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Association of soluble CD40L with short-term and long-term cardiovascular and all-cause mortality: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study

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HIGHLIGHTS

- The association of sCD40L with mortality in the Ludwigshafen Risk and Cardiovascular Health study has been investigated.
- There was no significant association of sCD40L with long-term cardiovascular mortality and all-cause mortality.
- No patient subgroup revealed a significant association between sCD40L and long-term all-cause or cardiovascular mortality.
- No previously published study ever investigated such a large number of patients over such a long follow-up period.
- Elevated levels of sCD40L seem only to be associated with short-term mortality in selected patient groups.

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ABSTRACT

Background and aims: The CD40^{-}CD40 Ligand (CD40L) system has an important role in vascular inflammation. For this reason, we assessed the association of soluble CD40L with cardiovascular and all-cause mortality in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study.
Methods: Plasma levels of sCD40L were determined in 2759 persons using an enzyme immunoassay. Cox proportional hazard regressions were performed to evaluate the association between plasma concentration of sCD40 ligand and short-term (12 months) and long-term (10 years) mortality. Subpopulation analyses were conducted in seven different risk groups. Cox regression models were adjusted for traditional risk factors.
Results: The present study did not reveal significant association between sCD40L plasma levels and all-cause mortality, as well as cardiovascular mortality at one-year follow-up. In selected subgroups only, significant association between elevated sCD40L plasma levels and short-term all-cause and cardiovascular mortality could be observed. With regard to long-term all-cause and cardiovascular mortality analyses, no significant correlation with increased plasma levels of sCD40L could be detected, neither overall nor in any subgroup.
Conclusions: Soluble sCD40L is not associated with cardiovascular and all-cause mortality in this large cohort. Only in selected patient subgroups elevated levels of sCD40L correlate with short-term mortality but this correlation disappears in long-term analysis.

1. Introduction

Atherosclerosis leads to cardiovascular diseases such as stroke, coronary heart disease and peripheral artery disease, which constitute the leading causes of death worldwide. In the past decades, it has widely been accepted that chronic inflammation initiates and mediates the progression of atherosclerotic diseases. Strong associations of circulating inflammatory markers with atherosclerotic diseases support

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the importance of chronic inflammation in the pathogenesis of atherosclerosis. Leukocytes and platelets interacting with endothelial cells play important roles in plaque formation as well as plaque rupture [1]. The CD40^{-}CD40 Ligand (CD40L) system has important roles in vascular inflammation: CD40L, also known as CD154, is a transmembrane glycoprotein of the tumor necrosis alpha superfamily, primarily located on T-cells and activated platelets, but also on mast cells, macrophages, basophils, B-lymphocytes, smooth muscle cells, endothelial cells, and epithelial cells [2–4]. Platelet stimulation and subsequent aggregation are known to cause the expression or release of several factors that could affect vascular pathology including CD40L. CD40L appears to be particularly relevant in contributing to long-term vascular pathology because this protein is known to be prothrombotic [5], to have a proven role in atherosclerotic lesion progression [6], and to be a risk factor for cardiovascular events [7].

With platelet activation, CD40L rapidly becomes exposed on the platelet surface [3]. By means of proteolysis from activated platelets, plasma soluble CD40L (sCD40L) is cleaved and released [8]. CD40L on platelets and sCD40L interact with the CD40 receptor expressed on macrophages, endothelial cells, vascular smooth muscle cells and glomerular mesangial cells leading to multiple inflammatory responses. These include the expression of chemokines such as interleukin-8 and monocyte chemotactic protein-1, tissue factor and the production of cellular adhesion molecules with the consequence of matrix degradation, plaque rupture and thrombus formation [3,9]. In mouse models, the disruption of CD40L function significantly reduced lesion progression of atherosclerosis [10,11]. In addition, three alternate receptors for CD40L have been described in recent years, the integrins Mac-1 (aMb2), VLA-5 (a5b1), and GPIIbIIIa (aIIbb3) [12]. While interaction of CD40L with Mac-1 has been shown to promote atherosclerosis and inflammatory cell recruitment to sites of injury, interaction with VLA-5 mediates additional pro-infalmmatory gene expression, and the interaction with GPIIbIIIa is important in thrombosis [13].

