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Original Research Paper

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# A PRELIMINARY STUDY TO IDENTIFY SEVERITY OF COVID-19 USING COMBINED LABORATORY PARAMETERS

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## ABSTRACT

**BACKGROUND:** As the coronavirus disease 2019 (COVID-19) pandemic rages on, there is an urgent need to identify clinical and laboratory predictors for progression towards severe and fatal forms of illness.So this study is aimed to analyse the ability of haematological and inflammatory parameters for predicting the severity in COVID-19 patients.

**METHODS:** This was a retrospective study of 120 patients with confirmed COVID-19. Clinical histories of these patients were taken, and the patients are categorized into mild group and severe group. The baseline demographic indicators like age, gender and laboratory indicators like WBC count, Neutrophil to lymphocyte ratio (NLR), D-dimer, CReactiveProtein(CRP), Prothrombin Time(PT), APTT,LDH were collected, analysed and compared between the two groups.

**RESULTS:** The mean age of the severe group was higher than that of mild group. White blood cell count, Neutrophil to lymphocyte ratio (NLR), D-dimer, and CRP levels were significantly higher in the severe group. Furthermore, compared to the mild group, total bilirubin, AST, ALT, and LDH were significantly higher and serum albimun was lower in the severe group. PT, APTT and INR were significantly prolonged in the severe group.

**CONCLUSION:** As the severity of COVID-19 increases, there is an abnormal increase in the rate of hematological and inflammatory parameters. Especially, an elevated Neutrophil to lymphocyte ratio may indicate that the disease was progressing towards exacerbation. Age > 65 years, Neutrophil to lymphocyte ratio, CRP, D-dimer were independent predictors of severity.

**KEYWORDS :** COVID-19, Neutrophil lymphocyte ratio, inflammatory parameters, mild group, severe group.

## INTRODUCTION

Coronavirus disease 19 (COVID-19), caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-COV-2), emerged in late December 2019 and rapidly evolved into an ongoing global pandemic.[1] Till date, more than one seventy-five million people have succumbed to infection.[2] SARS-COV-2 is a member of the -coronavirus family.[3] It has a single strand positive RNA with a large genome. Under the electron microscope, the virus looks like solar corona due to the club-shaped spikes, hence the name coronavirus. For the diagnosis of COVID-19, the standard method is the nucleic acid Real-TIme polymerase reaction chain (RT-PCR).[4]

In COVID-19 infection, leucocytes play a significant role in defence mechanism and thus provide an immune response. There will be an increase in the number of neutrophils to destroy the cell wall of the virus and for the disruption of its structure by the release of free radicals. There will also be a decrease in the number of lymphocytes due to the increase in the levels of cytokines like Interleukins and Tumor necrosis factor-α, which promote lymphocyte apoptosis.[5] .Thus there is an increase in the Neutrophil Lymphocyte Ratio (NLR). There is an excessive immune response & uncontrolled release of cytokines & chemokines in severe patients. Platelets, which have a significant role in hemostasis, coagulation and maintenance of vascular integrity, have been reported to be decrease in Covid-19 patients.[6]

The clinical features of Covid-19 range from mild to moderate upper respiratory tract infection to severe systemic infection involving many systems especially respiratory and also cardiovascular, immunological, hematopoietic, gastrointestinal and neurological systems[7]. In most of the confirmed covid-19 patients, there have been fluctuations in the various laboratory parameters like renal function tests, liver function tests, biochemical, coagulation, inflammatory and hemocytometric parameters[8].

As Covid-19 is associated with a higher mortality rate within a short span of time, to reduce mortality and improve the allocation of limited hospital resources, identification of early biomarkers like CRP, LDH, serum ferritin, D-dimer is essential to predict disease severity[9,10]. For the treatment decisions and for predicting the severity of Covid-19 haematological parameters, including complete blood cell counts and coagulation profile, have gained significance[7].

In this study, a combination of laboratory tests along with presenting symptoms have been evaluated to show the hyperinflammatory state and to predict the severity of the disease.

## STUDY DESIGN:

This is a retrospective study done on 120 confirmed Covid-19 patients hospitalised in a tertiary care centre from 20th April 2021 to 30th May 2021.

## PATIENTS:

A positive real-time polymerase chain test (RT-PCR) is taken as a confirmed case of Covid-19. Complete history, including age, gender, duration of symptoms and baseline saturation, were taken for all the patients included in the study.

