Clinical Microbiology and Infection 27 (2021) 786.e1–786.e7

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Single nucleotide polymorphism (SNP) rs3751143 in *P2RX7* is associated with therapy failure in chronic Q fever while rs7125062 in *MMP1* is associated with fewer complications☆

S.B. Buijs [1, *, †], A.F.M. Jansen [2, †], J.J. Oosterheert [1], T. Schoffelen [2], P.C. Wever [3], A.I.M. Hoepelman [1], E. van de Vosse [4], M. van Deuren [2], C.P. Bleeker-Rovers [2]

[1)] *Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands*
[2)] *Radboud Expertise Center for Q Fever, Radboud Center for Infectious Diseases, Department of Internal Medicine, Division of Infectious Diseases, Radboud University Medical Center, Nijmegen, the Netherlands*
[3)] *Department of Medical Microbiology and Infection Control, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands*
[4)] *Department of Infectious Diseases, Leiden University Medical Center, Leiden, the Netherlands*

ARTICLE INFO

Article history:
Received 10 February 2020
Received in revised form
15 June 2020
Accepted 16 June 2020
Available online 29 June 2020

Editor: S.J. Cutler

Keywords:
Chronic Q fever
Coxiella burnetii
Matrix metalloproteinase
P2RX7
Single nucleotide polymorphism

ABSTRACT

Objectives: Chronic Q fever is a persistent infection with the intracellular bacterium *Coxiella burnetii.* Development of chronic Q fever is associated with single nucleotide polymorphisms (SNPs) in genes encoding for pattern recognition receptors, for phagolysosomal pathway components and for matrix metalloproteinases (MMPs). We evaluated the association of SNPs in these innate-immunity and MMP genes with clinical outcomes.

Methods: SNPs were selected from previous association studies and analysed in a cohort of patients with chronic Q fever. The primary outcome was all-cause mortality; secondary outcomes were therapy failure and chronic Q fever–related complications. Subdistribution hazard ratios (SHR) were calculated.

Results: Nineteen SNPs were analysed in 134 patients with proven and 29 with probable chronic Q fever. In multivariable analysis, none of the selected SNPs was associated with all-cause mortality. However, SNP rs3751143 located in *P2RX7* appeared to be associated with therapy failure (SHR 2.42; 95% confidence interval, 1.16–5.05; p 0.02), which is in line with other reports, showing that a loss of function of the P2X7 receptor leads to inefficient killing of intracellular organisms. In addition, SNP rs7125062 located in *MMP1,* involved in the cleavage of extracellular matrix, was associated with fewer chronic Q fever–related complications such as acute aneurysms (SHR 0.49; 95% confidence interval, 0.29–0.83; p 0.008).

Conclusions: A polymorphism in *P2RX7,* known to lead to loss of function of the receptor and inefficient killing of intracellular organisms, and a polymorphism in *MMP1* were respectively associated with more therapy failures and fewer complications such as acute aneurysms in patients with chronic Q fever.
S.B. Buijs, Clin Microbiol Infect 2021;27:786.e1–786.e7

Introduction

Chronic Q fever, also known as persistent focalized Q fever infection, is an ongoing infection caused by the obligate intracellular bacterium *Coxiella burnetii.* After the initial Q fever infection, the disease progresses to chronic Q fever in 1% to 5% of patients [1]. From 2007 to 2010 the Netherlands was faced with the largest Q fever outbreak ever, with over 4000 confirmed cases and more than 40 000 estimated infections [2,3]. During and after the outbreak, 439 patients were diagnosed with chronic Q fever [4]. Patients with

☆ Presented in part as poster presentation at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), April 2019, Amsterdam, the Netherlands.

* Corresponding author. S. B. Buijs, Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Room F.02.126, PO Box 85500, 3508 GA, Utrecht, the Netherlands.
E-mail address: sb.buijs1@gmail.com (S.B. Buijs).

† The first two authors contributed equally to this article and both should be considered first author.

https://doi.org/10.1016/j.cmi.2020.06.016
1198-743X/

chronic Q fever have an impaired quality of life and a poor prognosis [4,5]. Known risk factors for the development of chronic Q fever, associated with the focus of the infection, are vascular prosthesis, aneurysms, and valvulopathy [6]. Genetic factors associated with the immune response to *C. burnetii* have recently been shown to contribute to the progression to chronic Q fever in individuals with these focalizing risk factors [7].

