

Effect of low high-density lipoprotein levels on mortality of septic patients: A systematic review and meta-analysis of cohort studies

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BACKGROUND: An increase in high-density lipoprotein (HDL) is well associated with a decreased cardiovascular risk, especially atherosclerosis. Recent studies suggest that lower levels of HDL may also be associated with an increased risk of sepsis and an increased rate of mortality in septic patients. However, this conclusion remains controversial.

METHODS: MEDLINE, EMBASE, and CENTRAL databases were searched from inception to September 30, 2019. All studies were conducted to evaluate the correlation of lipoprotein levels and the risk and outcomes of sepsis in adult patients. The primary outcomes were the risk and mortality of sepsis.

RESULTS: Seven studies comprising 791 patients were included. Lower levels of HDL had no marked relevance with the risk of sepsis (odds ratio [OR] for each 1 mg/dL increase, 0.94; 95% CI 0.86–1.02; $P=0.078$), whereas lower HDL levels were related to an increased mortality rate in septic patients (OR for below about median HDL levels, 2.00; 95% CI 1.23–3.24; $P=0.005$).

CONCLUSION: This meta-analysis did not reveal a significant association between lower HDL levels and an increase in the risk of sepsis, whereas it showed that lower HDL levels are associated with a higher mortality rate in septic adult patients. These findings suggest that HDL may be considered as a promising factor for the prevention and treatment of sepsis in the future.

KEY WORDS: High-density lipoprotein; Sepsis; Mortality; Meta-analysis

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INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by the dysregulation of a host's response to infections,^[1] which is further complicated by an altered metabolic state. The mortality rate of sepsis remains high,^[2,3] but the potential mechanism is unclear. It has been widely accepted that the inflammatory mediators which alter the body's metabolic state play an important role in the pathogenesis of sepsis.^[4] There are also no specific or effective treatments available for sepsis, therefore, it will be of great interest to find a new approach to prevent and treat sepsis.

Notably, the effects of high-density lipoproteins (HDL) on sepsis have become a hot topic. The 2016 European Guidelines for Cardiovascular Disease Prevention shows a lower risk of cardiovascular events when HDL levels are above 40 mg/dL in men or above 45 mg/dL in women.^[5] Nevertheless, when HDL levels of septic patients decrease to 33.6 mg/dL or even 20 mg/dL, there were significant correlations with a higher risk^[6] or mortality^[7] of sepsis. It is reported that HDL can clear lipopolysaccharides (LPS) and other pathogenic lipids through the liver, wherein receptors such as the HDL receptor, scavenger receptor and class B type I

are bonded to the pathogenic lipids during the sepsis process.^[8-10] Some studies^[11,12] reported HDL has the highest affinity to both toxin lipoteichoic acid and LPS, which is beneficial for decreasing the ability to actively regulate the innate immune response. HDL is able to maintain the endothelial function and repair,^[13] which are important for mediating the inflammatory response in the process of sepsis. In addition, HDL also prevents peroxide damage and stimulates the endothelial cells secreting endothelial nitric oxide synthetase.^[12, 14]

Given the evidence of its role in the pathogenesis of sepsis, HDL may be a potential predictor of the risk of sepsis or the prognosis in septic patients. In recent years, an increasing number of studies^[6, 15-20] have reported that lower HDL levels are related to an increased risk of sepsis and the mortality in septic patients. However, the results among the published studies remain controversial, and consolidating the available information to assess the association between HDL levels and sepsis is imperative.

METHODS

The methods of this meta-analysis is in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.^[21] We searched the MEDLINE (www.ncbi.nlm.nih.gov/pubmed), EMBASE (www.embase.com) and Cochrane CENTRAL (www.cochranelibrary.com) databases for articles published in English from the inception of the databases to September 30, 2019. The proceed of search was presented in Figure 1. We used the combination of “cholesterol”, “lipoprotein”, “low-density lipoprotein”, “high-density lipoprotein”, “severe sepsis”, “septic shock”, and “critically ill patients” as the keywords. We also manually-searched the references of the included articles. The literature searches were performed independently by HL and HL. When disagreement occurred between different evaluators, the final decision was made by the third researcher. In addition, the EndNote X7 software was used for literature screening process.

