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RESEARCH ARTICLE

The importance of LDL-cholesterol and infection in the etiology of cardiovascular disease: a meta-analysis of COVID-19 survivors and non-survivors

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ABSTRACT

Object: As cardiovascular mortality has increased during the COVID-19 epidemic, and as low-density-lipoprotein cholesterol (LDL-C) participates in the immune system, we examined whether infection is a more serious risk factor for cardiovascular disease (CVD) than elevated LDL-C.

Method: In a systematic search identifying cohort studies of COVID-19 patients we identified 21 studies including 25.647 patients with COVID-19 where LDL-cholesterol was compared with mortality.

Results: In 20 of the 21 cohorts where LDL-C was compared with mortality, LDL-C was lowest among the non-survivors and with statistical significance in 19 of the studies. LDL-C was highest among non-survivors in one cohort that included only 250 patients and the difference was not statistically significant. In three reviews, the authors found that severity of COVID-19 was also more prominent among patients with low LDL-C.

Conclusions: The results are in accordance with the hypothesis that LDL-C participates in the immune system by adhering to and inactivating almost all kinds of microorganisms and their toxic products. The results contradict the general view that low LDL-C protects against CVD. Obviously, infection is a more serious risk factor for CVD than high LDL-C. To verify this hypothesis, blood cultures should be performed in all patients with acute myocardial infarction (AMI) and if positive, appropriate antibiotic therapy should be administered.

Keywords: LDL-cholesterol • COVID-19 • inflammation • infection • hypothesis • statin • cardiovascular disease • ox-LDL • bacteremia • sepsis • mortality

Introduction

For almost a century high total cholesterol and in particular high LDL-C have been considered as the main cause of atherosclerosis and cardiovascular disease (CVD). However, during the past decades several researchers have identified many contradictions to the cholesterol hypothesis.[1-8] For instance, by reporting the relative risk reduction (RRR) instead of the absolute risk reduction (ARR), the benefit of cholesterol-lowering treatment has been exaggerated because in almost all trials the ARR of CVD mortality has been less than one percent,[1-4,6] and in some of the trials it has even increased.[3,4] Furthermore, no cholesterol-lowering trial has shown exposure-response;[4] the association between LDL-C and CVD disappears when corrected for other risk factors;[7-9] and there is much evidence that premature CVD mortality among people with familial hypercholesterolemia (FH) is not due to their high cholesterol, but to increased coagulation factors which a few of them have inherited as well.[10] Although CVD is the commonest cause of mortality in most countries, numerous studies have shown that elderly people with high LDL-C live just as long or longer than those with normal or low LDL-C, and no study has shown that high LDL-C shortens their lifespan.[11,12]

These contradictory observations and the frequent finding of inflammation in atherosclerotic arteries support the hypothesis that inflammation may be the cause of CVD.[13] According to this hypothesis LDL-C may enter the subendothelial layer where it becomes oxidized and causes inflammation, and many studies have shown that oxidized LDL-C is strongly associated with atherosclerosis and CVD. However, if oxidized LDL-C were the cause of atherosclerosis, its lowering should of course be beneficial, but in the REVERSAL trial, where a low statin dose was compared with a high dose, the outcomes on arterial lumen size or atheroma volume were unchanged despite a significant reduction of oxidized LDL biomarkers.[14] Another contradiction is that several large case-control studies, meta-analyses and controlled trials including more than 800,000 CVD patients and controls have demonstrated that treatment with anti-inflammatory drugs increases the risk of CVD.[15-18]

Several years ago, we presented the hypothesis that the etiology of CVD may be attributed to infections, because more than a dozen studies had demonstrated that LDL participates in the immune system by adhering to and inactivating almost all types of microorganisms and their toxic products.[19] In support of the infection hypothesis are the observations that about a third of patients with acute CVD have had an infection immediately before onset,[20] that bacteremia and periodontal infections are associated with an increased risk of CVD, and that treatment of periodontal infections improves endothelial function by reducing the intima-media thickening of the carotid arteries.[19-21]

As cardiovascular mortality has increased during the COVID-19 epidemic,[22-26] we decided to investigate the LDL-C values in patients with COVID-19, because if the cholesterol hypothesis is valid, LDL-C of those who died should be elevated, but if the infection hypothesis is valid, the LDL-C of those who died should be lower than that of the survivors.

