International Journal of Medical and Pharmaceutical Research
Website: https://ijmpr.in/ | Print ISSN: 2958-3675 | Online ISSN: 2958-3683
NLM ID: 9918523075206676
Volume: 4 Issue:3 (May-June 2023); Page No: 368-373

Original Article

IJMPR

Is SAA a better marker of acute exacerbation than other inflammatory markers like hsCRP, Ferritin and LDH? –A comparative study

Desai Vidya Sripad[1], Naga Guhan*[2], Nichenametla Gautam[3], Montosh Chakraborty[4], Bari Siddiqui[5], Saidaiah Ikkurthi[6], Krishna Rao[7], Mangayarkarasi[8], Rakesh UK[9], Arundhathi[10]

[1] MBBS, MD Biochemistry, Additional Professor, Department of Biochemistry, AIIMS Mangalagiri, India
[2] MBBS, MD Biochemistry, Assistant Professor, Department of Biochemistry, AIIMS Mangalagiri, India
[3] MBBS, MD Biochemistry, Assistant Professor, Department of Biochemistry, SRM Medical college, Trichy, India
[4] MBBS, MD Biochemistry, Associate Professor, Department of Biochemistry, AIIMS Mangalagiri, India
[5] MBBS, MD Biochemistry, Assistant Professor, Department of Biochemistry, AIIMS Mangalagiri, India
[6] MSc Biochemistry, Tutor, Department of Biochemistry, AIIMS Mangalagiri, India
[7] MSc PhD, Tutor, Department of Biochemistry, AIIMS Mangalagiri, India
[8] MBBS, MD Microbiology, Additional Professor, Department of Microbiology, AIIMS Mangalagiri, India
[9] MBBS, MD General Medicine, Assistant Professor, Department of General medicine, AIIMS Mangalagiri, India
[10] MBBS, MD Pathology, Associate Professor, Department of Pathology, AIIMS Mangalagiri, India

ABSTRACT

Introduction: Acute Phase proteins, which is part of a repertoire of cell responses to inflammation, can be used as diagnostic tool and may provide an alternative means of monitoring health. In this study, we aimed to explore the role of Serum Amyloid A (SAA) protein and other inflammatory markers like CRP, Ferritin, LDH, D-Dimer and Lymphocytes in acute and convalescent phase of SARS–Cov-2 cases.

Methodology: In this pilot study, 5ml of blood sample was taken from 30 SARS CoV2 positive patients and Serum inflammatory markers like SAA, CRP, D-Dimer, Ferritin, and Lactate dehydrogenase & Lymphocytes were estimated. According to the MOHFW guidelines, 16 out of 30 were categorized as non-severe Covid-19 and 14 of them as severe Covid-19 who had SPO2<90% or RR> 30/minute. There were 7 deaths out of the total 14 severe Covid-19

Results: SAA is elevated in acute phase (AP), and is decreased in convalescent phase (CP), with statistically significant p value ($p<0.01$). All other inflammatory markers exhibit similar pattern with a statistically significant p values between acute and convalescent phase except for inverse relation of Lymphocytes. Lymphocyte counts were strongly and significantly correlating with disease severity than compared to other inflammatory markers. Lymphocytes, ferritin and D-Dimer levels during admission also significantly correlates with mortality.

Conclusion: Serum SAA level is significantly increased in acute phase along with other inflammatory markers like CRP, Ferritin, LDH, D Dimer and lymphocyte count. But serum ferritin, D-Dimer and lymphocyte counts at baseline can be used to predict the worse outcome.

