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Review Article

Association between FcγRIIa-131R/H polymorphism and the risk of sepsis: a systematic review and meta-analysis

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Abstract: Objectives: Recent studies on the association between *FcγRIIa-131R/H* polymorphism and sepsis susceptibility showed inconsistent results. Thus, a meta-analysis was conducted to clarify the association between *FcγRIIa-131R/H* polymorphism and risk of sepsis. Methods: We systematically searched PubMed, Embase and Web of Knowledge databases for literature published between database inception and 31 December 2015, as well as reference lists of identified primary studies. The genotype number or allele frequency for case and control were compared by using odds ratios and 95% confidence intervals. Fixed or Random-effects models were used based on heterogeneity test. Results: A total of 10 studies comprising 4714 subjects fulfilled the inclusion criteria for the final analysis. Neither overall analysis nor subgroup analysis showed evidence of a significant association between *FcγRIIa-131R/H* polymorphism and sepsis risk under all genetic models. Conclusions: Our meta-analysis reveals that current evidence does not support a direct effect of *FcγRIIa-131R/H* polymorphism on the risk of sepsis. We need more studies based on larger sample sizes and homogeneous patients to confirm this finding.

Keywords: Sepsis, Fc gamma receptor, polymorphism, meta-analysis

Introduction

Sepsis is a systemic inflammatory response syndrome (SIRS) that caused by microorganism infection [1]. Despite the advances in the development of supportive care and antibiotics therapy, sepsis remains the most common cause of mortality in critically ill patients worldwide [2, 3]. Early diagnosis sepsis and timely treatment are the keys to improve patients' outcome [4]. Thus, there is an urgent need of a method which could help us identify patients who are at high risk of developing sepsis. Currently, experimental and epidemiological studies suggest that the host genetics may play an important role in the susceptibility to sepsis [5-7].

There are two families of human low affinity *Fcγ* receptors located on chromosome 1q23, that consists of *FcγIIa*, *IIb*, *IIc*, *IIIa*, and *IIIb* genes [8]. The most widely distributed class of *Fcγ* receptors is *FcγIIa*. Single nucleotide substitution (*T* or *C*) at the position 131 of *FcγIIa* encodes the amino acids histidine (*H*) or arginine (*R*), respectively [9]. These variants have markedly different in binding human IgG2. *FcγIIa-131H* is the high-binding allele, *FcγIIa-131R* is low-binding, and heterozygotes have intermediate function [10]. Phagocytosis of IgG2 opsonized bacteria by polymorphonuclear leucocytes is the main host defence against infection diseases, so *FcγIIa* alleles may be inherited susceptibility factors in sepsis.

Several studies have investigated the potential association between *FcγRIIa-131R/H* polymorphism and sepsis, but the results were not consistent and remained inconclusive [11-22]. This inconsistency may be due to insufficient sample sizes with low statistical power, racial differences, publication biases, and so on. Therefore, we conducted the meta-analysis based on the published papers to investigate the association between the *FcγRIIa-131R/H* polymorphism and sepsis susceptibility.

Table 1. Characteristics of the studies included in the meta-analysis

Study	Country	Case	Control	Case			Control			HWE
				HH	HR	RR	HH	HR	RR	
Bredius 1994	Netherlands	25	123	7	7	11	36	59	28	Yes
Norris 1996	America	60	60	18	27	15	7	30	23	Yes
Yee 2000	America	42	136	7	14	21	34	62	40	Yes
van 2001	Netherlands	138	239	34	81	23	58	134	47	Yes
Lehrn B 2005	Germany	68	34	23	31	14	10	16	8	Yes
Yuan 2008	Australia	85	409	20	32	33	86	239	84	No
Ende M 2009	Netherland	54	146	14	18	22	42	73	31	Yes
Davis 2010	America	28	63	6	15	7	19	24	20	Yes
Sole V 2011	Spain	1262	1224	321	638	303	284	630	310	Yes
Beppler 2015	Brazil	347	171	74	172	101	50	75	46	Yes

HWE: Hardy-Weinberg equilibrium.

Materials and methods

Search strategy

We systematically searched PubMed, Embase and Web of Knowledge databases to identify all published case-control studies up to 31 December 2015 that had evaluated the associations between *Fcγ* receptors polymorphism and sepsis. The combination of terms "*Fc gamma receptor*", "*Fcγ* receptor", "*FcγR*", "*FCGR*", "*rs1801274*", "sepsis", "septic shock", "septicemia", "polymorphism", "variation", and "mutation" was used without language restriction and publication date. Additionally, the reference lists of each primary study identified were hand-searched to identify potentially eligible studies. Authors were contacted by Email to obtain related data not revealed in original articles.

