Association of hyperlipidemia and statin use with severity of COVID-19

Wilnard YT Tan
National Centre for Infectious Diseases
Barnaby E Young
National Centre for Infectious Diseases
David Chien Lye
National Centre for Infectious Diseases
Daniel EK Chew
Tan Tock Seng Hospital
Rinkoo Dalan (rinkoo_dalan@ttsh.com.sg)
Tan Tock Seng Hospital https://orcid.org/0000-0001-9769-2696

Research Article

Keywords: COVID-19, hyperlipidemia, statins

Posted Date: July 7th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-40008/v1

Abstract

Background and Aims: We aim to study the association of hyperlipidemia and statin use with COVID-19 severity.

Methods: We analysed a retrospective cohort of 717 patients admitted to a tertiary centre in Singapore for COVID-19 infection. Clinical outcomes of interest were oxygen saturation ≤94% requiring supplemental oxygen, intensive-care unit (ICU) admission , invasive mechanical-ventilation and death. Logistic regression models were used to study the association between hyperlipidemia and clinical outcomes adjusted for age, gender and ethnicity. Statin treatment effect was determined , in a nested case-control design, through logistic treatment models with 1:3 propensity matching for age, gender and ethnicity. All statistical tests were two-sided, and statistical significance was taken as $p < 0.05$.

Results: One hundred fifty-six (21.8%) patients had hyperlipidemia and 97% were on statins. There were no significant associations between hyperlipidemia and clinical outcomes. Logistic treatment models showed a lower chance of ICU admission for statin users when compared to non-statin users (ATET: b-0.12(-0.23,-0.01); p=0.028). There were no other significant differences in other outcomes.

Conclusion: Treated hyperlipidemia was not an independent risk factor for severe COVID-19. Statin use independently associated with lower ICU admission. This supports current practice to continue prescription of statins in COVID-19 patients.

Introduction

The COVID–19 pandemic continues to grow around the world, with total number of cases around the crossing the 10 million mark on 30 June 20 [1]. Recent studies suggested that COVID–19, like SARS and MERS, are associated with dysregulated immune and inflammatory processes. Severe cases of COVID–19 had high levels of circulating pro-inflammatory cytokines, as well as high neutrophil counts and lymphopenia [2–4]. COVID–19 has been associated with hyperinflammatory states in children, cardiovascular disease and venous thromboembolism [5–7].

Hyperlipidemia is part of the metabolic syndrome associated with a pro-inflammatory state [8]. Statins are commonly used to treat hyperlipidemia and its pleiotropic effects have been shown to reduce cytokines in various non-infective conditions [9–10]. Patients on statin therapy who developed pneumonia in the setting of bacterial infections [11–12] and influenza [13] are known to have better outcomes.

Medical comorbidities such as diabetes, hypertension and cardiovascular diseases have been identified as risk factor for severe COVID–19 in numerous large case series from China, Italy and the United States [14–16]. Hyperlipidemia has not been identified as an independent risk factor [17], although it is associated with diabetes and hypertension, and contributes to cardiovascular diseases. We aimed to

study the association of hyperlipidemia with COVID–19 severity and the effects of the use of statin in COVID–19 patients.

Methods

We carried out a retrospective cohort study of patients with confirmed COVID–19 hospitalized at the National Centre of Infectious Diseases, Singapore, which has managed more than 60% of COVID–19 patients in Singapore. Patients may be identified by primary care and emergency doctors based on case definitions informed by evolving epidemiological risk factors, case detection from active contact tracing, enhanced pneumonia surveillance and diagnostic testing based on doctors' discretion [18]. Patients were included if they were hospitalized from 22 January 2020 to 4 April 2020. Inclusion criteria were: age ≥50 years old, presence of comorbidities and hyperlipidemia, or presence of pneumonia on chest radiography.