The immune response to *C. burnetii* is initiated after pattern recognition receptors such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domains (NOD) recognize the bacterium [8]. Through interaction with various adaptor proteins, including MyD88, proinflammatory cytokines are produced and antimicrobial mechanisms are activated. Despite the bacteriolytic properties of the phagolysosome that is being formed as part of the cellular response of macrophages, *C. burnetii* manages to survive and replicate itself in the *Coxiella*-containing vacuole. Proteins involved in this phagolysosomal pathway are Rab5, Rab7 and autophagy proteins, among others [9,10]. Eradication of *C. burnetii* is aided by reactive oxygen species, nitric oxide and innate immune receptor P2X7 [11].

We postulated that genetic variations in the phagolysosomal pathway, microbial killing pathways and autophagy pathway are not only related to the progression to chronic Q fever but also influence the course of the disease and prognosis.

More than 60% of patients with proven chronic Q fever develop one or more chronic Q fever–related complications, most frequently an acute aneurysm [4]. Matrix metalloproteinases (MMP) are able to degrade extracellular matrix proteins; they have been implicated in the formation and expansion of aneurysms [12–18]. Single nucleotide polymorphisms (SNPs) in these genes have been related to the progression to chronic Q fever in infected individuals with focalizing risk factors [19]. Expression of certain MMP genes is upregulated in response to *C. burnetii,* which leads to the release of at least MMP-1 and MMP-9 [19]. Therefore, the occurrence of complications in chronic Q fever patients may be linked to genetic variation in MMP genes.

In this retrospective cohort study involving patients with chronic Q fever, we investigated whether genetic variations in innate immunity and MMP genes play a role in mortality, therapy failure or chronic Q fever–related complications.

Methods

Patients and data collection

We enrolled all patients with proven and probable chronic Q fever [20] known to the Radboud Expertise Center for Q Fever, Nijmegen, the Netherlands, or participating hospitals located in high-incidence areas of the 2007–2010 Dutch Q fever epidemic [19,21]. The diagnosis of proven chronic Q fever was based on the presence of a positive *C. burnetii* PCR on blood or tissue (in the absence of an acute Q fever infection) and/or *C. burnetii* phase I IgG $\geq$1:1024 with a proven focus of infection as shown by imaging techniques [20]. The diagnosis of probable chronic Q fever was based on the presence of a titre of *C. burnetii* phase I IgG antibodies $\geq$1:1024 with a risk factor for persistence of the bacterium, such as aneurysm, heart valve abnormality or immunocompromised state, often in conjunction with symptoms of a chronic infection [20]. Data on patient characteristics and course of the disease were collected from electronically stored patient records and stored in an SPSS database, version 25.0 (IBM, Armonk, NY, USA).

Laboratory testing and SNP analysis

Indirect fluorescent-antibody assay for *C. burnetii* phase I and II IgG was used for serologic testing (Focus Diagnostics, Cypress, CA, USA; or Fuller Diagnostics, Anchorage, AK, USA). PCR was performed for detection of *C. burnetii* DNA in serum or tissue samples (in-house, real-time PCR targeting the repetitive element IS1111).

DNA from patients was isolated from venous blood or epithelial cells from a buccal swab (Isohelix; Cell Projects, Harristsham, UK) using standard methods [22]. SNPs were genotyped with the Sequenom (San Diego, CA, USA) mass spectrometry genotyping platform as described earlier [21]. Five per cent of the samples were duplicated within and across plates to perform quality control. The selection of SNPs was based on previously reported associations with chronic Q fever. All SNPs had a minor allele frequency of >5%.

Definitions

The primary outcome of this study was all-cause mortality. Secondary outcomes were therapy failure and chronic Q fever–related complications. Therapy failure was defined as a chronic Q fever–related complication or chronic Q fever–related death after at least 3 months of therapy and/or a new positive PCR test result after being negative for 3 months during treatment and/or a persistent positive PCR for 6 months during treatment. Cause of death was reviewed by two investigators in all cases (CPB-R and SBB); classification of the relationship between death and chronic Q fever was based on consensus. Definitions for chronic Q fever–related complications and mortality are listed in the online Supplementary Materials.

