Analysis of Adiponectin Levels in Covid-19 Patients and Their Relationship to the Occurrence of Multi-Organ Failure and Mortality

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Abstract
Chronic inflammation in comorbidities is thought to be the main cause of the low multiorgan dysfunction (MODS) threshold and death. The failure of the immune system's homeostatic feedback loop triggers ongoing inflammatory activation. Beginning with obesity as a pathological beginning of noncommunicable disease (NCD) and deficiency of adiponectin. Which has anti-inflammatory properties, inhibits the secretion and activation of various inflammatory cytokines (TNF-, IL-1, IL-6, and IFN-) and maintains innate immunity.
This is an analytic observational study with a cross-sectional design. The sampling technique is total sampling. The study was conducted in the COVID-19 isolation room at RSUD Dr. Soetomo Surabaya from May to June 2021. Blood samples were taken on day 0 of treatment, with autoanamnesis data and medical records. The normality test uses the Kolmogorv-Smirnov, and Contingency coefficient test was conducted to assess the correlation between nominal type variables.
There were 153 research subjects; MODS was experienced by 82.35% of subjects, and mortality was experienced by 32.68%. There was a relationship between MODS and mortality (P = 0.016). The median ADP level in the study was 2.8 ng/mL and was associated with multiorgan failure (P = 0.047) and mortality (P = 0.019). With a cut-off value of 3.15 g/mL, the ROC ADP area under the curve (AUC) is 0.378 (P = 0.048, CI 0.265-0.491).Length of stay (LoS) and degree of ARDS were significantly related to ADP levels (P = 0.007 and P = 0.004).
Initial ADP levels were associated with mortality and MODS. ADP levels are related to LoS and the degree of ARDS, or the initial P/F ratio value.

Keywords: adiponectin, comorbidity, mortality, MODS, COVID-19

1. Introduction

Corona virus disease 2019 (COVID-19), a respiratory infection caused by the severe acute respiratory syndrome virus corona 2 (SARS-CoV-2), was originated in Wuhan, China, and become a pandemic momentarily.(1) The mortality rate of oid-19 was reported to be 4% in Shout East Asia.(2) COVID-19 severity was influenced by comorbidities of the patients. The most prevalent comorbidities are hypertension, diabetes mellitus, chronic obstructive pulmonary disease. Approximately, 25.1% of severe COVID-19 had at least 1 comorbidity and 8.2% of them had at least 2 comorbidities. Hypertension became the highest comorbidity responsible for the severe COVID-19 manifestation, which accounted for 16.9%, followed by diabetes mellitus in 8.2%.(3)

Obesity was closely correlated with all of those metabolic conditions and became the root of inflammation pathologies and COVID-19 risk of infection.(4) patients with obesity had an increasing demand of physical compliance anatomically from adipose tissue to expand, nevertheless, lack of blood supply and oxygenation leads to chronic ‘low-grade’ inflammation or meta-inflammation and worse, para-inflammation.(5) Low-grade inflammations chronically trained the innate immunity to immediately activate long-term phenotype after the stimulation, in this circumstances, the cytokines and saturated fatty acid.(6) In obesity, adipose hormones of Adiponectin (ADP) was decreasing and became the stimulant of atherogenic disease, diabetes mellitus, and inflammation. Hypoadiponectinemia was associated with coronary artery disease, type 2 diabetes mellitus, primary hypertension, and metabolic syndromes. SARS-CO-2 infection was correlated with Angiotensin Converting Enzyme-2 (ACE2), which was widey distributed in adipose tissue. (7) Angiotensin II binding with

AT1 receptor generates the pro-inflammatory and prothrombotic milieu, free radical of reactive oxygen species, fibrosis and pathologic alterations of the cells.(6)

Adiponectin is a hormone and also a cytokine that regulates energy metabolism of glucose and fat, insulin resistance, and homeostasis regulation of immune system and anti-inflammatory agents. Hypoadiponectinemia causes the insulin resistance and dyslipidemia.(8) normal value of Adiponectin is in the range of 3 to 30 µg / ml in a healthy body. Adiponectin prevents oxidative stress, reduces inflammatory cytokines, and lipid levels. Decrease of Adiponectin stimulates the activation of cellular kinases.(5) Therefore, we aimed to investigate Adiponectin (ADP) levels in COVID-19 patients, and the relationship between ADP levels to the incidence of multiorgan dysfunction (MODS) and mortality.