Inclusion criteria

Studies were considered suitable for inclusion in this meta-analysis if they met the following criteria: (1) patients with sepsis, severe sepsis or septic shock were enrolled; (2) when the studies observed the risk of sepsis, not all of the enrolled patients were septic patients; (3) the levels of HDL were divided into lower or higher level groups according to the median concentration or

the levels were set by the designers in the initial studies; (4) the mortality or risk of sepsis was measured; (5) all the patients were adults; and (6) language was English. Studies were excluded if they lacked outcome data, were animal researches, provided only an association of lipoprotein levels and patients with other illnesses but not sepsis, or reported outcomes that were between non-HDL lipoprotein levels and sepsis. If the full text was not available or the article was a review, it would be excluded.

Data extracted

All the suitable data were independently extracted based on the aforementioned inclusion and exclusion criteria. The objective outcomes were the risk odds ratios (ORs) or mortality of sepsis among septic patients. The data of each study were listed as: the last name of the first author, publication year, country, study design, population, mean age, mean levels of HDL, study period and reported outcomes.

Bias of risk assessment

In this meta-analysis, the risk of bias in each study was assessed using the Newcastle-Ottawa Scale (NOS).^[22] The highest score that would be awarded from the NOS assessment was nine: in cohort selection, the comparability of the cohort design and analysis and the adequacy of the outcome measures were awarded a maximum of four points, two points and three points, respectively; higher than or equal to seven points was considered as high quality.^[22]

Primary outcome

In this article, we extracted the outcomes including risk^[6,23] and mortality^[7,20,24-26] of sepsis as primary outcomes.

Statistical analysis

The outcomes of this study were mortality and risk odds ratio between lower and higher HDL levels in septic adult patients. The pooled effect of each outcome was conducted. In order to assess the heterogeneity among the included studies, we used a random effects model to calculate *OR* and 95% *CI* from each included study. The *I*² and *P* values were used to evaluate the heterogeneity of each included studies, in which the variability was caused by heterogeneity rather than sampling error.^[27, 28] When *I*² equaled 51%–74% or greater than 74%, the heterogeneity was considered as moderate or high, respectively. Because the number of each outcome was relatively small, the publish bias was not performed in

this meta-analysis. The statistical analyses in this study was performed by using STATA 14.0.

RESULTS

Study selection

Totally 1,524 articles were identified from these databases, and 250 articles were removed due to duplication. Forty-one studies remained after preliminary screening by title and abstract, and finally seven articles comprising 791 patients met inclusion criteria and were enrolled in this study. The selection process of this study is presented in Figure 1.

Study characteristics

Seven eligible articles reported the association of septic patients and HDL levels. Two articles^[6,23] indicated the relation of lower HDL levels and the risk of sepsis, five studies^[7,20,24-26] presented the outcomes that were associated with HDL levels in septic patients. Then, we extracted the *ORs* and 95% *CI*s for dichotomous data. Any missing data were calculated based on the raw data

provided by the included study. The baseline information about the analyzed studies is presented in Table 1.

Risk of bias assessment

According to the score of risk of bias in the NOS assessment, the quality of included studies was considered as a high quality and therefore showed a low risk of bias in this meta-analysis. The details of the risk of bias of included studies are reported in Table 2.

Effects of low HDL levels on sepsis

The primary outcome in the 7 observational studies^[6,7,20,23-26] showed that lower HDL had no significant relationship with the risk of sepsis (*OR* for each 1 mg/dL increase, 0.94; 95% *CI*s 0.86–1.02; Figure 2), whereas lower HDL levels were related to an increased mortality rate in septic patients (for below about median HDL levels 2.00; 95% *CI*s 1.23–3.24; Figure 3). Unfortunately, due to the reason that the HDL levels in both survivors and non-survivors were performed as median and interquartile, we could not pool the outcomes among included studies.

Publication bias assessment

We used the funnel plots (Figure 4) and Egger's regression (Figure 5) asymmetry tests to assess the potential publication bias in included studies, which evaluated the mortality between lower and higher HDL levels in septic patients. The result showed that there was a significant publication bias ($P=0.01$).

Trim and fill analysis

The trim and fill analysis (Figure 6) were performed to evaluate the robust model of the included articles that evaluated the mortality in lower and higher HDL levels among septic patients. The result showed that there was a need to add a new study that may be a source of the potential publication bias, and the model was not robust.

DISCUSSION

This meta-analysis demonstrated that lower HDL levels are related to an increased mortality in septic patients. This is the first systematic review study and meta-analysis to elucidate the association between lipoprotein levels and the risk of sepsis as well as the mortality of septic patients. The results of this meta-analysis indicate that HDL levels can be considered as an interesting factor for prevention and treatment of sepsis.

