Mortality in American Veterans with the HLA-B27 Gene

Jessica A. Walsh, Xi Zhou, Daniel O. Clegg, Chiachen Teng, Grant W. Cannon, and Brian Sauer

ABSTRACT. ***Objective.*** To compare survival in American veterans with and without the HLA-B27 (B27) gene.

Methods. Mortality was evaluated in a national cohort of veterans with clinically available B27 test results between October 1, 1999, and December 31, 2011. The primary outcome was the mortality difference between B27-positive and B27-negative veterans, adjusted for age, sex, race, and diagnoses codes for diseases that may have influenced both B27 testing and mortality, including psoriasis, inflammatory bowel disease, spondyloarthritis (SpA), and other types of inflammatory arthritis. The secondary outcomes were the adjusted mortality HR for B27+ and B27– veterans, in subgroups with and without SpA.

Results. Among veterans with available B27 test results, 27,652 (84.7%) were B27– and 4978 (15.3%) were B27+. The mean followup time was 4.6 years. Mortality was higher in the B27+ group than in the B27– group (HR 1.15, 95% CI 1.03–1.27). Mortality was also higher in the B27+ subgroups with SpA (HR 1.35, 95% CI 1.06–1.72) and without SpA (HR 1.11, 95% CI 0.99–1.24), but the difference was significant only in the subgroup with SpA.

Conclusion. B27 positivity was associated with an increased mortality rate in a cohort of veterans clinically selected for B27 testing, after adjustment for SpA. In the subgroup with SpA, the mortality rate was associated with B27 positivity, and in the subgroup without SpA, there was a nonsignificant association between B27+ and mortality. (First Release Feb 15 2015; J Rheumatol 2015;42:638–44; doi:10.3899/ jrheum.140675)

Key Indexing Terms:
MORTALITY SPONDYLOARTHRITIS EPIDEMIOLOGY

HLA genes produce molecules that help the immune system identify unhealthy cells. HLA-B27 (B27) is a subclass of HLA genes that is carried by 6%–8% of Americans[1,2]. B27 is strongly associated with spondyloarthritis (SpA) and has been reported in 60%-95% of individuals with SpA[3]. SpA occurs in 1.3% of North Americans and is characterized by inflammation at multiple sites including the spine, peripheral joints, intestine, eyes, and entheses[2]. Despite the strong association between SpA and B27, SpA occurs in only 7% of B27+ individuals[4].

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SpA has been associated with premature mortality in some studies[5,6,7]. Nevertheless, little is known about the relationship between B27 and mortality in the general population. Recently published data from the 2009 US National Health and Nutrition Examination Survey (NHANES) revealed a lower prevalence of B27 in randomly selected people older than 50, compared to younger people (7.3% vs 3.6%, OR 0.4, CI 0.3–0.8)[1]. These data suggested that B27 positivity may be associated with an increased mortality risk. The NHANES data were limited by a small number of B27+ participants (n = 124), and the potential contribution of SpA to mortality was unknown. The purpose of our study was to better characterize the relationship between the B27 positivity and mortality by comparing mortality in B27+ and B27– individuals in a large population of veterans who were clinically selected for B27 testing.

MATERIALS AND METHODS

Design, setting, and data sources. We did an observational historical cohort study of American veterans enrolled in the Veterans Health Administration (VHA). Data were collected from veterans as part of routine clinical care and standard VHA administrative procedures. To be included in this database study, veterans needed to be tested for B27 within the VHA system between October 1, 1999, and December 31, 2011. Veterans were excluded for missing birth or death dates and unavailable or uninterpretable B27 test results. Veterans fulfilling inclusion and exclusion criteria were followed from the date of their first B27 test (cohort entry) until their date of death or the end of the study (December 31, 2011).

