Clinical Infectious Diseases

MAJOR ARTICLE

The Role of *FER* rs4957796 in the Risk of Developing and Dying from a Bloodstream Infection: A 23-Year Follow-up of the Population-based Nord-Trøndelag Health Study

Tormod Rogne,[1,2,3] Jan Kristian Damås,[1,4,5] Helene Marie Flatby,[1,3] Bjørn Olav Åsvold,[1,6,7] Andrew Thomas DeWan,[1,2,a] and Erik Solligård,[1,3,a]

[1]Gemini Center for Sepsis Research, Department of Circulation and Medical Imaging, NTNU, Norwegian University of Science and Technology, Trondheim, Norway, [2]Department of Chronic Disease Epidemiology, Yale University School of Public Health, New Haven, Connecticut, USA, [3]Clinic of Anaesthesia and Intensive Care, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [4]Centre of Molecular Inflammation Research, Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway, [5]Department of Infectious Diseases, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway, [6]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway, and [7]Department of Endocrinology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

Background. Bloodstream infection and sepsis are major causes of health loss worldwide, and it is important to identify patients at risk of developing and dying from these conditions. The single-nucleotide polymorphism most strongly associated with sepsis mortality is *FER* rs4957796. However, it is not known how this variant is associated with bloodstream infection incidence and mortality.

Methods. We used prospective data from 1995–2017 from the population-based HUNT Study. Genotypes were ascertained from blood samples, and additional genotypes were imputed. Information on bloodstream infection and diagnosis codes at hospitalization were collected through record linkage with all hospitals in the area.

Results. A total of 69 294 patients were included. Patients with the rs4957796 CC genotype had an increased risk of developing a bloodstream infection compared with the TT genotype (hazard ratio [HR], 1.20; 95% confidence interval [CI], 1.00–1.43). However, there was a protective additive effect of the C allele in terms of mortality in the total study population (HR, 0.77; 95% CI, .64–.92 per copy of the C allele) and among bloodstream infection patients (odds ratio, 0.70; 95% CI, .58–.85 per copy of the C allele). The results did not appear to be affected by selection bias.

Conclusions. The rs4957796 CC genotype was associated with an increased risk of contracting a bloodstream infection but with a reduced risk of dying from one. The latter finding is in line with studies of sepsis case fatality, while the former expands our understanding of the immunoregulatory role of this polymorphism.

Keywords. FER tyrosine kinase; genetic association studies; prospective studies; bacteremia; sepsis.

Bacteremia associated with infection, or bloodstream infection (BSI), is an important cause of morbidity and mortality globally [1, 2] and is closely linked to organ dysfunction and sepsis [3]. It is therefore key to identify patients at risk of developing BSI or sepsis. Several lifestyle factors and comorbidities have been associated with risk of BSI, such as smoking habits and adiposity [4]. While some studies have evaluated the genetic susceptibility to BSI or sepsis, much is still unknown about how specific mutations affect these conditions [5–7].

The single-nucleotide polymorphism (SNP) most robustly associated with BSI or sepsis is rs4957796 in the *FER* gene [5]. This gene encodes for a widely expressed cytoplasmic tyrosine kinase that acts downstream of cell-surface receptors and is involved in many pathways relevant to infection, such as neutrophil chemotaxis and endothelial permeability [8]. A genome-wide association study of patients hospitalized with sepsis due to pneumonia found that patients with the C allele (minor allele) of this SNP had a markedly reduced risk of dying within 28 days [5]. Similarly, a study found that patients with severe acute respiratory distress syndrome had improved survival rates if they carried the C allele [9]. Another study, however, found no association between rs4957796 and case fatality among sepsis patients, but this may be due to lower statistical power [10]. To date, no studies have determined whether rs4957796 is associated with risk of developing an infectious disease, such as BSI, or its association with BSI mortality.

Our aims in this study were to determine whether rs4957796 in the *FER* gene is associated with the risk of contracting or dying from a BSI in the general population

Received 12 February 2020; editorial decision 20 May 2020; accepted 12 June 2020; published online June 17, 2020.

[a]A. T. D. and E. S. contributed equally to this work.

Correspondence: T. Rogne, Department of Circulation and Medical Imaging, NTNU, Prinsesse Kristinas gate 3, Akutten og Hjerte-lunge-senteret, 3. etg, Trondheim 7491, Norway (tormod.rogne@ntnu.no). ORCiD: https://orcid.org/0000-0002-9581-7384.

Clinical Infectious Diseases® 2021;73(2):e297–303

DOI: 10.1093/cid/ciaa786

and with case fatality among BSI patients and to determine whether subtypes of BSI were differentially distributed by the rs4957796 genotype. To explore these questions, we evaluated a genotyped cohort of approximately 70 000 patients representative of the adult Norwegian population followed between 1995 and 2017.

