The Role of High Sensitivity C-Reactive Protein as a Predictor of Clinical Outcome Among Admitted Adult COVID-19 Patients

Jan Paulo S. Pereira, MD; Florido A. Atibagos, Jr., MD, FPSP and Mari Karr A. Esguerra, MD, FPSP

ABSTRACT

Background: Elevated levels of interleukin-6 (IL-6) and the presence of cytokine storm is associated with a poorer outcome in COVID-19. IL-6 is the primary cytokine involved in the production of C-reactive protein (CRP) which is uniformly increased in cytokine storm. CRP also shows correlation with the severity of COVID-19 making it a promising predictor of clinical outcomes. It can be measured using monoclonal antibody-based test referred to as high sensitivity C-reactive protein (HS-CRP). This method has superior assay precision and accuracy in comparison to conventional means of CRP measurement.
Objectives: To determine the role of HS-CRP as a predictor of clinical outcomes among admitted adult COVID-19 patients.
Methods: This is a retrospective cohort study. Randomly selected medical records of 110 adult COVID-19 patients who were admitted in a tertiary hospital were used. HS-CRP measurement was used as a predictor of outcomes which were divided into good outcome (improvement and recovery) and poor outcome (deterioration and death).
Results: Of the 110 patients, 62 were males while 48 were females. Their ages ranged from 22 to 95 years old with a median age of 60 years old. Among these patients, 85 were discharged while 25 died. As for the HS-CRP measurements, patients with > 20 final HS-CRP were 7.667 times more likely to expire compared to patients with < 20 final HS-CRP. It was observed that for every 1.0 unit increase in patient's first HS-CRP, the odds of mortality also increase by 0.81%. There will also be a 1.21% increase in the odds of mortality for every 1.0 unit increase in patient's final HS-CRP.
Conclusion: The present study supports that an HS-CRP value > 20.00 mg/L be used as a predictor of poor outcome, particularly death.

Key words: COVID-19, high sensitivity C-reactive protein, retrospective cohort study

In December of 2019, Wuhan, China was struck by an outbreak of corona virus disease 2019 (COVID-19) which was caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) that eventually led to a pandemic affecting millions of lives. The disease is highly contagious where an overall effective treatment plan is yet to be established. It is therefore necessary to identify patients who are likely to progress or succumb to the disease early in its course in order to come up with an individualized treatment and risk stratification plan. Unfortunately, as of now, there are no dependable prognostic markers for predicting the outcome of this dreaded infectious disease.

Recent studies have shown that C-reactive protein (CRP) levels are elevated among COVID-19 patients and it correlates well with severity and progression. CRP is an acute phase reactant that rises depending on the degree of inflammation and returns easily to baseline levels after resolution of the inciting condition. Its half-life does not change in between health and disease making it a useful marker for monitoring disease severity. Studies

* From the Department of Pathology and Clinical Laboratory

have also shown that CRP levels progress with the size of the largest lung lesion among patients with pneumonia. It was also observed that patients with low oxygen saturation have higher CRP levels in comparison to those who have normal levels. However, common limitations identified among these previous studies were small sample size and lack of effective treatment plan that might have contributed to poorer outcomes. Aside from that, CRP levels were not consistently ordered among patients involved in these previous studies.

The general objective of this study was to determine the role of HS-CRP as a predictor of clinical outcomes among COVID-19 patients admitted in this institution. Information from this study may be helpful in the early detection of COVID-19 patients who are at risk of progression into a more severe course and death. This may also aid in early decision making and preparation of an individualized treatment plan. Lastly, information from this study may be used as a basis for future studies.

COVID-19 signs and symptoms may range from being asymptomatic to life-threatening such as pneumonia and multiorgan failure[8]. Although the exact mechanism of lung injury and multiorgan failure is still under investigation, it was identified that the presence of cytokine storm is central to having a poorer outcome[8]. Despite the variations of laboratory findings in cytokine storm, it was observed that CRP is uniformly increased[7,8]. It has also been shown to have correlation with COVID-19 severity and disease progression[7,8].