Study selection

Eligibility of a study for the meta-analysis was based on the following selection criteria: (1) evaluate the association between *FcγRIIa-131R/H* polymorphism and sepsis risk; (2) case-control study or cohort study; (3) the study provided sufficient information to infer the results. The exclusion criteria were as follows: (1) review, comment, abstract, editorial, and case report; (2) articles that did not provide the detailed genotype data. If data were reported in more than one study, only the one with the largest dataset was included.

Data extraction

Two investigators (S.L.L and Z.H.D) reviewed all eligible studies and extracted data independently. The following data was extracted from each included study: first author's name, year of publication, study design, sepsis type, country origin and ethnicity of study population, genotype number or allele frequency for case and control. Disagreements were resolved by referral to a third investigator (W.X.P). We contacted the authors of the included studies by email if further information was needed. If there was no response, the study was excluded.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) for each study was calculated again in our meta-analysis, and the Chi square goodness of fit was used to test deviation from HWE. We assessed the strength of the association between *FcγRIIa-131R/H* polymorphism and sepsis susceptibility by calculating the pooled odds ratio (OR) with their 95% confidence interval (95% CI). The significance of pooled OR was tested by Z-test ($P<0.05$ was considered statistically significant). The following comparison models were evaluated: an allele model (*H* vs. *R*), a co-dominant model (*HH vs. RR*), a dominant model (*HH+HR* vs. *RR*), and a recessive model (*HH* vs. *HR*+RR). We used Cochran's Q test and the I^2 statistic to examine the heterogeneity among the studies. Significant heterogeneity was considered when the *p* value was less than 0.05 and the I^2 value was greater than 50%. If there was significant heterogeneity, we chose a random model (the DerSimonian and Laird method); if there was no heterogeneity, we chose a fixed model (the Mantel-Haenszel method). Galbraith plots were performed to investigate the source of between-study heterogeneity. Sensitivity analysis was performed to assess the stability of the results.

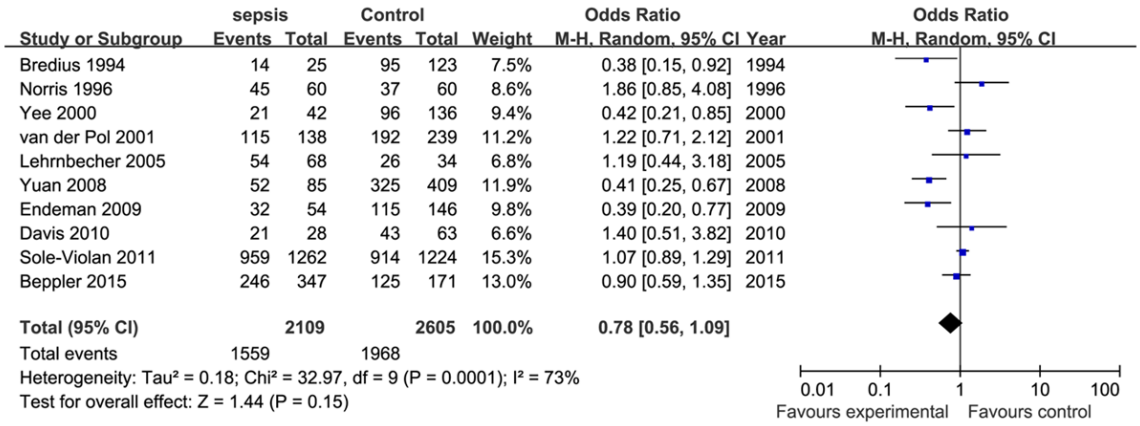

Figure 1. Forest plot of sepsis susceptibility associated with FcγRIIa-131R/H polymorphism under the dominant model (HH+HR vs. RR).

