Diagnostic accuracy of pathogens in positive blood culture broths by Sepsityper Kit

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Research

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Abstract

Background: Sepsis is a global medical problem and consistently the leading cause of death. Quick identification can help clinicians to determine the appropriate antibiotic treatment and reduce mortality. Sepsityper Kit is fast and easy-to-operate method. However, the studies on its performance is inconsistent. Thus, in other to fill the gap, we conducted data analysis to evaluate the effectiveness of the Sepsityper kit on pathogen identification.

Methods: Relevant literature were searched in PubMed, Embase, Cochrane Library, and Web of Science. The correct identification rate of gram-positive bacteria, gram-negative bacteria, and fungi at the species and genus level were analyzed. Stata 12.0 was used to explore the publication bias of the included literature.

Results: 30 articles were included. The diagnostic performance in gram-negative bacteria genus level was 96% (P = 0.000; I^2 = 80.9%), in gram-negative bacteria species level was 88% (P = 0.000; I^2 = 89.2%), in gram-positive bacteria genus level was 85% (P = 0.000; I^2 = 94.0%), in gram-positive bacteria species level was 65% (P = 0.000; I^2 = 89.2%), in genus level of fungi was 85% (P = 0.000; I^2= 90.0%), and in the of species level of fungi was 59% (P = 0.000; I^2 = 97.0%), respectively. There is no publication bias in the study.

Conclusions: The Sepsityper kit is a good method for the rapid diagnosis of all kinds of pathogenic microbes. Moreover, it is also very prominent in the identification of Gram-negative bacteria.

Keywords: Sepsityper Kit, gram-negative bacteria, gram-positive bacteria, fungi, Sepsis

Introduction:

Sepsis is the main causative agent of human death, the mortality is no less than 40% [1]. Sepsis is an organs dysfunction caused by the host's maladjusted response to infection, even life-threatening, which has been listed as a global health priority by the World Health Organization(WHO)[2]. It often leads to multiple organs dysfunction. The high cost of treatment of sepsis consumes a lot of medical resources, greatly damages human health and their living qualification. At present, limited drugs could effectively cure it. Matrix-assisted laser desorption ionizationetime-of-flight mass spectrometry (MALDI-TOF MS) is one of the most promising technologies for the identification of microbial pathogens directly from positive blood culture bottles[31]. And the Sepsityper® kit is the most widely used pretreatment protocol[3]. Faster and more accurate diagnosis can be achieved with matrix assisted laser desorption / ionization MALDI Bioanalyzer and Sepsityper diagnostic tool. The quick identification and correct diagnosis of sepsis are necessary to prevent septic shock. The experimental use of broad-spectrum antibiotics in the early treatment of sepsis induce more and more pathogenic bacteria resistance. Rapid diagnosis can significantly reduce the incidence rate and mortality rate of patients, optimize therapy, and even release the medical economic burden.

Gold standard:

In the clinical setting, it is well known that bacteremia and sepsis are associated with morbidity and mortality. The early initiation of treatment with the appropriate antibiotic is a key criterion for a reduction in the morbidity and mortality rates[44]. However, the identification of bacteria by subculture and subsequent biochemical reactions take up to 48 h, depending on the species and system used[13].Current routine laboratory practice for the identification

of yeast from blood cultures has a turnaround time of 24 – 72 h [35,45]. In contrast, MALDI-TOF MS can be performed with minimal amounts of bacteria and takes only a few minutes[13]. Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS) is capable of reducing turnaround times by up to 48 hours compared to standard laboratory protocols.[43]. The results of positive blood culture broths prepared with MBT Sepsityper kit facilitate physicians to control blood infections, reduce the resistance of pathogens to antimicrobial agents, and improve the treatment of sepsis. However, this sample processing method lacks systematic review, so here we analyzed the related publication and performed the systematic evaluation.

Methods

Study design

This study has been carried out from 23 September 2020. The diagnosis effect of the Sepsityper kit on direct detection of gram-positive bacteria, fungi, and gram-negative bacteria in inoculated positive blood culture broths was systematically evaluated.

Search Strategy

Cochrane Library, EMBASE, PubMed, and Web of Science were conducted by systematic search using the following terms:(Sepsityper kit OR Sepsityper) AND (bacterial species[all synonyms] OR Bacterial Gene Product[all synonyms] OR Protein, Bacterial[all synonyms]). This study only includes English literature as of September 2019.