In three recent reviews the authors had studied a total of almost 10,000 COVID-19 patients and found that LDL-C was significantly lower among those who died or had a serious type

of COVID-19.[27-29] As the difference between mild and serious disease is difficult to define, we decided to search only for those studies where the authors have measured LDL-C of the survivors and the non-survivors:

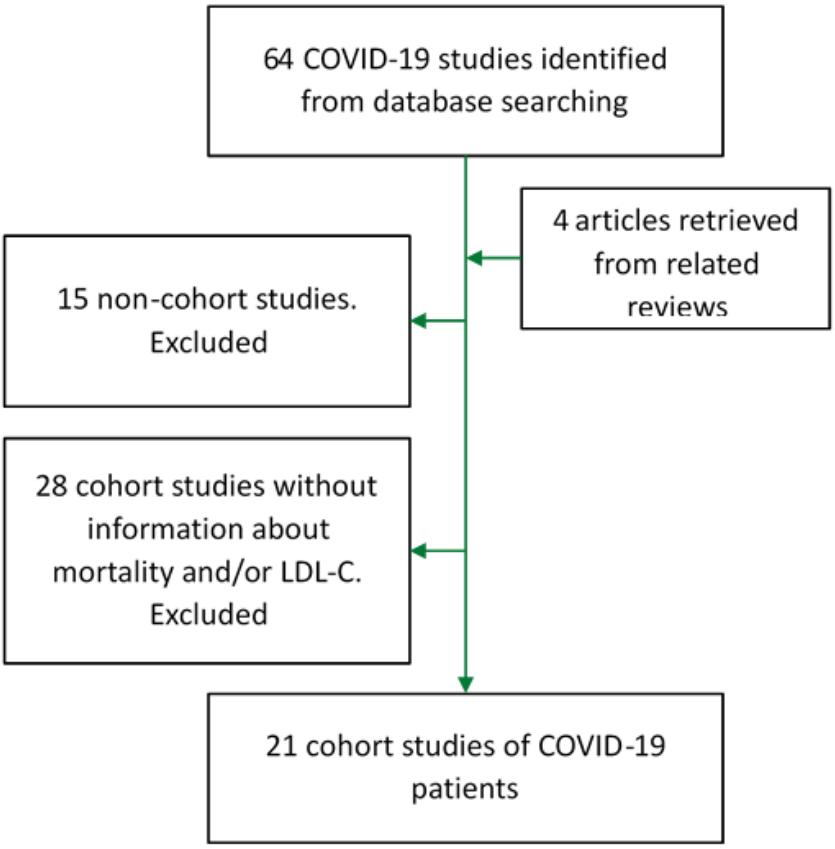
Methods

We performed a PubMed literature search from the years 2020-2023 employing the following search terms (COVID-19 OR Sars-COV-2) AND (LDL OR low-density-lipoprotein) AND mortality and selected those studies where the authors had compared LDL-C with the outcome of the survivors of COVID-19 with the LDL-C of the non-survivors.

Results

Our search disclosed a total of 64 studies of patients with COVID-19. We excluded 15 non-cohort studies and 28 cohort studies with insufficient information. Taken together, we identified 21 relevant cohort studies including 25.647 COVID-19 patients (flow chart).[30—50]

Flow chart



In 20 cohorts LDL-C was lowest in the non-survivor group and with statistical significance in 18 of the cohorts. In two cohorts[31,47] the numbers of non-survivors were not presented. In only one cohort,[43] LDL-C was highest in the non-survival group, but not with statistical significance. In five studies information about statin treatment was present. In all of them, more non-survivors were on such treatment (table 1).[31-33,44,46]

Table 1. The number of survived and non-survived in 21 cohort studies of COVID-19 patients.