METHODS

We used data from the Nord-Trøndelag Health Study (HUNT Study), which is a series of cross-sectional surveys conducted in Nord-Trøndelag County, Norway. Roughly 130 000 inhabitants live in the county, and the demographics are largely comparable to the adult Norwegian population, except for a slightly lower average education and income and the lack of major cities in the county [11]. The present study is based on patients aged ≥20 years from the HUNT2 and HUNT3 surveys conducted in 1995–1997 and 2006–2008, respectively.

Background characteristics such as sex, age, lifestyle factors, and self-reported history of diseases were collected in the HUNT surveys. Body mass index was calculated as measured weight in kilograms divided by squared measured height in meters. Information on date of emigration out of Nord-Trøndelag and date of death was obtained from the Norwegian population registry; registered date was rounded to the 15th of the actual month.

There are 2 local hospitals in the county (Levanger and Namsos hospitals), and St. Olavs Hospital in Trondheim serves as a tertiary referral center. By use of the personal identification number that all Norwegian citizens have, information on positive blood cultures and diagnosis at discharge were collected through record linkage with these hospitals for the period between 1995 (from 1999 in Namsos Hospital) through December 2017 (through February 2017 for diagnosis codes).

The presence of a positive blood culture of pathogenic bacteria (excluding bacteria associated with contamination, such as coagulase-negative *Staphylococcus*) was defined as a BSI [12]. BSI mortality was defined as death within 30 days of BSI. Diseases were classified according to the *International Classification of Diseases, Ninth Revision* and *Tenth Revision* (Supplementary Table 1).

Three Illumina HumanCoreExome arrays were used to genotype the study participants (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1, and UM HUNT Biobank v1.0). Samples with a call rate <99%, with large chromosomal copy number variants, contamination >2.5% as estimated with BAF Regress [13], with genotypic and phenotypic sex discordance, and not of European ancestry were excluded. Genetic variants out of Hardy-Weinberg equilibrium (P value < .0001) or with a call rate <99% were excluded. Imputation was done using Minimac3 with 2201 whole-genome reference sequences from HUNT and HRC v1.1.

Of the 78 973 patients participating in HUNT2 or HUNT3, genotypic information was available for 69 423 (87.9%). We excluded patients who had a BSI between 1995 and 2017 but before participating in the HUNT study (n = 73) and patients who moved out of the catchment area before study participation (n = 56). This yielded a final study population of 69 294 patients. Note that for the mortality analyses and the secondary analyses (eg, mortality from BSI or incidence of lower respiratory tract infections), the number of patients excluded due to an event occurring before HUNT study participation varied slightly, yielding a different population under study.

Statistical Analyses

The a priori main analyses were to evaluate the association between carrying the minor allele of rs4957796 and risk of contracting or dying from a BSI in the whole study population and the 30-day case fatality among those hospitalized with BSI. In secondary analyses, we examined different strains of infecting bacteria and organ-specific sites of infection.

In time-to-event analyses, we used Cox proportional hazards regression, censoring patients when they moved out of the county or died from something other than BSI. As date of death was rounded to the 15th of the current month, time-to-event analyses were deemed inappropriate in analyses restricted to patients with BSI, and we conducted logistic regression instead. Analyses of ordered outcomes were evaluated using ordered logistic regression. Ancestry-informative principal components were estimated with the TRACE software package, with 938 individuals from the Human Genome Diversity Project serving as the reference [14, 15]. All regression analyses were adjusted for age at first HUNT participation, sex, and the first 5 ancestry-informative principal components. Hard calls were created as dosages rounded to the nearest integer and were used when considering the effect of carrying the TC or the CC genotype compared with the TT genotype (wild type). Dosages were used in analyses of the additive effect of an extra C allele.

In analyses of BSI incidence, we considered the first event. Some patients had multiple hospitalizations with BSI. To make sure that we included the relevant hospitalization in the mortality analyses, we evaluated the last BSI event in these analyses.

When considering the case fatality among patients with BSI by genotype, selection bias may be introduced at the point of restriction to patients with BSI [16]. We tried to mitigate this bias in sensitivity analyses by weighting patients from the total study population with the inverse probability of developing BSI [17]. The weights were based on rs4957796 genotype, first 5 ancestry-informative principal components, HUNT2 or HUNT3 survey participation, and the first HUNT baseline characteristics of age, sex, body mass index, smoking habits, alcohol consumption, and self-reported health (asthma, myocardial infarction, stroke, diabetes, blood pressure medication use, fractured hip, cancer, chronic diseases, and quality of health). The weights

were trimmed at the 99th percentiles. The inverse-probability weighted analyses relied on nonmissing information of the covariates used to construct the weights. Thus, these analyses were compared with unweighted analyses restricted to the patients included in the inverse-probability weighted analyses.

