Added Value of Soluble Tumor Necrosis Factor-α Receptor 1 as a Biomarker of ESRD Risk in Patients With Type 1 Diabetes

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OBJECTIVE

Recent studies have suggested that circulating levels of the tumor necrosis factor-α receptor 1 (sTNFαR$_1$) may be a useful predictor for the risk of end-stage renal disease (ESRD) in patients with diabetes. However, its potential utility as a biomarker has not been formally quantified.

RESEARCH DESIGN AND METHODS

Circulating levels of sTNFαR$_1$ were assessed in 429 patients with type 1 diabetes and overt nephropathy from the Finnish Diabetic Nephropathy (FinnDiane) cohort study. Predictors of incident ESRD over a median of 9.4 years of follow-up were determined by Cox regression and Fine-Gray competing risk analyses. The added value of sTNFαR$_1$ was estimated via time-dependent receiver operating characteristic curves, net reclassification index (NRI), and integrated discrimination improvement (IDI) for survival data.

RESULTS

A total of 130 individuals developed ESRD (28%; ESRD incidence rate of 3.4% per year). In cause-specific modeling, after adjusting for baseline renal status, predictors of increased incidence of ESRD in patients with overt nephropathy were an elevated HbA$_{1c}$, shorter duration of diabetes, and circulating levels of sTNFαR$_1$. Notably, sTNFαR$_1$ outperformed estimated glomerular filtration rate in terms of R^2. Circulating levels of the sTNFαR$_1$ also remained associated with ESRD after adjusting for the competing risk of death. A prediction model including sTNFαR$_1$ (as a −0.5 fractional polynomial) was superior to a model without it, as demonstrated by better global fit, an increment of R^2, the C index, and area under the curve. Estimates of IDI and NRI(>0) were 0.22 (95% CI 0.16–0.28; $P < 0.0001$) and 0.98 (0.78–1.23; $P < 0.0001$), respectively. The median increment in the risk score after including sTNFαR$_1$ in the prediction model was 0.18 (0.12–0.30; $P < 0.0001$).

CONCLUSIONS

Circulating levels of sTNFαR$_1$ are independently associated with the cumulative incidence of ESRD. This association is both significant and biologically plausible and appears to provide added value as a biomarker, based on the absolute values of NRI and IDI.

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The presence and severity of chronic kidney disease (CKD) are the strongest predictors of adverse outcome in patients with type 1 diabetes (1). However, an adverse prognosis is not inevitable in patients with overt nephropathy. Some patients do not develop end-stage renal disease (ESRD) or die. Developing new ways to identify those patients with a good prognosis from those with poor prognostic outcomes remains important for the management of patients with type 1 diabetes and CKD. A number of recent articles have highlighted the potential importance of small circulating proteins as biomarkers for progressive kidney disease, including the soluble tumor necrosis factor-α receptor 1 ($TNF\alpha R_1$) (2–10). But while there may be biological plausibility for an independent association with progressive renal disease, small proteins accumulate in proportion to the deterioration in renal function, much in the same way as occurs with cystatin C, a known biomarker of renal function. In addition, although each of these proteins may be associated with prognosis, the "lead time bias" of renal impairment in determining renal outcomes like ESRD (i.e., people with the most severe renal impairment are more likely to develop ESRD because they have less renal function to lose before they get there) means that the true association may be confounded or insignificant. Moreover, many cause-specific analyses are also potentially confounded by the competing risks of death and ESRD, whereby those dying without first developing ESRD are either inappropriately coded as having a healthy renal outcome (last value carried forward) or censored (estimation in a scenario where it is impossible for the patient to undergo the competing event, i.e., dead patients cannot then develop ESRD) (11,12). In addition, the utility of a (new) biomarker is not necessarily inferred from the magnitude of the odds/hazard ratio in a multivariate predictive model (13) nor the change in the receiver operating characteristic (ROC) curve area (14); rather, recently described metrics (integrated discrimination improvement index [IDI] and the net reclassification index [NRI]) for evaluating novel biomarkers must be canvassed (15,16). Such assessment should also incorporate appropriate adjustment for censoring in time-to-event data (17). In this article, we explore the recently proposed association between soluble $TNF\alpha R_1$ and ESRD using both a cause-specific and competing risks paradigm, showing that even after adjusting for other factors, it remains an independent predictor of ESRD in patients with type 1 diabetes and CKD, and provides modest to substantial added value as a biomarker for ESRD risk.

