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Efficacy and Safety of EBUS-TBNA and EUS-B-FNA in Children: A Systematic Review and Meta-analysis

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Abstract

Background: Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) and Transesophageal Bronchoscopic Ultrasound-guided fine-needle aspiration (EUS-B-FNA) are established modalities for evaluation of mediastinal/hilar lymphadenopathy in adults. Limited literature is available on the utility of these modalities in the pediatric population. Herein, we perform a systematic review and meta-analysis on the yield and safety of EBUS-TBNA and EUS-B-FNA in children. Methods: We performed a systematic search of the PubMed and EMBASE databases to extract the studies reporting the utilization of EBUS-TBNA/EUS-B-FNA in children (<18 years of age). Pooled diagnostic yield and sampling adequacy (proportions with 95% confidence intervals) were calculated using the random-effects model. Details of any procedure-related complications were noted. Results: The search yielded 12 relevant studies (five case series and seven case reports on EBUS-TBNA/EUS-B-FNA, 173 patients). Data from five case series (164 patients) were summarized for the calculation of sampling adequacy and diagnostic yield. Safety outcomes were extracted from all publications. The pooled sampling adequacy and combined diagnostic yield of EBUS TBNA/EUS-B-FNA were 98% (95% CI, 92-100%) and 61% (95% CI, 43-77%) respectively. A procedure-related major complication was reported in 1 patient (1/173, Major complication rate 0.6%), and minor complications occurred in 6 patients (6/173, Minor complication rate 3.5%). Conclusions: EBUS-TBNA and EUS-B-FNA are safe modalities for evaluation of mediastinal lymphadenopathy in the pediatric population. EBUS-TBNA/EUS-B-FNA may be considered as the first-line diagnostic modalities for this indication as they have a good diagnostic yield and can avoid the need for invasive diagnostic procedures.

Introduction

Mediastinal and hilar lymphadenopathy is a common clinical problem in adults and children. (1) The traditional approach for the diagnosis of mediastinal lymphadenopathy / mediastinal masses in children have included various invasive techniques. These include procedures like Mediastinoscopy, Video-Assisted Thoracoscopic Surgery (VATS), Thoracotomy or Image-guided percutaneous biopsy. (2) However, these modalities have inherent risks and potential for severe complications due to the invasive nature of the procedure. (3)

Endobronchial Ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has revolutionized the diagnostic approach of mediastinal lymphadenopathy in adults. (4, 5) EBUS-TBNA involves the use of a dedicated ultrasound equipped bronchoscope that enables real-time sampling from mediastinal and hilar lymph nodes. The EBUS bronchoscope can also be introduced through the oesophagus to sample mediastinal lymph nodes. This technique is described as Transesophageal Bronchoscopic Ultrasound-guided fine-needle aspiration (EUS-B-FNA). (6) While these techniques were initially developed for diagnosis and staging of lung cancer, their application has now extended for the determination of various benign diseases as well.

The first report of EBUS-TBNA in children in 2009 followed the initial description of EBUS-TBNA in

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2003. (7) Since then, few studies reporting the utilization of EBUS-TBNA and EUS-B-FNA in children have been published. Most of the studies in children include retrospective case series and case reports that have reported a variable diagnostic yield and peculiar issues related to the procedure in children. The benefit of these minimally invasive modalities over the invasive approaches has also been highlighted. In this systematic review, we summarize the various studies describing the utility and safety of EBUS TBNA/EUS-B-FNA in children. We also perform a meta-analysis of the relevant studies to calculate the diagnostic yield and sampling adequacy of these modalities in the pediatric population.

Methods

Search strategy and initial review

The authors performed a systematic search of the two databases: PubMed and EMBASE (2004–2017) to identify the relevant studies on EBUS-TBNA/EUS-B-FNA in children (<18 years). The following free text search terms were used: (ebus OR ebus-tbna OR ebus tbna OR tbna OR endobronchial ultrasound OR endobronchial Ultrasonography OR endobronchial ultrasound-guided OR endobronchial ultrasound-guided OR tbna OR eus b fna) AND (pediatric OR pediatric OR child OR children). The authors also reviewed their personal files to identify relevant studies. All the retrieved references were imported into reference management software (EndNote). Duplicate references were removed. References were screened through the title and abstracts. The reference lists of the extracted studies were reviewed. The finally retrieved studies were independently screened by two authors (HI and KM). Full texts of the relevant articles were obtained. The following types of studies were excluded – (a) studies that did not report the utilization of either EBUS-TBNA/EUS-B-FNA or were not related to paediatrics (b) studies describing the use of conventional TBNA for mediastinal lesions in children (c) studies not in the English language (d) review articles, editorials and letters without any case description. Any disagreement between the authors was resolved after mutual discussion. The systematic review methodology is summarized in Figure 1.