Stata/MP version 16.0 (Colleges Station, TX), R version 3.4.1 (packages ipw, survey, Hmisc), and PLINK version 1.9 were used [18]. The level of statistical significance was set at $P < .05$.

Ethical Approval

The Regional Committee for Medical Research, Health Region IV, in Norway (REK) approved the HUNT study, and this project is regulated in conjunction with the Norwegian Social Science Data Services.

RESULTS

The 69 294 study patients included in the main analyses were followed for a median of 20.8 years, with a total time at risk of 1 140 218 years. The *FER* rs4957796 was accurately imputed ($R^2 = .97$) and had a minor allele frequency of 19.6%. The genotype distribution was 44 818 (64.7%), 21 749 (31.4%), and 2727 (3.9%) for TT, TC and CC, respectively, which is in Hardy-Weinberg equilibrium ($P = .159$).

Baseline characteristics, based on the first HUNT survey of participation, are provided in Table 1, stratified by rs4957796 genotype. Compared with the TT genotype, those with the TC genotype smoked slightly more cigarettes at baseline, but this was not the case for the CC genotype, and there was no clear

Table 1. Baseline Characteristics by rs4957796 Genotype

Characteristic	All (N = 69 294)	TT (n = 44 818)	TC (n = 21 749)	CC (n = 2 727)	*P* Value		
					TC vs TT	CC vs TT	Additive
HUNT2	56 542 (81.6)	36 607 (81.7)	17 715 (81.5)	2220 (81.4)	.519	.465	.332
HUNT3 (and not HUNT2)	12 752 (18.4)	8211 (18.3)	4034 (18.5)	507 (18.6)			
Time followed (years)	20.8 (10.4–21.6)	20.8 (10.4–21.6)	20.8 (10.3–21.6)	20.8 (10.3–21.6)	.192	.638	.207
Age (years)	46.4 (34.4–60.5)	46.3 (34.5–60.3)	46.4 (34.3–60.6)	46.6 (35.1–61.4)	.967	.128	.377
Male sex	32 575 (47.0)	21 035 (46.9)	10 250 (47.1)	1290 (47.3)	.630	.703	.656
Smoking habits							
Never smoked	29 483 (44.6)	19 192 (44.8)	9104 (43.9)	1187 (45.3)	.013	.452	.188
<5 pack years	9837 (14.9)	6346 (14.8)	3115 (15.0)	376 (14.4)			
5–15 pack years	13 854 (20.9)	8945 (20.9)	4366 (21.0)	543 (20.7)			
≥15 pack years	13 001 (19.7)	8324 (19.5)	4615 (20.0)	512 (19.6)			
Alcohol intake							
<1 glass/2 weeks	22 088 (34.3)	14 365 (34.5)	6854 (34.0)	869 (34.0)	.138	.026	.013
1–5 glasses/2 weeks	26 748 (41.6)	17 306 (41.6)	8419 (41.8)	1023 (40.0)			
6–10 glasses/2 weeks	10 465 (16.3)	6750 (16.2)	3273 (16.2)	442 (17.3)			
11–15 glasses/2 weeks	2935 (4.6)	1860 (4.5)	939 (4.7)	136 (5.3)			
≥16 glasses/2 weeks	2103 (3.27)	1337 (3.2)	678 (3.4)	88 (3.4)			
Physical activity							
None	4387 (7.2)	2839 (7.2)	1371 (7.1)	177 (7.3)	.606	.277	.753
Slight	18 003 (29.4)	11 640 (29.4)	5667 (29.4)	696 (28.7)			
Moderate	22 759 (37.1)	14 662 (37.0)	7204 (37.4)	893 (36.8)			
High	16 160 (26.4)	10 489 (26.5)	5009 (26.0)	662 (27.3)			
Current health							
Poor	1159 (1.7)	747 (1.7)	369 (1.7)	43 (1.6)	.725	.138	.608
Not so good	16 185 (23.6)	10 434 (23.5)	5137 (23.9)	614 (22.7)			
Good	39 624 (57.8)	25 689 (57.9)	12 346 (57.4)	1589 (58.8)			
Very good	11 631 (17.0)	7499 (16.9)	3674 (17.1)	458 (16.9)			
Body mass index (kg/m^2)	25.9 (23.5–28.7)	25.9 (23.5–28.6)	25.8 (23.5–28.7)	25.9 (23.6–28.7)	.561	.433	.492
Type 1 or type 2 diabetes	2123 (3.1)	1388 (3.1)	649 (3.0)	86 (3.2)	.312	.890	.426
Blood pressure medication	8974 (13.0)	5834 (13.1)	2766 (12.8)	374 (13.8)	.139	.549	.418
Myocardial infarction	1922 (2.8)	1238 (2.8)	607 (2.8)	77 (2.8)	.843	.804	.704
Stroke	1230 (1.8)	808 (1.8)	368 (1.7)	54 (2.0)	.206	.690	.509
Asthma	6514 (9.4)	4179 (9.4)	2092 (9.7)	243 (9.0)	.213	.492	.587
Fractured hip	1033 (1.6)	657 (1.5)	330 (1.6)	46 (1.8)	.704	.429	.467
Cancer	2390 (3.6)	1578 (3.6)	720 (3.4)	92 (3.5)	.130	.571	.119
Chronic diseases	23 313 (34.4)	15 056 (34.4)	7346 (34.5)	911 (34.2)	.873	.405	.686

Abbreviation: HUNT, Nord-Trøndelag Health Study.