Adoption Criteria and Screening Guidelines

For the applicability of the research, the exclusion and inclusion criteria were established, and the included 30 studies were evaluated. The following are the inclusion criteria: (1) Sepsityper kit was evaluated; (2) the subjects should be human positive blood culture broths; (3) Sepsityper kit as index text
; (4) the correct recognition rate of species or genera containing gram-positive bacteria, fungi, or gram-negative bacteria. The exclusion criteria were as follows: (1) meeting abstracts were excluded; (2) letters were excluded because data could not be extracted.

Data presented in the studies

The following information are extracted from the selected publication by two individuals independently, they are authors, year, blood culture system, correct identification rate in various pathogen. The differences between the two groups were compared and the reasons for the differences were discussed.

Research quality assessment of the included studies

After data extraction, the quality of included studies were evaluated according to the Cochrane Collaboration quadas-2 standard [41], in which the answers of "no", "unclear" and "yes" were used for evaluation (Figure 2)

Data analysis

Stata 12.0 was used to integrate the specificity of gram-positive bacteria, gram-negative bacteria, and fungus. It also provides the function of heterogeneity test and publication bias.

Results

Search results

According to collection criterial, 52 studies are selected, Then, 22 unrelated studies were excluded after reviewing the abstracts. Finally, 30 studies were included for further analysis(Figure 1)[3-33]. The species identification accuracy of these studies is summarized in Table 1.

Quality assessment of the studies

Using Cochrane Collaboration quadas-2 as the standard, the quality of 30 studies was evaluated. The results of the quality evaluation are shown in Figure 2.
The quality assessment of 30 included studies is shown in Figure 2 and Figure 3. In the field of patient selection, 13 studies (43.3%) were rated as at the risk of "Unclear" bias because it not clear whether the inappropriate exclusion was avoided. Analysis of the index test indicated an unclear risk of bias in 18 studies (60.0%) because the details of sample processing were not reported, and a high risk of bias in the other 5

studies (16.7%), because the results of 3 studies were conducted when the gold standard was known, and the gold standard of 3 studies was not determined in advance. Analysis of patient flow and timing indicated that 3 studies (10.0%) had a high risk of bias, because the cases in a study received two cut-off scores, and the 2 studies did not include all cases of the analysis. In the domain of reference standard, 3 studies (10%) had a higher risk of bias. While 19 studies (63.3%) were rated as having an "Unclear" risk of bias, because the blind method was not used to interpret the gold standard of 3 studies, and 19 studies were not clear. Analysis of applicability concerns indicated low concerns in all three categories.

An analysis of the overall situation

Among the 30 papers, 16 papers described the identification of gram-negative bacteria to genus level while 25 publication reach to species level. 16 papers described the identification of gram-positive bacteria to genus level while 24 publication reach to species level. 10 papers described the identification of fungi to genus level while 16 publication reach to species level.

(1) The accuracy of Sepsityper kit in the identification of Gram-negative bacteria at genus level and species level was 96% (P = 0.000; P = 0.000); I2 = 80.9%) and 88% (P = 0.000; I2 = 89.2%)(Figure 4).
(2) The accuracy of Sepsityper kit in the identification of gram-positive bacteria at genus level and species level was 85% (P = 0.000; I^2 = 90.0%) and 65% (P = 0.000; I^2 = 89.2%)(Figure 5).
(3) The accuracy of Sepsityper kit in the identification of fungi in genus level and species level was 85% (P = 0.000; I^2 = 90.0%) and 59% (P = 0.000; I^2 = 97.0%)(Figure 6).

Assessment of publication bias of the included studies

The funnel plot was generated by Stata12.0 software. The P-value in the Gram-negative bacteria at genus level and species level was 0.084(P > 0.05) and 0.119(P > 0.05)(Figure 7). The P-value in the gram-positive bacteria at genus level and species level was 0.981(P > 0.05) and 0.149(P > 0.05)(Figure 8). The P-value in fungi genus level and species level was 0.669(P > 0.05) and 0.424(P > 0.05)(Figure 9).

Heterogeneity

There is obvious heterogeneity in this study. The I^2 values of gram positive bacteria, gram negative bacteria and fungi were 80.9%, 94.0% and 90.0% respectively. The I^2 values of gram-negative bacteria, gram-negative bacteria, gram-positive bacteria, and fungus are more than 50%, indicating a high degree of heterogeneity.