Statistical analysis

Continuous data were compared by Mann-Whitney *U* test or independent sample *t* test as appropriate. Categorical data were compared by the Fisher exact test or the chi-square test, as appropriate. For regression analysis, a dominant model analysis was used. The genetic variants were chosen on the basis of candidate genes that earlier studies had identified as having an association with chronic Q fever [19,21]. Therefore, correction for multiple testing was not applied.

For all-cause mortality, age, gender, past or current smoking, heart failure, diabetes mellitus, chronic kidney disease, presence of prosthetic material before diagnosis of chronic Q fever, immunocompromised state and selected SNPs were analysed in univariable analysis with Kaplan-Meier estimates and compared by a log-rank test. The threshold for excluding variables in the multivariable Cox proportional hazards model was set at a p value of 0.20.

Covariates for secondary outcomes were selected on the basis of previously identified predictors for these outcomes [23]. For chronic Q fever–related complications, age, presence of prosthetic material before diagnosis of chronic Q fever and PCR positivity were used as covariates in the model. For therapy failure, age and presence of prosthetic material before diagnosis of chronic Q fever were used as covariates. All selected SNPs were analysed with univariable Cox regression analysis; the threshold for excluding SNPs in the Cox proportional hazards model was set at a p value of 0.20.

Subdistribution hazard ratios (SHR) were calculated for all outcomes with a competing risks analysis. The Cox regression models were fitted with the 'survival' and 'cmprsk' packages in RStudio 3.4.1 (https://rstudio.com/). The proportional hazard assumption was verified with both formal tests and graphically by using Schoenfeld residuals. Level of significance was set at a p value of <0.05. Descriptive data were generated by SPSS 25.0 software (IBM, Armonk, NY). Figures were made by RStudio.

Ethical statement

This study was approved by the medical ethics committee of Arnhem-Nijmegen (NL35784.091.11). Written informed consent was obtained from all participants.

Results

Patient characteristics

A total of 163 patients were included, of whom 134 (82%) had a proven chronic Q fever infection (Table 1). Median age was 76 years (interquartile range, 68-81), and most patients were male (82%). In 158 patients (97%), antibiotic therapy was initiated, and treatment regimens consisted of at least doxycycline and hydroxychloroquine in 154 patients (97%). Reasons for withholding therapy were chronic Q fever not recognized by clinician ($n = 3$) and unknown ($n = 2$). Fifty patients (31%) died during the study period; in 20 (12%) of them, the cause of death was definitely or probably related to chronic Q fever. Therapy failure occurred in 64 chronic Q fever patients (41%). In 85 patients, 148 chronic Q fever–related complications were observed.

SNP analysis

Table 2 lists details of the selected SNPs, in which gene they are located, their frequency in the study population, and associations as reported in earlier studies. Results of the univariable analysis of the association between each SNP and the primary and secondary outcomes are depicted in Supplementary Tables S1, S2 and S3.

All-cause mortality

In Kaplan-Meier analysis, only *MMP1* SNP rs1144393 was found to be associated with all-cause mortality (p 0.04, Fig. 1, Supplementary Table S1). However, after correcting for covariates with multivariable analysis, this association did not hold (Table 3).

Table 1
Patient characteristics, comorbidity, disease characteristics, and outcomes