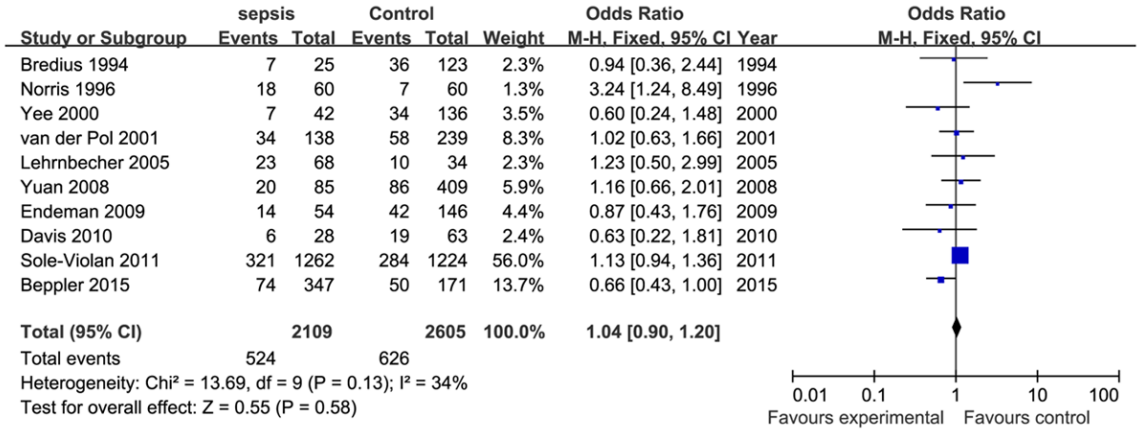

Figure 2. Forest plot of sepsis susceptibility associated with FcγRIIa-131R/H polymorphism under the recessive model (HH vs. HR+RR).

Publication bias was examined by funnel plot and Egger test. All statistical analyses were performed by using Review Manager 5.2 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 12.0 software (STATA Corp, College Station, TX).

All analyses are based on previous published studies, thus no ethical approval and patient consent are required.

Results

Characteristics of eligible studies

In our database search, we retrieved 125 articles, of which 94 were eliminated for various reasons based on the title and/or abstract. After full-text reviews, we excluded a further 24 studies: 4 studies' reference group or control group did not correspond to our criteria; 4 articles were conference abstracts or comments; 15 articles were reviews; 1 study's data had been duplicately published. Searches of the reference lists identify 3 additional relevant articles. Finally, 10 relevant articles were included in final meta-analysis. The characteristics and data of each included studies are shown in **Table 1**. Among the 10 publications, 5 studies were performed in European populations, 4 in American populations, 1 in Australian populations. Six records were performed in adult, and the others were in pediatric populations. In total, the 10 eligible studies provided 2109 cases and 2605 controls about the relationship between *FcγRIIa-131R/H* polymorphism and sepsis.

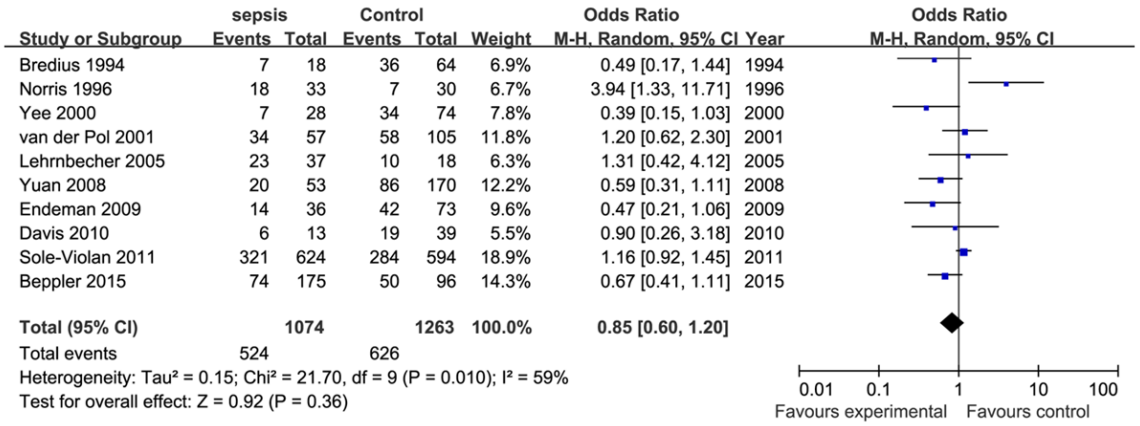

Figure 3. Forest plot of sepsis susceptibility associated with FcγRIIa-131R/H polymorphism under the co-dominant model (HH vs. RR).