## INCLUSION & EXCLUSION CRITERIA:

The individuals who were tested positive for SARS-COV-2 according to the WHO guidelines for detection and diagnosis of Covid-19 were included in this study.

Individuals with missing data were excluded from the study.

## DATA EXTRACTION AND COLLECTION:

These patients were categorized into mild (asymptomatic & patients with mild symptoms, $SpO_2$ > 94% @ Room air and Respiratory rate <24/min.), moderate ( symptoms with mild to moderate pneumonia with no signs of severe disease, $SpO_2$90 – 94% @ room air and respiratory rate 24–30/min.) and severe

group ( symptomatic patients with severe pneumonia with respiratory rate >30/min, $SpO_2$ < 90% @ room air) accordingly.

All the laboratory parameters including WBC, neutrophil count, lymphocyte count, platelet count, D-dimer, CRP, PT, APTT, INR, renal function tests, liver function tests and LDH were collected.

NLR was calculated as the ratio of absolute neutrophil count to the absolute lymphocytic count.

## STATISTICAL ANALYSIS:

Statistical analyses were performed using SPSS trial version 26. Descriptive statistics were used to summarize the data. Mean and Standard deviation was used for the comparision of continuous variables, ensuring normal distribution. An independent sample t-test was applied to compare mild/moderate group biochemical and haematological findings to severe group Covid-19 patients. P-value of <0.05 was considered statistically significant.

## RESULTS:

### Characteristics of study population:

Of the 120 confirmed cases of Covid-19 reviewed, 71 were males and 49 were females(Fig 1). The age distribution ranging from 18 to 85 years old. In our study there were 86 patients in mild/moderate and 34 patients in severe group(Fig 2). The median age of mild/ moderate and severe group were 43 and 65 years old respectively.

**Fig 1-Pie Diagram showing sex distribution among two groups**

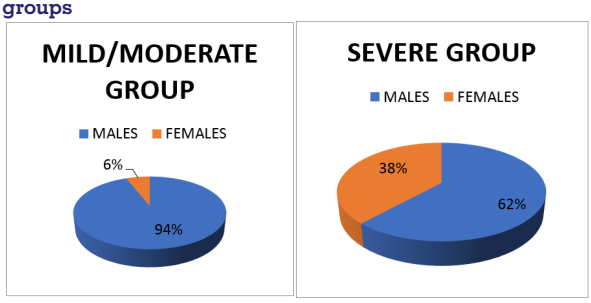


**Fig-2: Graph dipicting Age distribition among two groups**

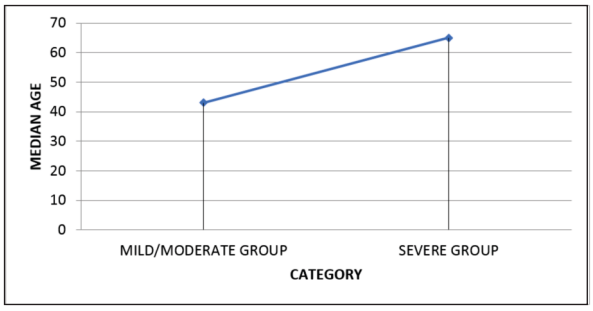


**Table 1: Baseline demographic study**

| NUMBER OF CASES | | ALL CASES | MILD/MODERATE GROUP | SEVERE GROUP | P-VALUE |
|---|---|---|---|---|---|
| | | 120 | 86 | 34 | |
| AGE (yrs) | MEAN±SD | 47.4 ± 15.2 | 42.2 ± 12.9 | 63.3 ± 10.8 | p<0.001 HS |
| | RANGE | 18-85 | 18-70 | 35-85 | |
| SEX | MALE | 71 | 50 | 21 | p = 0.56 NS |
| | FEMALE | 49 | 36 | 13 | |

The mean age of the patients of the severe group was significantly higher (p-value<0.001)

**SD :** Standard deviation ; HS : Highly significant ; NS : Not significant

### Clinical Laboratory Indicator Analysis:

The laboratory parameters were compared between the patients of mild/moderate and severe groups. The haematological parameters like Total white blood cell count, Neutrophil count, Neutrophil % and Neutrophil to lymphocyte ratio (NLR) were significantly higher in the patients of severe group as compared to that of patients of mild group. Whereas, Lymphocyte count and Lymphocyte % were significantly decreased in the severe group.