Electronic medical records of hospitalised patients with COVID–19 confirmed by PCR performed on respiratory samples were reviewed to extract information on demographic data on age, gender and ethnicity, presence of comorbidities and concomitant medications, laboratory investigations including full blood count, renal and liver function tests, C-reactive protein (CRP) and lactate dehydrogenase (LDH) and clinical outcomes of COVID–19. Clinical outcomes of interest were: hypoxia with oxygen saturation ≤94% requiring supplemental oxygen, intensive care unit (ICU) admission and invasive mechanical ventilation (IMV) and death. All study procedures and data collections were performed in accordance with institutional guidelines. Waiver of informed consent for data collection was provided by the Ministry of Health under provision of the Infectious Disease Act.

Continuous and categorical variables are presented as median (interquartile range) and frequency (%), respectively. We used the logistic regression models to study the association between hyperlipidemia and outcomes of hypoxia, ICU admission, IMV and death, adjusted for age, gender and ethnicity. Linear regression models to assess the association between each of the complete blood count variables and inflammatory markers, and hyperlipidaemia with adjustment for age, gender and ethnicity were built. To assess the possible treatment effect of statin use on these outcomes we used a nested case control design, wherein after excluding patients with diabetes and hypertension, we estimated the statin treatment effect through logistic treatment models with 1:3 propensity matching for age, gender and ethnicity. All statistical tests were two-sided, and statistical significance was taken as $p < 0.05$. All statistical analyses were performed using Stata version 15.

Results

Within our cohort of 717 patients, one hundred fifty-six (21.8%) patients had hyperlipidemia. Individuals with hyperlipidemia were older (62.5 years, IQR 55–68 years versus 37 years, IQR 27–52 years) and more likely to be of Malay ethnicity (18.6% versus 8.9%). There were more patients with concomitant cardiovascular risk factors with 24 to 59% of patients having coexisting diabetes, hypertension and cardiovascular disease. In terms of inflammatory markers, those with hyperlipidemia were more likely to

have higher CRP, LDH, procalcitonin, white cell count and neutrophil count but lower lymphocyte count. Patients with hyperlipidemia were more likely to require supplemental oxygen, ICU admission and IMV. The risk of death was higher (P <0.05). See Table 1 and 2.

After adjusting for age, gender and ethnicity, there were no significant associations between hyperlipidemia and clinical outcomes of hypoxia, ICU admission, IMV and death. Hyperlipidemia was associated with higher white cell count and neutrophil count but not the other inflammatory markers. See Table 2 and 3.

Of those who had hyperlipidemia, 151 (96.7%) were on statins, 11 (7.1%) were on fibrates and 9 (5.8%) were on ezetimibe. In the nested case control analysis after excluding patients with diabetes and hypertension, 40 patients were on statins and 509 were non-statin users. Logistic treatment models using propensity matching showed a lower chance of ICU admission for statin users when compared to non-statin users (Average treatment effect of statins (ATET): −0.12(−0.23,−0.01); p = 0.028). There were no other significant differences in other outcomes (Table 4).

Discussion

While comorbidities such as diabetes, hypertension and cardiovascular disorders are associated with poorer outcomes with COVID−19, we did not find hyperlipidemia which is part of the metabolic syndrome to be independently associated with severe COVID−19. Most of the patients in this cohort were already treated with statins (97%) and this maybe a reason for these non-significant results. Cholesterol has been implicated to have a possible role in the increased risk of infection in the elderly patients wherein higher tissue cholesterol has been shown to increase the endocytic entry of SARS-CoV−2 along with increased trafficking of angiotensin converting enzyme—2 (ACE−2) in a preprint [19]. However, this increased transmission is more related to tissue cholesterol concentrations rather than the blood concentrations [19].

In our small observational cohort, we did see a significant trend towards a significantly higher white cell counts and neutrophil counts in hyperlipidemia status. Statin use was associated with a lower chance of requiring ICU admission. A key pathological process that leads to cardiovascular disease is inflammation. Statins have been shown to have anti-inflammatory and immunomodulatory effects [20–26] in patients with hyperlipidemia, independent of its ability to reduce low-density lipoprotein [27]. Even in rheumatological disease statins are known to modulate the inflammatory response [28]. Additional to its beneficial effects in cardiovascular disease, statins may be beneficial in patients with bacterial sepsis [29–30], community acquired pneumonia [31] and influenza [13]. Hence, we suggest that statins should not be discontinued in those who require them. This is especially important in COVID−19 as severe disease is related to cardiovascular comorbidities [14–16].