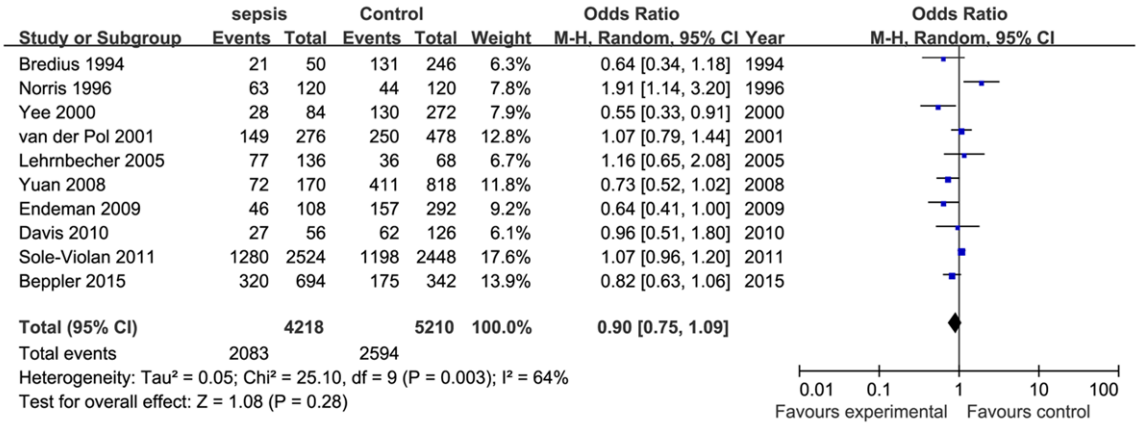

Figure 4. Forest plot of sepsis susceptibility associated with FcγRIIa-131R/H polymorphism under the allele model (H vs. R).

Quantitative data synthesis

To evaluate the association between *FcγRIIa-131R/H* polymorphism and sepsis susceptibility, we performed both the overall meta-analysis and the subgroup meta-analysis based on ethnicity and age according to the 10 eligible studies. There was no significant association between *FcγRIIa-131R/H* polymorphism and sepsis risk for overall analysis (*HH+HR* vs. *RR*: OR=0.78, 95% CI 0.56-1.09, P=0.15; *HH* vs. *HR+RR*: OR=1.04, 95% CI 0.90-1.20, P=0.58; *HH* vs. *RR*: OR=0.85, 95% CI 0.60-1.20, P=0.36; *H* vs. *R*: OR=0.90, 95% CI 0.75-1.09, P=0.28) (**Figures 1**-**4**). After removing the study which was not consistent with Hardy-Weinberg equilibrium testing, the results remained unchanged. Similarly, the results of the subgroup analyses showed that this polymorphism was not significantly associated with sepsis risk. Summary results of comparisons are listed in **Table 2**.

Sensitivity analysis

To examine the stability of the results of our meta-analysis, we removed each study sequentially. None of the results were significantly changed, which confirmed the robustness of our results.

Publication bias

Funnel plot and Egger test were done to estimate the publication bias of literatures. Dots in the funnel plot were mostly symmetrically distributed. Egger's test did not show obvious evidence of publication bias.

Table 2. Summary of meta-analysis results

Groups	Studies	Case	Control	Test of association				Heterogeneity		
				OR [95% CI]	*p* value	Z	Model	X^2	*p* value	I^2 (%)
Overall										
HH+HR vs. RR	10	2109	2605	0.78 [0.56-1.09]	0.15	1.44	RE	32.97	0.0001	73
HH vs. HR+RR	10	2109	2605	1.04 [0.90-1.20]	0.58	0.55	FE	13.69	0.13	34
HH vs. RR	10	1074	1263	0.85 [0.60-1.20]	0.36	0.92	RE	21.70	0.01	59
H vs. R	10	4218	5210	0.90 [0.75-1.09]	0.28	1.08	RE	25.10	0.003	64
Child										
HH+HR vs. RR	4	238	626	0.74 [0.33-1.66]	0.47	0.73	RE	13.27	0.004	77
HH vs. HR+RR	4	238	626	1.35 [0.93-1.98]	0.12	1.58	FE	4.09	0.25	27
HH vs. RR	4	141	282	1.06 [0.43-2.59]	0.90	0.12	RE	10.39	0.02	71
H vs. R	4	476	1252	1.00 [0.61-1.63]	1.00	0.00	RE	11.56	0.009	74
Adult										
HH+HR vs. RR	6	1871	1979	0.83 [0.58-1.18]	0.29	1.05	RE	14.96	0.01	67
HH vs. HR+RR	6	1871	1979	1.00 [0.86-1.16]	0.98	0.03	FE	7.73	0.17	35
HH vs. RR	6	933	981	0.81 [0.55-1.18]	0.26	1.12	RE	11.16	0.05	55
H vs. R	6	3742	3958	0.87 [0.71-1.08]	0.20	1.27	RE	13.35	0.02	63
European										
HH+HR vs. RR	5	1547	1766	0.79 [0.49-1.26]	0.32	0.99	RE	13.27	0.01	70
HH vs. HR+RR	5	1547	1766	1.10 [0.93-1.29]	0.26	1.14	FE	0.77	0.94	0
HH vs. RR	5	772	854	1.07 [0.88-1.30]	0.51	0.66	FE	6.62	0.16	40
H vs. R	5	3094	3532	1.03 [0.94-1.14]	0.51	0.66	FE	7.56	0.11	47
American										
HH+HR vs. RR	4	477	430	0.95 [0.53-1.71]	0.87	0.17	RE	8.60	0.04	65
HH vs. HR+RR	4	477	430	0.91 [0.45-1.86]	0.80	0.26	RE	9.59	0.02	69
HH vs. RR	4	249	239	0.94 [0.39-2.23]	0.88	0.15	RE	10.81	0.01	72
H vs. R	4	954	860	0.94 [0.59-1.50]	0.80	0.26	RE	12.38	0.006	76

