# Wet- *versus* dry-suction techniques for EUS-FNA of solid lesions: A systematic review and meta-analysis

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## ABSTRACT

The optimal sampling techniques for EUS-FNA remain unclear and have not been standardized. To improve diagnostic accuracy, suction techniques for EUS-FNA have been developed and are widely used among endoscopists. The aim of this study was to compare wet-suction and dry-suction EUS-FNA techniques for sampling solid lesions. We performed a comprehensive literature search of major databases (from inception to June 2020) to identify prospective studies comparing wet-suction EUS-FNA and dry-suction EUS-FNA. Specimen adequacy, sample contamination, and histologic accuracy were assessed by pooling data using a random-effects model expressed in terms of odds ratio (OR) and 95% confidence interval (CI). Six studies including a total of 418 patients (365 wet suction *vs*. 377 dry suction) were included in our final analysis. The study included a total of 535 lesions (332 pancreatic lesions and 203 nonpancreatic lesions). The pooled odds of sample adequacy was 3.18 (CI: 1.82–5.54, $P = 0.001$) comparing wet- and dry-suction cohorts. The pooled odds of blood contamination was 1.18 (CI: 0.75–1.86, $P = 0.1$). The pooled rate for blood contamination was 58.33% (CI: 53.65%–62.90%) in the wet-suction cohort and 54.60% (CI 49.90%– 59.24%) in the dry-suction cohort ($P = 0.256$). The pooled odds of histological diagnosis was 3.68 (CI 0.82–16.42, $P = 0.1$). Very few adverse events were observed and did not have an impact on patient outcomes using either method. EUS-FNA using the wet-suction technique offers higher specimen quality through comparable rates of blood contamination and histological accuracy compared to dry-suction EUS-FNA.

**Key words:** dry suction, EUS, FNA, solid lesions, wet suction

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## INTRODUCTION

Tissue acquisition using EUS-FNA was first introduced 25 years ago and has become an important part of the diagnostic and staging algorithm for both benign and malignant diseases of the GI tract.[1] As such, various suction techniques for EUS-FNA have been developed to improve diagnostic accuracy. To this end, the dry- and wet-suction techniques have been proposed as methods for tissue acquisition using EUS-FNA.

The dry-suction or traditional technique involves removal of the stylet and the use of a 10 ml prevacuum syringe to generate negative pressure to aid in the acquisition of tissue specimen. However, this technique has associated flaws which may impact the quality of the aspirate.[2,3] This technique has been shown to increase the cellularity of a sample but also increases the chance of blood contamination.[4]

Alternatively, the wet-suction technique involves the use of saline or heparin to preflush the needle prior to aspiration.[5,6] Prior to puncturing the lesion, the stylet is removed and the needle is preflushed with about 5 ml of liquid. Left attached to the proximal port and later used for aspiration is a 10 ml syringe prefilled with 3 ml of liquid. Once the needle is passed into the lesion, the needle is moved back and forth roughly three times and suctioned to acquire tissue aspirate. This is repeated about four times prior to air flushing the sample onto a slide for review.

Compared to dry-suction EUS-FNA, the wet-suction technique has been shown to increase cellularity and adequacy of specimens without adding blood contamination.[7] To this end, we conducted a systematic review and meta-analysis to evaluate the differences between wet- and dry-suction techniques for the sampling of solid lesions.

## METHODS

### *Search strategy*
We conducted a comprehensive search of several databases and conference proceedings including PubMed, EMBASE, and Google-Scholar databases to April 2020. An experienced medical librarian using inputs from the study authors helped with the literature search. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using a predefined protocol to identify studies

reporting the use of wet suction and dry suction during EUS FNA [Supplementary Table 1].[8,9]

Keywords used in the literature search included a combination of "endoscopic ultrasound", "fine needle aspiration", "FNA," "dry-suction", "wet-suction" "pancreatic mass", and "solid lesions." The search was restricted to studies performed on human subjects and published in the English language in peer-reviewed journals [Supplementary Table 2]. Two authors (DR and JS) independently reviewed the title and abstract of studies identified in the primary search and excluded studies that did not address the research question, based on prespecified exclusion and inclusion criteria. The full text of the remaining articles was reviewed to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus and in discussion with a co-author.

