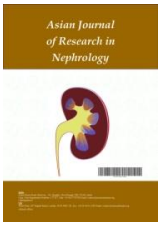

Asian Journal of Research in Nephrology

4(2): 1-10, 2021; Article no.AJRN.69803

Association between D Dimer and Inflammatory Markers in COVID-19 Patients with Preexisting Chronic Kidney Disease

N. S. Madhura[1], R. Kowsalya[1*], S. Mythri[1], N. Shashikala[1] and K. M. Mythri[1]

[1]Institute of Nephrourology, Bangalore, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author NSM designed the study, wrote the protocol, performed the statistical analysis, Author RK managed the study methodology and the analyses of the study. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Prof. Eduesley Santana-Santos, Universidade Federal de Sergipe, Brazil.
(2) Dr. P.Kiranmayi, GITAM University, India.
(3) Prof. Darko Nozic, Military Medical Academy, Serbia.
Reviewers:
(1) S K Agarwal, EPIC Hospital, India.
(2) Taklo Simeneh Yazie , Debre Tabor University, Ethiopia.
(3) Eric Loic Bana, Université Cheikh Anta Diop de Dakar, Senegal.
(4) Maria do Carmo, Centre Hospitalier Universitaire, Belgium.
(5) Mahzuz Karim, Norfolk and Norwich University Hospital and Norwich Medical School, UK.
Complete Peer review History: http://www.sdiarticle4.com/review-history/69803

Original Research Article

Received 01 May 2021
Accepted 06 July 2021
Published 09 July 2021

ABSTRACT

Background: Renal involvement in Covid 19 disease is an independent predictor of mortality in Covid 19 patients. Hyperinflammation and hypercoagulability are the important key factors for assessing severity of Covid 19 disease. Management of Covid 19 infection in preexisting CKD patients is a challenge.
Aim: 1.To compare D- Dimer, CRP, PCT, Lactate, LDH and Ferritin of Covid 19 CKD patients with that of Covid 19 patiets without CKD.
2. To evaluate the correlation between D-Dimer levels and Inflammatory markers in Covid 19 CKD patients.
Study Design: An observational cross sectional study
Place and Duration of Study: Dept of Biochemistry, Institute of nephrourology, Bangalore, India. from July 2020 to Dec 2020

**Corresponding author: E-mail: r.kowsalya@gmail.com;*

Methodology: Study popoulation were categorised into 3 groups, Group 1 (Covid 19 with preexisting CKD), Group 2 (Covid 19 without CKD) and Group 3 (CKD without Covid 19) . All the groups were assayed for D dimer, CRP, PCT, Lactate and LDH using Abbott ci4000 chemistry and immuno assay analyser, in Biochemistry laboratory. Student t test was used to to analyse the significance between Group 1&2 also Group 1&3. Pearson correlation was done to analyse the association between d dimer and inflammatory markers in Group 1.

Results : In our study, a peaked and statistically significant *(P* value = <0.0001) D-Dimer values were observed in Group 1 (7.4±2.5), compared to Group 2 (3.4±2.1) and Group 3 (1.5±0.4)]. Similarly CRP, PCT, LDH, Ferritin, and Lactate levels were higher in Group 1 compared to other two groups.

D- Dimer had strong positive correlation with CRP (r= 0.702), PCT (r= 0.66) , LDH (r=0.67) and moderately positive correlation with Lactate (r=0.42) in Group1.

Conclusion: This study shows Covid -19 patients with preexisting CKD had significantly higher levels of hypercoagulability marker (D-Dimer) and of hyperinflammatory markers (CRP. PCT, Lactate, and Ferritin). Therefore, it is possible that COVID-19 infection in CKD is more likely to cause severe hyperinflammatory and hypercoagulable state with a worse prognosis.

Keywords: D dimer; CRP; PCT; Lactate; Covid19 disese; chronic kidney disease.

1. INTRODUCTION

Corona virus disease-2019 (COVID-19) which was originally discovered in China, later infected the whole world, has emerged as a fatal disease in last one year, as the severity rate and case fatality rate of the disease, are increasing day by day [1,2]. The disease manifestations range from asymptomatic, mild influenza-like illness to severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, leading to death [3]. So far, Biochemical markers like serum C-reactive protein (CRP), Procalcitonin (PCT), Ferritin, Lactate dehydrogenase (LDH), and Lactate levels are proven to be strongly associated with the severity of Covid-19 [4-7].

