C-Reactive Protein - A Promising Marker for Patients with Ischemic Heart Disease along with Covid-19 among South Indian Population

Chitra Siva Sankari Gandhi[1], Amuthavalli Vasudevan[2], Ramya Subramani[3], Ramadevi Kanaka Sabapathi[4]

[1, 2, 3, 4] Institute of Biochemistry, Madras Medical College, Chennai, Tamilnadu, India.

ABSTRACT

BACKGROUND

New corona virus respiratory syndrome is a health emergency due to high infectivity and high case fatality in patients with comorbid conditions like ischemic heart disease. The diagnostic methods of corona virus disease (Covid-19) are still in experimental stage. Hence, a sensitive and specific disease progression marker of Covid-19 is needed. CRP (C-reactive protein) is synthesised by liver. It is elevated in infection and inflammatory conditions as it is an acute phase protein. The purpose of this study was to evaluate CRP as a promising marker for predicting severity of Covid-19 in ischemic heart disease patients and to correlate the impact of CRP with other circulating cardiac biomarkers in different age groups and both sexes.

METHODS

This is a cross sectional study done among south Indian population mostly from Tamil Nadu and Andhra Pradesh. 232 cases were selected and divided into two groups based on age, sex and confirmed Covid-19 positive cases by RT-PCR (Reverse transcription-polymerase chain reaction), admitted and treated in Rajiv Gandhi Government General Hospital, Chennai.

RESULTS

In this study, CRP levels were elevated in the age group of 50 - 70 years (66.96 ± 70.09 mg/dL) than CRP levels of age group 30 - 50 years (82.31 ± 90.23 mg/dL) and P value was found to be significant in the age group of 50 - 70 years. Lactate dehydrogenase (LDH) levels were elevated in the age group of 30 - 50 years (380.77 ± 252.23 U/L) than the LDH levels of age group 50 - 70 years (393.53 ± 206.83 U/L) and P value was found to be significant in the age group of 30 - 50 years. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatine kinase (CK) levels are the additional cardiac enzymes found to be elevated in this study. CRP showed a positive correlation with LDH (r = 0.221 P < 0.001) in both males (r = 0.06 and P < 0.001) and females (r = 0.45 and P < 0.001) with a significant P value. Receiver operating characteristics (ROC) curves for CRP Vs age group shows a sensitivity of 91.15 % and specificity of 92.52 % and area under curve of 0.556.

CONCLUSIONS

CRP can be used as a promising marker for early detection and timely intervention of ischemic heart disease in Covid-19 patients especially in the age group of 50 - 70 years and thereby reduces the mortality.

KEYWORDS

Biomarkers, Heart Disease, Mortality, Prognosis

BACKGROUND

Severe acute respiratory syndrome-2 (SARS-2), caused by corona virus emerged as a pandemic on March 11, 2020. Covid-19 originated in China, developed as an alarm of public health on January 31, 2020 and spread worldwide with increase in infectivity and disease severity.[1,2] Globally reported cases as on May 11,2020 was about 4,006,257 (88,891 new cases in last 24 hrs.) and number of deaths 2,78,892 (4531).[3] Many studies reveal that the person who was infected with SARS-CoV-2, had high degree of inflammation in innate immunity cells infiltration especially in those who have poor host immune response.[4,5] The novel corona viruses are a group of RNA viruses named after crown like spikes in its surface that infects both humans and animals. They are divided into four groups: α, β, γ, and δ. Among them, α and β causes infection in humans.[6] In humans, they predominantly affect respiratory as well as the cardiovascular system in addition to other systems. Common complications in respiratory system includes acute respiratory distress syndrome (ARDS) and pneumonia. In cardiovascular system, complications caused by coronavirus includes ischaemic heart disease (IHD), arrhythmia, heart failure and coronary vessel abnormalities.[7,8,9] Mortality due to Covid -19 is increased by other co-morbidities like diabetes, hypertension, renal disease, cancer and other immunosuppressive disorders. Covid-19 infection mortality is found to be higher in patients with pre-existing cardiac disease than newer patients with cardiac disease of acute onset.[10] Even though ACE-2 receptor for Covid-19 infection is expressed in various organs like heart, lung and whole of cardiovascular system, target organ is supposed to be heart as many studies revealed so far.[11,12] Many studies revealed elevation of cardiac biomarkers in Covid-19 infection but the correlation of severity and prognosis of cardiac disease with cardiac biomarkers were not clearly defined.[13]