Discussion

In this study, we focus on the accuracy performance of the rapid identification of positive blood culture broths of the Sepsityper kit. The Sepsityper kit is a very reliable method of detecting gram-negative bacteria in the blood, with an accuracy rate of 96%. The accuracy rate of gram-positive bacteria and fungi reach 85%. In addition, it is more convenient and quicker than the traditional detection method. The advantage of the Sepsityper kit is that it is fast and easy to operate. Compared with the standard laboratory protocol, MALDI-TOF MS can shorten the turnaround time by up to 48 hours. In addition to saving time with the Sepsityper kit, it is also possible to run analyses in parallel rather than sequentially, further speeding up the laboratory's progress[43]. This detection method can more quickly identify pathogens in infectious diseases and formulate appropriate treatment plans in time, so as to prevent improper treatment methods and the use of unnecessary broad-spectrum antibiotics[3]. Moreover, the Sepsityper kit has obvious advantages in the identification of gram-negative bacteria.

After analyzing 25 articles related to gram-negative bacteria, we found that the reasons for the high heterogeneity of identification in gram-negative bacteria may be as follows:(1)There may have been an outbreak of Salmonella typhi during the study period, resulting in a high proportion of Salmonella. In conventional practice, this bacterium accounts for only 1% of all pathogens isolated from positive blood culture broths. As we all know, MALDI-TOF mass spectrometry cannot identify these organisms at the serotype level[33]. (2)The sample contains anaerobic bacteria. The mass spectrometric identification of anaerobic organisms needs to be improved by developing standardized methods and updating databases [34]. (3)Pseudomonas putida was erroneously identified as Pseudomonas fulva. Pseudomonas putida and Pseudomonas fulva have similar phenotypic characteristics, and after rebuilding the genus structure based on the nucleotide sequence of the gyrB and rpoD genes, both are placed in the Pseudomonas putida complex in[38]. In view of the complex and controversial taxonomy of the genus, it is not surprising that MALDI-TOF MS mistook Aeromonas hydrophila for Aeromonas veronii in a polymeric bacterium[5]. (4)Enterobacter cloacae isolate was wrongly identified as Enterobacter asburiae. Enterobacter asburiae is closely related to E. cloacae and resides within the E. cloacae

complex. It is difficult to distinguish the species in this kind of complex by biochemical tests, which are often misidentified by automated systems[39, 40]. (5)The presence of charcoal had a significant effect on the identification of Gram Negative Bacilli.[9](6)Pseudomonas species was wrongly identified as Pasteurella beta Yae. This error was probably due to the lack of reference spectra for variants of some species in the MALDI-Biotyper 2.0 application software. By re-analyzing its spectra using MALDI-Biotyper 2.0 application software with Blood Culture Update v.3.1.0.4, the pathogen was correctly identified as a Pseudomonas species. After analyzing 16 studies on the identification of gram-positive bacteria, it is found that the reasons for the high heterogeneity of identification of gram-positive bacteria may be as follows:(1)Str. mitis isolates were wrongly identified as str. Pneumoniae. The error identification of these two closely related species is based on a known shortcoming of the MALDI-TOF mass spectrometry method, which has been described in previous BC identification and can be explained by phylogenetic relationships of the two species[34,36,37]. (2)The results of the biotype and Vitek MS in the identification of Bacillus species were not good. Since the formic acid and CHCA matrix cannot effectively decompose the cell wall of spores, the poor performance of the two systems in the identification of Bacillus species may be due to the nature of spore formation[12]. (3)The presence of charcoal had a significant effect on the identification of staphylococci and streptococci[9].

After analyzing 16 studies on the identification of fungi, we found that the reasons for the high heterogeneity of fungi identification may be as follows:(1)This may be due to the fact that the Sepsityperis not fully optimized for yeast. (2)Loss of pellet during processing was the likely factor leading to no identification in these cultures[19]. (3)In the process of analysis, insufficient washing of slides is the possible reason[19]. (4)Differences in accuracy can also be attributed to technical methods[8].
However, there are some limitations in the current research. First, we only include articles published in English, which may cause deviation. Second, our research only includes articles as of September 2020. Different inclusion and exclusion criteria may also lead to heterogeneity of included studies.