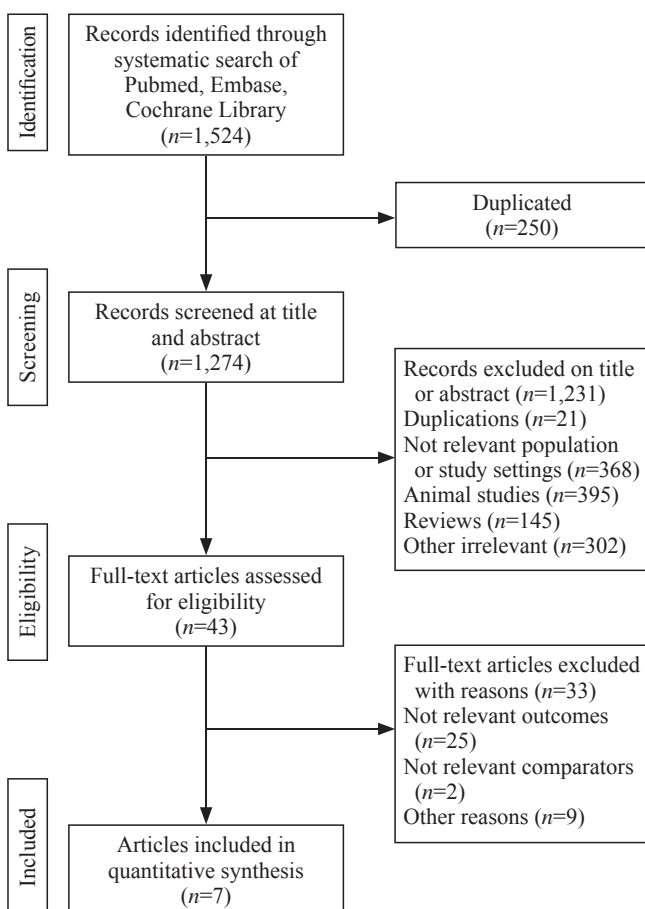


Figure 1. Flow-process diagram of the study selection.

Studies^[29-31] on animal models of sepsis have reported that HDL can ameliorate the adverse consequences of sepsis, for example, leading to decreased cytokine levels and organ dysfunction, increasing LPS clearance, and improving survival. One of the mechanisms by which the HDL improved the outcomes of sepsis in animal models is a higher affinity of the HDL receptors to LPS and other pathogenic lipids compared to the inflammatory factors, resulting in an increased clearance of those pathogenic compounds via the liver. Subsequently, the anti-endotoxin and anti-inflammation properties of HDL were confirmed in human studies.^[32,33] Moreover, Murch et al^[8] showed HDL can activate the sphingosines

binding to sphingosines receptors, and then exert the effect of bacterial killing or reduce the bacterial growth, thereby improving the inflammatory response in sepsis. In addition, HDL was found to protect LDL against oxidation,^[34] help to maintain normal microvascular structure and endothelial integrity during the period of infection^[35] and promote the removal of LPS from activated monocytes.^[36] Additionally, some studies have shown that patients with lower LDL levels had an increased risk of sepsis and worse outcomes.^[5,26] These potential protective effects of HDL may significantly decrease the risk of sepsis and improve the prognosis of septic patients, but this correlation requires further

