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The *IL20* Genetic Polymorphism Is Associated with Altered Clinical Outcome in Septic Shock

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Keywords
Sepsis · Organ dysfunction · Genetics · Critical care · Infection · *IL10* family gene

Abstract
Background: The *IL10* family of genes includes crucial immune regulators. We tested the hypothesis that single nucleotide polymorphisms (SNPs) in *IL10*, *IL19*, *IL20*, and *IL24* of the *IL10* family gene cluster alter the clinical outcome of septic shock. ***Methods:*** Patients with septic shock (n = 1,193) were genotyped for 13 tag SNPs of *IL10*, *IL19*, *IL20*, and *IL24*. *IL20* gene expression was measured in genotyped lymphoblastoid cells in vitro. Cardiac surgical ICU patients (n = 981) were genotyped for *IL20* rs2981573 A/G. The primary outcome variable was 28-day mortality. ***Results:*** Patients with the G allele of *IL20* rs2981573 had a significantly increased hazard of death over the 28-day period compared to patients with the A allele in the septic shock cohort (adjusted hazard ratio 1.27; 95% confidence interval 1.10–1.47; $p = 8.0 \times 10^{-4}$). Patients with the GG genotype had more organ dysfunction ($p < 0.05$). The GG genotype was associated with increased *IL20* gene expression in stimulated lymphoblastoid cells in vitro ($p < 0.05$). The cardiac surgical ICU patients with the GG genotype had an increased length of ICU stay ($p = 0.032$). ***Conclusions:*** The GG genotype of *IL20* rs2981573 SNP was associated with increased *IL20* gene expression and increased adverse outcomes in patients with septic shock and following cardiac surgery.

Introduction

Dysregulated immune response to infection is a fundamental element of developing septic shock and leads to adverse clinical outcomes [1, 2]. Interleukin (IL)-10 is a crucial immune regulator, which is produced after infection; it controls excessive activation of proinflammatory signaling and enhances tissue recovery after injury [3]. *IL19*, *IL20*, and *IL24* are grouped into the *IL10* family of genes, based on their similarities with regard

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to gene structure, protein structure, and receptors [4]. In addition to the similarities, these 3 genes and *IL10* are clustered within a 200-kb genomic DNA region of chromosome 1q32, called the *IL10* gene cluster region [4]. Despite their similarities, these 4 *IL10* family genes do not necessarily have similar biological functions. For instance, *IL20* appears to provoke inflammation via JAK/STAT signaling, which is dissimilar to *IL10* [5–7]. However, there is accumulating evidence that they play key roles in the pathophysiology of inflammatory diseases such as arthritis, asthma, ulcerative colitis, respiratory wheeze, palmoplantar pustulosis, and autoimmune diseases, and also in tissue injury [3, 8–12]. Importantly, increased *IL19* and *IL20* gene expression/IL-19 and IL-20 protein production in sepsis has been reported in vitro and in vivo [8, 13, 14]. Neutralization of IL-20 has been reported to be a potential therapeutic approach to inflammatory diseases including arthritis and asthma [7, 15, 16]. Thus, these genes may play a role in septic shock and may contribute to clinical outcomes.

Genetic variants are potential risk factors for susceptibility to sepsis and death [17, 18]. Genetic variants in key genes of the immune response, including *IL10*, have been studied in patients experiencing septic shock [18, 19]. In particular, single nucleotide polymorphisms (SNPs) in the promoter region of the *IL10* gene have been investigated. A recent meta-analysis suggested that *IL10* promoter SNPs were associated with altered susceptibility to sepsis [19]. However, there is no report of a genetic association of the *IL19*, *IL20*, and *IL24* variants with septic shock. A genetic association study focusing on this gene cluster found associations of *IL19* and *IL20* SNPs with recurrent wheeze after respiratory syncytial virus bronchiolitis [10]. There is also increasing evidence that *IL19* and *IL20* SNPs are associated with the development of inflammatory diseases such as ulcerative colitis [9] and systemic juvenile idiopathic arthritis [11].

