Role of Tumour Necrosis Factor-Alpha promoter 308A/G polymorphism in sepsis and sepsis mortality: A Meta-Analysis

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Abstract

Background: Sepsis is the most common health problem because of which an increased proportion of health resources are consumed. Tumour Necrosis factor alpha also plays an essential role in many diseased conditions like diabetes, cancer, etc. There have been findings suggesting a high level of correlation between TNF activity and sepsis susceptibility and mortality. Thus, the present meta-analysis was carried out to assess the role of Tumour Necrosis Factor-Alpha promoter 308A/G polymorphism in sepsis and sepsis mortality. Methods: The meta-analysis was carried out using the MOOSE guidelines. A total number of 782 articles were retrieved, out of which only 45 full-text articles were eligible. Out of that, 24 were used for meta-analysis after checking the quality of articles. The meta-analysis was carried out using MedCalc Software. The comparison of TNF factor alpha 1 and 2 among patients was calculated in the two groups. The odds ratio of these studies was used to construct the forest plot. Results: Eight studies evaluated the odds of having increased TNF1 in sepsis conditions. The plot shows that the cumulative statistics are significant at a 95% confidence level and have a p-value less than 0.05. The odds of increased TNF2 in sepsis conditions among Asians is more than in the case of TNF1. The odds ratio of 0.978 indicates that the odds of increased TNF1 in sepsis conditions among Caucasians are more than in the case of TNF2. Conclusion: The meta-analysis suggests an association between the G/A allele combination of TNF-α and sepsis risk in the Asian population compared to the Caucasian Population.

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Methods: The meta-analysis was carried out using the MOOSE guidelines. A total number of 782 articles were retrieved, out of which only 45 full-text articles were eligible. Out of that, 24 were used for meta-analysis after checking the quality of articles. The meta-analysis was carried out using MedCalc Software. The comparison of TNF factor alpha 1 and 2 among patients was calculated in the two groups. The odds ratio of these studies was used to construct the forest plot.

Results: Eight studies evaluated the odds of having increased TNF1 in sepsis conditions. The plot shows

that the cumulative statistics are significant at a 95% confidence level and have a p-value less than 0.05. The odds of increased TNF2 in sepsis conditions among Asians are more than in the case of TNF1. The odds ratio of 0.978 indicates that the odds of increased TNF1 in sepsis conditions among Caucasians are more than in the case of TNF2.

Conclusion: The meta-analysis suggests an association between the G/A allele combination of *TNΦ-α* and sepsis risk in the Asian population compared to the Caucasian Population.

Keywords: Tumor Necrosis Factor (TNF); 308 A/G Polymorphism; Sepsis; Sepsis Mortality; Asians; Caucasians.

What is already known about this topic?

Tumour Necrosis factor alpha plays a vital role in many body's diseased conditions like diabetes, cancer, etc. The studies conducted in the past have produced mixed results on the role of TNF-$\propto$ during weakened health conditions. Very few studies determined its role in sepsis and its associated mortality. However, few studies demonstrate that it has no role in the Caucasians.

What does this article add?

This is an updated meta-analysis of all the studies done so far on the TNF-α and its relationship with the sepsis and sepsis mortality especially, in the Asian population when compared to the Caucasians.

Introduction

Sepsis is defined as the infection that causes the immune system to attack the body, subsequently leading to an individual's death. Sepsis is the most common health problem because of which an increased proportion of health resources are consumed. It is most commonly seen in the elderly, preterm infants, or low birth weight infants.[1,2] Various studies in the past have shown an association between the polymorphism and sepsis-related mortality.[3] Several biomarkers have been seen to show an elevated level in sepsis condition like *TLR4* (toll-like receptor 4) single nucleotide polymorphisms, rs4986790, and rs4986791, but not the *SERPINE1* [Serpin Peptidase Inhibitor, Clade E (Nexin, Plasminogen Activator Inhibitor Type 1), Member 1] rs1799768 polymorphism.[4-8]

