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Pan -Immune- Inflammation Value to Predict Early Mortality in Adults with Severe Covid 19: An Observational Retrospective Study

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ABSTRACT

Background: The SARS-CoV-2 infection has triggered a worldwide outbreak of COVID-19. Infection with SARS-CoV-2 can cause a wide spectrum of symptoms, from no obvious illness at all to a life-threatening form of the virus called COVID-19 that necessitates hospitalization. Hospitalized patients frequently develop life-threatening cases of pneumonia and acute respiratory distress syndrome (ARDS).

Objective: The study's overall objective was to establish the predictive significance of pan-immune-inflammatory status for death in persons suffering from severe Covid-19.

Patients and methods: A retrospective study that was conducted on 200 cases of sever Covid 19 collected from ICU, Department of Internal Medicine, Menoufia University Hospital, Full analysis of medical history and laboratory investigations were taken during the period study from September 2021 to October 2022.

Results: Results showed that PIV (pan immune inflammation value) was increased in studied cases by mean of (343.28±127.9), and there was highly statistically significant +ve relationship among PIV and mortality in studied patients (higher in died group) P value <0.001 by mean of 526.01±72.81. PIV was the most important predictor of mortality in severe COVID-19 cases in univariate analysis of highly statistically significant.

Conclusion: It could be concluded that PIV is increased in severe COVID-19 cases and is an important predictor of mortality of these patients.

Keywords: COVID-19, Inflammation, Pan immune inflammation value, Prognosis

INTRODUCTION

The severe acute respiratory syndrome (SARS-CoV-2) may be caused by a coronavirus pandemic [(1)].

The global cost of treating this viral infection has overwhelmed healthcare and public health institutions. Researchers have been hard at work looking into biological factors as possible markers of COVID-19 risk and severity. Risk factor epidemiology aims to predict or discover persons who may become ill, be hospitalized, or pass away to provide more targeted public health interventions and relieve strain on already-stretched health care infrastructures [(2)]. T-cell adaptive immune responses are crucial in SARS-CoV-2 infection, as they are in other respiratory viral infections. Whether or not T cell responses are beneficial in COVID-19 is still up for debate; data has been shown for both suboptimal and dysfunctional and excessive T cell responses [(3)].

The pathophysiology of COVID-19 is a topic of ongoing research. Increased neutrophils and platelets, as well as decreased lymphocytes, have been linked by several studies [(4)]. Based on these results, it seems likely that immuno-inflammatory responses contribute significantly to the pathophysiology of COVID-19 and to the development of the disease (as well as its many consequences) [(5)]. Neutrophil, platelet, monocyte, and lymphocyte counts as well as their relative variations in PIV's value may be indicative of the equilibrium between the host's immunological and inflammatory status. Viral illnesses developed and progressed with the help of inflammatory cells [(1)].

The aim of the current work was to establish the predictive significance of pan-immune-inflammatory status for death in persons suffering from severe Covid-19.

PATIENTS AND METHODS

This retrospective study included a total of 200 cases with severe covid 19 collected from ICU, Department of internal medicine, Menoufia University Hospital. during the period from September 2021 to October 2022.

Inclusion criteria: Individuals who tested positive for COVID-19 infection via examination of nasopharyngeal and/or oropharyngeal swabs.

Exclusion criteria: Chronic inflammatory disease as (FMF, malignancy), patients on immunosuppressive therapy, and patients with viral infection other than COVID 19 (HIV)

The following were applied to all study participants:

Thorough Full medical history taking:

Paying particular attention to: age, gender, BMI, occupation, and any unusual or potentially harmful behavior (such as smoking). Duration and timing of symptoms such as (but not limited to) fever, cough, shortness of breath, muscular discomfort, disorientation, headache, sore throat, rhinorrhea, chest pain, diarrhea, nausea, and vomiting. Background comorbidities (such as a history of high blood pressure or diabetes), Drug history.

Laboratory investigations: Complete blood count (CBC), ALT & AST, PT & INR, Bilirubin (total &direct), albumin, virology, serum urea& creatinine,

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ESR, CRP, serum ferritin, D dimer, pro calcitonin & CT chest were done.

