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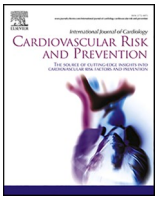

Extreme lipoprotein(a) in clinical practice: A cross sectional study

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ABSTRACT

Introduction: Measurement of lipoprotein(a) [Lp(a)] is recommended once in a lifetime to identify individuals at high risk of atherosclerotic cardiovascular disease (ASCVD). We aimed to analyze the clinical features of patients with extreme Lp(a).

Methods: Cross-sectional, case-control study of a single healthcare organization between 2015 and 2021. Individuals with extreme Lp(a) > 430 nmol/L (53 of 3900 tested patients) were compared to age- and sex-matched controls with normal range Lp(a).

Results: Mean patient age was 58 ± 14 years (49% women). Myocardial infarction (47.2% vs. 18.9%), coronary artery disease (CAD) (62.3% vs. 28.3%), and peripheral artery disease (PAD) or stroke (22.6% vs. 11.3%) were more prevalent in patients with extreme than normal range Lp(a). The adjusted odds ratio [95% confidence interval (CI)] associated with extreme compared to normal range Lp(a) was 2.50 (1.20–5.21) for myocardial infarction, 2.20 (1.20–4.05) for CAD, and 2.75 (0.88–8.64) for PAD or stroke. A high-intensity statin plus ezetimibe combination was issued by 33% and 20% of CAD patients with extreme and normal range Lp(a), respectively. In patients with CAD, low density lipoprotein cholesterol (LDL-C) <55 mg/dL was achieved in 36% of those with extreme Lp(a) and 47% of those with normal range Lp(a).

Conclusions: Extremely elevated Lp(a) levels are associated with an approximately 2.5-fold increased risk of ASCVD compared with normal range Lp(a) levels. Although lipid-lowering treatment is more intense in CAD patients with extreme Lp(a), combination therapies are underused, and attainment rates of LDL-C goals are suboptimal.

1. Introduction

Lipoprotein(a) [Lp(a)] is composed of a low-density lipoprotein (LDL)-like particle containing apolipoprotein B-100 (apoB-100) linked by a disulfide bond to a glycoprotein named apo(a) that shares homology with plasminogen [1]. Lp(a) is considered proatherogenic, proinflammatory, and prothrombotic, with cumulative data suggesting a causal relationship with atherosclerotic cardiovascular disease (ASCVD) [2,3]. Unlike LDL cholesterol (LDL-C), statins do not reduce Lp(a) levels, and the clinical benefit of reducing Lp(a) has yet to be proven [4,5]. However, PCSK9 inhibitors reduce Lp(a) concentration by up to 20–25%, concomitant with potent LDL-C lowering, and elevated Lp(a) levels may identify individuals with a greater absolute benefit from PCSK9 inhibition [6]. Furthermore, novel therapeutic approaches are underway, involving RNA-based therapies that inhibit apo(a) synthesis and can reduce Lp(a) by 70–90% [6]. These developments have led several scientific groups to recommend not only screening high-risk individuals but also measuring Lp(a) once in each adult's lifetime [7,8]. It is suggested that this approach may identify people with very high Lp(a) levels >430 nmol/L who may have a lifetime risk of ASCVD equivalent to those with heterozygous familial hypercholesterolemia (HeFH) [7]. Nevertheless, although the reporting of Lp(a) levels is increasing, it is still measured in only a minority of the population, and data on patients with very high Lp(a) levels in real-life clinical settings are lacking [9].

The aim of the present study was to analyze the clinical characteristics of patients with very high (extreme) Lp(a) levels >430 nmol/L, and to compare the prevalence of ASCVD, use of lipid-lowering therapies, and attainment of lipid treatment goals to those with normal range Lp(a) < 72 nmol/L.