Data abstraction

Data from the finally selected studies were abstracted on a data extraction form. The following information was retrieved after a thorough review of the full text – (a) author, (b) year, (c) number of patients, (d) height/weight, (e) sex, (f) number of centres involved, (g) study design, (h) operator experience, (i) EBUS bronchoscope type and procedure approach, (j) anaesthesia, (k) number of nodal stations sampled (l) duration of the procedure, (m) complications, (n) rapid on-site evaluation, (o) nodal size, (p) details of ancillary procedures, (q) needle gauge, (r) sampling adequacy, (s) diagnostic yield, and (t) need for additional procedures such as mediastinoscopy.

Assessment of study quality

The Qualsyst tool (3) was used to assess the quality of each selected study for meta-analysis. This tool incorporates ten questions (scored from 0 to 2). Two authors (KM and HI) evaluated the quality of the selected studies for meta-analysis. The inter-observer agreement for the quality assessment of the selected studies was performed using the Weighted Cohen's kappa ($\varkappa$) co-efficient.

Statistical analysis

Statistical analyses were performed using the STATA statistical analysis software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.) Proportional meta-analysis was performed using the random effects model. In the random-effects model, the observed difference between the proportions is not entirely attributed to error in sampling. The pooled estimate describes the mean of the distribution of the estimated parameters. The diagnostic adequacy and the diagnostic yield of EBUS-TBNA/EUS-B-FNA were calculated for the finally selected studies for meta-analysis. Proportions with 95% confidence intervals (CI) were calculated for individual studies. The data was subsequently pooled to estimate a summary proportion with 95% CI representing the combined diagnostic adequacy/yield. Using Metaprop, 95% confidence intervals were calculated using the score statistic and the exact binomial method.

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This method incorporates the Freeman-Tukey double arcsine transformation of proportions. Within-study variability is modelled using the binomial distribution using this method.

Heterogeneity assessment

The impact of heterogeneity on the pooled estimates of the outcome was assessed using the Cochran Q statistic and I2 test (measures the extent of inconsistency among the results of the studies).

Assessment of Publication Bias

The presence of publication bias was evaluated using the Begg's funnel plot (4), which is a measure of the proportion (in the X-axis) against the standard error of the proportion (in the Y-axis). Each open circle represents an individual study in the meta-analysis. The line in the centre indicates the pooled proportion and the other two lines indicate the 95% CI. The proportion estimates from smaller studies are expected to be scattered above and below the summary estimate, producing a triangular or funnel shape, if there is no publication bias.

Results

The initial search yielded 238 study results. No previously published systematic review or meta-analysis on the subject was found. After initial screening, 14 eligible articles on EBUS-TBNA/EUS-B-FNA in children were identified. Twelve studies (including 173 patients) described the utilization of EBUS-TBNA or EUS-B-FNA in pediatric mediastinal lymphadenopathy. Two articles were excluded as one described utilization of EUS-B-FNA for intra-abdominal pathology, and one case report described the use of EBUS for airway wall involvement assessment in a patient with mucoepidermoid carcinoma. (8, 9) Of the finally selected 12 articles, five were case series that included greater than five patients, and seven were single patient case reports (except one article that described EBUS-TBNA in two children)(10). The abstracted data of the five major case series are summarized in Table 1. These five case series (including 164 children) were included in the meta-analysis for calculation of the pooled summary statistics for diagnostic yield and sampling adequacy. (11-15) In all, a total of 173 patients underwent EBUS-TBNA/EUS-B-FNA.

