American Journal of Preventive Cardiology 12 (2022) 100428

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

Synergistic effect of lipoprotein (a) and C-reactive protein on prognosis of familial hypercholesterolemia

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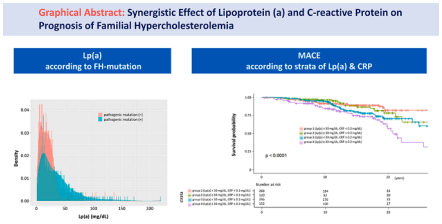
HIGHLIGHTS

- Lp(a) levels among patients with pathogenic variant FH were significantly elevated.
- Lp(a) and CRP levels were not associated with MACE by themselves.
- Lp(a) level was significantly associated with MACE only when the CRP level was elevated.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Familial hypercholesterolemia
LDL cholesterol
Genetics
Lipoprotein (a)
C-reactive protein

ABSTRACT

Objective: The synergistic effect of lipoprotein (a) [Lp(a)] and C-reactive protein (CRP) on major adverse cardiovascular events (MACE) among patients with familial hypercholesterolemia (FH) is unknown. This study aimed to investigate the relations between Lp(a) and CRP levels and MACE in patients with FH whose Lp(a) levels are elevated.

Methods: We retrospectively investigated associations between genotypes and phenotypes, including low-density lipoprotein (LDL) cholesterol level and the occurrence of MACE among patients with FH (N = 786, male/female: 374/412). A Cox proportional hazard model was used to identify factors associated with MACE, adjusting for traditional risk factors. Patients with FH were divided into four groups, based on their Lp(a) and CRP levels, and assessed using Kaplan–Meier curves.

Results: The median follow-up was 12.6 years (interquartile range [IQR], 9.5–17.9 years). During follow-up, 129 MACE were observed. Median Lp(a) and CRP levels were 21.4 (10.9–38.3) mg/dL and 0.20 (0.11–0.29) mg/dL, respectively. Under these conditions, natural log-transformed Lp(a) and CRP were not associated with MACE (hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.91–1.25; P = 0.220; and HR, 1.12; CI, 0.96–1.28; P = 0.190, respectively). However, in Group 4, Lp(a) and CRP were significantly associated with MACE (HR, 2.44; CI, 1.42–3.46; $P = 1.8 \times 10^{-7}$).

Conclusions: In patients with FH, Lp(a) was significantly associated with MACE only when the CRP level was elevated. Patients with FH whose Lp(a) and CRP levels are elevated should be treated aggressively.

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[1] Short tweet: #lipoprotein(a); #C-reactive protein; #familial hypercholesterolemiaIn patients with FH, Lp(a) was significantly associated with MACE only when the CRP level was elevated. Patients with FH whose Lp(a) and CRP levels are elevated should be treated aggressively.

https://doi.org/10.1016/j.ajpc.2022.100428
Received 19 July 2022; Received in revised form 26 September 2022; Accepted 9 November 2022
Available online 11 November 2022

1. Introduction

Familial hypercholesterolemia (FH) is one of the most common Mendelian disorders; its prevalence in the general population is believed to be 1/300 [1,2]. Patients with FH are often complicated with premature cardiovascular disease (CVD) due to an extremely high level since birth of low-density lipoprotein (LDL) cholesterol level. FH is caused by variants of genes associated with LDL metabolism, including LDL receptor (*LDLR*), apolipoprotein B (*APOB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*), and LDL receptor adaptor protein 1 (*LDLRAP1*) [3]. In past decades, several types of medication have been developed to reduce LDL cholesterol, including statins, ezetimibe, and PCSK9 inhibitors [4]. However, even with LDL-lowering therapies, there remain risks of CVD ("residual risks"), such as lipoprotein (a) [Lp(a)] and C-reactive protein (CRP) [5,6]. Among patients with FH, Lp(a) levels are significantly higher than in those without FH; the underlying mechanism remains unclear.

CRP level has been established as a residual risk for CVD among general populations receiving LDL-lowering therapies [7–10]. Furthermore, several studies conducted in patients without FH have suggested that Lp(a) and CRP have synergistic effects on CVD events [11,12]. However, there is only sparse data for clarifying Lp(a) and CRP as residual risk factors for CVD among patients with FH. Here we investigate the associations between these residual risk factors, Lp(a) and CRP, and the occurrence of major adverse cardiac events (MACEs) among patients who fulfill the clinical diagnostic criteria for FH.