Conclusions

This study evaluated the accuracy of the Sepsityper kit in identifying bacteria from positive blood culture broths and provided a new method for clinical diagnosis. Sepsityper kit is suitable for the identification of various bacteria, but it performs better in gram-negative bacteria

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Author Contribution

Xu-Guang Guo conceived the study. Le-Yao Qi and Min-Lin collected the data. Le-Yao Qi, Min-Lin and Ya-Ping Li analyzed the data, wrote the manuscript, amended the manuscript. The final manuscript was read and approved by all the authors.

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Abbreviations

QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies; UC, Unclear; Y, Yes; N, No; I^2, Inconsistency (I-square); MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

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Figures

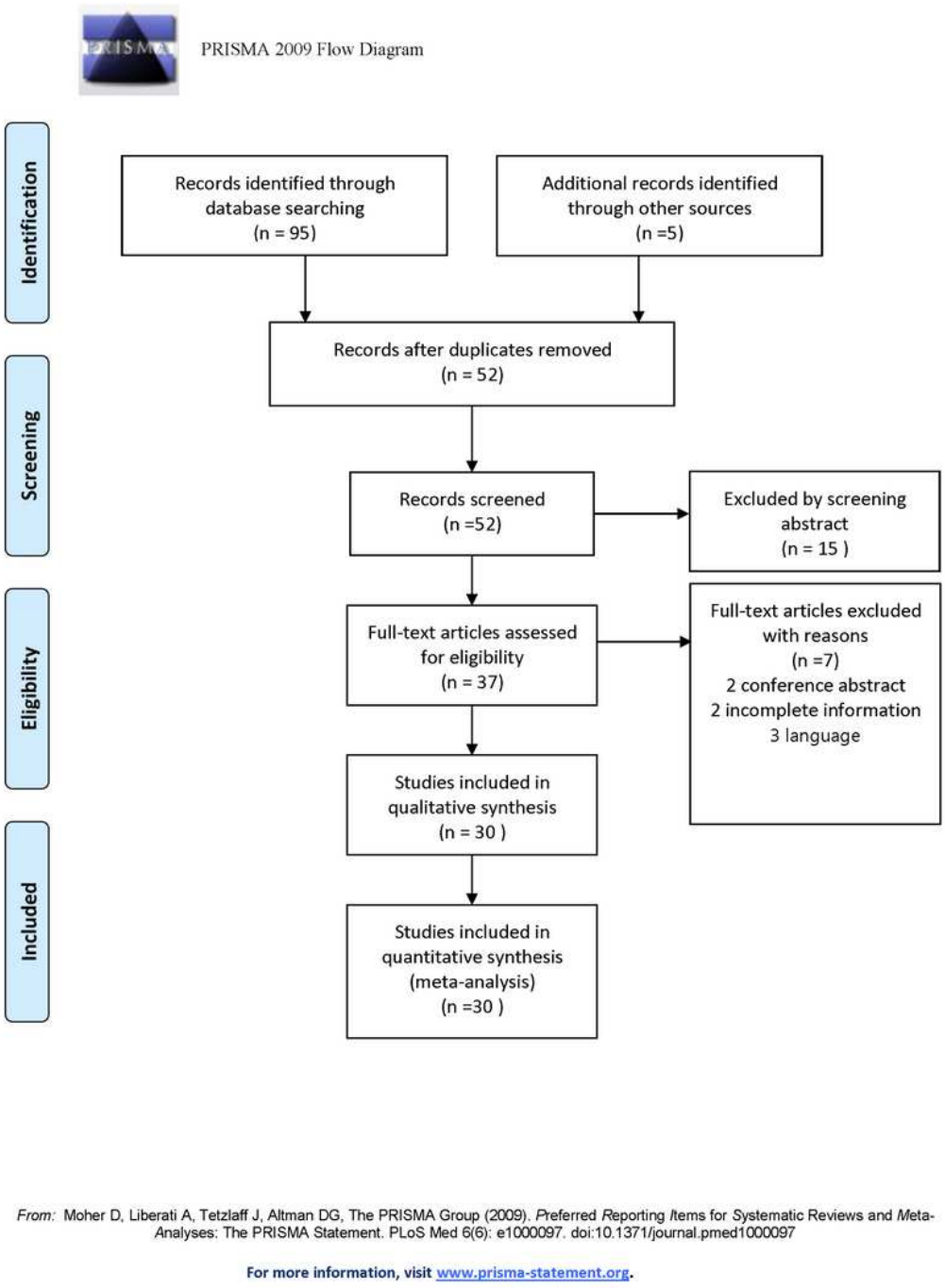

Figure 1

Flow diagram for systematic article search

Figure 2

Quality assessment of the individual studies according to QUADAS-2

Figure 3

Overall quality assessment of the included studies

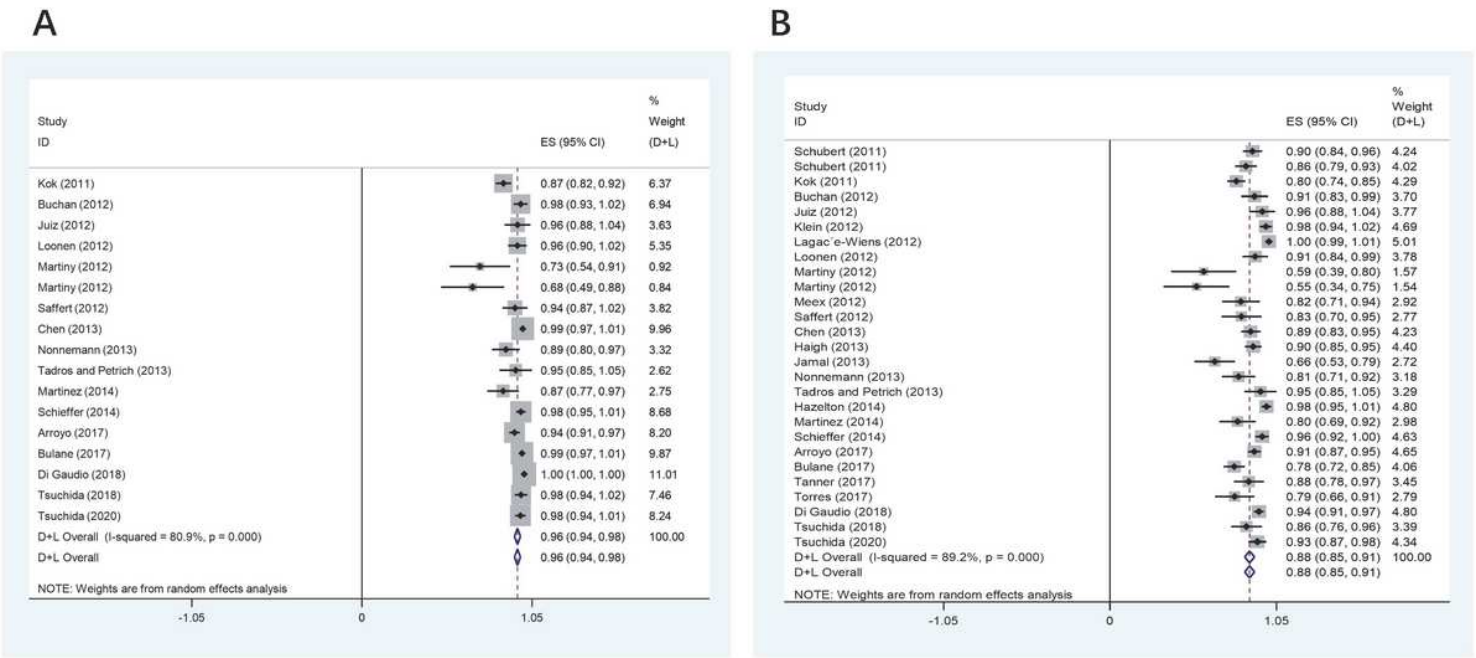

Figure 4

Forest plot for the analysis in the gram-negative bacteria identification ratio at the genus (A) and species(B) level.

