

87979\_Auto\_Edited.docx

***Retrospective Cohort Study*****Use of Inflammatory Markers as <sup>1</sup>Predictor for Mechanical Ventilation in COVID-19 Patients with Stages IIIb-V Chronic Kidney Disease?**

Inflammatory markers in CKD and COVID-19

Harinivaas Shanmugavel Geetha, Sushmita Prabhu, Abinesh Sekar, Maya Gogtay, Yuvaraj Singh, Ajay K Mishra, George M. Abraham, Suzanne Martin

**Abstract****BACKGROUND**

Studies have shown elevated C-reactive protein (CRP) to predict mechanical ventilation (MV) in patients with COVID-19. Its utility is unknown in patients with chronic kidney disease (CKD), who have elevated baseline CRP levels due to chronic inflammation and reduced renal clearance.

**AIM**

Our aim was to assess whether an association exists between elevated inflammatory markers and MV rate in patients with Stages IIIb-V CKD and COVID-19.

**METHODS**

We conducted a retrospective cohort study on patients with COVID-19 and Stages IIIb-V CKD. The primary outcome was the rate of invasive MV, the rate of noninvasive MV, and the rate of no MV. Statistical analyses used unpaired t-test for continuous variables

and chi-square analysis for categorical variables. Cutoffs for variables were CRP:100 mg/L, ferritin:530 ng/mL, D-dimer:0.5 mg/L, and LDH:590 U/L

## RESULTS

290 were screened, and 118 met the inclusion criteria. CRP, D-dimer, and ferritin were significantly different among the three groups. On univariate analysis for IMV, CRP had an OR-5.44; ferritin,OR-2.8; LDH,OR-7.7; D-dimer,OR-3.9, ( $p<0.05$ ). The admission CRP level had an AUROC:0.747 for the IMV group (sensitivity-80.8%,specificity-50%) and 0.663 for the NIMV group (AUC-ROC,sensitivity-69.2%,specificity-53%).

## CONCLUSION

Our results demonstrate a positive correlation between CRP, ferritin, and D-dimer levels and MV and NIMV rates in CKD patients. The AUROC demonstrates a good sensitivity for CRP levels in detecting the need for MV in patients with Stages IIIb-V CKD. This may be because of the greater magnitude of increased inflammation due to COVID-19 itself compared with increased inflammation and reduced clearance due to CKD alone.

**Key Words:** COVID-19; CKD; Inflammatory markers; CRP; Invasive Mechanical Ventilation; Non-invasive Mechanical ventilation

<sup>1</sup> Shanmugavel Geetha H, Prabhu S, Sekar A, Gogtay M, Singh Y, Mishra AK, Abraham GM, Martin S. Use of Inflammatory Markers as Predictor for Mechanical Ventilation in COVID-19 Patients with Stages IIIb-V Chronic Kidney Disease? . *World J Virol* 2023; In press

**Core Tip:** Our study demonstrates a positive correlation between the levels of inflammatory markers, including CRP, ferritin, and D- dimer, and the rate of invasive and non-invasive mechanical ventilation among COVID-19 patients with chronic

kidney disease, suggesting that these biomarkers are clinically useful to predict the need for mechanical ventilation in the CKD population.

## **INTRODUCTION**

A new variant of coronavirus lead to the pandemic of 2019 and <sup>7</sup> was described as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Initially assumed to be a pathogen affecting the respiratory system, its effects have now been shown to be widespread affecting multiorgan infection and disease manifestation. With more than six million admissions and more than 1 million deaths COVID-19 continues to be an infection with ongoing global concern. As we continue to discover the multitude of pathologies caused by the virus in different organ systems, the various associations and interactions between COVID-19 and existing chronic diseases slowly come to light. It was a sudden increase in the utility of inflammatory biomarkers, as they served as useful indicators of the severity of the underlying disease process. Severe COVID-19 disease is characterized by a hyperinflammatory condition, with multiorgan involvement due to a cytokine storm.<sup>1</sup> Multiple organ specific and nonspecific markers have been studied. Cardiac troponins, BNP and multiple other markers have been shown to predict outcome in patients with and without cardiovascular disease.<sup>2,3</sup> Similar inflammatory markers including cytokines, including IL-6 and C-reactive protein (CRP), have been validated in multiple studies to help predict the severity of disease and the need for mechanical ventilation.<sup>4-6</sup> Studies have shown baseline elevation in these same inflammatory markers in patients with chronic kidney disease alone, due to a chronic inflammatory milieu in Chronic Kidney Disease (CKD) and reduced renal clearance of these inflammatory markers.<sup>7</sup> Currently the clinical utility of these inflammatory markers to predict the need for mechanical ventilation among patients with COVID-19 and underlying chronic kidney disease is unclear. We aimed to assess if elevations in inflammatory markers can similarly predict the rate of invasive and non-invasive mechanical ventilation among COVID-19 patients with chronic kidney disease.