Key Words: *COVID 19, SAA, Inflammatory markers, CRP, Ferritin*

***Corresponding Author**
Naga Guhan
MBBS, MD Biochemistry, Assistant Professor, Department of Biochemistry, AIIMS Mangalagiri, India

INTRODUCTION

The Acute Phase Response which is part of a repertoire of cell responses to inflammation is characterized by increased or decreased plasma concentrations of acute phase proteins (APPs) along with a wide range of pathophysiological responses such as pyrexia, leukocytosis, hormone alterations, and muscle protein depletion [1]. APPs are divided as positive and negative APPs, respectively increasing or decreasing during the APR. Positive APPs include C Reactive protein (CRP), Serum Amyloid A, Ceruloplasmin, Ferritin, Haptoglobin, Orosomucoid, Fibrinogen etc. Albumin, transferrin, Retinol binding protein and transthyretin are examples of negative APPs. Hepatocytes are considered as the primary cell type expressing APPs. However, APP production is induced after cytokine-mediated systemic inflammation in other cell types, including intestinal epithelial cells, adipocytes, endothelial cells, fibroblasts and monocytes. Mediators of APP gene expression include pro-inflammatory cytokines such as IL-6, IL-1β and TNFα, glucocorticoids and growth factors, among which IL-6 is the major mediator for the hepatocytic secretion of most of the APPs [2]. The acute phase response with its changes in blood plasma composition is thought to be beneficial by preventing microbial growth and helping to restore homeostasis. Some APPs opsonize microorganisms and activate complement, others scavenge cellular remnants and free radicals, or neutralize proteolytic enzyme [3].

Besides these physiological roles, APPs can be used as diagnostic tool and may provide an alternative means of monitoring health. The maximum serum concentration of APPs is typically reached within 24 to 48 h after the initiation. A decline coinciding with the recovery from the infection is seen and feed-back regulations will limit the response leading to its resolution within 4–7 days after the initial stimulus. The major APPs that are routinely used as diagnostic tools in inflammatory conditions like COVID 19 are CRP, Ferritin, LDH, D-Dimer and lymphocyte counts. CRP, a beta-globulin with molecular weight of 115–140 kD and a stimulant of complement activity and macrophage phagocytosis, is an exquisitely sensitive systemic marker of acute-phase response in inflammation, infection, and tissue damage [4]. Ferritin, which is the storage form of iron, is also an acute phase reactant protein that is elevated in various inflammatory diseases, liver disease, chronic infection, autoimmune disorders, and malignancy. Within a couple of days after the onset of an infection, a rise in serum ferritin was seen, the magnitude of which was not dependent on the type of infection (bacterial or viral) [5]. D-dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. The circulating enzyme plasmin, the main enzyme of fibrinolysis, cleaves the fibrin gel to FDPs, the smallest of which are D-dimers [6]. Elevation of D-dimer indicates a hypercoagulable state which might be associated with most of the inflammatory conditions. Lactate dehydrogenase (LDH) can be considered as a biomarker of interest and their levels have been associated with worse outcomes in patients with COVID19 and other viral infections in the past. In contrast to other inflammatory markers, the lymphocyte counts were decreased in acute phase and increased during convalescent phase, indicating the inverse relationship with severity and disease outcome. The serum level of pro-inflammatory cytokines, such as TNF-α and IL-6, have been closely correlated with lymphopenia, while recovered patients have shown close to normal levels of such cytokines

Though these inflammatory markers are available, a more objective simple marker is a need of the hour, to monitor the disease progression in any acute inflammatory conditions. Recent studies have indicated the measurement of Serum Amyloid A Protein (SAA) has a better predictive value than C Reactive Protein (CRP), lymphocytes and neutrophils and SAA values raise proportionally to the severity or progression of the disease [7]. SAA which is also an acute phase protein gradually increases and reaches a peak at 3-4 days of post infection, and during the phase of recovery it decreases, and the rate of decrease is faster than that of CRP. SAA is a more sensitive parameter than CRP in detecting minor inflammatory stimuli in viral Infections and can be used as a noninvasive and early marker of both bacterial and viral infections. But there are very few studies in India establishing the role of Serum Amyloid A (SAA) as a prudent inflammatory marker. So our study is designed to estimate Serum Amyloid A (SAA) in acute and convalescent phase of COVID 19 infection and determine the correlation of Serum Amyloid A (SAA) protein with other inflammatory markers like CRP, Ferritin, LDH, D-Dimer and Lymphocytes in acute and convalescent phase of SARS –Cov-2 Cases.

