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SHORT REPORTS

Tumour necrosis factor receptor 1 and mortality in a multi-ethnic cohort: the Northern Manhattan Study

Jorge M. Luna[1,2], Yeseon Moon[1], Khin Liu[3], Steven Spitalnik[3], Myunghee Paik[4], Ralph Sacco[5], Mitchell S. V. Elkind[1,2]

[1]Department of Neurology, Columbia University, New York, NY, USA
[2]Department of Epidemiology, Columbia University, New York, NY, USA
[3]Department of Pathology, Columbia University, New York, NY, USA
[4]Department of Biostatistics, Columbia University, New York, NY, USA
[5]Department of Neurology, University of Miami, Miami, FL, USA

Address correspondence to: J. M. Luna. Tel: (+1) 2123055507; Fax: (+1) 2123051238. Email: jl2708@columbia.edu

Abstract

Objective: to study the association between soluble tumour necrosis factor receptor 1 (sTNFR1) levels and mortality in the population-based Northern Manhattan Study (NOMAS).
Methods: NOMAS is a multi-ethnic, community-based cohort study with mean 8.4 years of follow-up. sTNFR1 was measured using ELISA. Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals (HR, 95% CI) for the association of sTNFR1 with risk of all-cause mortality after adjusting for relevant confounders.
Results: sTNFR1 measurements were available in 1,862 participants (mean age 69.2 ± 10.2 years) with 512 all-cause deaths. Median sTNFR1 was 2.28 ng/ml. Those with sTNFR1 levels in the highest quartile (Q4), compared with those with sTNFR1 in the lowest quartile (Q1), were at an increased risk of all-cause mortality (adjusted HR: 1.8, 95% CI: 1.4–2.4) and non-vascular mortality (adjusted HR: 2.5, 95% CI: 1.5–3.6), but not vascular mortality (adjusted HR: 1.3, 95% CI: 0.9–1.9). There were interactions between sTNFR1 quartiles and medical insurance-status [likelihood ratio test (LRT) with 3 degrees of freedom, $P_{\text{interaction}} = 0.02$] and alcohol consumption (LRT with 3 degrees of freedom, $P_{\text{interaction}} < 0.01$) for all-cause mortality. In participants with no insurance or Medicaid, those with sTNFR1 in the top quartile had nearly a three-fold increased risk of total mortality than the lowest quartile (adjusted HR: 2.9, 95% CI: 1.9–4.4).
Conclusion: in this multi-ethnic cohort, sTNFR1 was associated with all-cause and non-vascular mortality, particularly among those of a lower socioeconomic status.

Keywords: *inflammation, insurance status, mortality risk, alcohol use, older people*

Introduction

Tumour necrosis factor (TNF) is a major pleiotropic regulator of immunity. Endogenous soluble TNF-receptor-1 (sTNFR1) increases in response to TNF-mediated inflammation; however, its exact role remains unclear [1–3]. In healthy individuals, sTNFR1 exists in concentrations orders of magnitude greater than circulating sTNF levels, and these concentrations are even higher in individuals with inflammatory disorders [4, 5]. The ubiquitous expression of TNFR1 in many tissue types and its increased serum levels in response to TNF-induced inflammation make it an ideal predictor of mortality across several disease categories [6–8]. Several TNF-mediated disorders have been targeted by exogenous recombinant sTNFR therapies, with possible implications for risk modification [9]. We previously reported on the association between sTNFR1 and vascular risk factors and atherosclerosis [10, 11]. In this analysis, for both vascular and non-vascular endpoints, we present

sTNFR1 findings on mortality. We sought to determine whether sTNFR1 levels are associated with the risk of all-cause mortality in the multi-ethnic urban Northern Manhattan Study (NOMAS) cohort, after adjusting for demographic and traditional risk factors.

Methods

Study population and study sample

As previously reported, NOMAS is a population-based, prospective cohort study ($n = 3,298$) [10–12]. Participants were identified using random digit dialling and selected using the following eligibility criteria: (i) no prior diagnosis of stroke, (ii) >39 years old and (iii) resided in Northern Manhattan for >3 months. Recruitment began in 1993 and ended in 2003. The race-ethnic distribution of this cohort consists of 63% Hispanic, 20% non-Hispanic black and 15% non-Hispanic white residents. This study received approval from the Institutional Review Board at Columbia University Medical Center and all participants provided informed consent. An analytic subsample was selected based on the availability of blood samples for sTNFR1 assays ($n = 1,862$).