2. Methods

2.1 Study design and population

This was an observational prospective analytical study using primary and secondary data to analyse the correlation of serum ADP levels with the incidence of MODs and mortality in COVID-19 patients hospitalized in infection unit. This study was held in infectious unit of Dr. Soetomo Genreal hospital, Surabaya, Indonesia, from May 2021 to June 2021.

We included all adult patients aged ≥ 18 years old who had COVID-19 confirmed by PCR swab test and who agreed to join this study and signed the informed consent. We excluded patients with uncomplete medical history, patients who died less than 24 hours upon the blood sampling. We also excluded patients who were against medical advice.

2.2 Variables and measurements

The independent variable was ADP serum levels in the confirmed COVID-19 patients, and compared to the MODs incidence and mortality as the dependent variable. The potential confounding variables in our study were age, gender, body mass index, and medications history of the patients.

MODs was defined as the organs function impairment in acute disease which causes the incapability to maintain homeostasis without medical intervention, involving > 2 organ systems. Acute respiratory distress syndrome (ARDS) is an acute condition marked with the P/F ratio of<300mmHg with a minimum PEEP of 5cmH2O from the serial blood gas analysis and chest X-ray. Organ systems that were affected in COVID-19 and were investigated in this research to be determined as the MODs is the respiratory, cardiovascular, central nervous system, and urinary systems, as well as hepatobiliary system.

Respiratory failure could be manifested as ARDS, which is a diffuse and acute disease causing the vascular hyperpermeability, loss of aired lungs, with a marked hypoxia, bilateral opacity, lung oedema relating to the increase of vein admixture and dead space as well as the decrease of lung compliance. Acute cardiovascular spectrums syndrome related to COVID-19 (AcovCS) is a collection of symptomatic cardiovascular disease during hospitalization in those whom without symptoms in the last 3 months or the patients with the increase of cardiac enzymes during the hospitalization. COVID-19 manifestation sin the central nervous system could be the decrease of consciousness, measured with Glasgow Coma scale, presence of cerebrovascular attack without other reason during COVID-19 care in infection unit.

COVID-19 complicated with acute kidney injury was defined as the increase of serum creatinine levels ≥ 0.3 mg/dL in 48 hours or the increase of serum creatinine levels more 1.5 times higher than the normal value, during the last 7 days, or decrease of urinary production < 0.5 ml/kg/hour in 6 hours. Acute non-specific hepatitis caused the increase of AST twice the normal levels without any secondary conditions. Coagulopathy was marked with the increase in D-dimer levels (0.5µg/mL) or FDP, thrombocyte < 100.000/mm3 of TEG results of hypercoagulation and/ or hyperfibrinolysis.

Mortality was determined according to the World Health Definition of mortality in COVID-19 patients.(9) Adiponectin (ADP) is a gelatin-28 (GBP28) binding protein, and was measured by ELISA method in this study.

2.3 Study Instruments and data collection

Study subjects was chosen based on the inclusion and exclusion criteria. The eligible patients were explained and asked to sign the informed consent for those who agreed to join the study. Demographical data, anamnesis, physical examinations, were documented in the data collection form. Blood plasma specimen was taken subsequently, using EDTA tube or heparin as the anticoagulant. Blood samples was stored not more than 5 days in the temperature of 2-8ºC or in the temperature of -80ºC for the storage of 6 months.

Samples were centrifugated 15 minutes with 2000-3000 RPM speed in the temperature of 2-8oC for 20 minutes. Reagents and standard solution in the ELISA kit was prepared and 50µl of standard solution was added into the ELISA's well without adding the antibody, followed by the addition of 40µl sample solution, 10µl antibody anti-ADP and 50µl streptavidin-HRP. The wells were incubated for 60 minutes in 37°C and soaked with 0.35 ml of buffer solution for 30 seconds- 1 minutes for each washing. The wells was dried using tissue paper and 50µl of substrate solution was added subsequently, followed by the incubation of 10 minutes in 37°C inside a dark room. After that, a stop solution was added 50µlin each well, until the color turned to yellow. Optical density (OD value) from each well was measured using set reader microplate with the wavelength of 450 nm for 10 minutes.
During the hospitalization, MODs incidence and mortality rate was documented in the data collection form.