2. Materials and methods

2.1. Study population

At Kanazawa University Hospital, from 1990 to 2020, we reviewed the information of 2,011 patients who were clinically diagnosed with FH using the 2017 Japan Atherosclerosis Society criteria [13]. All of these patients fulfilled at least two of the three essential clinical criteria as follows: [1] LDL cholesterol $\geq$ 180 mg/dL; [2] tendon xanthoma on the backs of the hands, elbows, knees, or other areas, Achilles tendon hypertrophy, Achilles tendon thickness $\geq$ 9 mm (as assessed by X-ray), and xanthoma tuberosum; and [3] a family history of FH or premature coronary artery disease (diagnosed in the patient's first- or second-degree relatives). We excluded 1,225 patients who lacked data (e.g., blood lipids, genetic analyses) or because patients were homozygous with compound heterozygous FH. We finally included 786 patients (Supplemental Fig. **1**).

2.2. Clinical data assessments

We defined hypertension as systolic blood pressure of $\geq$140 mmHg, diastolic blood pressure of $\geq$90 mmHg, or by the use of antihypertensive agents. We used the definition of diabetes of the Japan Diabetes Society [14]. Smoking was defined as current smoking. CVD was defined as the presence of angina pectoris, myocardial infarction, or severe stenotic region(s) in the coronary artery ($\geq$75% stenosis), identified using either angiography or computed tomography. Serum levels of total cholesterol, triglycerides, and high-density lipoprotein cholesterol were determined enzymatically using automated instrumentation. If triglyceride levels were <400 mg/dL LDL, cholesterol levels were calculated using the Friedewald formula; otherwise, they were determined enzymatically. Throughout the study period, an enzyme-linked immunosorbent assay was used to determine Lp(a) concentrations (N-Assay TIA Lp(a) Nittobo; Nitto Boseki, Tokyo, Japan) [15]. A previous study found that the coefficient of variation for this measurement of Lp(a) was <8%, within and between assays [15]. We evaluated high-sensitive CRP (Quoligent CRP reagent (Sekisui Medical Co, Ltd) using a Hitachi LABOSPECT-L instrument for laboratory measurements).

2.3. Genetic analyses

We assessed genotypes using next-generation sequencing for all of the study subjects. Briefly, the coding regions of *LDLR, APOB, PCSK9*, and *LDLRAP1* were sequenced, as previously described [16]. Copy number variations of *LDLR* were assessed using eXome Hidden Markov Model software, as previously described [17]. We assessed the pathogenicity of the genetic variants according to the standard American College of Medical Genetics and Genomics criteria [18]. We classified pathogenic variants as protein-truncating variants, including frameshift, large deletion/duplication, nonsense, and splice site.

2.4. Ethical considerations

This study was approved by the Ethics Committee of Kanazawa University. All procedures were conducted in accordance with the ethical standards of relevant human research committees (institutional and national) and with the Declaration of Helsinki (1975, revised in 2008). Informed consent for genetic analyses was obtained from all individuals included in this study.

2.5. Statistical analyses

Categorical variables are reported as numbers and percentages; comparisons between them were made using Fisher's exact test or the Chi-squared test. Normally distributed continuous variables are reported as means with standard deviations. Nonnormally distributed continuous variables are reported as medians with interquartile ranges (IQR). Mean values of continuous variables were compared using Student's t-test for independent variables. Median values were compared using the nonparametric Mann–Whitney U test (Wilcoxon rank-sum test). For categorical variables, Chi-squared or Fisher's post hoc tests were used, as indicated. A Cox proportional hazard model was used to assess relationships between all variables. Formal test for interaction between Lp(a) and CRP was performed. Comparisons of times to first MACE incidents were made using cumulative Kaplan–Meier survival curves, starting at baseline. Statistical analyses were performed using R software (https://www.r-project.org). A P-value of <0.050 was considered to indicate statistical significance.

3. Results

3.1. Clinical characteristics

Table 1 shows the study patients' clinical characteristics. Their mean age was 49 years; almost half were male. At baseline, their median LDL cholesterol level was 241 mg/dL; this reduced to 106 mg/dL during follow-up. A family history of FH and/or premature CVD was found in 620 patients (78.9%). A history of CVD was present in 230 patients (29.3%). When we divided the patients into two groups, based on the occurrence of MACE, we noted significant differences in all variables between the groups, except for family history of FH and/or premature CVD. Medical treatments at the end of follow-up period are summarized in Supplemental Table 1. Most of the patients used statins, most frequently ezetimibe and colestimide. We identified 84 different types of pathogenic variant FH among 582 patients (67.2%) (Supplemental Table 2).