## **MATERIALS AND METHODS**

### **Study design and participants**

We conducted a retrospective single-center cross-sectional study of hospitalized patients between Dec 1, 2019, to Jan 1, 2022, at a 329-bed community teaching hospital in central Massachusetts. In order to be recruited into the study participants had to meet the inclusion criteria

Inclusion criteria : 1) Inpatients admitted with clinical symptomatology and subsequently diagnosed with SARS-CoV-2 infection with PCR test; 2) Age >18 years; 3) Patients with history of Stages IIIb-V chronic kidney disease (eGFR <45 cc/min as per NKF guidelines); and 4) Patients with documented inflammatory markers within 24 h of admission to the hospital. Exclusion criteria included: 1) Pregnant patients; 2) Patients who had a history of renal transplantation; 3) Patients who required renal replacement therapy, 4) Patients who failed to meet the inclusion criteria or if the required information could not be collected. The data was obtained by reviewing medical records, including demographic information, past medical history, medications, labs, and hospitalization course. Two independent physician were involved with acquiring the data. All patient details were anonymized. Preformed proforma was used to acquire the study details such as age, sex, vaccination status, comorbidities such as hypertension, diabetes mellitus, chronic liver disease, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure and the use of medications such as steroids or remdesivir.

### **Exposure and Outcomes**

The primary endpoints measured included the rate of invasive mechanical ventilation (IMV)), the rate of non-invasive mechanical ventilation (NIMV), and the rate of no requirement of mechanical ventilatory support (No-MV). As per ATS guidelines, Invasive mechanical ventilation was defined as intubation and provision of mechanical ventilatory support for respiratory failure. Non-invasive mechanical ventilation

included bi-level positive airway pressure (BiPAP), high flow oxygen, and continuous positive airway pressure (CPAP) support. No mechanical ventilation was defined as requiring oxygen *via* nasal cannula, Oxymizer support, or those who did not require any oxygen supplementation. We assessed the levels of inflammatory markers among the three groups, including C-reactive protein, ferritin, lactate dehydrogenase, and D-Dimer levels using certain cutoffs above which the levels were considered elevated. These cutoffs was designated as per institution protocol and was  $\geq 100$  mg/L for CRP,  $\geq 530$  ng/mL for ferritin,  $\geq 590$  U/L for LDH, and  $\geq 0.5$  mg/L for D-dimer respectively. We collected the baseline demographic data of the study population. Relevant clinical data associated with increased risk of mechanical ventilation, including a history of hypertension, diabetes mellitus, chronic liver disease, chronic pulmonary disease, coronary artery disease, and congestive heart failure, were collected. We also collected data regarding the different treatment modalities that each patient population received.

## **Ethical Considerations:**

Institutional review board statement: The study was reviewed and approved by Saint Vincent- MetroWest Medical Center Institutional Review Board [(Approval No. 2020-035)].

Informed consent statement: The requirement of informed consent was waived by Saint Vincent- MetroWest Medical Center Institutional Review Board [(Approval No. 2020-035)].

## **Data gathering and Statistical Analyses**

The Data was collected in Microsoft excel and was analyzed using SPSS. Non-parametric tests were employed since the data showed a non-normalcy distribution when we assessed it using the Shapiro-Wilk test. Chi-square analysis was employed for analyzing categorical variables and the Mann-Whitney U test was employed for analyzing continuous variables. Univariate logistic regression was utilized to assess the association between covariates and outcomes. We also calculated the area under the

curve (AUC-ROC) for invasive and non-invasive mechanical ventilation for the different covariates, including C-reactive protein, ferritin, and lactate dehydrogenase. The modalities of Medline, Pubmed and RCA were utilized to analyze high impact articles relevant to the current field of study and were incorporated in the discussion

## **RESULTS**

### **Patient characteristics**

Of the 290 patients screened, 118 met the inclusion criteria, among which 26 (22%) required invasive mechanical ventilation, 26 (22%) required non-invasive mechanical ventilation, and 66 (56%) patients did not require any form of mechanical ventilatory support. There was an increased number of males in the group requiring invasive mechanical ventilation compared to those requiring non-invasive mechanical ventilation ( $P = 0.01$ ) (Table 1).<sup>4</sup> Baseline demographics, including age >60 years, vaccination status, and history of hypertension, diabetes mellitus, chronic liver disease, chronic pulmonary disease, coronary artery disease, and congestive heart failure, was similar among the three groups. In terms of medication administration, a significant difference was observed only in steroid use between patients on non-invasive mechanical ventilation compared to those without (84.6% *vs* 66.7%,  $P = 0.01$ ).