Baseline characteristics are based on the first HUNT survey of participation. Data are presented as n (%) for dichotomous characteristics and median (25th percentile–75th percentile) for continuous characteristics. *P* values are from logistic and ordered logistic regressions for dichotomous and ordinal characteristics (including rounded continuous characteristics), respectively. The additive effect of 1 additional C allele (using dosages) is tested in the right-most column. All statistical tests have adjusted for the 5 top principal components, age at first HUNT participation and sex.

sign of an additive effect of 1 additional C allele. Alcohol consumption was to a small extent positively associated with the C allele, but the baseline characteristics were otherwise comparable between the 3 genotype groups.

In the follow-up period, there were 2698 cases of BSI, of which 444 (16.5%) resulted in death within 30 days (Table 2). Compared with the wild type, those with the CC genotype had an increased risk of developing a BSI (Figure 1), a gram-negative BSI in particular (Supplementary Figures 1 and 2). Genotype was not clearly related to any specific infecting bacteria species. Participants with the CC genotype had a reduced risk of being hospitalized with lower respiratory tract infections (Supplementary Figure 3), but there was otherwise no association between genotype and organ-specific sources of infection (Supplementary Table 2).

In the total study population, the C allele was associated with a reduced risk of mortality from BSI, a gram-positive BSI in particular (Table 2, Figure 2). The CC genotype was associated with reduced mortality from lower respiratory tract infections (Supplementary Table 2 and Supplementary Figure 4). All-cause mortality was not affected by rs4957796 genotype (Supplementary Table 2).

Next, we determined whether genotype was associated with characteristics of BSI hospitalization (Table 3). The distribution of infecting bacteria and organ-specific origin of infection was comparable between the genotype groups. Those with the CC genotype were less likely to be diagnosed with sepsis and severe sepsis compared with the TT genotype. Finally, the TC and CC genotypes, compared with the TT genotype, were associated with a reduced risk of death within 30 days (Figure 3).

To limit the risk of selection bias explaining the protective effect of the C allele, we conducted a set of sensitivity analyses. First, when we restricted the study population to those who developed a BSI, we found that the baseline characteristics were comparable between the genotype groups (Supplementary Table 3). Next, we evaluated the characteristics and outcome of BSI infection among BSI patients using inverse-probability weighting (Supplementary Table 4). In brief, we observed the same findings as in the main analyses, albeit with less statistical power (eg, odds ratio, 0.72; 95% confidence interval, .55–.95) for death within 30 days per additional C allele).

Because of the small imbalance in alcohol consumption between genotype groups at baseline, we conducted a sensitivity analysis where we adjusted for alcohol consumption (in categories as defined in Table 1), in addition to age, sex, and 5 principal components, in analyses of BSI incidence and BSI mortality in the total population and among BSI patients. Effect estimates in these analyses were only marginally changed compared with the original analyses but with wider confidence intervals, in large part due to fewer patients under study (data not shown).

DISCUSSION

In the first prospective, population-based cohort study to evaluate the effect of *FER* rs4957796 on infection, we found that patients with the CC genotype had an increased risk of contracting a BSI, in general, and with gram-negative infections in particular. However, both in the total study population and among patients hospitalized with a BSI, the C allele was associated with a reduced 30-day mortality after BSI.

Table 2. Time-to-Event Analysis of Incidence and Mortality of Bloodstream Infection in the General Population by rs4957796 Genotype