Thus, we hypothesized that the genetic variants *IL10*, *IL19*, *IL20*, and *IL24* in the *IL10* gene cluster were associated with an altered clinical outcome in septic shock. We genotyped 13 tag SNPs for this gene cluster in a large septic shock cohort. The primary outcome was 28-day mortality. The secondary outcomes were measures of organ dysfunction. We tested for evidence of a biologically plausible mechanism, by measuring *IL20* gene expression in a genotyped cell line. We further tested for the replication of a genotypic effect in a separate cohort of patients with acute inflammation, namely, a postoperative cardiac surgery cohort.

Table 1. Allele frequency and effect on mortality of 13 tag SNPs in *IL10*, *IL19*, *IL20*, and *IL24* in septic shock

	Major/ minor allele	MAF	Trend test slope	*p* value (corrected)
IL10				
rs1518111	G/A	0.282	0.25	0.0040 (0.052)
rs1554286	C/T	0.256	0.27	0.0026 (0.034)
rs1878672	C/G	0.414	–0.0020	0.98
rs3024498	A/G	0.228	–0.080	0.42
rs3024505	C/T	0.118	–0.092	0.48
IL19				
rs1798	C/G	0.182	0.17	0.095
rs2243191	C/T	0.301	0.27	0.0020 (0.026)
rs2243193	G/A	0.315	0.24	0.0057 (0.074)
IL20				
rs1518108	C/T	0.402	–0.15	0.067
rs1713239	G/C	0.171	0.19	0.082
rs2981573	A/G	0.296	0.30	0.00072 (0.0094)
IL24				
rs1150258	A/G	0.410	–0.10	0.22
rs291109	A/G	0.435	–0.11	0.19

MAF, minor allele frequency. *p* values were calculated with the use of the Armitage trend test for 28-day mortality with correction for multiple testing using the Bonferroni test.

Materials and Methods

Study Cohorts

Septic Shock Cohort

St Paul's Hospital Cohort. All patients admitted to the ICU at the St Paul's Hospital (SPH) in Vancouver, Canada, between July 2000 and January 2004, were screened (n = 1,626). Of these, 589 patients had septic shock on admission and DNA available. Septic shock was defined as: the presence of a systemic inflammatory response syndrome [20], proven or suspected infection, at least one new organ dysfunction according to the Brussels score (online suppl. Table S1; see www.karger.com/doi/10.1159/000486104 for all online suppl. material), and hypotension despite adequate fluid resuscitation. Twelve patients who were also enrolled in the Vasopressin and Septic Shock Trial (VASST) [21] were excluded from this cohort. Thus, 577 SPH patients were included in the study cohort of septic shock. The institutional review board at SPH and the University of British Columbia (UBC) approved the study and as it was a fully anonymized analysis, the need for informed patient consent was waived.

VASST Cohort. The VASST was a multicenter, randomized, double-blind, controlled trial evaluating the efficacy of vasopressin in patients with septic shock [21]. Of 6,229 patients screened, 778 who had septic shock were assessed in the trial. Of these, 616 who had DNA available were included in the study cohort of septic shock. The research ethics boards of all participating institutions (online suppl. Table S4) approved the trial and written informed

Table 2. Baseline characteristics of 2 cohorts of septic shock patients by *IL20* rs2981573 genotype

	GG (n = 127)	GA (n = 453)	AA (n = 613)	p
Age, years	63 (49–72)	64 (49–73)	62 (50–73)	0.45
Male gender	46.5%	61.1%	63.6%	0.0015
APACHE II score	26 (21–32)	26 (21–32)	26 (20–31)	0.19
Preexisting conditions				
Chronic heart failure	8 (6.3)	32 (7.1)	44 (7.2)	0.94
Chronic pulmonary disease	22 (17.3)	84 (18.5)	99 (16.2)	0.59
Chronic liver disease	18 (14.2)	48 (10.6)	60 (9.8)	0.34
Chronic renal failure	14 (11.0)	38 (8.4)	53 (8.6)	0.64
Chronic corticosteroid use	17 (13.4)	59 (13.0)	86 (14.0)	0.89
Laboratory variables on day 1				
Norepinephrine, μg/min	15 (6–30)	13 (7–24)	13 (6–25)	0.85
Dobutamine, μg/kg/min	9 (3–10)	6 (4–10)	5 (3–8)	0.25
Body temperature, °C	38.2 (37.1–38.8)	38.2 (37.2–39.0)	38.2 (37.4–39.0)	0.45
Heart rate, beats/min	120 (105–136)	122 (105–135)	120 (105–135)	0.15
MAP, mm Hg	54 (48–60)	55 (50–60)	55 (50–60)	0.31
White blood cell count, $10^3/mm^3$	13.7 (9.3–18.2)	13.8 (8.2–20.3)	14.7 (9.3–21.3)	0.10
Platelet count, $10^3/mm^3$	134 (76–214)	158 (89–245)	171 (94–258)	0.035
PaO_2/FiO_2, torr	160 (106–223)	167 (107–240)	172 (117–233)	0.44
Blood creatinine, μmol/L	153 (86–273)	157 (91–267)	146 (90–258)	0.59