CRP belongs to the family of pentraxins. It has five subunits with pentameric cyclical symmetry.[14] The subunits are non-glycosylated and identical polypeptides each containing 206 aminoacid residues. Major functions of CRP includes the host defensive mechanism against the foreign pathogens and mediates inflammatory changes in damaged tissues. Though CRP and immunoglobulins are structurally different, some functional properties of CRP are similar to immunoglobulins like phagocytic activation, promotion of agglutination and activation of classical complement cascade.[15] This protein is synthesised by liver and it is early to rise in infection and inflammatory conditions.[16] This observational study was conducted to assess the impact of CRP with other cardiac enzymes and also assess the severity of ischemic heart disease in covid-19 patients.

METHODS

This is a cross sectional observational study with 232 patients (114 males and 118 females), divided into two groups based on age and sex. Group A with age group (30 - 50 years) which includes 57 males and 59 females comprises of 116 patients. Group B with age group (50 - 70 years) which includes 57 males and 59 females comprises of 116 patients. These patients were selected from confirmed covid-19 positive cases by RT-PCR by nasopharyngeal swab,[17] admitted and treated from June 17 to July 27, 2020 in Rajiv Gandhi Government General Hospital, Chennai. The study protocol was approved by local ethical committee.

The mean age was 51.1 years (ranging from 40 to 62 years). 5 mL of venous blood was drawn from antecubital vein of patients and collected in a plain vacutainer tube under aseptic precautions and serum separated by centrifugation at 3000 rpm for 15 minutes. Analytes were estimated using Roche automated clinical chemistry analyser. Quantitative measurements of serum aspartate aminotransferase and alanine aminotransferase done by dynamic extended stability modified IFCC method. Creatine kinase and LDH levels were estimated by ultraviolet spectrophotometric method. CRP levels were quantified by particle enhanced immunoturbidimetric assays.

Statistical Analysis

Statistical data was analysed using SPSS (Statistical Package for Social Science) version software 16.0.

RESULTS

Serum levels of AST, ALT, CK, LDH and CRP were estimated in patients with Covid-19 and ischemic heart disease. Mean and standard deviation were calculated. Student's t distribution was done to compare the values of mean. Calculation of P values were done and the value of significance was determined. A P value of less than 0.05 was considered to be significant. Pearson Spearman rank correlation of CRP with other variables like LDH, AST, ALT and CK was done. Receiver operating characteristic (ROC) curve was done to assess the sensitivity and specificity of CRP. Area under curve (AUC) was useful to find out the expected cases of ischemic heart disease with Covid-19.

Parameter	Age Group (30 - 50 Years)		Mean	SD	t-Value	P Value	Significance
	Males	Females					
CRP (mg/dL)	76.77	87.64	82.31	90.23	0.65	0.52	Not significant
LDH (U/L)	433.39	329.93	380.77	252.23	2.25	0.03	Significant
CK (U/L)	210.47	119.08	163.69	255.20	1.95	0.05	Significant
AST (U/L)	69.56	41.54	55.31	85.87	0.44	0.66	Not significant
ALT (U/L)	36.58	27.05	31.73	23.89	2.18	0.03	Significant

Table 1. Laboratory Findings of Cardiac Biomarkers in the Age Group of 30 - 50 Years

Parameter	Age Group (50 - 70 Years)		Mean	SD	t-Value	P Value	Significance
	Males	Females					
CRP (mg/dL)	52.27	81.16	66.96	70.09	2.26	0.03	Significant
LDH (U/L)	387.94	398.92	393.53	206.83	0.28	0.78	Not significant
CK (U/L)	244.89	103.34	172.90	431.28	1.78	0.08	Not significant
AST (U/L)	42.19	39.83	40.99	28.87	1.81	0.07	Not significant
ALT (U/L)	57.34	32.64	44.78	76.35	2.49	0.01	Significant

