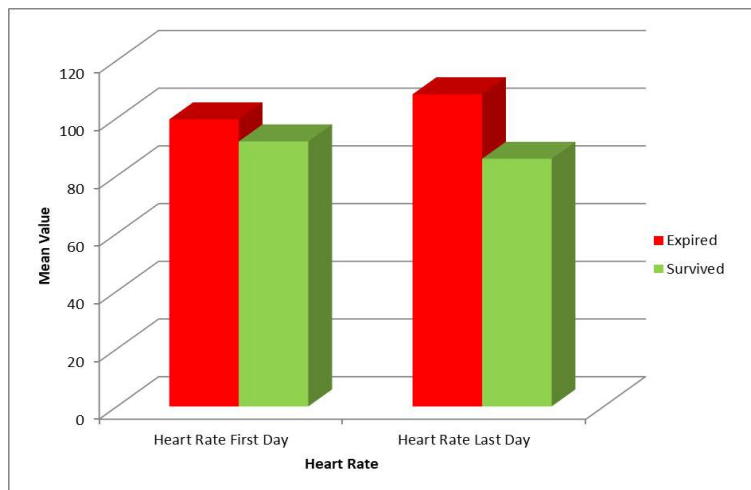

Graph 1: Heart Rate (beats per minute) on day of admission and last day of Hospitalisation

The mean Heart Rate on day of admission was 99.50 ± 20.51 bpm among those expired and 91.86 ± 16.40 bpm in those survived, and the difference was statistically significant (p value = 0.005). The mean Heart Rate on last day of hospitalisation was 108.21 ± 31.29 bpm among those expired and 85.85 ± 13.88 bpm in those survived, and the difference was statistically significant (p value = 0.001). The results were similar to that of study conducted by Chen

Q *et al*. [20] in 2020 among 39 severe and 15 critically ill patients in ICU, where they found that sinus tachycardia was seen in 23 out of 39 (59.0%) severe patients and 15 out of 15 (100%) critically ill patients. These findings were also similar to that of the study conduceted by Cecconi M *et al*. [21] in 2020 among 238 patients, where the mean Heart Rate was 82 ± 14 bpm.
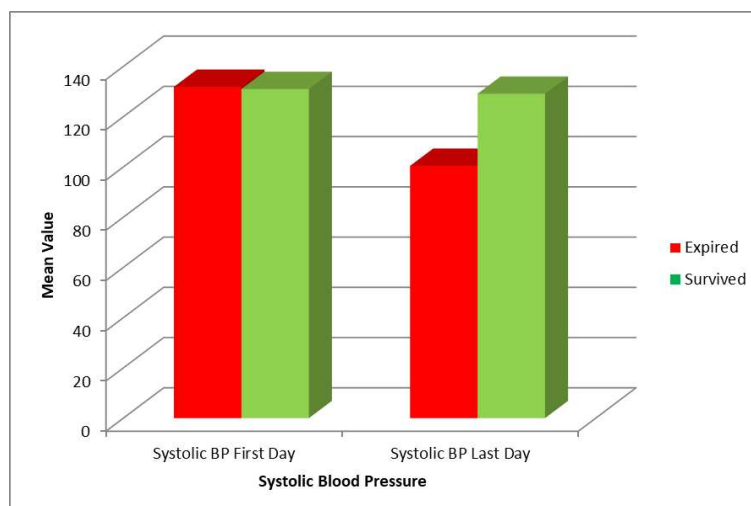
Graph 2: Systolic BP (mm Hg) on day of admission and last day of Hospitalisation
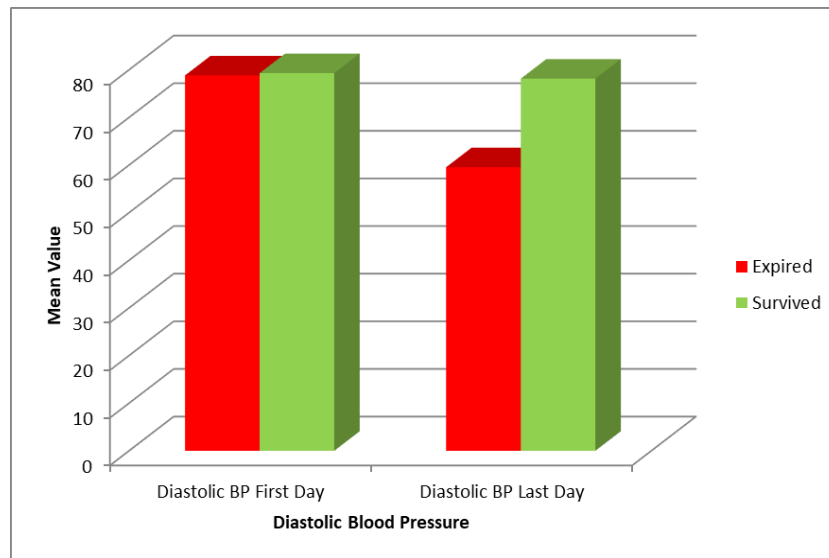
Graph 3: Diastolic BP (mm Hg) on day of admission and last day of Hospitalisation