Our study has several limitations. We did not have the quantitative lipid profile on admission to study detailed correlations with the lipid phenotype. Our cohort was small and adverse outcome rates, especially that of mortality, were low. This will affect the generalisability of our findings. Lastly, there was

a risk of channelling bias as patients on statins were more likely to have more severe cardiovascular disease than those without.

Conclusion

We found that treated hyperlipidemia was not an independent risk factor for severe COVID–19. There was a significant trend towards a higher innate immune response shown by higher white cell counts and neutrophil counts. Statin use was independently associated with lower requirement for ICU admission. This supports current practice to continue prescription of statins in hyperlipidemia and other metabolic disorders in COVID–19 patients. The effect of statin use on COVID–19 disease severity needs to be studied in larger observational studies or ideally in randomised controlled trials.

Declarations

The study protocol was reviewed and approved by the Singapore, Ministry of health who provided a waiver of informed consent from study participant for data collection under the Infectious Disease Act as part of national public health research.

Acknowledgments: The study is funded through NMRC COVID-19 research fund (COVID19RF-001). RD is supported in part by Ministry of Health, Clinician Scientist Award [MOH-000014]; and National Medical Research Council Centre Grant [NMRC/CG/017/2013].

Author contributions: RD, WT conceptualized the study, performed data analysis, data interpretation, literature review and wrote the manuscript. DEKC : data interpretation and critical review of manuscript. DCL and BEY conceptualized the study, data interpretation and critical review of manuscript. All authors reviewed the final manuscript.

Declaration of Interest: All authors state that they have no conflict of interest with regards to this manuscript.

Data Availability : The datasets are available from the corresponding author upon reasonable request.

References

[1] Situation Reports [Internet]. Situation Reports. 2020 [cited 2020May12]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200511-covid–19-sitrep–112.pdf?sfvrsn = 813f2669_2

[2] Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV–2 infected patients. EBioMedicine. 2020;55:102763.

[3] Konig MF, Powell M, Staedtke V, et al. Preventing cytokine storm syndrome in COVID–19 using α–1 adrenergic receptor antagonists [published online ahead of print, 2020 May 26]. J Clin Invest.

2020;139642..

[4] Chen X, Zhao B, Qu Y, et al. Detectable Serum Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load (RNAemia) Is Closely Correlated With Drastically Elevated Interleukin 6 Level in Critically Ill Patients With Coronavirus Disease 2019, Clinical Infectious Diseases,, ciaa449, https://doi.org/10.1093/cid/ciaa449

[5] Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID–19 pandemic. Lancet. 2020;395:1607–1608.

[6] Clerkin KJ, Fried JA, Raikhelkar J, et al. COVID–19 and Cardiovascular Disease. Circulation. 2020;141:1648–1655.

[7] Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID–19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. J Thromb Thrombolysis. 2020;50(1):211.

[8] Schonbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? Circulation 2004; 109:II18–26.

[9] Wassmann S, Faul A, Hennen B, Scheller B, Bohm M, Nickering G. Rapid effect of 3-

hydroxy–3-methylglutaryl coenzyme A reductase inhibition on coronary endothelial function. Circ Res 2003; 93:e98–103.

[10] Fang CH, Li JJ, Hui RT. Statins, like aspirin, should be given as early as possible in patients with acute coronary syndrome. Med Hypotheses 2005; 64:192–6.

[11] Novack V, Eisinger M, Frenkel A, Terblanche M, Adhikari NK, Douvdevani A, Amichay D, Almog Y. The effects of statin therapy on inflammatory cytokines in patients with bacterial infections: a randomized double-blind placebo controlled clinical trial. Intensive Care Med. 2009;17:1255–1260.

[12] Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The effect of prior statin use on 30-day mortality for patients hospitalized with community-acquired pneumonia. Respir Res 2005;17:82.

[13] Vandermeer ML, Thomas AR, Kamimoto L, et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. J Infect Dis 2012; 205: 13–19.