3.2. Lp(a) levels according to FH mutation status

The distribution of serum Lp(a) levels was skewed to the right, as previously shown (Fig. 1). When we divided the patients into two groups, based on the presence of pathogenic variant FH, those with pathogenic variants exhibited significantly higher Lp(a) levels (26.0 mg/dL [12.2–46.5]), compared with those without pathogenic variants (17.0 mg/dL [8.8–25.3]) (Fig. 2).

Table 1
Baseline characteristics.

Variables	All (N = 786)	MACE (N = 129)	No MACE (N = 657)	P-value
Age (years)	49 ± 18	60 ± 20	46 ± 16	$<2.2 \times 10^{-16}$
Male (%)	374 (47.6%)	88 (68.2%)	286 (43.5%)	4.7×10^{-7}
Hypertension (%)	211 (26.8%)	86 (66.7%)	125 (19.0%)	$<2.2 \times 10^{-16}$
Diabetes (%)	69 (8.8%)	25 (19.4%)	44 (6.7%)	7.3×10^{-6}
Smoking (%)	206 (26.2%)	71 (55.0%)	135 (20.5%)	9.4×10^{-16}
Total cholesterol (mg/dL)	318 [288–350]	341 [279–381]	321 [259–360]	6.8×10^{-5}
Triglyceride (mg/dL)	126 [84–168]	154 [96–188]	114 [79–170]	0.0032
HDL cholesterol (mg/dL)	47 [40–57]	45 [40–49]	48 [43–53]	0.00019
Lp(a) (mg/dL)	21.4 [10.9–38.3]	26.8 [12.3–41.4]	20.4 [10.5–36.3]	1.9×10^{-5}
CRP (mg/dL)	0.20 [0.11–0.29]	0.27 [0.15–0.36]	0.18 [0.09–0.26]	6.7×10^{-5}
LDL cholesterol (at baseline, mg/dL)	241 [206–275]	255 [214–296]	238 [202–268]	0.0018
LDL cholesterol (at follow-up mg/dL)	106 [90–118]	101 [88–112]	111 [94–120]	0.0044
Family history of FH and/or premature CVD (%)	620 (78.9%)	103 (79.8%)	517 (78.7%)	0.86
FH pathogenic variants (%)	528 (67.2%)	114 (88.4%)	414 (63.0%)	3.7×10^{-8}
History of prior CVD (%)	230 (29.3%)	105 (81.4%)	125 (19.0%)	$< 2.2 \times 10^{-16}$

Abbreviations: MACE, major adverse cardiac event; FH, familial hypercholesterolemia; CVD, cardiovascular disease; Lp(a), lipoprotein (a); CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

3.3. Factors associated with MACE

During a median follow-up period of 12.6 years, MACEs were experienced by 129 patients, which included myocardial infarction, unstable angina, staged revascularization, and death associated with CVD (Table 2). We used a multivariate Cox proportional hazard model to assess factors associated with MACE (Table 3). We found that the following were significantly associated with MACE: age (hazard ratio [HR], 1.08; 95% confidence interval [CI], 1.03–1.13; $P = 1.2 \times 10^{-12}$), male sex (HR, 1.59; CI, 1.09–2.09; P = 0.006), hypertension (HR, 3.04; CI, 2.04–4.04; $P = 2.2 \times 10^{-6}$), diabetes (HR, 1.92; CI, 1.40–2.54; P = 0.011), smoking (HR,.22; CI, 1.44–3.00; $P = 2.2 \times 10^{-4}$), LDL cholesterol (per 10 mg/dL) (HR, 1.01; CI, 1.00–1.02; P = 0.0034), prior CVD (HR, 3.03; CI, 2.00–4.06; $P < 2.2 \times 10^{-16}$), and the presence of pathogenic variant FH (HR, 1.88; CI, 1.08–2.68; P = 0.003). Under these conditions, natural log-transformed Lp(a) (HR, 1.08; CI, 0.91–1.25; P = 0.220) and CRP (HR, 1.12; CI, 0.96–1.28; P = 0.190) were not associated with MACE.

