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

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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, 0.64–0.92 per copy of the C allele) and among bloodstream infection patients (odds ratio, 0.70; 95% CI, 0.58–0.85 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...
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...
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 \textit{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 2,727 (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

| Characteristic | All (N = 69,294) | TT (n = 44,818) | TC (n = 21,749) | CC (n = 2,727) | TC vs TT | CC vs TT | Additive |
|---------------|-----------------|-----------------|-----------------|---------------|---------|---------|---------|
| **HUNT2**     | 56,542 (81.6)   | 36,607 (81.7)   | 17,715 (81.5)   | 2,220 (81.4)  | .519    | .465    | .332    |
| **HUNT3 (and not HUNT2)** | 12,752 (18.4) | 8,211 (18.3) | 4,034 (18.5) | 507 (18.6) | .192    | .638    | .207    |
| 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)   | 1,290 (47.3)  | .013    | .452    | .188    |

**Smoking habits**

- Never smoked: 29,483 (44.6%) vs 19,192 (44.8%) vs 9,104 (43.9%) vs 1,187 (45.3%)
- <5 pack years: 9,837 (14.9%) vs 6,346 (14.8%) vs 3,115 (15.0%) vs 376 (14.4%)
- 5–15 pack years: 13,854 (20.9%) vs 8,945 (20.9%) vs 4,366 (21.0%) vs 543 (20.7%)
- ≥15 pack years: 13,001 (19.7%) vs 8,324 (19.5%) vs 4,615 (20.0%) vs 512 (19.6%)

**Alcohol intake**

- <1 glass/2 weeks: 22,088 (34.3%) vs 14,365 (34.5%) vs 6,854 (34.0%) vs 869 (34.0%)
- 1–5 glasses/2 weeks: 26,748 (41.6%) vs 17,306 (41.6%) vs 8,419 (41.8%) vs 1,023 (40.0%)
- 6–10 glasses/2 weeks: 10,465 (16.3%) vs 6,750 (16.2%) vs 3,273 (16.2%) vs 442 (17.3%)
- 11–15 glasses/2 weeks: 2935 (4.6%) vs 1,860 (4.5%) vs 939 (4.7%) vs 136 (5.3%)
- ≥16 glasses/2 weeks: 2,103 (3.27%) vs 1,337 (3.2%) vs 678 (3.4%) vs 88 (3.4%)

**Physical activity**

- None: 4,387 (72) vs 2,839 (72) vs 1,371 (71) vs 177 (73)
- Slight: 18,003 (29.4%) vs 11,640 (29.4%) vs 5,667 (29.4%) vs 696 (28.7%)
- Moderate: 22,759 (37.1%) vs 14,662 (37.0%) vs 7,204 (37.4%) vs 893 (36.8%)
- High: 16,160 (26.4%) vs 10,489 (26.5%) vs 5,009 (26.0%) vs 662 (27.3%)

**Current health**

- Poor: 1,159 (1.7%) vs 747 (1.7%) vs 369 (1.7%) vs 43 (1.6%)
- Not so good: 16,185 (23.6%) vs 10,434 (23.5%) vs 5,137 (23.9%) vs 614 (22.7%)
- Good: 39,624 (57.8%) vs 25,689 (37.0%) vs 12,346 (57.4%) vs 1,589 (58.8%)
- Very good: 11,631 (17.0%) vs 7,499 (16.9%) vs 3,674 (17.1%) vs 458 (16.9%)

- Body mass index (kg/m²): 25.9 (23.5–28.7) vs 25.9 (23.5–28.6) vs 25.9 (23.5–28.7) vs 25.9 (23.5–28.7)
- Type 1 or type 2 diabetes: 2,123 (3.1%) vs 1,388 (3.1%) vs 649 (3.0%) vs 86 (3.2%)
- Blood pressure medication: 8974 (13.0%) vs 5,834 (13.1%) vs 2,766 (12.8%) vs 374 (13.8%)
- Myocardial infarction: 1,922 (2.8%) vs 1,238 (2.8%) vs 607 (2.8%) vs 77 (2.8%)
- Stroke: 1,230 (1.8%) vs 808 (1.8%) vs 368 (1.7%) vs 54 (2.0%)
- Asthma: 6,514 (9.4%) vs 4,179 (9.4%) vs 2,092 (9.7%) vs 243 (9.0%)
- Fractured hip: 1,033 (1.6%) vs 657 (1.5%) vs 330 (1.6%) vs 46 (1.8%)
- Cancer: 2,390 (3.6%) vs 1,578 (3.6%) vs 720 (3.4%) vs 92 (3.5%)
- Chronic diseases: 23,313 (34.4%) vs 15,056 (34.4%) vs 7,346 (34.5%) vs 911 (34.2%)

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. \textit{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

| Incidence of BSI | TC | Additive |
|------------------|------------------|-----------|
|                  | HR (95% CI) | P Value | HR (95% CI) | P Value |
| Any              | 0.99 (.91–1.08) | .829 | 1.20 (.100–1.43) | .050 |
| Gram-negative    | 0.95 (.85–1.06) | .380 | 1.28 (.102–1.61) | .034 |
| Gram-positive    | 1.04 (.92–1.18) | .497 | 1.08 (.81–1.44) | .589 |
| Streptococcus pneumonia | 0.80 (.61–1.04) | .102 | 1.32 (.79–2.20) | .281 |
| Staphylococcus aureus | 1.24 (.99–1.56) | .062 | 0.65 (.32–1.32) | .237 |
| Enterococcus faecalis | 0.91 (.60–1.40) | .679 | 1.10 (.44–2.73) | .833 |
| Escherichia coli | 0.93 (.80–1.09) | .394 | 1.27 (.92–1.75) | .147 |
| Mortality from BSI in total population | 1.01 (.89–1.14) | .903 |

**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).
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.

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 Pam3CSK4 (a synthetic gram-positive and gram-negative lipopeptide) [21, 22]. Toll-like receptors 1 and 2 are the target receptors of Pam3CSK4, 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...
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].

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.

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

| Type of Infection | TT (n = 1,733) | TC (n = 830) | CC (n = 130) | Additive |
|-------------------|--------------|-------------|-------------|---------|
| Number of Events  | n (%)        | n (%)       | n (%)       | OR (95% CI) |
| Number of Events  | n (%)        | n (%)       | n (%)       | OR (95% CI) |
| Number of Events  | n (%)        | n (%)       | n (%)       | OR (95% CI) |
| Number of Events  | n (%)        | n (%)       | n (%)       | OR (95% CI) |

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.

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).
**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**

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