Ethical Approval: The study was approved by the Ethics Board of Menoufia University and the patients were given all the information they need about the trial. An informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Using an IBM compatible computer, the data was processed with SPSS (statistical software for social science; SPSS Inc., Chicago, IL, USA) version 26.0. Quantitative "n (%)" and "Chi-square" and "Fisher's exact" tests were applied to the qualitative data. The Shapiro-Wilks test was used to check if the quantitative data were normally distributed (assuming normality at $P > 0.05$). Mean, standard deviation, and range were used to characterize quantitative data, which was tested with the Student's t-test for normality or the Mann-Whitney U-test and the Kruskal-Wallis test for non-normality. In this study, a value of P less than 0.05 was judged to be statistically significant.

RESULTS

This retrospective study included a total of 200 cases with severe covid 19.

Table (1) shows the descriptive data of the studied cases regarding age from 18 – 75 years with mean ±SD of 47.58±18.36 years and BMI with mean of (23.05±2.59). The studied group included 68 females (34%) and 132 males (66%). The prevalence of hypertension in the studied group was (46%), diabetes (50%)and Asthma (27.5%) . Most of the studied group was non-Smoker (56%). Analysis of symptoms among the studied group showed that fever appear in 165 patients (82.5%), cough appear with in 185 patients (92, 5%), shortness of breathing in 163 patients (81.5%), Git irritability in 113 patients (56.5%). (12.5 %) 0f the studied group have HBV, (7%) have HCV**.** Regarding vital signs, the current study showed that the mean RR was 35.66±4.3 **cycle/minute**, PR was 125±33.65 beats/min, and mean oxygen saturation was 80.5±3.70%. Within 2 days of admission, all patients had their lung CT scans completed. CT chests show Ground glass appearance complicated with bronchopneumonia within 150 patients (75%) and the others CT showing Ground glass appearance (25%). As regard treatment used all cases received antiviral therapy, 71.5% received anticoagulant, 42.5% received antibiotic, and steroids given in 33.5% of cases, 52% of cases received non-invasive mechanical ventilation, 36% Invasive mechanical ventilation & high oxygen flow nasal cannula given for 12% of cases **,** The prevalence of ICU early mortality after 7 days among the studied group was (56 patients) (28%)

Table (1): descriptive data of studied patients (No =200)

Variable	**No.**	**%**
Age (years) Mean ± SD.	47.58±18.36	
Sex (Male) (no, %)	132	66
Smoking (no, %)	88	44
BMI (Kg/m^2) Mean ± SD.	23.05±2.59	
comorbidities	**No.**	**%**
No (no, %)	59	29.5
Yes (no, %)	141	70.5
Hypertension (no, %)	92	46
Diabetes (no, %)	100	50
Asthma (no, %)	55	27.5
Symptoms	**No.**	**%**
Fever (no, %)	165	82.5
Cough (no, %)	185	92.5
Shortness of breath (no, %)	163	81.5
Digestive symptoms (no, %)	113	56.5
Respiratory rate (RR) (cycle/minute) mean	35.66±4.3	
Pulse rate (beats/minute) mean	125±33.65	
O2 saturation(%) mean	80.5±3.70	
CT chest	No	%
Bilateral ground glass appearance complicated with bronchopneumonia (no, %)	150	75
Bilateral ground glass appearance (no, %)	50	25
Treatment given Antiviral therapy (no, %)	200	100
Antibiotic (no, %)	85	42.5
Anticoagulant (no, %)	143	71.5
Steroids (no, %)	67	33.5
Oxygen therapy Noninvasive mechanical ventilation (no, %)	104	52
Invasive mechanical ventilation (no, %)	72	36
High flow nasal cannula (no, %)	24	12
ICU early mortality after 7 days (n = 200)		
No (no, %)	144	72
Yes (no, %)	56	28