The mean Systolic BP on day of admission was 131.90 ± 21.09 mm Hg among those expired and 131.03 ± 20.21 mm Hg in those survived, and the difference was not statistically significant (p value = 0.77). The mean Systolic BP on last day of hospitalisation was 100.43 ± 25.53 mm Hg among those expired and 129.13 ± 13.97 mm Hg in those survived, and the difference was statistically significant (p value < 0.001).

The mean Diastolic BP on day of admission was 78.82 ± 13.65 mm Hg among those expired and 79.30 ± 11.46 mm Hg in those survived, and the difference was not statistically significant (p value < 0.80). The mean Diastolic BP on last day of hospitalisation was 59.54 ± 14.79 mm Hg among those expired and 78.13 ± 9.41 mm Hg in those survived, and the difference was statistically significant (p value < 0.001). These finding were similar to that of the study conducted by Ran J et al. [22] in 2020 among 803 patients,

where they found that the mean SBP and DBP on admission were 137.0 mmHg (±19.7) and 84.2 mmHg (±12.8), respectively.

Also these results were similar to that of the study conducted by Chen T et al. [23] in 2020 among 274 patients, where they found that the median systolic blood pressure was significantly higher in 113 deceased patients 137 mm Hg (IQR : 122.0 - 147.0) than 161 recovered patients 125 mm Hg (IQR : 115.5 - 136.0). However this finding was contradictory to that of study conducted by E. Christiaan Boerma et al. [24] in 2021 among 28 mechanically ventilated covid-19 patients where they found that the mean arterial pressure increased from 77 ± 10 mmHg on day 1 to 84 ± 9 mmHg on day 21 (p = 0.04), in combination with the rapid tapering and cessation of norepinephrine and the gradual use of antihypertensive drugs in the vast majority of patients.
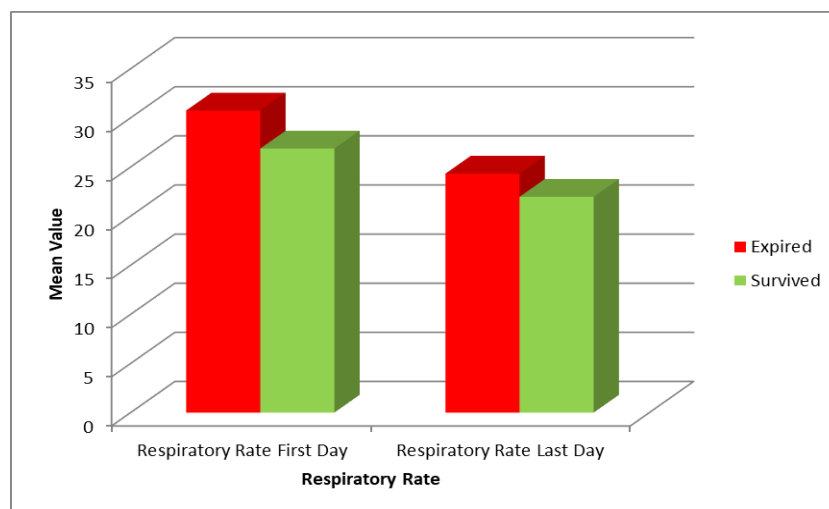
Graph 4: Respiratory Rate (breaths per minute) on day of admission and last day of Hospitalisation

The mean Respiratory Rate on day of admission was 30.75 ± 7.20 breaths per min among those expired and 26.88 ± 8.41 breaths per min in those survived, and the difference was statistically significant (p value < 0.0009). The mean Respiratory Rate on last day of hospitalisation was 24.33 ± 4.15 breaths per min among those expired and 21.97 ± 2.83 breaths per min in those survived, and the difference was

statistically significant (p value < 0.001). These results suggested that higher respiratory rate at presentation was associated with higher mortality. This finding was similar to that of the study conducted by Bahl A et al. [25] among 1461 patient where the median admission respiratory rate was 21.0 (IQR 19.0 - 24.0) for survivors and 24.0 (IQR 21.0 - 28.0) for non-survivors, respectively (p < 0.001).