RESEARCH DESIGN AND METHODS

Study Sample

This study is part of the ongoing prospective nationwide multicenter Finnish Diabetic Nephropathy (FinnDiane) Study, with the aim to identify genetic, clinical, and environmental risk factors for diabetic nephropathy in patients with type 1 diabetes (1,18,19). Type 1 diabetes was defined as an onset of diabetes before the age of 40 years and permanent insulin treatment initiated within 1 year of diagnosis. For this study, outcomes were ascertained in patients in the FinnDiane prospective cohort with type 1 diabetes and macroalbuminuria (n = 459). This was defined by an albumin excretion rate $\geq$200 μg/min or $\geq$300 mg/day in at least two out of three consecutive overnight or 24-h urine samples. None of these individuals had ESRD at baseline. These baseline assessments were performed between 1995 and 2006. The ethics committees of all participating centers approved the study protocol. Written informed consent was obtained from each patient, and the study was performed in accordance with the Declaration of Helsinki as revised in the year 2000.

Cohort Characteristics

At baseline, all patients also underwent a thorough clinical investigation in connection with a regular patient visit to their attending physician. Data on medication and diabetes complications were registered with the use of a standardized questionnaire, which was completed by the physician based upon medical files. Blood pressure was measured twice in the sitting position after a 10-min rest, and the average of these two measurements was used in the analysis. Height, weight, and waist-hip ratio were recorded, and blood was drawn for the measurements of HbA_{1c}, lipids, and creatinine. Macrovascular disease was defined as a history of myocardial infarction, a coronary artery procedure (bypass surgery or angioplasty), stroke, limb amputation, or peripheral artery procedure, which was verified from the medical files. HbA_{1c} was determined by standardized assays at each center. Serum lipid and lipoprotein concentrations were analyzed centrally by automated enzymatic methods (Hoffmann-La Roche, Basel, Switzerland). The glomerular filtration rate (eGFR) was consequently estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Measurement of Soluble $TNF\alpha R_1$

Frozen plasma samples obtained at baseline were subsequently thawed and assayed for soluble $TNF\alpha R_1$ levels using the EKF Diagnostics Human sTNFR1 EIA (product BIO94), according to the manufacturer's instructions. Intra-assay precision (mean % coefficient of variation), determined using six samples each assayed 16 times in a single assay, was 3.2%, range 1.8–5.3. Interassay precision (mean % coefficient of variation), determined using eight samples each assayed in duplicate across 10 separate assays, was 5.1%, range 3.6–6.8.

Ascertainment of Outcomes

Deaths from any cause through to 31 December 2010 were identified via a search of the Finnish National Death Registry and center databases. All deaths were confirmed with death certificate data. In each case, vitality status was verified from the Finnish National Death Registry. ESRD was defined as the requirement for dialysis or kidney transplantation and identified via a search of the Finnish Hospital Discharge Registry, renal registries, and center databases and verified from medical files.

Statistical Analysis

In the current article, we initially determined the predictive ability of various covariates, in particular the soluble $TNF\alpha R_1$, in a multivariate time-to-event analysis using both a cause-specific and a formal competing risk (non-ESRD death) analysis, with the end point as the development of ESRD. The former analysis used a Cox model with non-ESRD death censored, and the latter estimated the cumulative incidence of ESRD (non-ESRD death as the competing risk) using the Fine and Gray model (20), which extends the Cox proportional hazards model to competing risks data by consideration of the subdistribution hazard (21). We limit our analysis to the consideration of two (competing)

events: (the development of) ESRD and pre-ESRD deaths; deaths occurring after the development of ESRD are not considered. As opposed to a cause-specific analysis, which would censor the competing event(s), the Fine-Gray approach "carries forward" the competing event(s) into the risk set and does not censor them. All variables known to be associated with ESRD were assessed as candidates for the final model, along with any variables associated with ESRD in univariate analyses with a P value <0.01. The final model(s) did not incorporate "nonsignificant" parameters (on the basis of no meaningful improvement in information criteria). Model selection was guided by information criteria (Akaike and Bayesian information criterion [AIC and BIC]; the latter preferred in nonnested comparisons) (22). Nonlinear covariate effect was explored via multivariate fractional polynomials using a closed-test algorithm (simplification from the most complex permitted fractional polynomial, depending upon the degree) while maintaining the overall type I error rate at a prespecified nominal level, as implemented in the Stata module "mfp," final covariate form being determined by the plausible clinical effect of the fractional polynomial, i.e., subject knowledge, and overall model fit (23).

The Fine-Gray model was implemented in Stata statistical software (V13, 2013; College Station, TX) using the "stcrreg" module. Within the Cox model, the explained variation (R^2) was assessed using the user-written Stata module "str2d" (24). Although the cause-specific (Cox) and competing risk (cumulative incidence; Fine-Gray) models nominally address two separate questions of *1*) the biological effect of the covariate(s) of interest and *2*) the differences between proportions of patients experiencing the particular condition (ESRD) in time, respectively (12), both of these questions were adjudged pertinent in the current context, as were comparative assessments (BIC) of model fit (11). The proportional hazards assumption of the Cox model was assessed using the "phtest" of Stata, testing that the log hazard ratio function was constant over time. Rejection of the null hypothesis ($P < 0.05$) of a zero slope indicates deviation from the proportional hazards assumption.

