Case Series

Cholesterol Level in Covid-19 Patients Related to Severity and Mortality: A Case Series and Literature Review

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Abstract

Coronavirus Disease 2019 (COVID-19) is a communicable disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). December 2019 in Wuhan, China, is the time and place where the first pneumonia case which SARS-CoV-2 causes was found, and WHO designated COVID-19 as a pandemic by March 2020. There are reported cases of dyslipidemia associated with SARS patients, albeit rare. Several case reports showed lower cholesterol levels compared to healthy subjects. Therefore, some argued that dyslipidemia could occur in COVID-19. Several studies have revealed that hypolipidemia is positively correlated with the severity of COVID-19. In Ulin Regional Hospital Banjarmasin, several cases found higher cholesterol levels in asymptomatic and mild-moderate COVID—19 survivor compared to patients with severe/critical COVID-19and non-survivor. Two patients in the non-survivor group showed a significant decrease in cholesterol level compared to baseline, and five patients had <150 mg/dL cholesterol level during the examination. Four mild-moderate COVID-19 survivors had cholesterol levels that were greater than 150 mg/dL at the first examination and did not decrease during the evaluation. Cholesterol is thought to play an important role in the pathological development of COVID-19, and it is associated with severity and mortality, which requires further studies.

Keywords: cholesterol, COVID-19, severity, mortality

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] SARS-CoV-2 is a new type of Coronavirus that has never been identified previously in humans. At least two Coronavirus strains have been linked to severe symptoms, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). COVID-19 patients can be asymptomatic or symptomatic, with symptoms ranging from mild to severe to critical. Acute respiratory disease syndromes, such as fever, cough, and shortness of breath, are common signs and symptoms of COVID-19. The average

incubation period is 5-9 days, with the longest incubation time being 14 days.[2]

Severe cases of COVID-19 may cause pneumonia, acute respiratory syndrome, septic shock, multiple organ dysfunction/failure, and even mortality.[3] This disease started with the emergence of pneumonia cases of unknown etiology in Wuhan, China, at the end of December 2019. On Mar 11, 2020, WHO stated that COVID-19 is a pandemic.[4,5]

Coronavirus is a single-strain positive RNA virus that is encapsulated and not segmented. There are four structures of the main protein in Coronavirus; they are protein N (nucleocapsid), glycoprotein M (membrane), glycoprotein spike S (S spike), protein E (envelope). Coronavirus belongs to the order *Nidovirales*, family *Coronaviridae*.[1,6]

This Coronavirus may cause diseases to animals or humans. There are four genera: alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus. Before the presence of COVID-19, there are 6 types of coronavirus that can infect human, they are HCoV-229E (alpha coronavirus), HCoV-OC43 (beta coronavirus), HCoVNL63 (alpha coronavirus), HCoV-HKU1 (beta coronavirus), SARS-CoV (beta coronavirus), and MERS-CoV (beta coronavirus.[1,6]

The Coronavirus that becomes the etiology of COVID-19 belongs to the genus beta coronavirus. Generally, it has a round shape with a pleomorphic diameter of 60-140nm. The result of the phylogenetic analysis shows that this virus is included in a similar subgenus with the coronavirus that causes the SARS epidemic in 2002-2004, Sarbecovirus. 79% RNA sequence is similar to SARS-COV, and 50% resembles MERS-COV. Based on this data, the International Committee on Taxonomy of Viruses (ICTV) names the cause of COVID-19 as SARS-CoV-2.[1,7,8]

Dyslipidemia that is associated with SARS patients has been reported, although it rarely occurs. Some case reports show lower cholesterol levels when it is being compared to healthy subjects.[9] Other studies reported a lipid metabolism disorder in SARS patients who had been recovered after 12 years of infection.[10]

Based on this study, it is presumed that dyslipidemia may occur in patients with COVID-19. Doctors and researchers, on the other hand, haven't paid much attention to this problem yet. A study reported dyslipidemia in COVID-19 patients, and it demonstrated the relationship between lower cholesterol levels and severity and mortality.[11]

Cases of hypolipidemia show a positive correlation to the severity level of COVID-19.[9] This case study will describe the cholesterol levels of 21 COVID-19 patients in relation to their severity and survival.

CASE ILLUSTRATIONS

Ulin Regional Hospital Banjarmasin has treated COVID-19 patients since Mar 14, 2020, and up to Aug 8, 2020, the hospital has treated 442 confirmed COVID-19 patients. There are various severities of

COVID-19 in which they are treated with different laboratory characteristics according to the severity level. There is a phenomenon in confirmed COVID-19 patients without symptoms/mild-moderate symptoms with higher lipid profile levels compared to COVID-19 patients with severe/critical symptoms and non-survival. Below are the descriptions of some cases.

Case 1

A woman, 29 years old, full-term pregnant with mild COVID-19, was referred to Ulin Regional Hospital, Banjarmasin for a cesarean section surgery. The patient complained of fever and cough. Body mass index (BMI) was 23.2 kg/m^2, and blood pressure was 113/92 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit.

Result from laboratory test was random blood sugar (RBS) 89 mg/dl, neutrophil-lymphocyte ratio (NLR) 4.02%, absolute lymphocyte count (ALC) 1200/ul, C-reactive protein (CRP) <6 mg/L, lactate dehydrogenase (LDH) 455 U/L, Ferritin 271 ng/mL, D-dimer 1.16 mg/L, aspartate aminotransferase (AST) 41 U/L, alanine aminotransferase (ALT) 26 U/L, Cholesterol 281 mg/dL, Triglyceride 218 mg/dL, low density lipoprotein (LDL) 215 mg/dL, and high density lipoprotein (HDL) 49 mg/dL The patient recovered after 43 days of hospitalization.

Case 2

A woman, 30 years old, full-term pregnant with asymptomatic COVID-19, was referred to Ulin General Hospital, Banjarmasin, for a cesarean section surgery. BMI was 28.9 kg/m^2, and blood pressure was 120/80 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit. Result from laboratory test was RBS 107 mg/dl, NLR 2.6%, ALC 2650/ul, CRP 9.2 mg/L, LDH 184 U/L, Ferritin 39.28 ng/mL, D-dimer 0.46 mg/L, AST 15 U/L, ALT 13 U/L, Cholesterol 225 mg/dL, Triglyceride 218 mg/dL, LDL 172 mg/dL, and HDL 47 mg/dL. The patient recovered after 38 days of hospitalization.