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2. Methods

This study is part of a retrospective analysis of Lp(a) laboratory tests performed in insured members of the Clalit Health Services (CHS) in Israel, providing inclusive health care for about half of the country's population. The methodology and main features of the overall study population have been previously published [9]. In short, data on all individuals insured by the CHS in whom Lp(a) testing was performed during the years 2015–2021 were retrieved. The main analysis was limited to the adult population (aged ≥20 years; n = 3900) who were tested for Lp(a) during the study period. In the current study, we evaluated all patients with very high Lp(a) values > 430 nmol/L [defined as cases with extreme Lp(a)], and matched them by age and sex in a 1:1 ratio to controls with Lp(a) values < 72 nmol/L [defined as normal range Lp(a)] by random selection from the same overall cohort using statistical software. A flowchart of the study population is shown in Fig. 1. Demographic data, clinical variables, laboratory values, risk factors, and comorbidities were collected from electronic medical records based on discharge diagnosis, primary care physicians, and community clinic visits, including age, sex, body mass index, family history of ASCVD, hypertension, diabetes mellitus, hyperlipidemia, smoking, chronic kidney disease, prior malignancy, aspirin, lipid-lowering drugs, lipid profile, thyroid-stimulating hormone, glucose, and glycosylated hemoglobin levels. Data on ASCVD were documented prior to the date of Lp(a) testing, and included coronary artery disease (CAD), myocardial infarction, peripheral artery disease (PAD), ischemic stroke, and aortic valve stenosis.

LDL-C was calculated using the Friedewald formula and recorded at two time points: (a) baseline LDL-C levels, defined as the peak LDL-C value in the patients' history, and (b) the most recent lipid profile available. The attainment rates of LDL-C treatment goals were calculated in relation to the presence of CAD and Lp(a) group. Lp(a) concentrations were measured using a particle-enhanced quantitative turbidimetric immunoassay [Tina-quant® Lipoprotein(a) Gen.2, Roche Diagnostics International Ltd.].

The study was approved by the institutional ethics committee and CHS Data Extraction Committee in accordance with the Declaration of Helsinki, waiving the need for individual patient consent due to the retrospective design of the study.

2.1. Data analysis

Paired categorical data were compared using the McNemar test, and continuous data using the two groups paired T-test or Wilcoxon rank-sum test, when appropriate. Normality of distribution was assessed using the Shapiro-Wilk test and graphically by Q-Q-plots. Odds ratios (OR) with 95% confidence intervals (CI) for myocardial infarction, CAD, and PAD or stroke were calculated using a multivariate conditional logistic regression model adjusted for hypertension, smoking, diabetes mellitus, chronic kidney disease, family history of cardiovascular disease, obesity (body mass index ≥30 kg/m^2), prior malignancy, and baseline LDL-C levels (in addition to age and sex matching by design). The results were considered statistically significant when the 2-sided p-value was <0.05. Statistical Package for the Social Sciences (SPSS) software version 25.0 and MEDCALC version 16.8 were used to perform all statistical analyses.

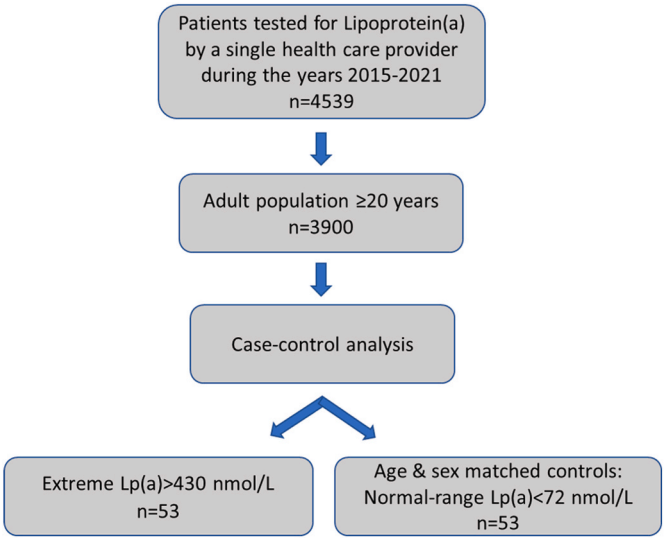

Fig. 1. Study population flow chart.