Authors	Covid-19 patients n	Survived n (%)	Non-survived n (%)	LDL-C of non-survivors compared with LDL-C of survivors
Anushiravani A. et al.[30]	109	71 (65)	38 (35)	Lower (p<0.014)
Aparisi A et al.[31] (X)	654	NI	NI	Lower (p<0.00001)
Aydin et al.[32] (X)	4118	3501 (85)	617 (15)	Lower (p=0.002)
Barman HA et al.[33] (X)	324	260 (80.2)	64 (19.8)	Lower (p<0.001)
Chen FF, et al.[34] (A)	681	577 (84.7)	104 (15.3)	Lower (p<0.05)
Fabre B, et al.[35]	193	129 (66.8)	64 (33.2)	Lower (p<0.0001)
Fan J. et al.[36] (B)	21	17 (81)	4 (19)	Lower (p<0.03)
Khalilzadeh F. et al.[37]	1078	556 (51.6)	522 (48.4)	Lower (p<0.001)
Li Y. et al.[38]	424	390 (92)	34 (8)	Lower (NS)
Mink et al. [39]	1046	928 (89.8)	118 (10.2)	Lower (p<0.001)
Mohammadshahi et al. [40]	300	274 (91.3)	26 (8.7)	Lower (p<0.001
Parra et al.[41]	125	99	26	Lower (p<0.009)
Rohani-Rasaf M. et al.[42]	1228	1140 (92.8)	88 (7.2)	Lower (p<0.014)
Salari, A. et al.[43]	250	147 (58.8)	103 (41.2)	Higher (NS)
Sampedro-Nuñez M. et al.[44] (X)	1489	1333 (89.5)	156 (10.5)	Lower (p<0.0001)
Senol A. et al.[45]	180	No info	No info	Lower (p=0.02)
Tanaka S, et al.[46] (X)	48	32 (66.7)	16 (33.3)	Lower (p<0.006)
Wu B. et al.[47]	9822	NI	NI	Lower (NS)
Yan X. et aL.[48] (B)	1004	964 (96)	40 (4)	Lower (p<0.001)
Yildirim ÖT et al.[49] (C)	139	113 (81.3)	26 (18.7)	Lower (p<0.001)
Yue J. et al.[50]	48	30 (62.5)	18 (37.5)	Lower (p<0.015)
Total	25.647			

NS: Not significant. NI: No information. X: More non-survivors were on statin treatment. n: numbers. A: From the meta-analyses by Mahat et al.[27] B: From the meta-analysis by Zinellu et al.[28] C: From the meta-analysis by Chidambaram et al.[29]

Discussion

Many studies have reported that both incidence and mortality from CVD among patients with COVID-19 are significantly increased.[22-26] Several authors have suggested that statin treatment may solve the problem. However, as LDL-C was significantly lower among non-survivors than among the survivors in almost all cohort studies of COVID-19 patients (Table 1) and as mortality was higher among those who were treated with statins, cholesterol-lowering treatment may not prevent mortality in COVID-19 patients.

A more likely hypothesis is that infections may be causal factors in the etiology of CVD, as suggested more than a hundred years ago. This hypothesis was supported by the observation of increased frequency of arterial lesions in patients who died from typhoid fever and by the high prevalence of arteriosclerotic radial arteries in those who survived.[19-21]

The infection hypothesis of CVD is in accordance with many clinical observations and experiments. It is a well-known fact that many polymorphonuclear leukocytes are frequently found within the myocardium of patients with AMI. Furthermore, cardiovascular mortality increases during influenza epidemics,[20-26] and about a third of patients with acute CVD have had an infection immediately before onset.[20]

In a follow-up study of 427 patients with CVD, elevated antibodies against C pneumoniae, Epstein-Barr virus and herpes simplex virus were associated with progression of atherosclerosis.[51]

Bacteremia and sepsis are found frequently in patients with cardiogenic shock due to myocardial infarction,[52] and bacterial remnants occur in atherosclerotic plaques but not in normal arterial tissue.[53,54]

