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Original Article

Increased susceptibility of sepsis associated with CD143 deletion/insertion polymorphism in Caucasians: a meta analysis

Hongming Yang, Yihe Wang, Lingying Liu, Quan Hu

Department of Burn & Plastic Surgery, The First Affilated Hospital of PLA General Hospital, Beijing, China

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Abstract: Background: Several lines of evidence have reported that serum angiotensin-converting enzyme (CD143) levels are genetically regulated by insertion/deletion (ins/del) polymorphism in intron 16 of the CD143 gene. In addition, published data on the association of ins/del polymorphism and sepsis risk yielded contradictory conclusions. Therefore, we determined to perform a meta-analysis to validate the association of much debate. Methods and major findings: Relevant literature was identified through weekly searches in databases and references of systematic reviews and the single studies incorporated in this meta-analysis. We combined ORs and its 95% CIs for several genetic models to evaluate the risk of sepsis associated with ins/del polymorphism. A total of seven studies were considered eligible for this analysis. We found significantly increased risk of sepsis in relation to the homozygote ins/ins (OR: 1.32, 95% CI: 1.04-1.68, *P*: 0.4201, for ins/ins vs. del/del), heterozygote del/ins (OR: 1.33, 95% CI: 1.11-1.61, *P*: 0.7937, for del/ins vs. del/del) and the two genotypes combined (OR: 1.33, 95% CI: 1.11-1.59, *P*: 0.7018, for ins/ins + del/ins vs. del/del). Subgroup analysis by age group showed a significant association in pediatric sepsis, but not in adult sepsis. Conclusions: The statistical data suggest that the CD143 gene ins/del polymorphism may influence the risk of sepsis, especially pediatric sepsis.

Keywords: CD143-ins/del polymorphism-sepsis

Introduction

Sepsis is an infection-initiated systemic inflammatory response syndrome (SIRS) characterized by leukopenia or leukocytosis, hypothermia or fever, tachypnea or supranormal minute ventilation, and tachycardia [1]. There has been a continuous increase in the occurrence rate during the past decades and this makes sepsis and sepsis-induced organ failures enormous challenges for clinicians and scientists [2, 3]. A number of groups have performed basic and clinic studies, attempting to identify the pathogens and to gain newest insights for the mechanism underlying sepsis [4-6]. These efforts, however, fail to unravel the nature of sepsis pathogenesis.

It is striking that Thomas nearly forty years ago first established a concept of host factors involved in susceptibility towards sepsis [7], and since then an increasing body of literature has emerged in an attempt to investigate the association of sepsis with sequence variations in the predisposition, low-penetrance genes [8].

Available data have shown that stimulation of inflammatory activities in conjunction with activation of coagulation leads to microvascular thrombosis, which ultimately causes multi-organ dysfunction and exacerbates the severity of sepsis [9, 10]. The renin-angiotensin system is of fundamental importance for the regulation of inflammatory reactions in addition to systemic blood pressure and intravascular volume. Angiotensin-converting enzyme (CD143) converts angiotensin I to angiotensin II, a major biological effector synthesized in various organs and functioning as a potent inducer of apoptosis in human endothelial cells [11-13].

Polymorphisms in the CD143 gene regulate the plasma CD143 levels, including the insertion/deletion (ins/del) polymorphism (dbSNPs: rs-

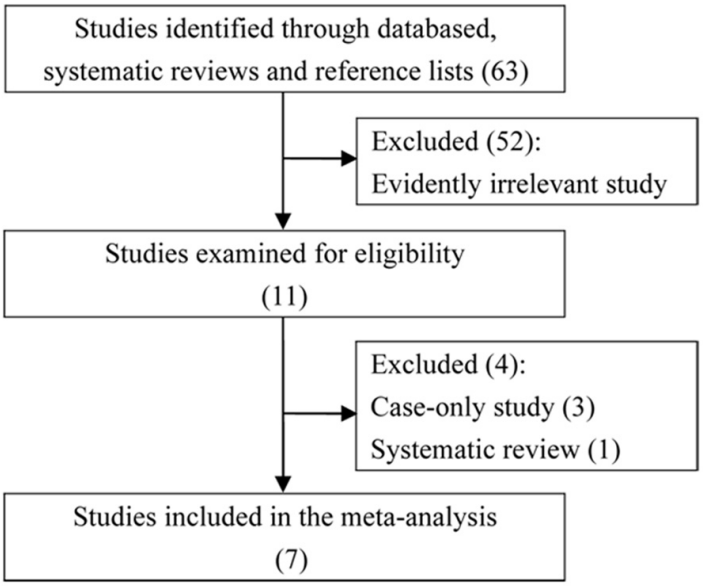

Figure 1. A flow diagram of study identification, exclusion and inclusion.