Data were obtained from the VHA Corporate Data Warehouse (CDW) and Vital Status File (VSF) through the Veterans Affairs (VA) Informatics and Computing Infrastructure. The CDW is a national repository of data

from the VHA medical record system and other VHA clinical and administrative systems. B27 tests were identified using the CDW Laboratory and Chemistry package. Variables indicating diseases were obtained from the CDW outpatient diagnosis table, and demographic data were obtained from the CDW patient table. Pharmacy data were obtained from the outpatient pharmacy package, inpatient pharmacy package, Barcode Medication Administration data, and Healthcare Common Procedure Coding System. The patient Integration Control Number (ICN) was used to link patients across VHA stations. The VHA VSF was used to determine date of death. Multiple data sources contribute to the VSF, including the Beneficiary Identification Records Locator Subsystem death file, VA Medicare VSF, and the Social Security Administration Death Master File. Cause of death data were not available.

Variables. The outcome was mortality and the primary independent variable was B27 positivity. Demographic variables associated with mortality differences were included as adjustment variables, including age, sex, and race. Clinical variables that may have influenced B27 testing and are potential risk factors for mortality were also included for statistical adjustment. These variables were diagnostic codes for systemic inflammatory diseases that occurred prior to the B27 testing, and included diseases associated with SpA [psoriasis and inflammatory bowel disease (IBD)], and diseases that may mimic SpA [rheumatoid arthritis (RA), connective tissue disease, vasculitis, crystal arthritis][5,6,7,8,9].

Veterans with SpA were identified with International Classification of Diseases, 9th ed (ICD-9) codes that originated from a rheumatology encounter. This method of identifying SpA was selected because ICD-9 codes from a VA rheumatology center have been reported to have excellent sensitivity and specificity[10]. ICD-9 codes for diseases associated with SpA and for diseases that mimic SpA did not require a rheumatology encounter.

For the purpose of better characterizing the study population, we described common comorbid conditions that were not suspected to lead to B27 testing and occurred within 1 year prior to the first B27 test. The Healthcare Cost and Utilization Project Clinical Classification Software (CCS) was used to categorize comorbidities according to ICD-9 codes. The single-level CCS software collapses over 14,000 diagnosis codes and 3900 procedure codes into 285 clinically meaningful categories[11]. To simplify the presentation of data, we further collapsed the CCS categories into broader categories of common diseases, including cancer, cardiovascular disease, diabetes, hypertension, infection, injury/trauma, kidney disease, liver disease, mood or anxiety disorders, and pulmonary disease. The CCS classification descriptions and codes for each comorbidity category are summarized in Appendix 1. Pharmacy data included lifetime exposure to biologic and nonbiologic disease-modifying antirheumatic drugs (DMARD). Biologic DMARD included etanercept, infliximab, adalimumab, golimumab, certolizumab, and ustekinumab. Nonbiologic DMARD included methotrexate, sulfalsalazine, leflunomide, hydroxychloroquine, mycofenolate mofetil, and azathioprine.

Statistics. Survival was assessed using Cox proportional hazard analyses. The time scale for the time-to-event comparisons between the B27+ and B27– groups was time between B27 testing (cohort entry) and death or the end of the study period on December 31, 2011. This time scale was selected rather than an age-based time scale, because events or conditions preceding B27 testing may have influenced both mortality and the likelihood of B27 testing, and these events could not be comprehensively identified or accounted for in the survival comparisons. The association between B27 status and mortality was examined separately for the entire B27 tested cohort and for the subgroups with and without SpA.

Covariates in the Cox proportional hazard models included age at B27 testing (age at study entry), sex, race, psoriasis, IBD, and inflammatory arthritis (RA, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, polymyositis, other connective tissue disease, cryoglobulinemia, polyarteritis nodosa, granulomatosis with polyangiitis, polymyalgia rheumatica, Takayasu arteritis, gout, pseudogout, and SpA). Exposure to biologic and nonbiologic DMARD and comorbidities not suspected to trigger B27 testing (cancer, cardiovascular disease, diabetes, hypertension, infection, injury/trauma, kidney disease, liver disease, mood or anxiety disorders, and pulmonary disease) were also added as covariates to the models to explore the potential effect of these variables on the mortality estimates. Conditions that were suspected to influence B27 testing but not mortality were not included in the adjustment models, because these conditions were not expected to influence of the mortality hazard estimates.

Nonparametric, fitted survival curves were used to illustrate the mortality differences from the adjusted Cox proportional hazard analysis in the B27+ and B27– groups[12]. We tested the proportionality assumption for all independent variables with log (-log) survival curves and Schoenfeld residuals. The resulting figures demonstrated that we did not violate proportionality, except for IBD, which was significant at the 0.05 level.