[14] W. Guan, Z. Ni, Yu Hu, W. Liang, C. Ou, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. NEJM 2020;382:1708–20.

[15] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID–19 in the New York City Area.JAMA

2020;323(20):2052–2059.

[16] Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid–19. N Engl J Med 2020;382:2431–2440.

[17] Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019—United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020;69:382–386. DOI: http://dx.doi.org/10.15585/mmwr.mm6913e2

[18] Ng YX, Li ZB, Chua YX, et al. Evaluation of the Effectiveness of Surveillance and Containment Measures for the First 100 Patients with COVID–19 in Singapore—January 2–February 29, 2020. MMWR Morb Mortal Wkly Rep 2020;69:307–311. DOI: http://dx.doi.org/10.15585/mmwr.mm6911e1.

[19] Wang, H.,Yuan Z, Pavel MA, Hansen SB. Cholesterol and COVID19 lethality in elderly. bioRxiv preprint 2020. doi: https://www.biorxiv.org/content/10.1101/2020.05.09.086249v2

[20] Ridker PM, Rifai N, Pfeffer MA, Sacks F, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. Circulation. 1999;100:230.

[21] McCarey DW, McInnes IB, Madhok R, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet 2004;363:2015.

[22] Albert MA, Danielson E, Rifai N, Ridker PM, PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. JAMA 2001;286:64.

[23] Zhang J, Osawa S, Takayanagi Y, et al. Statins directly suppress cytokine production in murine intraepithelial lymphocytes. Cytokine. 2013;61:540–545.

[24] Iwata A, Shirai R, Ishii H, et al. Inhibitory effect of statins on inflammatory cytokine production from human bronchial epithelial cells. Clin Exp Immunol. 2012;168:234–240.

[25] van der Meij E, Koning GG, Vriens PW, et al. A clinical evaluation of statin pleiotropy: statins selectively and dose-dependently reduce vascular inflammation. PLoS One. 2013;8:e53882.

[26] Duan HY, Liu DM, Qian P, et al. Effect of atorvastatin on plasma NT-proBNP and inflammatory cytokine expression in patients with heart failure. Genet Mol Res. 2015;14(4):15739–15748.

[27] Zeiser R. Immune modulatory effects of statins. Immunology 2018;154:69–75.

[28] Erkan D, Willis R, Murthy VL, et al. A prospective open-label pilot study of fluvastatin on proinflammatory and prothrombotic biomarkers in antiphospholipid antibody positive patients. Ann Rheum Dis. 2014;73:1176–1180.

[29] Liappis AP, Kan VL, Rochester CG, Simon GL. The effect of statins on mortality in patients with bacteremia. Clin Infect Dis. 2001;33:1352–1357.

[30] Ma Y, Wen X, Peng J, Lu Y, Guo Z, Lu J. Systematic review and meta-analysis on the association between outpatient statins use and infectious disease-related mortality. PLoS One. 2012;7:e51548.

[31] Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The effect of prior statin use on 30-day mortality for patients hospitalized with community-acquired pneumonia. Respir Res. 2005;6:82.

