Predictors of Mortality in People with Recent-onset Gout: A Prospective Observational Study

Zoë L. Vincent, Greg Gamble, Meaghan House, Julie Knight, Anne Horne, William J. Taylor, and Nicola Dalbeth

ABSTRACT. ***Objective.*** To determine mortality rates and predictors of death at baseline in people with a recent onset of gout.

Methods. People with gout disease duration < 10 years were recruited from primary and secondary care settings. Comprehensive clinical assessment was completed at baseline. Participants were prospectively followed for at least 1 year. Information about death was systematically collected from primary and secondary health records. Standardized mortality ratios (SMR) were calculated and risk factors for mortality were analyzed using Cox proportional hazard regression models.

Results. The mean (SD) followup duration was 5.1 (1.6) years (a total 1511 patient-yrs accrued). Of the 295 participants, 43 (14.6%) had died at the time of censorship (SMR 1.96, 95% CI 1.44–2.62). In the reduced Cox proportional hazards model, these factors were independently associated with an increased risk of death from all causes: older age (70–80 yrs: HR 9.96, 95% CI 3.30–30.03; 80–91 yrs: HR 9.39, 95% CI 2.68–32.89), Māori or Pacific ethnicity (HR 2.48, 95% CI 1.17–5.29), loop diuretic use (HR 3.99, 95% CI 2.15–7.40), serum creatinine (per 10 μmol/l change; HR 1.04, 95% CI 1.00–1.07), and the presence of subcutaneous tophi (HR 2.85, 95% CI 1.49-5.44). The presence of subcutaneous tophi was the only baseline variable independently associated with both cardiovascular (CV) cause of death (HR 3.13, 95% CI 1.38–7.10) and non-CV cause of death (HR 3.48, 95% CI 1.25–9.63).

Conclusion. People with gout disease duration < 10 years have an increased risk of death. The presence of subcutaneous tophi at baseline is an independent predictor of mortality, from both CV and non-CV causes. (First Release December 15 2016; J Rheumatol 2017;44:368–73; doi:10.3899/jrheum.160596)

Key Indexing Terms:
GOUT TOPHUS DEATH MORTALITY

Gout is a common form of inflammatory arthritis, affecting 3.9% of the adult US population[1]. Comorbid conditions including obesity, hypertension (HTN), Type 2 diabetes, chronic kidney disease, and cardiovascular disease (CVD) are common in people with gout[2,3]. It has been widely reported that gout is associated with an increased risk of CV events and mortality[4,5,6]. However, information regarding gout disease duration and severity is limited in these studies and it is unclear how gout affects mortality risk. Perez-Ruiz, *et al*[7] reported that a number of variables independently predicted mortality in patients with a wide range of disease duration (0–42 yrs) who attended a specialist gout clinic, including age, loop diuretic use, vascular event history, presence of subcutaneous tophi, and baseline serum urate. The aim of our prospective observational study was to determine mortality rates and predictors of mortality in people with recent-onset gout.

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Supported by Arthritis New Zealand (grant number R203), the University of Auckland Faculty Research Development Fund (grant number 9801/3623120), and the Henry Cotton Charitable Trust.

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Accepted for publication November 4, 2016.

MATERIALS AND METHODS

People with gout and disease duration of less than 10 years were recruited from primary and secondary care clinics as well as from local advertising in Auckland and Wellington, New Zealand. The disease duration of < 10 years was selected at the time of study design because prior natural history studies of untreated gout indicated that tophaceous gout commonly presents in people with disease duration of more than 10 years[8,9]. Key inclusion criteria were diagnosis of gout by a physician, confirmed by the 1977 American Rheumatism Association preliminary classification criteria[10] with the first

onset of gout-related symptoms in the preceding 10 years, and the ability to complete forms in English and provide written informed consent. The study was carried out in compliance with the Helsinki Declaration and was approved by the New Zealand Multi-Regional Ethics Committee (MEC/06/10/114).