4340) at intron 16 [14]. Individuals with ins/ins or ins/del genotype have markedly lower CD143 levels compared to the individuals with del/del genotype [15]. Earlier research provided ample evidence supporting an association of higher CD143 levels with del/del genotype [16, 17]. However, serum CD143 activity varies considerably between individuals. For example, significantly higher levels are detected in type II diabetic patients with macroalbuminuria relative to the patients with normoalbuminuria [18]. So it is interesting to investigate the effects of this CD143 polymorphism on sepsis. Nevertheless, there are controversial results with respect to the contribution of the CD143 polymorphism to sepsis [19-21].

In this meta-analysis, we incorporated all literature on the subject of interest to determine the association between CD143 ins/del polymorphism and sepsis risk.

Methods

This meta-analysis was conducted in agreement with the guidelines of preferred reporting items for systematic reviews and meta-analyses [22].

Search strategy and study eligibility

We performed weekly searches from Dec. 2013 to Feb. 2014 in multiple databases (PubMed, Embase, Web of Knowledge, Science Direct, Cochrane Library) to identify the literature addressing the association of CD-143 ins/del polymorphism with sepsis risk. The keywords embraced polymorphism, polymorphisms, angiotensin converting enzyme, CD-143, and sepsis. The online searches were supplemented by hand searching the references of two types of study: 1) systematic reviews; 2) the single studies incorporated in this meta-analysis. All publications, no matter what language was used, were included if: 1) the study addressed the association being investigated; 2) sepsis patients were analyzed; 3) reference group consisted of healthy controls; 4) genotype distribution between cases and controls were detailed; 5) subjects investigated must be unique. In cases of duplicates, we selected the largest study.

According to the inclusion criteria, two authors evaluated the titles, abstracts and full-texts whenever necessary to pick out the studies that provided usable data for this meta-analysis.

Data abstraction

A consensus on all items was reached prior to data abstraction. For each of the studies included, the pre-mentioned authors gathered first author's surname, year of publication, country where the study was completed, ethnicity of study population (Asian or Caucasian), genotyping assay, genotype count, study design (retrospective or prospective), age group (pediatric or adult), and Hardy-Weinberg equilibrium (HWE) wherever available.

Statistical analysis

Deviations from HWE were determined using a goodness-of-ft X^2-test in controls and $P < 0.05$ was considered statistically significant. The crude OR and its 95% CI were calculated for several genetic models to evaluate the association between CD143 ins/del polymorphism and sepsis risk. A Z test was used to assess the significance of pooled ORs, with $P < 0.05$ being considered significant. Between-study hetero-

Table 1. Summary information for the studies analyzed in the meta-analysis

Authors	Cases-controls	Age group	Study design	Country of origin	Ethnicity	Genotyping method	Deviation from HWE
Bunker-Wiersma et al.	53-135	Pediatric	Retrospective	Netherlands	Caucasian	Taqman	No
Celik et al.	98-100	Pediatric	Retrospective	Turkey	Caucasian	NA※	Yes
Cogulu et al.	98-287	Pediatric	Retrospective	Turkey	Caucasian	multiplex PCR	No
Davis et al.	28-53	Adult	Prospective	United States	Caucasian	Taqman	No
Spiegler et al.	246-963	Pediatric	Prospective	Germany	Caucasian	PCR-RFLP	No
Tsantes et al.	186-180	Adult	Retrospective	Greece	Caucasian	PCR, reverse-hybridisation technique	No
Villar et al.	212-364	Adult	Retrospective	Spain	Caucasian	PCR	No
Total	921-2082						

NA※: not available.