The added value of the marker of interest (soluble TNFαR$_1$) was assessed by two methods. First, time-dependent ROC curves were assessed using the R (V3.0.1, 2013) (25) software user-written module "risksetROC" (V1.0.4, 2012-09-26) (26,27). The module estimates time-specific versions of sensitivity and specificity calculated over risk sets as an alternative to the use of R^2 extensions for survival data. A subject may thus act as a control for an early time ($t < T_i$, where T_i is the survival time) or a case when $t = T_i$. The weighted average of the time-specific area under the curve (AUC) is a global concordance measure (the C index) (28).

Second, added value specific for survival data, including the NRI and IDI, was also assessed using the R module of survIDINRI (17). The NRI (theoretical range −2 to +2) is computed by assessing the change (movement "up" or "down" within categories) in the classification of the risk/probability of patients with respect to the end point (in this case ESRD) by the addition of the new marker in question (soluble TNFαR in the current study), that is, $\text{NRI} = P(\text{up}|\text{event}) - P(\text{down}|\text{event}) + P(\text{down}|\text{nonevent}) - P(\text{up}|\text{event})$. In the absence of understandable and well-verified risk categories, a category-free version is available NRI(>0) (29), which may be more robust as the NRI has been demonstrated to be computationally sensitive to the number of risk categories used (30). The NRI(>0) "...captures the marginal strength of the new predictor after accounting for correlations with variables included in the baseline model" (31). The IDI, a complement to the AUC, is defined as: $\text{IDI} = (\text{IS}_{\text{new}} - \text{IS}_{\text{old}}) - (\text{IP}_{\text{new}} - \text{IP}_{\text{old}})$, where IS is the integral of sensitivity over all possible cutoff values and IP is the corresponding integral of "1-specificity" (32). The IDI magnitude indicates the increase in the separation of mean predicted risks/probabilities for events and nonevents that has occurred by the incorporation of the new biomarker (31). The NRI and IDI represent new metrics for the formal assessment of renal biomarkers, to supplement the improvement in the AUC.

RESULTS

Cohort Characteristics

Outcomes were determined in 459 participants from the FinnDiane study with type 1 diabetes and overt nephropathy. Their baseline characteristics have been previously described in detail (1,18,19) and are summarized in Table 1. In brief, 56% of patients were male ($n = 260$). The mean age of participants was 42 years with a median duration of diabetes of 28 years. At baseline, 19% of the cohort had pre-existing macrovascular disease. Of patients with macroalbuminuria, 54% had an eGFR <60 mL/min/1.73 m^2, denoting the presence of moderate to severe renal impairment. Despite the use of insulin regimens and multiple antihypertensive and lipid-lowering therapies, less than half of all patients achieved standard therapeutic targets. In particular, 48% of the patients had an HbA$_{1c}$ $\geq$9.0% (75 mmol/mol). Seventy five percent of patients had a systolic blood pressure $\geq$130 mmHg, and 70% percent of patients had an LDL cholesterol $>$3.0 mmol/L.

Circulating Levels of the Soluble TNFαR$_1$

The median level of soluble TNFαR$_1$ was 2.0 ng/mL in patients with overt nephropathy, similar to that reported in previous studies (2–9). Circulating levels of soluble TNFαR$_1$ were highly correlated with eGFR ($R^2 = 0.69$) (Supplementary Fig. 1), especially within the subset of patients with an eGFR <60 mL/min/1.73 m^2 at baseline, a subset in which seven out of every eight cases of ESRD events were ultimately observed. This correlation was similar to that observed for cystatin C, a protein of a similar size and known biomarker of renal function ($R^2 = 0.64$) (Supplementary Fig. 2).