Soluble CD40L is found to be elevated in coronary artery disease [14,15] and peripheral arterial occlusive disease [16] and has been proposed as biomarker of atherothrombosis [17]. However, whether elevated plasma levels of sCD40L are causative or rather a surrogate parameter of cardiovascular disease ultimately remains to be shown. While biological activity has been proven for sCD40L, it has been reported to be much weaker than that of the membrane bound form of the protein [18]. Since sCD40L when cleaved exists in monomeric form and requires trimerization in plasma for biological activity, incomplete trimerization may be a reason for this phenomenon [19]. Beyond that, in the Women's Health Study, a nested case control study of 130 cases has suggested that elevated plasma levels of sCD40L represents an independent risk factor for future cardiovascular events [7].

Given this background, we assessed the association of sCD40L with cardiovascular (CV) mortality and all-cause mortality in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, which was designed to prospectively investigate the effect of clinical and biochemical factors on cardiovascular outcomes with short-term and long-term follow-up.

2. Materials and methods

2.1. Study design, participants and clinical characterization

3316 participants were enrolled in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study between July 1997 and January 2000. sCD40L levels were available for 2759 of the 3316 participants. Only patients with a coronary angiogram were included. Coronary artery disease (CAD) was assessed by coronary angiography based on maximal luminal narrowing of visual stenosis. The study protocol has been published previously [20]. All participants were followed over a median observation period of 9.9 years. Written informed consent was obtained from each participant prior to inclusion. The study was in accordance with the Declaration of Helsinki and approved by the ethics committee at the Medical Association of Rheinland-Pfalz (Ärztekammer Rheinland-Pfalz).

2.2. Follow-up and definition of clinical endpoints

Information about survival was obtained from local person registries. Two physicians blinded to baseline characteristics of the study participants classified causes of death by reviewing hospital records and death certificates. In the case of disagreement about classification, the final decision was made by one of the principal investigators of LURIC after appropriate review of the data.

Cardiovascular mortality was defined as death due to fatal MI, sudden cardiac death, death after cardiovascular intervention, stroke and other causes of death due to cardiovascular diseases.

2.3. Laboratory procedures

Patients were admitted in the morning hours for diagnostic or interventional coronary angiography to the Heart Centre Ludwigshafen, Germany. Fasting blood samples were collected, immediately centrifuged to obtain EDTA plasma and stored at −80 °C for later analysis.

Plasma levels of sCD40L were determined by using an enzyme immunoassay (R&D systems, Minneapolis, Canada). The inter-assay CV was 6.4% at 437 pg/mL and 6.2% at 2612 pg/mL. The sensitivity was 10.1 pg/mL and the entire measuring range 62.5–4000 pg/mL. Serum creatinine was determined by liquid chromatography tandem mass spectrometry (LC-MS/MS). Cystatin C was measured by immunonephelometry (N-Latex Cystatin C, Dade Behring, Marburg, Germany). Other laboratory analyses were performed using conventional laboratory methods as described earlier [21]. Kidney function was estimated with a combined cystatin C and creatinine Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI = 135 × min (Scr/κ, 1)α × max (Scr/κ, 1)−0.601 × min (Scys/0.8, 1)−0.375 × max (Scys/0.8, 1)−0.711 × 0.995 Age [× 0.969 if female]; Scr is serum creatinine, Scys is serum cystatin C, κ is 0.7 for females and 0.9 for males, α is −0.248 for females and −0.207 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1) [21,22]. Chronic kidney disease (CKD) was defined as eGFR between 15 and 59 mL/min/1.73 m^2 according to the Kidney Disease Outcomes Quality Initiative (KDIGO) definition [23].

2.4. Statistical analyses

Baseline characteristics are given according to tertiles of plasma sCD40L concentrations. Continuous data are shown as medians and categorical data with absolute and relative frequencies. Comparisons between groups were conducted by χ [2]-Test and Kruskal–Wallis test as appropriate.

Cox proportional hazard regressions were performed to evaluate the association between plasma sCD40L concentration and short-term and long-term mortality. Analyses were performed for six-months and one-year all-cause mortality (reflecting short-term mortality) and for 10-year all-cause mortality and cardiovascular mortality (representing long-term mortality) using two different models: model 1 adjusted for age and sex and model 2 additionally adjusted for traditional risk factors (age, sex, smoking (never, former and active), systolic blood pressure, diastolic blood pressure, low density lipoprotein cholesterol, high density lipoprotein cholesterol, CAD status (noCAD, stable CAD and ACS), eGFR (Cystatin C and creatinine) and C-reactive protein (CRP).