Case 3

A woman, 36 years old, full-term pregnant with moderate COVID-19, was referred to Ulin Regional Hospital, Banjarmasin, for a cesarean section surgery. Coughing was reported by the patient.BMI was 28.3 kg/m^2, and blood pressure was 130/80 mmHg. Rhonchi were heard in the right lower lobe during auscultation. Chest x-rays showed basal right pulmonary infiltrate. Result from laboratory test was RBS 93 mg/dl, NLR 2.25%, ALC 2360/ul, CRP 31.4 mg/L, LDH 507 U/L, Ferritin 370.83 ng/mL, D-dimer 5.08 mg/L, AST 14 U/L, ALT 10 U/L, Cholesterol 274 mg/dL, Triglyceride 214 mg/dL, LDL 218 mg/dL, and HDL 40 mg/dL. The patient recovered after 32 days of hospitalization.

Case 4

A woman, 27 years old, full-term pregnant with asymptomatic COVID-19, was referred to Ulin Regional Hospital

Banjarmasin for a cesarean section surgery. BMI was 27.8 kg/m^{2,} and blood pressure was 100/75 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit. Laboratory test result was RBS 79 mg/dl, NLR 3.13%, ALC 2600/ul, CRP 22.1 mg/L, LDH 242 U/L, Ferritin 29.85 ng/mL, D-dimer 6.74 mg/L, AST 12 U/L, ALT 11 U/L, Cholesterol 236 mg/dL, Triglyceride 165 mg/dL, LDL 187 mg/dL, and HDL 43 mg/dL. The patient was sent to a halfway house in stable condition after being treated for 18 days.

Case 5

A 22-year-old female with full-term pregnancy and asymptomatic COVID-19 was referred to Ulin Regional Hospital Banjarmasin for cesarean section surgery. BMI was 21 kg/m^2, and blood pressure was 110/70 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit. Laboratory test result was RBS 116 mg/dl, NLR 3.16%, ALC 1657/ul, CRP 4.2 mg/L, LDH 181 U/L, Ferritin 22.20 ng/mL, D-dimer 6.63 mg/L, AST 25 U/L, ALT 11 U/L, Cholesterol 263 mg/dL, Triglyceride 114 mg/dL, LDL 244 mg/dL, and HDL 38 mg/dL. The patient was declared cured after 27 days of treatment.

Case 6

A 54-year-old female with severe COVID-19, Chronic Kidney Disease (CKD) on regular dialysis, hypertension, and type 2 diabetes deteriorated on the 32nd day of treatment. Shortness of breath, cough, and fever were among the symptoms reported upon admission to the hospital. BMI was 24 kg/m^2, and blood pressure was 169/90 mmHg. There were bilateral basal rhonchi in physical lung examination. Basal right pulmonary infiltrates and cardiomegaly were shown on the chest radiograph.

Result of laboratory test was RBS 211 mg/dL, NLR 37.5%, ALC 605/ul, CRP 35.1 mg/L, LDH 885 U/L, Ferritin 2433.72 ng/mL, D-dimer 4.86 mg/L, AST 14 U/L, ALT 6 U/L, Cholesterol 191 mg/dL, Triglyceride 194 mg/dL, LDL 127 mg/dL, and HDL 25 mg/dL. The patient's lipid profile was examined again two weeks later, and a significant decrease was found. Cholesterol 73 mg/dL, Triglyceride 62 mg/dL, LDL 35 mg/dL, and HDL 16 mg/dL. The patient passed away after 34 days of treatment.

Case 7

A 42-year-old male with critical COVID-19, CKD on dialysis, heart failure, and hypertension. Shortness of breath, fever, cough, and nausea-vomitus were all mentioned by the patient. BMI was 22.91 kg/m^2, and blood pressure was 160/106 mmHg. There were rhonchi in all fields of the lungs during auscultation. Chest radiograph showed bilateral infiltrates on all lobes and cardiomegaly.

Result of laboratory test was RBS 138 mg/dL, NLR 39.8%, ALC 319.2/ul, CRP 78.8 mg/L, LDH 1356 U/L, Ferritin >2000 ng/mL, D-dimer 5.56 mg/L, AST 59 U/L, ALT 14 U/L, Cholesterol 126 mg/dL, Triglyceride 94 mg/dL, LDL 80 mg/dL, and HDL 30 mg/dL. After nine days, the lipid

profile was reevaluated and found, Cholesterol 90 mg/dL, Triglyceride 186 mg/dL, LDL 35 mg/dL, and HDL 9 mg/dL. The patient passed away after 14 days of treatment.

Case 8

A 58-year-old male with critical COVID-19, hypertension, and type 2 diabetes complained of shortness of breath, fever, cough, and sore throat.BMI was 25.3 kg/m^2, and blood pressure was 123/79 mmHg. Rhonchi were audible on both lungs during auscultation. Chest radiograph showed bilateral infiltrates on all lobes. Laboratory test result was RBS 416 mg/dL, NLR 23.3%, ALC 630/ul, CRP 278 mg/L, LDH 1446 U/L, Ferritin 4470.10 ng/mL, no data of D-dimer, AST 74 U/L, ALT 98 U/L, Cholesterol 145 mg/dL, Triglyceride 195 mg/dL, LDL 94 mg/dL, and HDL 19 mg/dL. The patient passed away after four days of treatment.

Case 9

An overweight, 47-year-old male with critical COVID-19 complained shortness of breath, cough, sore throat, and nausea upon hospital admission. BMI was 28.9 kg/m^2, and blood pressure was 123/71 mmHg. There were rhonchi in the right lung medial basal and left lung basal in physical lung examination. The chest x-ray showed infiltrates in all right lobes and middle-lower left lobes. Result of laboratory test was RBS 88 mg/dL, NLR 6.14%, ALC 1830/ul, CRP 194.6 mg/L, LDH 1056 U/L, Ferritin >2000 ng/mL, D-dimer 0.91 mg/L, AST 108 U/L, ALT 58 U/L, Cholesterol 136 mg/dL, Triglyceride 178 mg/dL, LDL 104 mg/dL, and HDL 20 mg/dL. The patient passed away after five days of treatment.