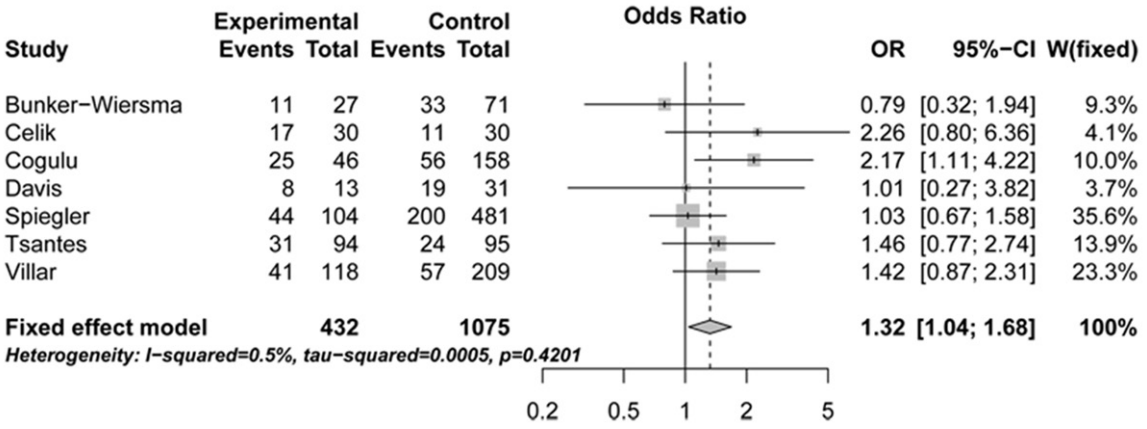

Figure 2. Forest plots illustrating the association between sepsis risk and CD143 gene ins/del polymorphism under ins/ins vs. del/del genetic model (fixed-effects model). OR, indicates odds ratio; CI, confidence interval.

geneity was examined by the chi-square-based Q-test, and the significance level was fixed at $P < 0.05$. We also quantified the variance across studies using the I^2 statistic and the I^2 values ≥ 50% represented large heterogeneity [23]. When lack of significant heterogeneity was indicated, we used the Mantel-Haenszel method (the fixed effect model) to combine effect estimates. Otherwise, the DerSimonian Laird method (the random-effects model) was performed.

In addition to global analysis, we also performed subgroup analyses according to age group. The funnel plots, described by Begg, were applied to detect the publication bias in this analysis [24]. The Egger's test was used to examine the symmetry of each funnel plot ($P < 0.05$ indicated asymmetric plots) [25]. Sensitivity analysis was performed to assess the stability of the combined results. Statistical analyses were done by R software (version 2.15.0) and Stata software (version 12.0).

Results

Characteristics of included studies

Database and hand searches yielded 63 publications. After excluding the evidently irrelevant study, we were left with 11 studies. We then read through the full-texts, and found three case-only studies [26-28] and one narrative review [29]. Our final dataset therefore combined seven research articles [19-21, 30-33]. A flow chat showing the selection process is displayed in **Figure 1**.

As described in **Table 1**, there were seven Caucasian studies, of which four studies investigated sepsis in children and three in adults. Five retrospective studies were conducted in four different countries: Netherlands, Turkey, Greece, and Spain. The two prospective studies were from the United States and Germany, respectively. Significant deviation from HWE was revealed in a Turkish study [31]. Genotyping