Participants attended a baseline visit that included a structured clinical assessment. Demographic data, gout history, medical history (including traditional CV risk factors), and concomitant medications were collected. Gout disease duration was defined as the time from the first clinical manifestation of gout (either flare or tophus) and flare frequency was self-reported as the number of flares in the preceding 3 months. Ethnicity was self-reported and is presented as recommended by the New Zealand Ministry of Health[11]. History of CVD was defined as coronary heart disease, heart failure, stroke, peripheral vascular disease, or current treatment with an anticoagulant as reported by Perez-Ruiz, *et al*[7]. Physical examination included the recording of weight and height for measurement of the body mass index (BMI) and assessment for subcutaneous tophi. Subcutaneous tophi were identified by 1 of 2 experienced clinical research assistants who had received training in tophus assessment by the site investigators (WJT and ND). Laboratory tests included serum urate and creatinine.

Participants were recruited from December 2006 until January 2014 and followed for at least 1 year. Data were censored at January 2, 2015, or date of death, whichever came first. Information about death was systematically collected from primary care and secondary care electronic health records and/or official death certificates. Participants were assumed to be alive in the absence of evidence of recorded death. Causes of death were classified as either CV [myocardial infarction (MI), aortic dissection, congestive heart failure, stroke, or pulmonary embolism] or non-CV (accident, cancer, infection, multiple organ failure, kidney disease, suicide, or unknown).

Standardized mortality ratios (SMR) were calculated from actual deaths observed in the study population for Māori and non-Māori men and women within the following age bands: 15–24, 25–44, 45–64, 65–74, and 75+ years, and expected deaths from Māori and non-Māori men and women mortality rates (/100,000) population for the same age bands (Mortality and Demographic Data 2011, www.health.govt.nz). The 95% CI were calculated using an exact mid-P method (www.openepi.com).

Univariate comparisons between groups were performed using the Student t test or Wilcoxon signed-rank test as appropriate and comparisons between categorical variables were made using exact methods where possible. Kaplan-Meier life table analysis (univariate analysis for presence/absence of tophi) and multivariable Cox proportional hazards models analyses were performed using SAS (version 9.4; SAS Institute Inc.) and graphs were prepared using PRISM version 6.07 (www.graphpad.com). Variables were chosen for entry into fully saturated models based on good clinical/scientific judgement. A reduced model was constructed from variables that consistently, across a variety of model building techniques (forward/backward and stepwise selection), produced p values < 0.15. Assumptions of proportionality were verified. All tests were 2-tailed and $p < 0.05$ was considered significant.

RESULTS

Clinical features at baseline. We recruited 295 people with gout disease duration < 10 years. The clinical features at the baseline visit are shown in Table 1. At the baseline visit, the mean age was 59.1 years and the mean (SD) disease duration was 5.0 years (3.0). Most participants were men (70.5%) and 115 (39.0%) of the participants had a history of CVD. There were 87 female participants. Compared with male participants, female participants were older (mean age was 67 yrs in women vs 56 yrs in men, $p < 0.001$) and had higher prevalence of HTN (57% vs 39%, $p = 0.005$), higher loop diuretic use (28% vs 14%, $p = 0.008$), lower colchicine use (23% vs 40%, $p = 0.007$), and lower serum urate concentrations (0.37 vs 0.43 mmol/l, $p = 0.002$). There were no significant differences between female and male participants in the other clinical features listed in Table 1.

SMR and causes of death. The mean (SD) followup duration was 5.1 (1.6) years (a total 1511 patient-yrs accrued). During the followup period, 43 participants died (14.6%). The expected number of deaths for this population and time period was 22 (SMR 1.96, 95% CI 1.44–2.62). Of the 43 participants who died, 26 deaths (60.5%) were because of a CV cause and 17 (39.5%) were because of a non-CV cause (Table 2).