Table (2) shows the descriptive analysis of the studied cases according to laboratory data. The Mean ±SD of Hb was 12.83±1.85 **g/dl** , median WBCs was 8.95(6.6-10.9)**10^9/L**, mean platelet count was (245.9±48.5)**10^9/L** , median neutrophil was 3.25(2.9-3.8)**10^9/L**, median lymphocyte was 1.2(.9-1.7) **10^9/L**, mean albumin was 4.65±0.56 **g/L**, median AST, ALT was 39 (35-43) **u/L**, 40 (37-43) **u/L** respectively, median total bilirubin 0.7 (0.5-1)**mg/dl**, median direct 0.29 (0.2-0.35)**mg/dl**, and median creatinine, urea nitrogen was 1 (0.8-1.2) **mg/dl**, 24 (19-27)**mmol/L** respectively . Median D-dimer 0.7(0.55-1.1) **mg/L**,

median CRP was 37(30-41)**mg/L**, median ferritin was 849.35(620.5-1309)**ng/ml**, mean procalcitonin was 0.78±2.89 **ng/ml** .according to virology **HBsAg (-ve)** in all patients , **HBcAb (+ve)** in 12.5% and **HCV Ab (+ve)** in 7%

Table (2): Descriptive analysis of the studied cases according to laboratory data (n = 200)

Laboratory parameters	
Hb (g/dl) mean±SD	12.83±1.85
WBCs (10^9/L) median	8.95 (6.6-10.9)
Neutrophil (10^9/L) median	3.25(2.9-3.8)
Monocyte median	0.46(0.3-0.7)
Lymphocyte (10^9/L) median	1.2(.9-1.7)
Platelet (10^9/L) mean±SD	245.9±48.5
AST (u/L) median	39 (35-43)
ALT (u/L) median	40 (37-43)
Albumin (g/L) mean±SD	4.65±0.56
Total bilirubin (mg/dl) median	0.7 (0.5-1)
Direct-bilirubin (mg/dl) median	0.29 (0.2-0.35)
PT mean±SD	11.13±0.54
Creatinine (mg/dl) median	1 (0.8-1.2)
Urea (mg/dl) median	24 (19-27)
Ferritin (ng/ml) median	849.35 (620.5-1309)
D-dimer (mg/L) median	0.7 (0.55-1.1)
CRP (mg/L) median	37 (30-41)
Procalcitonin (ng/ml) mean±SD	0.78±0.18
Virology	
HBsAg (-ve) (No, %)	200 100
HBcAb (+ve) (No, %)	25 12.5
HCVAb (+ve) (No, %)	14 7

CRP: highly sensitive C-reactive protein, Hb: hemoglobin, WBCS: white blood cells, AST: aspartate transaminase, ALT: alanine transaminase

Table (3) shows the PIV in the studied group which ranged from 147.93-642.88 with mean and SD (343.28±127.9). The distribution of the studied cases according to mortality as showed in **Table (4)** indicates that there was a statistically significant difference between mortality and PIV, with early ICU death within 7 days reaching 28% among included cases, that was higher in died group by mean of (526.01±72.81) (P value <0.001) as shown in **Table (5)**.

Table (3): PIV (pan immune inflammation value) in the studied group

Studied variables	Mean ± SD
PIV	343.28±27.9

Table (4): Distribution of the studied cases according to mortality

	No.	%
ICU early mortality after 7 days (n = 200)		
No	144	72
Yes	56	28

Table (5): Relation between PIV and mortality in the studied group

	Mortality		Test of sig.	P value
	Died No=56	Discharged No=144		
PIV Mean ± SD	526.01±72.81	272.22±50.63	t=23.93	<0.001

Table (6): The severity among the studied group (discharged group) (N= 144)

Severity	No.	%
Mild	40	20
Moderate	60	30
Severe	44	22

Regarding the severity among the studied group (discharged patients were 144) **Table (6)** shows The prevalence of Mild cases were (20%), the moderate cases were (30%) and severe cases were (22%) among the studied group, The correlation between illness onset and mortality of the studied cases in **Table (7)** which shows Median time from commencement of illness to death or discharge was 11.0 (7.0 -20.0) days, and mean time to ICU admission was 9.49±3.31 days.

