The circulating soluble TRAIL is a negative marker for inflammation inversely associated with the mortality risk in chronic kidney disease patients

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Abstract

Background. Chronic kidney disease (CKD) is associated with accelerated atherosclerosis and an inadequate inflammatory response which may account for the high morbidity and mortality observed in this population. In vitro and preclinical evidence suggests that the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) might be involved in both the atherosclerosis pathway and modulation of the inflammatory response. The aim of the present study was thus to (i) determine serum levels of soluble TRAIL (sTRAIL) in a cohort of CKD patients, (ii) assess the relationship between sTRAIL and other inflammatory biomarkers (C-reactive protein and albumin) and (iii) evaluate the association between serum sTRAIL levels and the mortality risk.

Methods. One hundred and thirty patients (mean ± SD age: 67 ± 12; 62% males; 8% at CKD stage 2, 26% at stage 3, 27% at stage 4, 8% at stage 5 and 31% at stage 5D) were assayed for sTRAIL and the selected biochemical parameters and then prospectively monitored for mortality.

Results. CKD stage 5D patients had significantly lower serum sTRAIL levels (median: 46 pg/ml) than patients at CKD stages 2 and 3 (median: 62 pg/ml) or stages 4 and 5 (median: 71 pg/ml). There was no correlation between serum sTRAIL and the estimated glomerular filtration rate (GFR) ($r^2 = 0.017$, $P = 0.22$) in pre-dialysis patients. In a multivariate regression analysis, the body mass index ($\beta = 1.48$, $P = 0.001$) and the serum C-reactive protein (CRP) level ($\beta = -8.841$, $P < 0.0001$) were independently associated with serum sTRAIL. During follow-up (mean: 772 ± 286 days), 36 patients died (19 from cardiovascular events, 8 from infectious events and 9 from other causes). The lowest sTRAIL levels (first tertile) were associated with the worst all-cause survival ($P = 0.010$). Cox regression analyses (with non-cumulative models including age, albumin and CRP as covariates) confirmed the low serum sTRAIL level (first tertile) as an independent predictor of all-cause mortality.

Conclusions. Circulating sTRAIL is a negative marker for inflammation and is inversely associated with the mortality risk in CKD patients. Further studies are needed to better understand the role of sTRAIL as an inflammatory marker and to confirm its protective role in the CKD population.

Keywords: chronic kidney disease; haemodialysis; inflammation; mortality; TRAIL

Introduction

The tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of TNF ligand superfamily [1]. TRAIL is a type II transmembrane protein which can be released as a vesicle-associated form [2] or a soluble form [3]. It has been detected in a range of cells and tissues [1]. Soluble TRAIL (sTRAIL) is generated by the enzymatic cleavage of the transmembrane protein’s carboxyl-terminal domain [4]. Five different sTRAIL receptors have been identified to date: two death receptors containing a death domain (TRAIL-R1 and TRAIL-R2), which are capable of rapidly inducing apoptosis; two decoy receptors (TRAIL-R3 and TRAIL-R4) that are unable to transduce apoptosis signals but may activate nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) and block apoptosis [5]; and, lastly, osteoprotegerin (OPG), a soluble decoy receptor [6].

In general, TRAIL has been studied in tumour immunology settings. It selectively induces apoptosis in the transformed cells while leaving the non-transformed cells unaffected [7]. Although it has been shown that TRAIL can activate both pro-apoptotic and anti-apoptotic pathways, the reasons for directing to one or other of these pathways are, however, less well understood [8].

It has notably been shown that TRAIL and its receptors (TRAIL-R2 and OPG) are present in human atheroscler-
ic lesions and that their expression levels are higher in vulnerable plaques than in stable ones [4,9]. Furthermore, TRAIL expression levels are low in patients with acute coronary syndrome [4] and those with angiographically documented coronary artery disease [10]. These findings supported that TRAIL has a role in atherosclerosis—possibly by modulating apoptosis.