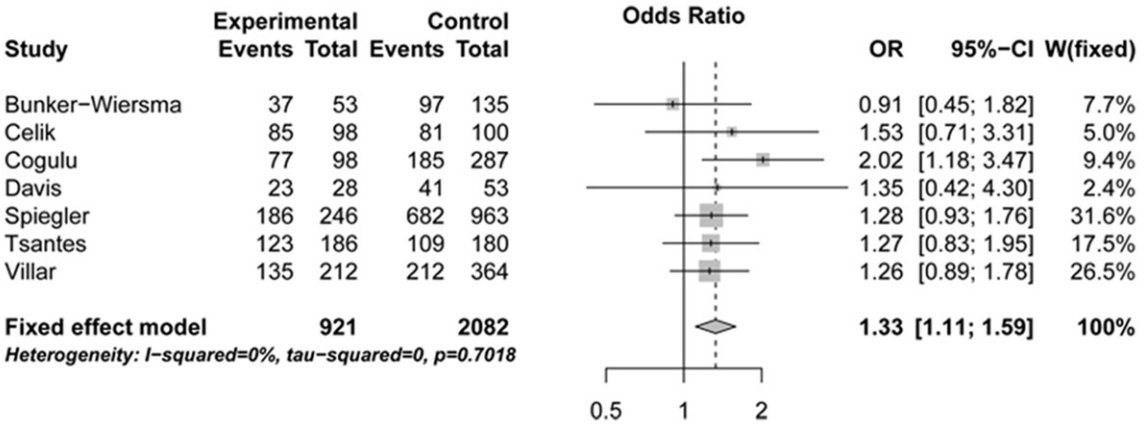

Figure 3. Forest plots illustrating the association between sepsis risk and CD143 gene ins/del polymorphism under ins/ins + del/ins vs. del/del genetic model (fixed-effects model). OR, indicates odds ratio; CI, confidence interval.

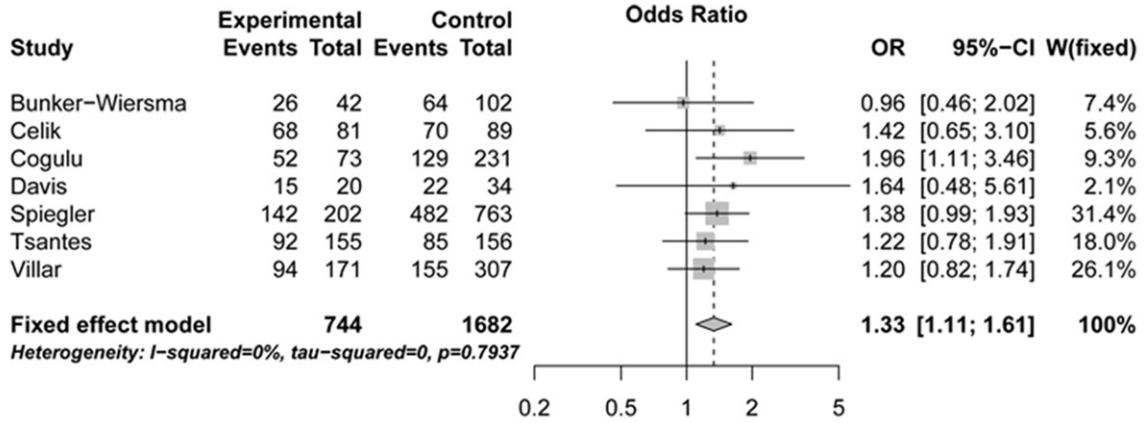

Figure 4. Forest plots illustrating the association between sepsis risk and CD143 gene ins/del polymorphism under del/ins vs. del/del genetic model (fixed-effects model). OR, indicates odds ratio; CI, confidence interval.

methods, including multiplex polymerase chain reaction (multiplex PCR), PCR-restriction fragment length polymorphism (PCR-RFLP), reverse-hybridization technique and Taqman were performed in identifying the genotypes of CD-143 polymorphism.

Association between CD143 polymorphism and sepsis

The association of CD143 polymorphism with sepsis risk was assessed in a meta-analysis combining 921 patients and 2 082 controls. All genetic models, with the exception of ins/ins vs. del/ins + del/del, provided statistical evidence for a significant association between the ins/del polymorphism and sepsis risk (OR: 1.32, 95% CI: 1.04-1.68, *P*: 0.4201, for ins/ins vs. del/del; OR: 1.33, 95% CI: 1.11-1.59, *P*: 0.7018, for ins/ins + del/ins vs. del/del; OR: 1.33, 95% CI: 1.11-1.61, *P*: 0.7937, for del/ins vs. del/del) (**Figures 2**-**4**; **Table 2**).