Tables

Table 1: Baseline characteristics and clinical outcomes of patients

		Hyperlipidemia	No Hyperlipidemia
Total number (%)	717 (100)	156 (21.8)	561 (78.2)
Males (%)	410 (57.2)	91 (58.3)	319 (56.9)
Age, median (IQR)	46 (19-57)	62.5 (55-68)	37 (27-52)
Chinese (%)	401 (55.9)	87(55.77)	314 (55.97)
Malays (%)	79 (11.02)	29 (18.59)	50 (8.91)
Indians (%)	83 (11.58)	22 (14.10)	61 (10.87)
Others (%)	154 (21.48)	18 (11.54)	136 (24.24)
Diabetes (%)	76 (10.60)	58 (37.18)	18 (3.21)
Hypertension (%)	139 (19.39)	92 (58.97)	47 (8.38)
Cardiovascular diseases^ (%)	50 (6.97)	38 (24.36)	12 (2.14)
Renal Failure (%)	6 (0.84)	5 (3.21)	1 (0.18)
Systolic BP (mmHg, IQR)	132 (120-143)	139 (132-153)	130 (119-140)
Diastolic BP (mmHg, IQR)	79 (70-87)	78.5 (71.5-88)	79 (70-87)
Presenting Inflammatory markers and peripheral blood indices			
CRP, median (mg/L, IQR)	5.3 (1.6-15.9)	12.8 (3.1-47.4)	4.1 (1.3-11.8)
LDH, median (U/L, IQR)	400 (342-500)	473 (377-610)	386 (334-474)
Procalcitonin, median (ug/L, IQR)	0.06 (0.04-0.11)	0.08 (0.04-0.19)	0.05 (0.04-0.08)
White cell count ($x10^9$/L, IQR)	4.9 (4-6.1)	5.3 (4.2-6.7)	4.8 (3.9-5.9)
Neutrophils ($x10^9$/L, IQR)	2.9 (2.11-3.8)	3.3 (2.5-4.4)	2.7 (2.2-3.7)
Platelets ($x10^9$/L, IQR)	204.5 (172-242)	208.5 (165.5-242)	204 (173-242)
Lymphocytes ($x10^9$/L, IQR)	1.3 (1.0-1.7)	1.2 (0.9-1.6)	1.3 (1.0-.8)
Monocytes ($x10^9$/L, IQR)	0.52 (0.39-0.70)	0.6 (0.4-0.7)	0.51 (0.39-0.70)
Clinical outcome parameters			
Supplementary O2 (%)	91 (12.7)	47 (30.1)	44 (7.8)
ICU admission (%)	47 (6.6)	24 (15.4)	23 (4.1)
Intubation (%)	25 (3.5)	14 (9.0)	11 (2.0)

Death (%)	12 (1.67)	7 (4.5)	5 (0.9)

^Ischemic heart disease, cerebrovascular accidents, peripheral vascular disease

Table 2: Logistic regression analysis for associations of clinical outcomes with hyperlipidemia

	Crude OR (95% CI)	P value	aOR(95%CI)	P value
Hypoxia	5.07 (3.20-8.03)	<0.001*	1.53 (0.88-2.65)	0.129
ICU admission	4.25 (2.33-7.77)	<0.001*	1.35 (0.66-2.75)	0.415
Intubation	4.93 (2.19-11.09)	<0.001*	1.51 (0.57-3.95)	0.405
Death	5.22 (1.63-16.69)	0.005*	0.82 (0.18-3.69)	0.800

Crude rate: unadjusted; aOR: Adjusted Odds risk (adjusted for age, gender and ethnicity); *p<0.05

Table 3: Associations of laboratory markers with hyperlipidemia

	P value#	b-Coefficient^	P value^
CRP	<0.0001*	5.8(-2.1-13.8)	0.151
LDH	<0.0001*	5.7(-32.0-43.3)	0.769
Procalcitonin	0.0069*	-0.03(-0.8-0.8)	0.931
White cell count	0.0009*	0.62(0.2-1.1)	0.005*
Neutrophil count	<0.0001*	0.64(0.3-1.0)	0.001*
Haemoglobin	0.0364*	0.21(-0.1-0.5)	0.115
Platelet count	0.8858	7.26(-8.0-22.5)	0.350
Lymphocyte count	0.0024*	-0.01(-0.15-0.12)	0.849
Monocyte count	0.5151	-0.02(-0.07-0.03)	0.535
Haematocrit	0.0110*	-2.0(-5.6-1.6)	0.282

^Linear regression adjusted for age, gender and ethnicity; #Wilcoxan Rank Sum Test;*p<0.05

Table 4: Logistic treatment models with 1:3 propensity matching (age, gender, ethnicity) to assess statin treatment effect on clinical outcomes

	ATET b (95% CI)	P value
Hypoxia	-0.06(-0.21,0.09)	0.449
ICU admission	-0.12(-0.23, -0.01)	0.028*
Intubation	-0.08(-0.19, 0.02)	0.114
Death	-0.04(-0.16,0.08)	0.488

*P value<0.05, ATET: Average treatment effect on statin