Mortality outcomes

Annual telephone follow-up was conducted for all participants. All deaths were prospectively evaluated and classified into either vascular or non-vascular causes. Cause of death was established by (i) medical-records/death-certificates (MRDC); (ii) family-members/nursing home staff (FMNHS) interviews or (iii) other sources. Deaths arising from stroke, myocardial infarction, congestive heart failure, pulmonary embolism, arrhythmia/sudden death, aortic aneurysm, aortic or mitral stenosis, and left ventricular hypertrophy were considered vascular death endpoints. Deaths ruled not of vascular origin were deemed non-vascular, and deaths without sufficient records were deemed unknown aetiology. The primary outcome was all-cause mortality. The two secondary outcome measures were vascular and non-vascular mortality.

sTNFR1 serum levels

Serum sTNFR1 levels were determined in baseline blood samples using an enzyme-linked immunosorbent assay (Biosource International, Camarillo, CA, USA). Whole blood was collected in 5cm^3 EDTA/anti-coagulated tubes by a trained phlebotomist. Blood samples were centrifuged at 3,000 r.p.m. for 10 min, with serum samples immediately aliquoted and stored in 1.2-ml cryule vials at −70°C until ready for batch testing. External commercial testing on a subset of NOMAS blood samples and internal testing on control bloods with known sTNFR1 values, confirmed reliability and validity of sTNFR1 assays (correlation with external testing: $r = 0.98$).

Covariates

Covariate definitions are described in Table 1, and were previously reported [10].

Data analysis

The baseline characteristics and their relations to sTNFR1 were calculated. We fitted Cox proportional hazard regression models to estimate hazard ratios and 95% confidence intervals (HR, 95% CI) for sTNFR1 levels, unadjusted and after adjusting for demographics, medical and behavioural risk factors: age, sex, race-ethnicity, education, insurance status, history of coronary artery disease, blood sugar, systolic blood pressure, waist circumference, HDL, LDL, cigarette smoking, alcohol consumption, physical activity, cholesterol medication and hsCRP levels. sTNFR1 was modelled by quartiles with the lowest quartile (Q1) as the reference. The primary outcome was all-cause mortality, and secondary outcomes were vascular and non-vascular mortality. Final models and models with interactions of sTNFR1 levels with covariates were examined using the likelihood ratio test (LRT) with specified degrees of freedoms (df) to ensure overall effects of sTNFR1 on mortality. After examining the proportional hazards assumption in final models, we censored follow-up at 10 years. All statistical analyses were conducted using SAS, version 9.2.3 (Cary, NC, USA).

Results

Baseline descriptive statistics, risk factors and associations with sTNFR1 are shown in Table 1. The median sTNFR1 was 2.28 (IQR: 1.75–2.97) ng/ml. There were 512 deaths, including 267 vascular deaths, 207 non-vascular deaths and 38 deaths of unknown aetiology during the mean follow-up of 8.4 years. For mortality assessment, 215 records were confirmed by FMNHS only, 112 records by MRDC only, 137 by both MRDC and FMNHS and 48 by other sources.

sTNFR1 quartiles and mortality: all-cause, vascular and non-vascular

Participants with sTNFR1 levels in the highest quartile had an increased risk of all-cause (adjusted HR: 1.8, 95% CI: 1.4–2.4) and non-vascular mortality (adjusted HR: 2.5, 95% CI: 1.5–3.6), but not vascular mortality (adjusted HR: 1.3, 95% CI: 0.9–1.9) in fully adjusted main effects models, when compared with the referent quartile (Table 2A). There were mild violations for proportionality among Q2 and Q3 of TNFR1, which was mainly due to cross-over after 10 years of the follow-up. Analyses were thus limited to 10 years of the follow-up. Quartiles 2 and 3 were not associated with mortality. Secondary analysis for a possible threshold effect found the highest quartile of sTNFR1 was associated with vascular mortality, when compared with the remaining quartiles combined (adjusted HR = 1.4, 95% CI:

Table 1. Population characteristics ($n = 1{,}862$)