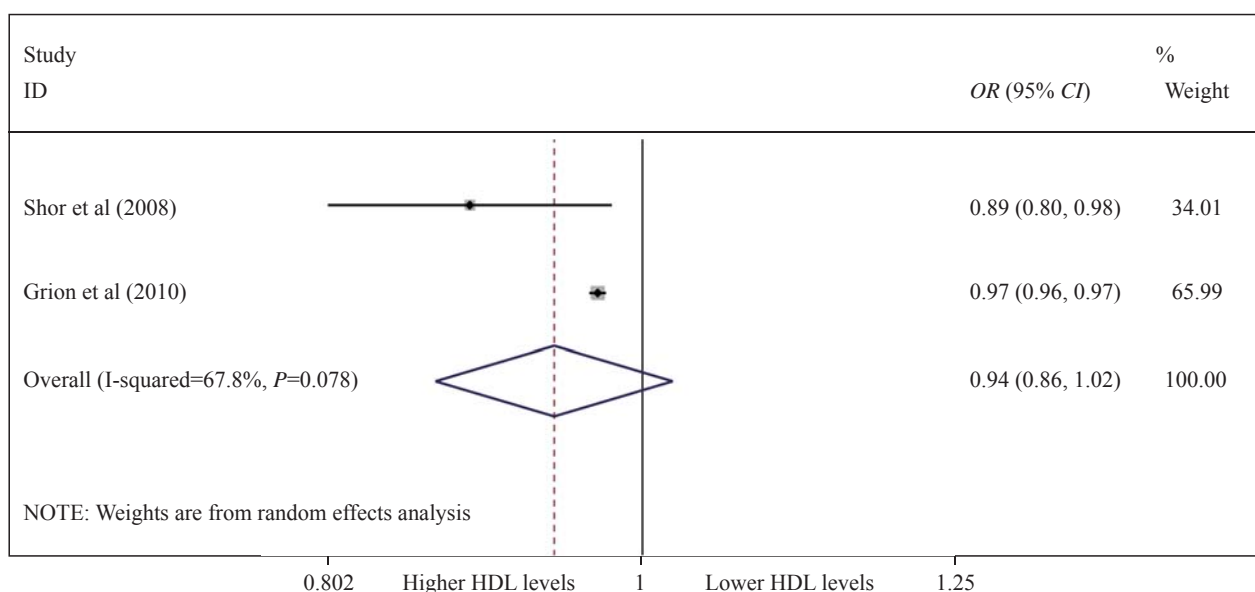


Figure 2. Forest plot showing the significance of the association between lower HDL levels (for each 1 mg/dL HDL) and risk of sepsis in the two groups according to the random effects model.

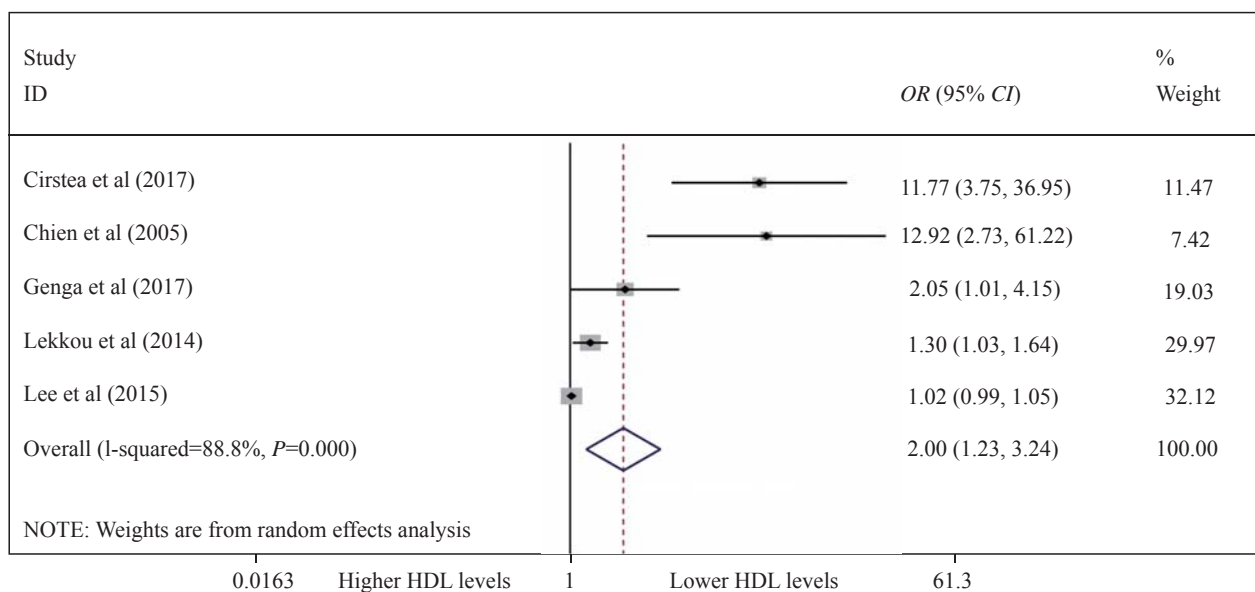


Figure 3. The association between lower HDL levels (for below median HDL levels) and mortality in the two groups according to the random effects model performed by forest plot.