CRP belongs to a class of protein known as acute phase reactants which are produced by the liver[4,10]. CRP is the fastest acute phase reactant to rise during inflammation and the fastest one to return to normal levels during the convalescent period[10]. CRP levels can also be elevated up to several thousand times in comparison to other acute phase reactants making it better in detecting pathologic conditions[10]. CRP binds to C-polysaccharide which is a phosphocholine substituted ribitol teichoic acid found in damaged and necrotic cells[4,5]. After binding, CRP will then activate the classical complement pathway leading to the formation of the membrane attack complex. This will result to cellular lysis and further tissue injury[5,6,9]. Its production is primarily induced by interleukin-6 (IL-6) which is the primary cytokine involved in the production of acute phase reactants.[4,8,9,10]. Studies have shown that a shorter survival among COVID-19 patients is associated with higher levels of IL-6 in comparison to those who have lower levels[8]. Since measurement of IL-6 levels is not routinely requested in a hospital setting, CRP levels may be used as an alternative parameter. CRP measurement is a simple, fast, and easy to perform laboratory test using blood samples. It is conventionally measured using nephelometry and enzyme immuno-assays (EIA)[12,13]. Another way of measuring it is using high sensitivity C-reactive protein (HS-CRP) which is a monoclonal antibody-based test[12,13]. HS-CRP has a superior assay precision, accuracy, availability, and the existence of standards for proper calibration in comparison to conventional CRP measurements[13].

In normal individuals, CRP ranges from 2 to 10 mg/L with a median concentration of around 1 mg/L[4,10]. Different studies have resulted to varying cutoff values for CRP in determining COVID-19 patients who are at risk of progression and deterioration[1,3,6,11]. Majority of these studies found out that a CRP level of at least 10 mg/L or greater is already associated with poorer outcomes[1,3] while some studies are at a cutoff value of 100 mg/L.[6,14] These variations among cutoff values may be attributed to differences in the study population and study designs used. Nevertheless, majority of these studies have shown that baseline CRP level is a simple and independent factor in determining progression and severity among COVID-19 patients.[1,2,3,5,6,7,11,15]

To determine the role of HS-CRP in predicting clinical outcomes categorized as good outcome composed of recovery and/or improvement, and bad outcome composed of deterioration and/or death.

MATERIALS AND METHODS

Research Design: Retrospective cohort study

Study Population and Study Site

Medical records of adult patients with COVID-19 admitted in Far Eastern University – Nicanor Reyes Medical Foundation from March 20, 2020 to March 20, 2021

Eligibility Criteria

Inclusion Criteria

1. Adult patients aged 19 years old and above.

2. The patient must have a SARS-CoV-2 infection confirmed by molecular testing such as Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), Genexpert or Nucleic acid testing.

3. The patient must be admitted in Far Eastern University – Nicanor Reyes Medical Foundation (FEU-NRMF) from March 20, 2020 to March 20, 2021.

Exclusion Criteria

1. Patients who were not diagnosed using molecular methods such as Rapid Antigen Test.

2. CRP measurements done using conventional methods.

Sampling Methodology

A simple random sampling method was utilized by a digital random number generator to facilitate sampling.

Recruitment of Participants

No participants were recruited since the study only used medical records.

Data Collection

A list of all COVID-19 patients from March 20, 2020 to March 20, 2021 was requested from the Infection Control Committee of FEU-NRMF. A random sampling method was used on the list where demographic, clinical and diagnostic data was anonymously collected using medical records and Case Investigation Form (CIF) Coronavirus Disease 19 (COVID-19) Version 8.

The following data were gathered:

1. Demographic data: age and sex

2. Clinical data: clinical signs and symptoms, COVID-19 severity status upon admission, comorbidities, and death (when applicable)

3. Diagnostic data: laboratory results
   - For HS-CRP, the initial value of each case on admission was used as baseline data. The highest HS-CRP value which led to an outcome was used as final data.