The five major case series included 164 patients (90 males, 54.9%). All the studies were retrospective in nature. Four out of the five were multicentric (except Gulla KM et al., India).(13) Two studies reported the use of only EBUS-TBNA(11, 15), two used both EBUS-TBNA and EUS-B-FNA(13, 14), while one study used Radial EBUS along with EBUS-TBNA.(12) For the study where both EBUS-TBNA and Radial EBUS were used, data is summarized for only the patients who underwent EBUS-TBNA. General anaesthesia (GA) was used in one study(12), three studies used both GA and moderate sedation(11, 14, 15), while in one study(13), procedures were performed only using moderate sedation. The most common EBUS bronchoscope used was the Olympus BF-UC-180F (6.9 mm outer diameter with a 2.2 mm working channel). 21G (13, 14) and 22G needle (11, 12) was used in two studies each. A total of 238 nodes were sampled. The most frequently sampled lymph node stations were Subcarinal (Station 7) and lower right paratracheal (Station 4R). Rapid On-Site Evaluation (ROSE) was performed in three of the five studies.(11, 12, 15) The mean procedure duration was 20 min (Range 18-30 min).(14)

Diagnostic yield and sampling adequacy

The sampling adequacy of EBUS TBNA/EUS-B-FNA in various series ranged from 92 to 100%. The sampling adequacy rates were available for four out of the five studies (134 patients). (11, 12, 14, 15) The overall pooled sampling adequacy was 98% (95% CI, 92-100%). The diagnostic yield of EBUS TBNA/EUS-B-FNA ranged from 37 to 100%. The overall pooled diagnostic yield was 61% (95% CI, 43-77%) (random-effects model). (Table 2) The summary data for the calculations of pooled adequacy and diagnostic yield are summarized in Figures 2 and 3.

There was presence of statistical heterogeneity among the studies (I square = 76.01) There was no evidence of publication bias on the visual examination of the funnel plot (Supplementary Figure 4). The inter-observer agreement for scoring the quality of studies was good. (Cohen's k 0.74).

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Safety and procedure-related complications

One study reported a major complication [(overall major complication rate (1/173, 0.6%)] in which oxygen desaturation occurred in a child leading to premature termination of the procedure.(13) Minor complications occurred in six patients [(overall minor complication rate (6/173, 3.5 %)] in a single study.(14) The minor complications included transient hypoxemia (n=2), transient tachycardia (n=1), transient hypotension (n=1), airway bleeding (n=1) and excessive coughing (n=1).

Case reports

The data from the single patient case reports are summarized in Table 3.(7, 10, 16-20) Two case reports described the utilization of EUS-B-FNA for the sampling of the subcarinal lymph node in two very young children (one year and three years old).(16, 17) Diagnostic material was obtained in both the patients without any complications. In one study, anaesthesia and procedural considerations of EBUS-TBNA performed under GA using a supraglottic airway were discussed.(18)

Discussion

In the present review, we summarize the safety and diagnostic utility of the minimally invasive endosonographic modalities, EBUS-TBNA and EUS-B-FNA in children. We found that EBUS-TBNA and EUS-B-FNA have an excellent safety profile as the major complication rate is minimal. The overall diagnostic yield (61%) is similar to the diagnostic yield of EBUS-TBNA in adults in real-world settings.(21) The excellent sampling adequacy has important clinical relevance. The findings highlight that when used as first-line investigations for evaluation of mediastinal lymphadenopathy in children, invasive surgical procedures may be avoidable in a majority of them.