We subsequently performed subgroup analysis according to age group. The statistical data revealed significantly increased risk of sepsis in relation to the combined ins/ins and del/ins genotypes (OR: 1.38, 95% CI: 1.08-1.76, *P*: 0.3056) or del/ins genotype alone (OR: 1.43, 95% CI: 1.11-1.84, *P*: 0.5133) (**Table 2**).

Sensitivity analysis

To examine if the combined results were affected by some single study, we performed sensitivity analyses through removing one study each time. The removals did not cause quantitative differences compared to the original results. This process confirmed the stability of our findings.

Table 2. Meta-analysis of the association between CD143 I/D polymorphism and sepsis risk

Comparisons	Subgroups	No. of cases and controls	Effect size	Heterogeneity test		Model※※
			OR (95% CI)	P_{Het}	I^2 (%)	
(ins/ins vs. del/del)	Total	921-2082	1.32 (1.04, 1.68)	0.4201	0.5	FEM
	Pediatric	495-1485	1.27 (0.93, 1.74)	0.1302	46.9	FEM
	Adult	426-597	1.39 (0.96, 2.02)	0.8833	0.0	FEM
(ins/ins + del/ins vs. del/del)	Total	921-2082	1.33 (1.11, 1.59)	0.7018	0.0	FEM
	Pediatric	495-1485	1.38 (1.08, 1.76)	0.3056	17.1	FEM
	Adult	426-597	1.27 (0.97, 1.65)	0.9936	0.0	FEM
(ins/ins vs. del/ins + del/del)	Total	921-2082	1.08 (0.88, 1.33)	0.3832	5.8	FEM
	Pediatric	495-1485	1.01 (0.78, 1.31)	0.2143	33.0	FEM
	Adult	426-597	1.21 (0.87, 1.68)	0.5448	0.0	FEM
(del/ins vs. del/del)	Total	921-2082	1.33 (1.11, 1.61)	0.7937	0.0	FEM
	Pediatric	495-1485	1.43 (1.11, 1.84)	0.5133	0.0	FEM
	Adult	426-597	1.23 (0.93, 1.62)	0.8928	0.0	FEM

Model※※: fixed-effects model.

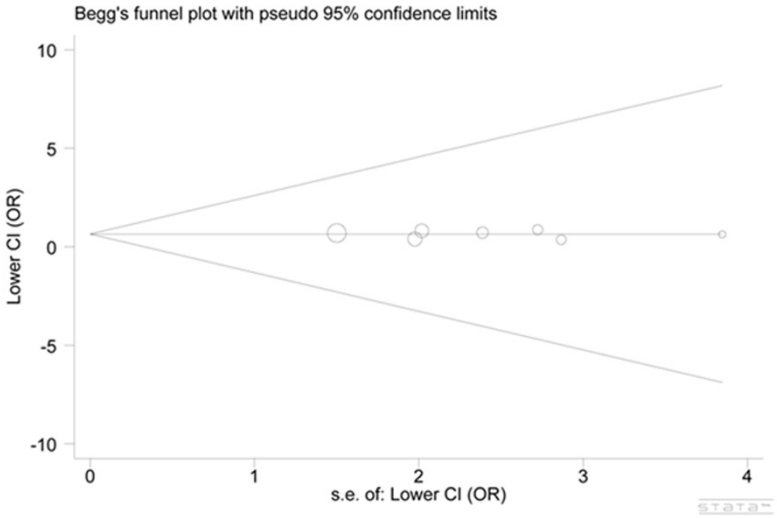

Figure 5. Egger's test and Begg's test of publication bias.

Publication bias

We evaluated the publication bias by use of the funnel plots along with the Egger's test. The studies were symmetrically distributed within the funnel plots (z: 0.30, *P*: 0.764 for ins/ins vs. del/del) (**Figure 5**). Evidence of asymmetry was not revealed by performing the Egger's test (z: -0.24, *P*: 0.822 for ins/ins vs. del/del).