Case 10

A 68-year-old male with hypertension and type 2 diabetes was diagnosed with critical COVID-19. Shortness of breath, fever, cough, and nausea were noted upon admission. BMI was 23.4 kg/m^2, and blood pressure was 139/90 mmHg. There were rhonchi in both middle-lower lobes in physical lung examination. There were bilateral peripheral infiltrates on chest radiograph. Laboratory test result was RBS 166 mg/dL, NLR 11.1%, ALC 751/ul, CRP 200.8 mg/L, LDH 591 U/L, Ferritin 555.63 ng/mL, no data of D-dimer, AST 50 U/L, ALT 35 U/L, Cholesterol 138 mg/dL, Triglyceride 168 mg/dL, LDL 83 mg/dL, and HDL 21 mg/dL. The patient passed away after three days of treatment.

Case 11

A 65-year-old woman with moderate COVID-19. The patient had hypertension, heart failure, and was overweight. She had a fever and a cough. During the course of treatment, the patient's condition deteriorated. BMI was 27.1 kg/m^2, and blood pressure was 130/81 mmHg. There were no rhonchi in the initial lung examination, but rhonchi were found in both lung fields during treatment. There was no infiltrate on the initial chest x-ray, but on chest x-ray evaluation, there were bilateral peripheral infiltrates.

Result of laboratory test was RBS 99 mg/dL, NLR 1.7%, ALC 1782/ul, CRP 32 mg/L, LDH 528 U/L, Ferritin >2000 ng/mL, D-dimer 1.23 mg/L, AST 139 U/L, ALT 87 U/L, Cholesterol 112 mg/dL, Triglyceride 148 mg/dL, LDL 74 mg/dL, and HDL 25 mg/dL. Six days later, laboratory evaluation was conducted, and the result was NLR 5.63%, ALC 1250/ul, CRP 229.9 mg/L, LDH 944 U/L, Ferritin 5505.42 ng/mL, D-dimer 5.10 mg/L, AST 129 U/L, ALT 115 U/L, Cholesterol 139 mg/dL, Triglyceride 180 mg/dL, LDL 67 mg/dL, and HDL 26 mg/dL. The patient passed away after 14 days of treatment.

Case 12

A 53-year-old male with a history of spondylitis TB was admitted to the hospital with diarrhea, nausea, and vomit. He was diagnosed with mild-COVID-19. BMI was 18.7 kg/m^2, and blood pressure was 105/88 mmHg. There was no abnormality from the physical lung examination. Chest x-ray was within normal limit.

Result of laboratory test was RBS 178 mg/dL, NLR 6.68%, ALC 1218/ul, CRP 38.6 mg/L, LDH 604 U/L, Ferritin 1969.52 ng/mL, D-dimer 2.48 mg/L, AST 20 U/L, ALT 44 U/L, Cholesterol 189 mg/dL, Triglyceride 171 mg/dL, LDL 158 mg/dL, and HDL 23 mg/dL. Laboratory evaluation was done two weeks later, and the result was NLR 3.94%, ALC 1070/ul, CRP 8 mg/L, LDH 144 U/L, Ferritin 804.64 ng/mL, D-dimer 0.96 mg/L, AST 12 U/L, ALT 14 U/L, Cholesterol 173 mg/dL, Triglyceride 218 mg/dL, LDL 143 mg/dL, and HDL 26 mg/dL. The patient was discharged after 20 days of hospitalization.

Case 13

An overweight, 33-year-old male was diagnosed with critical COVID-19.He complained of shortness of breath, fever, cough, and nausea. BMI was 28.7 kg/m^2, and blood pressure was 112/80 mmHg. There were rhonchi at the base of both lungs from auscultation. Chest CT showed peripheral opacity glass ground with consolidation >3cm multifocal in the right and left superior-inferior lobes.

Result from laboratory test was RBS 118 mg/dL, NLR 10.5%, ALC 448/ul, CRP 171.6 mg/L, LDH 397 U/L, Ferritin >2000 ng/mL, D-dimer 1.77 mg/L, AST 51 U/L, ALT 50 U/L, Cholesterol 146 mg/dL, Triglyceride 81 mg/dL, LDL 115 mg/dL, and HDL 34 mg/dL. Two weeks later, laboratory evaluation was conducted, and the result was NLR 3.57%, ALC 1000/ul, CRP 6.1 mg/L, LDH 251 U/L, Ferritin 1126.41 ng/mL, D-dimer 1.19 mg/L, AST 92 U/L, ALT 216 U/L, Cholesterol 162 mg/dL, Triglyceride 91 mg/dL, LDL 136 mg/dL, and HDL 37 mg/dL. The patient was treated for 23 days, and was discharged for self-isolation.

Case 14

A 60-year-old male smoker with hypertension and pulmonary TB was admitted for critical COVID-19.He complained of shortness of breath, fever, and cough. BMI was 20.8 kg/m^2, and blood pressure was 141/100 mmHg. There were rhonchi in the right middle-lower lobes and

all left lobes from the physical lung examination. The chest x-ray showed infiltrates in both lungs, predominantly left.

Result of laboratory test was RBS 112 mg/dL, NLR 8.5%, ALC 1330/ul, CRP 218.6 mg/L, LDH 1250 U/L, Ferritin 2568.08 ng/mL, D-dimer 5.40 mg/L, AST 207 U/L, ALT 181 U/L, Cholesterol 236 mg/dL, Triglyceride 105 mg/dL, LDL 233 mg/dL, and HDL 30 mg/dL. Three weeks later laboratory evaluation was conducted, and the result was NLR 24.67%, ALC 520/ul, CRP 78.8 mg/L, LDH 246 U/L, Ferritin 3359.02 ng/mL, D-dimer 4.83 mg/L, AST 45 U/L, ALT 93 U/L, Cholesterol 164 mg/dL, Triglyceride 112 mg/dL, LDL 133 mg/dL, and HDL 39 mg/dL. The patient was discharged after 57 days of treatment.