METHODOLOGY

A pilot study was conducted with a sample size of 30 considering flat rules of thumb as stated and explained by Machin et al. The study was conducted at Department of Biochemistry, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh. The patients who were diagnosed as SARS CoV2 positive through RT PCR and admitted in AIIMS Mangalagiri were recruited as study population. It was conducted between April – June 2021, for a period of 3 months. The Inclusion Criteria was all subjects who were in the age group of 20 – 70 years diagnosed and confirmed as SARS – CoV2 and admitted in AIIMS Mangalagiri. Subjects with Tuberculosis, Autoimmune Diseases, Arthritic Diseases, Cancer, CKD, Patients with HIV, HbsAg, HCV Positive were excluded from the study. Project was initiated after obtaining clearance from Institute Ethical Committee – AIIMS Mangalagiri (AIIMS/MG/IEC/2021-22/120 dated 01.11.2021). The study was carried according to the ICMR National Ethical Guidelines. Signed informed consent (confirmed by a witness) and appropriate clinical history was obtained before taking blood collection.

A Random 5ml of blood sample was taken in appropriate vacutainers both in acute and convalescent phase under aseptic precautions (for handling SARS- CoV2 samples) following appropriate HICC guidelines according to the SOP based on the ICMR guidelines and was transported to Department of Biochemistry, AIIMS Mangalagiri. Acute phase was considered as within 24 hours of presentation and convalescent phase was 48 hours before discharge. Serum Amyloid A and various serum inflammatory markers like CRP, D-Dimer, Ferritin, and Lactate dehydrogenate & Lymphocytes were estimated in both Acute and Convalescent phase. Serum inflammatory markers like CRP, D – Dimer were estimated using Beckman Coulter AU700 series autoanalyzer and Ferritin was estimated using Roche Cobas E 411 Immunoassay analyzer. SAA is estimated using SAA Human ELISA Kit, INVITROGEN using Multimode microplate ELISA reader and complete blood picture was done using a Horiba 5 part analyzer. Appropriate Calibration and Quality control protocol were followed before analysis of the samples.

All data were analysed using SPSS 22.0 software package. The Kolmogorov-Smirnov test was used to examine the normality of the distributions of continuous variables. For continuous variables that satisfied normal distribution, the data were expressed as mean ± standard deviation (SD) and were compared using paired t-tests between acute and convalescent phase. Otherwise, the data were expressed as medians and quartile ranges (QR), and compared using the Wilcoxon signed rank test. Correlation analysis were performed using the Pearson test or Spearmann test depending upon the variable. A two-sided p-value of < 0.05 was regarded as statistically significant.

RESULTS

The mean age of the patients recruited in the study was 54±13; there were 17 (57%) Male and 13 (43%) female patients. The most common symptom was cough, fever, fatigue. The median length of hospitalization was 12 days. According to the MOHFW guidelines, 16 out of 30 were categorized as non-severe Covid-19 and 14 of them as severe Covid-19 who had SPO2<90% or RR> 30/minute [8]. There were 7 deaths out of the total 14 severe Covid-19.

Serum SAA concentration was significantly increased in the acute phase of infection in all the patients, the extent of which was correlated with the disease severity. SAA is elevated in acute phase (AP), (median – 256.35mg/L with the IQR (227.47-261.17)) but is significantly decreased in convalescent phase (CP), (median – 208.56mg/L with IQR (167.95-222.83)) with statistically significant p value (p<0.01). All other inflammatory markers exhibit similar pattern with a statistically significant P values between acute and convalescent phase (Table /figure1) except for inverse relation of Lymphocytes. Lymphocytes were decreased in acute phase (median – 8%(IQR-5.25.16)) and are increased in convalescent phase (median-18% (IQR-12-25)) and the increase is statistically significant with (P<0.01) indicates the inverse relationship of lymphocytes with the disease outcome.