Chronic kidney disease (CKD) is a chronic inflammatory state caused by many factors including infection, oxidative stress, obesity, and immunologic factors, thus has a strong association with Inflammatory markers [8,9]. CRP and PCT are the key inflammatory markers, being used for assessing severity in CKD [10,11]. Hyperferritinemia is also known to be associated with high mortality in CKD patients on dialysis [12]. Coronary heart disease and Multi organ failure due to severe infection and sepsis are the major causes of morbidity and mortality in patients with chronic kidney disease (CKD) thus having an association with hypercoagulability marker D- Dimer [13,14].

D-Dimer, a fibrin degradation product, is being used as a specific biomarker for diagnosing of thromboembolic events in both Covid 19 and CKD patients [15-17].

Management of severe Covid 19 in preexisting CKD patients has become a challenge for nephrologists all over the world. Corrections on the upper limit of all of the above mentioned critical biomarkers in Covid 19 patients with preexisting CKD,becomes very important in managing the same. However, no study has investigated the effect of severe Covid 19 on these critical biomarkers in preexisting CKD patients. Hence in the present study we try to determine the variations in D Dimer, PCT, CRP, Ferritin, LDH, and Lactate in Covid 19 patients with preexisting CKD.

The severe inflammatory reaction is known to be followed by coagulation and fibrinolysis process which thus explains why does venous thromboembolic phenomenon arise as a complication of severe inflammations [18]. Hence in the present study we also try to establish the relation between D-Dimer and inflammatory markers in Covid 19 CKD patients.

2. MATERIALS AND METHODS

This was a cross sectional study conducted in The Institute of Nephrourology (INU), Bangalore, a tertiary care centre, from July 2020 to Dec 2020. All laboratory confirmed COVID-19 cases by Real Time Reverse Transcription Polymerase Chain Reaction (RTPCR) or Rapid Antigen Test (RAT) who were admitted at this centre in the above mentioned time period were included in the study. They were categorised into two groups, based on the preexisting kidney disease.

Covid 19 patients with preexisting CKD as Group 1 and Covid 19 without CKD as Group 2.

CKD patients who tested negative for Covid 19 were taken as controls, and were in Group 3.

Covid 19 patients were further triaged into mild, moderate and severe groups based on National guidelines as follows, Mild (Respiratory Rate <24/min, SpO2>94% at room air), Moderate(Respiratory rate: 24 -30/min, SpO2 90-94% at room air) and Severe(Respiratory rate >30/min, SpO2 <90%). As only moderate and severe cases were admitted in the hospital, we also enrolled only moderate to severe Covid 19 cases.

Analysis of various biochemical parameters including D Dimer assay, C-reactive protein (CRP), Procalcitonin (PCT), Ferritin, Lactate dehydrogenase (LDH), and Lactate levels were done in all the three groups.

2.1 Inclusion Criteria

1. Age 18 to 65 years
2. Patients attending outpatient department of nephrourology centre, and those admitted in the wards.
3. Group 1 - Covid 19 patients with preexisting CKD .
   Group 2- Covid 19 without CKD
   Group 3- CKD patients without Covid 19
4. Covid 19 patients with only moderate to severe disease were included, CKD patients of all stages were included.

2.2 Exclusion Criteria

1. Patients aged <18yrs,
2. Patients with a preexisting history of Venous thromboembolism, or on anticoagulants.
3. Mild Covid 19 cases .
4. Absence of informed consent.