Tumour Necrosis factor alpha also plays a vital role in many body's diseased conditions like diabetes, cancer, etc. The studies conducted in the past have produced mixed results on the role of TNF-$\propto$during weakened health conditions. One study reported this as a risk factor in the North Indian population, Japanese patients, Chinese, Turkish children. Studies in Germany and Hungary revealed a negative correlation between preterm infants and low birth weight infants.[8-19]

However, there are several genomic variants of the TNF factor-$\propto$of which the biallelic polymorphism at position 308 is associated with sepsis.[20,21] There have been findings suggesting a high level of correlation between TNF activity and sepsis susceptibility and mortality. [22-23.] However, there is an equal number of evidence contradicting the findings.[24] Thus, the present meta-analysis is carried out to assess the role of Tumour Necrosis Factor-Alpha promoter 308A/G polymorphism in sepsis and sepsis mortality.

Methods

The meta-analysis was carried out using the MOOSE guidelines. The studies selected were evaluated on two parameters: a)They must focus on TNF- $\propto$ 308 A/G polymorphism and b) They must focus on sepsis and sepsis mortality.

The keywords used were: TNF- $\propto$ 308 A/G, Tumour necrosis factor, sepsis, septic shock, and sepsis mortality. The search was carried out in MEDLINE, Scopus, and Web of Science databases. All articles up to 2019 were considered. A total of 782 articles were retrieved, out of which only 45 full-text articles were found to be eligible. Out of those, 24 were used for meta-analysis after checking the quality of articles. (Figure 1)

Figure 1 shows the selection of studies.

The studies were excluded for one of the following reasons: Duplicate Articles studies considered multiple organ dysfunction and/or sepsis not related to bacterial function. Three reviewers evaluated the titles, abstracts, and text of the articles searched. The final inclusion of articles was considered after the full agreement of the reviewers. It was also statistically analyzed using kappa statistics; the value of 0.87 indicated a high level of agreement between the reviewers, and hence the included studies were finalized. (Table 1)

The included studies compared G/G with G/A, G/A with A/A, and hence the meta-analysis compared the studies taking G/G with G/A or A/A allele combinations. G/A or A/A allele combination is referred to as TNF-2 and G/G as TNF1. The meta-analysis also considered the ethnicity of the study population, and it is believed to have a confounding role in the role of TNF towards sepsis and sepsis mortality.

The meta-analysis was carried out using MedCalc Software. The comparison of TNF factor alpha 1 and 2 among patients was calculated in the two groups. The odds ratio of these studies was used to construct the forest plot. The random-effects model was used with statistical significance at a p-value less than 0.05 to assess TNF factor alpha's association with sepsis response.

Results

Figure 2 shows the Forest Plot between the role of TNF alpha during sepsis. Less than 1 favors TNF1, and more than 1 favors TNF2 among Asian Population. The plot shows eight studies evaluated for the odds of having increased TNF1 in sepsis conditions. The plot shows that the cumulative statistics are significant at a 95% confidence level and have a p-value less than 0.05. The cumulative statistics for odds of increased TNF2 with confidence interval varying from 0.992 to 1.310. The odds ratio of 1.140 indicates that the odds of increased TNF2 in sepsis condition among Asians were more than the cases of TNF1. The I2 (inconsistency) is also more than 95%, indicating less heterogeneity between the studies included.

Figure 3 shows the Forest Plot between the role of TNF alpha during sepsis. Less than 1 favors TNF1 and more than 1 favors TNF2 among Caucasian Population. Fifteen studies evaluated the odds of having increased TNF1 in sepsis conditions. The cumulative statistics were significant at a 95% confidence level and had a p-value less than 0.05. The odds ratio of 0.978 indicates that the odds of increased TNF1 in sepsis condition among Caucasians is more than in the case of TNF2. The I2 (inconsistency) is less than 95% (82.31%), indicating moderate heterogeneity between the studies included.