**Table 2: Comparison of hematological parameters**

| Hematological parameters | Mild/Moderate Group | Severe Group | P-Value |
|---|---|---|---|
| WBC count ($10^9$/L) | 6.7 ± 3.45 | 12.3 ± 7.6 | <0.001 |
| Neutrophil count ($10^9$/L) | 3.25 ± 1.54 | 7.4 ± 4.08 | <0.001 |
| Neutrophil % | 60.41 ± 11.12 | 85.5 ± 8.18 | <0.001 |
| Lymphocyte count ($10^9$/L) | 1.65 ± 0.84 | 1.05 ± 0.8 | <0.001 |
| Lymphocyte % | 30.43 ± 9.38 | 7.25 ± 5.45 | <0.001 |
| NLR | 2.43 ± 1.24 | 4.08 ± 1.48 | <0.001 |

WBC : White blood cell; NLR : Neutrophil to lymphocyte ratio.

p-value <0.001 indicates significance.

Compared to the patients of mild/moderate group, the patients in the severe group have significantly increased levels of total bilirubin, ALT, AST, LDH, urea, CRP and decreased levels of albumin with significant P value.

**Table 3: Comparison of Biochemical and Inflammatory parameters**

| Parameters | Mild/Moderate group | Severe group | P-value |
|---|---|---|---|
| Total bilirubin(mg/dl) | 1.27 ± 0.66 | 1.73 ± 0.9 | <0.001 |
| Albumin (g/dl) | 3.94 ± 0.45 | 3.12 ± 0.43 | <0.001 |
| ALT (U/L) | 28.86 ± 23.22 | 51.72 ± 31.8 | <0.001 |
| AST (U/L) | 25.86 ± 11.76 | 57.57 ± 29.86 | <0.001 |
| LDH (U/L) | 171.52 ± 51.75 | 312.61 ± 116.92 | <0.001 |
| Urea (mg/dl) | 32.8 ± 16.52 | 67.4 ± 18.25 | <0.001 |
| Creatinine (mg/dl) | 0.62 ± 0.41 | 0.68 ± 0.45 | 0.26 (NS) |
| CRP (mg/dl) | 1.21 ± 0.92 | 4.56 ± 2.38 | <0.001 |

ALT : Alanine transaminase; AST : Aspartate amino transferase; LDH : Lactate dehydrogenase; CRP : C-reactive protein

PT, APTT and INR were prolonged in the patients of severe group compared to that of mild/moderate group patients. D-dimer levels were also significantly higher in the severe group patients as compared to those of mild/moderate group patients.

**Table 4: Comparison of coagulation profile**

| Parameters | Mild/Moderate group | Severe group | P-Value |
|---|---|---|---|
| PT (sec) | 11.6 ± 1.32 | 11.94 ± 1.45 | 0.18 (NS) |
| APTT (sec) | 28.58 ± 5.73 | 33.10 ± 4.47 | <0.001 |
| INR | 0.85 ± 0.21 | 1.3 ± 0.94 | <0.001 |
| D- DIMER (mg/ml) | 0.30 ± 0.21 | 1.93 ± 1.84 | <0.001 |

PT : Prothrombin time ; APTT : Activated partial thromboplastin time; INR : International normalized ratio. NS : not significant.

## DISCUSSION:

Since the outbreak of SARS-Cov-2 in December 2019, more than 175 million people are infected worldwide, with more than 25 million infections in India. The number continues to grow with a case fatality rate of 2.19%,1.44% respectively worldwide and India[2]. Lack of medical resources, especially in critical care, is the current day difficulty. So it is vital to

identify the early predictors of mortality which can help in the risk stratification and also in the appropriate utilization of medical resources.

In our study, the age distribution ranged from eighteen to eighty-five years old; the age of severely affected patients was older than that of mild or moderately affected patients. The median ages of mild and severe category patients were 43 and 65 years old, respectively. This observation suggests that elderly patients were at higher risk of severe Covid-19, which is consistent with other studies [11,12]. The compensatory ability of various organs of the individual decreases as age increases. Also, as one ages the immune system function and resistance will be lowered.

SARS-Cov-2 virus attributes to an overactive immune response and a cytokine storm. In our study, we observed increased CRP levels, which was considered to be related to the systemic acute-phase inflammatory response induced by the virus. Complete blood picture is inexpensive and can be easily performed. Parameters like total leukocyte count, neutrophil count and lymphocyte count, individually and in combination, can be used as indexes of the systemic immune response. In our study, patients of the severe group had higher leukocytes, neutrophils, and lower lymphocytes, similar to the findings of other studies.[13,14] There is an increase in neutrophils and a decrease in lymphocytes as a response to stress.