Wurzel et al. reported the first case of EBUS TBNA in children using an adult EBUS-TBNA bronchoscope (2009), for the diagnosis of Sarcoidosis. (7) After this, few studies and case reports have highlighted the use of broncho-endosonographic modalities in children and interest in this field has grown. There are particular concerns regarding the use of EBUS-TBNA and EUS-B-FNA in children. The available EBUS bronchoscopes have an outer diameter of 6.9 – 7.4 mm. Recently, a thinner EBUS bronchoscope has become available (6.3 mm diameter). The diameter of all the available EBUS scopes is larger than that of the conventionally used flexible bronchoscopes in children (usually 2.8-4.2 mm). Therefore, the performance of EBUS-TBNA is challenging in younger children with a smaller trachea.(16) Introduction of the EBUS bronchoscope through the oesophagus to perform mediastinal lymph node aspiration, a technique described as transesophageal bronchoscopic ultrasound-guided fine-needle aspiration (EUS-B-FNA) approach has been one of the most significant additions for pediatric mediastinal lymphadenopathy. (6) The first description of this modality in children was to sample the subcarinal lymph node in a 3-year-old child. (16) EUS-B-FNA allows successful sampling from oesophagal accessible lymph node stations (like subcarinal, lower left paratracheal and paraoesophagal) in children as young as one year.(17) This approach has the advantage of being complementary to the traditional EBUS and can be the sole approach in small children. Avoidance of tracheal entry during EUS-B-FNA minimizes the risk of impairment of ventilation and desaturation. The available literature suggests that traditional adult EBUS scopes can be easily used through the tracheal route in children more than 12 years of age or weighing more than 50kg.

Sedation and anaesthesia constitute an essential aspect of optimization of procedure comfort. In adults, EBUS-TBNA is routinely performed under moderate sedation, although deep sedation/GA is optional. In children, ensuring adequate anaesthesia is vital for safety and procedural success. As the scope for error during needle manipulation during sampling is minimal, a comfortably sedated child with proper ongoing ventilation is ideal. The sedation practices reported in the studies on EBUS in children are varied. While many operators have used general anaesthesia, studies have shown that the procedure can be very well be performed using moderate to deep sedation without an artificial airway.(13) While using general anaesthesia, either an LMA (laryngeal mask airway) or an endotracheal tube may be used. The diameter of the EBUS scope varies from 6.3–7.4 mm, hence the minimum size of endotracheal tube required for easy passage of the scope would be around 8 mm. This could be problematic in small children. Also, the use of an endotracheal

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tube may cause difficulty in accessing the upper and lower paratracheal lymph nodes.(14) An appropriately sized supraglottic airway (Laryngeal Mask Airway) can help circumvent this problem. The minimum size of the LMA recommended is 2.0 (IGel LMA). While using an artificial airway, the scope may be required to be removed intermittently to enable ventilation. While using general anaesthesia, inhalational sevoflurane and neuromuscular blockade using intravenous atracurium can be used. (18) Administration of anaesthesia and monitoring by a trained anesthesiologist is ideal.

Various gauge EBUS-TBNA needles are available like 21G, 22G, 19G and 25G. Most of the published literature in children describes the use of either a 21G or a 22G needle. The reported yield of either of the two needles in adults is similar. 19 G needles may allow one to obtain larger specimens. However, currently, no data is available with the use of 19G and 25G EBUS-TBNA needles in children. We believe that Rapid on-site evaluation (ROSE) by a pathologist is ideal during EBUS-TBNA/EUS-B-FNA in children as it may allow minimization of needle punctures and reduce the total duration of procedure thereby minimizing the duration and risks of anaesthesia.

EBUS was developed in adults mainly for staging and diagnosis of lung cancer. However, since then, the diagnostic utility of EBUS is established in many other benign diseases like Sarcoidosis. In children, tuberculosis and lymphoma constituted the two most common pre-clinical diagnosis. EBUS-TBNA has excellent diagnostic performance for Tuberculous mediastinal lymphadenopathy. (22) EBUS-TBNA can be a useful initial minimally invasive diagnostic modality in lymphoma if it is combined with immunophenotyping and molecular analysis. (23)

The pooled diagnostic yield of EBUS-TBNA in the meta-analysis was 61% which approximates the diagnostic yield of EBUS-TBNA in adults (around 63%) in real-world settings. (21) The excellent sampling adequacy (98%) signifies that representative lymph nodal tissue is nearly always obtained. The data for determination of sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were not provided in any study due to lack of a detailed follow-up. Gilbert et al. reported that EBUS TBNA helped in avoiding invasive surgical biopsy in 62% of cases. (15) In addition to the risk of complications, invasive procedures entail more cost.