2.4 Statistical analysis

The collected and documented data were re-checked before analysis and were tabulated and coded. Descriptive analysis was performed for the baseline characteristics of the subjects. Categorical data were displayed with frequency (n) and percentage (%). Numerical data were identified for the normality using Kolmogorov-Smirnov, with a α>0,05 determined to be normally distributed. Numerical data were presented by Mean and Standard deviation (SD). Bivariate analysis was performed using independent t-test for the normally distributed numerical data and Mann-Whitney test for the numerical data which were not normally distributed. The correlation of the variables were analysed using Pearson correlation test (normal distribution) and Spearman (not-normally distributed) or contingency test. A strong correlation was defined if the r =0,80- 1,00; moderate if the r =0,60-0,799; weak if the r =0,20-0,399; or very weak if the r =0,00-1,99. Statistical program used SPSS.

3. Results

3.1 Baseline characteristics of the subjects

Normality of the data was analysed using Kolmogorov-smirnov test, with the significancy of ($P < 0.05$) in all subjects' characteristics. Chi-squrae / Fisher's exact test was used to compare the differences of the subjects' characteristics towards MODs incidence and mortality, with the significance value of $P < 0.05$. Study participants were mostly male, and BMI ranged from 18.6 - 24.9 kg/m2, and P/F ratio 100-199. BMI and P/F ratio variables were significantly correlated to the MODs incidence and the mortality rate.
Variables related to the MODs incidence were the duration of hospitalization (P=0.001), dyspnea duration before hospital admission (P<0.001), SOFA score (P<0.001), albumin levels (P=0.026) and ADP levels (P=0.047). Mortality was significantly correlated to the albumin levels (P=0.001), ADP (P=0.019), SOFA score (P<0.001), and the length of stay (P<0.001).

Table 1. Baseline Characteristics of the subjects

Variables	**Total (N)**	MODS **(126)**			**Non survive (50)**		
		Cases	SD/ (%) MODS	**P**	**Cases**	SD/ (%) Non survive	**P**
Gender							
Male	80	70	55.6%	0.125*	28	44.0%	0.640*
Female	73	56	44.4%		22	56.0%	
BMI (kg/m2)							
< 18.5	12	5	4%	**0.01*** **	4	8.0%	**0.017*** **
18.5 -24.9	62	56	44.4%		14	28%	
25 - 29.9	59	49	38.9%		28	56.0%	
≥30	20	18	12.7%		4	100%	
P/F Ratio							
<100	31	31	24.6%	**0.000*** **	23	46.0%	**0.000*** **
100 - 199	53	50	39.7%		13	38.0%	
200 - 299	23	19	15.1%		3	6.0%	
300 - 399	30	23	18.3%		3	6.0%	
≥ 400	16	3	2.4%		2	4.0%	
Age	126	52.0	14.20	0.13**	52.46	15.81	0.36**
Illness duration	126	7.62	5.15	**0.001***	7.90	5.43	0.63*
Dyspnea	126	3.83	2.32	**0.000***	4.12	2.46	0.19*
SOFA score	126	5.04	3.22	**0.000***	7.74	2.46	**0.000**
Adiponectin level	126	3.19	1.31	**0.047***	3.59	1.40	**0.019***