3. Results

Lp(a) levels were tested in 3900 adults ≥20 years between the years 2015–2021. Of these, we identified 53 patients (1.3%) with extreme Lp(a) levels >430 nmol/L. The median concentration of the extreme Lp(a) group was 472 nmol/L [interquartile range (IQR) 453–552]. Controls with normal range Lp(a) concentrations were matched (n = 53) in a 1:1 ratio according to age and sex. The median Lp(a) level in the normal range control group was 16 nmol/L (IQR 10–38).

The median age was 60 years (IQR, 51–68 years), and 49% were women in both Lp(a) groups. Compared to patients with normal range Lp(a), those with extreme levels had a higher prevalence of family history of ASCVD, diagnosis of hyperlipidemia, and baseline LDL-C >190

Table 1
Baseline characteristics in patients with normal versus extremely high lipoprotein(a) levels.

Variable	Lp(a) < 72 nmol/L	Lp(a) > 430 nmol/L	P value
Number of patients	53	53	1
Age (years)	60 (51–68)	60 (51–68)	1
Gender (female)	26 (49.1%)	26 (49.1%)	1
Lipoprotein(a) - nmol/L	16 (10–38)	472 (452–552)	<0.001
Body mass index	27.5 (23.9–29.3)	27.6 (24.4–29.5)	0.719
Family history of ASCVD	4 (7.5%)	12 (22.6%)	0.038
Hypertension	24 (45.3%)	31 (58.5%)	0.167
Diabetes mellitus	14 (26.4%)	12 (22.6%)	0.814
Hyperlipidemia[a]	38 (71.7%)	47 (88.7%)	0.022
Smoking (ever)	18 (34%)	27 (50.9%)	0.078
Chronic kidney disease	1 (1.9%)	3 (5.7%)	0.625
Prior malignancy	8 (15.1%)	10 (18.9%)	0.774
Peripheral artery disease	5 (9.4%)	10 (18.9%)	0.226
Myocardial infarction	10 (18.9%)	25 (47.2%)	0.005
Coronary artery disease	15 (28.3%)	33 (62.3%)	<0.001
Prior ischemic stroke	1 (1.9%)	3 (5.7%)	0.625
PAD or stroke	6 (11.3%)	12 (22.6%)	0.146
Aortic valve stenosis	1 (1.9%)	3 (5.7%)	0.625
TSH - mIU/ml	2.15 (1.21–3.08)	2.31 (1.47–3.11)	0.623
Hgba1c (%)	5.8% (5.6%–6.3%)	5.8% (5.8%–6.2%)	0.837
Glucose - mg/dL	100 (91–114)	97 (86–111)	0.251
Aspirin	16 (30.2%)	31 (58.5%)	0.002
PCSK9 inhibitors	2 (3.8%)	1 (1.9%)	1
Statins	28 (52.8%)	41 (77.4%)	0.011
Ezetimibe	10 (18.9%)	18 (34%)	0.096
Most-recent LDL-C – mg/dL	96 ± 41	81 ± 37	0.088
Baseline LDL-C – mg/dL	161 ± 44	183 ± 33	0.009
Baseline LDL-C >190 mg/dL	10 (18.9%)	20 (37.7%)	0.087

Data are presented as number (percentage), mean ± standard deviation, or median (interquartile range).
ASCVD, atherosclerotic cardiovascular disease; CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PAD, peripheral artery disease; PCSK9, Proprotein convertase subtilisin/kexin type 9; TSH, thyroid-stimulating hormone.
[a] Diagnosis was made by primary care physicians according to clinical judgment and customary definitions.

mg/dL (uncorrected values) (Table 1). The prevalence of myocardial infarction (47.2% vs. 18.9%, p = 0.005) and overall CAD (62.3% vs. 28.3%, p < 0.001) was significantly higher in patients with extreme compared to normal range Lp(a). PAD (18.9% vs. 9.4%), ischemic stroke (5.7% vs. 1.9%), and aortic valve stenosis (5.7% vs. 1.9%) were also more prevalent in the extreme Lp(a) group, but the differences were not statistically significant (Table 1). After multivariable adjustment, the excess risk associated with extreme Lp(a) relative to normal range Lp(a) was significant for myocardial infarction [OR 2.50, 95% CI (1.20–5.21), p = 0.014] and CAD [OR 2.20, 95% CI (1.20–4.05), p = 0.011], but did not reach statistical significance for PAD or stroke [OR 2.75, 95% CI (0.88–8.64), p = 0.083] (Table 2).