Discussion

The present meta-analysis showed increased susceptibility among the population carrying TNF2 compared to the TNF1 allele. Teuffel et al. and Zhang et al. also reported an increased sepsis risk among GG or AA genotypes[25,26]. The inconsistency in previous studies' results does not give a direction to this biomarker's role. This study revealed an association between polymorphism and sepsis among Asian/Caucasian ethnic backgrounds. This result could help in further conduct of prospective research among the said ethnic background.

The meta-analysis used the definition of sepsis and considered different clinical conditions like sepsis, septicemia, septic shock for analysis. There was no difference found in the analysis because of the different conditions. Similarly, there was an inconsistent methodologic description in the studies considered. However, the meta-analysis helped in overcoming the shortcomings of the individual studies and produced a combined effect on TNF alpha's role during sepsis.

The study has few limitations, like fewer studies that have a larger sample size, thus affecting the statistical power. There was high heterogeneity among the different ethnic backgrounds, and lastly, there is a strong need for more studies to determine the clarification on genetic roles and cytokine production during sepsis.

The meta-analysis suggests an association between the G/A allele combination of *TNΦ-α* and sepsis risk in the Asian population compared to the Caucasian Population. It is also in line with Teufel et al. and Zhang et al. Furthermore, the present meta-analysis identifies the opportunity to get a more stratified focussed

analysis by considering similar studies in each stratum. Meta-Regression can also be carried out to examine the hidden factors affecting the phenomenon. Suggestive publication bias as no or fewer studies were focusing on TNF2 and sepsis's negative analysis.

Acknowledgment: None Declared.

Statement of Ethics: All procedures performed in the study were in accordance with the institutional and/or national research committee's standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest Statement: The authors declare that they have no competing interests.

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Author Contributions: HN and FL: Concept and designed the study, HM and LX: analyzed data and drafting of the manuscript; JC: Collected the data and helped in data analysis; MH: Proofreading and final editing along with guarantor of the manuscript. All authors read and approved the final version of the manuscript.