The temperature of vulnerable plaques is higher than the temperature of the surrounding tissue, a finding attributed to microbial infection.[55]

Before the year 1900, when infections were the commonest cause of death, the life span of people with FH was just as long or longer than in the general population.[56]

Children who die from an infection have narrowed coronary arteries.[57]

Several animal experiments have succeeded in producing early atherosclerotic plaques by infection with Herpes virus, Mycoplasma pneumonia, Chlamydia pneumonia, Helicobacter pylori, Porphyromonas gingivalis or Influenza virus,[58-63] and the lifespan of experimentally infected rats can be increased by injecting them with purified human LDL-C.[64]

Most investigators attribute myocardial infarction to ischemic myocardial necrosis resulting from rupture of a vulnerable plaque and thrombosis caused by high LDL-C. According to our interpretation,[19] most microorganisms are inactivated immediately in healthy individuals with normal or high LDL-C. However, if plasma LDL-C is too low, some of the microorganisms may succeed in entering the circulation where they aggregate and become phagocytosed by macrophages, producing foam cell formation and inflammation. In the presence of hyperhomocysteinemia, thiolation of LDL-C may cause increased aggregation and altered interaction with macrophages.[65,66] Because of the high extra-capillary tissue pressure around arteries, aggregates of foam cells may occlude their vasa vasorum, causing local vascular ischemia, intramural cell necrosis and creation of vulnerable plaques. Such plaques have many characteristics of a micro-abscess, and their rupture may initiate thrombotic occlusion and releasing the microorganisms into the blood circulation. If a coronary artery is totally occluded by thrombosis, acute myocardial infarction may occur, whereas a partial occlusion may cause myocarditis.[21]

The phagocytosed microorganisms within macrophages are inactivated by oxidation. As the microorganisms are complexed with LDL-C, the cholesterol of LDL-C may become oxidized as well. Thus, high levels of oxidized LDL-C may be a result of infections, but not the very cause.

The cholesterol hypothesis is apparently supported by several trials using Mendelian randomization, showing that lower genetically determined LDL-C concentrations are associated with lower all-cause mortality. But

as pointed out by Burgess et al., "Power, linkage disequilibrium, pleiotropy, canalization and population stratification have all been recognized as potential flaws in the Mendelian randomization approach.[67]

Conclusions

Our analysis of numerous cohort studies of the outcome of COVID-19 demonstrates that those who died had significantly lower LDL-C than the LDL-C of those who survived. As LDL-C participates in the immune system, these findings support the hypothesis that infections may contribute to the etiology and pathogenesis of CVD. We do not exclude the possibility that high LDL-C may be a risk factor for CVD, but the fact that LDL-C was higher among the survivors in almost all of the cohorts indicates that infections are a more important risk factor than a high LDL-C.

Since bacteremia and sepsis are common findings in severe AMI, a blood culture should be performed in all patients with an acute AMI and if it is positive, we recommend treatment with an appropriate antibiotic.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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References:

1. Ravnskov U. Cholesterol-lowering trials in coronary heart disease: frequency of citation and outcome. BMJ 1992;305:15-19

2. Diamond DM, Ravnskov U. How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease. Exp Rev Clin Pharm 2015;8:201–210.

3. Dubroff R. Cholesterol paradox: a correlate does not a surrogate make. BMJ Evidence-Based Med 2017;22:15-19.

4. Okuyama H, Hamazaki T, Hama R, et al. A critical review of the consensus statement from the European atherosclerosis society consensus panel 2017. Pharmacology 2018;101:184–218.

5. Ravnskov U, de Lorgeril M, Diamond DM, et al. LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature. Exp Rev Clin Pharm 2018;11:959–970.

6. Byrne P, Demasi M, Jones M, et al. Evaluating the association between low-density lipoprotein cholesterol reduction and relative and absolute effects of statin treatment. A systematic review and meta-analysis. JAMA Intern Med 2022;182:474-481.