Albumin	126	2.95	0.39	**0.026***	2.82	0.40	**0.001****
Length of stay	126	15.6	11.07	0.12*	8.32	6.31	**0.000**
Comorbidities							
Diabetes	78	72	57.1%	0.002*	30	60.0%	0.167*
Tiroid	3	3	2.4%	1.000**	2	4.0%	0.249**
Dislipidemia	51	45	35.7%	0.261*	20	40.0%	0.300*
Hematologi	62	52	41.3%	0.849*	24	48.0%	0.256*
Hipertensi	83	70	55.6%	0.625*	24	48.0%	0.364*
Stroke	15	12	9.5%	0.730**	5	10.0%	1.000**
DVT	4	3	2.4%	0.544**	2	4.0%	0.597**
Aritmia	6	4	3.2%	0.286**	2	4.0%	1.000**
HHD	59	48	38.1%	0.969*	17	34.0%	0.528*
CAD	17	16	12.7%	0.310**	8	16.0%	0.184**
Penyakit paru menahun	34	28	22.2%	1.000*	10	20.0%	0.800*
Penyakit ginjal menahun	48	42	33.3%	0.368*	21	42.0%	**0.048***
Autoimun	14	10	7.9%	0.274**	4	8.0%	0.750**
Penyakit hepar menahun	24	21	16.7%	0.573**	6	12.0%	0.524**
Keganasan	18	11	8.7%	**0.02****	4	8.0%	0.460*
Trauma	9	6	4.8%	0.197**	1	2.0%	0.273**
Infeksi sekunder	3	2	1.6%	0.444**	2	4.0%	0.249**
Hamil	11	8	6.3%	0.411**	4	8.0%	0.750**
Medications							
Steroid	6	5	3.96%	1.000**	1	2%	0.682
Imunodepresan	4	2	1.58%	0.144**	0	0%	0.304
Insulin	5	5	3.96%	0.587**	1	2%	1.000
sulfonilurea	3	2	1.58%	0.444**	0	0%	0.551
Metformin	6	6	4.76%	0.591**	1	2%	0.664
Thiazolidines	2	1	0.79%	0.323**	0	0%	1.000
Antilipid	3	3	2.38%	1.000**	1	2%	1.000
Fibrate	0	0	0%	-	0	0%	-
ACEI / ARB	14	13	10.3	0.466**	2	4%	0.147

Notes: DVT = deep vein thrombosis; HHD = hipertensive heart disease, CAD = Coronary artery disease; *Uji continuity correction, ** *Fisher's exact,* ***Pearson chi-square.

Comorbidities and medications data were not normally distributed, and Kolmogorov-smirnov was used to test it. Diabetes mellitus and malignancy had a strong correlation to the MODs incidence (P = 0.002 and P=0.02, respectively). Chronic kidney disease (CKD) was the only comorbid that was correlated to the mortality (P = 0.048). None of the medications was significantly correlated to mortality.

3.2 Characteristics distribution and their correlation to the Adiponectin levels

The Area under curve (AUC) of ROC in ADP level was 0.378. ADP levels as the predictor of MODs incidence showed a high false positive result (P=0.048 ; CI 0.265 -0.491). The cut-off value of ADP levels in predicting the MODs incidence was 3.15 µg/mL.

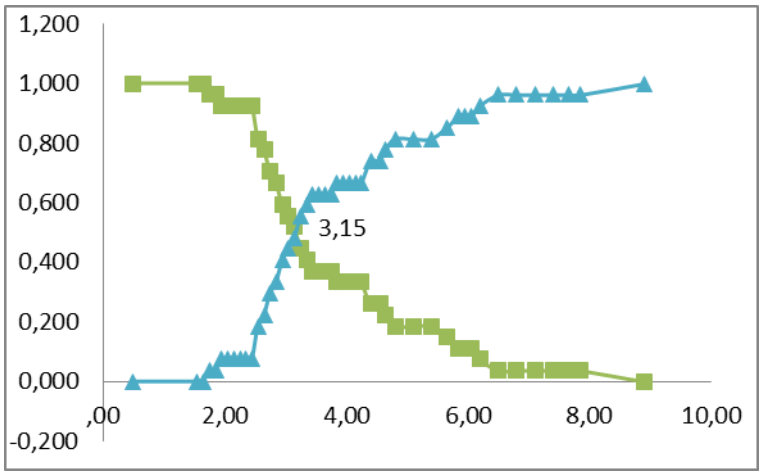

Fig.1. ADP levels cut-off of the sensitivity and specificity in predicting MODs incidence