Case 15

A 60-year-old male with history of stroke, hypertension, and CKD was taken to the hospital after an episode of seizure, shortness of breath, fever, cough, nausea, and vomit. He was diagnosed with moderate COVID-19. BMI was 25.6 kg/m^2, and blood pressure was 157/89 mmHg. No abnormality were found in the lung examination. The chest radiograph showed minimal infiltrates at the base of the right lung.

Laboratory result showed that RBS was 111 mg/dL, NLR 14.3%, ALC 1090/ul, CRP 357 mg/L, LDH 317 U/L, Ferritin >2000 ng/mL, D-dimer 5.16 mg/L, AST 37 U/L, ALT 9 U/L, Cholesterol 96 mg/dL, Triglyceride 77 mg/dL, LDL 72 mg/dL, and HDL 16 mg/dL. Blood work reevaluation result were NLR 1.98%, ALC 1420/ul, CRP 253.7 mg/L, LDH 144 U/L, Ferritin 2834.89 ng/mL, D-dimer 2.76 mg/L, AST 17 U/L, ALT 9 U/L, Cholesterol 180 mg/dL, Triglyceride 109 mg/dL, LDL 162 mg/dL, and HDL 26 mg/dL. The patient was discharged after 47 days of treatment.

Case 16

A 47-year-old female with hypertension and CKD came with shortness of breath and cough, and was diagnosed with moderate COVID-19. BMI was 22.9 kg/m^2, and blood pressure was 161/100 mmHg. From auscultation, there were rhonchi in both middle-lower lobes. The chest x-ray showed bilateral infiltrates in both middle-lower lobes.

Result of laboratory test was RBS 88 mg/dL, NLR 11.19%, ALC 660/ul, CRP 32 mg/L, LDH 395 U/L, Ferritin 2128,73 ng/mL, D-dimer 5.8 mg/L, AST 25 U/L, ALT 34 U/L, Cholesterol 162 mg/dL, Triglyceride 88 mg/dL, LDL 112 mg/dL, and HDL 39 mg/dL. Laboratory evaluation was conducted five weeks later, and the result was NLR 36.48%, ALC 560/ul, CRP 4.7 mg/L, LDH 306 U/L, Ferritin 4889.89 ng/mL, D-dimer 4.83 mg/L, AST 13 U/L, ALT 31 U/L, Cholesterol 174 mg/dL, Triglyceride 189 mg/dL, LDL 85 mg/dL, and HDL 51 mg/dL. The patient was discharged after 37 days of hospitalization.

Case 17

A 58-year-old female with a history of acute lymphoblastic leukemia (ALL) type L1 and hypertension came with shortness of breath, cough, and sore throat, and was diagnosed with moderate COVID-19. BMI

was 18.1 kg/m^2, and blood pressure was 158/100 mmHg. Rhonchi at the base of the right lung was heard during auscultation. The chest x-ray showed infiltrates in both lung bases.

Result of laboratory test was RBS 145 mg/dL, NLR 5.59%, ALC 240/ul, CRP 116.5 mg/L, LDH 810 U/L, Ferritin 2910.37 ng/mL, D-dimer 4.85 mg/L, AST 16 U/L, ALT 32 U/L, Cholesterol 234 mg/dL, Triglyceride 132 mg/dL, LDL 141 mg/dL, and HDL 37 mg/dL. Four weeks later there was laboratory evaluation, and the result was NLR 3.66%, ALC 4192.5/ul, CRP 15.7 mg/L, LDH 254 U/L, Ferritin 2111.74 ng/mL, D-dimer 3.89 mg/L, AST 18 U/L, ALT 10 U/L, Cholesterol 167 mg/dL, Triglyceride 169 mg/dL, LDL 124 mg/dL, and HDL 33 mg/dL Patient was discharged after 37 days of treatment.

Case 18

A 51-year-old female with a history of CKD and hypertension complained of shortness of breath and cough. She was diagnosed with moderate COVID-19. BMI was 19.9 kg/m^2, and blood pressure was 169/72 mmHg. Rhonchi were audible at the base of the lungs and chest radiograph showed infiltrates in the right middle-lower lobes and cardiomegaly. R

esult of laboratory test was RBS 96 mg/dL, NLR 8.6%, ALC 1020/ul, CRP 3 mg/L, LDH 1200 U/L, Ferritin 1215 ng/mL, no data of D-dimer, AST 112 U/L, ALT 66 U/L, Cholesterol 239 mg/dL, Triglyceride 411 mg/dL, LDL 142 mg/dL, and HDL 29 mg/dL. Two weeks later laboratory evaluation was reevaluated, and the results were NLR 1.74%, ALC 930/ul, CRP 0.6 mg/L, LDH 260 U/L, Ferritin 514.0 ng/mL, no data of D-dimer, AST 20 U/L, ALT 11 U/L, Cholesterol 177 mg/dL, Triglyceride 148 mg/dL, LDL 127 mg/dL, and HDL 39 mg/dL. The patient was discharged after 22 days of treatment.

Case 19

A 61-year-old female with previous history of type 2 diabetes, hypertension, and heart failure complained of shortness of breath and was diagnosed with severe COVID-19. BMI 25.8 kg/m^2 and blood pressure was 153/99 mmHg. Rhonchi was audible on auscultation especially in the right middle-lower lobes and left lower lobes. Infiltrates were prominent on the right middle-lower lobes and cardiomegaly was visible on chest radiograph.

Result of laboratory test was RBS 272 mg/dL, NLR 15.22%, ALC 900/ul, CRP 6.0 mg/L, LDH 490 U/L, Ferritin 295.71 ng/mL, D-dimer 5.50 mg/L, AST 29 U/L, ALT 25 U/L, Cholesterol 243 mg/dL, Triglyceride 132 mg/dL, LDL 172 mg/dL, and HDL 68 mg/dL. Laboratory evaluation was conducted two weeks later and the result was NLR 2.85%, ALC 1857/ul, CRP 54.4 mg/L, LDH 239 U/L, Ferritin 569.54 ng/mL, D-dimer 1.66 mg/L, AST 29 U/L, ALT 35 U/L, Cholesterol 186 mg/dL, Triglyceride 107 mg/dL, LDL 121 mg/dL, and HDL 67 mg/dL. The patient was discharged after 18 days of treatment.