### **Mechanical Ventilation and Inflammatory markers**

The association between the levels of inflammatory markers and the use of invasive, non-invasive, and no mechanical ventilatory support was evaluated.

#### **Invasive Mechanical Ventilation:**

We observed a significant difference in the levels of inflammatory markers, including CRP (65.4% *vs* 25.8%,  $P = 0.01$ ), ferritin (61.5% *vs* 36.4%,  $P = 0.01$ ), troponin (42.3% *vs* 22.7%,  $P = 0.03$ ), D-dimer (80.8% *vs* 51.5%,  $P = 0.01$ ), and LDH (26.9% *vs* 4.5%,  $P = 0.04$ ) between patients who required invasive mechanical ventilation and those who did not require mechanical ventilation (Table 2). This correlated with the significantly different



mean levels of inflammatory markers observed between the two groups as well [CRP (160.2 *vs* 67,  $P = 0.001$ ), ferritin (811 *vs* 295,  $P = 0.019$ ), LDH (452 *vs* 321,  $P = 0.001$ ) and D-dimer (2 *vs* 1,  $P = 0.001$ )]. Further univariate analysis between the inflammatory markers showed greater odds of having high inflammatory marker levels in patients who required invasive mechanical ventilation [CRP (OR 5.44, 95%CI: 2.04-14.48), ferritin (OR 2.8, 95%CI: 1.98-7.13), D-dimer (OR 3.95, 95%CI:1.33-11.74), LDH (OR 7.73, 95%CI: 1.821-32.87), but troponin levels were not statistically significant (OR 2.49, 95%CI: 0.947-6.56)].

#### **Non-Invasive Mechanical Ventilation:**

A similar phenomenon of significantly different levels of inflammatory markers was observed in patients who required non-invasive mechanical ventilation in comparison to those without mechanical ventilatory support requirements [CRP (53.8% *vs* 25.8%,  $P = 0.001$ ), ferritin (65.4% *vs* 36.4%,  $P = 0.03$ ), D-dimer (80.8% *vs* 51.5%,  $P = 0.01$ ), and LDH (7.7% *vs* 4.5%,  $P = 0.001$ ), but no significant difference was demonstrated in troponin levels (46.2% *vs* 22.7%,  $p=0.06$ )](Table 3). On assessing the mean levels of inflammatory markers between the two groups, we observed a significant difference in CRP (115.9 *vs* 67,  $P = 0.002$ ), ferritin (628 *vs* 295,  $P = 0.013$ ), and D-dimer (2 *vs* 1,  $P = 0.001$ ) but no significant difference in LDH (357 *vs* 321,  $P = 0.29$ ). We subjected these inflammatory biomarkers to univariate analysis, which showed increased odds of higher levels of all biomarkers except LDH among patients who required non-invasive mechanical ventilation [CRP (OR 3.63, 95%CI: 1.30-8.67), ferritin (OR 3.306, 95%CI: 1.27-8.55), D-dimer (OR 3.95, 95%CI:1.33-11.73), troponin (OR 2.94, 95%CI: 1.11-7.62) but no significant difference was demonstrated in LDH (OR 1.75, 95%CI: 0.27-11.12).

#### **Area under curve - receiver operator characteristic:**

In order to further confirm the role of the inflammatory biomarkers in predicting the need for mechanical ventilation, ROC analysis was carried out. The AUROC for invasive mechanical ventilation was the following: for CRP, AUROC 0.747 (95%CI:0.617-0.878,  $P = 0.001$ ) that yielded a sensitivity of 80.8% and specificity of 50%;



for ferritin, AUROC 0.658 (CI:0.528-0.788,  $P = 0.019$ ) with a sensitivity of 73% and specificity of 50%; for LDH, AUROC 0.699 (CI:0.579-0.820,  $P = 0.003$ ) with a sensitivity of 80.8% and specificity of 50%; and for D-dimer, AUC 0.751 (CI:0.625-0.876,  $P = 0.001$ ) with a sensitivity of 76.9% and specificity of 50% (Figure 1).