Data are expressed as n (%) or median (interquartile range), unless otherwise indicated. APACHE, Acute Physiology And Chronic Health Evaluation; MAP, mean arterial pressure. p values were calculated with the use of the Kruskal-Wallis and χ^2 tests.

consent was obtained from all patients or their authorized representatives. The research ethics board at the coordinating center (UBC) approved the genetic analysis.

We analyzed a total of 1,193 patients in the septic shock cohort (VASST plus SPH cohort).

Cardiac Surgical ICU Cohort

Patients admitted to the cardiac surgical ICU after surgery at SPH between July 2000 and January 2004 (n = 1,234) were screened. Of these, 981 patients who had DNA available were included in the analysis. The institutional review board at SPH and UBC approved the study. We analyzed length of ICU stay after cardiac surgery and postoperative cardiac output upon admission to the ICU.

Selection of Tag SNPs and Genotyping

Fourteen tag SNPs were identified in the 200-kb DNA region of the *IL10* gene cluster including *IL10*, *IL19*, *IL20*, and *IL24* on chromosome 1, using a linkage disequilibrium-based tag SNP selection method [22] based on genotyping data of subjects of European ancestry from the HapMap database (CEU), with an r^2 threshold of 0.65 for SNPs with a minor allele frequency of >5%.

DNA was extracted from the buffy coat of discarded blood samples using a QIAamp DNA maxi kit (Qiagen, Mississauga, ON, Canada) and genotyped using the Illumina Golden Gate assay (Illumina, San Diego, CA, USA). The patients in the septic shock cohorts were genotyped for 14 tag SNPs. The patients in the cardiac surgical ICU cohort were genotyped for *IL20* rs2981573.

We tested for Hardy-Weinberg equilibrium (HWE) of 14 tag SNPs using the χ^2 test primarily as a data quality check. The *IL10* rs1554286 SNP, which deviated significantly from the HWE threshold, p <0.00001, was excluded from the analysis. Thus, 13 tag SNPs were included in the analysis of the combined septic shock cohort.

IL20 mRNA Expression Analysis in vitro

Lymphoblastoid cell lines from 77 individuals of European ancestry genotyped by the HapMap project were stimulated using cytomix [23] (2.5 ng/mL each of TNF-α, IL-1β, and IFN-γ [R&D Systems] and 12.5 μM of CpG [Sigma-Aldrich]) for 6 h. RNA was extracted from the 3 stimulated samples and 2 control biological duplicates using the Qiagen RNeasy kit (Qiagen). *IL20* mRNA expression was measured using the HumanWG-6 v3 Expression BeadChip (Illumina, San Diego, CA; Génome Québec Innovation Centre, Montréal, QC, Canada) and normalized, and fold change was measured with the Flexarray package (v1.4.1) from Génome Québec.