Graph 5: Oxygen Saturation (SpO2 in %) on day of admission and last day of Hospitalisation

The Median SpO2 levels along with its interquartile range in Group A (Expired) versus Group B (Survivors) on day of admission was 82% (IQR: 74 - 86) and 88% (IQR: 84 - 93), and the difference was statistically significant (p value < 0.001). The Median SpO2 levels along with its interquartile range in Group A (Expired) versus Group B (Survivors) on last day of hospitalisation was 86 % (IQR: 78 - 93) and 97 % (IQR: 95 - 98), and the difference was statistically significant (p value < 0.0001). This finding was similar to that of study conducted by Ferrando C *et al*. [26] in 2020 among 663 patient admitted in ICU where they found that non-survivors were more hypoxemic with, median SpO_2 of 90 % (IQR 83-93) in comparison to survivors with median SpO2 of 91% (IQR 87-94); (p <0.001).
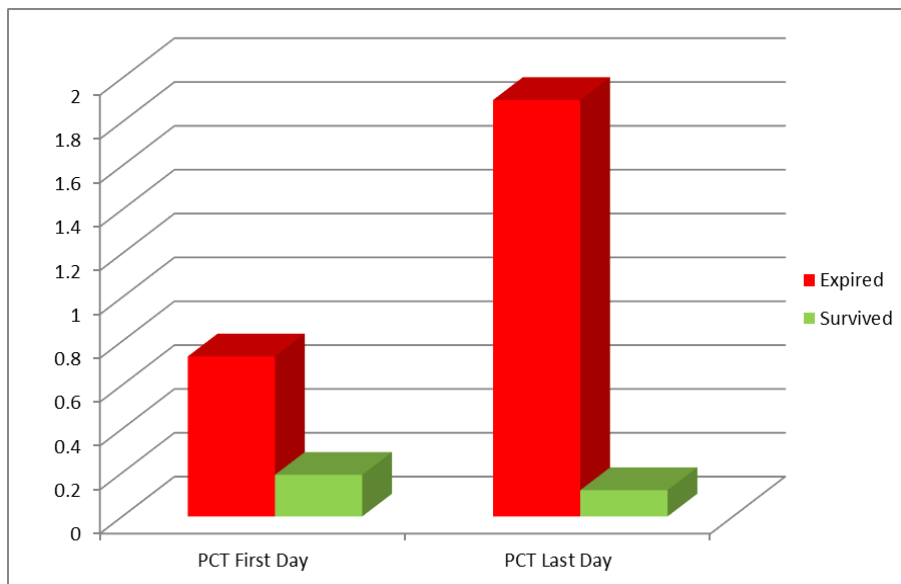
Graph 6: PCT (ng/ml) on day of admission and last day of Hospitalisation

The Median PCT levels along with along with its interquartile range in Group A (Expired) versus Group B (Survivors) on day of admission was 0.73 ng/ml (IQR: 0.24 – 2.0) and 0.19 ng/ml (IQR : 0.12 - 0.36), the difference was statistically significant (p value < 0.001). The Median PCT levels along with along with its interquartile range in Group A (Expired) versus Group B (Survivors) on last day of hospitalisation was 1.9 ng/ml (IQR: 0.56 - 7.6) and 0.12 ng/ml (IQR : 012 - 0.2), the difference was statistically significant (p value < 0.001). This finding was similar to that of study conducted by Hu R *et al*. [27] in 2020 among 95 Covid patients, where they found that the mean serum procalcitonin (PCT) levels were over four times higher in severe patients than in moderate patients and were over eight times higher in critical patients than in moderate patients. For discharged patients, both high-normal PCT levels and abnormal PCT levels decreased during recovery. However, in death cases, serum levels of PCT increased as the disease worsened.
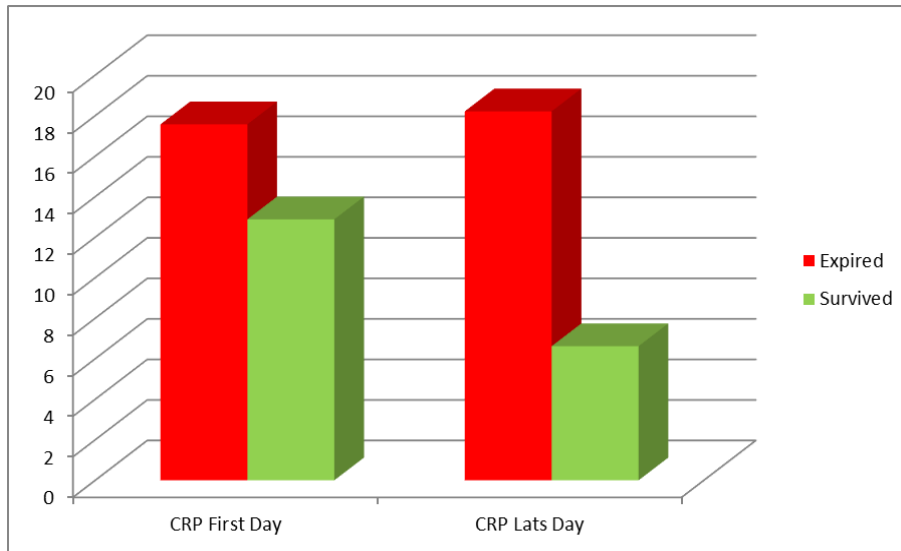
Graph 7: CRP (mg/dl) on day of admission and last day of Hospitalisation