Case 20

A 71-year-old male came with shortness of breath, fever, cough, diarrhea,

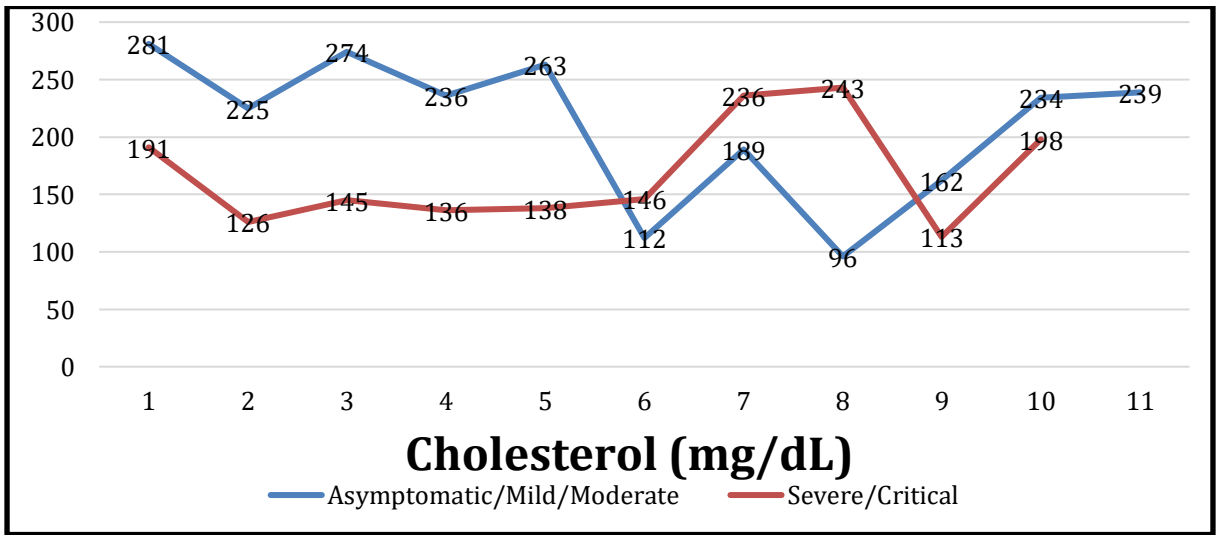
nausea and vomit, and was diagnosed with severe COVID-19. BMI was 23.4 kg/m^2, and blood pressure was 138/65 mmHg. Rhonchi in bilateral medial basal was found from auscultation. Chest x-ray showed infiltrates in both lungs.

Laboratory examination showed that RBS 87 mg/dL, NLR 8.7%, ALC 646/ul, CRP 207.2 mg/L, LDH 852 U/L, Ferritin 446.88 ng/mL, D-dimer 4.56 mg/L, AST 63 U/L, ALT 34 U/L, Cholesterol 113 mg/dL, Triglyceride 85 mg/dL, LDL 96 mg/dL, and HDL 17 mg/dL. Four weeks later there was laboratory evaluation, and the result was NLR 3.80%, ALC 1120/ul, CRP 6.0 mg/L, LDH 213 U/L, Ferritin 208.11 ng/mL, D-dimer 0.70 mg/L, AST 27 U/L, ALT 29 U/L, Cholesterol 156 mg/dL, Triglyceride 124 mg/dL, LDL 96 mg/dL, and HDL 17 mg/dL. After 43 days of treatment, the patient was discharged.

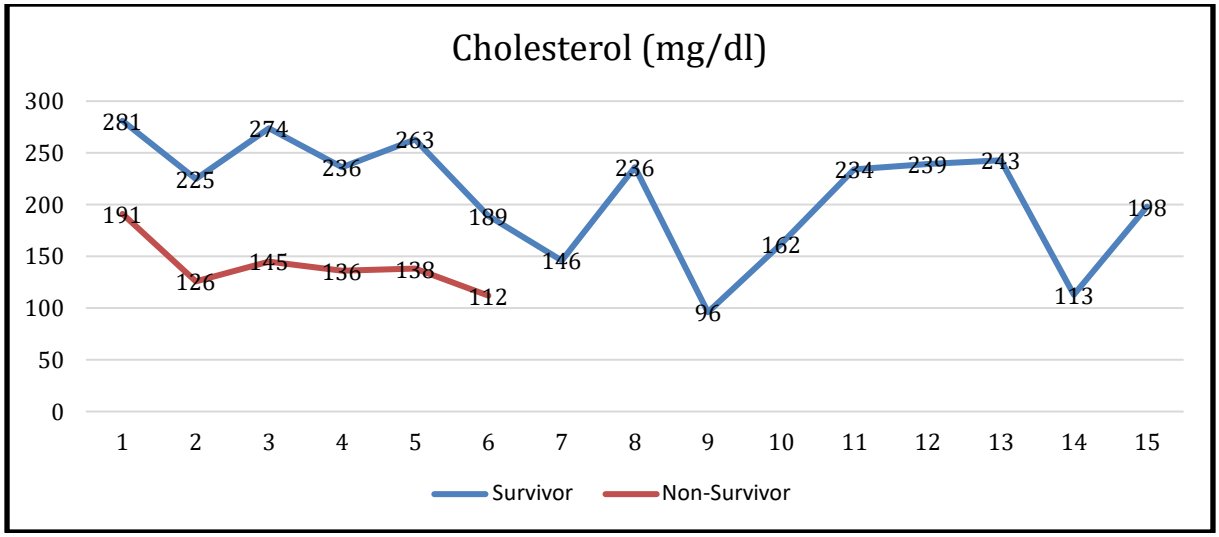
Case 21

A 58-year-old male with a history of hypertension was admitted with critical COVID-19. The patient complained of shortness of breath, fever, cough, diarrhea, epigastric pain, nausea, and vomit. BMI was 27.9 kg/m^2, and blood pressure was 149/100 mmHg. Rhonchi were audible especially in both middle-lower lobes.