	Number of Patients	Time at Risk (years)	Number of Events	Incidence Rate per 100 000	TC		CC		Additive	
					HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Incidence of BSI										
Any	69 294	1 140 218	2 698	236.6	0.99 (.91–1.08)	.829	1.20 (1.00–1.43)	.050	1.03 (.97–1.10)	.347
Gram-negative	69 294	1 140 218	1 537	134.8	0.95 (.85–1.06)	.380	1.28 (1.02–1.61)	.034	1.02 (.94–1.12)	.602
Gram-positive	69 294	1 140 218	1 161	101.8	1.04 (.92–1.18)	.497	1.08 (.81–1.44)	.589	1.04 (.94–1.16)	.403
Streptococcus pneumoniae	69 294	1 140 218	285	25.0	0.80 (.61–1.04)	.102	1.32 (.79–2.20)	.281	0.95 (.77–1.17)	.641
Staphylococcus aureus	69 294	1 140 218	323	28.3	1.24 (.99–1.56)	.062	0.65 (.32–1.32)	.237	1.07 (.88–1.29)	.504
Enterococcus faecalis	69 294	1 140 218	106	9.3	0.91 (.60–1.40)	.679	1.10 (.44–2.73)	.833	0.97 (.69–1.37)	.876
Escherichia coli	69 294	1 140 218	775	68.0	0.93 (.80–1.09)	.394	1.27 (.92–1.75)	.147	1.01 (.89–1.14)	.903
Mortality from BSI in total population										
Any	69 372	1 154 745	444	38.5	0.77 (.62–.95)	.014	0.63 (.36–1.10)	.107	0.77 (.64–.92)	.004
Gram-negative	69 372	1 154 745	217	18.8	0.76 (.56–1.03)	.073	0.81 (.40–1.64)	.555	0.80 (.62–1.04)	.090
Gram-positive	69 372	1 154 745	225	19.5	0.75 (.56–1.01)	.060	0.47 (.19–1.15)	.098	0.72 (.55–.93)	.012

Abbreviation: BSI, bloodstream infection; CI, confidence interval; HR, hazard ratio.

First event and last event are used for incidence and mortality, respectively. Mortality defined as death within 30 days of BSI. All analyses are Cox proportional hazards analyses adjusting for age at first HUNT participation, sex, and first 5 ancestry-informative principal components. The analyses compare genotype group to TT or the effect of each additional C allele (using dosages).

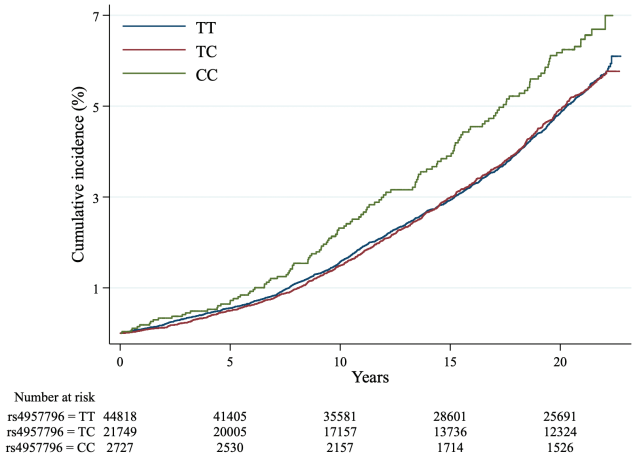

Figure 1. Bloodstream infection (BSI) incidence by rs4957796 genotype. Cumulative incidence of first BSI in the total study population.

Our observation of a protective effect of the rs4957796 C allele on mortality among patients with BSI adds to the previous findings of its protective effect among patients with sepsis due to pneumonia [5] and its protective effect among severe acute respiratory distress syndrome patients [9].

An important extension to the previous work is that our study is the first to determine whether rs4957796 is associated with the risk of developing an infectious disease in a population sample. We found that patients with the CC genotype had an increased risk of contracting BSI. Despite this, in the general population, the presence of the C allele was protective in terms of BSI mortality. Thus, the protective effect of the C allele among BSI patients appears to outweigh the increased risk of contracting BSI.

The observed protective effect of the C allele among patients with BSI, sepsis [5], and severe acute respiratory distress syndrome [9] could be due to selection bias. Given our observation that patients with the CC genotype had an increased risk of developing BSI, one would suspect that those who developed BSI for reasons other than the CC genotype had an accumulation of other risk factors (eg, smoking habits and chronic diseases). If these other risk factors among patients with the TT genotype were more strongly associated with mortality than the CC genotype, the CC genotype would erroneously appear to be protective. However, we found no evidence of an unequal distribution of baseline characteristics by genotype among those who developed BSI. Furthermore, in inverse-probability weighted analyses of mortality among BSI patients, which accounts for selection bias [17], we observed only a slight attenuation of the effect estimates compared with the main analyses. Thus, we argue that the observed protective effect of the rs4957796 C allele in terms of BSI mortality, and probably sepsis mortality and severe acute respiratory distress syndrome mortality, is not due to selection bias.