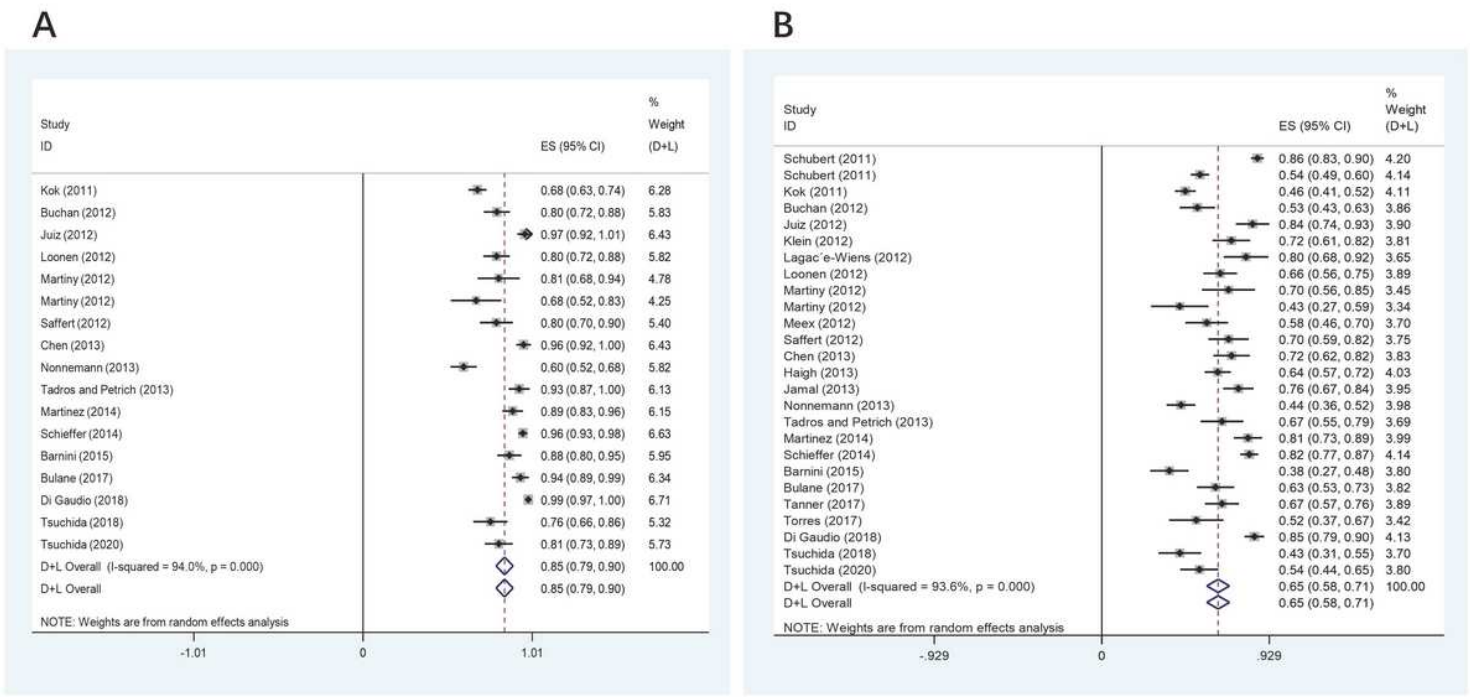

Figure 5

Forest plot for the analysis in the gram-positive bacteria identification ratio at the genus (A) and species(B) level.