Table (7): Distribution of the studied cases according to mortality

	No.	%
Time from illness onset to ICU admission in days (n= 200) Mean ± SD.	9.49±3.31	
Time from illness onset to death or discharge in days (n = 200) Median (IQR)	11(7-20)	

There was highly statistically significant +ve relationship among Ferritin, D-dimer, CRP, Procalcitonin and mortality that was higher in non-survivors than survivors by mean of **(1570.01± 41.2)**, (**1.35± 0.35**), (**44.65± 9**), (**0.46±0,1)** respectively as showed in **Table (8)** ,Univariate analysis was done to assess the association of parameters with mortality in sever COVID-19 patients as **Table (9)** shows that The most highly statistically significant parameter was PIV by HR (95%CI) was (0.547-1.350), p-value was <0.001 followed by Lymphocytes HR (95%CI) 1.076-1.563 (p-value.008), WBCs HR (95%CI) 1.110-33.650 (p-value 0.037), age HR (95%CI) 0.564-1.598 (p-value.041), Ferritin HR (95Percent CI) 0.529-0.990 (p-value .043), CRP HR (95 Percent CI) 0.544-0.995 (p-value 0.046) & D-dimer HR (95%CI) 0.522-0.993 (p-value 0.047) .

Table (8): spearman Relationship among early mortality & demographic data (n= 200)

	Survivor (n = 144)		**Non survivor (n = 56)**		**p**
	No.	**%**	**No.**	**%**	
Sex					
Male	99	68.75	33	58.92	**0.097**
Female	45	31.25	23	41.07	
Age (years) Mean ± SD.	**46.14** ± 17		**52.45± 18**		**0.041**
Diabetes	76	52.7	24	42.9	**0.039**
Hypertension	74	51.8	18	32.14	
Total bilirubin (mg/dl) Mean ± SD.	**0.747± 0.05**		**0.765± 0.05**		**0.043**
Direct bilirubin (mg/dl) Mean ± SD.	**0.266± 0.03**		**0.288± 0.085**		**0.166**
PT Mean ± SD.	**11.83± 0.6**		**11.802± 0.7**		**0.053**
D-dimer(mg/L) Mean ± SD.	**0.706± 0.03**		**1.35± 0.03**		**0.001***
CRP (mg/L) Mean ± SD.	**35.10 ± 1**		**44.65± 9**		0.001*
Ferritin (ng/ml) Mean ± SD.	**858.90± 93.7**		**1570.01± 41.2**		0.001*
Procalcitonin (ng/ml)					
mean± SD.	**0.34±0.01**		**0.46±0.01**		**0.057**
Hb (g/dl)	**12.7±3.15**		**13.23±2.1**		**0.883**
Mean ± SD.					
WBCs (10^9/L)	**8.19±0.23**		**12.08±3.8**		**0.014***
Mean ± SD.					
Platelet (10^9/L)					
Mean ± SD.	**259±17.2**		**185.5 ±16.8**		0.001*
Neutrophil(10^9/L)					
Mean ± SD.	**3.2±0.5**		**3.5±0.3**		**0.108**
Lymphocyte(10^9/L)					
Mean ± SD.	**1.4±0.04**		**0.7±0.07**		**0.030***
Albumin (g/L)					
Mean ± SD.	**4.7±0.03**		**4.75±0.09**		**0.557**
AST (U/L)					
Mean ± SD.	**38.89±8**		**38.84±5**		**0.567**
ALT (U/L)					
Mean ± SD.	**39.97±6**		**41.8±3.5**		**0.751**
Creatinine (mg/dl)	**1±0.03**		**1.05±0.06**		
Mean ± SD.					**0.654**
Urea (mg/dl)					
Mean ± SD.	**23.87±5**		**26.61±3**		**0.689**
PIV					
Mean ± SD	**272.22±5.63**		**526.01±7.81**		**<0.001**

R: spearman correlation test

Table (9): Univariate analysis for the parameters affecting early mortality in studied patients