Variable Description/ Operational Definitions

Patients were classified based on the Severity Classification of COVID-19 of the Philippine COVID-19 Living Recommendations:

Non-severe COVID-19

Mild COVID-19 – no pneumonia or hypoxia, acute onset of fever and cough or any three or more of the following: fever, cough, coryza, sore throat, diarrhea, anorexia/nausea/vomiting, loss of sense of smell or taste, general weakness/body malaise/fatigue, headache, myalgia

Moderate COVID-19

a. With pneumonia, no difficulty of breathing, RR <30 breaths/min, oxygen saturation $\geq$ 94%

b. Without pneumonia but with risk factors for progression: elderly and/or with comorbidities

Severe COVID-19 – with pneumonia and signs of respiratory distress, oxygen saturation < 94%. RR >30 breaths/minute, requiring oxygen supplementation

Critical COVID-19 – with pneumonia and impending respiratory failure requiring high flow oxygen, non-invasive or invasive ventilation, acute respiratory distress syndrome, sepsis, or shock, deteriorating sensorium, multi-organ failure. COVID-19 outcomes were divided into Good outcome composed of recovery and/or improvement and Poor outcome composed of death and/or deterioration and were defined as follows:

Good outcome:

a. Recovery: When a patient recuperated and was subsequently sent home.

b. Improvement: De-escalation of COVID-19 Severity status (e.g., from severe COVID-19 to moderate COVID-19).

Poor Outcome

a. Death: When the demise of the patient is due to COVID-19 or other complications or conditions associated with COVID-19.

b. Deterioration: Escalation of COVID-19 Severity status (e.g., from moderate COVID-19 to severe COVID-19).

Sample Size

One hundred thirty three (133) COVID-19 patients were randomly included in this study based on the census of 201 COVID-19 patients with confirmed results with an alpha of 95 %, beta of 20 %, margin of error of 5%, confidence level of 95%, and response distribution of 50%. Among the randomly selected 133 COVID-19 patients, 110 were accepted while 23 were rejected. The most common reason for rejection was the lack of HS-CRP measurement.

Data Management and Analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables and median and inter quartile range for non-normally distributed continuous variables. Mann-Whitney U test and Fisher's Exact/ Chi-square test was used to determine the difference of rank and frequency, respectively, between alive and expired patients. Odds ratio and corresponding 95% confidence intervals from binary logistic regression was computed to determine significant predictors for mortality. All statistical tests were two tailed tests. Missing values was neither replaced nor estimated. Null hypotheses rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

RESULTS

Table 1 shows a total of 110 admitted COVID-19 adult patients, 62 of which were males while 48 were females. The ages ranged from 22 to 95 years old with a median age of 60 years old. Among these patients, 85 were discharged while 25 died. Significant findings included severity class of mild, moderate, and critical along with comorbidities of coronary heart disease, pulmonary tuberculosis, chronic obstructive pulmonary disease, and cerebrovascular accident. Significant clinical findings included cardiac rate of > 100 bpm, systolic blood pressure of < 90mmHg, diastolic blood pressure of < 60 mmHg, and diastolic blood pressure of > 100mmHg. Laboratory findings included white blood cell count of > 10 x109/L, neutrophil count of < 0.55 and > 0.65, lymphocyte count of < 0.25, hemoglobin of < 120 g/L among females and > 160 g/L among males, D-Dimer > 0.5 mg/L, blood urea nitrogen > 7.14 mmol/L, procalcitonin of ≥ 10 ng/ml, and high sensitivity CRP of < 20 mg/L and > 20 mg/L. Treatment identified as significant include steroids, non-invasive oxygen therapy, and invasive mechanical ventilation.

Table 2 shows that the first HS-CRP measurement as well as a final HS-CRP measurement was greater than 20 mg/L. Both showed statistical significance in predicting the good and poor outcomes.

DISCUSSION

A significant finding is seen in the HS-CRP values of these patients. All of those who consistently had HS-CRP values of < 20 mg/L improved and were subsequently discharged. A total of 77 patients had at least one HS-CRP value of > 20 mg/L or which 25 died of the disease.