Characteristic	Proven chronic Q fever	Probable chronic Q fever	All patients
N (%)	134 (82)	29 (18)	163 (100)
Age (years), median (IQR)	76 (68-81)	73 (64.5-79.5)	76 (68-81)
Male gender	111 (83)	22 (76)	133 (82)
Focus of chronic Q fever			
Vascular/vascular prosthesis infection	80 (60)	15 (52)	95 (58)
Endocarditis	32 (24)	4 (14)	36 (22)
Endocarditis with vascular/vascular prosthesis infection	20 (15)	1 (3)	21 (13)
Other focus[a]	1 (1)	0	1 (1)
No focus identified	1 (1)	9 (31)	10 (6)
Comorbidity			
diabetes mellitus	18 (13)	6 (21)	24 (15)
past or current smoking	106 (81)	23 (82)	129 (81)
heart failure	10 (8)	4 (14)	14 (9)
chronic kidney disease	24 (18)	3 (10)	27 (17)
Risk factor			
Valvulopathy	13 (10)	10 (35)	23 (14)
Cardiac valve surgery	27 (20)	2 (7)	29 (18)
Vascular prosthesis	50 (37)	11 (38)	61 (37)
Aneurysm	24 (18)	3 (10)	27 (17)
Immunocompromised state	16 (12)	9 (31)	25 (15)
Complications[b]			
Total complications	148	4	152
Acute aneurysm, *n* (% of total complications)[c]	51 (34)	—	51 (34)
Fistula, *n* (% of total complications)	12 (8)	—	12 (8)
Abscess, *n* (% of total complications)	33 (22)	—	33 (22)
Spondylodiscitis/osteomyelitis, *n* (% of total complications)	10 (7)	—	10 (7)
Heart failure, *n* (% of total complications)[d]	25 (17)	2 (50)	27 (18)
Arterial embolic complications, *n* (% of total complications)	7 (5)	2 (50)	9 (6)
Other, *n* (% of total complications)[e]	10 (7)	—	10 (7)
Therapy failure			
N (%)	62 (46)	2 (7)	64 (39)
New positive PCR after being negative for 3 months	17 (13)	—	17 (10)
PCR positive for 6 months	6 (5)	—	6 (4)
Q fever–related complication during therapy	45 (34)	1 (3)	46 (28)
Q fever–related death during therapy	15 (11)	1 (3)	16 (10)
Mortality			
Deceased	41 (31)	9 (31)	50 (31)
Definitely/probably chronic Q fever related	18 (13)	2 (7)	20 (12)

Data are presented as *n* (%) unless otherwise indicated. IQR, interquartile range.
[a] Other focus: in a patient with pleuritis, pleural effusion was PCR positive for *Coxiella burnetii* DNA.
[b] Multiple complications per patient were possible.
[c] Definition of acute aneurysm: rupture of aneurysm, dissection of aneurysm, endoleak or symptomatic aneurysm (in absence of abscess, fistula, spondylodiscitis, rupture or dissection).
[d] Definition of heart failure: heart failure, fatal arrhythmia, cardiac arrest, tamponade.
[e] Other complications: amyloid-A amyloidosis, central sleep apnea syndrome, paraplegia postoperative, myocarditis, pacemaker implantation needed for arrhythmia, compartment syndrome postoperative, glomerulonephritis, complete atrioventricular block with syncopes, 2 × temporary need for haemodialysis after surgery.

Table 2
Selected SNPs, previously reported association, and frequency in study population

Gene	SNP	Nucleotide change	Association	No. of patients tested	Wild type, n (% of tested)	Hetero- or homozygote, n (% of tested)
TLR pathway						
TLR1	rs5743611	G > C	SNP is less prevalent in proven chronic Q fever patients; carriers show decreased IL-10 production after *Coxiella burnetii* stimulation [21]	125	105 (84)	20 (16)
NOD2	rs2066844	C > T	Protein involved in the recognition of *C. burnetii* [21]	130	115 (89)	15 (11)
NOD2	rs2066847	- > C	SNP is more prevalent in chronic Q fever patients [21]	125	114 (91)	11 (9)
MyD88	rs4988453	C > A	SNP is more prevalent in chronic Q fever patients [21]	125	108 (86)	17 (14)
Phagolysosomal pathway						
RAB5A	rs8682	C > G	SNP is less prevalent in chronic Q fever patients [7]	154	123 (80)	31 (20)
RAB7A	rs13081864	C > T	SNP is more prevalent in chronic Q fever patients; reduced *C. burnetii*–induced IL-6 production [7]	153	97 (63)	56 (37)
P2RX7	rs1718119	C > T; gain of function	SNP is less prevalent in chronic Q fever patients [7]	141	62 (44)	79 (56)
P2RX7	rs3751143	T > G; loss of function	SNP is more prevalent in chronic Q fever patients [7]	154	108 (70)	46 (30)
ATG5	rs2245214	C > G	SNP is less prevalent in chronic Q fever patients [7]	148	62 (42)	86 (58)
MAP1LC3A	rs1040747	C > G	SNP is less prevalent in chronic Q fever patients; increased *C. burnetii*–induced IL-6 production [7]	141	80 (57)	61 (43)
MMP pathway						
MMP1	rs1144393	T > C	Gene is upregulated and increased enzyme production after *C. burnetii* stimulation [19]	129	45 (35)	84 (65)
MMP1	rs7125062	T > C	Gene is upregulated after *C. burnetii* stimulation [19]	127	76 (60)	51 (40)
MMP2	rs1053605	C > T	Increased enzyme concentrations in past Q fever patients [19]	125	102 (82)	23 (18)
MMP2	rs243865	C > T	Increased enzyme concentrations in past Q fever patients [19]	130	74 (57)	56 (43)
MMP7	rs11568818	A > G	Gene upregulated after *C. burnetii* stimulation; SNP is more prevalent in chronic Q fever patients; serum *MMP7* levels higher in chronic Q fever patients [19]	129	31 (24)	98 (76)
MMP8	rs1940475	T > C	Gene is upregulated after *C. burnetii* stimulation in chronic Q fever patients [19]	130	39 (30)	91 (70)
MMP8	rs3765620	A > G	Gene is upregulated after *C. burnetii* stimulation in chronic Q fever patients[a] [19]	125	32 (26)	93 (74)
MMP9	rs17576	A > G	Increased enzyme production after *C. burnetii* stimulation; SNP is more prevalent in chronic Q fever patients [19]	130	47 (36)	83 (64)
MMP10	rs486055	C > T	Gene is upregulated after *C. burnetii* stimulation [19]	130	91 (70)	39 (30)