Table 1. The characteristics of included studies

The first author (year)	Country	Study design	No. of population (case/control)	Mean age of patients population	Mean age of control population	Sample source	Source divided into case/control group	Levels of HDL in case/control group (mg/dL)	Study period	Reported outcomes	Source of definition of sepsis/severe sepsis /septic shock
Shor (2008) ^[6]	Israel	RC	108/96	66.6	66.3	Serum	Levels of serum HDL	<20 /≥65	01/2005-12/2005	Risk of sepsis	ACCP/SCCM consensus conference definitions
Genga (2017) ^[7]	Canada	OC	11/24	55.8	53.7	Plasma	Levels of serum HDL	<33.06 /≥33.06	01/2011-07/2013	2-year mortality	Institutional Sepsis Protocol
Chien (2005) ^[6]	China	PC	30/33	72.5	72	Serum	Levels of serum HDL	<20 /≥20	10/2002-01/2003	30-day mortality	ACCP/SCCM consensus conference definitions
Lekkou (2014) ^[18]	Greece	PC	28/22	64.8	66.2	Serum	Levels of serum HDL	<25 /≥25	NA	Mortality	SIRS
Grion (2010) ^[21]	Brazil	PC	51/71	65.81	65.12	Serum	Levels of serum HDL	33.07 /40.33	05/2005-12/2005	Risk of sepsis	ACCP/SCCM consensus conference definitions
Cirstea (2017) ^[24]	Canada	OC	68/132	56.5	55.9	Serum	Levels of serum HDL	<25.1 /≥25.1	01/2011-06/2014	28-day mortality	Suspected sepsis protocol
Lee (2015) ^[25]	South Korea	PC	65/52	63	62.3	Serum	Survivors/non-survivors	21 /21	08/2008-12/2008	Mortality	The identification of an infection site + three or four SIRS

PC: prospective cohort; OC: observational cohort; RC: retrospective cohort; LDL: low density lipoprotein; HDL: high density lipoprotein; NA: not applicable; ACCP/SCCM: American College of Chest Physicians/Society of Critical Care Medicine; SIRS: systemic inflammatory response syndrome.

Table 2. The Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies

Author	Selection		Comparability		Assessment of outcome		Total quality score		
	Representativeness of exposure arm(s)	Selection of the comparative arm(s)	Demonstration that outcome of interest was not present at start of study	Origin of exposure source	Studies controlling the most important factors	Studies controlling the other main factors		Adequacy of follow-up length (to assess outcome)	Lost to follow-up acceptable (less than 10% and reported)
Shor (2008) ^[6]	*	*	*	*	*	*	*	-	7
Genga (2017) ^[7]	*	*	*	*	*	*	*	-	7
Chien (2005) ^[16]	*	*	*	*	*	*	*	-	7
Lekkou (2014) ^[18]	*	*	*	*	*	*	*	-	7
Grion (2010) ^[23]	*	*	*	*	*	*	*	-	8
Cirstea (2017) ^[24]	*	-	*	*	*	*	*	-	7
Lee (2015) ^[25]	*	*	*	*	*	*	*	-	8

clinical studies. Despite extensive research, lipid profiles are rarely measured or interpreted in the clinical management of sepsis^[37] and are not even mentioned in the Surviving Sepsis Campaign guidelines.^[38] Moreover, HDL like presepsin, is not only a diagnostic predictor

of early phase of sepsis but also a prognostic predictor of sepsis.^[39] However, whether HDL levels lead to an increased risk of sepsis and mortality in septic patients remains controversial. Therefore, our finding provides evidence that low HDL levels have no significant effect on the risk of sepsis, but increase the mortality rate in septic adult patients.

Dellinger et al^[40] showed that phospholipid emulsion did not reduce 28-day all-cause mortality of severe sepsis patients. Comparatively, Pajkrt et al^[33] suggested that reconstituted HDL infusion in human can inhibit LPS effects in humans. Additionally, Musher et al^[41] reported that the association between acute infection (including sepsis) and myocardial infarction (showing acute inflammation), in which acute infection could increase the risk of cardiovascular events, especially myocardial infarction. Interestingly, the author proposed a notable clinical problem of whether statins provided a benefit to all patients with acute infection. Statins are the first-line lipid-lowering medications that mainly decrease LDL levels and increase HDL levels. Willeit et al^[42] suggested that when baseline lipoprotein levels were 30 mg/dL, the hazard ratios (HRs) for cardiovascular events were 1.11 (95% CI 1.00–1.22); interestingly, the HRs for on-statin lipoprotein were 1.43 (1.15–1.76) for 50 mg/dL or higher. The results of the study indicated that an increased baseline and on-statin lipoprotein showed an independent, approximately linear relation with the risk of cardiovascular diseases. However, low HDL levels were associated with a higher mortality among septic patients as shown in this meta-analysis.