2.3 Laboratory Analysis of Biomarkers

All the parameters were assayed in our Biochemistry laboratory using Abbott CI 4100, Chemistry and Immunoassay analyser..

i. Urea was assayed by Urease method and Creatinine by Jaffe s method using serum sample.
ii. D-Dimer was assayed using plasma sample by Immunoturbidimetric method with reportable range of 0.5 -8.5 mg/L.
iii. Procalcitonin was measured using chemiluminescent microparticle immunoassay (CMIA), with a measuring range of 0.02-100 ng/ml.
iv. C-reactive protein (CRP) was measured using Immunoturbidimetric method, with the reportable range of 0.50 to 30.00 mg/dl.
v. Ferritin assay is done by Chemiluminescent Microparticle Immunoassay (CMIA) technique.
vi. Lactate levels are assayed using plasma sample based on method where lactic acid is converted to pyruvate and hydrogen peroxide (H2O2) by lactate oxidase, and increase in absorbance is measured colorimetrically.
vii. LDH is assayed using serum sample based on the method lactate dehydrogenase catalyzes the conversion of lactate to pyruvate and absorbance is measured colorimetrically.
viii. RT PCR- Detection of corona virus RNA in nasopharyngeal secretions,was based on single tube multiplex real time RT PCR assay using commercial kit from Q- line molecular. The E-gene, RdRP and Internal control Rnase were the primers and probes used, which were specific for covid 19. The test has a sensitivity of 98.7% and specificity of 100%.
ix. RAT - Detection of corona virus antigen in nasopharyngeal secretions, was based on the principle of antigen antibody reaction, using commercial rapid antigen kits from BIOCARD with a sensitivity of 92% and specificity of 100%.

2.4 Statistical Analysis

The complete date was compiled in an excel master sheet. Statistical analysis was performed using SPSS software. Continuous variables were expressed as the mean ± standard deviation. Unpaired independent t test was used to find out significance between Groups 1&2, also between Group 2 &3. *P* value <0.005 was was considered significant .

The correlation between D- Dimer and Inflammatory markers was done using Pearson correlation test. Pearson correlation coefficient(r) ranging −1 to +1 is considered to assess the correlation.

3. RESULTS

All patients enrolled in the study were divided into 3 study groups, Group 1 were Covid 19 with CKD (n=44), Group 2 were COVID 19 without CKD (n=45) , and Group 3 were CKD without

Covid19 (n=48). Male Female ratio (M/F) in all the three groups were 30/14, 31/14 and 33/15 in Group 1 , 2 & 3 respectively. Mean age of patients enrolled were 49±13 ,46±15 & 45±17 in Group 1 ,2 & 3 respectively[Table-1]. Among total Covid 19 patients(n=89), 54 patients (60%) had moderate disease, 30(33%) had severe disease and remaining 5 (6%) expired in the hospital. Among all Covid 19 patients recruited in the study, 85%(75 patients) were diagnosed based on RTPCR, and 15% (14 patients) were diagnosed based on RAT.

D- Dimer was significantly increased in Group1 (7.4±2.5), compared to Group 2 (3.4±2.1) and Group 3 (1.5±0.4) with *P* value <0.0001. CRP levels were significantly increased (*P* =<0.0001) in Group1 (7.0±8.3) compared to Group 3 (0.4±0.2). but the difference was not significant (p value- 0.12) compared to Group 2 (4.7±5.3). PCT levels were significantly increased (*P* =<0.0001) in Group1 (12.4±22.8) compared to Group 3 (1.5±0.5) , but the difference was not significant.

(P = 0.01) compared to Group 2 (3.2±2.4) .With respect to LDH levels, the difference was not significant *(P* = 0.53) in Group1 (347.8±108.9) compared to Group 2 (333±104.5) ,was significant (p = 0.004) compared to Group 3 (266±101).Also Lactate levels were significantly increased (*P* =<0.0001) in Group1 (3.2±1.2) compared to Group 2 (2.02±1.2) and Group 3 (1.9±1.2). [Table-1] .

In Group 1 (Covid 19 with CKD) on comparing D-Dimer levels with inflammatory markers, we found that there was strongly positive correlation (r- 0.66) between the D-Dimer levels and PCT which was statistically significant (*P* = 0.0003).[Table2 &Fig1]

Also, D dimer levels had strong positive correlation (r-0.702) with CRP levels in Covid 19 CKD patients which was significant.(p = 0.0009). [Table 3 &Fig 2]