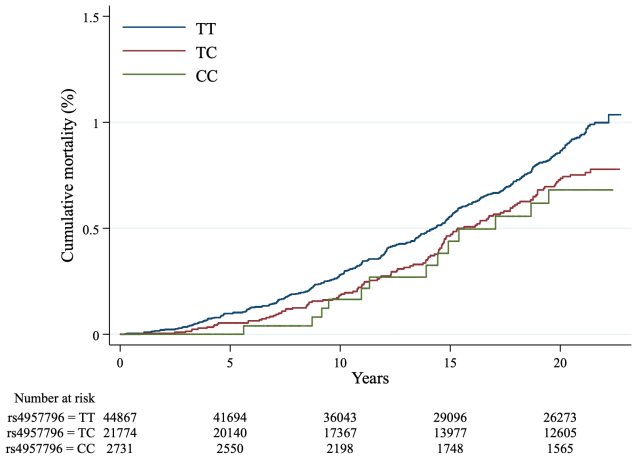

Figure 2. Bloodstream infection (BSI) mortality in the general population by rs4957796 genotype. Cumulative mortality of last BSI in the total study population.

At baseline, there was a slightly increased use of alcohol for each additional C allele of rs4957796. This link is not observed in other cohorts [19] and may be due to chance or pleiotropic effects with characteristics associated with alcohol consumption (eg, chronic diseases). Sensitivity analyses where alcohol consumption was added as a covariate yielded no substantial differences from the primary analyses.

As *FER* is both ubiquitously expressed and involved in multiple pathways, it is challenging to tease out the gene's role in systemic infectious diseases. Our observation that patients with the CC genotype had an increased risk of contracting BSI but reduced risk of dying from it could both be explained by an attenuated immune response. Impaired bacteria clearance would allow for an increased susceptibility to BSI, while the survival chances among BSI patients would be improved due to a reduced likelihood of an overwhelming immune response with subsequent organ dysfunction and death. In support of this, pathogen stimulation has been demonstrated to lead to reduced tyrosine kinase activity and antiinflammatory response in immune cells [20]. Also, in the case of *FER*, the C allele of rs4957796 is associated with an even more pronounced reduction in *FER* expression in monocytes after exposure to Pam_3CSK_4 (a synthetic gram-positive and gram-negative lipopeptide) [21, 22]. Toll-like receptors 1 and 2 are the target receptors of Pam_3CSK_4, which may suggest that more focus should be paid to these Toll-like receptors as potential therapeutic targets in sepsis [23]. However, this hypothesis has to be tested in experimental studies.

Given the relatively strong association between rs4957796 and mortality in our and other cohorts of patients with severe infectious diseases [5, 9] and the high minor allele frequency, we argue that this SNP should be evaluated for use in clinical decision-making. While information on genotype is generally unavailable at present, this is likely to change in the near future, and there are numerous ongoing initiatives, on many million patients, that work on integrating genetics in

Table 3. Type of Infection Among Patients Hospitalized With Bloodstream Infection

	Number of Events (n = 2 693)	TT (n = 1 733)	TC (n = 830)			CC (n = 130)			Additive	
		n (%)	n (%)	OR (95% CI)	*P* Value	n (%)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Type of infecting bacteria										
Gram-negative	1 541 (57.2)	996 (57.5)	464 (55.9)	0.94 (.80–1.12)	.491	81 (62.3)	1.22 (.84–1.76)	.300	1.01 (.88–1.15)	.913
Gram-positive	1 145 (42.5)	733 (42.3)	363 (43.7)	1.06 (.89–1.25)	.529	49 (37.7)	0.83 (.57–1.20)	.325	0.99 (.87–1.14)	.921
Streptococcus pneumoniae	278 (10.3)	185 (10.7)	78 (9.4)	0.87 (.66–1.15)	.314	15 (11.5)	1.12 (.64–1.96)	.690	0.96 (.77–1.20)	.721
Staphylococcus aureus	330 (12.3)	201 (11.6)	119 (14.3)	1.26 (.99–1.61)	.061	10 (7.7)	0.63 (.33–1.23)	.177	1.05 (.86–1.28)	.649
Enterococcus faecalis	110 (4.1)	72 (4.2)	34 (4.1)	0.98 (.64–1.49)	.923	4 (3.1)	0.72 (.26–2.00)	.526	0.94 (.66–1.32)	.703
Escherichia coli	751 (27.9)	487 (28.1)	226 (27.2)	0.96 (.80–1.16)	.685	38 (29.2)	1.06 (.71–1.57)	.776	0.99 (.85–1.15)	.898
Origin of infection										
Lower respiratory tract	480 (17.8)	314 (18.1)	144 (17.4)	0.95 (.76–1.18)	.621	22 (16.9)	0.89 (.55–1.44)	.637	0.96 (.80–1.14)	.610
Urinary tract	585 (21.7)	376 (21.7)	187 (22.5)	1.05 (.86–1.28)	.637	22 (16.9)	0.74 (.46–1.19)	.218	0.97 (.83–1.14)	.743
Gastrointestinal	225 (8.4)	141 (8.1)	67 (8.1)	0.99 (.73–1.34)	.960	17 (13.1)	1.67 (.97–2.86)	.063	1.14 (.91–1.44)	.264
Skin	117 (4.3)	80 (4.6)	30 (3.6)	0.77 (.50–1.19)	.243	7 (5.4)	1.20 (.54–2.66)	.653	0.93 (.66–1.29)	.648
Other	727 (27.0)	463 (26.7)	230 (27.7)	1.05 (.88–1.27)	.573	34 (26.2)	0.99 (.66–1.48)	.944	1.02 (.88–1.18)	.806
Severity of infection										
Sepsis not diagnosed	1 306 (48.5)	837 (48.3)	396 (47.7)	1.02 (.87–1.20)	.797	73 (56.2)	0.70 (.49–.99)	.046	0.94 (.82–1.06)	.307
Sepsis	1 158 (43.0)	747 (43.1)	360 (43.4)			51 (39.2)				
Severe sepsis	229 (8.5)	149 (8.6)	74 (8.9)			6 (4.6)				
Death within 30 days	444 (16.6)	314 (18.2)	117 (14.2)	.73 (.58–.92)	.009	13 (10.1)	0.46 (.25–.83)	.010	0.70 (.58–.85)	<.001