The bibliographic section of the selected articles, as well as the systematic and narrative articles on the topic, was manually searched for additional relevant articles.

### *Study selection*
We included comparative studies that evaluated and compared wet-suction and dry-suction techniques for EUS FNA. Studies irrespective of the sample size, inpatient/outpatient setting, and geography were included as long as they provided data needed for the analysis.

Inclusion criteria were (1) comparative studies. Exclusion criteria included (1) pediatric (age <18 years) studies, (2) case reports or case series with less than 10 patients, and (3) studies not published in the English language. In the event of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were retained.

### *Data abstraction and quality assessment*
Study references and citations were collected in EndNote X9 (Thomson Reuters, New York, NY). Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia: https://www. covidence. org/) was used to further screen and extract relevant studies. The full text of each selected article was reviewed to verify that it contained relevant information. To identify other potentially eligible publications, the bibliographic section of the selected articles was manually searched for additional

relevant articles. Data on study-related outcomes in the individual studies were abstracted by two authors (DR and JS) and the two authors (DR and JS) did the quality scoring independently. The Jadad scale for RCT was used to assess the quality of studies.[10] The Newcastle–Ottawa scale was used for cohort studies.[10,11]

### Outcomes assessed in study cohorts were as follows

1. Odds ratio (OR) of specimen adequacy
2. Pooled rate of specimen adequacy
3. OR of sample blood contamination
4. Pooled rate of sample blood contamination
5. OR of histologic accuracy
6. Pooled rate of histologic accuracy.

### Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird using the random-effects model.[12] We assessed heterogeneity between study-specific estimates using Cochran Q statistical test for heterogeneity and the $I^2$ statistics.[13-16] In this, values of <30%, 30%–60%, 61%–75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.[17-20]

Publication bias was ascertained qualitatively, by visual inspection of the funnel plot and quantitatively by the Egger test.[21,22] $P$ value <0.05 was considered statistically significant for comparison of groups. Statistical analyses were conducted using STATA software, version 16.0 (College Station, TX: StataCorp LLC).

### RESULTS

### Search results and study characteristics

From an initial total of 558 studies, 520 records were screened after deduplication, and 16 full-length articles were assessed. Six studies were ultimately included in the final meta-analysis.[4,7,23-26] The schematic diagram of study selection is illustrated in Figure 1.

A total of 418 patients (365 wet suction *vs.* 377 dry suction) were included in the final analysis. This analysis included a total of 535 lesions (332 pancreatic lesions and 203 nonpancreatic lesions). Patient age ranged from 26 to 87 years. Four studies used 22G needles for EUS-FNA, 1 study used 19G, 1 study used 25G, and 1 study used either 19G or 22G. Additional details
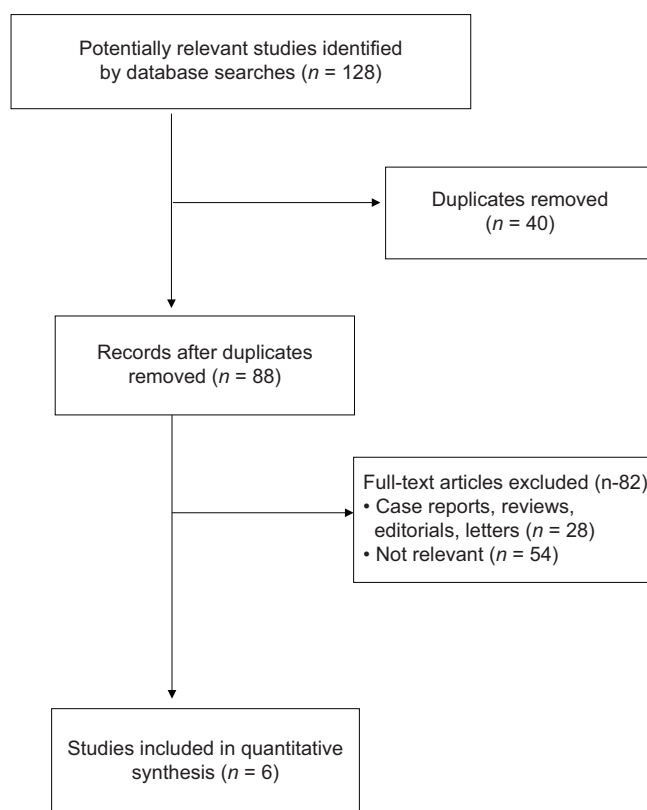


**Figure 1.** Study Prisma chart

of study characteristics with patient demographics are summarized in Table 1.