3.3.1. Prognosis according to risk groups classified by Lp(a) and CRP

When we divided the patients into four groups, according to Lp(a) and CRP levels, we found that the Lp(a) and CRP levels of patients in Group 4 were significantly associated with MACE (HR, 2.44; CI, 1.42–3.46; $P = 1.8 \times 10^{-7}$, Table 4). A significant interaction was observed between Lp(a) and CRP (P = 0.021). We assessed the groups' survival curves and found that patients in Group 4 exhibited the worst outcomes (Fig. 3).

3.4. Discussion

Our study aimed to determine whether Lp(a) and CRP levels were associated with MACE among patients with FH. We found that [1] Lp(a) levels among patients with pathogenic variant FH were significantly higher than in those among without pathogenic variants, [2] Lp(a) and CRP levels were not associated with MACE by themselves, and [3] the Lp (a) level was significantly associated with MACE only when the CRP level was elevated.

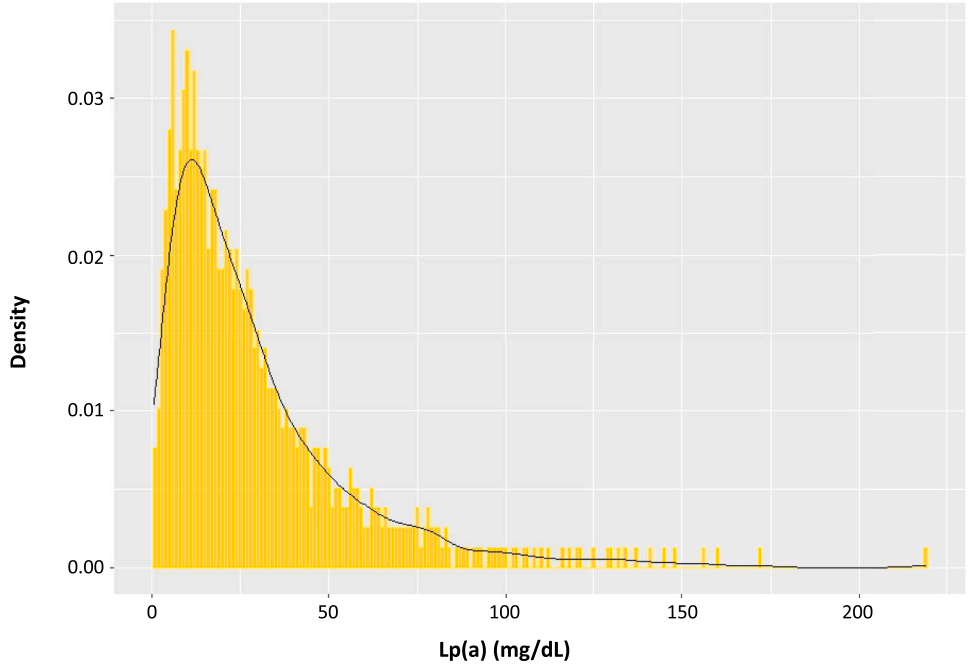

Fig. 1. Histogram of Lp(a).
X-axis represents Lp(a) (mg/dL). Y-axis represents density.
Abbreviations: Lp(a), lipoprotein (a).