Table/figure 1: Comparison of various biomarkers between acute phase & convalescent phase

VARIABLE	ACUTE PHASE	CONVALASCENT PHASE	STATISTICAL TEST	p VALUE
SAA(mg/L) (median(IQR))	256.35(227.47-261.17)	208.56(167.95-222.83)	Wilcoxon signed rank test	<0.001
CRP (mg/L) (median(IQR))	63.4(23.05-80.0)	8.05(2.6-23.13)	Wilcoxon signed rank test	<0.001
Ferritin (ng/ml) (median(IQR))	567.45(433.35-921.28)	272.3(216.375-416.4)	Wilcoxon signed rank test	<0.001
D Dimer (µg/ml) (median(IQR))	3.44(0.53-8.0)	1.0(0.30-1.47)	Wilcoxon signed rank test	<0.001
LDH (IU/L) (median(IQR))	556.0(398.75-746.0)	300.5(232.270-403.5)	Wilcoxon signed rank test	<0.001
Lymphocytes(%) (median(IQR))	8(5.25-16.5)	18(12-25)	Wilcoxon signed rank test	<0.001

A positive and statistically significant correlation is observed with SAA & CRP and SAA & Ferritin in acute phase and with SAA & CRP in convalescent phase (Table/figure – 2)

Table/figure 2: Association of serum amyloid A with other biomarkers

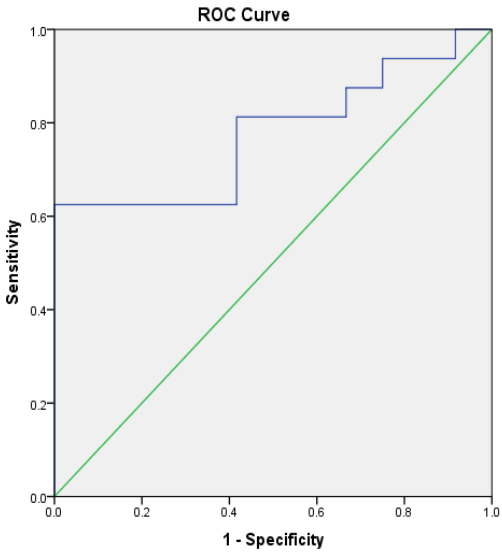
VARIABLES	ACUTE PHASE		CONVALASCENT PHASE	
	r value	p value	r value	p value
SAA vs CRP	0.675	<0.001	0.615	<0.001
SAA vs Ferritin	0.423	0.025	0.111	0.574
SAA vs D Dimer	-0.004	0.985	0.117	0.554
SAA vs LDH	-0.086	0.664	0.272	0.161
SAA vs Lymphocytes	-0.272	0.161	-0.109	0.582

Among the various inflammatory markers, lymphocyte count during admission inversely correlates significantly with the severity of the disease. (Table/figure-3). Lymphocytes are decreased in survivors in Acute phase (median-8 (IQR-6.5-16)) and in non-survivors they are further decreased to 4 (3.5-6) with (P< 0.006); showing statistically significant P value. In addition to lymphocytes, serum ferritin and D-Dimer levels during admission also significantly correlates with mortality. (Table/figure – 3).

Table/figure 3: Correlation of various biomarkers in acute phase with severity & mortality

VARIABLES	SEVERITY		MORTALITY	
	r value	p value	r value	p value
SAA	0.144	0.511	0.111	0.613
CRP	0.119	0.588	0.176	0.421
Ferritin	0.341	0.111	0.429	0.041
D Dimer	0.344	0.108	0.489	0.016
LDH	0.203	0.354	0.167	0.447
Lymphocytes	-0.561	0.005	-0.591	0.003

Using a Receiver operating characteristic curve, the optimal cutoff point of SAA related to COVID Severity was 202.4mg/L with a sensitivity of 81.3% and specificity of 58% respectively, and the area under the curve was 0.776(Table/Figure4)