**Neutrophil-Lymphocyte Ratio:**

In Covid-19 disease, one of the best predictors of severity of the disease is lymphopenia. The causes of lymphopenia in Covid-19 disease are: 1) The T-lymphocytes express ACE 2 receptor on their surface. The SARS-COV2 virus attaches to the ACE 2 receptors on lymphocytes via the spike protein and causes their lysis[15]. 2) The increased levels of cytokines produced in response to systemic inflammation cause lymphocyte apoptosis. 3) There will be an impairment in the lymphocyte turnover due to the atrophy of lymphoid organs[16]. 4) Inhibition of lymphocyte proliferation in some at-risk patients due to coexisting lactic acidosis[17].

NLR is a widely used marker not only for the assessment of the severity of bacterial infections but also for the prognosis of patients with pneumonia and tumour. Several studies[14,18-22] except Kalabin et al[22] have shown a positive correlation between NLR and the risk of Covid-19 and also elevated NLR as an independent prognostic marker in Covid-19 patients. Our study with NLR ratio 4.08 in severe group is in comparison with many other studies(Table 5).

**Table 5 Comparision of NLR ratio in different groups of COVID 19 infection.**

| S No | Author | N | NLR in severe group. |
|---|---|---|---|
| 1. | Sun S et al[14] | 116 | 2.9 |
| 2. | Yang AP et al[18] | 93 | 2.46 |
| 3. | Liu J et al[19] | 61 | 3.1 |
| 4. | Man Ma et al[20] | 149 | 2.5 |
| 5. | Wang X et al[21] | 131 | 2.3 |
| 6. | Kalabin et al[22] | 184 | NA (non significant) |
| 7. | Our study | 120 | 4.08 |

Along with haematological parameters, various inflammatory markers measured by inexpensive and readily available tests have been suggested to assess the severity of the disease. Our study showed a significant increase in the inflammatory markers like CRP, D-dimer and LDH levels of the patients of the severe group compared to those of the mild or moderate group.

**C-Reactive Protein:**

CRP binds to phosphocholine on membranes of host cells, acts as an opsonin to enhance phagocytosis and facilitate clearance. It also efficiently activates the classical pathway of the complement system, an important component of innate host defence.

Elevated CRP concentrations have been reported in severe viral infections, including H1N1 influenza pneumonia.In a prior study of 298 patients with COVID-19, patients who died had an initial CRP that was 10-fold higher than that of survivors[23]. Our study had shown that severe COVID infection is associated with elevation of CRP more than 4.5mg/dl, which is on par with many other studies[24-28](Table 6).

**Table 6 Comparision of CRP in different studies of COVID 19 infection.**

| S No | Author | N | CRP mg/dL (cut off for severe disease) |
|---|---|---|---|
| 1. | Smilowitz NR et al[24] | N=2782 | 108 |
| 2. | Chen et al[25] | N=274 | 113 |
| 3. | Wang et al[26] | N=209 | 43.8 |
| 4. | Guar et al[27] | N=1099 | NA |
| 5. | Chilimuri S et al[28] | N=375 | 200 |
| 6. | Our study | N= 120 | 456 |

**D Dimer:**

The causes of elevation of D-dimer includes 1) viremia and the cytokine storm syndrome (IL-2, IL-6, IL-8, IL-17, TNF- ) is inadequately controlled by the anti-inflammatory factors which triggers the coagulation cascade[29].2) Hypoxia itself activates transcription factor-dependent signaling pathway, predisposing to thrombosis. 3)The disease most commonly affects elderly and comorbid patients. Like many other studies[30-35] our study have shown the elevation of D Dimer 1.93mg/ml is seen in severe category of COVID 19 infection(Table 7).

**Table 7 Comparision of D Dimer in different groups of COVID 19 infection.**

| S No | Author | N | D – Dimer |
|---|---|---|---|
| 1. | Poudel A et al[30] | N = 182 | Cut of 1.5mg/ml |
| 2. | Guan et al[31] | N=560 | >0.5mg/ml |
| 3. | Zhang et al[32] | N=343 | Cut of 2mg/ml |
| 4. | Soni M et al[33] | NA | Cut of 2.1mg/ml |
| 5. | Naymagon et al[34] | N=1065 | NA |
| 6. | Rostami et al[35] | N= 2259 | 3.55 |
| 7. | Our study | 120 | 1.93 |