Table 1. Clinical and biochemical data

Parameters	Ref range	Group 1 Covid19 CKD (N=44) Mean±SD	Group 2 Covid19 without CKD (N=45) Mean±SD	Group 3 CKD without Covid 19 (N=48) Mean±SD	*P*1 value	*P*2 value
Age(yrs)	18-65	49±13	46±15	45±17	0.312	0.3
Sex(n) M/F	NA	30/14	31/14	33/15	NA	NA
Urea(mg/dl)	10-44	166±56	30.96±9.6	155±45	<0.0001	0.3
Creatinine(mg/dl)	0.57-1.1	10.1±3.7	0.9±0.3	9.6±1.3	<0.0001	0.38
D Dimer(mg/lt)	< 0.5	7.4±2.5	3.4±2.1	1.5±0.4	<0.0001	<0.0001
CRP(mg/dl)	< 0.5	7.0±8.3	4.7±5.3	0.4±0.2	0.12	<0.0001
PCT(ng/ml)	<0.08	12.4±22.8	3.2±2.4	1.5±0.5	0.01	<0.0001
LDH (U/lt)	122-220	347.8±108.9	333±104.5	266±101	0.53	0.004
Lactate (mmol/lt)	<0.5	3.2±1.2	2.02±1.2	1.9±1.2	<0.0001	<0.0001
Ferritin (ng/ml)	13-150	1682±399	650±152	380±95	<0.0001	<0.0001

P1- Comparision bw group 1 & 2, P2 - Comparision bw group 1 & 3
CRP- C-reactive protien, PCT- Procalcitonin, LDH- lactate dehydrogenase

Table 2. Correlation Between D Dimer and PCT in Covid 19 CKD Patients

Covid19 CKD	D- Dimer	PCT	Pearson correlation	P value
	7.4±2.5	347.8±108.9	r =0.66	0.0003

Table 3. Correlation between D-Dimer and CRP in Covid 19 CKD patients

Covid19 CKD	D- Dimer	CRP	Pearson correlation	*P* value
	7.4±2.5	7.0±8.3	r =0.702	0.00009

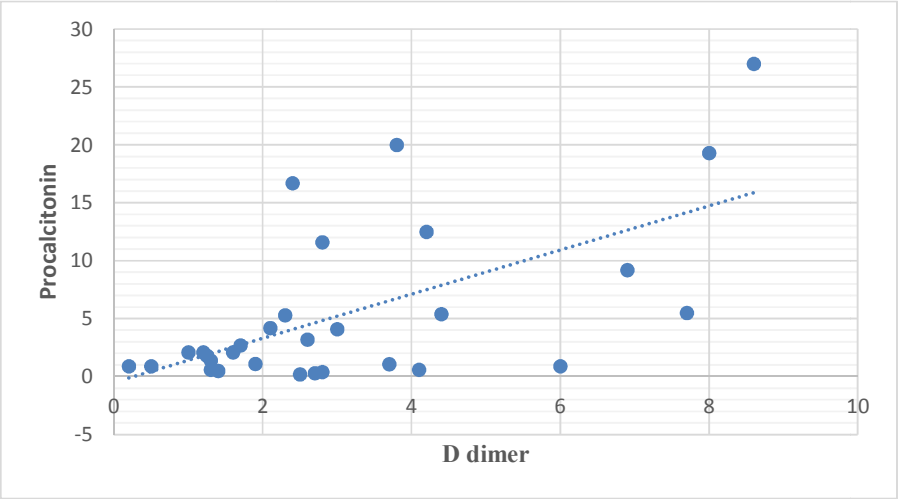

Fig 1. Scatter diagram showing correlation b/w D dimer and PCT in Covid 19 CKD

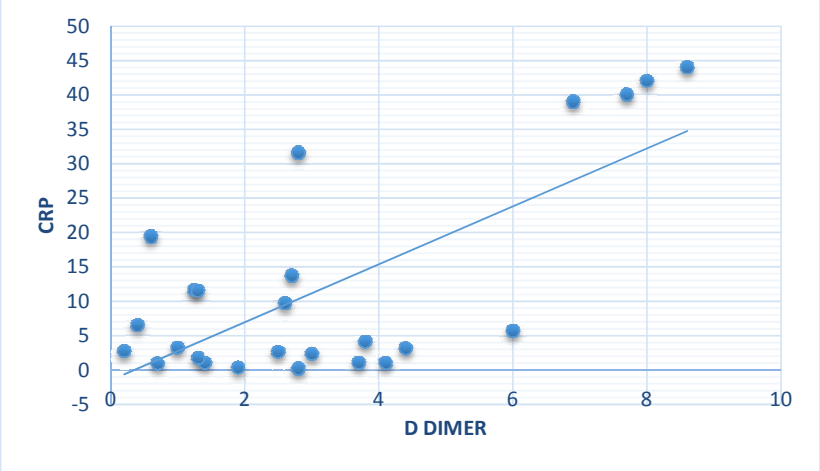

Fig 2. Scatter diagram showing correlation b/w D- Dimer and CRP in Covid 19 CKD patients