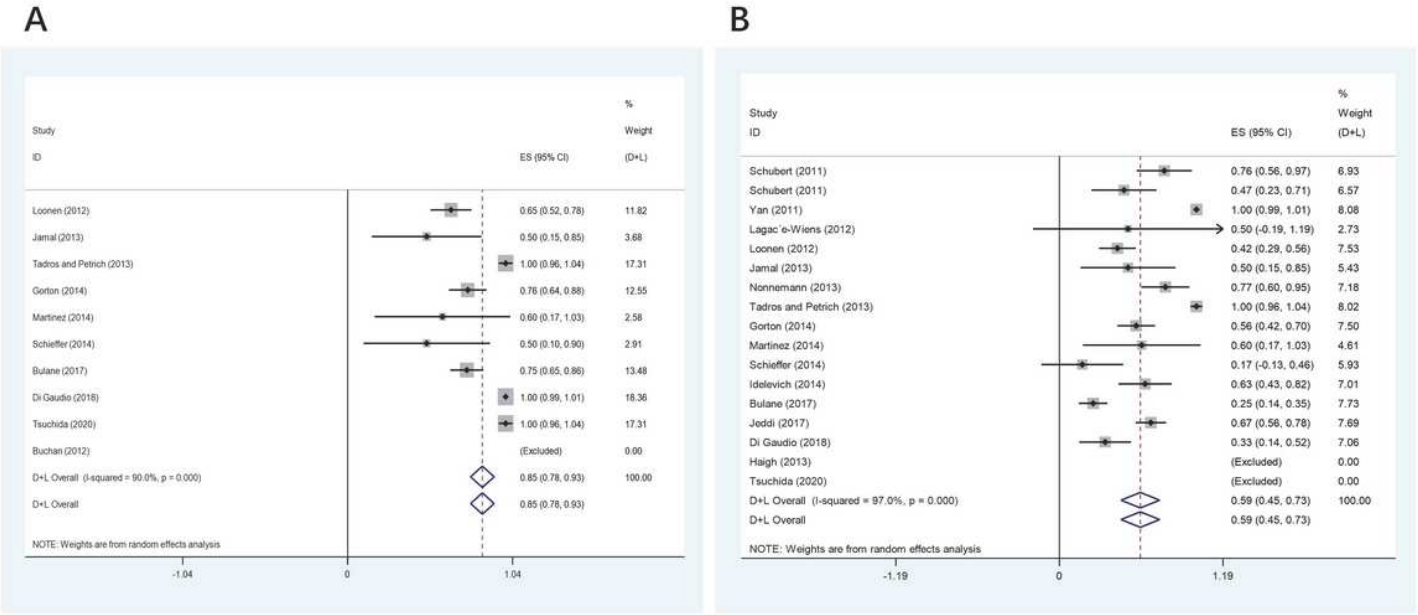

Figure 6

Forest plot for the analysis in fungi identification ratio at the genus (A) and species(B) level.

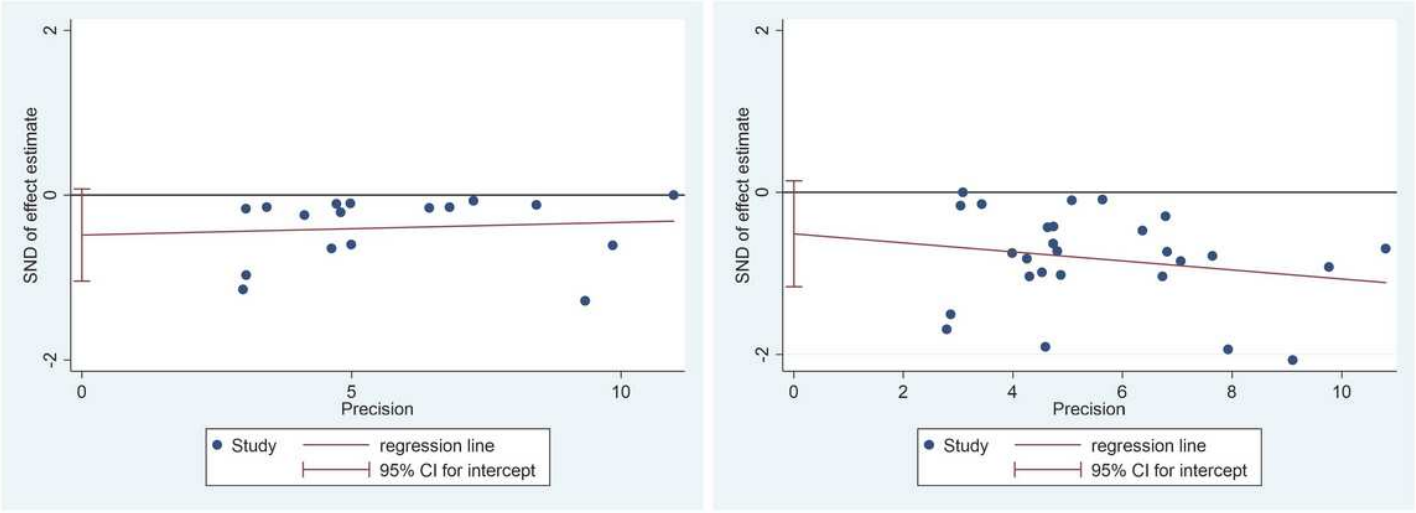

Figure 7

Funnel plot of gram-negative bacteria at genus (A) and species(B) level.