The present study showed that for every 1.0 unit increase in patient's first HS-CRP, the odds of mortality also increase by 0.81%. There will also be a 1.21% increase in the odds of mortality for every 1.0 unit increase in patient's final HS-CRP. The difference between the first and final HS-CRP value is explained by patients dying before a second measurement can be performed. It also showed that patients with more than 20 mg/L final HS-CRP are 7.667 times more likely to die compared to patients with less than 20 mg/L final High Sensitivity C-Reactive Protein.

These findings show that an HS-CRP value of < 20.00 mg/L is a predictor of good outcome while a value of > 20.00 mg/L as a predictor of poor outcome, particularly mortality. The difference in the cutoff value obtained in the present study compared to other studies[1,2,7,14,15] done overseas may be attributed to numerous factors. This may be due to differences in the study design and study

Table 1. Clinico-demographic characteristics of admitted adult COVID-19 patients.

Demographics and Comorbidities	Total (N=110)	Discharged (n=85)	Expired (n=25)	p value at α .05 Level of Significance	Interpretation
Age					
21-40	19 (17%)	19 (22%)	0 (0%)	p=.0059	Significant
41-60	40 (36%)	34 (40%)	6 (24%)		
61-80	42 (38%)	28 (33%)	14 (56%)		
81 and above	9 (8%)	4 (5%)	5 (20%)		
Sex					
Male	62 (56%)	48 (56%)	14 (56%)	p=.9669	Not Significant
Female	48 (44%)	37 (44%)	11 (44%)		
Comorbidities					
Hypertension	69 (63%)	50 (59%)	19 (76%)	p<.1237	Not Significant
Diabetes	37 (34%)	25 (29%)	12 (48%)	p=.0778	Not Significant
Coronary Heart Disease	26 (24%)	15 (18%)	11 (44%)	p=.0077	Significant
Bronchial Asthma	12 (11%)	12 (14%)	0 (0%)	p=.0486	Significant
CKD	7 (6%)	4 (5%)	3 (12%)	p=.2171	Not Significant
Malignancy	6 (5%)	4 (5%)	2 (8%)	p=.5707	Not Significant
Cerebrovascular Accident	3 (3%)	0 (0%)	3 (12%)	p=.0013	Significant
PTB	4 (4%)	0 (0%)	4 (16%)	p=.0002	Significant
Thyroid Disease.	3 (3%)	3 (4%)	0 (0%)	p=.3119	Not Significant
COPD	3 (3%)	0 (0%)	3 (12%)	p=.0013	Significant
BPUD	2 (2%)	1 (1%)	1 (4%)	p=.3074	Not Significant
Atrial Fibrillation	2 (2%)	1 (1%)	1 (4%)	p=.3074	Not Significant
Clinical Findings					
Respiratory Rate (breaths/min)					
<12	0 (0%)	0 (0%)	0 (0%)	p=.3641	Not Significant
>20	90 (82%)	68 (80%)	22 (88%)		
Cardiac rate (beats/min)					
<60	4 (4%)	2 (2%)	2 (8%)	p=.1454	Not Significant
>100	59 (54%)	38 (4%)	21 (84%)	p<.0001	Significant
Blood Pressure					
Systolic BP					
< 90mmHg	12 (11%)	2 (2%)	10 (40%)	p<.0001	Significant
>140mmHg	31 (28%)	23 (27%)	8 (32%)	p=.6266	Not Significant
Diastolic BP					
< 60mmHg	13 (12%)	3 (4%)	10 (40%)	p<.0001	Significant
>100mmHg	2 (2%)	2 (2%)	0 (0%)	p=.0001	Significant
Fever					
(To≥37.8°C)	76 (69%)	56 (66%)	20 (80%)	p=.1847	Not Significant
Cough	78 (71%)	58 (68%)	20 (80%)	p=.2486	Not Significant
Shortness of breath	73 (66%)	54 (63%)	19 (76%)	p=.2300	Not Significant
General body weakness	14 (13%)	12 (14%)	2 (8%)	p=.4295	Not Significant
Diarrhea	12 (11%)	10 (12%)	2 (8%)	p=.5773	Not Significant
Loss of smell and taste	9 (8%)	9 (11%)	0 (0%)	p=.0844	Not Significant
Myalgia	3 (3%)	3 (4%)	0 (0%)	---	---
Headache	3 (3%)	3 (4%)	0 (0%)	---	---