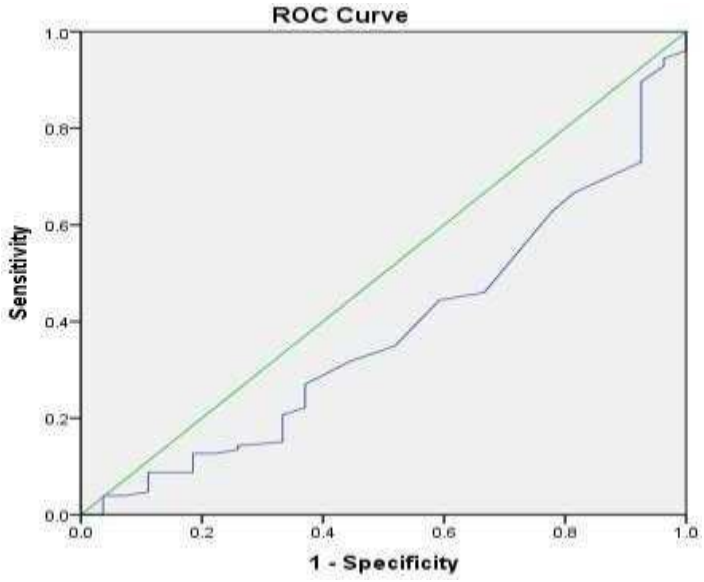

Fig.2. ROC curve of ADP levels in predicting MODs incidence

Patients with the ADP levels < 3.15 µg/mL had a significant difference in the variables of P/F ratio, ARDS incidence, outcome, and the length of stay, compared to patients whose ADP levels was ≥ 3.15 µg/mL .

Table 2 Frequency distribution of patients' characteristics toward the ADP levels

Characteristics	Total	ADP < 3.15 µg/mL (95)		ADP ≥ 3.15 µg/mL (58)		P
		N	% ADP	N	% ADP	
Gender						
Female	73	50	52.6	23	39.7	0.164*
Male	80	45	47.4	35	60.3	
Age (years)						
17-44	51	31	32.6	20	34.5	0.263**
45-64	69	47	49.5	22	37.9	
≥ 65	33	17	17.9	16	27.6	
BMI (kg/m^2)						
< 18.5	12	8	8.4	4	6.9	0.497**
18.5 -24.9	62	34	35.8	28	48.3	
25 - 29.9	59	40	42.1	19	32.8	
>30	20	13	13.7	7	12.1	
P/f ratio						**0.047****
<100	31	14	14.7	17	29.3	

100 - 199	53	36	37.9	17	29.3	
200-299	23	18	18.9	5	8.6	
300-399	30	20	21.1	10	17.2	
≥400	16	7	7.4	9	15.5	
ARDS						
Tidak	16	7	7.4	9	15.5	**0.004****
Mild	32	22	23.2	10	17.2	
Moderate	54	42	44.2	12	20.7	
Severe	51	24	25.3	27	46.6	
Albumin (gr/dL)						
< 3.15	96	58	63.7	38	69.1	0.631*
> 3.15	50	33	36.3	17	30.9	
Outcome						
Survive	103	72	75.78	31	53.44	**0.007****
Non survive	50	23	24.21	27	46.55	

Characteristics	**ADP < 3.15 µg/mL (95)**			**ADP ≥ 3.15 µg/mL (58)**			**P**
	Range	**Median**	**Mean**	**Range**	**Median**	**mean**	
Lama sakit (hari)	0 - 30	7.00	7.24 ± 7.00	0 – 33	7.00	7.71 ± 7.03	0.800***
Gejala Sesak (hari)	0 – 8	3.00	3.40 ± 2.25	0 - 12	3.50	3.34 ± 2.73	0.691***
SOFA score	0 - 10	3.00	4.06 ± 2.99	0 - 12	5.00	5.29 ± 3.56	0.052***
LoS (hari)	2 - 50	13.00	16.4 ± 11.18	1 - 47	10.00	12.02 ± 9.7	**0.007*****

notes: * continuity correction test, ** Pearson Chi-Square test,
***NPar / Mann-Whitney U test.