### Characteristics and quality of included studies

Full manuscript publications included three randomized control trials[4,7,25] and three prospective cohort studies.[23,24,26] One study was published as an abstract.[23] Four studies originated from the USA,[7,23,25,26] one from China,[4] and one from Japan.[24] The detailed assessment of study quality is given in Supplementary Table 3.

### Meta-analysis outcomes

1. OR of sample adequacy: The pooled odds of sample adequacy was 3.18 (confidence interval [CI]: 1.82–5.54), favoring wet over dry suction EUS FNA, this was statistically different ($P = 0.001$) [Figure 2]
2. Pooled rate of sample adequacy: The pooled rate of sample adequacy was 91.90% (CI: 89.10%–94.18%) in the wet-suction cohort and 77.32% (CI 73.37%-80.94%) in the dry-suction cohort (comparison $P$ value <0.001)
3. OR of blood contamination: The pooled odds of blood contamination was 1.18 (CI: 0.75–1.86) comparing the two study cohorts and this was not statistically different ($P = 0.1$)
4. Pooled rate of blood contamination: The pooled rate for blood contamination was 58.33%
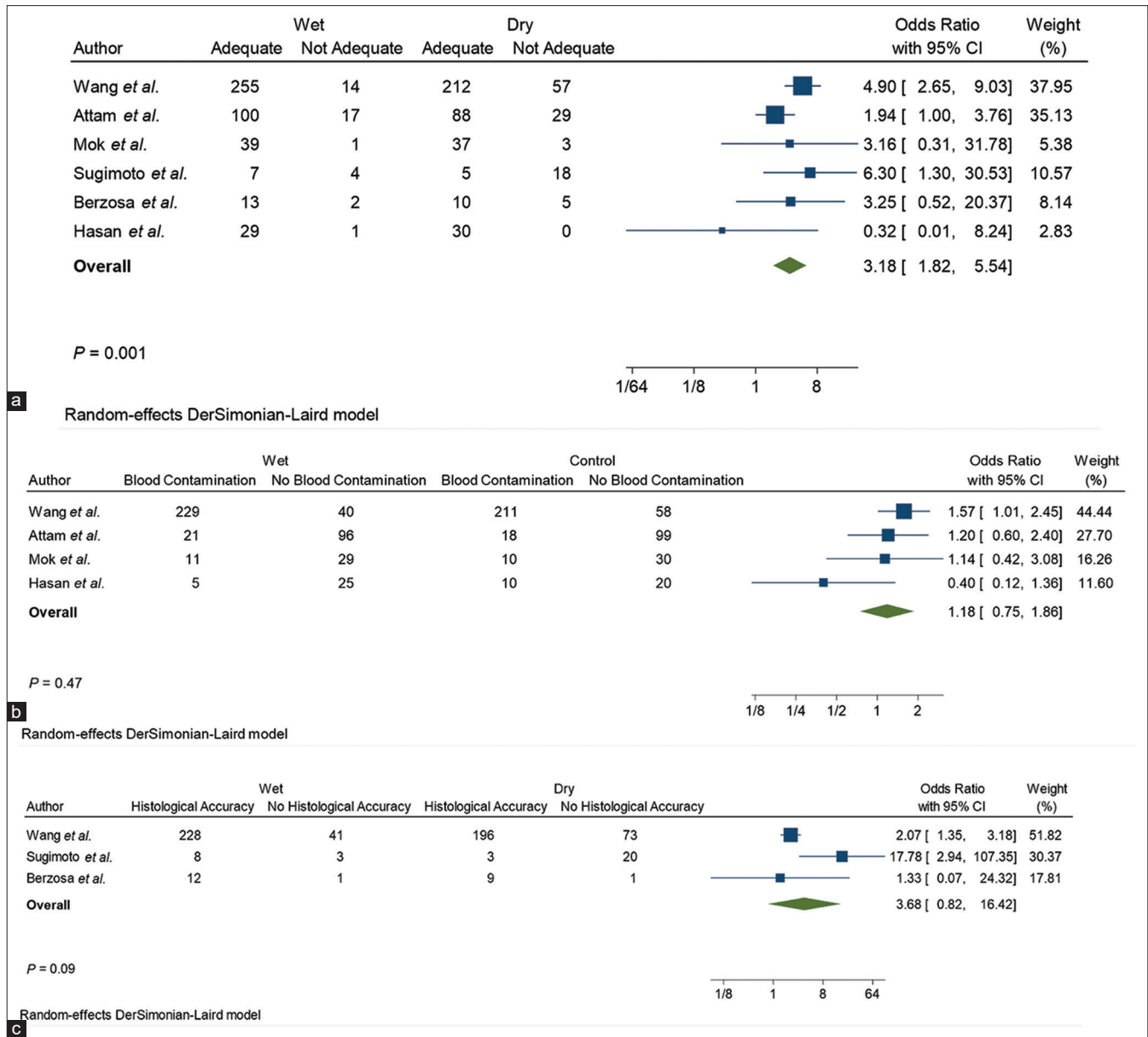
| Author | Wet Adequate | Not Adequate | Dry Adequate | Not Adequate | | Odds Ratio with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|---|
| Wang *et al.* | 255 | 14 | 212 | 57 | | 4.90 [ 2.65, 9.03] | 37.95 |
| Attam *et al.* | 100 | 17 | 88 | 29 | | 1.94 [ 1.00, 3.76] | 35.13 |
| Mok *et al.* | 39 | 1 | 37 | 3 | | 3.16 [ 0.31, 31.78] | 5.38 |
| Sugimoto *et al.* | 7 | 4 | 5 | 18 | | 6.30 [ 1.30, 30.53] | 10.57 |
| Berzosa *et al.* | 13 | 2 | 10 | 5 | | 3.25 [ 0.52, 20.37] | 8.14 |
| Hasan *et al.* | 29 | 1 | 30 | 0 | | 0.32 [ 0.01, 8.24] | 2.83 |
| **Overall** | | | | | | 3.18 [ 1.82, 5.54] | |