RESULTS

Population. We identified 17,763,277 veterans with unique patient ICN from the CDW patient table (Figure 1). B27 testing was ordered between October 1, 1999, and December 31, 2011, in 36,980 veterans (0.2%). Forty-one veterans (0.01%) were excluded for missing birth or death dates, and 4309 (11.7%) were excluded for unavailable or uninterpretable B27 test results. Common entries classified as unavailable or uninterpretable results included "needs redraw," "cancelled," and "pending." The study population consisted of 32,630 veterans with interpretable B27 test results, of whom 4978 were B27+ (15.3%).

The mean age was 52.1 for B27– and 52.5 for B27+ veterans (Table 1). Male sex was identified in 88.4% of B27– veterans and 92.9% of B27+ veterans. White race was reported by 69.9% of B27– veterans and 76.8% of B27+ veterans. The mean followup time between B27 testing and the end of the study was 4.6 and 4.8 years in B27– and B27+ veterans, respectively. Biologic DMARD exposure was recorded in 6.1% and 21.6% of B27– and B27+ veterans, respectively. Nonbiologic DMARD exposure was recorded in 4.5% and 12.9% of B27– and B27+ veterans, respectively. Several comorbidities that were not suspected to lead to B27 testing were more common in the B27– group than the B27+ group, including diabetes, injury/trauma, lipid disorders, mood or anxiety disorders, and pulmonary disease.

Among diseases suspected to influence both B27 testing and mortality, SpA was more common in the B27+ group than the B27– group (34.8% vs 8.7%, respectively; Table 2). Conversely, other types of inflammatory arthritis (excluding SpA) were less common in the B27+ group than in the B27– group (2.4% vs 11.4%, respectively). Among diseases suspected to influence B27 testing but not mortality, uveitis was more common in the B27+ group, while the remainder of conditions were more common in the B27– group.

Survival analyses. The Cox proportional hazard analysis demonstrated higher mortality for the B27+ veterans than the B27– veterans, after adjustment for age, sex, race, diseases suspected to influence B27 testing and mortality, and SpA (HR 1.15, 95% CI 1.03-1.27; Table 3). Figures 2 and 3 illustrate the adjusted survival curves for all

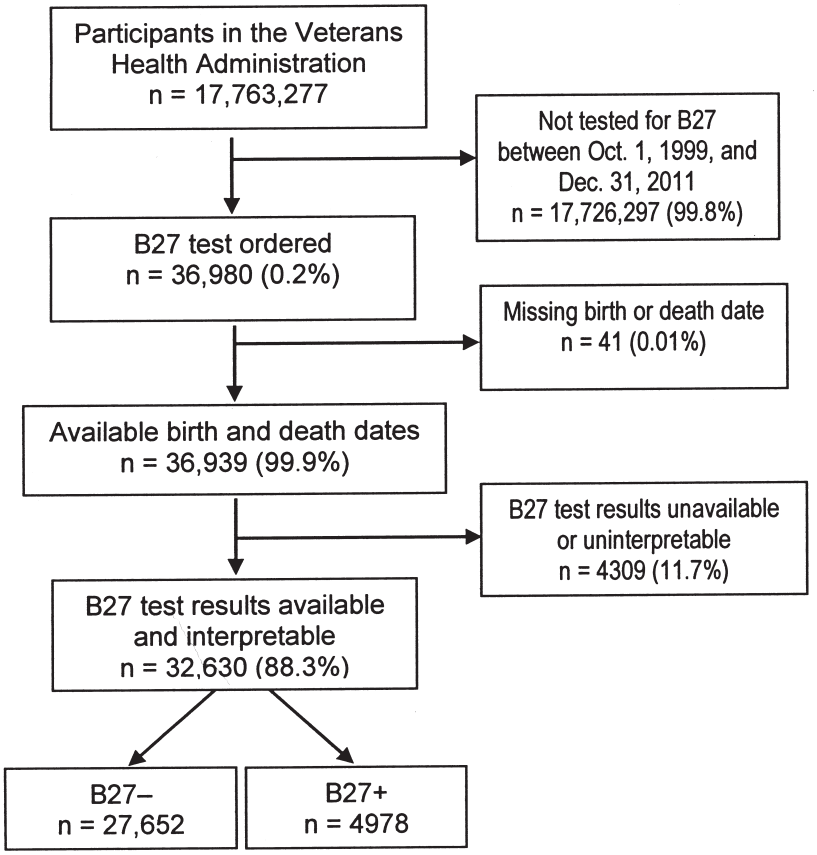

Figure 1. Study population.