This meta-analysis has several strengths. First, the included articles were from cohort studies, of which 4 were prospective cohort studies. Second, the risk of bias assessment showed a low risk of bias. Third, we used generic inverse variance to calculate the pooled effect of ORs and their 95% CIs evaluated the association of lower HDL levels and risk or mortality levels. Finally, the result of the sensitivity analysis showed that this pooled effect model was robust and reliable.

In addition, this study has some weaknesses. Although we aimed to perform a comprehensive search of the relevant articles, some studies may not have been published due to negative outcomes. Second, statins can decrease the levels of LDL and increase the levels of HDL, and many included studies did not report whether statins were used or not; thus, the conclusion needs to be drawn from original studies to control this main confounding factor. Third, there were various definitions of lower HDL levels, which may be confounding factors

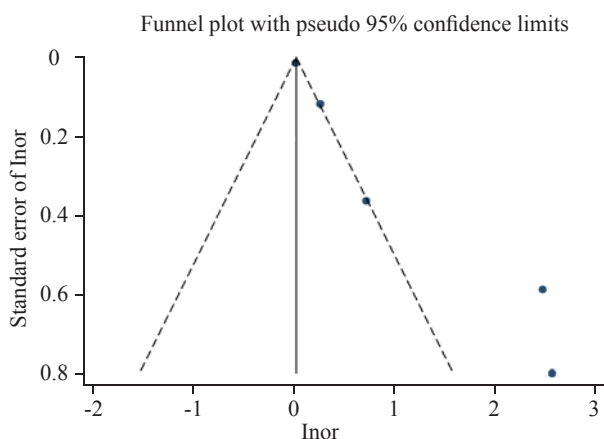


Figure 4. Funnel plot showed that it was asymmetry, suggesting potential publication bias may exist in mortality rates of lower and higher HDL levels among septic patients.

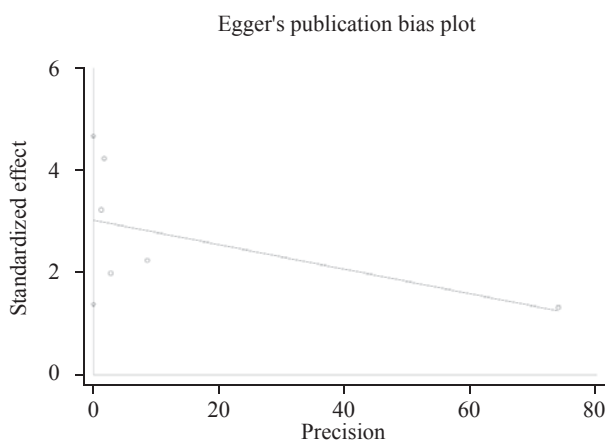


Figure 5. Egger's linear regression showed there was a significant publication bias existing in mortality of lower and higher HDL levels among septic patients.

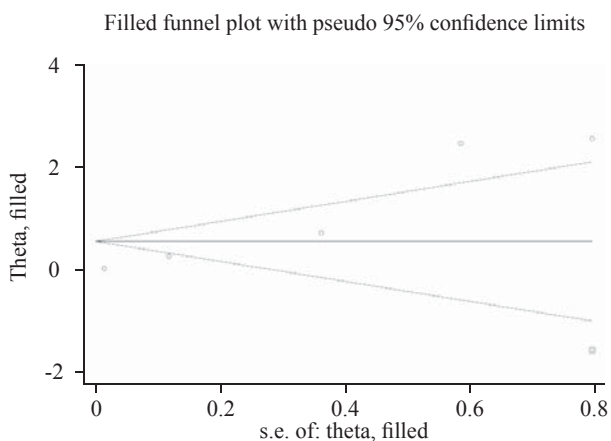


Figure 6. Trim and fill analysis to confirm whether the robust model for mortality in septic patients with lower and higher HDL levels.

for the pooled results. Finally, this is a limitation that no randomized controlled trials included in this meta-analysis.

CONCLUSION

This is the first systematic review and meta-analysis to evaluate an association between lower HDL levels and the risk of sepsis and mortality in septic patients. These results suggest that lower HDL levels are associated with an increased mortality rate of septic patients, but not with the risk of sepsis. Further original studies are needed to support these findings. Furthermore, the information on this article indicated that the HDL may be considered as a predictor for prognosis in septic patients. More importantly, the question from this study should be considered whether the cutoff value of HDL levels for preventing the sepsis are the same as that for cardiovascular disease, which may be confirmed in the further clinical researches.

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Contributors: SL proposed and wrote the paper. All authors read and approved the final version.

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