	Parameter	Overall, $n = 1862$ [n (%)] OR [mean (SD)]	sTNFR1 Q1 [n (%)] OR [mean (SD)]	sTNFR1 Q2 [n (%)] OR [mean (SD)]	sTNFR1 Q3 [n (%)] OR [mean (SD)]	sTNFR1 Q4 [n (%)] OR [mean (SD)]	K–W or X^2 (P-value)
A. Baseline descriptive statistics (overall and sTNFR1 quartiles)							
Demographics	Age, mean, SD, y	69 (10.2)	66.8 (10)	67.2 (9.6)	68.9 (9.4)	73.2 (10.6)	<0.001
	Sex,						
	Male	633 (34.0)	170 (36.5)	165 (35.3)	143 (30.8)	155 (33.4)	0.21
	Race/ethnicity						
	Non-Hispanic White	353 (19.0)	79 (22.4)	71 (20.1)	90 (25.5)	113 (32.0)	<0.01
	Non-Hispanic Black	426 (23.6)	133 (31.2)	101 (23.7)	93 (21.8)	99 (23.2)	
	Hispanic	1029 (56.9%)	244 (53.5%)	279 (61.9%)	269 (59.5%)	237 (52.8%)	
	Education level						
	≥High school	816 (43.9)	232 (28.4)	199 (24.4)	197 (24.1)	188 (23.0)	0.03
	Insurance status						
	No insurance/medicaid	872 (47.1)	203 (23.3)	213 (24.4)	231 (26.5)	225 (25.8)	0.22
	Private insurance/medicare	978 (52.9)	262 (26.8)	249 (25.5)	232 (23.7)	235 (24)	
Behavioural risk factors	Smoking status						
	Non-smoker	896 (48.2)	225 (25.1)	231 (25.8)	213 (23.8)	227 (25.3)	0.95
	Past smoker	646 (34.7)	159 (24.6)	159 (24.6)	170 (26.3)	158 (24.5)	
	Current smoker	318 (17.1)	82 (25.8)	77 (24.2)	81 (25.5)	78 (24.5)	
	Moderate alcohol consumption						
	Yes	605 (32.6)	166 (27.4)	173 (28.6)	155 (25.6)	111 (18.4)	<0.001
	Physical activity						
	Moderate or heavy	145 (7.8)	55 (37.9)	37 (25.5)	27 (18.6)	26 (17.9)	<0.01
	Waist, inches, mean, SD	36.6 (4.9)	35.7 (4.8)	36.2 (4.3)	36.8 (4.7)	37.7 (5.3)	<0.001
Clinical risk factors	Hx coronary artery disease	409 (22)	78 (19.1)	92 (22.5)	102 (24.9)	137 (33.5)	<0.001
	Diabetes mellitus	400 (21.5)	92 (23)	79 (19.8)	93 (23.3)	136 (34)	<0.001
	Cholesterol Rx	264 (14.2)	43 (16.3)	58 (22.0)	75 (28.4)	88 (33.3)	<0.01
	HDL, mg/dl, mean, SD	46.9 (14.5)	48.9 (15.3)	47.5 (14.3)	46.6 (14.3)	44.6 (13.6)	<0.001
	LDL, mg/dl, mean, SD	129.5 (36.3)	131.7 (37.8)	132.9 (35.1)	130.9 (37.0)	122.7 (34.4)	<0.001
	Systolic blood pressure, mm Hg mean + SD	143.7 (21.1)	142.9 (20.7)	141.2 (20.6)	143.5 (20.5)	147.3 (22.3)	<0.001
	hsCRP, mg/l, mean, SD	5.5 (9.3)	3.6 (4.4)	4.0 (5.1)	5.3 (8.1)	9.0 (14.7)	<0.001
Model parameters	sTNFR1, ng/ml, mean, SD	2.57 (1.7)	Q1 < 1.75	1.75 ≤ Q2 < 2.28	2.28 ≤ Q3 < 2.97	Q4 ≥ 2.97	
	Events						
	All-cause deaths	512 (27.5)	98 (21.0)	96 (20.6)	100 (21.5)	218 (47.0)	<0.001
	Non-vascular deaths	267 (14.3)	41 (15.4)	47 (17.6)	57 (21.4)	122 (45.7)	<0.001
	Vascular deaths	207 (11)	48 (23.2)	41 (19.8)	34 (16)	84 (40.6)	<0.001
	Time to all-cause mortality, mean, SD, years	8.4 (2.5)	9.0 (2.0)	8.7 (2.2)	8.6 (2.3)	7.1 (3.1)	<0.001

B. Covariates: acronyms, measurements, categorisation for modelling			
#	Parameter	Measurement	Categorisation
1,2	Age; sex	Self-report during standardised interview	Continuous; male, female (ref)
3	Race/ethnicity	Self-report during standardised interview	Hispanic, Black, White(REF)
4	Education level	Self-report during standardised interview	>High school, ≤High school (ref)
5	Insurance status	Self-report during standardised interview	No insurance or medicaid, private insurance or medicare (ref)
6	Smoking status	Self-report during standardised interview	Current smokers, past smokers, never smokers (ref)