**Liver Function Tests:**

Also, there was a significant increase in the biochemical parameters like total bilirubin, AST, ALT, Urea, Creatinine. There was a significant decrease in albumin and prolongation in the coagulation profile of the patients in the severe group, indicating that SARS-Cov2 virus could cause multiorgan damage. Which is multifactorial like microthrombotic endothelialitis, immune dysregulation, drug-induced liver injury, and hepatic ischemia related to hypoxia and Multi organ failure could all play a role[36,37]. Elevation of liver enzymes can be due to 1) Patients with chronic liver disease may be more vulnerable to the severe clinical consequences of COVID.19, including oxygen desaturation and hypoxemia due to severe pneumonia or the cytokine storm 2) liver biochemistry abnormalities are the consequence of drug toxicity[38,39]. Our study have showed that the severe group had high levels of ALT AST and decreased albumin which is on par with many other studies as shown in table 8 [40-44].

**Table 8 Comparision of Liver function tests in various studies of COVID 19 infection.**

| S No | Author | N | LFT |
|---|---|---|---|
| 1 | Zhang et al[40] | 115 | Increase in ALT AST TBIL Decrease in Albumin |
| 2 | Phipps MM et al[41] | 2273 | 5 times ULN |
| 3 | Weber S et al[42] | NA | INCREASED |

| | | | |
|---|---|---|---|
| 4 | Wander P et al[43] | NA | INCREASED |
| 5 | Chen N et al[44] | N+99 | INCREASED |
| 6 | Our study | 120 | increased with P<0.001 |

The results of our study show that all these combined laboratory parameters had high predictive values in terms of severity in Covid-19 disease.

**Limitations:**

Our study had some limitations. The sample size was small, and all the patients could not be followed up after the discharge for the re-assessment of the laboratory indices.

**Conclusion:**

As the severity of Covid-19 increases, there is an abnormal increase in the rate of hematological and inflammatory parameters. Thus, the use of combined laboratory parameters will help in the early prediction of disease severity, thereby early allocation of the critical care resources to the required patients is possible.