Predictors of mortality. In univariate analysis, participants who died were more likely to be older ($p < 0.0001$), have Type 2 diabetes ($p = 0.001$), and have a history of CVD ($p < 0.0001$; Table 1). They were more likely to be taking loop diuretics ($p < 0.0001$) and colchicine ($p = 0.01$), have subcutaneous tophi ($p < 0.0001$), and have higher serum creatinine ($p = 0.002$). The proportion of women was higher among those who died (44% vs 24%, $p = 0.03$). There was no difference between groups in disease duration, flare frequency, smoking status, BMI, or serum urate, and there was a similar prevalence of HTN and hypercholesterolemia (all $p \geq 0.06$). In survival analysis, the presence of subcutaneous tophi was associated with decreased survival from all-cause mortality (unadjusted $p < 0.0001$; Figure 1A).

The fully saturated Cox proportional hazards regression model (consisting of the following variables: age, sex, Māori or Pacific ethnicity, disease duration, flare frequency, smoking status, HTN, hypercholesterolemia, Type 2 diabetes, history of CVD, loop diuretic use, allopurinol use, colchicine use, BMI, subcutaneous tophus presence, serum urate, and serum creatinine) is shown in Supplementary Table 1 (available with the online version of this article). Variables with $p < 0.15$ in the fully saturated analysis were included in a reduced multivariable Cox proportional hazards model. HTN, hypercholesterolemia, BMI, and serum urate did not achieve this level of significance and therefore were not included in the reduced model. In the reduced Cox proportional hazards model, older age (70–80 yrs: HR 9.96, 95% CI 3.30–30.03; 80–91 yrs: HR 9.39, 95% CI 2.68–32.89), Māori or Pacific ethnicity (HR 2.48, 95% CI 1.17–5.29), loop diuretic use (HR 3.99, 95% CI 2.15–7.40), serum creatinine (per 10 μmol/l change; HR 1.04, 95% CI 1.00–1.07), and the presence of subcutaneous tophi (HR 2.85, 95% CI 1.49–5.44) were independently associated with an increased risk of death from all causes (Table 3).

Predictors of mortality from CV and non-CV causes. In survival analysis, the presence of subcutaneous tophi was associated with decreased survival from both CV-related mortality (unadjusted $p = 0.0002$) and non-CV–related mortality (unadjusted $p = 0.0005$; Figure 1B and Figure 1C).

In the reduced Cox proportional hazards model, these factors were independently associated with increased risk of

Table 1. Characteristics of participants at baseline visit**.** Data are presented as n (%) unless otherwise specified.

Characteristics	All, n = 295	Dead, n = 43	Alive, n = 252	p
Age, yrs, mean (SD)	59.1 (14.7)	69.9 (12.3)	57.2 (14.3)	< 0.0001
Female sex	87 (29.5)	19 (44)	68 (27.0)	0.03
Māori or Pacific ethnicity	77 (26.1)	16 (37)	61 (24.2)	0.09
Disease duration, yrs, mean (SD)	5.0 (3.0)	5.8 (3.2)	4.9 (3.0)	0.06
Flare frequency, preceding 3 mos, mean (SD)	1.7 (2.8)	2.3 (0.2)	1.5 (2.6)	0.1
Smoker	38 (12.9)	4 (9)	34 (13.5)	0.62
HTN	132 (44.8)	23 (53)	109 (43.3)	0.25
Hypercholesterolemia	139 (47.1)	22 (51)	117 (46.4)	0.62
Type 2 diabetes	41 (13.9)	14 (33)	27 (10.7)	0.001
History of CVD	115 (39.0)	32 (74)	83 (32.9)	< 0.0001
Diuretic use	70 (23.7)	25 (58)	45 (17.9)	< 0.0001
Loop diuretics	53 (18.0)	24 (56)	29 (11.5)	< 0.0001
Allopurinol use	184 (62.4)	32 (74)	152 (60.3)	0.09
Colchicine use	103 (34.9)	23 (53)	80 (31.8)	0.01
BMI, kg/m^2, mean (SD)	31.2 (6.5)	32.2 (8.2)	31.0 (6.2)	0.28
Presence of subcutaneous tophus	51 (17.3)	19 (44)	32 (12.7)	< 0.0001
Serum urate, mmol/l, mean (SD)	0.41 (0.12)	0.41 (0.11)	0.40 (0.10)	0.25
Serum creatinine, μmol/l, mean (SD)	104.8 (65.1)	133.6 (101.5)	99.9 (55.4)	0.002

HTN: hypertension; CVD: cardiovascular disease; BMI: body mass index.