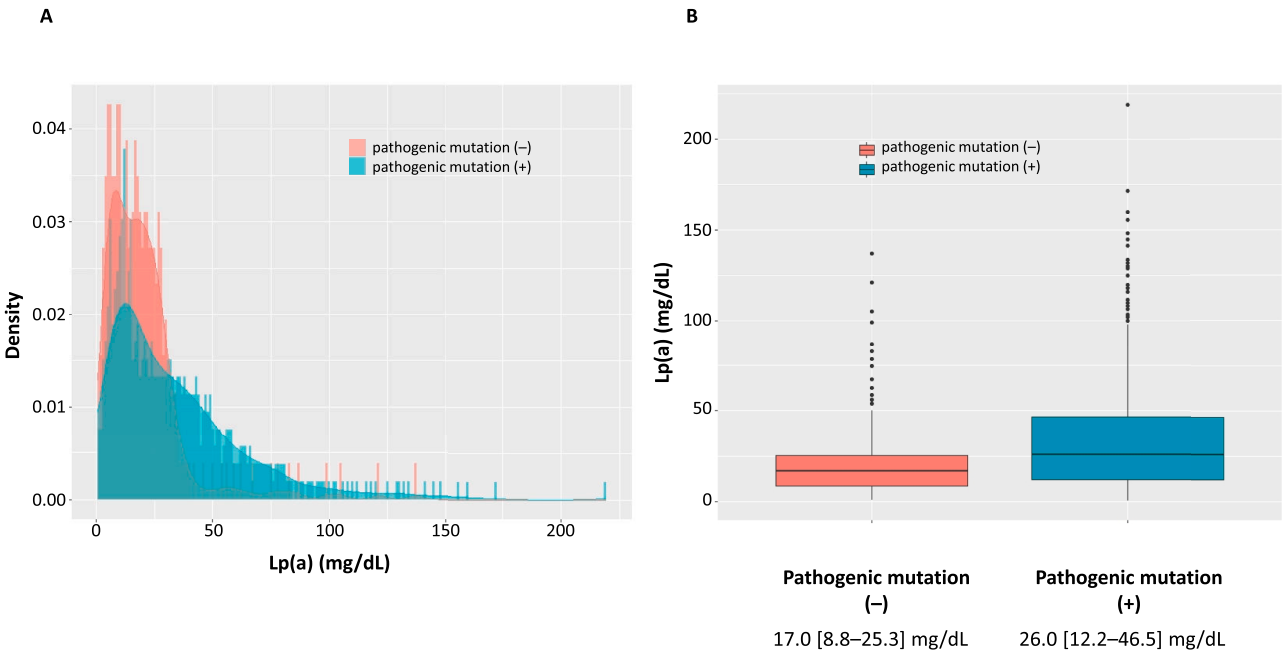

Fig. 2. Lp(a) according to FH mutation status.
(A) Histogram of Lp(a): X-axis represents Lp(a) (mg/dL). Y-axis represents density. Red indicates patients without pathogenic variants. Green indicates patients with pathogenic variants. (B) Box plots of Lp(a): Y-axis represents Lp(a) (mg/dL). Red indicates patients without pathogenic variants. Green indicates patients with pathogenic variants.
Abbreviations: Lp(a), lipoprotein (a); FH, familial hypercholesterolemia.

Table 2
Type of MACE.

Type of MACE	All (N = 786)
Death associated with CVD	46 (5.9%)
Myocardial infarction	19 (2.4%)
Unstable angina	23 (2.9%)
Staged revascularization	41 (5.2%)
Total	129 (16.4%)

Abbreviations: MACE, major adverse cardiac event; CVD, cardiovascular disease.

Table 3
Factors associated with MACE.

Variable	HR	95% CI	P-value
Age (per year)	1.08	1.03–1.13	1.2×10^{-12}
Male (yes vs. no)	1.59	1.09–2.09	0.0057
Hypertension (yes vs. no)	3.04	2.04–4.04	2.2×10^{-6}
Diabetes (yes vs. no)	1.92	1.40–2.54	0.011
Smoking (yes vs. no)	2.22	1.44–3.00	0.00022
LDL cholesterol (per 10 mg/dl)	1.01	1.00–1.02	0.0034
Prior CVD (yes vs. no)	3.03	2.00–4.06	$<2.2 \times 10^{-16}$
FH pathogenic variants	1.88	1.08–2.68	0.0033
ln (CRP)	1.12	0.96–1.28	0.19
ln [Lp(a)]	1.08	0.91–1.25	0.22

Abbreviations: MACE, major adverse cardiac events; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; Lp(a), lipoprotein (a); CRP, C-reactive protein; LDL, low-density lipoprotein; FH, familial hypercholesterolemia.

Over recent decades, the prognosis of patients with familial FH has greatly improved due to early diagnosis, based on universal and cascade screening, and initiation of LDL cholesterol-lowering therapies, including statins, ezetimibe, and PCSK9 inhibitors [19–22]. However, in this LDL-lowering era, there remain so-called residual risk factors for CVD, such as Lp(a) and CRP. Although Lp(a) and LDL have common structures, statins have been shown to be neutral in terms of their effect on Lp(a) levels, the reason for which remains unclear [23,24]. There are no available agents that can effectively reduce Lp(a) levels.

Table 4
Prognosis according to risk groups classified by Lp(a) and CRP.