Baseline uncorrected LDL-C levels were higher in patients in the extreme group than in those in the normal range Lp(a) group (183 ± 33 mg/dL vs. 161 ± 44 mg/dL, respectively, p = 0.009). In patients with CAD, high-intensity statin was used by 76% of those with extreme Lp(a) compared to 47% of those with normal range Lp(a), whereas combination therapy with high-intensity statin and ezetimibe was used by 33% and 20%, respectively (p < 0.05) (Fig. 2a). PCSK9 inhibitors were administered to only three patients. In patients with CAD, attainment rates of LDL-C treatment goal <70 mg/dL were 60% and 55% in those with a normal range compared to the extreme Lp(a) group, respectively (p = 0.724), whereas LDL-C <55 mg/dL was achieved in 47% and 36% of patients with a normal range compared to extreme Lp(a) levels, respectively (p = 0.499) (Fig. 2b).

4. Discussion

In this cross-sectional case-control analysis, we demonstrated that extreme Lp(a) concentration is associated with an excess risk for myocardial infarction and CAD, with an odds ratio of up to 2.5, compared to age- and sex-matched individuals with normal range Lp(a). Although lipid-lowering therapy is more intense in patients with extreme Lp(a), attainment rates of LDL-C treatment goals are suboptimal because of insufficient use of combination therapy with high-intensity statins and ezetimibe, as well as scant utilization of PCSK9 inhibitors.

Lp(a) concentrations in middle-aged individuals were shown to predict incident ASCVD in both primary and secondary prevention contexts, with a linear gradient in risk across the Lp(a) distribution [10]. Similar to our findings, recent data from Amsterdam reported an approximately 3-fold higher prevalence of ASCVD and myocardial infarction in adults with Lp(a) levels >99th percentile than in those with levels ≤20th percentile [11]. In both studies, the prevalence of PAD and stroke was higher in the extreme Lp(a) group, but the difference was not statistically significant; the evidence regarding the association of Lp(a) with stroke is generally less clear than that for CAD [12].

Recent guidelines recommend measuring Lp(a) at least once in each person's lifetime to identify those with very high inherited Lp(a) levels >430 nmol/L, as they may have a lifetime risk of ASCVD equivalent to those with HeFH [7]. As this threshold is associated with approximately the 99th percentile of a tested population, there is real potential to identify high-risk individuals and their family members at risk due to an autosomal dominant pattern of inheritance. Moreover, genetic studies suggest that only a robust Lp(a) reduction would be able to significantly reduce ASCVD-related events [13,14], and therefore, patients with extreme Lp(a) levels will ideally be targeted for novel Lp(*a*)-lowering therapies that are under development and can dramatically reduce Lp(a) levels [6].

The baseline LDL-C level of the study population was relatively high. This cannot be attributed solely to the cholesterol content of Lp(a), as LDL-C was also elevated in those with normal range Lp(a) levels. It is possible that Lp(a) is more commonly measured in individuals with high cholesterol levels, as Lp(a) measurement is recommended in patients with HeFH. Nevertheless, we have shown that the association between extreme Lp(a) levels and CAD risk is retained after additional adjustment to high LDL-C levels above 190 mg/dL in a multivariate model. Although this numerical cutoff is often used clinically to diagnose probable HeFH, other potential causes for very high LDL-C levels are possible, including polygenic hypercholesterolemia, high Lp(a) concentration, and secondary precipitation. Of note, LDL-C was not corrected for Lp(*a*)-cholesterol, as there is currently no gold standard method available to determine true LDL-C by subtracting Lp(*a*)-cholesterol, and corrected LDL-C is not routinely reported or validated in clinical practice [15].