Statistical Analysis

The primary outcome variable was 28-day mortality of septic shock. The secondary outcome variables for septic shock were days alive and free of organ dysfunction and organ support. To test for evidence of biological plausibility, we used measurements of mRNA expression in genotyped lymphoblastoid cell lines in vitro. For the cardiac surgical ICU patients, the primary outcome was length of ICU stay after cardiac surgery. The secondary out-

Table 3. Days alive and free of organ dysfunction and artificial organ support by the genotype of *IL20* rs2981573

	GG (n = 127)	GA (n = 453)	AA (n = 613)	p
Organ dysfunction				
Cardiovascular	6 (0–23)	13 (0–23)	18 (2–24)	0.0008
Respiratory	1 (0–18)	3 (0–19)	7 (0–20)	0.019
Renal	10 (1–27)	16 (1–28)	21 (3–28)	0.0007
Hematologic	15 (1–28)	23 (4–28)	25 (7–28)	0.0003
Hepatic	10 (1–28)	21 (3–28)	27 (6–28)	<0.0001
Neurologic	13 (0–26)	18 (1–27)	19 (4–27)	0.043
Artificial support				
Vasopressor use	10 (0–25)	17 (0–24)	20 (3–25)	0.0078
Ventilator	2 (0–18)	6 (0–21)	9 (0–21)	0.013
Renal replacement therapy	9 (1–28)	20 (2–28)	25 (5–28)	<0.0001

The numbers in this table are the number of days, out of the 28 study days, that patients were alive and free of organ dysfunction and artificial organ support. Data are median (interquartile range) for continuous variables. p values were calculated with the use of the χ^2 test and the Kruskal-Wallis test. Organ dysfunction was recorded if the patient met the Brussels organ dysfunction criteria (moderate, severe, or extreme).

come variable was postoperative cardiac output upon admission to the ICU.

We used the Armitage trend test to test for association of 28-day mortality with the genotypes of the 13 tag SNPs. We corrected for multiple comparisons using the Bonferroni correction. For the primary analysis, we chose the Cox regression to test for differences in the hazard of death over 28 days according to genotype, in order to allow for the correction of potential confounding factors including age, gender, a surgical versus a medical primary diagnosis, ancestry, and APACHE II score as covariates. We used the Kruskal-Wallis test to test for differences in baseline characteristics for continuous data, days alive and free of organ dysfunction (Brussels criteria) during 28 days [21], fold change in *IL20* gene expression, length of ICU stay, and postoperative cardiac output. Baseline characteristics for categorical data were analyzed using the χ^2 test. Differences were considered significant using a two-tailed $p < 0.05$. Analyses were performed using SPSS v21 (Armonk, NY, USA).

Results

A total of 1,193 patient with septic shock were successfully genotyped for 13 tag SNPs of *IL10*, *IL19*, *IL20*, and *IL24* in the DNA region (200 kb) of the *IL10* gene cluster on chromosome 1 (Table 1). The allele frequencies of these 13 tag SNPs are similar to those in the HapMap database. In the initial screening using the Armitage trend test for 28-day mortality in septic shock, 3 tag SNPs, including *IL10* rs1554286, *IL19* rs2243191 and *IL20* rs2981573 SNP, were significantly associated with altered 28-day mortality after Bonferroni correction. Of these 3, *IL20* rs2981573 A/G SNP had the lowest p value (p = 0.0094) after the Bonferroni correction (Table 1); we further studied the *IL20* rs2981573 A/G SNP.

There were no significant differences in characteristics at baseline including age, APACHE II score, and pre-existing conditions by the *IL20* rs2981573 genotype; however, GG genotype patients had a lower frequency of male gender and a lower platelet count, which may have been due to random baseline differences or to outcomes related to genotype (Table 2).

Patients who had the G allele of *IL20* rs2981573 had a significantly increased hazard of death over the 28-day observation period compared to patients with the A allele in the septic shock cohort (adjusted hazard ratio [HR] 1.26; 95% confidence interval [CI] 1.09–1.44; p = 0.0013) (online suppl. Table S2; Fig. 1). This result remained highly significant after including the APACHE II score in the Cox regression model (adjusted HR 1.27; 95% CI 1.10–1.47; $p = 8.0 \times 10^{-4}$). GG patients had more organ dysfunction and needed more artificial support (Table 3).

To test for biological plausibility, we measured *IL20* gene expression in stimulated lymphoblastoid cells in vitro. Lymphoblastoid cells with the GG genotype of *IL20* rs2981573 SNP had a significantly increased fold change of *IL20* gene expression by mixed inflammatory stimulation (p = 0.011) (Fig. 2).