Risk groups	MACE/total (%)	HR (95% CI)	P-value
Group 1 (Lp(a) < 30 mg/dL, CRP < 0.2 mg/dL)	28/268 (10.4%)	1.00 (reference)	NA
Group 2 (Lp(a) ≥ 30 mg/dL, CRP < 0.2 mg/dL)	16/120 (13.3%)	1.21 (0.97–1.45)	0.11
Group 3 (Lp(a) < 30 mg/dL, CRP ≥ 0.2 mg/dL)	44/246 (17.9%)	1.32 (1.04–1.60)	0.033
Group 4 (Lp(a) ≥ 30 mg/dL, CRP ≥ 0.2 mg/dL)	41/152 (27.0%)	2.44 (1.42–3.46)	1.8×10^{-7}

Abbreviations: MACE, major adverse cardiac event; HR, hazard ratio; CI, confidence interval; Lp(a), lipoprotein (a); CRP, C-reactive protein.

Lp(a) has been suggested to be a causal factor for CVD, based on Mendelian randomization studies [25]. In this context, new Lp(a)-lowering drugs are being developed, such as antisense oligonucleotide- and siRNA-based drugs [26,27].

When there is an innately elevated serum Lp(a) level, the association between Lp(a) and CVD events among patients with FH produces controversial results [28,29]. Several studies among general populations have suggested that Lp(a) and CRP appear to have synergistic effects in the development of CVD events [11,12]. However, there are few data regarding this issue among patients with FH who have extremely high risk for CVD. We found that the serum Lp(a) level was significantly associated with MACE only when the CRP level was elevated among patients with FH.

In vivo and *in vitro* studies have shown that Lp(a) has proinflammatory properties [30,31]. A post hoc analysis of the ACCELERATE trial of evacetrapib also suggested that Lp(a) was significantly associated with MACE only when CRP was elevated [11].

In our situation, among patients with FH (who are mostly under intensive LDL-lowering therapies), the serum Lp(a) could be considered