7. Nilsson G, Leppert J, Ohrvik J. Enigma of the cholesterol paradox in acute myocardial infarction: lessons from an 8-year follow-up of all-cause mortality in an age-matched and sex-matched case–control study with controls from the patients' recruitment area. BMJ Open 2022;12:e057562.

8. Georgoulis M, Chrysohoou C, Georgousopoulou E, et al. Long-term prognostic value of LDL-C, HDL-C, Lp(a) and TG levels on cardiovascular disease incidence, by body weight status, dietary habits and lipid-lowering treatment: the ATTICA epidemiological cohort study (2002–2012). Lipids Health Dis 2022;21:141-153.

9. Durai V., Redberg R. Statin therapy for the primary prevention of cardiovascular disease: Cons. Atherosclerosis 2022;356:46-49.

10. Ravnskov U, de Lorgeril M, Kendrick M, Diamond DM. Importance of coagulation factors as critical components of premature cardiovascular disease in familial hypercholesterolemia. Internat J Mol Sci. 2022;23:9146

11. Ravnskov U, Diamond DM, Hama R, et al. Lack of an association or an inverse association between low-density lipoprotein cholesterol and mortality in the elderly: a systematic review. BMJ Open 2016, 6:e010401. [PubMed].

12. Ravnskov U, de Lorgeril M, Diamond DM, et al. The LDL paradox: higher LDL-cholesterol is associated with greater longevity. Ann Epidemiol Pub Health 2000;3:1040-1047.

13. Ridker PM, Bhatt DL, Pradhan AD. et al. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials. Lancet 2023;401:1293-1301.

14. Choi SH, Chae A, Miller E, et al. Relationship between biomarkers of oxidized low-density lipoprotein, statin therapy, quantitative coronary angiography, and atheroma volume. J Amer Coll Cardiol 2008;52:24-32.

15. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroid-anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005;330:1366.

16. Johnsen SP, Larsson H, Tarone R, et al. Risk of hospitalization for myocardial infarction among users of refecoxib, celecoxib, and other NSAIDS. Arch Intern Med. 2005;165:978-984.

17. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomized trials. Lancet 2013;382:769-779.

18. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. BMJ 2017;357:j1909

19. Ravnskov U, McCully KS. Review and hypothesis: Vulnerable plaque formation from obstruction of vasa vasorum by homocysteinylated and oxidized lipoprotein aggregates complexed with microbial remnants and LDL autoantibodies. Ann Clin Lab Sci 2009;39:3-16.

20. Ravnskov U, McCully KS. Infections may be causal in the pathogenesis of atherosclerosis. Amer J Med Sci. 2012;344;391-394.

21. Ravnskov U, Alabdulgader A, McCully KS. Infections may cause arterial inflammation, atherosclerosis, myocarditis and cardiovascular disease. Med Res Arch. 2023;11,1-8.

22. Changal K, Veria S, Mack S, et al. Myocardial injury in hospitalized COVID-19 patients: a retrospective study, systematic review, and meta-analysis. BMC Cardiovasc Disord 2021;21:626.

23. Chang W-T, Toh HST, Liao CT, Yu WL. Cardiac involvement of COVID-19: A comprehensive review. Amer J Med Sci. 2021;361:14-20.

24. Gharibzadeh A, Shahsanaei F, Petrudi NR. Clinical and cardiovascular characteristics of patients suffering st-segment elevation myocardial infarction after Covid-19: A systematic review and meta-analysis. Curr Probl Cardiol. 2023;48:101045

25. Zuin M, Rigatelli G, Battisti V, et al. Increased risk of acute myocardial infarction after COVID-19 recovery: A systematic review and meta-analysis. Internat J Cardiol 2023; 372:138-143.

26. Tolu-Akinnawo O, Poku FA, Elimihele T, et al. Acute cardiovascular complications of COVID-19: A systematic review. Cureus 2023;15:e38575.

27. Mahat RK, Rathore V, Singh N, et al. Lipid profile as an indicator of COVID-19 severity: A systematic review and meta-analysis. Clin Nutr ESPEN. 2021, 45, 91-101.