Recent studies have also underlined TRAIL's important role as a modulator of the immune response [11]. In human cytomegalovirus (CMV) infection, TRAIL expression is induced by interferon-γ and TNF-α. The CMV-infected cells show an upregulation of the death receptors TRAIL-R1 and TRAIL-R2 and thus become more susceptible to TRAIL-induced apoptosis [12,13]. Additionally, TRAIL knockout mice infected with influenza virus display a low specific T cell-mediated cytotoxic response (which is otherwise necessary for viral clearance) and more severe diseases [14]. It has also been shown that TRAIL deficiency or blockade result in the disease exacerbation in a murine model of autoimmune diabetes; this suggests that TRAIL plays a crucial role in inhibiting autoreactive T cell activation [15].

Chronic kidney disease (CKD) is associated with accelerated atherosclerosis and an exacerbated but ineffective inflammatory response. Both factors are known to contribute to the high morbidity and mortality experienced by CKD patients. The above-cited in vitro and preclinical evidence suggests that the TRAIL might be involved to some extent in both the atherosclerosis disease pathway and the modulation of the inflammatory response. Thus, the aim of the present study was to (i) determine serum sTRAIL levels in a well-characterized cohort of CKD patients, (ii) assess the relationship between serum sTRAIL levels and the well-established biomarkers for inflammation (C-reactive protein and albumin) in the CKD setting and (iii) evaluate the association between serum sTRAIL levels and the mortality risk in this population.

Materials and methods

Patient selection

Over an 18-month period (from January 2006 to June 2007), a total of 150 Caucasian prevalent CKD patients were recruited by the Nephrology Department's outpatient clinic at Amiens University Hospital. All patients gave their informed, written consent. The study was approved by the local ethics committee and was performed in accordance with the ethical principles of the Declaration of Helsinki.

The included patients had to be over the age of 40, with a confirmed diagnosis of CKD (defined as ongoing haemodialysis or having two previous, estimated Cockcroft and Gault [16] creatinine clearance values <90 ml/min/1.73 m² 3–6 months apart). CKD stage 5D patients had been receiving a thrice-weekly haemodialysis for at least 3 months. The non-inclusion criteria included the presence of chronic inflammatory disease, atrial fibrillation, complete heart block, abdominal aorta aneurism, aortic and/or femoral artery prosthesis, primary hyperparathyroidism, kidney transplantation or any other acute cardiovascular event in the 3 months prior to screening. The 130 patients who met all inclusion criteria and had available serum sTRAIL measurements were included in the present analysis.

Study protocol

Each patient was day-hospitalized for laboratory tests and blood pressure measurements. Haemodialysis patients were preferentially seen on a dialysis-free day or, when the latter was not possible, in the morning before the dialysis session. A patient interview focused on the patient's comorbidities and personal disease history (and especially any previous vascular events). Medical records were reviewed in order to identify and describe any concomitant medications. For descriptive purposes, the patients who reported the current or previous use of insulin and/or oral hypoglycaemic drugs were considered to be diabetics. Previous cardiovascular disease was defined as a history of any of the following: myocardial infarction, stroke, heart failure, angina pectoris or surgical procedures for angina or coronary/peripheral artery disease (including percutaneous transluminal angioplasty).

Laboratory tests

Blood samples were collected on the same morning and before the other investigations were performed. Selected variables were measured after the samples had been frozen and stored at –80°C. Serum calcium, phosphate, cholesterol, haemoglobin and creatinine (Scr) levels were assessed in an on-site biochemistry laboratory using standard auto-analyser techniques (the Modular II® system from Roche Diagnostics, Basel, Switzerland). Serum intact parathyroid hormone (iPTH 1–84) was determined in a chemiluminesometric immunoassay (Liaison N-tact PTH CLIA®, Diasorin, Stillwater, USA). Serum sTRAIL levels were quantified in a sandwich enzyme immunoassay technique (Quantikine® R&D Systems, Minneapolis, MN, USA) with a mean limit of detection of 2.86 pg/ml and a mean reference value of 76 pg/ml, according to the information provided by the manufacturer. Osteoprotegerin serum levels were determined by ELISA with a mean reference value of 5.7 ± 0.42 pmol/l (Metrà®, OSTEomedical, Paris, France). C-reactive protein (CRP) (normal value 2.87 mg/l, ranging from non-detectable to 3.0 mg/l), albumin and cystatin C (CysC) levels were determined by laser nephelometry (BNProSpec, Siemens Healthcare, Dade Behring, Marburg, Germany). In order to better estimate the true glomerular filtration rate, the estimated glomerular filtration rate combining Scr and serum cystatin C measurements [eGFR(CysC)] was calculated for all non-dialysis patients according to the following recently published equation: 177.6 × Scr−0.67 × CysC−0.57 × Age−0.20 (× 0.82 for females) [17]. For descriptive purposes, the patients were then classified by CKD stages according to the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [18].