Discussion

Single nucleotide polymorphisms in pro-inflammatory genes that catalyze the stimuli of bacterial pathogens affect the biological function of the protein and thus confer individual susceptibility to the development of various human diseases, such as sepsis [34]. The human CD143 at chromosome 17q23 is an exopeptidase with a pivotal role in regulating inflammatory responses. Several studies have investigated the genetic alternations in CD143 gene and demonstrate that these variations impair the innate immune system by upregulating CD143 activity and consequently promote inflammation process [35, 36]. All genotypes of the ins/del polymorphism, including ins/ins, ins/del, and del/del are associated with plasma CD143 activities, with the heterozygote ins/del accounting for almost half (47%) of the total phenotypic variance, indicating most circulating CD143 concentration is determined by its genetic variations [16].

Recently, the effects of a functional polymorphism, CD143 ins/del, have been extensively studied in sepsis community because of the regulatory role in plasma CD143 levels [19-21, 33]. The previous studies, however, may have reported false-negative or false-positive results most likely due to poor study design and methodological limitations [37]. In an effort to clarify whether or not CD143 ins/del polymorphism

affects susceptibility to sepsis, we determined to carry out a meta-analysis.

Meta-analysis as a known analytical method could supply strong evidence of genotype-phenotype relationships for human ma-lignancies [38]. Herein, we analyzed 3 003 subjects and found a significant association between the ins/del polymorphism and overall sepsis risk. To be more specific, the carriage of ins/ins or ins/del alone, or ins/ins and ins/del combined had approxi-mately 33% greater risk of sepsis compared to the carriage of del/del. Strikingly, the observed association only persisted in pediatric subjects and was lost in adult subjects when data were stratified by age group. As reported by Felehgari et al., CD143 levels are significantly lower in patients harboring normoalbuminuria in comparison to patients with macroalbuminuria [18], showing plasma CD143 activities vary substantially even in patients with the same type of disease. Therefore, we hypothesize that the ins/del polymorphism modify susceptibility towards common diseases possibly by interacting with various confounders, such as age, gender, environmental pathogens and other predisposition genes. In addition, several lines of evidence have shown that there is no clear connection between the ins/del polymorphism and circulating CD143 levels. Thus we cannot rule out the possibility that the ins/del polymorphism exerts no influence on CD143 function, and does not modulate sepsis susceptibility [39-41]. Whether the ins/del polymorphism plays a major role in sepsis remains to be elucidated.

Previous reports have demonstrated wide differences in terms of the impact of ins/del polymorphism on CD143 activities as a result of disparate ethnicities. Tiret et al. found increased CD143 levels in Caucasian populations [16, 17]. A study by Bloem et al. revealed a clear association between serum CD143 activity and CD143 gene ins/del polymorphism in whites, but not in blacks, suggesting ethnic variation plays an important role in genetic regulation of serum CD143 levels and the relation of ins/del polymorphism with human diseases [42]. In this meta-analysis, only Caucasian studies were identified and the effects on other ethnic populations remain unknown. We expect that studies of various ethnicities will be conducted to determine the role of the CD143 gene ins/del polymorphism in sepsis.

Several limitations should be noted when interpreting the results of this meta-analysis. First, the small number of included studies, with each of them conducted with an inadequate sample, may likely make our analysis less powerful. Second, a positive association which requires further studies to validate was observed among Caucasian subjects in this work. It is still unclear whether the individuals of different ethnicities have higher risk of sepsis. Third, while no asymmetry was revealed in the funnel plots and no statistical evidence of significant publication bias was shown by performing the Egger's test, the bias may be introduced as we failed to include the unpublished studies and the studies written in other languages.

However, we incorporated all genetic association studies reporting on CD143 ins/del polymorphism and sepsis risk and the results were more powerful than any of the previously published studies concerning the same topic. We noted that although the ins/del polymorphism showed a significant association with sepsis risk in general populations, it seemed to not associate with the adult sepsis.

To sum up, we found some evidence supporting that the ins/del polymorphism in intron 16 of the CD143 gene was associated with risk of sepsis, pediatric sepsis in particular. The inadequate sample size of this investigation emphasizes the necessity for future studies to be larger and better designed to evaluate the effects the ins/del polymorphism has on sepsis.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hongming Yang, Department of Burn & Plastic Surgery, The First Affilated Hospital of PLA General Hospital, 51 Fu ChengRoad, Beijing 100037, China. E-mail: hongmvng@163.com

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