Table/Figure 4: ROC for SAA for predicting the severity of the disease

DISCUSSION

In late December 2019, pneumonia cases of unknown etiology took the entire China bystorm, which was later confirmed as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) by the International Committee on Taxonomy of Viruses the 2019, caused by novel Coronavirus (2019-nCoV) [9]. It transcended international borders in no time, reaching the worldwide tally of 513,955,910 confirmed cases and 6,249,700 deaths, reported as per World Health Organization (WHO) Situation Report of 8th May [10]. The SARS-CoV-2 belongs to a group of β-coronavirus, which is an enveloped positive-sense RNA virus of subgenus sarbecovirus [11]. nCOV genome is 30 kb in size comprised of 29891 nucleotides encoding for 9860 proteins. The presence of spike glycoproteins(S) on the envelope, gives it a crown-like appearance under an electron microscope which help in anchoring to the host cell receptors [12].

Receptor binding domain of S protein binds to ACE2 receptors in lungs and other tissues after primed by serine proteases. Virus attaches to the receptor, then is internalized into host cell and results in release of the viral RNA into the cytoplasm [13]. The RNA (uncoated) encodes two polyproteins; pp1a and pp1ab, which translate the NSP sequence, and collectively make replication-transcription complex (RTC) in double-layered vesicle (21, 22). RTC continuously replicates and form a network of sub genomic RNAs, which translates structural and accessory proteins [14]. These envelope glycoproteins, nucleocapsid proteins and new genomic RNA amalgamate together to produce virus particles. Finally, the vesicles containing virion fuse with the cell membrane to discharge the new viruses. These replicated viruses later bring out a dysregulation to immunomodulatory system and cytokine storm [15]. As the damage of SARS-CoV-2 appears to be more related to the immunopathology of the host reaction than to the replication of the virus, estimation of inflammatory markers and acute phase proteins can predict the disease severity rather than the quantification of viral load.

In our study, serum SAA is significantly elevated in acute phase than compared to convalescent phase (Table/figure 1). In addition to SAA, other inflammatory markers like CRP, Ferritin, LDH and D Dimer were also significantly elevated in acute phase and lymphocytes significantly decreased in acute phase. Thus, the elevated serum levels of inflammatory markers, which are associated with inflammatory process and recruitment of inflammatory cells, could reflect the ongoing inflammation at the infection site. According to a study conducted by Xiao merg MO, Zhu Suan SE their results declared that SAA could be an independent predictive factor of severe covid-19 with accuracy of 89.1% in predicting acute exacerbation (cut off value 122.9) [16]. Similarly, a study conducted by Jun Fu, Pian-Pian Huang, revealed that the SAA & CRP could predict severe Covid-19, with the AUC of SAA & CRP were 0.818 & 0.84 respectively which show high predictive efficiency. Also, linear regression result show that SAA & CRP are negatively co-related with the treatment days in the recovered patients in their study [17].

Serum Amyloid–A, a precursor of amyloid protein which is a nonspecific acute phase reactant produced by liver as pro inflammatory cytokines IL-1β, IL-6 and TNF α secreted by activated monocytes [18]. SAA is an endogenous TLR2 ligand mediating inflammatory angiogenic mechanisms and found to promote inflammatory response at an exceptionally low concentration through activating chemokines and inducing chemotaxis [19]. Various studies have revealed there is activation of TH1 cell by the cytokine storm and large amount of IL-1 β, IFN –γ, IL-10, MCP-1, MIP-1, IL-6, TNF- α are produced which in turn boosts the liver cells to produce more serum amyloid A (SAA) [20]. The large amounts of

various cytokines produced like the Il-1, IFN–γ, Ip-10, MCP cause activation of Th1 cells, and increased SAA, CRP, lymphocytes, PCT, WBC and Platelets hence these inflammatory factors can be used to indicate body's response towards inflammation. Among them SAA gradually increases and reaches a peak at 3-4 days of post infection, and during the phase of recovery it decreases, and the rate of decrease is faster than that of CRP. The activated monocytes and the IL-6 rapidly induces 1000 fold increase in SAA in a synergetic manner, and thus SAA can be associated with disease severity [21].