Table 2. Causes of death.

Cause	n (%)
Cardiovascular	
Myocardial infarction	10 (23)
Heart failure	8 (19)
Stroke	6 (14)
Abdominal aortic aneurysm	1 (2)
Pulmonary embolism	1 (2)
Noncardiovascular	
Cancer	6 (14)
Multiple organ failure	3 (7)
Accident	2 (5)
Infection	2 (5)
Unknown	2 (5)
Renal disease	1 (2)
Suicide	1 (2)

mortality from a CV cause: female sex (HR 2.59, 95% CI 1.14–5.91), history of CVD (HR 4.05, 95% CI 1.20–13.66), and the presence of subcutaneous tophi (HR 3.13, 95% CI 1.38–7.10; Supplementary Table 2 and Supplementary Table 3, available with the online version of this article).

In the reduced Cox proportional hazards model, these factors were independently associated with increased risk of mortality from a non-CV cause: older age (70–80 yrs: HR 9.21, 95% CI 2.03–41.71), Māori or Pacific ethnicity (HR 4.24, 95% CI 1.42–12.72), loop diuretic use (HR 3.98, 95% CI 1.51–10.41), and the presence of subcutaneous tophi (HR 3.48, 95% CI 1.25–9.63; Supplementary Table 4 and Supplementary Table 5, available with the online version of this article).

DISCUSSION

Our prospective observational study has shown that people with gout for less than 10 years have a 2-fold increased risk of death over an average of 5 years of observation compared with the general population. The presence of tophi at baseline is an important risk factor for death from all causes and is independently associated with both CV and non-CV causes of death. The presence of tophi at baseline was associated with an almost 3-fold increased risk of death from all causes.

In the absence of urate-lowering therapy, tophi typically develop more than a decade after the initial presentation of gout and are thought to signify poorly controlled disease[8]. The cohort had a short disease duration (mean disease duration 5 yrs), and clinically apparent tophi were present in 17% of participants at the baseline visit. We have previously reported that early development of tophi in this cohort is associated with reduced kidney function[12]. It is possible that development of tophi early in the course of disease reflects other comorbid conditions, such as kidney disease, that are true risk factors for mortality. Importantly, there was no independent association of serum creatinine and risk of death in the Cox proportional hazards model, suggesting that the association between tophi and mortality is not primarily because of the effects of comorbid kidney disease. It is also possible that the low-grade chronic inflammation induced by deposits of urate crystals within tophi contributed to accelerated vascular disease[13]. Although this may explain the association with vascular disease, it does not explain the association between tophi and non-CV causes of death.

Our results can be compared with the study by Perez-Ruiz, *et al*[7] that described risk factors for mortality in patients with gout with a wide range of disease duration who attended a specialist rheumatology clinic. In that study, the SMR was