The AUROC for non-invasive mechanical ventilation was as follows: for CRP, AUROC 0.663 (95%CI:0.527-0.799,  $P = 0.015$ ) that yielded a sensitivity of 69.2% and specificity of 53%; for ferritin, AUROC 0.667 (CI:0.555-0.778,  $P = 0.013$ ) with a sensitivity of 80.8% and specificity of 53%; and for D-dimer, AUROC 0.740 (CI:0.62-0.86,  $P = 0.004$ ) with a sensitivity of 80.8% and specificity of 50% (Figure 2).

## **DISCUSSION**

This study is unique in assessing the utility of inflammatory markers, such as CRP, ferritin, LDH, and D-dimer in predicting the need for non-invasive as well as invasive mechanical ventilation in COVID-19 disease in patients with CKD. We observed that a higher proportion of COVID-19 patients with CKD who had elevated inflammatory marker levels ultimately required mechanical ventilation. The average inflammatory marker levels in all 3 groups (MV, NIMV and no MV) were high. Elevated levels of inflammatory markers were highly predictive of the need for invasive mechanical ventilation with corresponding AUROC of 0.747, 0.658, 0.699, and 0.751 for CRP, ferritin, LDH, and D-dimer, respectively. Although not all markers were predictive of the need for non-invasive mechanical ventilation, CRP, ferritin, and D-dimer were predictive, with corresponding AUROCs of 0.663, 0.667, and 0.74, respectively. Although the pathophysiology explaining elevated LDH levels in patients requiring invasive mechanical ventilation but not amongst patients requiring non-invasive mechanical ventilation is not explicitly clear, we hypothesize that this could be secondary to the LDH cutoff that was used to define levels as elevated. LDH enzyme plays a prominent role in active metabolism and levels are elevated with minor abnormalities such as tissue hypoxia and lysis necessitating a higher cutoff to detect

significantly elevated LDH levels.<sup>8</sup> The results of our study reinforced the predictive value of CRP, ferritin, and D-Dimer in patients with COVID-19 and underlying Stages IIIb-V CKD. Among patients with chronic kidney disease alone, studies have shown baseline elevated inflammatory marker levels, due to a chronic inflammatory milieu and decreased renal clearance of these inflammatory markers.<sup>7</sup> Our study highlighted the positive correlation of these markers with invasive as well as non-invasive mechanical ventilation in COVID-19 patients with Stages IIIb-V CKD; the high sensitivity of these markers demonstrated by the AUROC signifies their predictive potential.

In our study, the demographic variables were similar to the previous studies.<sup>4,5</sup> Male sex was associated with an increased risk of the need for invasive and non-invasive mechanical ventilation.<sup>3</sup> Sex may influence the severity of SARS-CoV-2 as the X-chromosome contains a higher density of immune-related genes and immunoregulatory elements related to innate and adaptive immunity.<sup>9</sup> There was an equal distribution of the need for mechanical ventilation in the presence of associated comorbidities, such as hypertension, diabetes mellitus, chronic liver disease, chronic obstructive pulmonary disease, coronary artery disease, and congestive heart failure.<sup>4</sup> We noticed a significantly increased steroid administration rate in the non-invasive mechanical ventilation group compared to the no mechanical ventilation group, possibly due to the greater severity of the disease.

Biomarkers are a clinical reflection of the underlying disease process and help us assess the disease activity. This was frequently employed in COVID-19 disease with studies showing a correlation between elevated inflammatory marker levels and severe COVID-19 disease.<sup>5,6</sup> Although markers such as interleukin-6 (IL-6) were initially explored, they are cost-prohibitive and thus unsuitable for routine monitoring in COVID-19 patients.<sup>4</sup> This led to research on more routine biomarkers, including CRP, ferritin, LDH, and D-dimer, which have been shown to correlate well with the severity

of COVID-19 disease.<sup>10</sup> Despite the use of different values of CRP to define elevation in multiple studies, <sup>6</sup> such as Koozi *et al* - >1000mg/L, Ryoo *et al* - >140mg/L, and Liu *et al* - > 41.8mg/L, there was a uniformly observed greater risk of severe COVID-19 disease. <sup>11-14</sup>