Overall endosonographic procedures (EBUS-TBNA/EUS-B-FNA) have an excellent safety profile and favourable cost-benefit. The complication rate is low, approximately 0.05%. (24) Although EUS-B-FNA is complimentary to EBUS TBNA, it has a small risk of oesophagal perforation (0.02%) which may occur due to puncture of the node as the needle traverses the oesophagal wall. (25) Ideally, these procedures in children should be performed by experienced bronchoscopists who are regularly performing these procedures in adults. Paediatric bronchoscopists can quickly gain skills in this modality with training.

Conclusions

EBUS TBNA/EUS-B-FNA are excellent first choice modalities for undiagnosed mediastinal lymphadenopathy in children. Invasive procedures may be avoided in a vast majority by their use. It is necessary to include this procedure in the teaching curriculum of pediatric pulmonologists to enable its extensive use. Also, there is a need to develop customized scopes for use in children which will help in enhancing patient comfort and optimizing the yield of the procedure.

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Legends to figures

Figure 1 : Systematic review methodology for the identification of relevant studies describing the utility of EBUS-TBNA and EUS-B-FNA in Children.

Figure 2 : Meta-analysis of proportion of children undergoing EBUS-TBNA/EUS-B-FNA where adequate aspirates were obtained (pooled sampling adequacy)

Figure 3 : Meta-analysis of proportion of children undergoing EBUS-TBNA/EUS-B-FNA where diagnostic aspirates were obtained (pooled diagnostic yield)

Supplementary Figure 4 : Funnel plot comparing proportion vs the standard error of proportion for the diagnostic yield. Open circles represent trials included in the meta-analysis. The line in the centre indicates the summary proportion. The other lines represent the 95% confidence intervals.

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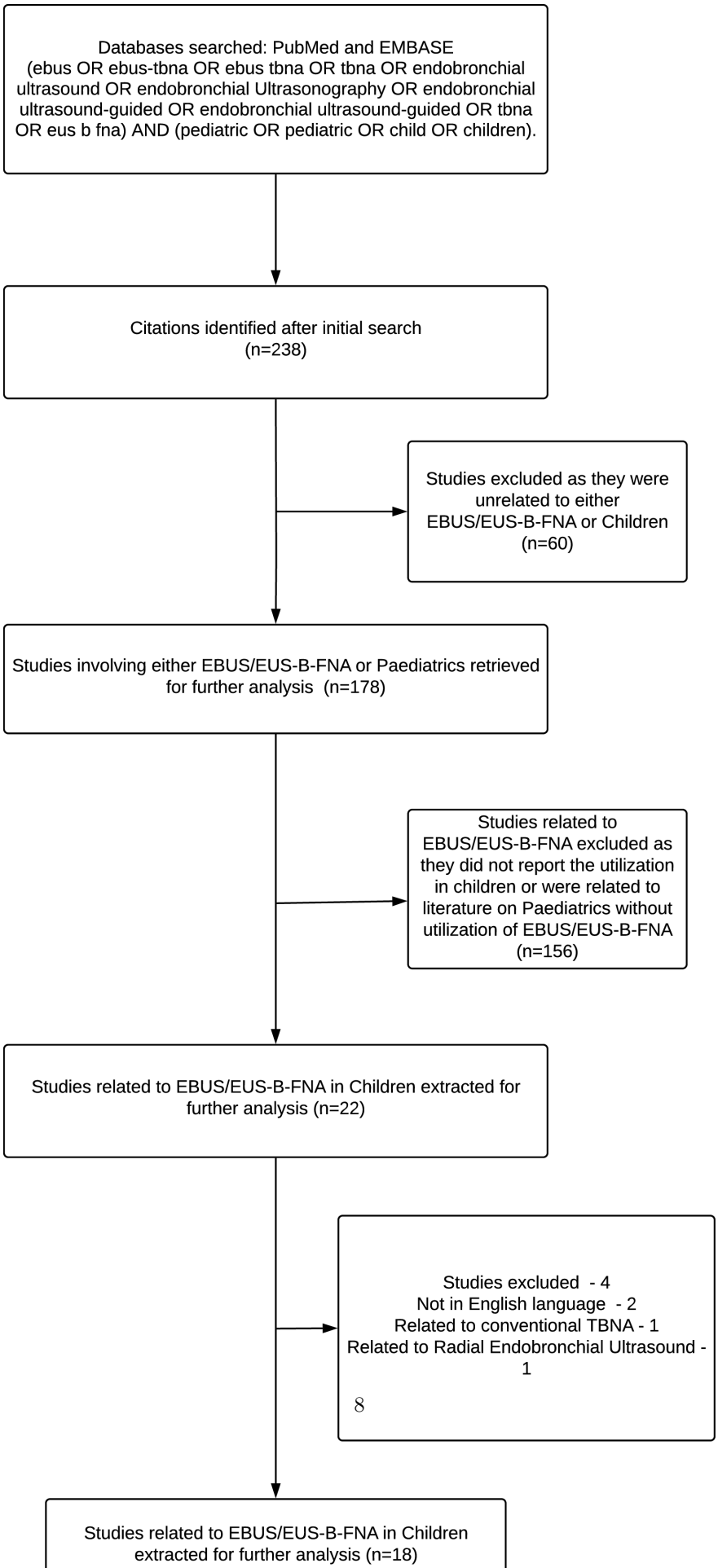