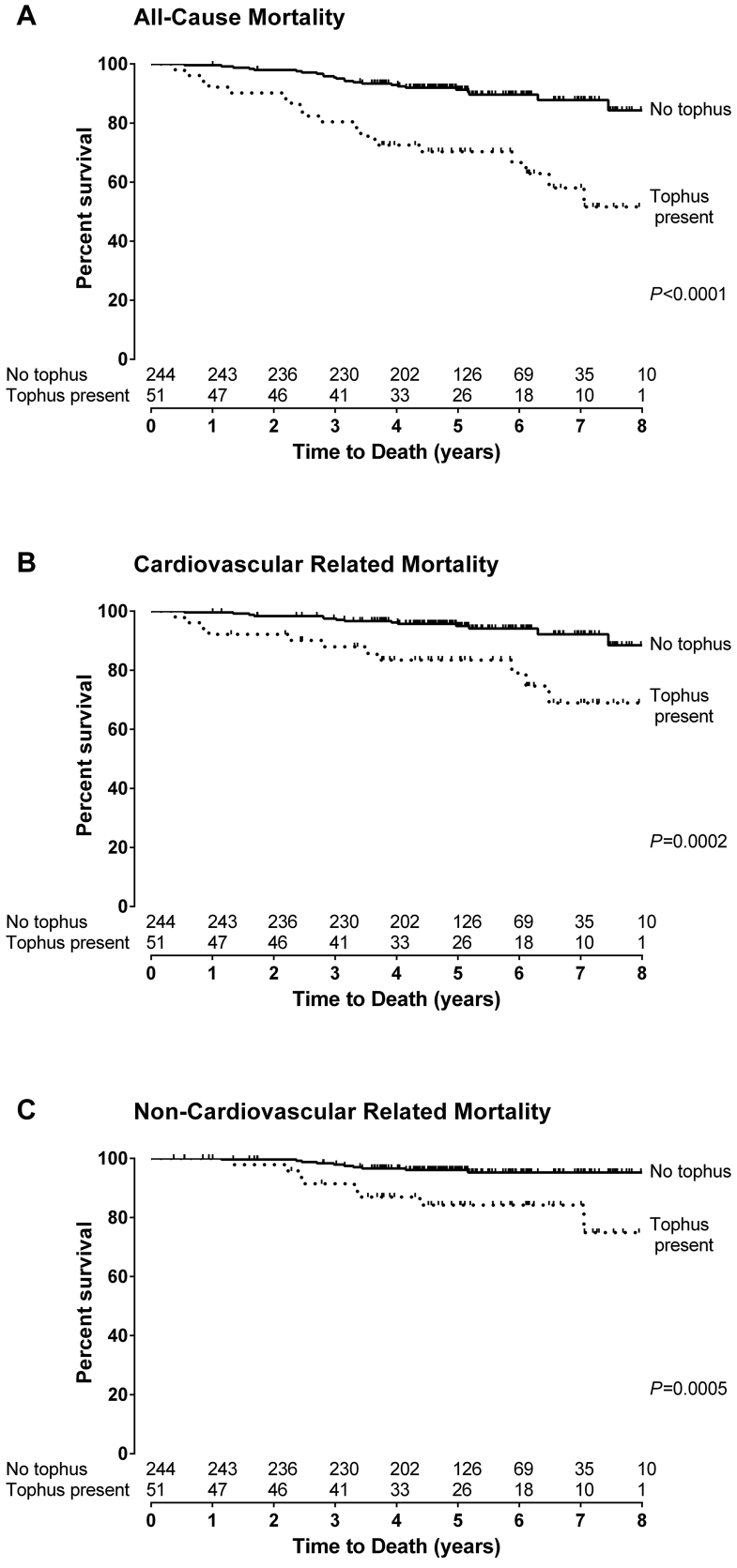

Figure 1. Effect of tophi on mortality. Kaplan–Meier survival plots comparing participants with tophi present at baseline with participants with no tophi at baseline for (A) all-cause mortality, (B) cardiovascular-related mortality, and (C) noncardiovascular-related mortality. Time axis in years. Unadjusted p values are shown.

Table 3. Multivariate-adjusted proportional hazards for baseline predictors of all-cause mortality. Cox proportional hazards reduced model includes all variables with p < 0.15 in the fully saturated model.

Variables	HR (95% CI)	p
Age, yrs		
< 50	Reference	—
50–60	1.15 (0.27–4.85)	0.85
60–70	2.08 (0.70–6.24)	0.19
70–80	9.96 (3.30–30.03)	< 0.001
80–91	9.39 (2.68–32.89)	0.0005
Māori or Pacific ethnicity	2.48 (1.17–5.29)	0.018
Loop diuretic use	3.99 (2.15–7.40)	< 0.001
Presence of subcutaneous tophi	2.85 (1.49–5.44)	0.0015
Serum creatinine, per 10 μmol/l change	1.04 (1.00–1.07)	0.03

also high at 2.37 (95% CI 1.82–3.03). Consistent with our results in patients with gout early in their disease course, Perez-Ruiz, *et al* also identified the presence of subcutaneous tophi as an important independent risk factor for mortality, with an adjusted HR of 2.05. In the Perez-Ruiz, *et al* study, baseline serum urate concentration was also identified as an independent risk factor for all-cause mortality, noting that the mean baseline serum urate concentration was 0.52 mmol/l (range 0.41–0.91 mmol/l), and the association between serum urate and mortality was only significant for very high levels of serum urate (0.52 mmol/l and above). In our present study, we did not observe a relationship between baseline serum urate and mortality. It is possible that the differences in the study population, particularly the lower baseline serum urate concentrations in our participants, explain the differences in the serum urate results between studies.