In patients with CAD, the attainment rates of LDL-C levels <55 mg/dL were suboptimal, with less than half of those with extreme Lp(a) achieving the treatment goal. Contemporary data show that the gaps between guidelines and clinical practice for lipid management across Europe persist, with only 33% of very high-risk patients achieving LDL-C <55 mg/dL, attributed to the limited use of combination lipid-lowering therapies [16]. Notably, similar to our findings, the real-world use of PCSK9 inhibition in patients with ASCVD remains limited [17]. As PCSK9 inhibitors have a modest Lp(*a*)-lowering effect in addition to their potent LDL-C-lowering capability, and have been shown to have added clinical benefit in patients with elevated Lp(a) [18,19], their use in subjects with extreme Lp(a) levels seems to be compelling as part of a combination lipid-lowering therapy.

This study has several limitations. The overall number of patients tested for Lp(a) was low, with only 0.1% of the insured population being tested in recent years by the largest healthcare provider in the country. Accordingly, in the absence of routine Lp(a) testing, the number of participants found to have extreme Lp(a) levels was small, which may have affected the significance of the results. As the Lp(a) level distribution differs between ethnic groups, the generalizability of the results to individuals from other racial groups may be limited. In addition, PCSK9 inhibitors are mainly administered through insurance plan management criteria, and therefore, the study cohort may not be a representative sample of patients treated with PCSK9 inhibitors in other healthcare systems. Finally, we did not analyze the proximity of Lp(a) measurements to acute illness or ASCVD events. Although Lp(a) may be elevated as an acute-phase reactant, Lp(a) is largely genetically determined and values are relatively stable throughout lifetime; therefore, it is likely that extreme Lp(a) concentrations reflect very high levels, regardless of the timing of Lp(a) measurement.

Table 2
Odds ratio for the association of extreme Lp(a) with cardiovascular outcomes.

Variable	Odds ratio (univariate)	P value	Odds ratio (multivariate[a])	P value
Myocardial infarction	3.84 (1.60–9.20)	0.003	2.50 (1.20–5.21)	0.014
Coronary artery disease	4.18 (1.85–9.54)	0.001	2.20 (1.20–4.05)	0.011
PAD or stroke	2.29 (0.79–6.66)	0.127	2.75 (0.88–8.64)	0.083
Overall ASCVD	2.72 (1.24–5.97)	0.012	1.65 (0.95–2.88)	0.077

ASCVD, atherosclerotic cardiovascular disease; PAD, peripheral artery disease.
[a] Adjusted for hypertension, smoking, diabetes mellitus, chronic kidney disease, family history of cardiovascular disease, obesity (body mass index ≥30 kg/m2), prior malignancy, and baseline LDL-C levels (in addition to age- and sex-matching by design).

5. Conclusions

In a real-life nationwide cohort of patients from a single health care provider tested for Lp(a), ASCVD, particularly CAD, was significantly more prevalent in subjects with extreme Lp(a) levels than in matched controls with normal range Lp(a), supporting recent recommendations to measure Lp(a) once in each person's lifetime. Although several therapeutic groups for cholesterol reduction are available, attainment rates of LDL-C treatment goals are suboptimal due to underutilization of combination lipid-lowering therapy and minimal use of PCSK9 inhibitors, which may have added clinical benefit in those with elevated