The Mean CRP levels on day of admission was 17.57 ± 13.12 mg/dl among those who expired and 12.88 ± 11.67 mg/dl among those survived, but the difference was not statistically significant (p value < 0.01). The mean CRP levels on last day of admission was 18.21 ± 12.85 mg/dl among those who expired and 6.62 ± 8.75 mg/dl among those survived, further the difference was statistically significant (p value < 0.001). The results were similar to that of studies conducted by Sharifpour M *et al*. [28] in 2020 where they found that the median CRP was significantly higher amongst the patients who died, compared to those who survived [206 mg/L (IQR: 157–288 mg/L) vs 114 mg/L (IQR : 72–160 mg/L), *p<0.001*].
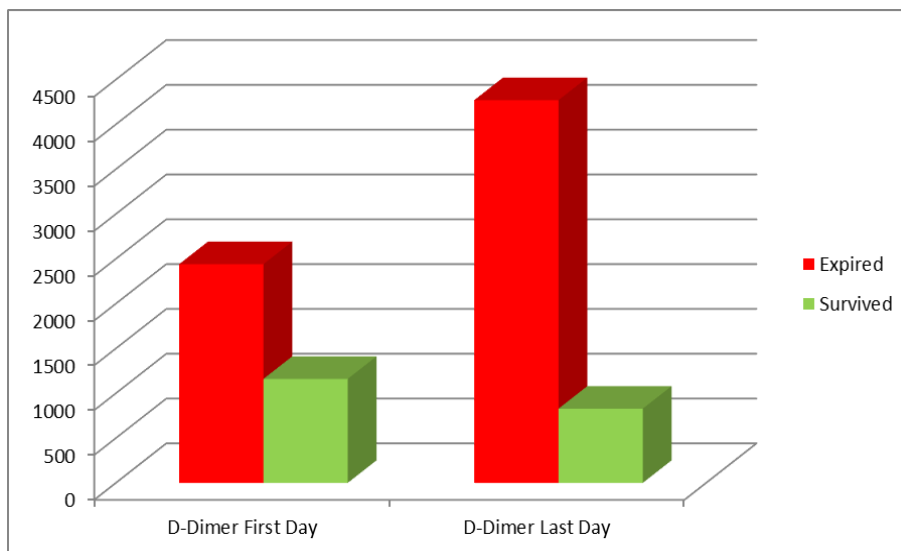
Graph 8: D-dimer (mcg/L) on day of admission and last day of Hospitalisation