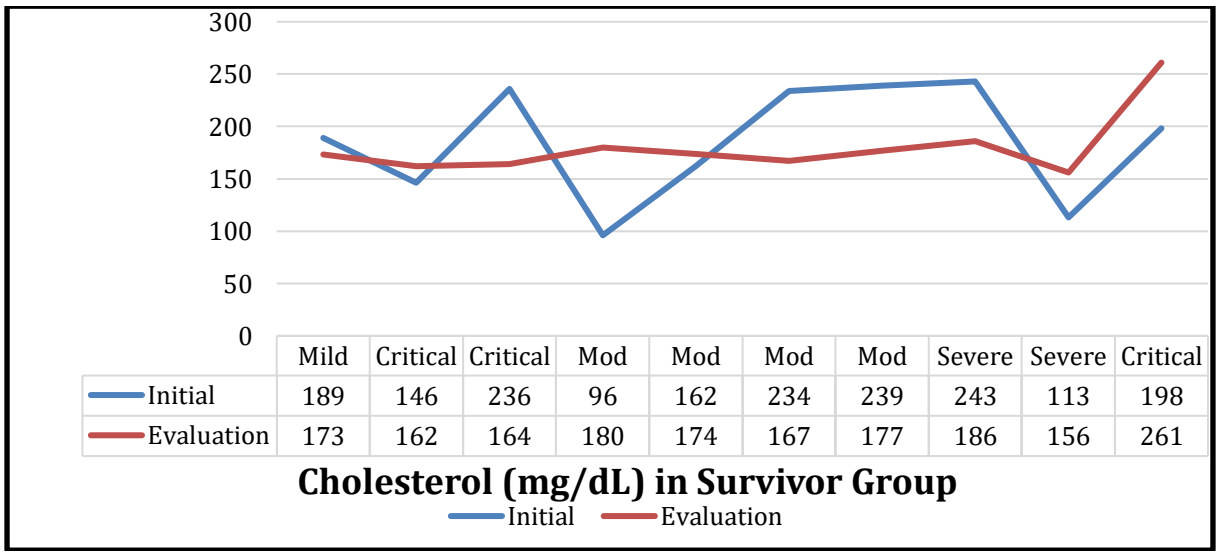
Results of chest x-ray showed infiltrates in both lungs. Result of laboratory test was RBS 140 mg/dL, NLR 6.56%, ALC 960/ul, CRP 59.8 mg/L, LDH 880 U/L, Ferritin 5835.82 ng/mL, D-dimer 1.92 mg/L, AST 92 U/L, ALT 91 U/L, Cholesterol 198 mg/dL, Triglyceride 193 mg/dL, LDL 112 mg/dL, and HDL 47 mg/dL. Laboratory evaluation was conducted four weeks later, and the result was NLR 2.0%, ALC 1725/ul, CRP <0.2 mg/L, LDH 239 U/L, Ferritin 1272.6 ng/mL, D-dimer 0.44 mg/L, AST 49 U/L, ALT 101 U/L, Cholesterol 261 mg/dL, Triglyceride 372 mg/dL, LDL 171 mg/dL, and HDL 44 mg/dL. The patient was discharged after 33 days of hospitalization.



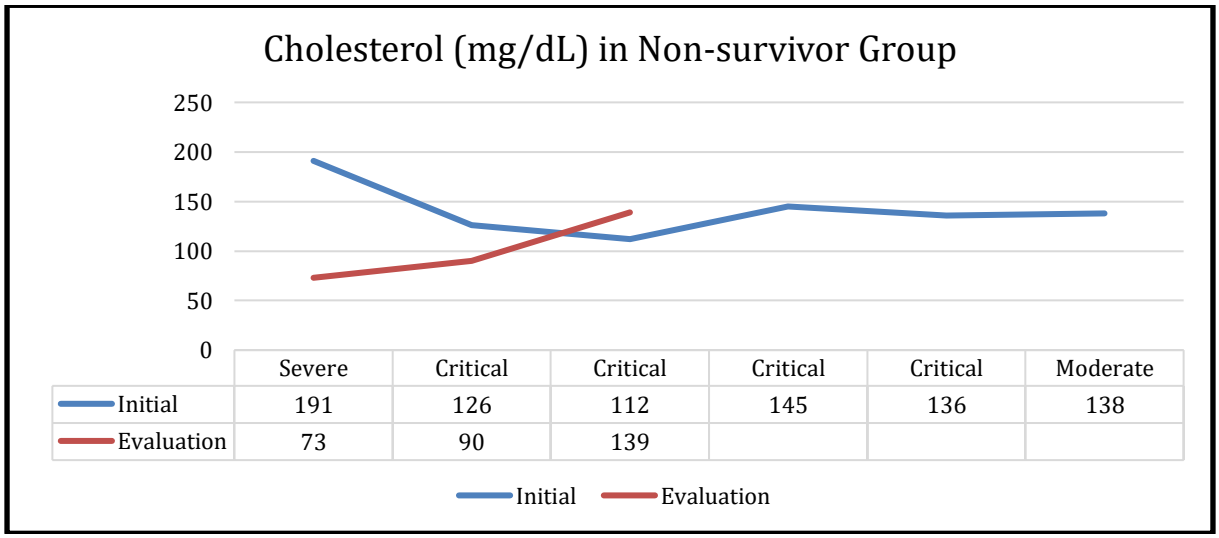
Graphic 1. Cholesterol level according to the severity of COVID-19 patients



Graphic 2. Cholesterol level in survivor and non-survivor of COVID-19 patients



Graphic 3. Cholesterol level in COVID-19 survivors (initial and reevaluation)



Graphic 4. Cholesterol level in the non-survivor group of COVID-19 patients (initial and reevaluation)

DISCUSSION

Recently, dyslipidemia cases were reported in COVID-19 patients, and it shows that cholesterol level decrease is associated with severity level and mortality.[4,5] In a cohort study of 21 patients, lipid profile was examined before the virus infection and during the disease. The patient's cholesterol level, LDL, and HDL decreased when treated in the hospital, and those levels remain low during the hospitalization. Cholesterol and LDL levels return to the baseline of the outpatients. However, a continuous decrease of those levels occurs in non-survivors.[5]

In another cohort study with more samples (n=597), lipid profile data is classified as mild, moderate, severe, or critical.The level of cholesterol and LDL decreased in COVID-19 patients compared to healthy subjects, and the decreased level correlates with the progress of the symptoms.[4]