We next tested for the genotypic effect in patients admitted to the ICU after cardiac surgery. There was no difference in baseline characteristics by the genotype of *IL20* rs2981573 in the cardiac surgical ICU cohort (online sup-

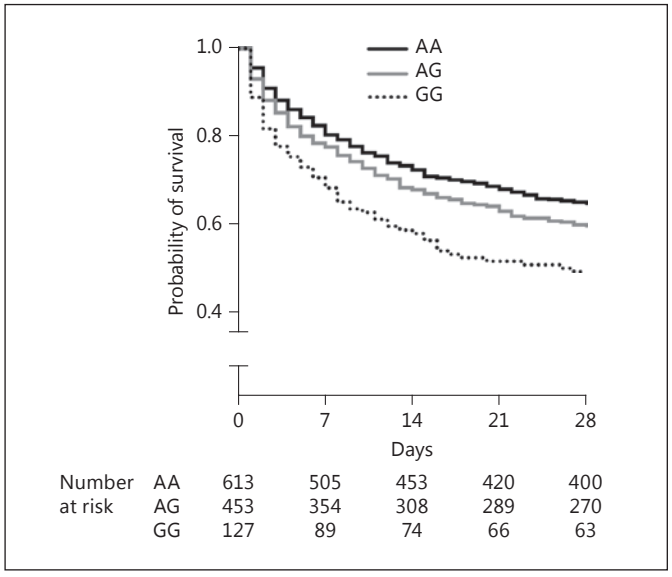

Fig. 1. Survival curves for the septic shock patients by the *IL20* rs2981573 genotype. Patients with the *IL20* rs2981573 G allele had significantly increased 28-day mortality compared to those with the A allele in the septic shock cohort (adjusted HR 1.27; 95% CI 1.10–1.47; $p = 8.0 \times 10^{-4}$). The *p* value was calculated using the Cox regression analysis corrected for age, gender, a medical versus a surgical diagnosis, ancestry, and APACHE II score.

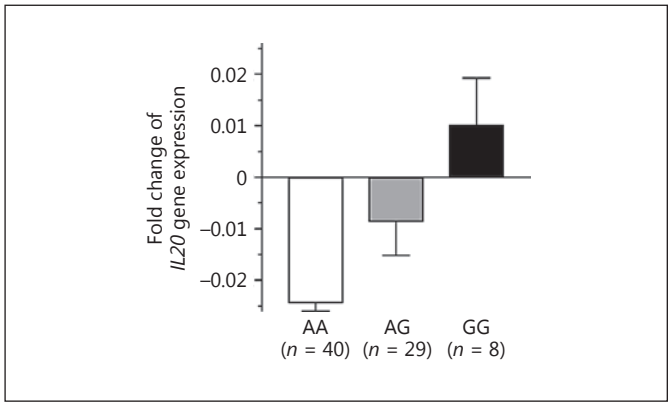

Fig. 2. *IL20* gene expression in stimulated lymphoblastoid cells in vitro. Lymphoblastoid cells with the GG genotype of *IL20* rs2981573 SNP had a significantly increased fold change of *IL20* gene expression by mixed inflammatory stimulation (AA vs. AG vs. GG genotype, $p = 0.011$). The *p* value was calculated using the Kruskal-Wallis test.

pl. Table S3). Patients with the GG genotype had a significantly increased length of ICU stay ($p = 0.032$). There was a nonsignificant trend of decreased cardiac output in patients with the GG genotype ($p = 0.068$) (Fig. 3).

Discussion

In this study on septic shock, patients who had the G allele of *IL20* rs2981573 SNP had a significantly increased 28-day mortality and more organ dysfunction than those with the A allele. In vitro, the G allele was associated with increased *IL20* gene expression in stimulated cells. Furthermore, in the postoperative cardiac surgery cohort, GG genotype patients had an increased length of ICU stay and a decreased postoperative cardiac output.