The Median D-dimer levels along with its interquartile range in Group A (Expired) versus Group B (Survivors) on day of admission was 2440 mcg/L (IQR : 1210 - 8160) and 1160 mcg/L (IQR : 722 - 660), and the difference was statistically significant (p value < 0.001). The Median D-dimer levels along with its interquartile range in Group A (Expired) versus Group B (Survivors) on last day of admission was 4270 mcg/L (IQR : 1970 - 9580) and 828 mcg/L (IQR : 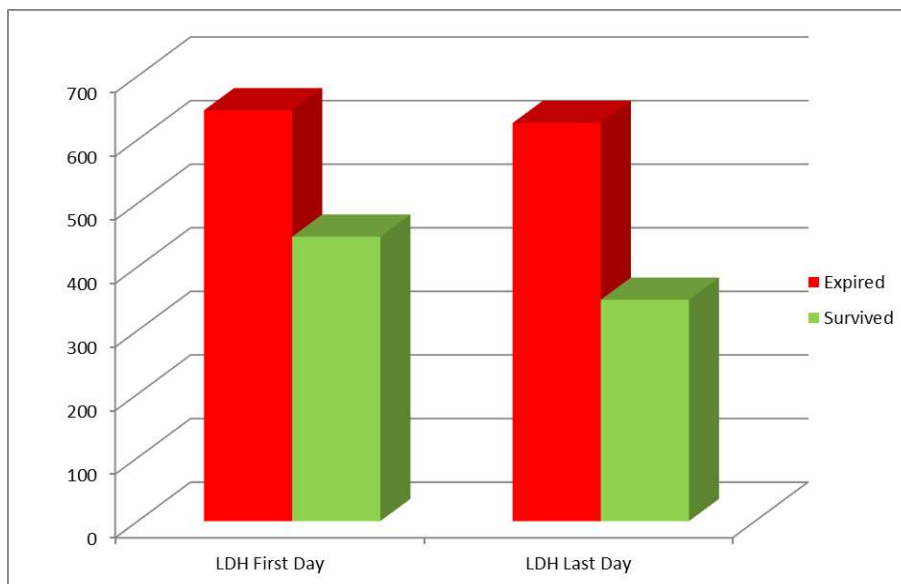528 - 1570), and the difference was statistically significant (p value < 0.001). These results were similar to that of the study conducted Zhang L *et al*. [29] in 2020 among 334 patients. Out of these 67 patients had D-dimer ≥2000 mcg/L, and 267 patients with D-dimer <2000 mcg/L on admission. During hospitalisation 13 deaths occurred. On analysis patients with D-dimer levels ≥2000 mcg/L had a higher incidence of mortality when comparing with those who with D-dimer levels <2000 mcg/L (12/67 vs 1/267, *P* < 0.001).
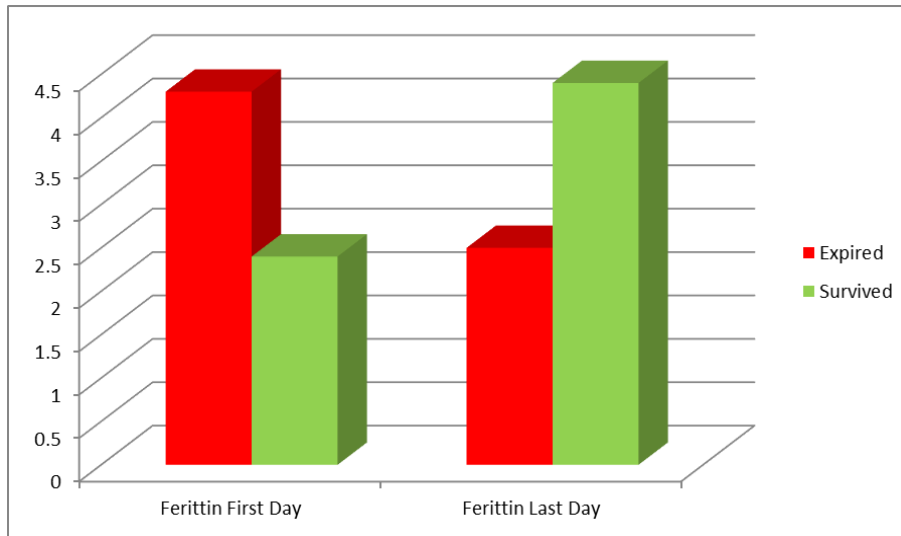
Graph 9: Ferritin (ng/ml) on day of admission and last day of Hospitalisation

The Median Ferritin levels along with its interquartile range in Group A (Expired) versus Group B (Survivors) on day of admission was 717 ng/ml (IQR: 387.8 - 1247) and 438 ng/ml (IQR: 187 - 801.3), and the difference was statistically significant (p value < 0.0003). The Median Ferritin levels along with its interquartile range in Group A (Expired) versus Group B (Survivors) on last day of hospitalisation was 896 ng/ml (IQR: 439 - 1312.4) and 396 ng/ml (IQR: 184 - 586), and the difference was statistically significant (p value < 0.001). These findings were similar to those of the meta-analysis study conducted by Cheng L *et al*. [30] in 2020 among 10614 patients where they found that the ferritin level was significantly increased in severe patients compared with the level in non-severe patients [Mean difference 397.77 (95% CI 306.51-489.02), *P* <.001]. Non-survivors had a significantly higher ferritin level compared with the one in survivors [Mean 677.17 (95% CI 391.01-963.33), *P* <.001]. Also in study conducted by Dahan S *et al*. [31] in 2021 among 39 patients it was found that severe patients had significantly higher levels of ferritin (2817.6 ng/ml) than non-severe patients (708.6 ng/ml) (p = 0.02).