	Univariate	
	p	HR (95%C.I)
Sex (male)	0.09	0.732-0.985
Age (years)	0.041	0.564-1.598
PT	0.448	1.538-4.998
D-dimer (mg/L)	0.047*	0.522-0.993
CRP (mg/L)	0.046*	0.544-0.995
Ferritin (ng/ml)	0.043*	0.529-0.990
Procalcitonin (ng/ml)	0.891	0.584-1.596
Hb (gm/dl)	0.067	0.999-1.041
WBCs (10^9/L)	0.037*	1.110-33.650
Red cell count (10^{12}/L	0.145	0.693-1.072
Platelet (10^9/L)	0.041*	1.234-5256.4
Neutrophil (10^9/L)	0.309	0.551-6.587
Lymphocyte (10^9/L)	0.008*	1.076-1.563
Albumin (g/L)	0.458	0.489-4.893
AST (u/L)	0.835	0.107-15.973
ALT (u/L)	0.248	1.330-5.852
Total bilirubin (mg/dl)	0.314	0.565-5.895
Direct-bilirubin(mg/dl)	0.844	0.389-3.177
Creatinine (mg/dl)	0.121	0.107-15.973
Urea (mg/dl)	0.245	0.674-1.76
PIV	0.001*	0.547-1.350

HR: Hazard ratio P: P value (probability value) C.I: Confidence interval

Table 10 shows that The dividing line between those who make it and those who don't D dimer levels were found to be significantly higher (0.234 - 4.618) in deceased individuals compared to living individuals using univariate and multivariate logistic regression analyses. In deceased patients compared to living patients, CRP was (0.507-9.993), Ferritin was (0.416-5.721), lymphocytes were (0.986-1.022), and PIV was (0.335-1.084).

Table (10): Univariate and multivariate logistic regression analysis

	Univariate		#Multivariate	
	p	HR (95%C.I)	p	HR (95%C.I)
Sex (male)	**0.024***	**0.732-0.985**	0.308	0.503 – 8.866
D-dimer (mg/L)	**0.047***	**0.522-0.993**	0.959	0.234 – 4.618
CRP (mg/L)	**0.046***	**0.544-0.995**	0.286	0.507 – 9.993
Ferritin (ng/ml)	**0.043***	**0.529-0.990**	**0.512**	0.416 – 5.819
WBCs (10^9/L)	**0.037***	**1.110-33.650**	**0.541**	0.854 – 1.352
Platelet (10^9/L)	**0.041***	**1.234-5256.4**	**0.999**	0.976 – 1.025
Lymphocyte (10^9/L)	**0.008***	**1.076-1.563**	**0.682**	0.986 – 1.022

DISCUSSION

There has been no conclusive research into the pathogenesis of COVID-19. Researchers have identified a link between low lymphocyte counts and higher illness severity and mortality, whereas others have shown the opposite to be true [(4)]. These results indicate that immuno-inflammatory responses are involved in the pathophysiology of COVID-19 and the development of the disease (as well as its many consequences) [(6)]. Neutrophil, platelet, monocyte, and lymphocyte count as well as their relative fluctuations may provide insight into the state of the host's immunological and inflammatory systems thanks to the novel biomarker PIV. There was a specific function for each type of inflammatory cell in the onset and course of viral illnesses [(7)].

Our study showed that age varies with a mean of (47.58±18.36 years**)** & BMI with a mean of (23.05 ± 2.59). The occurrence of severe COVID-19 increased with age & BMI as in the study of **Popkin *et al.*** [(8)]. The prevalence of hypertension in the studied group was (46%) and diabetes (50%). Most of the studied group were non-Smoker (56%), there was statistically significant between severity of covid-19 and presence of comorbidity as the severity increased with presence of comorbidity as in the study of **Barrera *et al.*** [(9)].

Within 2 days of hospitalization, all patients had a CT scan of their lungs .CT chest show Ground glass appearance complicated with bronchopneumonia within 150 patients (75%) and the others CT showing Ground glass appearance.as in the study of **Thomas C, Robert M**, [(10)].

There is no statistically significant differences between sex, virology (HBsAg, HBcAb, HCVAb), hemoglobin, ALT, AST, creatinine, urea and mortality in covid 19 patients, these findings as in the study of **Sattar *et al.*** [(11)]**, Majeed *et al.*** [(12)] and against the study of **Balderramo *et al.*** [(13)]**.**

There was statistically significant difference between TLC, lymphocytes, bilirubin, Prothrombin time & mortality in covid 19 cases. These findings were nearly agreed with study results of **Zhang *et al.*** [(14)].