IL10, *IL19*, *IL20*, and *IL22* are located in the 200-kb genomic DNA region in the q32 region of chromosome 1 and are *IL10* family genes. *IL10* family genes are pleiotropic, and they play essential roles in infectious and inflammatory diseases [24]. In sepsis, the potential role of the genetic variants of IL-10 on immune regulation has been widely studied [25, 26]. However, the importance of genetic variations in other IL-10 family members is unknown. In particular, the effect of *IL20* genetic polymorphisms on clinical outcomes in patients with sepsis has never been reported. In this study, we report the effect of the *IL20* rs2981573 SNP in the survival of patients with septic shock.

IL20 is a member of the *IL10* family gene cluster in chromosome 1q32. This genetic study of *IL10* family genes therefore included *IL20*. While there are similarities with regard to gene structure, protein structure, and receptors in the IL-10 family, there is relatively weak similarity of amino acid sequences [4]. There is no more than 40% amino acid identity between IL-10 family members, and that of amino acid sequences of IL-20 and IL-10 is only 28% [4, 6, 27].

The IL-10 family members do not necessarily have similar biological functions [4]. For instance, IL-10 is known as an anti-inflammatory cytokine, while IL-20 has dissimilar biological functions including provoking inflammation, angiogenesis, and neutrophil chemotaxis [5, 7, 15]. IL-20 is produced by multiple types of cells, including monocytes, dendritic cells, endothelial cells, keratinocytes, the synovial fibroblasts of rheumatoid arthritis, and the mesangial cells of lupus nephritis [7, 28, 29]. Since gene expression of IL-20 peaked 6 h after lipopolysaccharide stimulation, IL-20 is likely to act in the early phase of inflammation [13]. IL-20 is recognized by the heterodimer complex of either IL-20 or IL-22 receptor and activates JAK/STAT signaling [12], which enhances the production of inflammatory mediators such as IL-6, IL-8, and MCP-1 [5, 29]. Increased expression of the *IL20* gene has been observed in inflammatory diseases including rheumatoid arthritis and atherosclerosis [7]. Neutraliza-

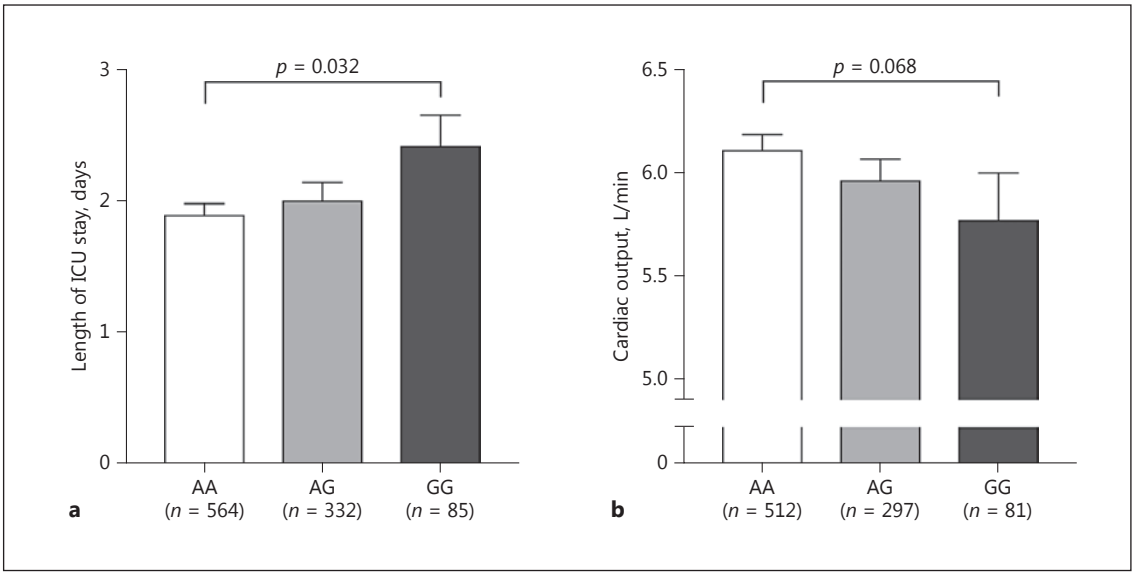

Fig. 3. Length of ICU stay and cardiac output in the postoperative cardiac surgery cohort by the *IL20* rs2981573 genotype. Patients with the GG genotype had significantly increased length of ICU stay (**a**, AA vs. AG vs. GG genotype, $p = 0.032$). There was a nonsignificant trend of decreased cardiac output in patients with the GG genotype (**b**, AA vs. AG vs. GG genotype, $p = 0.068$). The p values were calculated using the Kruskal-Wallis test.

tion of IL-20 by monoclonal antibody or small interfering RNA has been reported to be a potential therapeutic approach to inflammatory diseases including arthritis and asthma [7, 15, 16].