Graph 10: LDH (IU/L) on day of admission and last day of Hospitalisation

The Mean LDH levels on day of admission was 646 ± 314.83 IU/L among those who expired and 447.21 ± 187.1 IU/L among those survived, and the difference was statistically significant (p value < 0.001). The median LDH levels along with its interquartile range in Group A (Expired) versus Group B (Survivors) on last day of hospitalisation was 626 IU/L (IQR : 429 - 800) and 348 IU/L (IQR : 250 - 519), and the difference was statistically significant (p value < 0.001). These findings were similar to that of the study conducted by Dong X *et al*. [32] among 119 patients where they found that the mean LDH among 54 patient who expired was significantly higher (559.5 IU/L) (IQR : 172 - 7575) than 65 patients who survived (228 IU/L) (IQR : 117 - 490). Also in study conducted by J. Hari Kishan *et al*. [33] in 2020 among 108 patients, they found that there was a significant association between outcome and serum LDH levels. Among subjects with normal LDH levels (140 to 280 U/L), 21.1% required O2 and 5.3% were intubated, further among subjects with increased LDH levels (>280 U/L), 47.7% required O2, 27.3% required NIV and 4.5% were intubated.
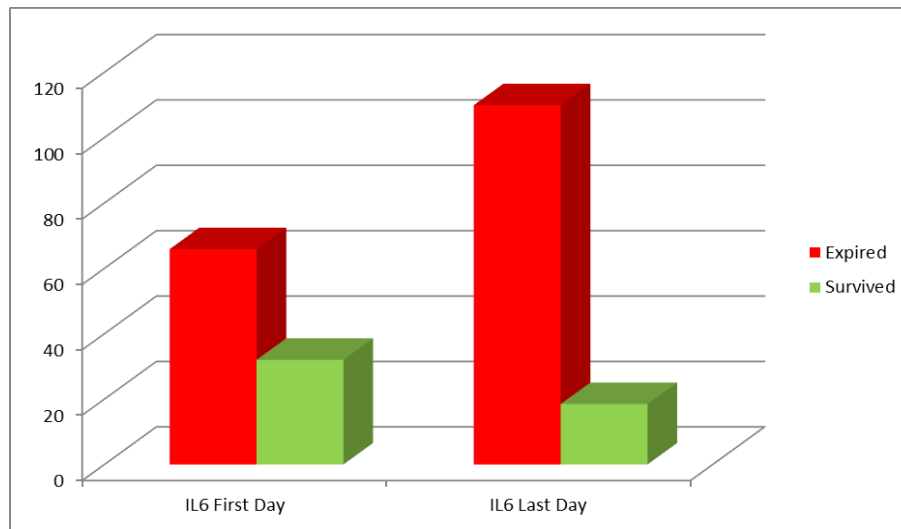
Graph 11: IL-6 (pg/ml) on day of admission and last day of Hospitalisation

The Median IL-6 levels along with its interquartile range in Group A (Expired) versus Group B (Survivors) on day of admission was 65.86 pg/ml (IQR: 31.13 - 180) and 32 pg/ml (IQR: 15.55 – 61.0), and the difference was statistically significant (p value < 0.001). The median IL-6 levels along with its interquartile range in Group A (Expired) versus Group B (Survivors) on last day of hospitalisation was 109.9 pg/ml (IQR: 41.2 - 465.17) and 18.48 pg/ml (IQR: 8.0 – 49.0), and the difference was statistically significant (p value < 0.001). These findings are similar to the results of comparative study conducted by Guirao JJ *et al*. [34] in 2020 among 50 patients of which survivors were 36 and those expired were 14. The mean IL-6 value among survivors was 24.31 ± 9.90 pg/ml and in those expired was 166.46 ± 97.36 pg/ml, and the difference was significant (p = 0.003). Similar findings were seen in the study conducted by Jurado A *et al*. [35] in 2020 among 178 severe patients, wherein the Median IL-6 levels along with its interquartile range on the day of admission, 87.45 pg/ml (IQR : 30.4 – 239.7) were significantly higher than that on discharge 24.86 pg/ml (IQR : 9.1 – 59.63).

Conclusion
On comparison of the two arms of study, clinical parameters such as Heart Rate, Systolic Blood Pressure, Respiratory Rate and Oxygen Saturation on the day of admission had significant difference among those who expired (Group A) versus the Survivors (Group B), further the raised levels in Expired group corresponded with the severity, poor outcome and higher mortality in critically ill patients in ICU. In addition to clinical parameters, the raised levels of biomarkers such as PCT, CRP, D-dimer Ferritin, LDH and IL-6 in the expired patients in comparison to the survivors on the day of admission and subsequently compared with those of the last day of hospitalisation are reliable indicator of progression towards severity, poor prognosis and outcome.