Cause-Specific (Cox) Analysis of ESRD

During a median of 9.4 years of follow-up, 130 individuals with overt nephropathy developed ESRD (28%; ESRD incidence rate of 3.4% per year). Independent predictors for ESRD in this cohort were baseline renal function, HbA$_{1c}$, duration of diabetes, and circulating levels of soluble TNFαR$_1$ (all $P < 0.01$) (Fig. 1*A* and Supplementary Table 1). Notably, patients with overt nephropathy and a shorter duration of diabetes were more likely to develop ESRD, reflecting their more rapid disease-progression trajectory when compared with individuals with a longer history of diabetes at baseline (Fig. 2). In addition, patients who developed ESRD during follow-up also had much lower eGFR at baseline, reflecting their lead time (proximity) to this end point. However,

Table 1—Baseline parameters in 459 participants from the FinnDiane Study with type 1 diabetes with overt nephropathy, stratified according to outcome

Baseline parameters	Alive without ESRD (*n* = 270)	ESRD (*n* = 130)	Dead without ESRD (*n* = 59)
Male sex, *n* (%)	143 (53%)	77 (59%)	39 (66%)#
Age (years)	40 ± 10	42 ± 10	48 ± 12 *
Duration of diabetes (years)	29 ± 8	28 ± 8	33 ± 9*
BMI (kg/m^2)	26 ± 4	26 ± 5	26 ± 4
Waist-hip ratio (cm/cm)	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1*
Ever smoking (%)	154 (57%)	83 (64%)#	38 (65%)
Macrovascular disease, *n* (%)	39 (14%)	27 (21%)	21 (36%)#
Laser treatment, *n* (%)	208 (77%)	109 (84%)	46 (78%)
HbA_{1c} (%)	8.8 ± 1.5	9.6 ± 1.6*	9.0 ± 1.4
HbA_{1c} (mmol/mol)	72 ± 18	78 ± 25*	75 ± 15
Insulin dose (units/kg)	0.7 ± 0.2	0.6 ± 0.2*	0.7 ± 0.2
Antihypertensive medication, *n* (%)	250 (94%)	123 (95%)	52 (88%)
Renin-angiotensin system blockade, *n* (%)	240 (89%)	110 (85%)	48 (81%)
Systolic blood pressure (mmHg)	139 ± 16	147 ± 22*	149 ± 23*
Diastolic blood pressure (mmHg)	81 ± 10	84 ± 10	81 ± 10
Lipid-lowering medication (%)	49 (18%)	46 (35%)#	12 (20%)
Total cholesterol (mmol/L)	5.2 ± 0.9	5.5 ± 1.2*	5.4 ± 1.0
LDL cholesterol (mmol/L)	3.5 ± 0.8	3.4 ± 1.1	3.4 ± 0.8
Triglycerides (mmol/L)	1.4 ± 0.7	2.1 ± 1.4*	1.8 ± 1.0*
HDL cholesterol (mmol/L)	1.4 ± 0.4	1.2 ± 0.3	1.2 ± 0.4
eGFR (mL/min/1.73 m^2)	68 ± 26	36 ± 21*	58 ± 26*

Data shows mean values ± SD, unless otherwise stated. *P value < 0.05 vs. patients alive without ESRD, calculated by Student t test. #P value $<$ 0.05 vs. patients alive without ESRD, calculated by χ^2 test.

after adjusting for these potentially confounding factors, as well as glycemic control, circulating levels of the soluble $TNF\alpha R_1$ remained predictive for ESRD. In this cause-specific Cox mode, soluble $TNF\alpha R_1$ outperformed eGFR in terms of R^2 (adjusted for model dimension) (Supplementary Table 2), as previously suggested by Krolewski and colleagues (9). Notably, cystatin C was not associated with ESRD after adjusting for eGFR, HbA_{1c}, and the duration of diabetes (P = 0.53). In addition, achieved blood pressure, lipid levels, smoking, and the use of blockers of the renin-angiotensin system were not significantly associated with the risk of ESRD after adjusting for these other variables.

Competing Risks in the Development of ESRD

Fifty-nine participants died without first developing ESRD (incidence rate of 1.5% per year). After taking into account the competing risk of death using a Fine-Gray model (8), predictors of increased cumulative incidence of ESRD in patients with overt nephropathy remained a reduced baseline eGFR, elevated HbA_{1c}, and a shorter duration of diabetes (all $P < 0.01$) (Supplementary Table 2). After adjusting for each of these factors as well as the competing risk of death, circulating levels of the soluble $TNF\alpha R_1$ also remained associated with ESRD (Fig. 1*B*). By contrast, cystatin C was not associated with ESRD after adjusting for eGFR, HbA_{1c}, and the duration of diabetes (P = 0.12). Despite its potential advantages, the Fine-Gray competing risk model demonstrated a statistically inferior global fit compared with the cause-specific Cox model, as assessed by the respective BIC in a nonnested comparison (1,256 vs. 1,220, threshold for preference of 5–10).