Table 2. Laboratory Findings of Cardiac Biomarkers in the Age Group of 50 - 70 Years
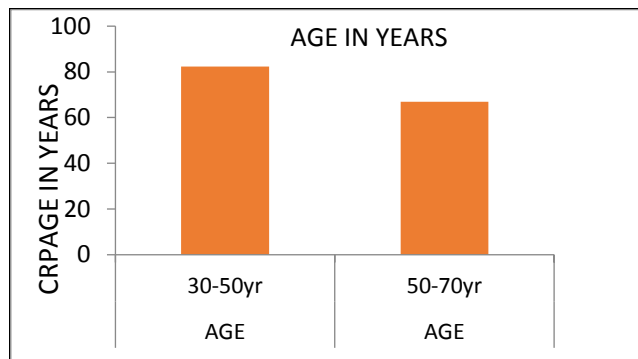
**Figure 1. Mean Concentration of C-Reactive Protein among Study Groups**

Figure 1 reveals the mean concentration of CRP on Y-axis and two different age groups (30-50 years and 50-70 years) on X-axis.

CRP	Number of Cases	Mean ± SD	t-Value	p Value	Significance
Total cases	232	74.63 ± 80.98	1.88		
Male	114	64.52 ± 73.34		0.06	Not significant
Female	118	84.40 ± 86.94			
Age group (30 – 50 years)	116	82.31 ± 90.23	0.65		
Male	57	76.77 ± 85.20		0.52	Not significant
Female	59	87.64 ± 95.27			
Age group (50-70 years)	116	66.96 ± 70.09	2.26		
Male	57	52.27 ± 57.35		0.03	Significant
Female	59	81.16 ± 78.40			

Table 3. CRP Levels in Various Age and Sex Matched Cases and Their Statistical Significance

	CRP	CK	LDH	SGOT	SGPT
Total	Correlation (r)	0.09	0.221	0.02	0.03
	Significant (p)	-	0.001	-	-
Male	Correlation (r)	0.05	0.06	0.03	0.12
	Significant (p)	-	-	-	-
Female	Correlation (r)	0.27	0.45	0.05	-0.06
	Significant	0.03	0.001	-	-
CRP (Age group 30 - 50)					
Male	Correlation (r)	0.01	-0.02	0.01	0.12
	Significant (p)	-	-	-	-
Female	Correlation (r)	0.30	0.46	-0.03	-0.12
	Significant (p)	0.05	0.01	-	-
CRP (Age group 50 - 70)					
Male	Correlation (r)	0.11	0.21	-0.04	-0.11
	Significant (p)	-	-	-	-
Female	Correlation (r)	0.22	0.52	0.18	0.12
	Significant (p)	-	0.01	-	-

Table 4. Pearson's Spearman Rank Correlation between CRP and Other Variables
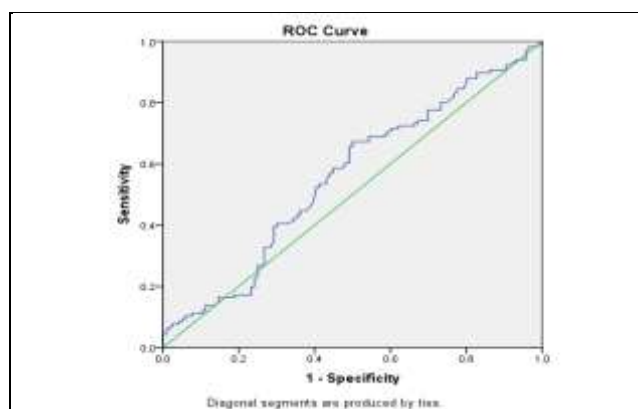
Area Under the Curve				
Test Result Variable(s): CRP				
Area	Std. Error	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.556	.038	.140	.482	.630