IL = interleukin; MMP, matrix metalloproteinases; SNP, single nucleotide polymorphism; TLR, Toll-like receptor.
[a] Gene analysis derived from publically available whole transcriptome microarray approach (GEO series accession number GSE66476).

P2RX7 SNP rs3751143 is associated with higher risk of therapy failure

In multivariable analysis, *P2RX7* SNP rs3751143 was found to be associated with a higher risk of therapy failure (SHR 2.21; 95% confidence interval, 1.05–4.68; p 0.04). The P2X7 receptor is an ATP-gated receptor that is ubiquitously expressed on immune cells. This innate immune receptor, which has many functions in inflammatory mediation, serves immune-cell recognition and phagocytosis of nonopsonized particles and apoptosis [24].

MMP1 SNP rs7125062 is associated with lower risk of complications

In multivariable analysis, rs7125062 was found to be associated with a lower risk of complications. This SNP is an intronic SNP located in *MMP1*. This SNP is an expression quantitative trait locus leading to an altered expression of the *MMP1* gene, but this effect appears to be highly tissue dependent (GTEx project, dbGaP accession no. phs000424.vN.pN).

Discussion

In the current study, the influence of genetic variations in immunity and MMP genes on the course of chronic Q fever infection in terms of mortality, therapy failure, and complications was evaluated. *P2RX7* SNP rs3751143 was associated with therapy failure and *MMP1* SNP rs7125062 carriers were at a lower risk for chronic Q fever–related complications.

Years after the major Q fever outbreak in the Netherlands, better care for chronic Q fever patients during the course of the infection remains an important issue. Mortality and morbidity during chronic Q fever are high, so there is a need to identify those at risk for death and the most important factors related to this—that is, therapy failure and complications. It was previously shown that SNPs in immunologically relevant genes influenced the progression to chronic Q fever [7,21]. The current study focused on whether these genetic factors may also affect the course of the disease.

Three major gene groups were identified: (a) genes of pattern recognition receptors involved in early innate recognition of *C. burnetii;* (b) genes associated with the intracellular processing and killing of *C. burnetii;* and (c) genes of MMPs, a group of zymogens that degrade collagen or elastin. SNPs present in these gene groups were previously found to be more prevalent in chronic Q fever patients than patients without chronic Q fever, or resulted in an altered gene regulation or cytokine production upon stimulation with *C. burnetii* [7,19,21]. Thus, carriers of the analysed SNPs were previously shown to react differently to *C. burnetii* specifically. Additionally, correction for confounders was performed to identify causative associations with clinical outcomes.