OR: Odds ratio; CI: Confidence interval; RE: Random-effects model; FE: Fixed-effects model.

Discussion

Sepsis remains a major global health problem with a high mortality in critically ill patients. Examining why certain patients continue to have a high risk of sepsis may provide clues to early therapeutic interventions. Recently more and more studies have explored the hypothesis that common genetic variations, particularly single nucleotide polymorphisms (SNPs), may contribute to or influence the susceptibility of sepsis and had some exciting results [23-25]. Therefore, it is significant to continue to explore the association between genetic variations and sepsis risk.

The *FcγRIIa* molecule is the primary receptor of human polymorphonuclear leukocytes that interacts with the IgG2 antibodies. A point mutation in exon 4 of *FcγRIIa* causes an arginine (*R*)-to-histidine (*H*) amino acid substitution. Initial researches have indicated that the affinity for IgG2 would be affected by this polymorphism [26-28]. IgG2 is the predominant subclass of antibodies produced by the immune system in response to bacteria. Therefore, *FcγRIIa* polymorphisms of patients could contribute to an underlying susceptibility to bacterial infection. Endeman et al. indicated that the *FcγRIIa-131R/H* genotype is associated with sepsis susceptibility [17]. However, others researchers didn't support a role of *FcγRIIa-131R/H* polymorphism in susceptibility to sepsis [19, 20]. So far, we don't get a consistent result.

In our study, we identified 10 genetic association studies and used meta-analysis to evaluate the association of *FcγRIIa-131R/H* polymorphism with sepsis under the dominant, codominant model, recessive and allelic genetic model respectively. Our results demonstrated

that there was no association between *FcγRIIa-131R/H* polymorphism and sepsis risk. Subgroup analyses according to ethnicity and age also showed no obvious association between this polymorphism and sepsis risk.

Though many published studies have indicated the *FcγRIIa-131R/H* polymorphism affect the affinity for IgG2 and some meta-analyses demonstrated the polymorphism associate with malaria, Kawasaki Disease and systemic lupus erythematosus [29-32]. Our research indicated there was no significant association between the polymorphism and sepsis. There were some possible reasons for this. Sepsis is a complex clinical syndrome and associate with many genes. A single gene mutation may have limited impact on the association. Ethnicity is related to the frequency and effect of gene mutation. Our study only included European, American, and Australasian populations. So this study only can indicate that the polymorphism isn't association with sepsis in these populations. However, the polymorphism may have strong association with sepsis in Asians and Africans. The heterogeneity in our meta-analysis still existed in both overall comparisons and subgroup analyses. It may affect the accuracy of the results.

Our meta-analysis also has some other limitations. First, this meta-analysis included only 10 studies, though we did our best to search eligible studies. One reason for this was that we only searched PubMed, Embase and Web of Knowledge databases. Secondly, we could not address gene-gene interactions in our study due to the lack of the detail information. Third, the study was based on unadjusted data, whereas a more precise analysis could be performed if all individual data were available. This would allow for adjustment by other covariables, including age, gender, severity of sepsis, and so on. Finally, we could not ensure the consistency in study samples of all included studies, which may play an important role in drawing an accurate conclusion.

Conclusions

In conclusion, this meta-analysis suggested that the *FcγRIIa-131R/H* polymorphism have no strong association with the risk of sepsis. However, the impact of limitations cannot be ignored. We need more association investigations on large samples and homogeneous population to further clarify the role of the *FcγRIIa-131R/H* polymorphism in the susceptibility of sepsis.

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Disclosure of conflict of interest

None.

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