The possibility of dyslipidemia occurrence in COVID-19 patients because of the side effects of the intervention is very slight as the patient's cholesterol level decreases before the intervention. The patients receive various kinds of medicine during the treatment, and their cholesterol levels improve along with their symptoms.[5] A study of proteomic and metabolism of COVID-19 patients showed massive suppression of metabolism. It included dysregulation of some apolipoproteins (Apo), for example, Apo A1, Apo A2, Apo H, Apo L1, Apo D, and Apo M.[12]

Hypolipidemia is a rare illness caused by multifactorial inheritance, including genetic alterations and other secondary factors. Hypolipidemia is frequently asymptomatic and is discovered during a lipid profile screening test. In COVID-19, it was stated that the decrease in lipid levels was most likely the result of SARS-CoV-2 infection with a complex pathological process. Because there is no consented limit for cholesterol levels, it is referred to as hypolipidemia.[9]

The cholesterol level that is mainly used for hypolipidemia is 120-150 mg/dL. Several other studies used the median or cut-off obtained in their research.[9,13] There are three causes of primary hypolipidemia that rarely occur abetalipoproteinemia, hypobetalipoproteinemia, and chylomicron retention disease. Secondary hypolipidemia occurs more often and may be caused by acute or chronic infection, malabsorption, malnutrition, anemia, critical illness, chronic inflammation, malignancy, hyperthyroidism, chronic liver disease, and the effect of therapy with statin.[13,14]

In acute or chronic bacterial infection, viral infection and parasite infection may cause hypolipidemia/ hypocholesterolemia because of the pro-inflammatory cytokine effect on lipoprotein metabolism.[15] In 2012, Metwally et al. reported a preliminary report about hypocholesterolemia at the patient with TB.[16] Since then, hypercholesterolemia is often found during the acute phase of bacterial infection.[15]

These changes are mediated by various pro-inflammatory cytokines such as Interleukin (IL)-1, IL-6, and Tumour Necrosis Factor (TNF) alpha involved during the acute phase in sepsis.[17]

For critically ill patients, the decreased cholesterol level marks the presence of infection. A recent cross-sectional study demonstrated the importance of lipid changes in sepsis and found low plasma lipid levels but could not determine whether these were pathogenic findings, reflecting more severe severity or higher microbial burden and lipopolysaccharides (LPS) levels. Cholesterol may play a role in host defense in sepsis, as suggested by the observation that circulating lipids and lipoproteins bind to and neutralize endotoxins.[18]

Some researchers believe that hypocholesterolemia is a more sensitive marker of infection presence than leukocytosis.[15,19] Besides that, hypocholesterolemia is significantly correlated to the acute phase in sepsis in line with CRP level.[17]

Other studies about cholesterol and viral infection also reported, such as hepatitis and dengue infection. Lipid levels are altered in HCV patients, regardless of day infection. In studies in acute HCV patients, LDL and total cholesterol levels were linked to early infection.[19,20] In Hepatitis B, chronic infection with cirrhosis, LDL, and HDL level decrease seems to happen.[21] Lima et al. found a decrease in total serum level of cholesterol and LDL in patients with dengue infection.[22]

Several cases above described Pregnant women who were going on cesarean sections with asymptomatic and mild-moderate COVID-19. Laboratory test results show a high level of the lipid profile of the patients. Dyslipidemia is predicted to correlate with the severity level of COVID-19 but is a dyslipidemia condition in pregnant women related to the severity of COVID-19. Pregnancy in healthy women occurs when a normal change of fat metabolism benefits fetus growth and development, thus increasing lipid levels. Deposition and maternal adipose hypertrophy occur during the first trimester of pregnancy due to an increase in insulin receptor expression.[23]

The increased maternal insulin, besides progesterone production, causes lipogenesis with reduced lipolysis, lipid production increases which then being transported to the fetus through placenta for fetus growth. This change is generally non-atherogenic, and lipid profile level will decrease to pre-pregnancy level after birth.[23] Dyslipidemia in pregnancy may risk premature birth, hypertension in pregnancy, preeclampsia, and gestational diabetes. These risks increase in high triglyceride, low HDL, and small dense-high LDL atherogenic fraction. As a result, the risk of cardiovascular disease will increase.[24,25]

Pregnant females with asymptomatic and mild-moderate COVID-19 in this case series were allowed to be discharged, no complications associated with dyslipidemia such as premature birth, hypertension, preeclampsia, and gestational diabetes

were noted.There is a study about characteristics of the pregnant females with COVID-19 in Wuhan, from 118 pregnant females, 109 of them were mild-moderate (92%), and nine were severe to critical (8%).[26]

No data supports the severity level increase of COVID-19 in pregnant females.[3] Another study by Zhu et al. reported that clinical manifestations of the pregnant females with confirmed COVID-19 were similar with the non-pregnant females with COVID-19 infection and had relatively good clinical outcomes.[27,28] Our case series showed no clear relationship between dyslipidemia in pregnant women with the severity of COVID-19.

From the non-survivor group, two patients had a significant decrease in cholesterol level compared to the initial examination. The other five patients had low cholesterol levels (<150 mg/dL) from the beginning.

In four mild-moderate survivors, initial cholesterol levels were>150 mg/dl, and there was no decrease until <150 mg/dl. Meanwhile, one moderate COVID-19 patient with initial cholesterol <150 mg/dl increased to >150 mg/dl. In two survivors with severe/critical infection who had initial cholesterol <150 mg/dL and increased during evaluation, while three other patients from the beginning had initial cholesterol above >150 mg/dL.

Based on this data, cholesterol levels tend to be low in patients with poor prognoses. Non-survivor who already had high levels of cholesterol also experience progressive declines. Meanwhile, mild-moderate patients showed high initial cholesterol level and did not decrease during observation. Those with low cholesterol levels showed elevation during observation.