B27 tested veterans and for veterans with and without SpA. In the subgroup with SpA, the HR was 1.35 (95% CI 1.06–1.72), after adjustment for demographics and diseases suspected to influence B27 testing and mortality. In the subgroup without SpA, the adjusted HR was 1.11 (95% CI 0.99–1.24; Table 3). When biologic and nonbiologic therapy were added as covariates to the model, the HR was 1.15 (95% CI 1.04–1.28) for the entire B27 tested cohort, 1.39 (95% CI 1.09-1.77) for the SpA subgroup, and 1.11 (95% CI 0.99–1.25) for the subgroup without SpA (data not shown). When comorbidities not suspected to lead to B27 testing were added to the model, the HR was 1.15 (95% CI 1.04–1.28) for the entire B27-tested cohort, 1.32 (95% CI 1.03–1.69) for the SpA subgroup, and 1.12 (95% CI 0.99–1.26) for the non-SpA subgroup (data not shown).

DISCUSSION

The purpose of our study was to better describe the relationship between the B27 gene and mortality. The possibility of a link between B27 and increased mortality risk was unexpectedly raised by an NHANES study that reported a lower prevalence of B27 in older Americans than younger Americans. The primary outcome from our study was consistent with the NHANES observation, with higher mortality in B27+ veterans than B27– veterans, in a population clinically selected for B27 testing. This mortality difference was not explained by age, sex, race, SpA, or other evaluated systemic inflammatory diseases suspected to have influenced both B27 testing and mortality.

The subgroup analyses in veterans with and without SpA similarly demonstrated higher mortality in B27+ veterans than B27– veterans, but the adjusted difference was only statistically significant in the SpA subgroup, during the mean 4.6-year followup interval. In the entire B27 tested population, we adjusted for SpA to minimize the chance that the mortality difference was driven by SpA. It is unclear whether the lack of a significant difference in the subset without SpA occurred because of a reduction in power with the smaller sample size or whether the mortality difference is smaller in people without SpA compared to people with SpA.

Exposure to biologic and nonbiologic DMARD therapies had minimal influence on the mortality estimates. However, these data should be interpreted cautiously, because we were unable to account for disease severity. For example, therapies may have positively influenced mortality, but this positive influence may have been countered by a negative influence of more severe disease in veterans exposed to therapies, compared to untreated veterans. Alternatively, DMARD therapies may have had little effect on survival, regardless of disease severity.

Table 1. Baseline characteristics.

	B27–, n = 27,652, ± SD or (%)	B27+, n = 4978 ± SD or (%)	p
Age at B27 testing (study entry), yrs	52.1 ± 14.5	52.5 ± 14.3	0.157
Male	24,447 (88.4)	4624 (92.9)	< 0.001
Race			
White	19,331 (69.9)	3824 (76.8)	< 0.001
Black	5189 (18.8)	437 (8.8)	< 0.001
Asian	134 (0.5)	35 (0.7)	< 0.001
Other*	509 (1.8)	102 (2.1)	< 0.001
Unknown/declined to answer	2489 (9.0)	580 (11.7)	< 0.001
Years of followup after B27 testing (mean)	4.6 ± 3.4	4.8 ± 3.4	< 0.001
Biologic DMARD exposure**	1677 (6.1)	1076 (21.6)	< 0.001
Nonbiologic DMARD exposure†	1245 (4.5)	642 (12.9)	< 0.001
Comorbidities not suspected to trigger B27 testing‡			
Cancer	1727 (6.3)	281 (5.6)	0.104
Cardiovascular disease	3627 (13.1)	653 (13.1)	0.998
Diabetes	5357 (19.4)	877 (17.6)	0.004
Hypertension	11,903 (43.1)	2090 (42.0)	0.164
Infection	8298 (30.0)	1482 (29.8)	0.736
Injury/trauma	3958 (14.3)	556 (11.7)	< 0.001
Kidney disease	1242 (4.5)	217 (4.4)	0.677
Lipid disorders	10,800 (39.1)	1835 (36.9)	0.003
Liver disease	2302 (8.3)	387 (7.8)	0.193
Mood or anxiety disorder	10,439 (37.8)	1569 (31.5)	< 0.001
Pulmonary disease	7639 (27.6)	1266 (25.4)	0.001