**REFERENCES:**


1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020 Feb 20; 382(8):727-733.
2. World Health Organization. Available online: https://covid19.who.int/ (accessed on 1 June 2021).
3. Walls AC, Park YJ, Tortorici MA et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020. S0092-8674.
4. https://www.who.int/dg/speeches/detail/who-director-general-s-opening (accessed 1June 2021).
5. Liao YC, Liang WG, Chen FW et al. IL-19 induces production of IL-6 and TNF-alpha and results in cell apoptosis through TNF-alpha. J Immunol 2002; 169(8): 4288-4297.
6. Fan BE, Chong VCL, Chan SSW, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;95(6): E131-E153.
7. Tang N, Li D, Wang X, Sun Z, Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia, J. Thromb. Haemostasis 18 (4) (2020) 844–847.
8. Mousavi SA, Rad S, Rostami T, et al. Hematologic predictors of mortality in hospitalized patients with COVID-19: a comparative study. Hematology. 2020;25(1):383-388.
9. C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, The lancet 395 (10223) (2020) 497–506.
10. Shang W, Dong J, Ren Y, et al (2020) The value of clinical parameters in predicting the severity of COVID-19. J Med Virol.
11. Yanez, N.D., Weiss, N.S., Romand, JA. et al. COVID-19 mortality risk for older men and women. BMC Public Health 20, 1742 (2020).
12. Clara Bonanad, Sergio García-Blas, et al., The Effect of Age on Mortality in Patients With COVID-19: A Meta-Analysis With 611,583 Subjects, Journal of the American Medical Directors Association, Volume 21, Issue 7, 2020, Pages 915-918, ISSN 1525-8610
13. Danying Liao, Fen Zhou, Lili Luo, et al., Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study, The Lancet Haematology, Volume 7, Issue 9, 2020, Pages e671-e678, ISSN 2352-3026
14. Suyu Sun, Xuejiao Cai, Huaguo Wang, et al., Abnormalities of peripheral blood system in patients with COVID-19 in Wenzhou, China, Clinica Chimica Acta, Volume 507, 2020, Pages 174-180, ISSN 0009-8981
15. Xu, H., Zhong, L., Deng, J. et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 12, 8 (2020).
16. Chan JF, Zhang AJ, Yuan S, et al. Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. Clin Infect Dis. 2020 Dec 3;71(9):2428-2446.
17. Fischer K, Hoffmann P, Voelkl S, et al. Inhibitory effect of tumor cellderived lactic acid on human T cells. Blood. 2007;109(9):3812-3819.
18. Yang AP, Liu JP, Tao WQ,et al. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020 Jul;84:106504.
19. Liu J, Liu Y, Xiang P, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020 May 20;18(1):206.
20. Man MA, Rajnoveanu R-M, Motoc NS, et al. (2021) Neutrophil-to-lymphocyte ratio, platelets-to-lymphocyte ratio, and eosinophils correlation with high-resolution computer tomography severity score in COVID-19 patients. PLoS ONE 16(6): e0252599.
21. Wang X, Li X, Shang Y, Wang J, et al, Ratios of neutrophil-to-lymphocyte and platelet-to-lymphocyte predict all-cause mortality in inpatients with coronavirus disease 2019 (COVID-19): a retrospective cohort study in a single medical centre. Epidemiol Infect. 2020 Sep 9;148:e211. doi: 10. 1017/S0950268820002071. PMID: 32900409; PMCID: PMC7506174.
22. Kalabin A, Mani VRK, Valdivieso SC, Donaldson B. Role of neutrophil-to-lymphocyte, lymphocyte-to-monocyte and platelet-to-lymphocyte ratios as predictors of disease severity in COVID-19 patients. Infez Med. 2021 Mar 1;29(1):46-53. PMID: 33664172.
23. Liang W , Liang H , Ou L , et al; China Medical Treatment Expert Group for COVID-19. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med 2020;180:1081–1089
24. Smilowitz NR, Kunichoff D, Garshick M, et al. C-reactive protein and clinical outcomes in patients with COVID-19. Eur Heart J. 2021 Jun 14;42(23):2270-2279. doi: 10.1093/eurheartj/ehaa1103. PMID: 33448289; PMCID: PMC7928982.
25. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368.
26. Wang S, Lin D, Yang X, et al. Prognostic value of C.reactive protein in patients with COVID.19.InfectDis.2020;9:2445.2453.
27. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708.1720.
28. Chilimuri S, Sun H, Alemam A, et al. Predictors of Mortality in Adults Admitted with COVID-19: Retrospective Cohort Study from New York City. West J Emerg Med. 2020 Jul 8;21(4):779-784.
29. Wool GD, Miller JL. The Impact of COVID-19 Disease on Platelets and Coagulation. Pathobiology. 2021; 88: 15–27.
30. Poudel A, Poudel Y, Adhikari A et al. (2021) D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLoS ONE 16(8):e0256744.
31. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Dis- ease 2019 in China. N Engl J Med. 2020; 382: 1708–1720.
32. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mor- tality in patients with Covid-19. J Thromb Haemost. 2020; 18: 1324–1329. https://doi.org/10.1111/jth. 14859 PMID: 32306492
33. Soni M, Gopalakrishnan R, Vaishya R, et al. D-dimer level is a useful predictor for mortality in patients with COVID-19: Analysis of 483 cases. Diabetes Metab Syndr Clin Res Rev. 2020; 14: 2245– 2249. https://doi.org/10.1016/j.dsx.2020.11.007 PMID: 33395786
34. Naymagon L, Zubizarreta N, Feld J, et al. Admission D-dimer lev- els, D-dimer trends, and outcomes in COVID-19. Thromb Res. 2020; 196: 99–105. https://doi.org/10. 1016/j.thromres.2020.08.032 PMID: 32853982
35. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol. 2020; 13: 1265–1275.
36. Clark R, Waters B, Stanfill AG. Elevated liver function tests in COVID-19: Causes, clinical evidence, and potential treatments. Nurse Pract. 2021;46(1):21-26.
37. Pirola CJ, Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: Putative mechanisms of liver involvement in COVID-19. Liver Int. 2020 Aug;40(8):2038-2040.
38. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol 2020;5:529-530.
39. Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020 Apr;14(2):185-192.
40. Zhang Y, Zheng L, Liu L et al. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver Int. 2020 Sep;40(9):2095-2103.
41. Phipps MM, Barraza LH, LaSota ED, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. Hepatology. 2020 Sep;72(3):807-817.
42. Weber S, Mayerle J, Irlbeck M, Gerbes AL. Severe liver failure during SARS-CoV-2 infection. Gut. 2020 Jul;69(7):1365-1367.
43. Wander P, Epstein M, Bernstein D. COVID-19 Presenting as Acute Hepatitis. Am J Gastroenterol. 2020 Jun;115(6):941-942.
44. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-513.