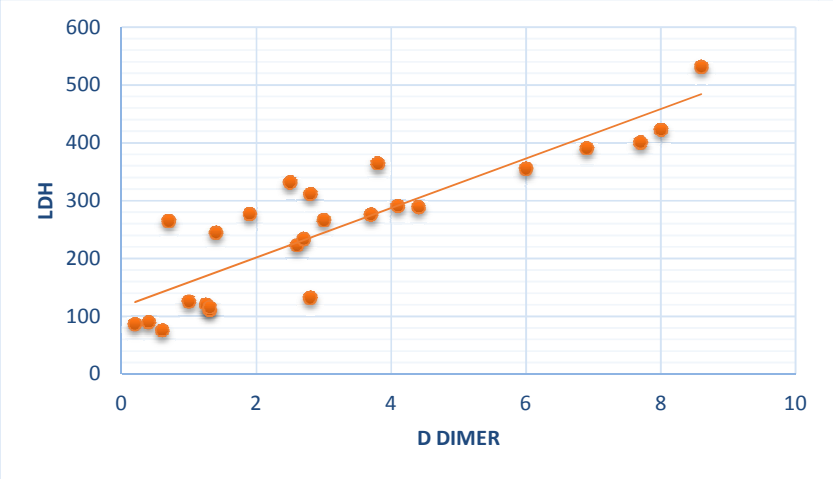

Fig 3. Scatter diagram showing correlation b/w D-Dimer and CRP in Covid 19 CKD patients

Table 4. Correlation between D dimer assay and LDH in covid 19 CKD patients

Covid 19 CKD	D Dimer	LDH	Pearson correlation	*P* value
	7.4±2.5	347.8±108.9	r=0.67	0.0002

Table 5. Correlation between D-Dimer assay and Lactate in Covid 19 CKD patients

Covid 19 CKD	D dimer	Lactate	Pearson correlation	*P* value
	7.4±2.5	3.2±1.2	r =0.42	0.036

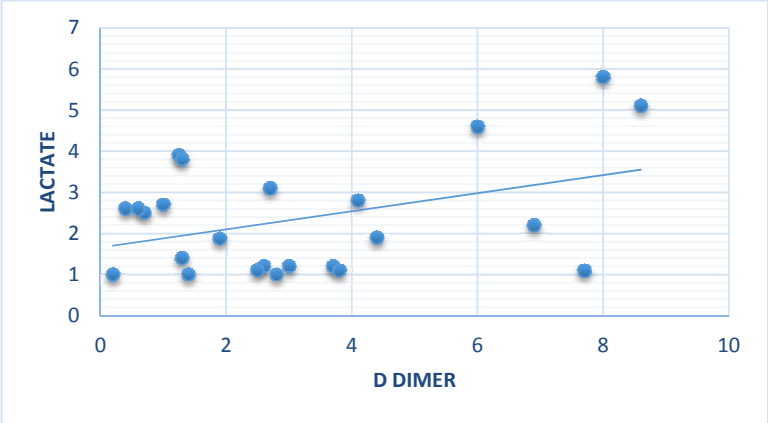

Fig 4. Scatter diagram showing correlation b/w D dimer and Lactate in Covid 19 CKD

Similarly, LDH levels also had strong positive correlation (r=0.607) with D-Dimer levels in the same group which was significant (*P*=0.0002). [Table4 &Fig3]

However, with respect to Lactate levels, there was moderately positive correlation (r= 0.42) between D-Dimer levels and Lactate levels in Covid 19 CKD patients which was not significant (*P* = 0.036) [Table 5 &Fig 4].