Key Message: As per our evidence based study, the elevated levels of biomarkers (PCT, CRP, D-dimer, Ferritin, LDH, IL-6) have significant association with mortality and poor outcome, and play an important role in deciding the severity and prognosis in Covid-19 patients. Hence they should be repeated at appropriate intervals to take a decision as to when to escalate or descalate the treatment and choose further line of management.

References
1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273. doi: 10.1038/s41586-020-2012-7. Epub 2020 Feb 3. PMID: 32015507; PMCID: PMC7095418.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J *et al*. China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733. doi: 10.1056/NEJMoa2001017. Epub 2020 Jan 24. PMID: 31978945; PMCID: PMC7092803.
3. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). Geneva, Switzerland 2020. Available on https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov).
4. World Health Organization; 2020. Coronavirus disease (COVID-2019) Situation Reports. Available on https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513. doi: 10.1016/S0140-6736(20)30211-7. Epub 2020 Jan 30. PMID: 32007143; PMCID: PMC7135076.
6. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H *et al*. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-481. doi: 10.1016/S2213-2600(20)30079-5. Epub 2020 Feb 24. Erratum in: Lancet Respir Med. 2020;8(4):e26. PMID: 32105632; PMCID: PMC7102538.

7. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239-1242. doi: 10.1001/jama.2020.2648. PMID: 32091533.

8. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. Int J Infect Dis. 2020;95:304-307. doi: 10.1016/j.ijid.2020.04.061. Epub 2020 Apr 25. PMID: 32344011; PMCID: PMC7194601.

9. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet. 2020;395(10229):1014-1015. doi: 10.1016/S0140-6736(20)30633-4. Epub 2020 Mar 17. PMID: 32197108; PMCID: PMC7138151.

10. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395(10239):1763-1770. doi: 10.1016/S0140-6736(20)31189-2. Epub 2020 May 19. PMID: 32442528; PMCID: PMC7237188.

11. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020;368(6490):473-474. doi: 10.1126/science.abb8925. Epub 2020 Apr 17. PMID: 32303591.

12. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017;39(5):529-539. doi: 10.1007/s00281-017-0629-x. Epub 2017 May 2. PMID: 28466096; PMCID: PMC7079893.

13. Chen R, Sang L, Jiang M, Yang Z, Jia N, Fu W et al. Medical Treatment Expert Group for COVID-19. Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. J Allergy Clin Immunol 2020;146(1):89-100. doi: 10.1016/j.jaci.2020.05.003. Epub 2020 May 11. PMID: 32407836; PMCID: PMC7212968.

14. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y et al. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020;71(15):762-768. doi: 10.1093/cid/ciaa248. PMID: 32161940; PMCID: PMC7108125.

15. Mahat RK, Panda S, Rathore V, Swain S, Yadav L, Sah SP. The dynamics of inflammatory markers in coronavirus disease-2019 (COVID-19) patients: A systematic review and meta-analysis. Clin Epidemiol Glob Health 2021;11:100727. doi: 10.1016/j.cegh.2021.100727. Epub 2021 Mar 20. PMID: 33778183; PMCID: PMC7979575.

16. Kayina CA, Haritha D, Soni L, Behera S, Nair PR, Gouri M et al. Epidemiological & clinical characteristics & early outcome of COVID-19 patients in a tertiary care teaching hospital in India: A preliminary analysis. Indian J Med Res 2020;152(1,2):100-104. doi: 10.4103/ijmr.IJMR_2890_20. PMID: 32811801; PMCID: PMC7853262.

17. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507-513. doi: 10.1016/S0140-6736(20)30211-7. Epub 2020 Jan 30. PMID: 32007143; PMCID: PMC7135076.

18. Serafim RB, Póvoa P, Souza-Dantas V, Kalil AC, Salluh JIF. Clinical course and outcomes of critically ill patients with COVID-19 infection: A systematic review. Clin Microbiol Infect 2021;27(1):47-54. doi: 10.1016/j.cmi.2020.10.017. Epub 2020 Oct 23. PMID: 33190794; PMCID: PMC7582054.

19. Larsson E, Brattström O, Agvald-Öhman C, Grip J, Campoccia Jalde F, Strålin K et al. Karolinska Intensive Care COVID-19 Study Group. Characteristics and outcomes of patients with COVID-19 admitted to ICU in a tertiary hospital in Stockholm, Sweden. Acta Anaesthesiol Scand 2021;65(1):76-81. doi: 10.1111/aas.13694. Epub 2020 Sep 15. PMID: 32892337; PMCID: PMC7756749.