Subpopulation analyses (adjusted for age and sex) were conducted in seven different risk groups. The risk populations were defined by the following criteria: Arterial hypertension (defined as blood pressure systolic ≥ 140 mmHg and/or blood pressure diastolic ≥ 90 mmHg and/or the use of antihypertensive drugs), HFpEF, heart failure with

preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; no CAD, no coronary artery disease by angiography, CAD, stable coronary artery disease by angiography, ACS, acute coronary syndrome; diabetes mellitus and CKD (defined as eGFR combined cystatin C and creatinine based estimated glomerular filtration rate, 15–59 mL/min/1.73 m^2). The adjustment was adapted to the subpopulation in which the model was executed. In patients with hypertension, no further adjustment was conducted for systolic and diastolic blood pressure. In patients with CAD and HFpEF the adjustment for CAD status was excluded.

Data were analysed using SPSS 25.0 statistical package (SPSS Inc., Chicago, IL, USA). The hazard ratio plots were drawn using R v3.5.1 (http://www.r-project.org) and the 'rms' package (v 5.1–3, https://CRAN.R-project.org/package=rms).

3. Results

3.1. Baseline characteristics and covariates

Baseline characteristics of the study population according to tertiles of sCD40 ligand plasma concentration are shown in Supplementary Table 1. A complete data set was available for 2759 participants, corresponding to 83.2% of the initial LURIC study population. Participants in the highest tertile of sCD40L were significantly younger, had significantly lower systolic blood pressure and higher eGFR than those in the first quartile. In addition, participants in the highest tertile were more often active smokers, showed higher heart rates, were more often diagnosed with acute coronary syndrome upon presentation and had fewer medication with vitamin K antagonist oral anticoagulants.

3.2. Association of sCD40 ligand with short-term mortality

Results of short-term all-cause and cardiovascular mortality analyses and sCD40L plasma levels are given in Table 1. Over an observation period of 12 months, 111 patients died. With regard to one-year all-cause mortality, elevated sCD40L plasma levels in the third tertile were significantly associated with increased all-cause mortality in Model 1 (adjusted for age and sex) (HR (95%CI) 1.65 (1.03–2.63); $p = 0.04$). However, after full adjustment, this association lost significance (Model 2). With regard to one-year cardiovascular mortality, we could not observe significant associations between sCD40L plasma levels and cardiovascular mortality.

Subpopulation analyses regarding all-cause mortality revealed significant associations between elevated sCD40L plasma levels and one-year all-cause mortality in patients with stable CAD, hypertension and HFpEF (Supplementary Table 2, models adjusted for age and sex). This association remained significant after further adjustment in patients with stable CAD (HR (95%CI) 2.17 (1.15–4.09); $p = 0.02$), hypertension (HR (95%CI) 2.33 (1.19–4.55); $p = 0.01$) and in patients with HFpEF (HR (95%CI) 5.35 (1.42–20.13); $p = 0.01$) (Supplementary Table 3).

Kaplan-Meier plots for short-term all-cause mortality according to tertiles of sCD40L plasma concentrations are provided in Supplementary Figs. 1 and 2.

Subpopulation analyses regarding cardiovascular mortality (Supplementary Table 2, models adjusted for age and sex) revealed significant associations between elevated sCD40L plasma levels and increased one-year cardiovascular mortality in patients with HFpEF and stable CAD. After full adjustment, significance remained for one-year cardiovascular mortality in patients with HFpEF (HR (95%CI) 7.80 (1.54–39.59); $p = 0.01$) (Supplementary Table 3).

3.3. Association of sCD40 ligand with long-term mortality

Over an observation time of 9.9 years, 819 patients died of all causes and 517 died of cardiovascular causes. Results of Cox proportional hazard analyses of sCD40L for all-cause mortality and cardiovascular mortality are shown in Table 2. No significant association was found between elevated sCD40L plasma levels and long-term all-cause mortality or CV mortality after full adjustment for traditional risk factors. The same is true when sCD40L is modelled as a continuous variable (graphical abstract). Cox proportional hazard analyses (adjusted for age and sex) of sCD40L for all-cause and CV mortality in seven different subpopulations are given in Supplementary Table 4. Overall, we obtained no significant association of elevated and increasing plasma sCD40L with all-cause mortality and with CV mortality after full adjustment in any subgroup.