4. DISCUSSION

This was the first study to analyze severity markers of Covid infection in moderate to severe covid 19 patients with preexisting kidney disease. Overall, our study revealed a significant increase in D-Dimer,CRP, PCT, Lactate, Ferritin and LDH levels in Covid 19 with preexisting CKD group compared to other two groups - patients with covid without CKD Group and CKD without Covid 19 Group.

CRP is an acute phase inflammatory protein produced by the liver which may be elevated in few conditions, like inflammation, infection post-surgery, and cardiovascular disease [19]. In our study, 40 out of 44 (90.9%) patients had high crp levels with 20 of them (45%) had CRP levels >10mg/dl. However, there is no general agreement on a cutoff point for CRP to determine the severity of Covid -19, many studies have used a cutoff of >10mg/dl to be associated with poor outcome in severe inflammatory states [20-23]. Our findings in the present study, would suggest that, a slight change in the CRP cutoff would help the nephrologist to use CRP levels appropriately in monitoring the progression of moderate to severe Covid infection in preexisting CKD patients.

PCT a peptide precursor of the hormone Calcitonin, the production of which is triggered by bacterial infection and thus PCT has been widely used as a promising biomarker for early detection of systemic bacterial infections [24-26]. Raised PCT levels in Covid 19 patients is believed to be due to associated bacterial infection [6]. Similarly raised PCT in severe CKD patients is believed to be due to either associated bacterial infection or due to Immuno modulator therapy that increase pro inflammatory cytokines [27-29]. In the present study, we observed very high levels of PCT in in Covid 19

patients with preexisting CKD Group which explains the high probability of associated severe bacterial infection in the this group.

D-Dimer is a fibrin degradation product, which indicates fibrinolytic activity in blood, is known to be elevated in hypercoagulable states [29]. So far, many studies have reported that D-Dimer levels are significantly elevated in moderate to severe Covid 19 cases, and are associated with high case fatality rate in the same [29-32]. Elevated D dimer levels in Covid 19 patients is probably due to Severe hypoxia of acute respiratory distress syndrome (ARDS) which can lead to activation of extrinsic coagulation pathway, thus increasing the blood viscosity leading to hypercoagulable state [33]

Many studies have also demonstrated correlation between elevated D-Dimer levels and disease severity in CKD patients [34-37]. Raised D-Dimer level in CKD can be attributed to the fact that the decline of GFR may cause endothelial dysfunction with the release of the Von willebrand factor, which promotes platelet adhesion and aggregation followed by micro thrombi formation, and increased D-Dimer levels[28]. Endothelial dysfunction might impair ,protein c activation, thus enhancing hypercoagulability status [38]. In the present study, we found that, there was eight fold increase in D-Dimer levels in the Covid19 with CKD group indicating the increased risk of hypercoagulability in the same group of patients

We also found that, in the Covid 19 CKD group, the D-Dimer levels had strong positive correlation with inflammatory markers like CRP, PCT, LDH, and Ferritin, a moderately positive correlation with serum Lactate levels. This suggest that there exists a a positive relation between hypercoagulable state and hyperinflammatory state.

5. CONCLUSION

This study concludes that marker of hypercoagulability namely D-Dimer levels are markedly raised in moderate to severe Covid patients with preexisting CKD suggesting D-Dimer should be continuous marker for managing CKD patients if they contract Covid 19 infection. Strong positive correlation between D-Dimer and inflammatory markers suggests considering prophylaxis for venous thromboembolism in Covid CKD patients having raised inflammatory markers alone.

Study also suggests that cut off for hypercoaulability marker namely D-Dimer and hyperinflammatory markers like CRP, PCT, Lactate, and Ferritin need to be revised and more studies are required in this context.

6. LIMITATIONS OF THE STUDY

1)The study was carried out in small sample size
2) The age group of patients was restricted to 18 to 65 years, we believe to carry out the same in age group <18 and >65 with large sample size.

CONSENT

Informed consent was taken from all the patients enrolled in the study.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

ACKNOWLEDGEMENTS

We thank our technicians both in biochemistry lab and in rt pcr lab for all the help. We also thank our director for being supportive throughout.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
DOI: 10.1001/jama.2020.1585.
2. Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA. 2020;323(15):1488-94.
DOI: 10.1001/jama.2020.3204.
3. 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):507-13. Epub 2020/02/03.
DOI: 10.1016/s0140-6736(20)30211-7. PubMed
PMID: 32007143; PubMed Central PMCID: PMCPMC7135076.