Continued

Table 1. Continued

	Parameter	Overall, $n = 1862$ [n (%)] OR [mean (SD)]	sTNFR1 Q1 [n (%)] OR [mean (SD)]	sTNFR1 Q2 [n (%)] OR [mean (SD)]	sTNFR1 Q3 [n (%)] OR [mean (SD)]	sTNFR1 Q4 [n (%)] OR [mean (SD)]	K–W or X^2 (P-value)
7	Alcohol consumption	National Cancer Institute Food Frequency Questionnaire			Moderate use (>1 drink/month and <2 drinks daily), all others (ref).		
8	Physical activity	National Health Interview Survey			Moderate to heavy activity, no activity to low activity (ref)		
9	Waist size	Measured by trained study researcher			Continuous		
10	Hx coronary artery disease	Self-report or provider Dx			History of coronary artery diease, no history (ref)		
11	Diabetes mellitus	Fasting glucose >126 mg/dl, self-report or hypoglycaemic drug			Diabetes mellitus, no diabetes mellitus (ref)		
12	Cholesterol Rx	Self-report during standardised interview			Any cholesterol medications at baseline, no cholesterol medications (ref)		
13,14	HDL, LDL	Fasting lipid panels, Hitachi 705 spectrometer (Boehringer) |			Continuous		
15	Systolic blood pressure	Mean of 2× calibrated aneroid sphygmomanometer measures			Continuous		
16	hsCRP	BNII nephelometric assay system (Dade-Behring, Deerfield, IL, USA)			>3 mg/l, <3 mg/l (ref)		

Q, quartile; SD, standard deviation; K–W, Kurts–Wallace test; X^2, Chi-squared test; y, years.

1.1–2.0). Sensitivity analysis restricting outcomes to those confirmed by MRDC did not materially affect the results.

Interactions of sTNFR1 with covariates on all-cause mortality

The insurance status (LRT, df = 3, $P_{interaction} = 0.02$) as well as moderate alcohol consumption (LRT, df = 3, $P_{interaction} < 0.01$) were the only interactions detected with quartiles of sTFNR1 (Table 2B). Compared with the lowest, the effects of highest quartile of sTNFR1 with all-cause mortality, was greater among those with no insurance or Medicaid (adjusted HR: 2.9, 95% CI: 1.9–4.4) than among participants with private insurance or Medicare (adjusted HR: 1.4, 95% CI: 1.0–1.9). Among participants with moderate amounts of alcohol consumption, compared with the lowest, a protective effect in sTNFR1 third quartile against all-cause mortality (adjusted HR: 0.5, 95% CI: 0.3–0.9, $P < 0.01$) was observed, while there were no associations among their counterpart.

Discussion

In this well-characterised population-based cohort study, elevated sTNFR1 levels predicted all-cause mortality. For example, sTNFR1 levels >2.97 ng/ml (upper quartile) were associated with a 1.8 times higher risk of dying from all causes, compared with those with levels <1.75 ng/ml (referent quartile). The effect of sTNFR1 on mortality differed by some population characteristics: the effect of sTNFR1 on mortality was greater among those with no insurance or Medicaid than among those with private insurance or Medicare. The absence of effect among intermediate quartiles and risk elevation in the highest quartile of sTNFR1 suggests a threshold pattern relationship with mortality, and it is unclear whether the association persists for longer than 10 years of the follow-up.

Our findings of elevated sTNFR1 and mortality risk are supported by other studies. sTNFR1 has been linked to non-vascular mortality through neurodegenerative processes [13, 14], cancer survival [15, 16] and autoimmune disease [17]. TNFR1 has been linked to vascular mortality through several risk factors and cardiovascular disorders, including pulmonary embolism [18], left ventricular hypertrophy [11], homocysteine [19], carotid atherosclerosis [10] and heart failure [20]. Having Medicaid or no insurance is likely a proxy for a socioeconomic status and correlates with poor management of health conditions, and may lead to increased mortality [21]. Alcohol consumption suppresses inflammatory responses [22] and may confer protective effects below a critical sTNFR1 threshold, above which may correlate with advanced disease and mortality risk [23].