Some studies have reported that allopurinol use has beneficial effects on CVD and mortality[14,15,16]. The use of colchicine in gout populations has also been reported to reduce the risk of MI, stroke, and transient ischemic attack, as well as all-cause mortality[17,18]. The published literature is conflicting, with some recent studies reporting no difference in CV events or survival following exposure to these medications[19,20,21]. In our study, baseline use of allopurinol was not independently associated with a reduced risk of mortality. Further, colchicine use was higher among the group of subjects who died, but was not independently associated with mortality. We cannot exclude immortal time bias influencing these findings[22]; this study did not recruit participants at the time of their first presentation with disease, and those enrolled in our study had to survive up to the baseline date (mean duration of 5 yrs). Therefore, the origin of followup is not from the diagnosis of gout, but from some time after initial diagnosis. Prescription patterns may change during the course of disease, and urate-lowering therapy such as allopurinol is not usually prescribed early in the course of disease.

Female participants were overrepresented in the group of patients who died. Consistent with other studies of gout[23], women were older and had more HTN and loop diuretic use. Sex was included in all models, and after adjusting for age, comorbidities, loop diuretic use, and presence of tophi, sex was not a significant predictor of all-cause mortality. Given the relatively low numbers of female participants, our study does not have sufficient power to separately analyze risk factors for death in men and women.

Our study has the following limitations. Because of the method of tophus ascertainment, the presence of intraarticular tophi cannot be excluded and we may have missed subclinical tophi in some participants. However, the methods for assessing tophi were uniform throughout our study. The cohort used for our study is unique in that the disease duration was less than 10 years. Because of this, the results reported here may not be applicable to all people with gout. Further, 26% of the cohort identified as Māori or Pacific Islander, and Māori or Pacific ethnicity was independently associated with death from all-causes and non-CV causes. Gout prevalence is higher and disease severity worse in Māori and Pacific people[24]; thus, these results may not be internationally generalizable. A further potential limitation is the relatively low number of events over the followup period (43 deaths). We have endeavored not to overfit these data. The choice of variables to model was based on expert opinion and independence sought through consistency and parsimony using a variety of model-building techniques. Although there were a limited number of events in each of the final models, the effect estimates were consistent when age was modeled with a single degree of freedom as with the more informative decade of life, and the number of variables in each model was small enough to be unlikely to result in biased or inflated regression coefficients[25]. Although the inclusion criteria were broad, the convenience sampling scheme may have led to patients with more severe health problems volunteering to participate in a research study, potentially overestimating the standardized mortality rate compared with an analysis of people with gout in the general population. However, the baseline clinical characteristics of participants (including frequency of comorbidities) were similar to large population studies and clinical trials of people with gout[3,26]. Further, this convenience sampling scheme should not have influenced the analysis of variables associated with mortality in the recruited group.

The strengths of our study are the standardized and detailed clinical assessment at baseline, and the systematic collection of followup data. Electronic hospital records were used to confirm the date of death for all participants and cause of death information was collected from electronic records (primary and secondary care) and/or official death certificates. Therefore, there was excellent coverage of the cohort for death status and cause-of-death information. A further strength of our study is the recruitment strategy that included community advertising and primary care, ensuring that our sample has similarities with the real-world gout population.

Our study has shown that older age, diuretic use, and the presence of subcutaneous tophi are independent risk factors for all-cause mortality in people with gout early in their disease course (< 10 yrs of disease duration). The presence of subcutaneous tophi predicts mortality, both from CV and non-CV causes.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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