Survival

Death records were compiled prospectively by considering all patients included at least 20 months before the study end date (1 March 2009). Each set of medical records was reviewed, and the cause of death was assigned by a physician on the basis of the available clinical information. For out-of-hospital deaths, the patient's general practitioner was interviewed to gain pertinent information on the cause.

Statistical analyses

Data were expressed as the mean ± SD, median and range or the frequency, as appropriate. For analytical purposes, the patients were divided according to the tertiles of serum sTRAIL levels (i.e. sTRAIL first tertile ≤48.52 pg/ml, second tertile >48.52 pg/ml and third tertile >71.80 pg/ml). Inter-group comparisons were performed using chi-square test for categorical variables and analysis of variance (ANOVA) or Kruskal–Wallis test for continuous variables. Univariate linear regression analyses were used to identify variables that were significantly associated with serum sTRAIL levels. Thereafter, a multivariate linear regression analysis was used to select the variables independently associated with serum sTRAIL levels.

The Kaplan–Meier actuarial methodology was used to estimate the overall survival by sTRAIL tertile. A log-rank test was used to compare survival curves. The univariate and multivariate analyses of mortality were performed by using a Cox proportional hazards model of death as a function of the sTRAIL tertile. The variables that were significantly associated with death in the univariate analyses were fed into predefined, non-cumulative models in the multivariate analysis. A multiplicative interaction term (sTRAIL first tertile × haemodialysis exposure) was also considered during the development of the prediction models. A P-value ≤0.05 was considered to be statistically significant. All the statistical analyses were performed using SPSS software (SPSS Inc, Chicago, IL), version 13.0 for Windows (Microsoft Corp, Redmond, WA).
Results

Tables 1 and 2 summarize the demographic, clinical and biochemical characteristics of the 130 analysed patients [mean age of 67 ± 12 years; 62% male; mean body mass index (BMI): 28 ± 6 kg/m²]. Forty percent of the patients had diabetes as a comorbid condition, 41% were previous or actual smokers and 32% had a history of cardiovascular events. Concerning CKD, 8% of the patients were classified as KDOQI stage 2, with 26% at stage 3, 27% at stage 4, 8% at stage 5 and 31% at stage 5D. The mean serum sTRAIL level in the study population was 63 ± 35 pg/ml (median: 62 pg/ml; range: 35–201 pg/ml). By dividing the patients into tertiles according to the serum sTRAIL level, we observed that the patients in the first tertile (sTRAIL ≤48.52 pg/ml) had a significantly lower BMI than the patients in the third tertile (sTRAIL >71.80 pg/ml). The prevalence of CKD stage 5D was significantly higher in the patients from the first sTRAIL tertile than in the second and third tertiles. Serum levels of albumin were significantly lower in the patients from the first sTRAIL tertile, whereas iPTH and CRP levels in these patients were significantly higher than in the patients in the second and third sTRAIL tertiles.

Figure 1 illustrates the serum sTRAIL distribution by CKD stage. CKD stage 5D patients presented significantly lower serum levels of sTRAIL (mean: 45 ± 30 pg/ml; median 46 pg/ml) than the patients at CKD stages 2 and 3 (mean: 64 ± 28 pg/ml; median 62 pg/ml) or stages 4 and 5 (mean: 79 ± 40 pg/ml, median 71 pg/ml). When restricting the analysis to pre-dialysis patients, there was no association between serum sTRAIL levels and the estimated GFR ($r^2 = 0.017$, $P = 0.22$).