*Other races included American Indian or Alaska Native, Native Hawaiian, or Other Pacific Islander. **Biologic DMARD included etanercept, infliximab, adalimumab, golimumab, certolizumab, and ustekinumab. †Nonbiologic DMARD included methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, mycophenolate mofetil, and azathioprine. ‡Category descriptions and Clinical Classification Software codes are included in Appendix 1. DMARD: disease-modifying antirheumatic drug.

Table 2. Diseases that may have led clinicians to order B27 tests.

	ICD-9	B27– (%), n = 27,652	B27+ (%), n = 4987	p
Diseases previously associated with increased mortality				
SpA	720.0, 696.1, 720.2, 720.8, 720.9, 099.3, 711.1x, 713.1 with 555.x, 713.1 with 556.x	2414 (8.7)	1732 (34.8)	< 0.001
Psoriasis	696.1	1387 (5.0)	230 (4.6)	0.237
Inflammatory bowel disease	556.x, 555.x	702 (2.5)	118 (2.4)	0.485
Other inflammatory arthritis, excluding SpA*	714.x, 710.x 273.2, 446.0, 446.4, 446.5, 446.7, 725, 274.x, 712.x	3161 (11.4)	118 (2.4)	< 0.001
Diseases not previously associated with increased mortality				
Uveitis	364.3, 364.0	2157 (7.8)	666 (13.4)	< 0.001
Osteoarthritis	715.x	10,371 (37.5)	1607 (32.3)	< 0.001
Back disorders other than SpA	721.x, 722.x, 723.x, 724.x, 847.x	15,413 (55.7)	2507 (50.4)	< 0.001
Fibromyalgia, generalized pain, chronic pain	780.96, 729.1, 338.4	3073 (11.1)	429 (8.6)	< 0.001
Other joint disorders/unspecified arthropathies	716.x, 719.x	15,478 (56.0)	2370 (47.6)	< 0.001
Other peripheral musculoskeletal disorders (synovium, tendon, bursa, muscle, ligament, fascia, other soft tissue)	726.x, 727.x, 728.x, 729.x	11,305 (40.9)	1603 (32.2)	< 0.001

*Other inflammatory arthritis includes rheumatoid arthritis, systemic lupus erythematous, systemic sclerosis, dermatomyositis, polymyositis, cryoglobulinemia, granulomatosis with polyangiitis, polyarteritis nodosa, giant cell arteritis, polymyalgia rheumatic, gout, and pseudogout. ICD-9: International Classification of Diseases, 9th ed; SpA: spondyloarthritis.

The mortality estimates were minimally affected by the unequal distribution, between the B27+ and B27– groups, of comorbidities not suspected to influence B27 testing. There were methodological concerns with adjusting for these comorbidities because they could have been in the causal pathway for death (i.e., B27 status may have influenced the risk of death related to specific comorbidities, and adjusting for these comorbidities could have reduced our ability to

Table 3. Mortality in veterans clinically selected for B27 testing.