Table 3. Frequency distribution and the correlation of comorbidities toward the ADP levels

Comorbidities	**Total**	**ADP < 3.15 µg/dL (95)**		**ADP ≥ 3.15 µg/dL (58)**		**P**
		N	**ADP (%)**	**N**	**ADP (%)**	
Diabetes	78	45	47.4	33	56.9	0.329*
Thyroid disease	3	0	0	3	5.2	0.053**
Dislipidemia	51	31	32.6	20	34.5	0.953*
Hematology	62	41	43.2	21	36.2	0.497*
Hypertension	83	50	52.6	33	56.9	0.729*
Stroke	15	11	11.6	4	6.9	0.506*
DVT	4	1	1.1	3	5.2	0.153**
Arrhythmia	6	3	3.2	3	5.2	0.674**
Hypertensive heart disease	59	35	36.8	24	41.4	0.698*
Coronary artery disease	17	12	12.6	5	8.6	0.617*
COPD	34	22	23.2	12	20.7	0.876*
CKD	48	30	31.6	18	31.0	1.000*
Chronic liver diasease	24	17	17.9	7	12.1	0.464*
Autoimunity	14	9	9.5	5	8.6	1.000*
Malignancy	18	10	10.5	8	13.8	0.762*
Trauma	9	7	7.4	2	3.4	0.484**
Secondary infections	3	2	2.1	1	1.7	1.000**
Pregnancy	11	8	8.4	3	5.2	0.535**

Medications	**Total**	**ADP < 3.15 µg/dL (95)**		**ADP ≥ 3.15 µg/dL (58)**		**P**
		N	**ADP (%)**	**N**	**ADP (%)**	
Steroid	6	5	16.7	1	1.7	0.409**
Imunosupressant	4	3	3.2	1	1.7	1.000**
Insulin	5	1	1.10	4	6.9	0.069**
sulfonilurea	3	1	1.1	2	3.4	0.558**
Metformin	6	2	2.1	4	6.9	0.201**
Thiazolidines	2	1	1.1	1	1.7	1.000**
Antilipid	3	3	3.2	0	0	0.289**
Fibrate	0	0	0	0	0	-
ACEI / ARB	14	10	10.5	4	6.9	0.641*

P< 0.05, *Uji continuity correction, ** *Fisher's* exact, ***Pearson chi-square.

There was no correlation between comorbidities and medications with their ADP levels (P >0.05).

4. Discussion

Most of the patients had the BMI range of 18.5-24.9 kg/m2, and with the highest frequency of mortality found in the BMI group of 25 - 29.9 kg/m2 (overweight). There was a significant correlation of the BMI range with the MODs incidence and mortality. This results were supported by the study from Cao et.al., 2021(10) that the risk of septic shock and mortality was 1.04 times higher by the increasing of BMI. The severity of the disease was also increased alongside with overweight and obesity, from 1.84 in overweight into 3.4 times higher in obesity. The median levels of ADP was 2.8 µg/mL in our study; on the contrary, another study stated that the average ADP levels in COVID-19 patients was 14.8 µg/mL.(11). In our study age was not correlated with the ADP levels significantly.

Normally, ADP hormone is circulating in 3 forms: HMW (80%), hexameric (<10%), and trimeric (<10%). In female group, ADP in HMW and LMW are distributed homogenously, whereas in LMW is dominant in male, thus the ADP level looks like to be higher in female. Our study showed a different result that the ADP levels were not correlated to gender differences. The two conclusions above are in accordance with the results of study by Poehls et al. (2009) with her study (Health ABC study)(12).