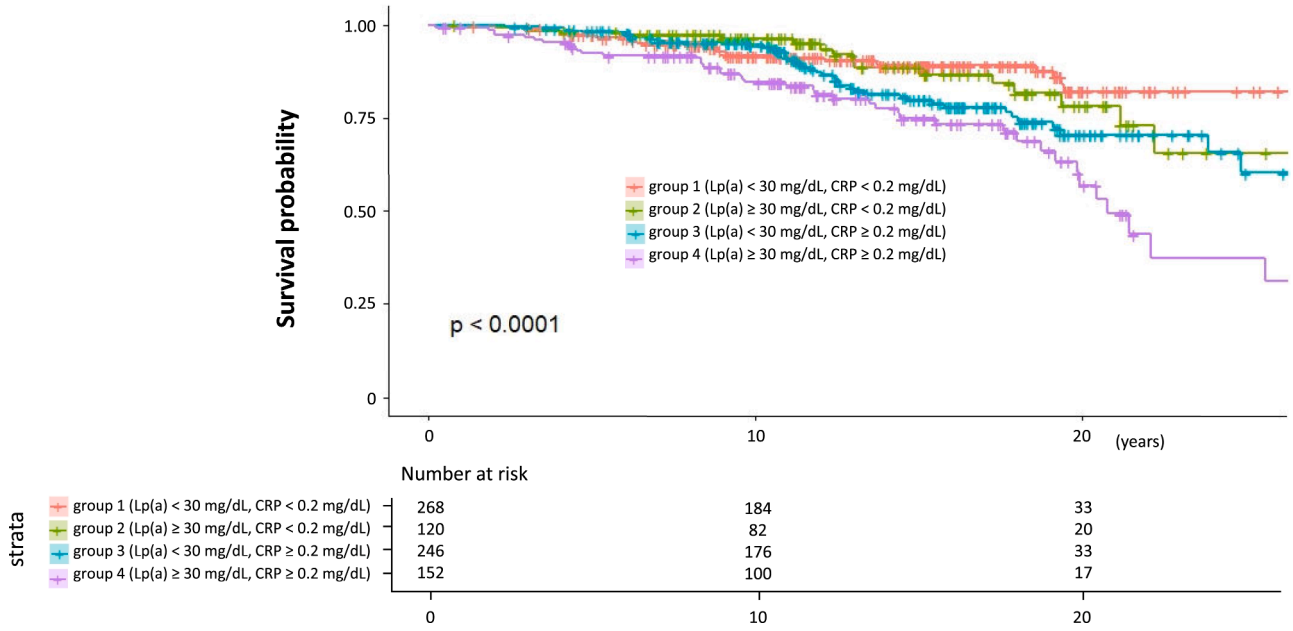

Fig. 3. Kaplan–Meier survival curves of MACE incidence.
X-axis represents age (years). Y-axis represents proportion of patients without MACE. Red: Group 1 [Lp(a) < 30 mg/dL, CRP < 0.2 mg/dL]. Green: Group 2 [Lp(a) ≥ 30 mg/dL, CRP < 0.2 mg/dL]. Blue: Group 3 [Lp(a) < 30 mg/dL, CRP ≥ 0.2 mg/dL]. Purple: Group 4 [Lp(a) ≥ 30 mg/dL, CRP ≥ 0.2 mg/dL].
Abbreviations: Lp(a), lipoprotein (a); CRP, C-reactive protein; MACE, major adverse cardiac event.

as a residual risk for CVD when the CRP level is elevated. New agents that can greatly reduce Lp(a), in addition to antiinflammatory agents (e.g., canakinumab, colchicine), should be considered [32,33].

Interestingly, we found that Lp(a) levels in patients with pathogenic variant FH were significantly higher than in those without pathogenic variants. However, there is a controversy regarding whether the Lp(a) level in FH is actually elevated or not. It was previously reported that an elevated Lp(a) level increases the likelihood of diagnosis of FH based on increased LDL cholesterol and a family history of CVD [34]. Our study clearly suggests that LDL receptor is likely to play an important role in Lp(a) metabolism. Further studies with sufficient data regarding pathogenic variant FH are needed in order to clarify this important issue.

This study has several limitations. First, it is a retrospective study conducted at a single center. Thus, the observations may not be generalizable. However, our institute, with a long history of treating patients with FH, has one of the largest datasets in Japan. Second, we could not account for treatments during the follow-up, which might affect our results. Third, many patients were excluded from analysis due to a lack of data or were lost to follow-up, which may affect our results. Fourth, we did not perform functional analyses to validate the pathogenicity of genetic variants. Fifth, a proportion of patients were treated with PCSK9 inhibitor, which might reduce Lp(a) levels. In addition, statins which has been shown to reduce CRP level might have impacted our results [35,36], although we used CRP level at baseline where no medication, including statins, was given to patients. Sixth, 1 in 3 patients in this study do not have FH-mutation who could have hypercholesterolemia with other cause rather than FH, although they met clinical criteria of FH in Japan. In this regard, the proportion of mutation positive among patients with clinical-FH looks like to be similar to other reports [37,38]. Seventh, among 556 patients under the primary prevention settings, only 24 MACEs were observed during the follow-up period of 12.6 years. So, it is impossible to investigate the associations focusing on these population due to lack of statistical power. Accordingly, it should be noted that our results may only be applicable to the patients under the secondary prevention settings. Finally, we could not identify concomitant inflammatory diseases and associated therapies, which might affect CRP levels.

In conclusion, we found that, among patients with FH, the Lp(a) level was significantly associated with MACE only when the CRP level was elevated. Patients with FH whose Lp(a) and CRP levels are elevated should be treated aggressively for modifiable risk factors.

CRediT authorship contribution statement

H.T. and M.K. conceived of the presented idea. H.T., N.K., K.Y., A.N., A.N., S.U., K.S., N.F., M.T., and M.K. collected clinical data. H.T., N.K, K.Y., and A.N. performed genetic analyses. H.T. performed statistical analyses. M.T. and M.K. supervised the findings of this work. All authors contributed to write the manuscript. All authors discussed the results and contributed to the final manuscript.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

We are thankful to Ms. Kazuko Honda and Mr. Sachio Yamamoto for their outstanding technical assistance.

Funding disclosure

This work has been supported by JSPS KAKENHI (20H03927, 21K08066, and 21H03179); a grant from Ministry of Health, Labour and Welfare of Japan (21FC1009) and Japanese Circulation Society (project for genome analysis in cardiovascular diseases); and the Japan Agency for Medical Research and Development (16ek0210075h0001) to Dr. Hayato Tada.

Supplementary materials

Supplementary material associated with this article can be found, in

the online version, at doi:10.1016/j.ajpc.2022.100428.

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