Abbreviation: CI, confidence interval; OR, odds ratio.

Hospitalization for last bloodstream infection is used. All analyses are logistic regression, except for ordered logistic regression for sepsis categories, and are adjusted for age at first Nord-Trøndelag Health Study participation, sex, and the 5 first principal components. The analyses compare genotype group to TT or the effect of each additional C allele (using dosages). Severe sepsis was defined as sepsis with additional diagnosis code of organ dysfunction or the use of diagnosis codes for severe sepsis.

healthcare [24]. Machine learning has already been demonstrated to be of use in predicting survival from sepsis based on clinical information [25], and it is feasible that inclusion of the rs4957796 genotype may further improve prediction. Given that genotype is static from birth, risk prediction may be done years before eventual disease onset. It is important to note that the predictive value may vary between populations, and the minor allele frequency ranges from 29.9% in Amish populations to 12.2% and 6.2% in African and East Asian populations, respectively [26].

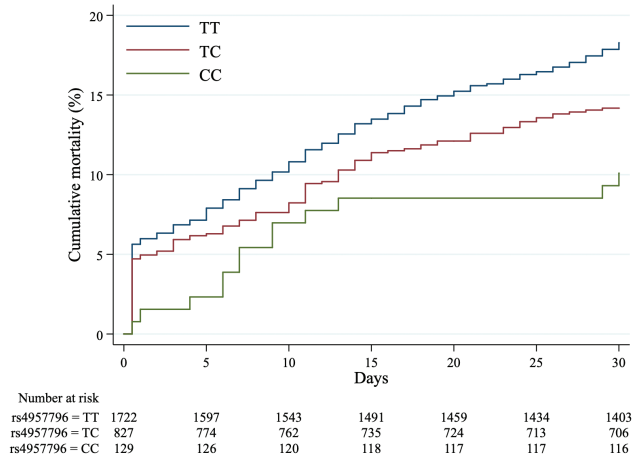

Figure 3. Thirty-day mortality among bloodstream infection (BSI) patients by rs4957796 genotype. Cumulative mortality of last BSI among patients with BSI. Fifteen observations were excluded from analyses as mortality status was unavailable. Note that the accurate date of death was unavailable (see *Statistical Analyses* in the Methods section).

There are several strengths and limitations of this study to be mentioned. A major strength of this study is that we used data from a large, population-based cohort representative of the adult Norwegian population. This population was followed over a 23-year period, which allowed for calculation of incidence rates, along with mortality rates by genotype. However, these findings need to be evaluated in cohorts with different ancestries. Prehospital information was key to reduce the risk of selection bias in mortality analyses among BSI patients. Furthermore, through record-linkage, we had information on all hospitalizations in the county. That said, additional clinical data (eg, laboratory test results and sequential organ failure assessment scores) would allow us to learn more about how genotype affected disease severity and trajectories.

In conclusion, we observed that the rs4957796 CC genotype was associated with an increased BSI incidence but reduced BSI mortality. These results support investigation into the immunological effects of rs4957796 polymorphism and add to previous work that suggests that this SNP may be informative in risk evaluation of critical care patients.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The Nord-Trøndelag Health Study (HUNT Study) is a collaboration of the HUNT Research Centre (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Disclaimer. The funding sources had no role in study design; collection, analysis, and interpretation of data; writing the article; or the decision to submit the article for publication.