	Person-time (person-yrs after B27 test)	Dead (%)	Unadjusted		Adjusted for Demographics*		Adjusted for Demographics* and ID**		Adjusted for Demographics*, ID**, and SpA	
			HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
B27–, entire cohort	127,532	2260 (8.2)	Ref.		Ref.		Ref.		Ref.	
B27+, entire cohort	24,004	465 (9.3)	1.10 (0.99–1.22)	0.058	1.10 (0.99–1.21)	0.075	1.11 (1.00–1.22)	0.05	1.15 (1.03–1.27)	0.010
B27– with SpA	11,264	157 (6.5)	Ref.		Ref.		Ref.		—	
B27+ with SpA	7988	138 (8.0)	1.24 (0.99–1.56)	0.066	1.32 (1.04–1.66)	0.021	1.35 (1.06–1.72)	0.014	—	—
B27– without SpA	116,268	2103 (8.4)	Ref.		Ref.		Ref.		—	
B27+ without SpA	16,016	327 (10.1)	1.14 (1.02–1.28)	0.026	1.11 (0.98–1.24)	0.090	1.11 (0.99–1.24)	0.089	—	—

*Demographics included age at B27 testing, sex, and race. **ID: inflammatory diseases including psoriasis, inflammatory bowel disease, and other inflammatory arthritis (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, polymyositis, other connective tissue disease, cryoglobulinemia, polyarteritis nodosa, granulomatosis with polyangiitis, polymyalgia rheumatica, Takayasu arteritis, gout, and pseudogout). SpA: spondyloarthritis.

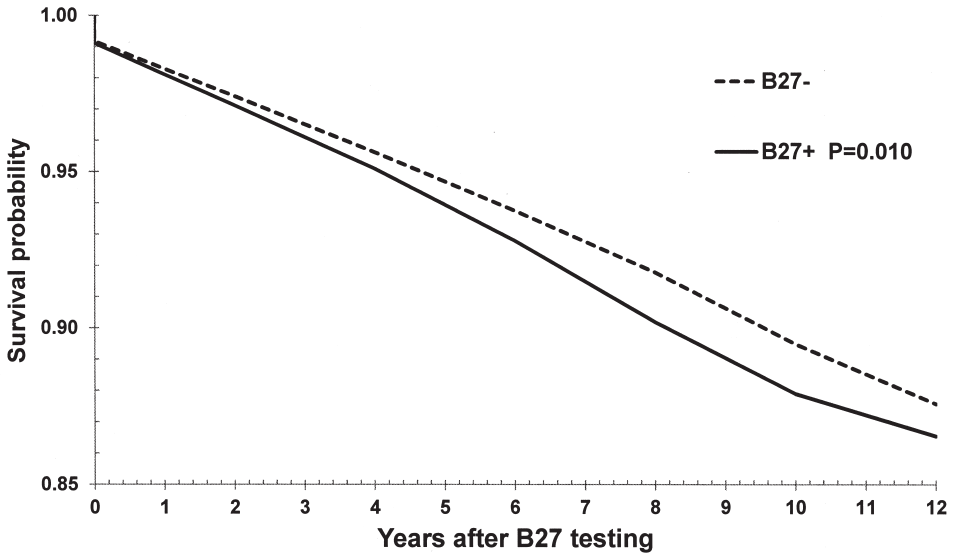

Figure 2. Adjusted survival curves for B27 tested veterans.

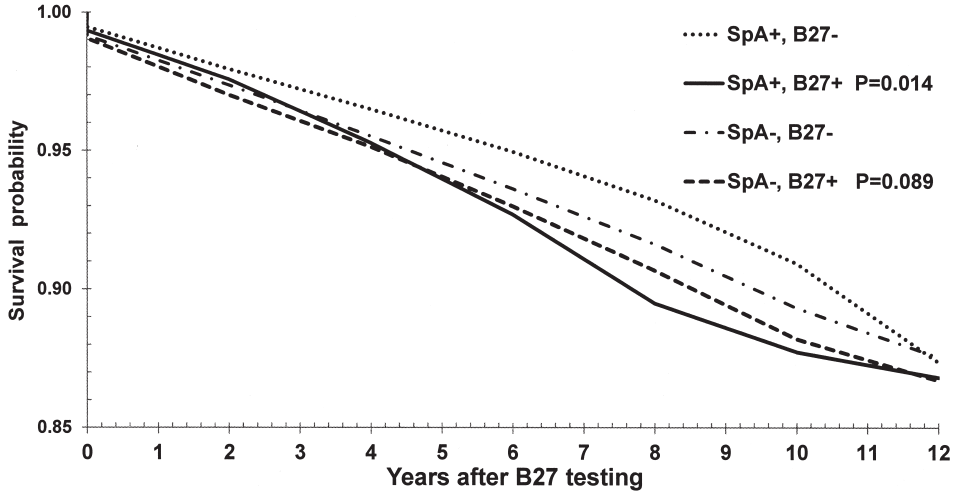

Figure 3. Adjusted survival curves for veterans with and without spondyloarthritis (SpA).

detect a mortality difference driven by the comorbidities). However, mortality estimates before and after adjustment for these comorbidities were very similar, demonstrating that the unequal distribution of comorbidities did not have a meaningful effect on the mortality estimates.