Added Value of Soluble $TNF\alpha R_1$

For the purposes of exploring the added value of soluble $TNF\alpha R_1$ as a biomarker, a base model (model 1) with three predictors, estimated GFR (as a -2 fractional polynomial), HbA_{1c}, and duration of diabetes (linear form), was compared with a "full" model (model 2) containing these three predictors with the addition of soluble $TNF\alpha R_1$ (as a -0.5 fractional polynomial). Notably, the second model containing soluble $TNF\alpha R_1$ demonstrated better global fit than the model without it (nested comparison; AIC 1,203 [model 2] vs. 1,306 [model 1]) and an increment of R^2 (0.67 vs. 0.60). Both models demonstrated proportional hazards ($P \geq 0.23$). When compared with model 1, model 2 also demonstrated an increment of both the C index (0.84 [model 1]; 0.87 [model 2]) and the AUC estimated over the whole data set (0.67 [model 1]; 0.74 [model 2]). As computed by the R module "risksetROC", comparable estimates (at T_i = 10 years survival time) for global concordance and AUC were found: 0.72 and 0.63 [model 1] and 0.86 and 0.81 [model 2], respectively. However, the time profile of the AUC was quite different between the two models (Fig. 3), confirming clear superiority for model 2, which included soluble $TNF\alpha R_1$.

We also explored the added value of soluble $TNF\alpha R_1$ as a biomarker for ESRD using NRI and IDI (29). Estimates of IDI and NRI($>$0) were 0.22 (95% CI 0.16–0.28; $P < 0.0001$) and 0.98 (0.78–1.23; $P < 0.0001$), respectively, also suggesting substantial added value of measuring soluble $TNF\alpha R_1$. The median increment in the risk score (the Cox model linear predictor) between model 2 and model 1 was 0.182 (95% CI 0.12–0.30; $P < 0.0001$). This is shown graphically in Fig. 4, in which the shaded area and the span of NRI($>$0) demonstrates the clear added value