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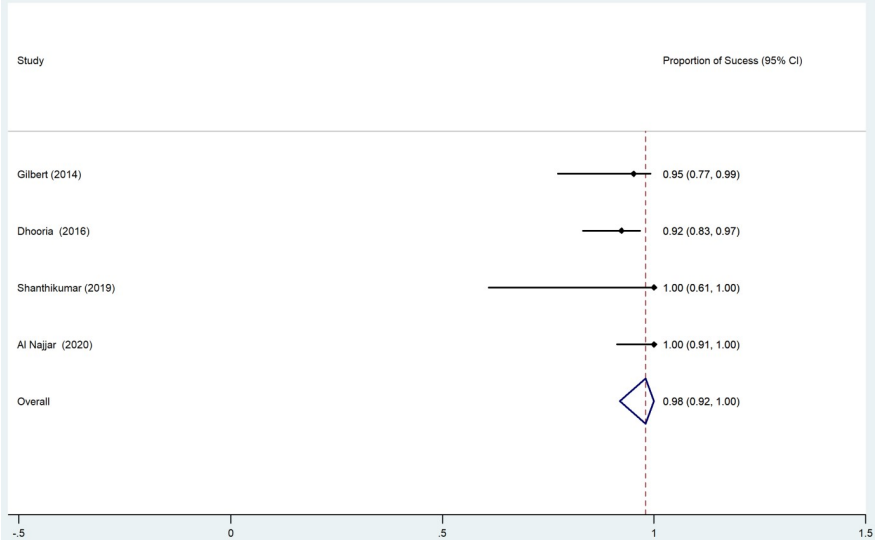

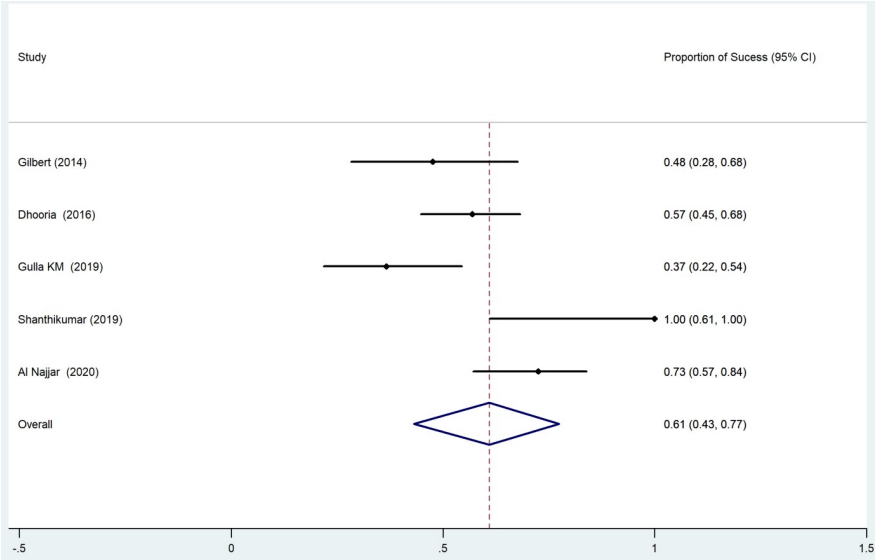

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