Financial support. This work was supported by the Norwegian University of Science and Technology, NTNU, the Research Council of Norway/NORDFORSK (the PERAID-project), and the Liaison Committee for Education, Research and Innovation in Central Norway.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Laupland KB, Pasquill K, Dagasso G, Parfitt EC, Steele L, Schonheyder HC. Population-based risk factors for community-onset bloodstream infections. Eur J Clin Microbiol Infect Dis **2020**; 39:753–8.
2. Holmbom M, Giske CG, Fredrikson M, et al. 14-year survey in a Swedish county reveals a pronounced increase in bloodstream infections (BSI). Comorbidity—An independent risk factor for both BSI and mortality. PLoS One **2016**; 11:1–16.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). JAMA **2016**; 315:801–10.
4. Paulsen J, Askim Å, Mohus RM, et al. Associations of obesity and lifestyle with the risk and mortality of bloodstream infection in a general population: a 15-year follow-up of 64 027 individuals in the HUNT Study. Int J Epidemiol **2017**; 46:1573–81.
5. Rautanen A, Mills TC, Gordon AC, et al; ESICM/ECCRN GenOSept Investigators. Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study. Lancet Respir Med **2015**; 3:53–60.
6. Scherag A, Schöneweck F, Kesselmeier M, et al. Genetic factors of the disease course after sepsis: a genome-wide study for 28-day mortality. EBioMedicine **2016**; 12:239–46.
7. DeLorenze GN, Nelson CL, Scott WK, et al. Polymorphisms in HLA class II genes are associated with susceptibility to *Staphylococcus aureus* infection in a white population. J Infect Dis **2016**; 213:816–23.
8. Dolgachev VA, Goldberg R, Suresh MV, et al. Electroporation-mediated delivery of the *FER* gene in the resolution of trauma-related fatal pneumonia. Gene Ther **2016**; 23:785–96.
9. Hinz J, Büttner B, Kriesel F, et al. The *FER* rs4957796 TT genotype is associated with unfavorable 90-day survival in Caucasian patients with severe ARDS due to pneumonia. Sci Rep **2017**; 7:1–8.
10. Schöneweck F, Kuhnt E, Scholz M, Brunkhorst FM, Scherag A. Common genomic variation in the *FER* gene: useful to stratify patients with sepsis due to pneumonia? Intensive Care Med **2015**; 41:1379–81.
11. Krokstad S, Langhammer A, Hveem K, et al. Cohort profile: the HUNT Study, Norway. Int J Epidemiol **2013**; 42:968–77.
12. Pien BC, Sundaram P, Raoof N, et al. The clinical and prognostic importance of positive blood cultures in adults. Am J Med **2010**; 123:819–28.
13. Jun G, Flickinger M, Hetrick KN, et al. Detecting and estimating contamination of human DNA samples in sequencing and array-based genotype data. Am J Hum Genet **2012**; 91:839–48.
14. Wang C, Zhan X, Bragg-Gresham J, et al; FUSION Study. Ancestry estimation and control of population stratification for sequence-based association studies. Nat Genet **2014**; 46:409–15.
15. Wang C, Zhan X, Liang L, Abecasis GR, Lin X. Improved ancestry estimation for both genotyping and sequencing data using projection procrustes analysis and genotype imputation. Am J Hum Genet **2015**; 96:926–37.
16. Munafò MR, Tilling K, Taylor AE, Evans DM, Davey Smith G. Collider scope: when selection bias can substantially influence observed associations. Int J Epidemiol **2018**; 47:226–35.
17. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology **2004**;15:615–25.
18. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet **2007**; 81:559–75.
19. Clarke TK, Adams MJ, Davies G, et al. Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). Mol Psychiatry **2017**; 22:1376–84.
20. Gopinathan U, Redalen KR, Trøseid AM, et al. Large-scale reduction of tyrosine kinase activities in human monocytes stimulated in vitro with *N. meningitidis*. PLoS One **2018**; 13:1–23.
21. Quach H, Rotival M, Pothlichet J, et al. Genetic adaptation and Neandertal admixture shaped the immune system of human populations. Cell **2016**;167:643–656.e17.
22. Kerimov N, Hayhurst JD, Manning JR, et al. eQTL catalogue: a compendium of uniformly processed human gene expression and splicing QTLs. bioRxiv **2020**; [preprint].
23. Savva A, Roger T. Targeting Toll-like receptors: promising therapeutic strategies for the management of sepsis-associated pathology and infectious diseases. Front Immunol **2013**; 4:387.
24. Shilo S, Rossman H, Segal E. Axes of a revolution: challenges and promises of big data in healthcare. Nat Med **2020**; 26:29–38.
25. Shimabukuro DW, Barton CW, Feldman MD, Mataraso SJ, Das R. Effect of a machine learning-based severe sepsis prediction algorithm on patient survival and hospital length of stay: a randomised clinical trial. BMJ Open Respir Res **2017**; 4:e000234.
26. Karczewski KJ, Francioli LC, Tiao G, et al; Genome Aggregation Database Consortium. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature **2020**; 581:434–43.