Further, in our study, there is a significant correlation between SAA and CRP in acute as well as convalescent phase. There is also correlation between SAA and FERRITIN in acute phasethat is statistically significant too. In contrast to other inflammatory markers, the lymphocyte counts were decreased in acute phase and increased during convalescent phase, indicating the inverse relationship with severity and disease outcome. Lymphocyte counts were strongly and significantly correlating with disease severity than compared to other inflammatory markers. J Wagner et al, in their retrospective cohort review, also had concluded that lymphocytopenia is related to disease severity and clinical outcomes in Covid- 19 patients [22]. The inflammatory cytokine storm is likely a key factor behind the observed lymphopenia. The serum level of pro-inflammatory cytokines, such as TNF-α and IL-6, have been closely correlated with lymphopenia, while recovered patients have shown close to normal levels of such cytokines [23].

In our study, Serum ferritin, D-Dimer and lymphocyte count in acute phase showed statistically significant difference between dead and alive patients and all these parameters were statistically correlating with mortality. According to Aditi Parimoo et al, higher ferritin levels at baseline, were associated with a greater probability of an adverse outcome [24]. Gandini O et al, in their study, concluded that Hyperferritinemia could be an independent risk factor for acute respiratory distress syndrome (ARDS) and mortality in COVID-19 [25]. The cytokine storm due to the release of pro-inflammatory factors, akin to that reported in other infections, has been attributed to be a major cause of death in patients with severe COVID-19 disease [26]. Hence the inflammatory markers were increased among the survivors than compared to non-survivors. To our knowledge, this is one of the few studies in India to compare the serum levels of SAA and other inflammatory markers between acute and convalescent phase and explore their relationship with severity and mortality of the disease. However, there are still several limitations in this study. Since it was a single-center study and the sample size is less, the results may lack external validity and may not be generalizable.

CONCLUSION

Serum SAA level is significantly increased in acute phase along with other inflammatory markers like CRP, Ferritin, LDH, D Dimer and lymphocyte count. But serum ferritin, D-Dimer and lymphocyte counts at baseline can be used to predict the worse outcome.

Financial disclosure: Self-funded

Ethical disclosure: Project was initiated after obtaining clearance from Institute Ethical Committee – AIIMS Mangalagiri (AIIMS/MG/IEC/2021-22/120 dated 01.11.2021)

REFERENCES

1. Jain S, Gautam V, Naseem S. (2011). Acute-phase proteins: As diagnostic tool. *J Pharm Bioallied Sci*. 3(1):118-127. doi:10.4103/0975-7406.76489
2. Zhou, Z., Xu, MJ. & Gao, B. (2016). Hepatocytes: a key cell type for innate immunity. *Cell Mol Immunol* **13**, 301–315.
3. Gruys E, Toussaint MJ, Niewold TA, Koopmans SJ. (2005). Acute phase reaction and acute phase proteins. *J Zhejiang Univ Sci B*. 6(11):1045-1056.
4. Bodman-Smith KB, Melendez AJ, Campbell I, Harrison PT, Allen JM, Raynes JG. (2002). C-reactive protein-mediated phagocytosis and phospholipase D signalling through the high-affinity receptor for immunoglobulin G (FcgammaRI). Immunology. 107(2):252-260.
5. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. (2010). Serum ferritin: Past, present and future. *BiochimBiophys Acta*. 1800(8):760-769. doi:10.1016/j.bbagen.2010.03.011
6. John D. Olson. (2015). Chapter One - D-dimer: An Overview of Hemostasis and Fibrinolysis, Assays, and Clinical Applications. Editor(s): Gregory S. Makowski. Advances in Clinical Chemistry, Elsevier. Volume 69, Pages 1-46
7. Cheng L, Yang JZ, Bai WH, et al. (2020). Prognostic value of serum amyloid A in patients with COVID-19. Infection. 48(5):715-722.
8. https://www.mohfw.gov.in/pdf/UpdatedDetailedClinicalManagementProtocolforCOVID19adultsdated24052021.pdf
9. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 5, 536–544 (2020).
10. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data(https://covid19.who.int/)
11. Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G.F., Tan, W. (2020). A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733