The test result variable(s): CRP has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the non-parametric assumption

b. Null hypothesis: true area = 0.5

Table 5. Receiver Operating Characteristic Curve CRP VS Age Group

DISCUSSION

Covid-19 infection is marked by dry cough, difficulty in breathing, fever and myalgia which leads to interstitial pneumonia progressing to acute respiratory distress syndrome with multiorgan failure.[18,19] Myocardial damage in Covid-19 occurs due to high levels of inflammatory cytokines circulating in the body which damages the healthy tissues of the body especially the heart. Moreover, corona virus affects the endothelial cells which lines the inner surface of the small blood vessels leading to blood clots that affects the blood flow to the heart and ends up with ischemic heart disease. To face the challenges due to mortality and severity of mild to moderate cases, biomarkers are needed which are easy to do and are more specific.[20,21] Many studies reveal the changes in blood marker levels which help in assessing the severity.[22] Five such markers were selected for this study. They include aspartate aminotransferase, alanine aminotransferase, total creatine kinase, lactate dehydrogenase and acute phase reactant protein, C-reactive protein (CRP).

CRP

Among the above five biomarkers, serum C-reactive protein proved to be a vital marker that alters significantly in Covid-19 patients of age group 50 - 70 years, as seen in table -2.

The normal circulating CRP level is found to be less than 10 mg/L.[23] CRP levels are elevated in ischemic heart disease, hypertension, diabetes, metabolic syndrome, peripheral artery disease and stroke. After infection or inflammation, CRP rises abruptly within 6 - 8 hours and reaches a peak in 48 hours and concentration begins to decline in the recovery phase.[24] Half-life of CRP is 19 hours. CRP adheres to phosphocholine in infected cells and stimulates the immune system; the classical complement pathway. The phagocytic activity is altered to eliminate the microbes and infected cells. CRP levels correlate with inflammation and concentration of CRP is affected by factors like age and sex as shown in table 3 which confirms the role of CRP as the vital biomarker for assessing the severity of Covid-19 infection.[25] In this study, table 2 shows significantly elevated level of CRP (mean levels in males - 52.7 mg/dL, in females - 81.16 mg/dL) with P value 0.03 and it is found to be highly significant. It is similar to the study done by Nurshad ali et al. where they found significant increase in CRP up to 50 mgms/L in about 86 % of patients.[20] In addition, table 4 reveals that CRP shows a positive correlation with LDH. CRP can also be correlated with IL-6 (interleukin-6) since IL-6 has anti-inflammatory and pro inflammatory actions. Patients with mild to moderate grades of Covid infection present with symptoms which may be severe due to viral cytotoxicity and inflammatory response.[26] Inflammatory cells release IL-6 immediately when compared to CRP. CRP levels can be used along with IL-6 for assessing the severity of Covid infection in ischaemic heart disease.[27] Since sources of IL-6 include vascular smooth muscle, lymphocytes, adipose tissue and skeletal muscle, it is highly non-specific during inflammatory conditions when compared to CRP synthesised by hepatocytes which confers the significance of

CRP.[28] Previous studies also reveal that concentration of CRP levels are not affected by age, sex and physical condition as compared to IL-6.[29] Moreover, CRP is a more economical biomarker when compared to IL-6. Hence, CRP can be used as a pivotal biomarker in assessing the severity of ischemic heart disease in Covid-19 patients. Epidemiological studies and clinical trials proved CRP to be useful in addition to troponin-I and troponin-T during management of ischemic heart disease patients at high risk in intensive care units with dosage of antiplatelet drugs and statins. Interventional cardiologist uses CRP level for monitoring the patients undergoing percutaneous coronary angiography. CRP levels help in identifying the patients who are at more risk of metabolic syndrome since obese individuals with high CRP values are having high triglycerides, low HDL and high blood glucose levels.[30] Diet, regular exercise, smoking cessation and alcohol withdrawal decreases CRP levels. CRP can be used as a best parameter for motivating the patients to undergo lifestyle modification. Classical acute phase protein CRP is associated with risk of IHD which leads to cardiac complications like arrhythmias and death.