No association was found between SNPs and clinical outcomes in the genes for pattern recognition receptors involved in the early innate recognition of *C. burnetii. P2RX7* encodes for a purinergic

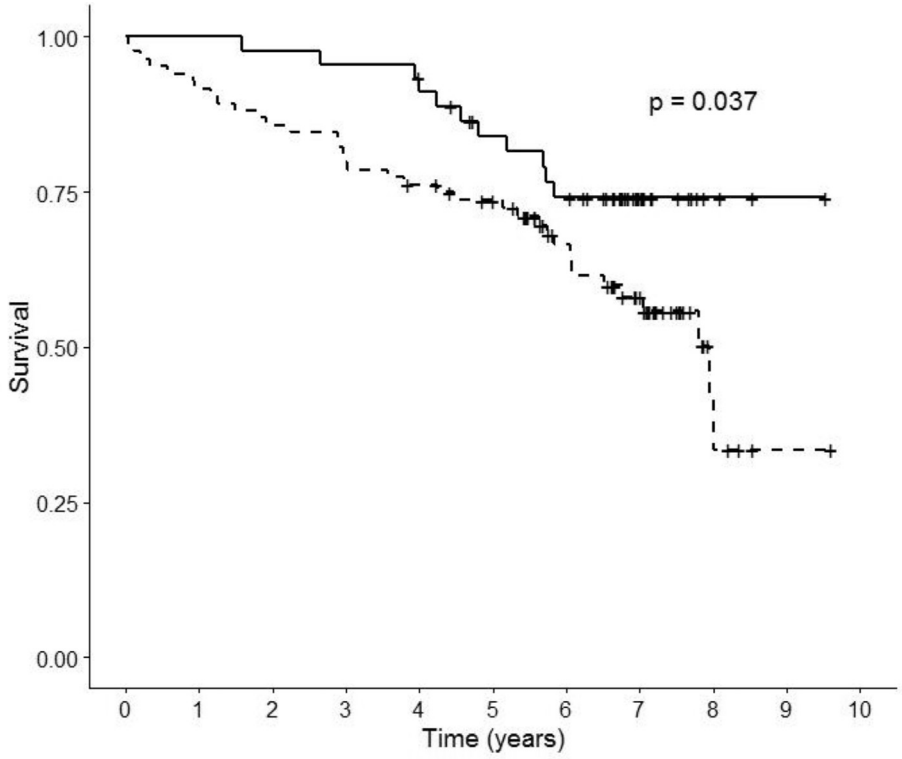

Fig. 1. Kaplan-Meier curve for all-cause mortality comparing patients with chronic Q fever with and without *MMP1* SNP rs1144393. Solid line indicates wild type; dashed line indicates heterozygote or homozygote for rs1144393.

receptor, ubiquitously present on immune cells, with several functions like recognition, phagocytosis of unopsonized particles, inflammasome activation, and apoptosis. SNP rs3751143 leads to a loss of function of the receptor [30] and has been associated with increased susceptibility to tuberculosis and less effective killing of other intracellular pathogens such as *Toxoplasma gondii* [25,26]. This SNP was previously found to be more prevalent in chronic Q fever patients than in individuals with resolved Q fever having similar clinical risk factors for progression to chronic Q fever [7]. In the same study, SNP rs1718119 resulting in a gain of function of the P2X7 receptor played a protective role for the development to chronic Q fever [7], which underscored the role of the P2X7 receptor in the pathogenesis of chronic Q fever. We found here that SNP rs3751143 is also associated with failure of therapy in patients

Table 3
Multivariable Cox regression analysis for all-cause mortality, therapy failure, and chronic Q fever–related complications

Variable	*N* with SNP[a]	*N* with SNP and event[a]	SHR (95% CI)	p
All-cause mortality (47 events)[b]				
MMP1 SNP rs1144393	84	36	1.49 (0.49–4.50)	0.48
MMP9 SNP rs17576	83	34	1.25 (0.42–3.75)	0.69
Therapy failure (36 events)[c]				
TLR1 SNP rs5743611	14	3	0.52 (0.12–2.24)	0.38
NOD2 SNP rs2066847	11	7	0.74 (0.23–2.38)	0.61
P2RX7 SNP rs1718119	62	18	0.71 (0.36–1.40)	0.32
P2RX7 SNP rs3751143	29	17	2.42 (1.16–5.05)	0.02*
MMP9 SNP rs17576	65	26	1.20 (0.55–2.62)	0.66
Chronic Q fever–related complications (56 events)[d]				
TLR1 SNP rs5743611	18	6	0.88 (0.38–2.01)	0.76
P2RX7 SNP rs3751143	35	19	1.23 (0.79–1.91)	0.37
ATG5 SNP rs2245214	66	34	1.27 (0.80–2.00)	0.31
MMP1 SNP rs7125062	45	17	0.49 (0.29–0.83)	0.008*
MMP8 SNP rs1940475	77	40	1.26 (0.79–2.03)	0.33