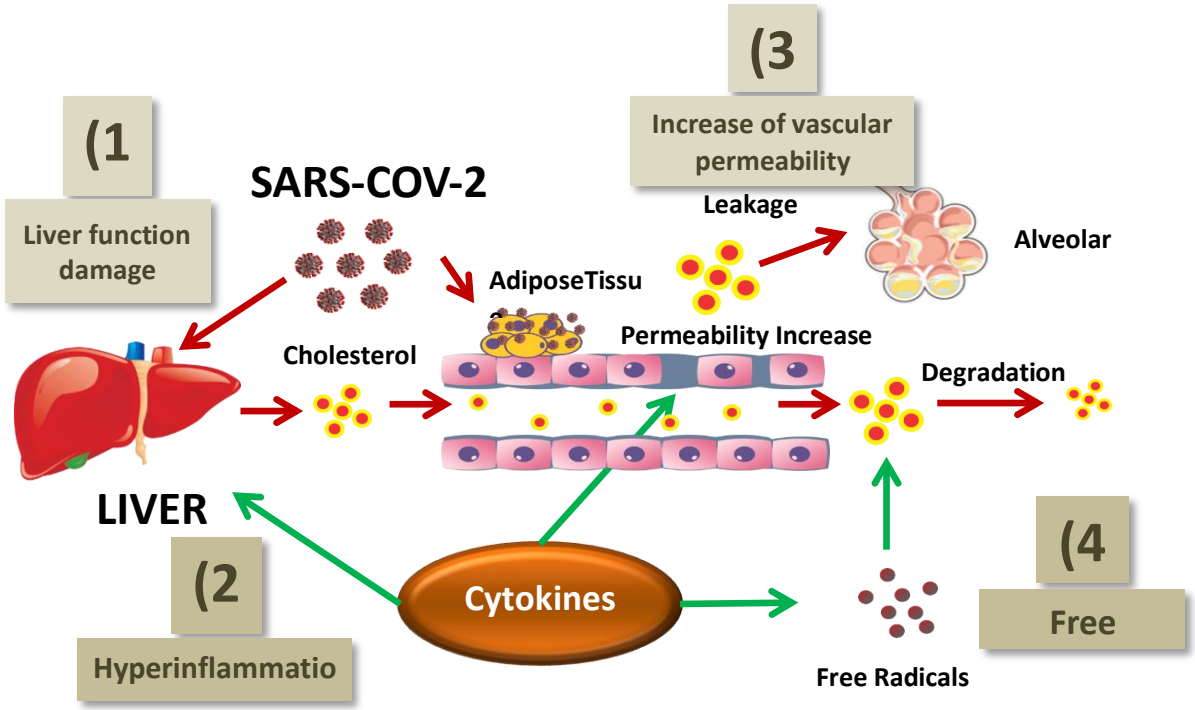


Figure 1. Mechanism of dyslipidemia in COVID-19[29]

The dyslipidemia condition in COVID-19 is interesting; some mechanisms assumed to play roles in the occurrence of dyslipidemia in COVID-19 showed in Figure 1.[29] Damage to liver function occurs as a result of SARS-COV-2 infection, which can interfere with LDL uptake and reduce cholesterol biosynthesis. However, AST and ALT only show a slight increase in less than 50% of the patients.[4,5,30]

This minimal increase of AST and ALT does not accurately describe the liver's LDL uptake and cholesterol biosynthesis ability. As shown in some cases explained previously, the increase of AST and ALT does not always occur in patients with dyslipidemia. Sterol regulatory-element binding protein (SREBPs) is the main transcription factor that manages the expression of various enzymes needed for lipid synthesis. Intracellular lipid homeostasis is regulated by the endoplasm reticulum, where on its membrane there is SREBP cleavage-activating protein (SCAP), squalene monooxygenase (SM), and nuclear factor erythroid two related factor-1 (Nrf1).[31]

When the body needs cholesterol, SCAP will bind SREBPs in the endoplasm reticulum, deliver it to Golgi, and facilitate SREBPs proteolysis to produce the factor domain release of SREBP transcription the entry of the nucleus to increase cholesterol synthesis and uptake. It is very reasonable to speculate that cholesterol synthesis and uptake path has changed in COVID-19 patients because recently, there is evidence that SARS-CoV-2 can suppress the amount of protein associated with the cholesterol mechanism.[12,30]

The hyper-inflammatory response generated by SARS-CoV-2 infection alters lipid metabolism. Inflammatory cytokines such as TNF alpha, IL-6, and IL-1 beta have been proven to change lipid composition, function, and transportation in HIV patients.[32] Cytokines storm in COVID-19 is considered mortality-causing factor in COVID-19 patients. Interleukin-6 increases to 96% of patients in the research of Fan et al.[11] It shows that cytokines may contribute to LDL abnormalities in COVID-19 patients.[5] In some cases that have been described above, cholesterol level decrease is correlated with the inflammatory level that occurs, which is marked by the increase of NLR, CRP, LDH, and Ferritin.[3]

The increase of vascular permeability in SARS-CoV-2 infection causes cholesterol leakage to the alveolar and forms exudate that contains proteins and cholesterol.[29] Exudate has been found in the pulmonary autopsy of SARS patients, such as in pulmonary pathology of COVID-19 patients.[33]

Free radicals are commonly increased in viral infection.[5] It fastens lipid degradation in COVID-19. Oxidized LDL examination is needed to confirm this possibility. Besides that, cholesterol facilitates SARS protein S bonded with Angiotensin Converting Enzyme (ACE) 2 for entering into the target cells. Adipose tissues may function as a reservoir for SARS-CoV-2.[29,34]

There were some limitations in this case series. First, this case report only

explains some cases that cannot describe the complete profiles of COVID-19 patients in Ulin Regional Hospital Banjarmasin yet. It needs further research of a bigger scale to prove the correlation between cholesterol level with severity level and mortality of COVID-19 patients and find the roles of cholesterol in SARS-CoV-2 infection. Second, equal treatment among groups should also be noticed regarding the disease onset with the time of cholesterol examination, cholesterol evaluation examination schedule, and the time of cholesterol sample taking. Third, viral load examination may help to determine the virulence level of SARS-CoV-2 and whether it is related to the patients' cholesterol level.

CONCLUSION

This study showed several cases of a higher cholesterol level in asymptomatic and mild-moderate COVID-19 survivors compared to severe-critical and non-survivors. Cholesterol is thought to play an important role in the pathological development of COVID-19 and was thought to be associated with severity and mortality, which requires further studies.

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