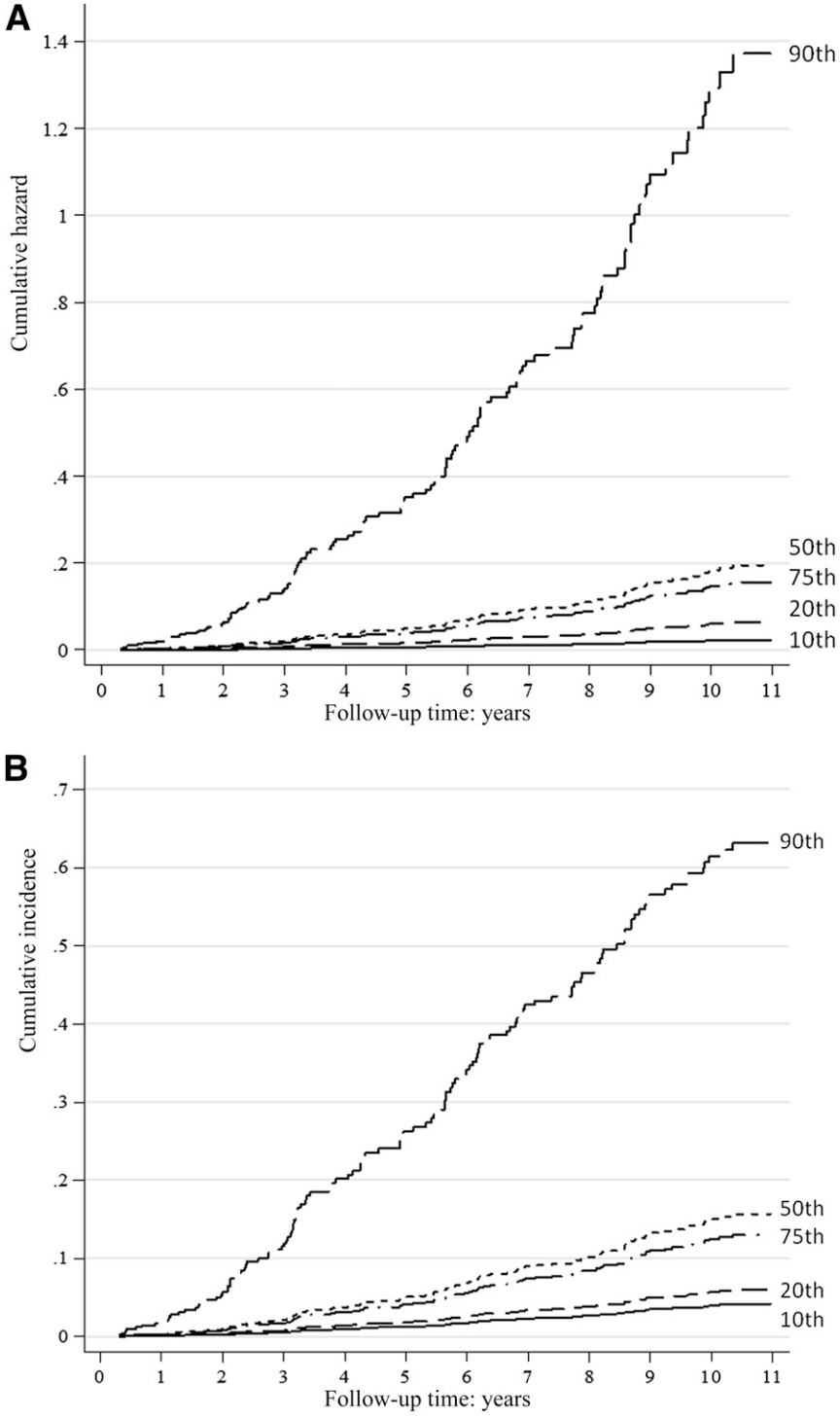

Figure 1—Graphical interpretation of the association between soluble TNFαR$_1$ levels and the development of ESRD. Data show percentiles of soluble TNFαR$_1$ modeled using cause-specific Cox regression (*A*) and Fine-Gray competing risk modeling (*B*). Full models are detailed in Supplementary Table 2.

(paired difference between risk scores) of the soluble TNFαR$_1$ biomarker. With respect to the estimate of the NRI, the proportion of patients in whom the risk scores with model 2 were higher than the risk scores with model 1 among the "event" group was 72.3% and in the "nonevent" group 24.5%.

CONCLUSIONS

TNF-α is known to play a role in the inflammation, renal hypertrophy, and fibrogenesis associated with progressive kidney disease. The plasma soluble TNFαR$_1$ concentration is generally regarded as a surrogate of TNF-α system activity. A number of recent studies have reported elevated soluble TNFαR$_1$ levels in patients with type 2 diabetes with renal structural injury (33) or renal impairment (2–8). In addition, some prospective cohort studies have suggested that the soluble TNFαR$_1$ concentration is associated with the progressive decline of renal function (2–8) and/or ESRD (9). In

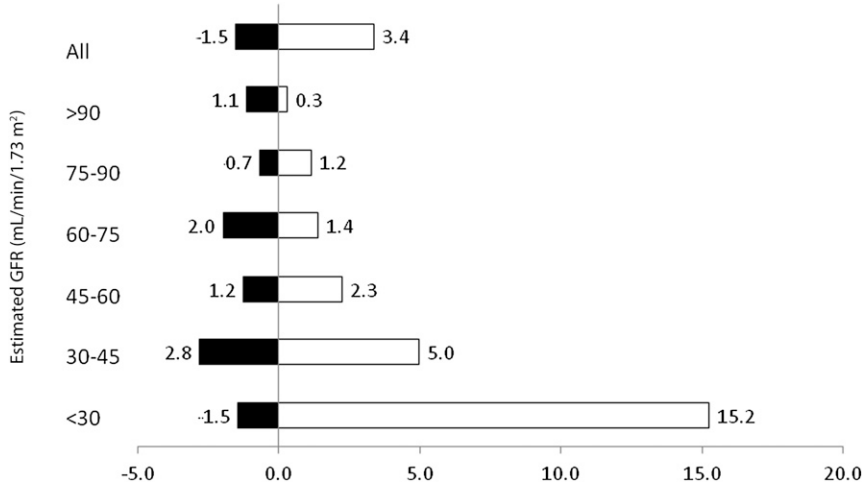

Figure 2—The competing risk of ESRD and pre-ESRD death. Figure shows the incidence of ESRD in patients with type 1 diabetes and overt nephropathy increases with decreasing renal function due to a lead time bias, while pre-ESRD death is a competing risk at all stages of renal function. Data show incidence as percent of patients per year of follow-up.

recent findings from the Diabetes Control and Complications Trial (DCCT), soluble TNFαR_1 and soluble TNFαR_2 were both associated with an increased risk for the development of overt nephropathy (10). In support of these studies, we confirm that the soluble TNFαR_1 concentration is also independently associated with the cumulative incidence of ESRD in adults with type 1 diabetes and established nephropathy.

Beyond simply an association, there are some data to suggest a plausible pathogenic link to renal progression. It has been argued that increased soluble TNFαR_1 concentrations are simply a marker for activity of the volatile cytokine TNF-α, although circulating TNF-α and soluble TNFαR_1 are only weakly correlated in diabetic patients (9). However, it may be that (unmeasured) tissue activity is elevated. Increased activity of sheddase enzymes leading to the release of soluble TNFαR_1 into the circulation may also be responsible for the shedding of other renoprotective proteins, including ACE2 (34). Finally, a