CI, confidence interval; SHR, subdistribution hazard ratio; SNP, single nucleotide polymorphism. Boldface values were indeed used for statistically significant p-values.
[a] Dominant model analysis.
[b] A total of 129 cases were analysed. SNP selection was based on Kaplan-Meier analysis (Supplementary Table S1) and corrected for age, heart failure and chronic kidney disease.
[c] A total of 103 cases were analysed. SNP selection was based on univariable Cox regression analysis (Supplementary Table S2) and corrected for age and presence of prosthetic material before diagnosis.
[d] A total of 113 cases were analysed. SNP selection was based on univariable Cox regression analysis (Supplementary Table S3) and corrected for age, presence of prosthetic material before diagnosis and serum PCR positivity.
* Statistically significant.

with chronic Q fever. Although this is outside the scope of our study, we speculate that patients with chronic Q fever carrying this SNP may benefit from additional therapeutic interventions.

The expression and production of MMPs, among them MMP-1, is induced by *ex vivo* stimulation of immune cells with heat-killed *C. burnetii* [19]. In light of their association with aneurysm expansion and other vascular complications such as coronary artery disease [27], genetic alterations in *MMP1* may influence the course of chronic Q fever infection. However, patients carrying the SNP rs7125062 seem to be less prone to have chronic Q fever–related complications. rs7125062 is an intronic SNP, which has been studied for its potential role in gastric cancer and resolution of cutaneous leishmaniasis lesions, although attempts to show association failed [28,29]. The association found in the current study has yet to be supported by other studies.

The current study assessed what is to our knowledge the largest cohort of chronic Q fever patients in whom SNPs were analysed. Therefore, a unique opportunity became available to evaluate a possible association between SNPs in candidate genes and clinical outcomes of chronic Q fever infection.

Only patients with proven and probable chronic Q fever were included; this cohort is known to be at high risk for mortality or complications. Another strength of this study is that data were collected on comorbidity and risk factors of chronic Q fever patients, enabling proper adjusting for covariates in multivariable analyses. A possible limitation is that only the association with all-cause mortality and not chronic Q fever–related mortality was evaluated. Although all-cause mortality is the only nonsubjective endpoint, one might argue that chronic Q fever–related mortality would have been a better endpoint. However, the number of chronic Q fever–related deaths was too small for reliable evaluation. In this study, all-cause mortality occurred in 31% of patients and chronic Q fever mortality in 12%. These mortality rates are lower than the mortality rates seen in the entire cohort of chronic Q fever patients after the Dutch outbreak, and can be explained by the fact that for participation in this study, patients had to have survived the first months of their chronic Q fever infection [4]. This may lead to survivor bias and thus to an underestimation of the true effect of the evaluated SNPs. Although the number of SNPs analysed was limited to 19, a correction for multiple testing was not made, and these findings might be the result of a type I error. However, the selection of the SNPs was not at random but based on their presence in genes involved in the killing machinery for *C. burnetii* according to previous gene analysis studies, on transcriptome analysis and on validated *in vitro* cytokine studies [19,21]. In these studies, the prevalence of selected SNPs were compared to control patients with exposure to *C. burnetii* but without chronic Q fever infection. Because the outcomes of this study were chronic Q fever–related endpoints, no comparison to the prevalence of SNPs in patients without chronic Q fever was made.

To our knowledge, this is the first study on SNPs in chronic Q fever patients that examined clinical endpoints. Future research should focus on validating our results in more chronic Q fever patients.

Conclusions

A polymorphism in *P2RX7,* known to lead to loss-of-function of the P2X7 receptor and inefficient killing of intracellular organisms, was associated with therapy failure in chronic Q fever patients. A polymorphism in *MMP1,* one known to lead to altered *MMP1* gene expression, was inversely associated with chronic Q fever–related complications in chronic Q fever patients.

Acknowledgements

We gratefully acknowledge S. Shamelian, M. Pronk, M. Wegdam-Blans, T. Sprong, K. Slieker, M. Leclercq, M. van Kasteren and L. Kampschreur for their effort in collecting patient material.

Transparency declaration

AFMJ was supported by the Q Support Foundation. TS was supported by grant 205520002 from the Netherlands Organization for Health Research and Development. All authors report no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.06.016.

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