Table 1. Clinical and demographic characteristics of the study population

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>All n = 130</th>
<th>First tertile n = 43</th>
<th>Second tertile n = 44</th>
<th>Third tertile n = 43</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>67 ± 12</td>
<td>67 ± 13</td>
<td>70 ± 12</td>
<td>65 ± 12</td>
<td>0.195</td>
<td></td>
</tr>
<tr>
<td>Male gender [n (%)]</td>
<td>81 (62)</td>
<td>28 (65)</td>
<td>29 (66)</td>
<td>24 (56)</td>
<td>0.560</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 ± 6</td>
<td>27 ± 5*</td>
<td>27 ± 5*</td>
<td>31 ± 8</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes [n (%)]</td>
<td>52 (40)</td>
<td>18 (42)</td>
<td>13 (29)</td>
<td>21 (49)</td>
<td>0.177</td>
</tr>
<tr>
<td>Smoking habit [n (%)]</td>
<td>52 (41)</td>
<td>20 (50)</td>
<td>20 (45)</td>
<td>12 (29)</td>
<td>0.112</td>
</tr>
<tr>
<td>Previous CVD [n (%)]</td>
<td>41 (32)</td>
<td>13 (30)</td>
<td>14 (32)</td>
<td>14 (33)</td>
<td>0.972</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>152 ± 26</td>
<td>147 ± 27</td>
<td>156 ± 27</td>
<td>153 ± 21</td>
<td>0.216</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>81 ± 12</td>
<td>79 ± 14</td>
<td>82 ± 12</td>
<td>82 ± 11</td>
<td>0.572</td>
</tr>
</tbody>
</table>

Table 2. Biochemical characteristics of the study population

<table>
<thead>
<tr>
<th>iPTH (pg/ml)</th>
<th>All n = 130</th>
<th>First tertile n = 43</th>
<th>Second tertile n = 44</th>
<th>Third tertile n = 43</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>138 ± 139</td>
<td>168 ± 134*</td>
<td>113 ± 135</td>
<td>133 ± 145</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>82 (95–197)</td>
<td>128 (77–217)</td>
<td>70 (40–127)</td>
<td>67 (41–192)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>12.1 ± 1.8</td>
<td>11.6 ± 1.7</td>
<td>12.2 ± 1.8</td>
<td>12.4 ± 1.7</td>
<td>0.095</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>38 ± 6</td>
<td>35 ± 5*</td>
<td>40 ± 5</td>
<td>38 ± 7</td>
<td>0.001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>10.5 ± 23.6</td>
<td>21.1 ± 37.1*</td>
<td>6.9 ± 11.2</td>
<td>3.7 ± 4.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3.5 (1.2–7.7)</td>
<td>5.1 (3.5–21.2)</td>
<td>1.9 (0.8–7.2)</td>
<td>2.0 (0.7–4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.8 ± 1.2</td>
<td>4.9 ± 1.3</td>
<td>4.7 ± 1.0</td>
<td>5.0 ± 1.2</td>
<td>0.602</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.6 ± 0.9</td>
<td>2.6 ± 1.0</td>
<td>2.6 ± 0.8</td>
<td>2.8 ± 1.0</td>
<td>0.555</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.2 ± 1.3</td>
<td>2.4 ± 1.7*</td>
<td>1.6 ± 0.8</td>
<td>2.0 ± 1.15</td>
<td>0.030</td>
</tr>
<tr>
<td>sTRAIL (pg/ml)</td>
<td>63 ± 35</td>
<td>28 ± 16</td>
<td>62 ± 7</td>
<td>101 ± 27</td>
<td>N/A</td>
</tr>
<tr>
<td>OPG (pmol/l)</td>
<td>12 ± 6</td>
<td>13 ± 7</td>
<td>12 ± 5</td>
<td>12 ± 5</td>
<td>0.977</td>
</tr>
<tr>
<td>11 (8–16)</td>
<td>10 (8–15)</td>
<td>11 (8–15)</td>
<td>11 (9–16)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1. Serum levels of the soluble fraction of the tumour necrosis factor-related apoptosis-inducing ligand (sTRAIL) by CKD stage. *P < 0.05, a statistically significant difference versus CKD stages 2 and 3 and CKD stages 4 and 5; the dotted line indicates the mean reference value (76 pg/ml) for serum sTRAIL, according to the information provided by the manufacturer.