Abdominal pain	2 (2%)	2 (2%)	0 (0%)	---	---
Joint pain	2 (2%)	2 (2%)	0 (0%)	---	---
White Blood Cells Count (x10^9/L)					
< 5	17 (15%)	12 (14%)	5 (20%)	p=.4666	Not Significant
> 10	35 (32%)	22 (26%)	13 (52%)	p=.0147	Significant
Neutrophils					
< 0.55	13 (12%)	13 (15%)	0 (0%)	p=.0404	Significant
> 0.65	75 (68%)	53 (62%)	22 (88%)	p=.0148	Significant
Lymphocytes					
< 0.25	80 (73%)	58 (68%)	22 (88%)	p=.0499	Significant
> 0.35	8 (7%)	7 (8%)	1 (4%)	p=.4953	Not Significant
Hemoglobin (g/L)					
Female: < 120	12 (11%)	6 (7%)	6 (24%)	p<.0001	Significant
> 140	5 (5%)	3 (4%)	2 (8%)	p=.4179	Not Significant
Male: <140	4 (4%)	3 (4%)	1 (4%)	p=1.000	Not Significant
> 160	7 (6%)	5 (6%)	2 (8%)	p=.0006	Significant
D-Dimer					
> 0.5 mg/L	62 (56%)	53 (62%)	9 (36%)	p=.0219	Significant
Blood Urea Nitrogen					
> 7.14 mmol/L	22 (20%)	10 (12%)	12 (48%)	p=.0001	Significant
Creatinine					
Female: >80 mmol/L	9 (8%)	5 (6%)	4 (16%)	p=.1122	Not Significant
Male: > 106 mmol/L	18 (16%)	12 (14%)	6 (24%)	p=.2359	Not Significant
Lactate Dehydrogenase					
> 225 U/L	86 (78%)	63 (74%)	23 (92%)	p=.0569	Not Significant
Ferritin					
>435 (Men)	32 (29%)	21 (25%)	11 (44%)	p=.0678	Not Significant
> 160 (non-menopausal)	7 (6%)	7 (8%)	0 (0%)	p=.1461	Not Significant
>280 (menopausal)	20 (18%)	13 (15%)	7 (28%)	p=.1384	Not Significant
Procalcitonin					
>/= 10 ng/ml	3 (3%)	0 (0%)	3 (12%)	p=.0013	Significant
High Sensitivity CRP					
< 20mg/L	33 (30%)	33 (39%)	0 (0%)	p=.0009	Significant
> 20 mg/L	77 (70%)	52 (61%)	25 (100%)	p=.0002	Significant
Radiologic Findings					
Consolidation	1 (1%)	1 (1%)	0 (0%)	---	
Ground-glass opacity	5 (5%)	4 (5%)	1 (4%)	p=.8374	Not Significant
Unilateral Pul, Inf.	8 (7%)	7 (8%)	1 (4%)	p=.4953	Not Significant
Bilateral Pul. Inf.	82 (75%)	60 (71%)	22 (88%)	p=.0864	Not Significant
Treatment					
Antibiotics	88 (80%)	65 (76%)	23 (92%)	p = .152	Not Significant
Antiviral treatment	27 (25%)	19 (22%)	8 (32%)	p = .324	Not Significant
Steroids	68 (62%)	41 (48%)	25 (100%)	p <.001	Significant
Intravenous IgG	16 (15%)	10 (12%)	6 (24%)	p = .127	Not Significant
Non-invasive oxygen therapy	39 (35%)	37 (44%)	2 (8%)	p = .001	Significant