While the precise pathophysiology of *IL20* in sepsis has not yet been clearly elucidated [12], excessive *IL20* production may be potentially harmful in septic shock. In this study, the GG genotype of *IL20* rs2981573 SNP was associated with increased *IL20* gene expression in stimulated lymphoblastoid cells in vitro. In line with this, patients with septic shock who had the G allele had increased 28-day mortality compared to those who had the A allele.

We found an association of altered clinical outcome with the *IL20* rs2981573 SNP in the septic shock and postoperative cardiac surgery cohorts. There are few reports of the genotypic effects of the *IL20* rs2981573 SNP on clinical outcomes. However, the *IL20* rs2981573 genetic variant has been reported to be associated with several inflammatory diseases. The minor allele frequency was found to be lower than that of healthy controls in patients with ulcerative colitis in a Mexican population [30], in patients with recurrent wheeze after respiratory syncytial bronchiolitis in a Dutch population [10], and in patients with palmoplantar pustulosis in an Estonian (Caucasian) population [31].

Inflammatory cytokines including TNF-α or IL-6 are upregulated after cardiac surgery [32]. Similarly, *IL20* gene expression increases after cardiopulmonary bypass [33]. The excessive inflammatory cytokines may contribute to worsening the clinical outcome of cardiac surgery [32]. Patients with higher levels of inflammatory cytokines after cardiac surgery have more hemodynamic instability or more suppressed myocardial performance [34, 35]. In line with these results, we found that patients with the GG genotype, associated with increased gene expression in vitro, had an increased length of ICU stay and a decreased cardiac function.

This study has several limitations. First, all 3 cohorts were retrospective. Second, according to the lowest p value in the initial test on 13 SNPs, we focused on *IL20* rs2981573. There is linkage disequilibrium between *IL20* rs2981573, *IL19* rs2243191, and *IL19* rs2243188 in individuals of European ancestry [10]. Thus, whether *IL20* rs2981573 was the functional SNP or another SNP was in linkage disequilibrium with the causal SNP was not determined. Third, we found altered *IL20* gene expression by the genotype of *IL20* rs2981573 in stimulated cells in vitro. Further investigation regarding the genetic effect on levels of cytokines including IL-20 or other proinflammatory cytokines in either septic shock or cardiac surgical ICU patients would therefore strengthen the results of this study.

To conclude, we analyzed the effect of genetic variants of the IL-10 family (*IL10*, *IL19*, *IL20*, and *IL24*) in septic shock. We found that patients who had the G allele of the *IL20* rs2981573 SNP had increased 28-day mortality and more organ dysfunction than patients with the A allele. The GG genotype was associated with increased *IL20* gene expression in stimulated cells in vitro. In a separate, independent cohort of acute inflammation after cardiac surgery, we found that the patients with the GG genotype had an increased length of ICU stay after cardiac surgery.

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Disclosure Statement

The authors declare no conflicts of interest.

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Author Contributions

Study concept and design: T. Nakada, Russell, Boyd, Walley. Acquisition of data: T. Nakada, Wacharasint, Russell, Boyd, Thair, Walley. Analysis and interpretation of data: T. Nakada, Wacharasint, Russell, Boyd, E. Nakada, Thair, Shimada, Walley. Drafting of the manuscript: T. Nakada, Wacharasint, E. Nakada. Critical revision of the manuscript for important intellectual content: T. Nakada, Wacharasint, Russell, Boyd, E. Nakada, Thair, Shimada, Walley. Statistical analysis: T. Nakada, Walley. Administrative, technical, or material support: T. Nakada, Wacharasint, Russell, Boyd, Walley. Supervision: Walley.

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