20. Chen Q, Xu L, Dai Y, Ling Y, Mao J, Qian J et al. Cardiovascular manifestations in severe and critical patients with COVID-19. Clin Cardiol 2020;43(7):796-802. doi: 10.1002/clc.23384. Epub 2020 Jun 20. PMID: 32562427; PMCID: PMC7323347.

21. Cecconi M, Piovani D, Brunetta E, Aghemo A, Greco M, Ciccarelli M et al. Early Predictors of Clinical Deterioration in a Cohort of 239 Patients Hospitalized for Covid-19 Infection in Lombardy, Italy. J Clin Med 2020;9(5):1548. doi: 10.3390/jcm9051548. PMID: 32443899; PMCID: PMC7290833.

22. Ran J, Song Y, Zhuang Z et al. Blood pressure control and adverse outcomes of COVID-19 infection in patients with concomitant hypertension in Wuhan, China. Hypertens Res 2020;43:1267-1276. https://doi.org/10.1038/s41440-020-00541-w.

23. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ 2020;368:m1091. doi: 10.1136/bmj.m1091. Erratum in: BMJ 2020;368:m1295. PMID: 32217556; PMCID: PMC7190011.

24. Christiaan Boerma E, Carina Bethlehem, Franciena Stellingwerf, Fellery de Lange, Koen W Streng, Peter M Koetsier et al. Hemodynamic Characteristics of Mechanically Ventilated COVID-19 Patients: A Cohort Analysis. Critical Care Research and Parctice 2021.

25. Bahl A, Van Baalen MN, Ortiz L, Chen NW, Todd C, Milad M et al. Early predictors of in-hospital mortality in patients with COVID-19 in a large American cohort. Intern Emerg Med 2020;15(8):1485-1499. doi: 10.1007/s11739-020-02509-7. Epub 2020 Sep 24. PMID: 32970246; PMCID: PMC7512216.

26. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Bordell A et al. de la Red de UCI Española para COVID-19. Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: A prospective, cohort, multicentre study. Rev Esp Anestesiol Reanim (Engl Ed) 2020;67(8):425-437. English. doi: 10.1016/j.redar.2020.07.003. Epub 2020 Jul 13. PMID: 32800622; PMCID: PMC7357496.

27. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. Int J Antimicrob Agents 2020;56(2):106051. doi: 10.1016/j.ijantimicag.2020.106051. Epub 2020 Jun 10. PMID: 32534186; PMCID: PMC7286278.

28. Sharifpour M, Rangaraju S, Liu M, Alabyad D, Nahab FB *et al*. C-Reactive protein as a prognostic indicator in hospitalized patients with COVID-19. PLOS ONE 2020;15(11):e0242400.

29. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z *et al*. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020;18(6):1324-1329. doi: 10.1111/jth.14859. PMID: 32306492; PMCID: PMC7264730.

30. Cheng L, Li H, Li L, Liu C, Yan S, Chen H *et al*. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal 2020;34(10):e23618. doi: 10.1002/jcla.23618. Epub 2020 Oct 19. PMID: 33078400; PMCID: PMC7595919. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci 2020;57(6):389-399. doi: 10.1080/10408363.2020.1770685. Epub 2020 Jun 5. PMID: 32503382; PMCID: PMC7284147.

31. Dahan S, Segal G, Katz I, Hellou T, Tietel M, Bryk G *et al*. Ferritin as a Marker of Severity in COVID-19 Patients: A Fatal Correlation. Isr Med Assoc J 2020;22(8):494-500. PMID: 33236582.

32. Dong X, Sun L, Li Y. Prognostic value of lactate dehydrogenase for in-hospital mortality in severe and critically ill patients with COVID-19. Int J med Sci 2020;17(14):2225-2231.doi:10.7150/ijms.47604.

33. Dr. Hari Kishan J, Dr. Karthikeya Byalya, Dr. Sharvan Kumar V. Serum ferritin, serum LDH and d-dimer in correlation with the outcome in Covid-19. Int J Med Res Rev [Internet]. 2021Feb.28 [cited 2021;9(1):46-3.

34. Guirao JJ, Cabrera CM, Jiménez N, Rincón L, Urra JM. High serum IL-6 values increase the risk of mortality and the severity of pneumonia in patients diagnosed with COVID-19. Mol Immunol 2020;128:64-68. doi: 10.1016/j.molimm.2020.10.006. Epub 2020 Oct 14. PMID: 33075636; PMCID: PMC7556792.

35. Jurado A, Martín MC, Abad-Molina C *et al*. COVID-19: age, Interleukin-6, C-reactive protein, and lymphocytes as key clues from a multicentre retrospective study. Immun Ageing 2020;17:22.