Invasive Mechanical Ventilation	25 (23%)	3 (4%)	22 (88%)	p <.001	Significant
Renal replacement therapy	4 (4%)	3 (4%)	1 (4%)	p = 1.000	Not Significant
Severity Class					
Mild	23 (21%)	23 (27%)	0 (0%)	p=.0036	Significant
Moderate	37 (34%)	37 (44%)	0 (0%)	p<.0001	Significant
Severe	24 (22%)	18 (21%)	6 (24%)	p=.7501	Not Significant
Critical	26 (16%)	7(8%)	19 (76%)	p<.0001	Significant

CKD – Chronic Kidney Disease, PTB – Pulmonary Tuberculosis, COPD – Chronic Obstructive Pulmonary Disease, BPUD – Bleeding Peptic Ulcer Disease, Unilateral Pul, Inf. – Unilateral Pulmonary Infiltrate, Bilateral Pul. Inf. – Bilateral Pulmonary Infiltrate.

Table 2. Logistic regression analysis of High Sensitivity C-Reactive Protein (HS-CRP) to predict mortality.

Parameters	Total (n=110)	Expired (n=25)	Alive (n=85)	Crude odds ratio (95% CI)	p-value
	Frequency (%); Median (IQR)				
1st High Sensitivity C-Reactive Protein	86 (12 to 178)	132 (96 to 238)	46 (7 to 115)	1.0081 (1.003 to 1.01)	**0.001**
> 20 mg/L	77 (70)	25 (100)	52 (61.18)	(reference)	-
< 20 mg/L	33 (30)	0	33 (38.82)	-	-
Final High Sensitivity C-Reactive Protein	20 (4 to 53)	94 (26 to 179)	8 (3 to 28)	1.0121 (1.003 to 1.02)	0.009
> 20 mg/L	25 (50)	10 (83.33)	15 (39.47)	(reference)	-
< 20 mg/L	25 (50)	2 (16.67)	23 (60.53)	7.667 (1.47 to 40)	**0.016**

population (race, ethnicity, vulnerability to the disease, comorbidities, accessibility of healthcare, and their initial presentation at the emergency room)[1,2,7,14,15]. The difference between the employed laboratory principle such as conventional CRP measurement used in previous studies versus HS-CRP measurement done in the present study may had contributed as well.

It can be shown that the age of the patient is significant in predicting COVID-19 outcome where the proportion of the patients who died were in the age group of 61 to 80 years old. Severity classifications of mild and moderate are predictors of good outcome wherein all patients were discharged while a total of 19 of the 26 patients who were classified as critical died. The severe category appeared to be insignificant which may be attributed to fewer number of cases for analysis. Cardiovascular, cerebrovascular, and pulmonary comorbidities were all identified as predictors of poor outcome particularly death. Tachycardia, hypertensive, and hypotensive episodes were all attributed to poor outcomes. Tachypnea alone does not appear to be significant, however, it is significant for those patients who require oxygen support. These include non-invasive oxygen therapy and invasive mechanical ventilation. Another significant finding is the use of steroids for treatment. A total of 68 patients were given steroids, 41 of these patients recovered while 25 died. Another significant finding is neutrophil count > 0.65 coupled with a lymphocyte count of < 0.25. This laboratory profile shows a possible concurrent bacterial infection or a shift towards inflammation as evidenced by neutrophilia with reduced viral defenses brought about by lymphocytopenia. Other significant laboratory findings include derangement in hemoglobin, blood urea nitrogen, and D-dimer levels which may be attributed to the hypoxic and inflammatory process brought about by COVID-19 leading to multiple organ involvement. Procalcitonin values ≥10 ng/ml is also a significant finding. All 3 patients who had elevated levels of procalcitonin died. One of the patients had a positive endotracheal tube aspirate culture of *Pseudomonas aeruginosa* with a procalcitonin value of 23 ng/ml. One patient had a negative blood culture result with a procalcitonin value of 40 ng/ml. Another patient had a procalcitonin

value of 40 ng/ml, however, no bacteriologic tests were done prior to his demise. Poor outcomes among patients with elevated procalcitonin may be attributed to concurrent bacterial infection. A negative culture result may not entirely rule out a concurrent bacterial infection. Using a different type of sample may be needed to totally rule it out. Radiologic findings may not show any clinical significance in determining the outcome among COVID-19 patients. This could be due to effect of early treatment, radiographic studies done early in the course of the disease, or due to lack of necessity doing serial imaging

LIMITATIONS AND RECOMMENDATIONS

Since data collection is done retrospectively and observational in nature, the study is limited only to the available information gathered from the patients' charts and CIF-COVID-19 Version 8. Serial testing of HS-CRP to monitor the progression of the disease is also recommended.