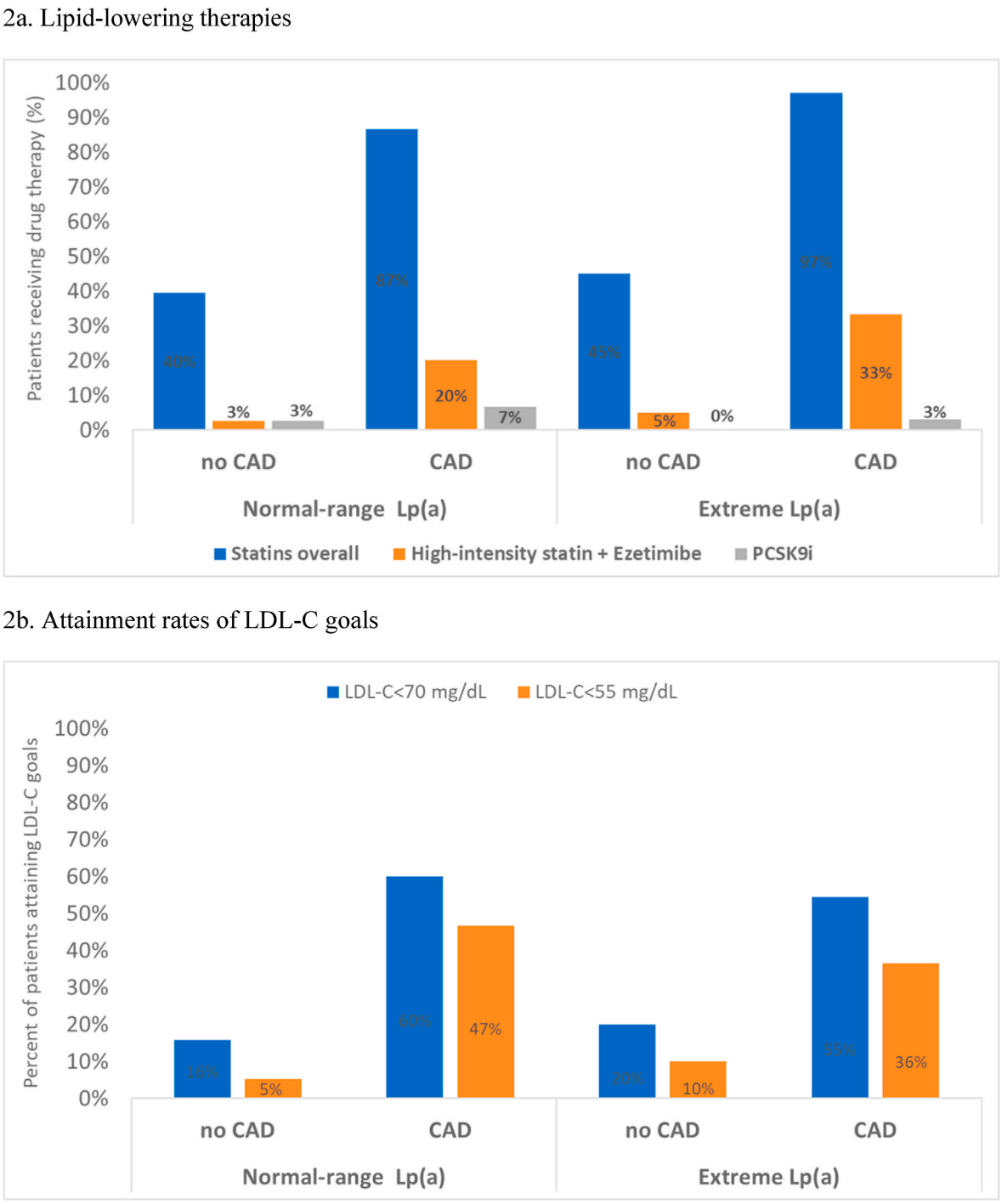

Fig. 2. Lipid-lowering therapies and attainment rates of LDL-C treatment goals according to presence of coronary artery disease and lipoprotein(a) levels.

Lp(a).

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Credit authors statement

Barak Zafrir: Conceptualization, Formal analysis, writing – original draft. Amir Aker: Conceptualization, Data curation, Investigation, Writing, review, and editing. Walid Saliba: Data curation, Methodology, Writing – Review, and Editing.

Declaration of competing interest

The authors report no relationships that could be construed as conflicts of interest.

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