There was a highly statistically significant +ve correlation between Ferritin, D-dimer, CRP, PLT, procalcitonin and mortality that was higher in non-survivors than survivors. As the study of **Marielen *et al.*** [(15)].

In the present study the prevalence of Mortality among the studied group was (56 patient) (28%), there is significant correlation between mortality and PIV, PIV was higher in dead group (P value <0.001).

LIMITATIONS

First, our study is limited in its persuasive power by its retrospective nature. The results of our investigation require cautionary explanation due to the presence of potential confounders. Second, the number of people we studied who have COVID-19 was rather modest. To confirm our findings, more studies with larger populations and prospective designs are required.

CONCLUSION

It could be concluded that PIV is increased in severe COVID-19 cases and is an important predictor of mortality of these patients.

There was highly statistically significant +ve correlation between Ferritin, D-dimer, CRP, procalcitonin and mortality that was higher in non-survivors than survivors, The PIV was significantly higher among the dead than in the living, indicating a strong statistical relationship between the two.

DECLARATIONS

- **Consent for publication:** I attest that all authors have agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** no conflicts of interest.

REFERENCES

1. **Lu Y, Huang Z, Wang M *et al*. (2021):** Clinical characteristics and predictors of mortality in young adults with severe COVID-19: a retrospective observational study. Annals of Clinical Microbiology and Antimicrobials, 20(1): 1–9.
2. **Wynants L, Van Calster B, Collins G *et al*. (2020):** Prediction models for diagnosis and prognosis of covid-19: a systematic review and critical appraisal. BMJ., 369: m1328.
3. **Kuri-Cervantes L, Pampena M, Meng W *et al*. (2020):** Comprehensive mapping of immune perturbations associated with severe COVID-19. Science immunology, 5(49): 7114.
4. **Wu F (2020):** A new coronavirus associated with human respiratory disease in China. Nature, 579: 265-269.
5. **Conti P, Ronconi G, Caraffa A, Gallenga C *et al.* (2020):** Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents, 34(2):327-331. doi: 10.23812/CONTI-E.
6. **Tay M, Poh C, Rénia L (2020):** The trinity of COVID-19: immunity, inflammation and intervention. Nat RevImmunol., 20(6):363-374. doi: 10.1038/s41577-020-0311-8.
7. **Hendrickson C, Matthay M (2013):** Viral pathogens and acute lung injury: investigations inspired by theSARS epidemic and the 2009 H1N1 influenza pandemic. Semin Respir Crit Care Med., 34: 475-486. https://doi.org/10.1055/s-0033-1351122
8. **Popkin B, Du S, Green W *et al.* (2020):** Individuals with obesity and COVID-19: a global perspective on the epidemiology and biological relationships. Obes Rev., 21(11):e13128. doi: 10.1111/obr.13128.
9. **Barrera F, Shekhar S, Wurth R *et al*. (2020):** Prevalence of Diabetes and Hypertension and Their Associated Risks for Poor Outcomes in Covid-19 Patients. J Endocr Soc.,4(9):bvaa102. doi: 10.1210/jendso/bvaa102.
10. **Thomas C, Robert M (2020):** Chest CT in COVID-19: What the Radiologist Needs to Know. doi: 10.1148/rg.2020200159
11. **Sattar N, Ho F, Gill J (2020):** BMI and future risk for COVID-19 infection and death across sex, age and ethnicity: preliminary findings from UK biobank. Diabetes Metab Syndr., 14:1149–1151.
12. **Majeed A, Shajar M (2020):** Is hemoglobin the missing link in the pathogenesis of COVID-19? Anaesth Pain Intensive Care, 24:9-12.
13. **Balderramo D, Mattos A, Mulqui V *et al*. (2021):** Abnormal Liver Tests during Hospitalization Predict Mortality in Patients with COVID-19: A Multicenter Study from South America. Can J. Gastroenterol. Hepatol.,2021:1622533. doi: 10.1155/2021/1622533.
14. **Zhang X, Cai H, Hu J *et al*. (2020):** Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. Int J Infect Dis., 94:81-87
15. **Marielen R, Ana Luísa H, Paulo V *et al*. (2021):** Immunity and inflammatory biomarkers in COVID-19.doi: 10.1002/rmv.2199.