CONCLUSION

An HS-CRP value of < 20.00 mg/L is a predictor of good outcome while a value of > 20.00 mg/L is a predictor of poor outcome, particularly mortality. Other predictors of poor outcome are age (61 to 80 years old), critical severity status, comorbidities (pulmonary diseases, cardiovascular diseases, and cerebrovascular diseases), cardiorespiratory distress (tachycardia, tachypnea requiring oxygen support, hypotensive and hypertensive episodes), complications requiring the use of steroids as part of treatment, and procalcitonin values of >/= 10 ng/ml.

Budgetary Requirement: None.

REFERENCES

1. Ahnach M, Zbiri S, Nejjari S, Ousti F & Elkettani C. C-reactive protein as an early predictor of COVID-19 severity. J Med Biochem 2020; 39(4): 500–7. https://doi.org/10.5937/jomb0-27554.
2. 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 Nov;92(11):2409-11. doi: 10.1002/jmv.26097. Epub 2020 Jun 9.
3. Clinical Chemistry Techniques, Principles, Correlations – 6th Edition. Chapter 10 (Amino acids and Proteins) page 223-65.
4. Fajgenbaum DC, June CH. Cytokine Storm. Reply. N Engl J Med 2021 Apr 22;384(16):e59. doi: 10.1056/NEJMc2036236.
5. Gulhar R, Ashraf MA, Jialal I. Physiology, acute phase reactants. 2021 Apr 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–.
6. Henry's Clinical Diagnosis and Management by Laboratory Methods – 23rd Edition. Chapter 19 (Specific Proteins) page 253-266.
7. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis 2020 Jan-Dec;14:1753466620937175. doi: 10.1177/1753466620937175.
8. Mark B Pepys, C-reactive protein predicts outcome in COVID-19: is it also a therapeutic target? Eur Heart J 2021; 42(23): 2280–3, https://doi.org/10.1093/eurheartj/ehab169
9. Knight ML. The application of high-sensitivity c-reactive protein in clinical practice: A 2015 update. US Pharm 2015;40(2):50-3.
10. Nehring SM, Goyal A, Patel BC. C reactive protein. [Updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441843/
11. Philippine COVID-19 Living Clinical Practice Guideline – May 09, 2021.
12. Robbins & Cotran Pathologic Basis of Disease - 10th Edition. Chapter 3 (Inflammation and Repair) page 71-113.
13. Sadeghi-Haddad-Zavareh M, Bayani M, Shokri M, et al. C-reactive protein as a prognostic indicator in COVID-19 patients. Interdiscip Perspect Infect Dis 2021 Apr 23;2021:5557582. doi: 10.1155/2021/5557582.
14. Sharifpour M, Rangaraju S, Liu M, Alabyad D, Nahab FB, Creel-Bulos CM, Jabaley CS & Emory COVID-19 Quality & Clinical Research Collaborative (2020). C-reactive protein as a prognostic indicator in hospitalized patients with COVID-19. PloS One 2020; 15(11), e0242400. https://doi.org/10.1371/journal.pone.0242400
15. Stringer D, Braude P, Myint PK, et al. COPE Study Collaborators . The role of C-reactive protein as a prognostic marker in COVID-19. Int J Epidemiol 2021; 50(2): 420–9. https://doi.org/10.1093/ije/dyab012
16. Wang L. C-reactive protein levels in the early stage of COVID-19. Medecine et maladies Infectieuses 2020; 50(4): 332–4. https://doi.org/10.1016/j.medmal.2020.03.007