Inflammatory markers are used for risk stratification and prognostication in several infectious diseases and malignancies, which are characterized by inflammation.<sup>15,16</sup> The pro-inflammatory nature of COVID-19 infection and associated organ dysfunction is well established.<sup>17,18</sup> Inflammatory markers, including CRP, erythrocyte sedimentation rate (ESR), LDH, and procalcitonin (PCT) are found to be elevated in patients with COVID-19.<sup>19,20</sup> Studies such as those by Herold *et al* have demonstrated the utility of these biomarkers in prediction models that help detect the need for invasive and non-invasive mechanical ventilation in patients with COVID-19 disease. They demonstrated an AUROC value of 0.97 and 0.86 for IL-6 and CRP with optimal cutoff values (IL-6: 80pg/mL and CRP: 97mg/L) that correctly classified 80% of their study population regarding their risk of respiratory failure.<sup>4</sup> The study by Li W *et al* used a multivariate stepwise logistic regression model to show the use of a glucocorticoid, increased neutrophil count, and procalcitonin level in COVID-19 as predictive indicators for non-invasive mechanical ventilation and <sup>3</sup> the use of glucocorticoid increased neutrophil count and LDH level as effective predictors for invasive mechanical ventilation.<sup>5</sup> In another single-center retrospective observational study, ferritin, LDH, absolute lymphocyte count, and CRP were found to predict the probability of early MIV with an accuracy of 88%. <sup>21</sup>

The inflammatory markers are renally cleared, and hence reduced kidney function is associated with elevated levels of serum inflammatory markers. In addition, CKD is associated with chronic inflammation. Studies have demonstrated an elevation of CRP levels in patients with CKD and a negative correlation between CRP levels and GFR. There is evidence <sup>7</sup> that inflammation, as measured by CRP level, increases with

declining renal function in CKD patients.<sup>22-24</sup> A study by Keller C, *et al* showed that in patients with initial stages of CKD and with ESRD, the levels of CRP, fibrinogen, D-dimer, coagulation factor VII, factor VIII were increased, either due to increased production *vs* decreased clearance.<sup>25</sup> CKD stages IIIb-V was selected since there was a significant increase in mortality rate amongst patients with CKD IIIb-V.<sup>26</sup>

In our study, the mean CRP levels at admission in COVID-19 patients with Stages IIIb-V CKD requiring invasive mechanical ventilation were remarkably higher than those who did not require mechanical ventilation (160.19 *vs* 67.02,  $P = 0.001$ ). This finding likely reflects the impact of acute, severe COVID-19-related illness on the existing chronic inflammation in CKD, and concomitant reduced renal clearance of inflammatory markers. We found CRP, ferritin, LDH, and D-dimer to be good predictors of invasive mechanical ventilation and CRP, ferritin, and D-dimer to be good predictors of non-invasive mechanical ventilation. Regardless of the negative correlation of inflammatory biomarkers with GFR in CKD, our study validated their high sensitivity in predicting COVID-19 prognosis in this specific population.

### **Limitations:**

One of the limitations of our study includes a small study population. We also did not include patients who had a history of renal transplantation, in order to minimize the influence of immunosuppressive medications in our study population. Another limiting factor includes the absence of information about baseline inflammatory marker levels in the setting of their underlying CKD. There are multiple factors that influence inflammatory marker levels, such as age, BMI, sex, use of nicotine, blood pressure, and

liver injury.<sup>20</sup> We did not study more specific markers such as IL-6, IL-1 $\beta$ , and IL-8, which are more sensitive but are cost-prohibitive in the real-world setting. We did not study the interactions of other comorbidities, interventions and various medications with these inflammatory markers and the disease severity.<sup>27,28,29</sup> We also did not have the long term follow up details of these patients.

#### **Future implications:**

Further prospective studies are needed to establish the correlation between the levels of inflammatory markers and the need for mechanical ventilation in COVID-19 patients with chronic kidney disease. Validation of these inflammatory biomarkers is key in establishing their use as predictive indices. With the clinical utility of these inflammatory markers being described, it is imperative to study the impact of different disease processes on these inflammatory markers before employing them as clinical tools to guide the diagnosis and management of acute COVID-19 infection.