Kaplan-Meier plots for long-term all-cause mortality and CV mortality according to tertiles of sCD40L plasma concentrations are provided in Supplementary Fig. 3.

4. Discussion

The key finding of the current study is the absence of a significant association of sCD40L plasma levels with short-term and long-term cardiovascular and all-cause mortality regarding the entire study population.

The impact of the CD40$^-$CD40L-system and particularly sCD40L on cardiovascular outcome and all-cause mortality has been discussed controversially for many years already. Various publications previously

Table 1
Cox proportional hazards regression analyses for short-term all-cause and cardiovascular mortality according to tertiles of sCD40 ligand plasma concentrations.

sCD40L	Deaths	All-cause mortality	Deaths	CV mortality		
	N	HR (95%CI)	*p*-value	N	HR (95%CI)	*p*-value
Model 1[a]	111			80		
Tertile I	31	1.0 reference		25	1.0 reference	
Tertile II	39	1.27 (0.79–2.03)	0.33	28	1.12 (0.66–1.93)	0.67
Tertile III	41	1.65 (1.03–2.63)	0.04	27	1.34 (0.78–2.33)	0.29
Model 2[b]	111			80		
Tertile I	31	1.0 reference		25	1.0 reference	
Tertile II	39	1.23 (0.77–1.98)	0.39	28	1.07 (0.62–1.84)	0.81
Tertile III	41	1.50 (0.93–2.41)	0.10	27	1.18 (0.68–2.06)	0.56

CI, confidence interval; HR, hazard ratio; n, total number of deaths.
[a] Model 1 adjusted for age and sex.
[b] Model 2 adjusted for age, sex, smoking (never, former and active), blood pressure systolic, blood pressure diastolic, CAD status (noCAD, CAD, ACS), HDL cholesterol, LDL cholesterol; eGFR estimated by cystatin C and creatinine, and CRP.

Table 2
Cox proportional hazards regression analyses for *long-term* all-cause and cardiovascular mortality according to tertiles of sCD40 ligand plasma concentrations.

sCD40L	Deathss	All-cause mortality		Deaths	CV mortality	
	N	HR (95%CI)	*p*-value	N	HR (95%CI))	*p*-value
Model 1[a]	819			517		
Tertile I	307	1.0 reference		201	1.0 reference	
Tertile II	269	0.89 (0.76–1.05)	0.17	158	0.80 (0.65–0.98)	0.03
Tertile III	243	0.94 (0.79–1.11)	0.44	158	0.92 (0.75–1.14)	0.45
Model 2[b]	819			517		
Tertile I	307	1.0 reference		201	1.0 reference	
Tertile II	269	0.90 (0.76–1.06)	0.20	158	0.81 (0.66–1.00)	0.05
Tertile III	243	0.92 (0.77–1.09)	0.33	158	0.89 (0.72–1.09)	0.26

CI, confidence interval; HR, hazard ratio; n, total number of deaths.
[a] Model 1 adjusted for age and sex.
[b] Model 2 adjusted for age, sex, smoking (never, former and active), blood pressure systolic, blood pressure diastolic, CAD status (noCAD, CAD, ACS), HDL cholesterol, LDL cholesterol; eGFR estimated by cystatin C, creatinine and CRP.

addressed short-term and longer-term effects of sCD40L in a number of patient groups and prospective studies.

Pusuroglu et al. found a significant association between high sCD40 L at admission and an increased in-hospital and 1-year mortality in 499 patients with ST-segment elevation myocardial infarction [24]. In 195 patients with acute coronary syndromes, Varo et al. found that elevated sCD40L identified patients at higher risk for death and recurrent myocardial infarction independently of C-reactive protein and cardiac troponin I during a follow-up of ten months [25]. In contrast to these results, the subgroup of patients with acute coronary syndromes in our study had no evidence for a significant association between plasma CD40L and all-cause or cardiovascular mortality. Supporting our results, a previous study by Setianto et al. reported that circulating sCD40L was not significantly associated with an increasing risk of in-hospital events in 77 patients with acute coronary syndrome [26]. Similarly, Olenchock et al. found no association between sCD40L and the risk of death or myocardial infarction in 2403 patients with acute coronary syndrome in the OPUS TIMI-16 study [27].