LDH

LDH is involved in production of energy in anaerobic conditions. LDH is synthesised by heart, muscle, lung, liver and kidney.[31] LDH is an intracellular enzyme composed of two subunits. Five isoenzymes of LDH includes LDH-1, 2, 3, 4 and 5. LDH–1 in heart, LDH-2 in RBC, LDH-3 in brain, LDH-4 in liver, LDH-5 in skeletal muscle. Samples should be monitored for haemolysis before analysis because haemolyzed samples also show similar flipped pattern. LDH concentration is increased in other conditions like stroke, cardiomyopathy, muscular dystrophy, pancreatitis and haemolytic anaemia. Hence, it is a nonspecific marker. So, compared to LDH, CRP proves to be useful as a promising marker for detecting patients with ischemic heart disease and Covid-19. The circulating level of LDH ranges from 125 - 220 U/L. Elevated LDH reflect multiple organ injury and failure which plays a more prominent role in this pathology in influencing the clinical outcomes of patients with Covid 19.[32,33] In these patients, the cardiac isoenzymes play a major role as it correlates well with CRP. In this study, table 1 shows significantly elevated level of LDH (mean levels in male - 433.39 U/L, in females - 329.93 U/L) with P value 0.03 and it is found to be highly significant. In table 4, correlation analysis reveals that there is significant correlation between CRP and LDH (r- 0.45, P < 0.001).

In 1955, a study by Karmen and associates revealed the drastic raise of enzymes like AST, ALT and LDH in serum of patients with ischaemic heart disease.[34] Based on the above study, enzyme analysis of AST, ALT and CK were also done.

CK

CK is an enzyme that is released when there is muscle damage. The circulating level of CK in the blood is around 20 - 200 U/L.[35] In this study also, there is a significant increase in CK especially in the age group of 30 - 50 years. Significant P value (P - 0.05) obtained for total CK in both males and females of age group 30 - 50 years (males - 210.47 U/L, females – 119.08 U/L). CK has three isoenzymes: CK-MM (Muscle), CK-MB (Heart) and CK-BB (Brain). CK-MB activity is 5 % of total CK activity. Since CK is present widely in heart, muscle and brain, the rise in CK is not tissue specific. Any hypoxia or cell injury will release CK into the circulation making it as a non-specific marker for ischemic heart disease. Creatine kinase levels are elevated in conditions like myocardial infarction, muscular dystrophy, rhabdomyolysis, acute kidney injury and malignant hyperpyrexia. Table - 4 reveals that the correlation between CRP with CK is not significant in males, but it is significant in females. (males r = 0.05, P - 0.06, females r = 0.27, P - 0.03) which has to be evaluated in further studies.

AST

AST is found in heart, liver, skeletal muscles, brain, kidneys, and red blood cells. Damage to plasma membrane and programmed cell death are the most common causes for the elevation of aspartate transaminase levels in blood circulation[36] Moreover, elevation of AST also occurs in liver disease of viral or alcoholic aetiology, toxicity due to drug intake, shock due to sepsis and trauma leading to skeletal injury. AST levels being elevated was used as a tool for diagnosing acute myocardial infarction and staging of necrosis in ischaemic heart disease.[37] After the onset of myocardial infarction, AST starts to rise in 6 - 8 hours of onset of symptoms and reaches its peak in 24 - 36 hours and return back to normal in 3 - 7 days. So, it lacks specificity and also it is widely present in all tissues of the body. Even though AST levels were raised in IHD patients with Covid infection, it is not significant (P - value 0.66).

ALT

ALT is another non-specific marker of ischaemic heart disease but mainly used to indicate the inflammation of liver or liver involvement.[38] Reference range of ALT is about 0 - 40 IU/L. ALT levels are elevated in diseases like viral hepatitis, congestive heart failure, diabetes, bile duct problems, liver damages, infectious mononucleosis and myopathies. Moreover, fluctuation of ALT levels occurs normally during the course of the day and also in response to strenuous physical exercise. So, ALT is a non-specific marker compared to CRP. In this study, ALT level was found to be significantly raised in both age groups as shown in table 1 and 2 (age group 30-50 years with ALT levels 31.73 ± 23.89 U/L with P value 0.03 and age group 50 - 70 years with ALT levels 44.78 ± 76.35 U/L with P value 0.01).This may indicate involvement of liver which is to be evaluated further.