Only the highest quartile of sTNFR1 was predictive of mortality, and this was similar in our secondary analysis for vascular mortality. sTNFR1 is believed to have dual roles, responsible for sequestering TNF and inhibiting

Table 2. Tumour necrosis factor receptor 1 (TNFR1) quartiles as a predictor of mortality

	Model 1. All-cause mortality						Model 2. Non-vascular mortality						Model 3. Vascular mortality					
	Unadjusted			Adjusted[a]			Unadjusted			Adjusted[a]			Unadjusted			Adjusted[a]		
sTNFR1 quartile	HR	95% CI	*P*-value*	HR	95% CI	*P*-value*	HR	95% CI	*P*-value*	HR	95% CI	*P*-value*	HR	95% CI	*P*-value*	HR	95% CI	*P*-value*
A. Association of soluble tumour necrosis factor 1 and mortality																		
Quartile 1 (referent)	1		<0.01	1		<0.01	1		<0.01	1		<0.01	1		<0.01	1		0.07
Quartile 2	1.02	0.77–1.35		1.11	0.83–1.49		0.94	0.51–1.73		0.88	0.47–1.65		2.35	1.48–3.72		1.11	0.64–1.95	
Quartile 3	1.08	0.82–1.43		1.03	0.76–1.38		1.30	0.74–2.28		1.17	0.65–2.09		0.75	0.50–1.11		0.52	0.27–0.99	
Quartile 4	2.97	2.33–3.77		1.81	1.39–2.36		4.03	2.49–6.53		2.42	1.45–4.04		2.26	1.63–3.14		1.10	0.65–1.85	

B. Association of soluble tumour necrosis factor 1 and all-cause mortality, stratified by insurance status and alcohol consumption

	Model 1. All-cause mortality							Model 1. All-cause mortality				
Stratum-specific estimates	sTNFR1 quartile	Adjusted[a]			Stratum-specific estimates	sTNFR1 quartile	Adjusted[a]		
		HR	95% CI	*P*-value**			HR	95% CI	*P*-value**
Private insurance or medicare	Quartile 1 (referent)	1			Low or no alcohol consumption	Quartile 1 (referent)	1		
	Quartile 2	1.06	0.74–1.53	0.74		Quartile 2	1.19	0.84–1.68	0.34
	Quartile 3	0.95	0.65–1.37	0.77		Quartile 3	1.30	0.93–1.82	0.12
	Quartile 4	1.35	0.97–1.87	0.07		Quartile 4	1.79	1.32–2.42	<0.01
Uninsured or medicaid	Quartile 1 (referent)	1			Moderate alcohol consumption	Quartile 1 (referent)	1		
	Quartile 2	1.27	0.77–2.11	0.57		Quartile 2	0.93	0.53–1.62	0.47
	Quartile 3	1.24	0.66–2.31	0.39		Quartile 3	0.49	0.26–0.91	<0.01
	Quartile 4	2.86	1.85–4.43	<0.01		Quartile 4	2.00	1.23–3.24	0.70

CI, confidence interval; HR, hazard ratio.

[a]Models were adjusted for age, sex, race-ethnicity, education, insurance status, smoking, alcohol consumption, physical activity, diabetes mellitus, cholesterol treatment, high-density lipoprotein, low-density lipoprotein, systolic blood pressure and high-sensitivity C-reactive protein.

**P*-value: based on the likelihood ratio test; df, degrees of freedom.

***P*-value: based on the Wald Chi-square test following a significant likelihood test.

inflammation [1], and alternately, enhancing TNF function by protecting active TNF trimer states [2, 3, 24]. It may be that high concentrations of sTNFR increase mortality risk through induction of pro-inflammatory pathways.

Convergence of the hazard functions for Q2 and Q3 occurred after 10 years. We were therefore only able to demonstrate the effects of sTNFR1 on all-cause death out to 10 years.

Limitations

There are limitations in this study. First, cause of death was reported by family members or nursing home staff in 50% of deaths, raising measurement error concerns. However, restricting samples to only those with medically confirmed cause of death did not change the results. Secondly, several potential confounders were not measured, including immune status, antioxidant supplements and liver function. These variables may explain part of the observed effect, but it is unlikely that unmeasured positive confounders account for the full observed magnitude of effect. Finally, a limitation of this study is a lack of the measurements of serum levels of TNF, to correlate with circulating sTNFR1 levels. It may be that unbound TNF and not sTNFR1 is aetiologically responsible for increased mortality risk, but this does not preclude the prognostic value of sTNFR1 in clinical settings. The increased stability of sTNFR1 measurements compared with TNF may also make it a better assay for population-based studies.

Conclusion

In conclusion, sTNFR1 levels predict 10-year risk of mortality in this urban, community-dwelling population—particularly in individuals without health insurance or with Medicaid. If these findings can be replicated in other studies, sTNFR1 may improve mortality risk assessment in clinical practice.

Key points

- Identify early mortality risk.
- Measuring underlying inflammation.
- Interaction with an insurance status.

Conflicts of interest

None declared.

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