However, patients with stable CAD in our subpopulation analysis revealed a significant association between elevated sCD40L plasma levels and an increased one-year all-cause mortality, even after additional full adjustment. With longer follow-up and for long-term mortality, this association was not significant anymore.

In 86 patients with chronic heart failure, Yan et al. measured significantly elevated sCD40L and platelet expression of CD40L compared to controls. These levels correlated with the NYHA class, left ventricular ejection fraction and blood brain natriuretic peptide concentrations [28].

Ueland et al. reported elevated sCD40L levels in 236 patients with acute and chronic heart failure. Soluble CD40L levels were persistently high during longitudinal follow-up and actually correlated with disease severity [29]. Indeed, and apparently supporting this observation, in our study, patients with HFpEF and soluble CD40L levels in the highest tertile had significantly increased one-year all-cause mortality and cardiovascular mortality. On the other hand, we provide evidence that with longer follow-up, elevated sCD40L levels did not significantly correlate with long-term all-cause mortality and with long-term cardiovascular mortality in the subgroup of patients with HFpEF.

Xie et al. reported that increased circulating sCD40L was also an independent predictor of a prospective decline in eGFR in 1750 patients with chronic kidney disease from any cause at one year of follow-up [30]. In contrast to these results, in an eight year follow-up, sCD40L concentrations were higher in 489 type 1 diabetic patients who developed nephropathy compared to those who did not, but in the same study, sCD40L levels were not predictive of all-cause mortality, cardiovascular mortality, progression to end-stage renal disease (ESRD) or the rate of decline in kidney function over time [31]. Similarly, our study was not able to detect any significant association between plasma levels of sCD40L and all-cause or cardiovascular mortality in the subpopulation with either diabetes mellitus or chronic kidney disease. However, we were not able to assess the association between sCD40L levels and the decline in renal function or incident diabetes mellitus due to lack of kidney specific follow-up data.

In summary, the present study did not reveal a significant association of soluble CD40L with long-term cardiovascular mortality and all-cause mortality. Additionally, no patient subgroup revealed a significant association between plasma levels of sCD40L and all-cause or cardiovascular mortality over a long-term follow-up.

It is noteworthy, that no previously published study ever investigated such a large number of patients over such a long follow-up period. Further, we provide data on short-term as well as long-term mortality in one study cohort. Moreover, and because of this, our findings could explain the heterogeneity of previous studies since significant associations between sCD40L plasma levels and mortality rather apply to short-term mortality in defined patient subgroups than to long-term mortality and the general population. Hence, long-term effects on outcome and mortality over several years according to our present results are not cohesive with baseline plasma levels of sCD40 L at study inclusion.

Limitation and a possible explanation for the negative predictive results of a significant correlation of sCD40L with mortality could be that plasma levels of sCD40 L at baseline were only measured once. Since plasma levels of sCD40L could show some fluctuation over day and days, this might have influenced measurements and statistical results. In addition, event rates in some subgroups were rather small and low statistical power for at least some subgroup analyses may be existent. Possible confounding factors such as for example emotional and physical stress and infections could also have affected sCD40L plasma levels. In this regard, no dependable data is available, but adjustment for CRP has been made in the present study.

Conflicts of interest

All authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Ingrid Gergei: Data interpretation, statistical analysis, writing the manuscript, critical review of the manuscript throughout the editorial

process. Thorsten Kälsch: Data interpretation, writing the manuscript, critical review of the manuscript throughout the editorial process. Hubert Scharnagl: Data acquisition, data interpretation. Marcus E. Kleber: Study concept and design, data acquisition, data interpretation, statistical analysis, critical review of the manuscript throughout the editorial process. Andreas Zirlik: Data interpretation. Winfried März: Study concept and design, data acquisition, data interpretation, statistical analysis, writing the manuscript, critical review of the manuscript throughout the editorial process. Bernhard K. Krämer: Study concept and design, data interpretation, writing the manuscript, critical review of the manuscript throughout the editorial process. Anna-Isabelle Kälsch: Data interpretation, writing the manuscript, critical review of the manuscript throughout the editorial process.

All authors agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the publication and all authors have given approval of the final manuscript draft submitted for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.09.004.

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