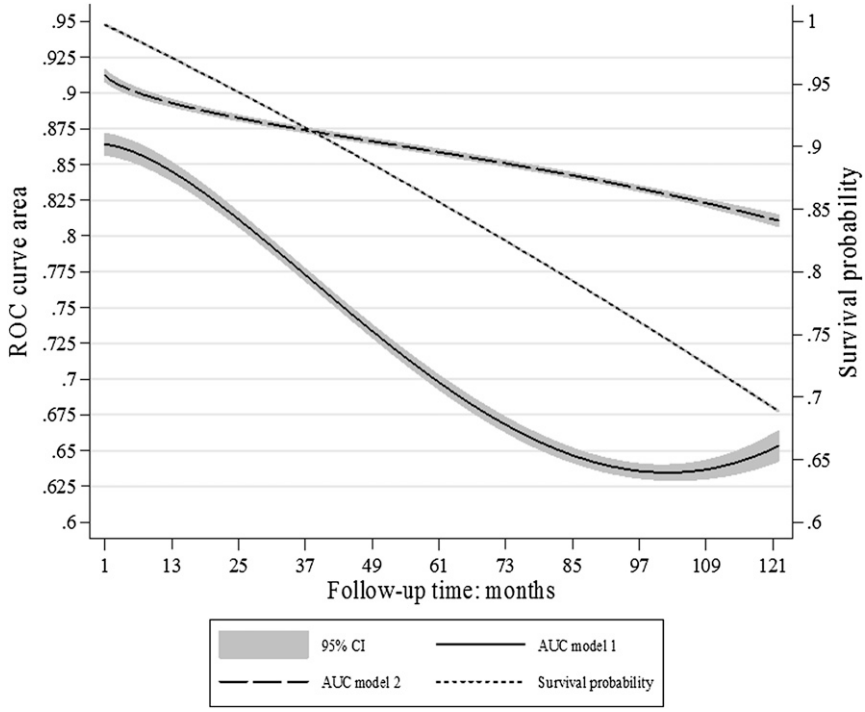

Figure 3—The additional value of soluble TNFαR_1 as assessed by the area under ROC curves. The AUC of model 2 (which includes estimated GFR as a -2 fractional polynomial, HbA_{1c}, duration of diabetes, and soluble TNFαR_1 as a -0.5 fractional polynomial) is superior over time when compared with the AUC of model 1 (solid line; including only eGFR, HBA_{1c}, and duration of diabetes). The overall survival probability is indicated by the short-dashed line.

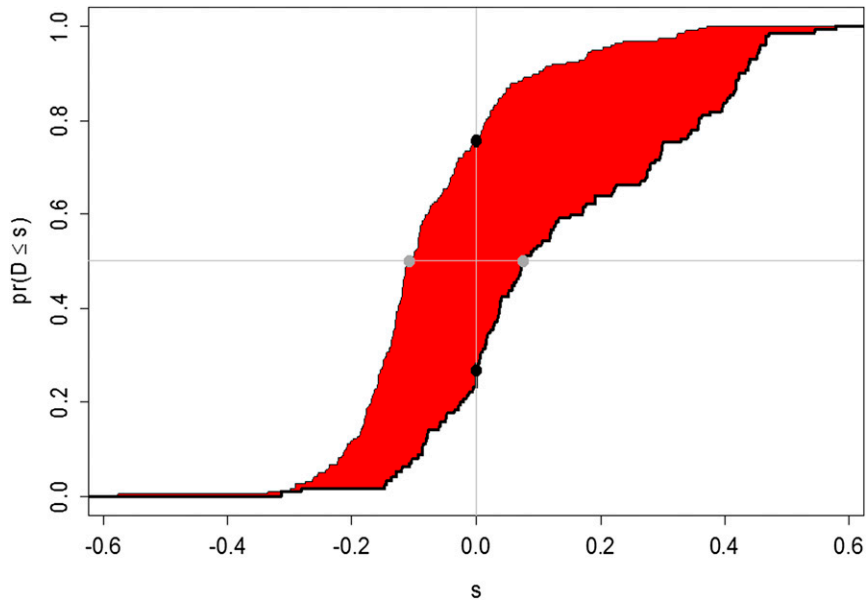

Figure 4—The additional value of soluble TNFαR$_1$ as assessed by the paired difference of risk scores. Figure shows the empirical distribution function of the paired difference ($\hat{D}$) between the risk scores (on the probability scale) estimated at T_i = 10 years using models with and without the inclusion of soluble TNFαR$_1$. The added value of soluble TNFαR$_1$ is proportional to the area of the shaded graphic. The vertical difference at s = 0 (between the two black dots; where s scales the graphic between −1 and +1) is NRI(>0), and the horizontal difference (between the two gray dots) equals the median risk-score difference. *y*-axis, cumulative probability; *x*-axis, s = $\hat{D}$, difference between two model risk scores.

direct effect for soluble TNFαR1 in the kidney has also been proposed including the inhibition of TNF-α priming of oxidative burst activity in neutrophils (5).