The mortality difference in this cohort may have been conservative. Veterans who died at younger ages had fewer opportunities for B27 testing and inclusion in this study than veterans surviving to older ages. If B27+ veterans from the general population died at younger ages than B27– veterans, a lower proportion of B27+ deaths would have been detected in this study than B27– deaths.

The clinical significance of the observed mortality difference between B27+ and B27– veterans remains to be determined. We want to know the effect of B27 positivity on the entire population of veterans; however, we were only able to estimate the effect of B27 positivity in the subpopulation with clinical indications for B27 testing. The study population was not representative of the general population in that B27 tested veterans (both B27+ and B27–) were likely sicker than the general population, because sicker veterans with more frequent medical encounters had more opportunities for B27 testing than healthier veterans with fewer medical encounters. Thus, the generalizability of these data is restricted to veterans with clinically available B27 test results.

Our study was also limited by the short study duration. The 4.6-year mean duration of followup was brief for an outcome as infrequent as death. A longer study duration may have enabled more confident conclusions about mortality differences, particularly in the subgroup without SpA.

Our study is novel in demonstrating that B27 positivity was associated with reduced survival in veterans clinically selected for B27 testing, after adjustment for SpA. Additional research in randomly selected individuals is required to confirm an association between the B27 gene and premature mortality and to determine whether mortality risk differs between subsets of people with and without SpA. Identifying causes of death and diseases that contribute to mortality risk in B27+ populations may also provide mechanistic insights into B27 functions and lead to interventions that improve survival for B27+ individuals.

REFERENCES

1. Reveille JD, Hirsch R, Dillon CF, Carroll MD, Weisman MH. The prevalence of HLA-B27 in the US: data from the US National Health and Nutrition Examination Survey, 2009. Arthritis Rheum 2012;64:1407-11.
2. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008;58:15-25.
3. Khan MA. Epidemiology of HLA-B27 and arthritis. Clin Rheumatol 1996;15 Suppl 1:10-2.
4. Colbert RA, DeLay ML, Klenk EI, Layh-Schmitt G. From HLA-B27 to spondyloarthritis: a journey through the ER. Immunol Rev 2010;233:181-202.
5. Mok CC, Kwok CL, Ho LY, Chan PT, Yip SF. Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. Arthritis Rheum 2011;63:1182-9.
6. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. Ann Rheum Dis 2011;70:1921-5.
7. Prati C, Claudepierre P, Pham T, Wendling D. Mortality in spondylarthritis. Joint Bone Spine 2011;78:466-70.
8. Toledano E, Candelas G, Rosales Z, Martínez Prada C, León L, Abásolo L, et al. A meta-analysis of mortality in rheumatic diseases. Reumatol Clin 2012;8:334-41.
9. Lottmann K, Chen X, Schädlich PK. Association between gout and all-cause as well as cardiovascular mortality: a systematic review. Curr Rheumatol Rep 2012;14:195-203.
10. Singh JA, Holmgren AR, Krug H, Noorbaloochi S. Accuracy of the diagnoses of spondylarthritides in Veterans Affairs Medical Center databases. Arthritis Rheum 2007;57:648-55.
11. Agency for Healthcare Research and Quality, Rockville, MD: Healthcare Cost and Utilization Project (HCUP). [Internet. Accessed Dec 5, 2014]. Available from: www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp
12. Kleinbaum DG, Klein M. Survival analysis on the computer. In: Gail M, Krickeberg K, Samet J, Tsiatis A, Wong W, eds. Statistics for biology and health: survival analysis, a self-learning text. New York: Springer; 2011:588-90.