ROC Curve was done to assess the sensitivity and specificity of CRP. Area under curve was useful to find out the expected cases of ischemic heart disease with Covid-19. ROC curves for CRP Vs age group as in table 6 shows a sensitivity of 91.15 % and specificity of 92.52 % and area under curve of 0.556.

Studies revealed that when CT findings were correlated with CRP levels, CRP levels showed an early significant

elevation than the CT scores in Covid-19 patients. Though CT findings predict outcomes of adverse events in Covid-19 patients, it is not available in emergency departments in all primary and some secondary health care centres. This makes CRP a unique inflammatory biomarker and its economical value provides an access for early detection of patients and prompt management in all levels of hospital set ups. Many clinical trials proved that patients with low oxygen saturation ($SpO_2 \leq 90$ %) had elevated levels of CRP compared to patients with high oxygen saturation ($SpO_2 \geq$ 90 %). This indicates that elevated CRP levels also helps in identifying early lung injury. In this study, CRP levels were found to be elevated in the age group of 50 - 70 years (66.96 ± 70.09 mg/dL) and age group of 30 - 50 years (82.31 ± 90.23 mg/dL).[39] Age groups are differentiated in this study as chances for improvement are greater in younger age group as they are expected to have lesser complications.[40] Gender comparison was done to find whether the risk threshold varies among groups as females tend to have more CRP levels than males which requires further evaluation. In addition, the risk for complications are less in females than males. So, the cut off value of CRP predicting the risk may vary among genders.[41,42] In this study even though the correlation is weak (as r value is 0.3), the trend is significantly along with other clinical findings.[43]

CONCLUSIONS

A cross sectional study was conducted during pandemic among ischemic heart disease patients with Covid infection.[44,45] Since the prognosis depends on proper management, inflammatory markers play a major role in determining the management.[46] Covid positive patients has lesser oxygen saturation than normal patients (Covid negative). Higher levels of CRP in this study indicates more severe disease course (due to added lung involvement).[47] In ischemic heart disease patients who are already under treatment have only a mild raise of CRP. When they are infected with Covid, there is a drastic raise of CRP values up to 80 % in severe Covid-19 patients. Since CRP has a half-life of only 19 hours, patients with IHD when infected with Covid showed a markedly elevated CRP level. Hence, CRP can be used as a promising marker for early detection and timely intervention of ischemic heart disease in Covid-19 patients especially in the age group of 50 - 70 years and thereby reduces the mortality.

Limitations of the Study
Number of cases in the study may be increased. CRP levels were studied in IHD patients who are infected with Covid, follow up was not possible at the time of study as some of them are discharged after becoming Covid negative and some expired. Further studies need to be conducted in review outpatient department. This study does not include IHD caused by various strains of the virus.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

REFERENCES

[1] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475-81.
[2] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507-13.
[3] Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20(5):533-534.
[4] Liu PP, Blet A, Smyth D, et al. The science underlying COVID-19: implications for the cardiovascular system. Circulation 2020;142(1):68-78.
[5] Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020;27(5):1451-1454.
[6] Zhang SF, Tuo JL, Huang XB, et al. Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010-2015 in Guangzhou. PloS One 2018;13(1):e0191789.
[7] Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46(5):846-848.
[8] Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5(7):802-810.
[9] Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5(7):811-818.
[10] Madjid M, Safavi-Naeini P, Solomon SD, et al. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol 2020;5(7):831-840.
[11] Sharma S. COVID-19: a concern for cardiovascular disease patients. Cardiovascular Toxicology 2020;20(5):443-447.
[12] Gallagher PE, Ferrario CM, Tallant EA. Regulation of ACE2 in cardiac myocytes and fibroblasts. Am J Physiol Heart Circ Physiol 2008;295(6):H2373-H2379.
[13] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine 2020;382(18):1708-1720.
[14] Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003;111(12):1805-1812.
[15] Ansar W, Ghosh S. C-reactive protein and the biology of disease. Immunol Res 2013;56(1):131-142.
[16] Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol 2005;117(2):104-111.

[17] Afzal A. Molecular diagnostic technologies for COVID-19: limitations and challenges. J Adv Res 2020;26:149-159.

[18] Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol 2020;92(7):856-862.