Fig. 2. Kaplan–Meyer estimates of overall mortality for all patients as a function of the serum sTRAIL tertiles.
In the univariate regression analyses, serum sTRAIL levels were positively correlated with BMI ($r^2 = 0.044$, $P = 0.017$) and albumin ($r^2 = 0.058$, $P = 0.006$), and negatively associated with age ($r^2 = 0.030$, $P = 0.049$), CRP level ($r^2 = 0.110$, $P < 0.0001$) and iPTH ($r^2 = 0.036$, $P = 0.031$). In the multivariate regression analysis including all the variables that were significantly associated with serum sTRAIL levels in the univariate analyses, the BMI ($\beta = 1.48$, 95% confidence interval (CI) = 0.58–2.38, $P = 0.001$) and the CRP level ($\beta = -8.841$, 95% CI = −12.67 to −5.01, $P < 0.0001$) were identified as the only independently associated variables.

During the follow-up period (mean duration: 772 ± 286 days; median: 809; range: 10–1129), 36 patients died (19 from cardiovascular events, 8 from infectious events and 9 from other causes). The Kaplan–Meier curves showed that the lowest serum levels of sTRAIL (i.e. the first tertile) were associated with the worst all-cause survival ($P = 0.010$) (Figure 2). Other variables that had been shown to significantly influence the mortality risk in this population included age, per 1 year increment, relative risk (RR) = 1.05; $P = 0.002$; haemoglobin, per 1 g/l increment, RR = 0.72, $P = 0.001$; albumin, per 1 g/l increment, RR = 0.95, $P = 0.026$; CRP (log-transformed), per 1 standard deviation increment, RR = 1.25, $P = 0.037$ and haemodialysis treatment, RR = 3.10, $P = 0.001$). Further univariate and multivariate Cox regression analyses using the non-cumulative models including possible confounders (i.e. age, albumin and CRP) confirmed that the lowest serum sTRAIL levels (first tertile) were independent predictors of all-cause mortality (Table 3, models 1–3). There was a statistically significant interaction between the effects of haemodialysis exposure and having the lowest serum sTRAIL levels (first tertile).

### Table 3. Cox regression models

<table>
<thead>
<tr>
<th>Models of patient survival (event $n = 36$)</th>
<th>RR (95% CI)$^a$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.65 (1.37–5.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, albumin</td>
<td>2.42 (1.24–4.72)</td>
<td>0.010</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, CRP (log-transformed)</td>
<td>2.47 (1.24–4.92)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

$^a$RR (95% CI), risk ratio (95% confidence interval); summarizing the effect of sTRAIL ≤48.52 pg/ml versus higher values on the overall mortality risk, for unadjusted models and models adjusted for multiple covariates. For other abbreviations, please refer to Tables 1 and 2.

![Graph showing Kaplan–Meier estimates of infectious mortality for all patients as a function of the serum sTRAIL tertiles.](https://academic.oup.com/ndt/article-abstract/25/8/2596/1893379)
tertile) for mortality in the study cohort ($P = 0.0006$ in a likelihood ratio test).

Additional crude survival analyses showed that the lowest serum sTRAIL levels were significantly associated with infectious mortality in the study population (log-rank $P = 0.012$, Figure 3) but not with cardiovascular mortality (log-rank $P = 0.124$).

**Discussion**

In a well-characterized cohort of CKD patients, we first established that CKD stage 5D patients presented significantly lower serum sTRAIL levels than stage 2 to 5 patients. It is noteworthy that there was no association between the eGFR and serum sTRAIL levels in pre-dialysis CKD stage 2 to 5 patients. This suggests that sTRAIL levels were more affected by haemodialysis than by renal dysfunction itself. Little is known about the mechanisms of sTRAIL clearance and, to date, there is no information regarding the protein's ability to cross the haemodialysis membrane. Since TRAIL is a 281-amino acid protein weighing 32kDa, one can infer that it is poorly dialysable [1,7]. It has been shown that the circulating sTRAIL decoy receptor OPG is present at the increased concentrations in CKD patients [19] and does not cross the haemodialysis membrane [20]. Notably, higher OPG serum levels have been associated with the presence and severity of coronary artery disease in the general population [21] and in CKD patients [22,23]. In the present study, we did not find any relationship between the circulating sTRAIL levels and OPG levels; this might be due to the fact that the OPG assay we used does not distinguish free OPG from sTRAIL-bound OPG. Furthermore, one could hypothesize that the low serum sTRAIL levels in haemodialysed patients might be the result of a higher expression of membrane-bound TRAIL in atherosclerotic plaques and a correspondingly decrease in the soluble form. Indeed, it is known that TRAIL is expressed in the atherosclerotic plaques in humans and in atherosclerotic ApoE knockout mice [4] but not in non-diseased vessels.