APPENDIX 1. Clinical Classification Software (CCS) descriptions and codes for each comorbidity category.

Comorbidity Category	Clinical Classification Software descriptions and codes
Cancer	"Cancer of bone and connective tissue" (CCS 21), "Cancer of brain and nervous system" (CCS 35), "Cancer of other GI organs; peritoneum" (CCS 18), "Cancer of stomach" (CCS 13), "Cancer of pancreas" (CCS 17), "Cancer of uterus" (CCS 25), "Cancer; other respiratory and intrathoracic" (CCS 20), "Cancer of ovary" (CCS 27), "Cancer of esophagus" (CCS 12), "Cancer of liver and intrahepatic bile duct" (CCS 16), "Cancer of other female genital organs" (CCS 28), "Cancer of other urinary organs" (CCS 34), "Cancer of other male genital organs" (CCS 31)
Cardiovascular	"Coronary atherosclerosis and other heart disease" (CCS 101), "Congestive heart failure; nonhypertensive" (CCS 108), "Acute cerebrovascular disease" (CCS 109), "Acute myocardial infarction" (CCS 100)
Diabetes	"Diabetes mellitus without complication" (CCS 49), "Diabetes mellitus with complications" (CCS 50)
Hypertension	"Essential hypertension" (CCS 98)
Infection	"Other upper respiratory infections" (CCS 126), "Mycoses" (CCS 4), "Skin and subcutaneous tissue infections" (CCS 197), "Viral infection" (CCS 7), "Sexually transmitted infections (not HIV or hepatitis)" (CCS 9), "Other infections; including parasitic" (CCS 8), "Pneumonia (except that caused by tuberculosis or sexually transmitted disease)" (CCS 122), "Infective arthritis and osteomyelitis (except that caused by tuberculosis or sexually transmitted disease)" (CCS 201), "HIV infection" (CCS 5), "Bacterial infection; unspecified site" (CCS 3), "Intestinal infection" (CCS 135), "Influenza" (CCS 123), "Acute and chronic tonsillitis" (CCS 124), "Tuberculosis" (CCS 1), "Meningitis (except that caused by tuberculosis or sexually transmitted disease)" (CCS 76), "Peritonitis and intestinal abscess" (CCS 148), "Gangrene" (CCS 248), "Encephalitis (except that caused by tuberculosis or sexually transmitted disease)" (CCS 77), "Other CNS infection and poliomyelitis" (CCS 78)
Injury/trauma	"E Codes: Motor vehicle traffic (MVT)" (CCS 2607), "E Codes: Pedestrian; not MVT" (CCS 2609), "Other injuries and conditions due to external causes" (CCS 244), "Joint disorders and dislocations; trauma-related" (CCS 225), "Intracranial injury" (CCS 233), "Other fractures" (CCS 231), "Fracture of lower limb" (CCS 230), "Fracture of upper limb" (CCS 229), "Suicide and intentional self-inflicted injury" (CCS 662), "Crushing injury or internal injury" (CCS 234), "Burns" (CCS 240), "Spinal cord injury" (CCS 227), "Skull and face fractures" (CCS 228), "Fracture of neck of femur (hip)" (CCS 226), "E Codes: Fire/burn" (CCS 2604), "E Codes: Suffocation" (CCS 2615), "E Codes: Firearm" (CCS 2605)
Kidney disease	"Chronic renal failure" (CCS 158), "Other diseases of kidney and ureters" (CCS 161), "Acute and unspecified renal failure" (CCS 157), "Nephritis; nephrosis; renal sclerosis" (CCS 156)
Liver disease	"Other liver diseases" (CCS 151), "Hepatitis" (CCS 6), "Biliary tract disease" (CCS 149)
Lipid disorders	"Disorders of lipid metabolism" (CCS 53)
Mood or anxiety disorder	"Mood disorders" (CCS 657), "Anxiety disorders" (CCS 651)
Pulmonary disease	"Other lower respiratory disease" (CCS 133), "Other upper respiratory disease" (CCS 134), "Chronic obstructive pulmonary disease and bronchiectasis" (CCS 127), "Asthma" (CCS 128)

GI: gastrointestinal; CNS: central nervous system.