[19] Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. J Med Virol 2020;92(10):1875-1883.

[20] Wang G, Wu C, Zhang Q, et al. C-reactive protein level may predict the risk of COVID-19 aggravation. Open Forum Infect Dis 2020;7(5):ofaa153.

[21] Ali N. Is SARS-CoV-2 associated with liver dysfunction in COVID-19 patients? Clinics and Research in Hepatology and Gastroenterology 2020;44(4):e84.

[22] Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. J Med Virol 2020;92(10):1733-1734.

[23] Vacchi E, Cazzola W. Neverlang: a framework for feature-oriented language development. Computer Languages, Systems & Structures 2015;43:1-40.

[24] Young B, Gleeson M, Cripps AW. C-reactive protein: a critical review. Pathology 1991;23(2):118-124.

[25] Bilgir O, Bilgir F, Calan M, et al. Comparison of pre-and post-levothyroxine high-sensitivity c-reactive protein and fetuin-a levels in subclinical hypothyroidism. Clinics 2015;70(2):97-101.

[26] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.

[27] Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol 2018;9:754.

[28] Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol 2020;146(1):128-136.

[29] Bilgir O, Bilgir F, Calan M, et al. Comparison of pre-and post-levothyroxine high-sensitivity c-reactive protein and fetuin-a levels in subclinical hypothyroidism. Clinics 2015;70(2):97-101.

[30] Packard RR, Libby P. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem 2008;54(1):24-38.

[31] Ballou SP, Kushner I. C-reactive protein and the acute phase response. Adv Intern Med 1992;37:313-336.

[32] Sepulveda JL. Challenges in routine clinical chemistry analysis: proteins and enzymes. In: Dasgupta A, Sepulveda J, eds. Accurate results in the clinical laboratory. 2nd edn. Elsevier 2019:141-163.

[33] McFadden RG, Oliphant LD. Serum lactate dehydrogenase in interstitial lung disease. Chest 1991;100(4):1182.

[34] Khalid N, Chen Y, Case BC, et al. COVID-19 (SARS-Cov-2) and the heart–an ominous association. Cardiovasc Revasc Med 2020;21(8):946-949.

[35] Nochioka K, Roca GQ, Claggett B, et al. Right ventricular function, right ventricular–pulmonary artery coupling, and heart failure risk in 4 US Communities: the Atherosclerosis Risk in Communities (ARIC) Study. JAMA Cardiol 2018;3(10):939-948.

[36] McGill MR. The past and present of serum aminotransferases and the future of liver injury biomarkers. EXCLI J 2016;15:817-828.

[37] Ladue JS, Wróblewski F, Karmen A. Serum glutamic oxaloacetic transaminase activity in human acute transmural myocardial infarction. Science 1954;120(3117):497-499.

[38] Ioannou GN, Weiss NS, Boyko EJ, et al. Contribution of metabolic factors to alanine aminotransferase activity in persons with other causes of liver disease. Gastroenterology 2005;128(3):627-635.

[39] Ahnach M, Zbiri S, Nejjari S, et al. C-reactive protein as an early predictor of COVID-19 severity. J Med Biochem 2020;39(4):500-507.

[40] Wyczalkowska-Tomasik A, Czarkowska-Paczek B, Zielenkiewicz M, et al. Inflammatory markers change with age, but do not fall beyond reported normal ranges. Arch Immunol Ther Exp 2016;64(3):249-254.

[41] Khera A, McGuire DK, Murphy SA, et al. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol 2005;46(3):464-469.

[42] Richardson MR, Johnson TM, Katzmarzyk PT, et al. Gender differences in c-reactive protein and muscle strengthening activity. J Phys Act Health 2015;12(12):1582-1588.

[43] Xie J, Covassin N, Fan Z, et al. Association between hypoxemia and mortality in patients with COVID-19. Mayo Clin Proc 2020;95(6):1138-1147.

[44] Chen T, Wu DI, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1295.

[45] Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol 2020;92(7):791-796.

[46] Lala A, Johnson KW, Januzzi JL, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol 2020;76(5):533-546.

[47] Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J Med Virol 2020;92(11):2409-2411.