Secondly, we showed that serum sTRAIL was positively associated with albumin and negatively associated with CRP and thus behaved as a negative acute inflammatory phase marker. Furthermore, the higher CRP levels and a lower BMI were identified as the only independent predictors of lower serum sTRAIL levels in the study cohort. Strong associations between malnutrition, inflammation and atherosclerosis have been observed in CKD patients and suggest the presence of a so-called malnutrition, inflammation and atherosclerosis (MIA) syndrome [24] (subsequently referred to as a protein-energy wasting (PEW) state [25]). Therefore, serum sTRAIL could be an alternative biomarker for PEW in the CKD setting.

Thirdly, the lowest levels of serum sTRAIL were associated with a higher risk of all-cause mortality in the study population. Since most of the deaths were attributable to cardiovascular causes, we initially hypothesized that the observed association between serum sTRAIL and all-cause mortality would effectively reflect its effect on the cardiovascular disease pathway. Remarkably, low serum sTRAIL levels have been observed in patients with acute coronary syndrome [4] and those with angiographically documented coronary artery disease [10]. In fact, it has been recently demonstrated that TRAIL is expressed in the atherosclerotic plaques from humans and atherosclerotic ApoE knockout mice to a greater extent than in non-atherosclerotic control vessels [4]. Moreover, in an animal model of atherosclerosis, a repeated injection of recombinant human TRAIL significantly attenuated the overall extension of the atherosclerotic plaques and contributed to their stabilization [26]. In view of these observations, one can hypothesize a protective role for sTRAIL in plaque stability. However, a crude analysis of cardiovascular mortality alone failed to reveal a significant association between cardiovascular mortality and serum sTRAIL levels in our study population. This may reflect the low proportion of ischaemic cardiovascular deaths ($n = 2$) in our cohort. Of interest, we observed a statistical interaction between the effects lower serum sTRAIL levels and haemodialysis treatment on mortality in our cohort, suggesting that the simultaneous exposure to these two factors would expose the patient to a higher risk of mortality than each of these factors separately (i.e. lower sTRAIL and haemodialysis treatment) [27].

Further analysis of the study cohort revealed an association between infectious mortality and serum sTRAIL levels. There is experimental evidence to suggest that TRAIL can indeed modulate the immune response by either inducing apoptosis of viral infected cells [12,13] or influencing the T cell-mediated cytotoxic response (which is necessary for viral clearance).

To the best of our knowledge, this is the first study to assess serum sTRAIL levels in patients with variable degrees of renal dysfunction and to evaluate the protein's relationship with inflammation and mortality. The study limitations include the relatively short follow-up, the small cohort and the non-inclusion of some patients with conditions associated with high morbidity–mortality (atrial fibrillation, aortic aneurism, recent acute cardiovascular ischaemic event), which might have biased the survival analysis. Furthermore, since the biological effects of serum sTRAIL are known to be largely receptor and cell type-specific, the measurement of serum sTRAIL and its soluble decoy receptor OPG will not enable us to determine the disease mechanisms in which sTRAIL levels could affect survival. Additionally, one must bear in mind the fact that only one membrane receptor for TRAIL (with high homology to human death receptor TRAIL-R2) has been identified in mice [28]; this suggests that TRAIL regulation in humans is probably much more complex than in mice.

In conclusion, we have demonstrated that circulating sTRAIL behaved as a negative marker of inflammation and was inversely associated with the all-cause and infectious mortality risk in a CKD population. The present data highlight the potential importance of sTRAIL in this setting. Further studies are needed to better understand the role of sTRAIL as an apoptotic modulator and inflammatory marker and to confirm its role in reducing mortality in a CKD population.
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Conflict of interest statement. None declared.

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