It is well known that serum soluble TNFαR$_1$ levels are dependent on kidney function (7) and soluble TNFαR$_1$ accumulates as a result of the loss of renal function (5). In our cohort, there was a strong correlation between eGFR and serum soluble TNFαR$_1$ levels that was similar to that observed for cystatin C, a known biomarker of renal function that is cleared predominantly by glomerular filtration (Supplementary Figs. 1 and 2). This association is important when considering the potential predictive utility of soluble TNFαR$_1$, as renal impairment is by far the dominant risk factor for ESRD, largely reflecting the "proximity" or lead time of patients with lower renal function to ESRD (Fig. 2). However, after adjusting for eGFR, soluble TNFαR$_1$ remained associated with ESRD, on both cause-specific and competing risk regression modeling (see Supplementary Tables 1 and 2).

Patients with overt nephropathy also have an increased risk of ESRD as well as death. These outcomes have important competing effects that potentially confound a cause-specific analysis. In contradistinction to the latter form of analysis, we have developed a formal competing risks model that looks at the cumulative incidence of an ESRD while also taking into consideration (in an estimation sense) competing risk of death prior to ESRD. And after taking into account the competing risk of death, soluble TNFαR$_1$ remained associated with the cumulative incidence of ESRD (Fig. 1*B* and Supplementary Table 2). Notably, however, the cause-specific (Cox) model had statistical (overall fit) advantage compared with the competing risk (Fine-Gray) model, as assessed by the difference in respective BIC (1,256 vs. 1,220; threshold for difference of 5–10). This may be understood in that the cause-specific Cox model has inferential advantage with respect to pathophysiology, whereas in a therapeutic/trial sense, a competing risk model may be apposite.

It has previously been argued that plasma concentration of soluble TNFαR$_1$ "outperformed all tested clinical variables with regard to predicting ESRD" in patients with type 2 diabetes (9). However, no robust tests of added value were performed in this article. As noted in recent clinical commentaries "...the *P* value (or the corresponding HR) do not indicate whether a given variable will be a good predictor. Markers... are often mistakenly defined as 'predictors,' whereas they are in fact only correlated (albeit strongly) with... outcome" (35); and more formally "...the value of hypothesis testing in evaluating new biomarkers is, at best, limited" (32). Consequently, to explore the "added value" of soluble TNFαR$_1$ as a biomarker, we have specifically incorporated in the present article a range of appropriate statistical techniques suitable for time-to-event analysis, including two newly described metrics, IDI and NRI. Alongside the incremental AUC, these complementary parameters may be considered the new standards for evaluating incremental value of biomarkers. Notably, soluble TNFαR$_1$ showed added value in each of these metrics. Moreover, the absolute values of NRI and IDI achieved when using soluble TNFαR$_1$ were substantive, when compared with other recognized biomarkers in both the general literature (31,36) and specifically in diabetes. We note, however, that the current clinical study may be one of the first to use such indices for survival data; the (absolute) values of the INR and IDI metrics may not be comparable.

Modern improvements in diabetes care and cardiovascular survival have meant that many patients with type 1 diabetes live long enough to require renal replacement. One key strength of this study is the large number of ESRD events, at least four times greater than reported in previous studies of patients with type 2 diabetes (9). In our cohort, 28% of participants developed ESRD during follow-up (n = 130). Other strengths of the FinnDiane Study include its large cohort of individuals with type 1 diabetes, high participation rate, long follow-up period, access to subsidized care (75–100% of costs), and contemporary treatment regimens, including a range of insulin regimens, statins, blockers of the renin-angiotensin system, and self-monitoring technologies. We used validated methods to identify deaths, and all deaths in our cohort were confirmed through death records. Surveillance bias is unlikely given the uniform vital status follow-up procedures used by our staff masked to participant CKD status levels. In our questionnaire, we had broad data on tobacco or alcohol use, diet, education, socioeconomic status, other possible confounders, and the severity of disease. Few changes in diabetes treatment and health care over the short study period would have affected mortality results.

In conclusion, despite conventional treatment, many patients with type 1 diabetes and overt nephropathy develop ESRD and/or succumb to a premature death. The strongest risk factors are impaired renal function, a historically rapid disease course, and poor glycemic control. However, after adjusting for these factors and also taking into account the competing risk of death, circulating levels of soluble TNFαR$_1$ were independently associated with the cumulative incidence of ESRD, consistent with a previous report in a smaller cohort of patients with type 2 diabetes (9). This association was both significant and biologically plausible, and soluble TNFαR$_1$ was assessed as providing modest to substantial incremental value as a biomarker.

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