28. Zinellu A, Paliogiannis P, Fois AG, et al. Cholesterol and triglyceride concentrations, COVID-19 severity, and mortality: A systematic review and meta-analysis with meta-regression. Front Pub Health. 2021, 9, 705916.

29. Chidambaram V, Geetha HS, Kumar A, et al. Association of lipid levels with COVID-19 infection, disease severity and mortality: a systematic review and meta-analysis. Front Cardiovasc Med 2022, 9, 862999.

30. Anushiravani A, Khosravi B, Saberzadeh-Ardestani B, et al. A reliable prognostic marker for liver dysfunction in COVID-19 infection. Middle East Digest Dis. 2021;13:193-199

31. Aparisi A, Iglesias-Echeverria C, Ybarra-Falcón C, et al. Low-density lipoprotein cholesterol levels are associated with poor clinical outcomes in COVID-19. Nutrit Metabol Cardiovasc Dis 2021;31,2619-2627.

32. Aydin SS, Aksakal E, Aydinyilomaz F, et al. Relationship between blood lipid levels

and mortality in hospitalized COVID-patients. Angiology 2022;73:724-733.

33. Barman HA, Pala AS, Dogan O, et al. Prognostic significance of temporal changes of lipid profile in COVID-19 patients. Obes Med. 2021;28:34671707

34. Chen FF, Zhong M, Liu Y, et al. The characteristics and outcomes of 681 severe cases with COVID-19 in China. J Crit Care. 2020;60:32-37.

35. Fabre B, Machulsky NF, Olano C, et al. Remnant cholesterol levels are associated with severity and death in COVID-19 patients. Sci Reports. 2022;12:17584.

36. Fan J, Wang H, Ye G, et al. Low-density lipoprotein is a potential predictor of poor prognosis in patients with coronavirus disease 2019. Metabolism 2020;107:154243.

37. Khalilzadeh F, Sakhaee F, Sotoodehnejadnematalahi F, et al. Angiotensin-converting enzyme 2 rs2285666 polymorphism and clinical parameters as the determinants of COVID-19 severity in Iranian population. Internat J Immunogen 2022;49: 325-332.

38. Li Y, Zhang Y. Dai M, et al. Lipid metabolism changes in patients with severe COVID-19. Clin Chim Acta 2021;517:66-73.

39. Mink S, Saely CH, Frick M, et al. Association between lipid levels, anti-SARS-CoV-2 spike antibodies and COVID-19 mortality: A prospective cohort study. J Clin Med. 2023;12:5068.

40. Mohammadshahi J, Ghobadi H, Matinfar G, et al. Role of lipid profile and its relative ratios (cholesterol/HDL-C, triglyceride/HDL-C, LDL-C/HDL-C, WBC/HDL-C, and FBG/HDL-C) on admission predicts in-hospital mortality COVID-19. J Lipids. 2023: Article ID 6329873

41. Parra S, Saballs M, DiNubile M, et al. Low HDL-C levels at admission are associated with greater severity and worse clinical outcomes in patients with COVID-19 disease. Atherosclerosis Plus 2023;50:1-8.

42. Rohani-Rasaf M, Mirjalili K, Vatannejad A, et al. Are lipid ratios and triglyceride-glucose index associated with critical care outcomes in COVID-19 patients? PLoS One 2022;17: e0272000.

43. Salari A, Mahdavi-Roshan M, Ghorbani Z, et al. An investigation of risk factors of in-hospital death due to COVID-19: a case-control study in Rasht, Iran. Irish J Med Sci. 2021;190:1321–1333.

44. Sampedro-Nuñez M, Aguirre-Moreno N, García-Fraile Fraile L. et al. Finding answers in lipid profile in COVID-19 patients. Endocrine 2021;74:443-454.

45. Senol A, Orhan D. The relationship of lipid profile with severity of disease and mortality in patients with COVID-1. Bratislava Med J 2022;123:589-593

46. Tanaka S, De Tymowski C, Assadi M, et al. Lipoprotein concentrations over time in the intensive care unit COVID-19 patients: Results from the ApoCOVID study. PLoS One 2020;15:e0239573.