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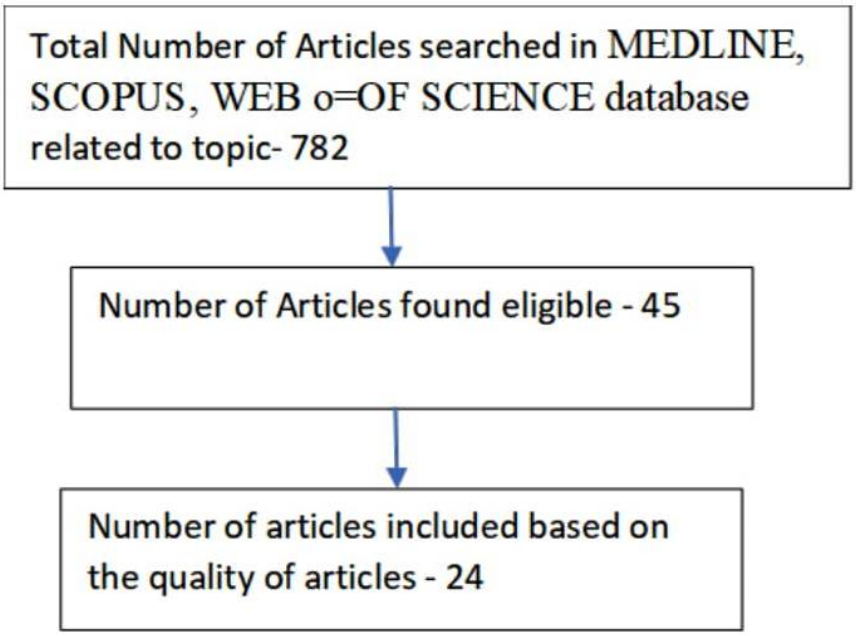
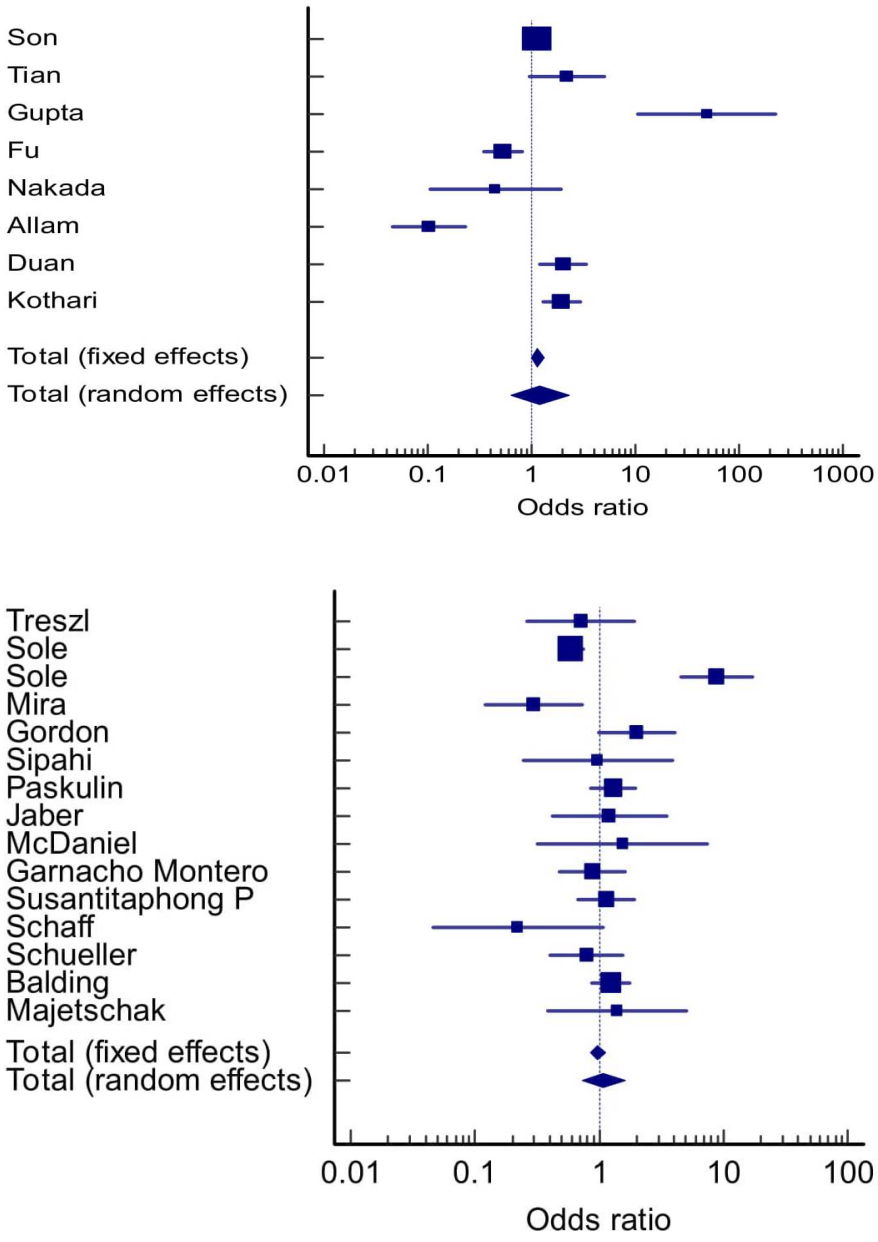
FIGURE LEGENDS

Figure 1 shows the selection of studies.

Figure 2 shows the Forest Plot between the role of TNF alpha during sepsis.

Figure 3 shows the Forest Plot between the role of TNF alpha during sepsis.





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