In the acute inflammation reaction such in COVI-19 infection, HMW is degraded into the active trimeric form to overcome the acute inflammation. Dissociation of the ADP could be not detected by the conventional device that only could measure the LMW form of ADP and the total ADP. Female tends to respond the inflammation faster ant intensely thus making the faster degradation of ADP too, and affecting the MODs incidence and mortality rate which were relatively lower compared to those in the male.(13)

Adipose tissue had a high expression of ACE2 especially in white adipose tissue (WAT). SARS-COV-2 binding to ACE2 receptor causes the increasing levels of Angiotensin II. Angiotensin II subsequently binds to AT1 receptor and stimulate prothrombotic and pro-inflammatory conditions as well as cell growth, Reactive oxygen species production (ROS) and fibrosis. ADP degradation to its active trimeric form will overcome the inflammation response and the exposure of TNF-α, IL-6 /sIL-6R, IL-1b and IFN-γ which in long-term period could suppress the total ADP levels secretion (delipidizing adipocytes).(14) A decrease in ADP levels in the beginning of infection was also proved by Hillebrand, et. al (2016).(15)

Our study showed that although there were significant differences between ADP levels in patients with MODs and non-survivor patient, but ADP levels could not predict the MODs incidence in COVID-19 patients (AUC= 0.378, P = 0.048 , 95% CI 0.265 – 0.491). ADP levels was measured upon admission and might be different if it was followed-up as the serial measurement of ADP levels in COVID-19 patients. A case control study investigated that Adiponectin levels were significantly lower in patients with COVID-19 respiratory failure, even after adjustment for age, sex, BMI, and other covariates.(16) Another study observing the correlation of ADP in COVID-19 infection showed that ADP level was indeed higher in COVID-19 patients with severe manifestation compared to patients with moderate to severe illness, but was not statistically significant, ADP level was strongly correlated with the increase of IL-6, ceramides, glycerophospholipids, which represented the mobilization of ADP from the adipose tissue to counteract the inflammation.(17)

The continuity correction test in our analysis showed a relationship between COVID-19 patients' outcome (survive or not) with the cut-off of ADP levels of 3.15 µg/dL with value 7.187 (α = 0.05, df 1 and Standard deviation 3.841, P=0.007) and risk estimate analysis showed an odd ratio of 2.77, which means that COVID-19 patients with ADP levels of < 3.15 µg/dL had a 2.7 times higher chance to survive compared to those with the higher ADP levels (95% CI 1.357 – 5.477).

ADP is a family of adipokine whose levels decrease with visceral fat accumulation.. ADP contributes to insulin sensitivity, fatty acid oxidation, and diminution of gluconeogenesis pathways. ADP stimulate the Th1 polarization thus has a role in the antiviral inflammation.(18) in the condition of abdominal obesity, there was an unbalanced of leptin production and low-grade inflammation at the expense of ADP or lipocalin-2.(19) Ang1-7 has an active role in regulating the effects of adipokines, reciprocally, ADP attenuates Angiotensin II, which is increased as the effect of SARS-COV-2 binding to ACE2 receptor. Ang 1-7's role as a strong capillary barrier and anti-oxidative profile is altered in patients with visceral fat activation and could help to prevent ARDS.(20) ACE2 receptor deficiency also could become another underlying reason in the inflammatory condition of patients with lipid dysregulation and may interfere with the COVID-19 patients outcome. ACE2 receptor deficiency and a higher titer of pro-inflammatory cytokines in mice with glucose intolerance was correlated to the meta-inflammation(20),

suggesting that Ang1-7, ACE-2 and adipokines are reciprocally influencing the outcomes in COVID-19 patients relating to the lipid dysregulation. Therefore, a further study analyzing the ADP levels towards the COVID-19 outcome needs to be performed and elaborated to the extend of COVID-19 patients' waist circumference to describe visceral fat metabolism, ACE2 receptor expression and the Ang1-7 levels, and a serial measurement of ADP. A larger study sample size and multicenter study will also contribute to the significant result of this study field.

5. Conclusion

Median ADP levels in COVID-19 patients was 2.8 µg/mL (1.5-7.9) with mean of 3.28 ± 1.36 µg/mL. Cut-off value of ADP level 3.15 µg/mL (AUC ROC 0.378, P=0.048, (CI 0.265 -0.4910)) could not reliable to predict the MODs incidence and mortality in COVID-19 patients. ADP levels of COVID-19 patients with different range of BMI and ARDS stage were significantly different. The average length of stay was also significantly different by the increasing level of ADP in COVID-19 patients. Although ADP level could not predict the MODs and mortality, ADP level was significantly correlated to MODs and mortality in COVID-19 patients (P=0.047 and P=0.019, respectively).

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