47. Wu B, Zhou J, Wang W, et al. Association analysis of hyperlipidemia with the 28-day all-cause mortality of COVID-19. Clin Med Sci J. 2021;36:17-26.

48. Yan X, Li F, Wang X, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study. J Med Virol. 2020;92:2573-2581.

49. Yildirim ÖT, Kaya S. The atherogenic index of plasma as a predictor of mortality in patients with COVID-19. Heart & Lung 2021; 50:329-333.

50. Yue J, Xu H, Zhou Y, et al. Dyslipidemia is related to mortality in critical patients with coronavirus disease 2019: A retrospective study. Endocrinology 2021;12:611526.

51. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. Impact of infectious burden on progression of carotid atherosclerosis. Stroke 2002;33:2581-2586.

52. Kohsaka S, Menon V, Lowe AM, et al. Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. Arch Intern Med. 2005;165:1643-1650.

53. Ott SJ, El Mokhtari NE, Musfeldt M, et al. Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. Circulation 2006;113: 929-937.

54. Shi Y, Tokunaga O. Herpesvirus (HSV-1, EBV and CMV) infections in atherosclerotic compared with non-atherosclerotic aortic tissue. Pathol Internat. 2002;52:31-39.

55. Madjid M, Naghavi M, Malik BA, et al. Thermal detection of vulnerable plaque. Am J Cardiol 2002;90:36L-39L.

56. Sijbrands EJ, Westendorp RG, Defesche JC, et al. Mortality over two centuries in large pedigree with familial hypercholesterolaemia: Family tree mortality study. BMJ 2001;322: 1019–1022.

57. Liuba P, Persson J, Luomac J, et al. Acute infections in children are accompanied by oxidative modification of LDL and decrease of HDL cholesterol, and are followed by thickening of carotid intima–media. Eur Heart J 2003;24:515–521.

58. Fabricant CG, Fabricant J, Litrenta MM, Minick CR. Virus-induced atherosclerosis. J Exp Med. 1978;148:335-40.

59. Damy SB, Higuchi ML, Timenetsky J, et al. Mycoplasma pneumoniae and/or Chlamydophila pneumoniae inoculation causing different aggravations in cholesterol-induced atherosclerosis in apoE KO male mice. BMC Microbiol. 2009;9:194-201

60. Birck MM, Pesonen E, Odermarsky M. et al. Infection-induced coronary dysfunction and systemic inflammation in piglets are dampened in hypercholesterolemic milieu. Am J Physiol - Heart Circul Physiol. 2011;300: 1595–1601.

61. Rothstein NM, Quinn TC, Madico G, et al. Effect of azithromycin on murine arteriosclerosis exacerbated by Chlamydia pneumoniae. J Infect Dis. 2001;183:232–238.

62. Ayada K, Yokota K, Hirai K, et al. Regulation of cellular immunity prevents Helicobacter pylori-induced atherosclerosis. Lupus 2009; 18:1154–1168.

63. Amar S, Wu SC, Madan M. Is Porphyromonas gingivalis cell invasion required for atherogenesis? Pharmacotherapeutic implications. J Immunol. 2009;182:1584–1592.

64. Feingold KR, Funk JL,Moser AH, et al. Role for circulating lipoproteins in protection from endotoxin toxicity. Infect Immun. 1995; 63:2041-2046.

65. Naruszewicz M, Mirkiewicz E, Olszewski AJ, McCully KS. Thiolation of low-density lipoprotein by homocysteine thiolactone causes increased aggregation and altered interaction with cultured macrophages. Nutr Metabol Cardiovasc Dis. 1994;4:70-77.

66. McCully KS. Infections, hyperhomocysteinemia, suppressed immunity and alteration of oxidative metabolism in

atherosclerosis and dementia. Front Aging Neurosci. 2017;9:324.

67. Burgess S, Timpson NJ, Ebrahim S, et al. Mendelian randomization: where are we now and where are we going? Int J Epidemiol. 2015;44:379–388.