#### **CONCLUSION**

Our study explored the efficacy and predictive ability of inflammatory markers in detecting the risk of respiratory failure and the subsequent need for invasive and non-invasive mechanical ventilation among COVID-19 patients with pre-existing chronic kidney disease. We demonstrated that inflammatory markers, including CRP, ferritin, and D-dimer are useful predictive indicators of invasive and non-invasive MV in COVID-19 patients with Stages IIIb-V CKD. The AUROC demonstrates good sensitivity for CRP levels in predicting the need for MV in the general population as well as in patients with Stages IIIb-V CKD. This could be explained by the rationale that COVID-19 creates a greater magnitude of increased inflammation compared with increased inflammation due to CKD alone. With an increased need for better prognostic tools to help predict the severity of disease, especially among high-risk populations, and with the rising use of inflammatory markers to risk-stratify patients with COVID-19, large-



scale, prospective studies are needed to delineate the optimal utilization of these biomarkers.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Inflammatory markers have been validated in multiple studies to help predict the severity of disease and the need for mechanical ventilation. Studies have shown baseline elevation in these same inflammatory markers in patients with chronic kidney disease alone, due to a chronic inflammatory milieu in Chronic Kidney Disease (CKD) and reduced renal clearance of these inflammatory markers. The clinical utility of these inflammatory markers to predict the need for mechanical ventilation among patients with COVID-19 and underlying chronic kidney disease is unclear.

### ***Research motivation***

The use of Biomarkers has been progressively increasing since the COVID-19 pandemic and the need for establishing the utility of these biomarkers in the presence of multiple comorbidities becomes essential to establish their clinical utility. Hence there is utmost need for this study to assess use of CRP level in assessing Mechanical ventilation risk in CKD patients.

### ***Research objectives***

Our aim was to assess whether an association exists between elevated inflammatory markers and MV rate in patients with Stages IIIb-V CKD and COVID-19.

### ***Research methods***

We conducted a retrospective single-center cross-sectional study of hospitalized patients between Dec 1, 2019, to Jan 1, 2022, at a community hospital. The primary outcome was the rate of invasive MV, the rate of noninvasive MV, and the rate of do



MV. Statistical analyses used unpaired t-test for continuous variables and chi-square analysis for categorical variables.

### **Research results**

290 were screened, and 118 met the inclusion criteria. CRP, D-dimer, and ferritin were significantly different among the three groups. On univariate analysis for IMV, CRP had an OR-5.44; ferritin, OR-2.8; LDH, OR-7.7; D-dimer, OR-3.9, ( $p < 0.05$ ). The admission CRP level had an AUROC: 0.747 for the IMV group (sensitivity-80.8%, specificity-50%) and 0.663 for the NIMV group (AUC-ROC, sensitivity-69.2%, specificity-53%).

### **Research conclusions**

Our results demonstrate a positive correlation between CRP, ferritin, and D-dimer levels and MV and NIMV rates in CKD patients. The AUROC demonstrates a good sensitivity for CRP levels in detecting the need for MV in patients with Stages IIIb-V CKD.

### **Research perspectives**

Validation of these inflammatory biomarkers is key in establishing their use as predictive indices. With the clinical utility of these inflammatory markers being described, it is imperative to study the impact of different disease processes on these inflammatory markers before employing them as clinical tools to guide the diagnosis and management of acute COVID-19 infection.

# 11%

SIMILARITY INDEX

### PRIMARY SOURCES

1	<a href="https://referencecitationanalysis.com">referencecitationanalysis.com</a> Internet	208 words — 5%
2	<a href="https://www.gavinpublishers.com">www.gavinpublishers.com</a> Internet	44 words — 1%
3	<a href="https://www.ncbi.nlm.nih.gov">www.ncbi.nlm.nih.gov</a> Internet	43 words — 1%
4	<a href="https://nmji.in">nmji.in</a> Internet	39 words — 1%
5	Hui Chen, Jianbin Tong, Haixia Zhu, Kaiyuan Song, Xichang Tang, Huan Xu, Qingxiang Liu, Canhui Peng. "Neurosymptoms of COVID-19: results of cerebrospinal fluid and blood biomarkers and assessment of diagnostic efficacy of risk factors", Research Square Platform LLC, 2023 Crossref Posted Content	36 words — 1%
6	<a href="https://www.wjgnet.com">www.wjgnet.com</a> Internet	36 words — 1%
7	<a href="https://www.ajol.info">www.ajol.info</a> Internet	28 words — 1%
8	<a href="https://f6publishing.blob.core.windows.net">f6publishing.blob.core.windows.net</a> Internet	15 words — < 1%

9

daten-quadrat.de

Internet

14 words — &lt; 1%

10

Tobias Herold, Vindi Jurinovic, Chiara Arnreich,  
Brian J. Lipworth et al. "Elevated levels of IL-6 and  
CRP predict the need for mechanical ventilation in COVID-19",  
Journal of Allergy and Clinical Immunology, 2020

Crossref

13 words — &lt; 1%

EXCLUDE QUOTES ON

EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES &lt; 12 WORDS

EXCLUDE MATCHES &lt; 12 WORDS