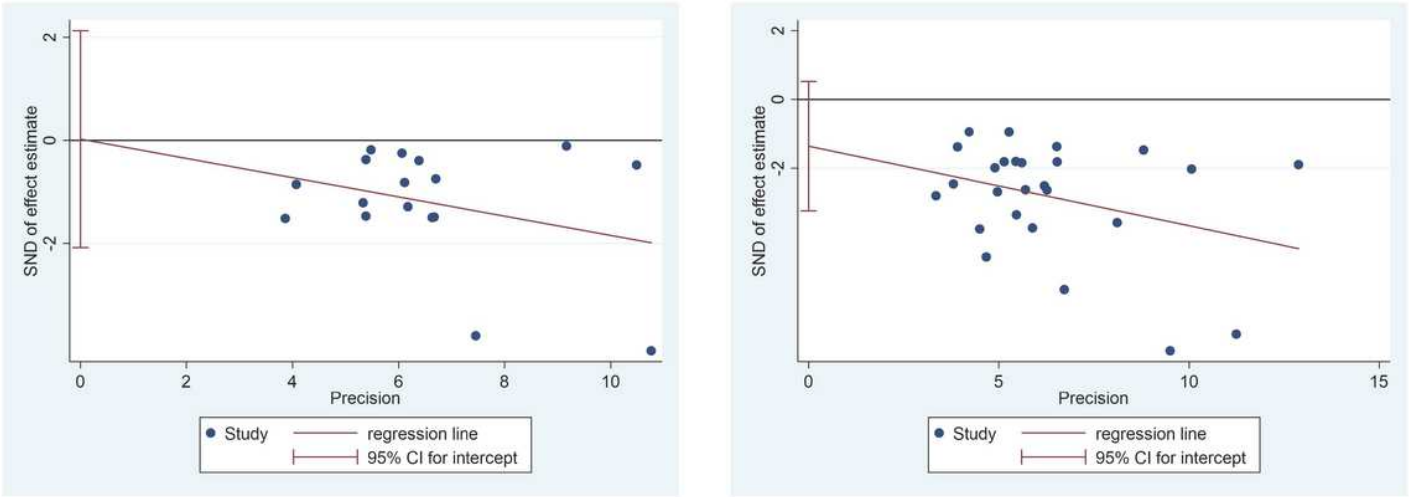

Figure 8

Funnel plot of gram-positive bacteria at genus (A) and species(B) level.

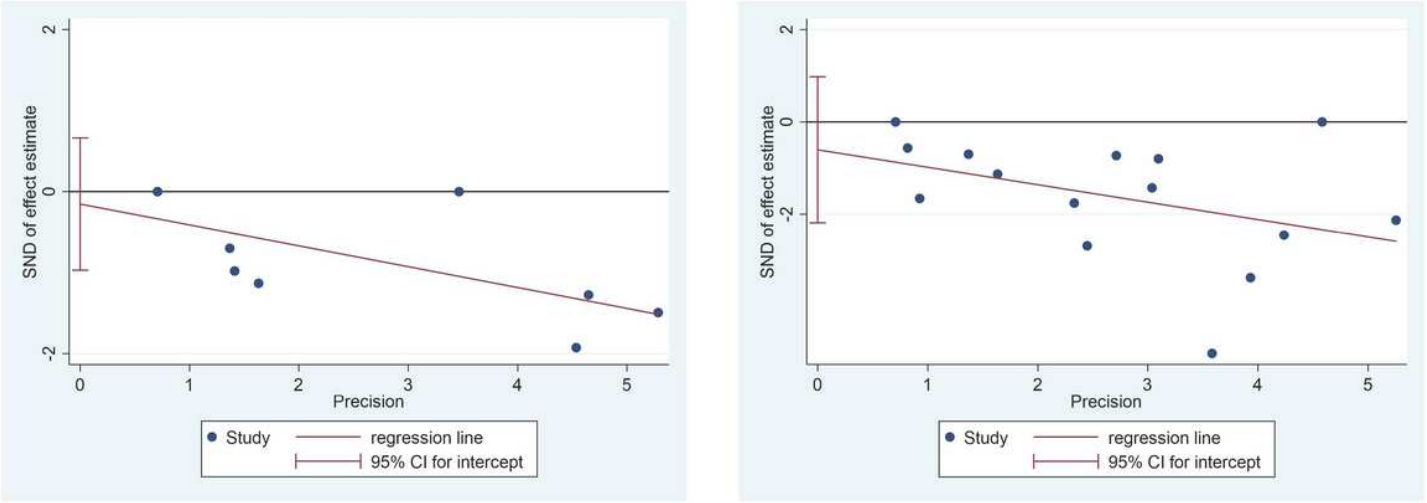

Figure 9

Funnel plot of fungi at genus (A) and species(B) level.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- S2.TableChecklistofthissystematicreview.doc
- Table1.Summaryofthecharacteristicsofincludedstudies.png