4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4. Epub 2020/03/21.
DOI: 10.1016/s0140-6736(20)30628-0. PubMed
PMID: 32192578; PubMed Central PMCID: PMCPMC7270045.
5. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43. Epub 2020/03/14.
DOI: 10.1001/jamainternmed.2020.0994. PubMed
PMID: 32167524; PubMed Central PMCID: PMCPMC7070509.
6. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(13):382-6. Epub 2020/04/03.
DOI: 10.15585/mmwr.mm6913e2. PubMed
PMID: 32240123; PubMed Central PMCID: PMCPMC7119513 Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.
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):1239-42. Epub 2020/02/25.
DOI: 10.1001/jama.2020.2648. PubMed
PMID: 32091533.
8. Jofré R, Rodriguez-Benitez P, López-Gómez JM, Pérez-Garcia R. Inflammatory syndrome in patients on hemodialysis. Journal of the American Society of Nephrology. 2006;17(12suppl3):S274-S80.
9. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. Ann Intern Med. 2004;140(1):9-17. Epub 2004/01/07.
DOI: 10.7326/0003-4819-140-1-200401060-00006. PubMed
PMID: 14706967.
10. Wu SC, Liang CX, Zhang YL, Hu WP. Elevated serum procalcitonin level in patients with chronic kidney disease without infection: A case-control study. J Clin Lab Anal. 2020;34(2):e23065. Epub 2019/10/17.
DOI: 10.1002/jcla.23065. PubMed
PMID: 31617251; PubMed Central PMCID: PMCPMC7031592.
11. Arici M, Walls J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? Kidney Int. 2001;59(2):407-14. Epub 2001/02/13.
DOI: 10.1046/j.1523-1755.2001.059002407.x. PubMed
PMID: 11168922.
12. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol. 2005;16(10):3070-80. Epub 2005/07/22.
DOI: 10.1681/asn.2005040423. PubMed
PMID: 16033854.
13. Dalrymple LS, Katz R, Kestenbaum B, de Boer IH, Fried L, Sarnak MJ, et al. The risk of infection-related hospitalization with decreased kidney function. Am J Kidney Dis. 2012;59(3):356-63. Epub 2011/09/13.
DOI: 10.1053/j.ajkd.2011.07.012. PubMed
PMID: 21906862; PubMed Central PMCID: PMCPMC3288732.
14. James MT, Quan H, Tonelli M, Manns BJ, Faris P, Laupland KB, et al. CKD and risk of hospitalization and death with pneumonia. Am J Kidney Dis. 2009;54(1):24-32. Epub 2009/05/19.
DOI: 10.1053/j.ajkd.2009.04.005. PubMed
PMID: 19447535.
15. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of 2019 novel coronavirus infection in China. medRxiv. 2020:2020.02.06.20020974.
DOI: 10.1101/2020.02.06.20020974.
16. Nwose EU, Richards RS, Jelinek HF, Kerr PG. D-dimer identifies stages in the progression of diabetes mellitus from family history of diabetes to cardiovascular complications. Pathology. 2007;39(2):252-7. Epub 2007/04/25.

DOI: 10.1080/00313020701230658. PubMed PMID: 17454757.

17. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7. Epub 2020/02/20.
DOI: 10.1111/jth.14768. PubMed PMID: 32073213; PubMed Central PMCID: PMCPMC7166509.
18. Epaulard O, Foote A, Bosson J-L, editors. Chronic infection and venous thromboembolic disease. Seminars in thrombosis and hemostasis; 2015: Thieme Medical Publishers.
19. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol. 2018;9:754. Epub 2018/05/01.
DOI: 10.3389/fimmu.2018.00754. PubMed PMID: 29706967; PubMed Central PMCID: PMCPMC5908901.
20. Koozi H, Lengquist M, Frigyesi A. C-reactive protein as a prognostic factor in intensive care admissions for sepsis: A Swedish multicenter study. J Crit Care. 2020;56:73-9. Epub 2019/12/20.
DOI: 10.1016/j.jcrc.2019.12.009. PubMed PMID: 31855709.
21. Song J, Park DW, Moon S, Cho HJ, Park JH, Seok H, et al. Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: a prospective controlled study according to the Sepsis-3 definitions. BMC Infect Dis. 2019;19(1):968. Epub 2019/11/14.
DOI: 10.1186/s12879-019-4618-7. PubMed PMID: 31718563; PubMed Central PMCID: PMCPMC6852730.
22. Miguel-Bayarri V, Casanoves-Laparra EB, Pallás-Beneyto L, Sancho-Chinesta S, Martín-Osorio LF, Tormo-Calandín C, et al. Prognostic value of the biomarkers procalcitonin, interleukin-6 and C-reactive protein in severe sepsis. Med Intensiva. 2012;36(8):556-62. Epub 2012/04/13.
DOI: 10.1016/j.medin.2012.01.014. PubMed PMID: 22495097.
23. Ryoo SM, Han KS, Ahn S, Shin TG, Hwang SY, Chung SP, et al. The usefulness of C-reactive protein and procalcitonin to predict prognosis in septic shock patients: A multicenter prospective registry-based observational study. Sci Rep. 2019;9(1):6579. Epub 2019/05/01.
DOI:10.1038/s41598-019-42972-7.PubMed
PMID: 31036824; PubMed Central PMCID: PMCPMC6488613.
24. Grace E, Turner RM. Use of procalcitonin in patients with various degrees of chronic kidney disease including renal replacement therapy. Clin Infect Dis. 2014;59(12):1761-7. Epub 2014/09/18.
DOI: 10.1093/cid/ciu732. PubMed PMID: 25228701.
25. Hatzistilianou M. Diagnostic and prognostic role of procalcitonin in infections. ScientificWorldJournal. 2010;10:1941-6. Epub 2010/10/05.
DOI: 10.1100/tsw.2010.181. PubMed PMID: 20890583; PubMed Central PMCID: PMCPMC5763968.
26. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis. 2018;18(1):95-107. Epub 2017/10/19.
DOI: 10.1016/s1473-3099(17)30592-3. PubMed PMID: 29037960.
27. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. Journal of clinical medicine. 2020;9(5):1417.
28. Shorr AF, Thomas SJ, Alkins SA, Fitzpatrick TM, Ling GS. D-dimer correlates with proinflammatory cytokine levels and outcomes in critically ill patients. Chest. 2002;121(4):1262-8.
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. Journal of Thrombosis and Haemostasis. 2020;18(6):1324-9.
30. Gupta N, Zhao Y-Y, Evans CE. The stimulation of thrombosis by hypoxia. Thrombosis research. 2019;181:77-83.
31. Vahdat S, Shahidi S. D-dimer levels in chronic kidney illness: a comprehensive and systematic literature review. proceedings of the national academy of sciences, india section b: biological sciences. 2020:1-18.
32. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. Journal of thrombosis and thrombolysis. 2021;51(4):1107-10.

33. Mohammed NMS, Khalil HBE. D-dimer levels in patients presenting chronic kidney disease in Sudan. Am J Med Med Sci. 2016;6:120-2.
34. Gordge M, Faint R, Rylance P, Ireland H, Lane D, Neild G. Plasma D dimer: a useful marker of fibrin breakdown in renal failure. Thrombosis and haemostasis. 1989;61(03):522-5.
35. Jenkins PV, O'Donnell JS. ABO blood group determines plasma von Willebrand factor levels: a biologic function after all? Transfusion. 2006;46(10):1836-44.
36. Scaldaferri F, Sans M, Vetrano S, Graziani C, De Cristofaro R, Gerlitz B, et al. Crucial role of the protein C pathway in governing microvascular inflammation in inflammatory bowel disease. The Journal of clinical investigation. 2007;117(7):1951-60.
37. Shibata T, Magari Y, Kamberi P, Ishii T, Tomo T, Yasumori R, et al. Significance of urinary fibrin/fibrinogen degradation products (FDP) D-dimer measured by a highly sensitive ELISA method with a new monoclonal antibody (DD E72) in various renal diseases. Clinical nephrology. 1995;44(2):91-5.
38. Pettilä V, Hynninen M, Takkunen O, Kuusela P, Valtonen M. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive care medicine. 2002;28(9):1220-5.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/69803