12. Mousavizadeh L, Ghasemi S. (2021). Genotype and phenotype of COVID-19: Their roles in pathogenesis. J Microbiol Immunol Infect. 54(2):159-163.
13. Anne M. Davidson, Jan Wysocki and Daniel Batlle. Interaction of SARS-CoV-2 and Other Coronavirus with ACE (Angiotensin-Converting Enzyme)-2 as Their Main Receptor. Hypertension. 2020;76:1339–1349.
14. Gioia M, Ciaccio C, Calligari P, et al. (2020). Role of proteolytic enzymes in the COVID-19 infection and promising therapeutic approaches. Biochem Pharmacol. 182:114225.
15. Tahaghoghi-Hajghorbani S, Zafari P, Masoumi E, et al. (2020). The role of dysregulated immune responses in COVID-19 pathogenesis. Virus Res. 290:198197.
16. Mo XN, Su ZQ, Lei CL, et al. (2020), Serum amyloid A is a predictor for prognosis of COVID-19. Respirology. 25(7):764-765.
17. Fu J, Huang PP, Zhang S, et al. (2020). The value of serum amyloid A for predicting the severity and recovery of COVID-19. Exp Ther Med. 20(4):3571-3577.
18. Urieli-Shoval S, Linke RP, Matzner Y. (2000). Expression and function of serum amyloid A, a major acute-phase protein, in normal and disease states. Curr Opin Hematol. 7(1):64-9.
19. Connolly M, Rooney PR, McGarry T, Maratha AX, McCormick J, Miggin SM, Veale DJ, Fearon U. (2016). Acute serum amyloid A is an endogenous TLR2 ligand that mediates inflammatory and angiogenic mechanisms. Ann Rheum Dis. 75(7):1392-8.
20. Damsker JM, Hansen AM, Caspi RR. Th1 and Th17 cells: adversaries and collaborators. Ann N Y Acad Sci. 2010;1183:211-221.
21. Guo G, Zhu Y, Wu Z, et al. Circulating monocytes accelerate acute liver failure by IL-6 secretion in monkey [published correction appears in J Cell Mol Med. 2021 Dec;25(23):11035-11036]. J Cell Mol Med. 2018;22(9):4056-4067.
22. Wagner J, DuPont A, Larson S, Cash B, Farooq A. (2020). Absolute lymphocyte count is a prognostic marker in Covid-19: A retrospective cohort review. Int J Lab Hematol. 42(6):761-765.
23. Popko K, Gorska E, Stelmaszczyk-Emmel A, et al. (2010). Proinflammatory cytokines Il-6 and TNF-α and the development of inflammation in obese subjects. Eur J Med Res. 15 Suppl 2(Suppl 2):120-122
24. Lucijanic M, Demaria M, Gnjidic J, et al. (2022). Higher ferritin levels in COVID-19 patients are associated with hyperinflammation, worse prognosis, and more bacterial infections without pronounced features of hemophagocytosis. Ann Hematol. 101(5):1119-1121.
25. Gandini O, Criniti A, Ballesio L, Giglio S, Galardo G, Gianni W, Santoro L, Angeloni A, Lubrano C. (2020). Serum Ferritin is an independent risk factor for Acute Respiratory Distress Syndrome in COVID-19. J Infect. 81(6):979-997
26. Fara A, Mitrev Z, Rosalia RA, Assas BM. (2020). Cytokine storm and COVID-19: a chronicle of pro-inflammatory cytokines. Open Biol. 10(9):200160.