$P = 0.001$

1/64   1/8   1   8

**a**   Random-effects DerSimonian-Laird model

| Author | Wet Blood Contamination | No Blood Contamination | Control Blood Contamination | No Blood Contamination | | Odds Ratio with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|---|
| Wang *et al.* | 229 | 40 | 211 | 58 | | 1.57 [ 1.01, 2.45] | 44.44 |
| Attam *et al.* | 21 | 96 | 18 | 99 | | 1.20 [ 0.60, 2.40] | 27.70 |
| Mok *et al.* | 11 | 29 | 10 | 30 | | 1.14 [ 0.42, 3.08] | 16.26 |
| Hasan *et al.* | 5 | 25 | 10 | 20 | | 0.40 [ 0.12, 1.36] | 11.60 |
| **Overall** | | | | | | 1.18 [ 0.75, 1.86] | |

$P = 0.47$

1/8   1/4   1/2   1   2

**b**   Random-effects DerSimonian-Laird model

| Author | Wet Histological Accuracy | No Histological Accuracy | Dry Histological Accuracy | No Histological Accuracy | | Odds Ratio with 95% CI | Weight (%) |
|---|---|---|---|---|---|---|---|
| Wang *et al.* | 228 | 41 | 196 | 73 | | 2.07 [ 1.35, 3.18] | 51.82 |
| Sugimoto *et al.* | 8 | 3 | 3 | 20 | | 17.78 [ 2.94, 107.35] | 30.37 |
| Berzosa *et al.* | 12 | 1 | 9 | 1 | | 1.33 [ 0.07, 24.32] | 17.81 |
| **Overall** | | | | | | 3.68 [ 0.82, 16.42] | |

$P = 0.09$

1/8   1   8   64

**c**   Random-effects DerSimonian-Laird model

**Figure 2.** Forest plots of specimen adequacy (a), blood contamination (b), and histological accuracy (c)

## Table 1. Study characteristics

| Author | Country | Center type | Study design | Number of patients (*n*) Dry | Wet | Male/ female | Lesions type Pancreatic, *n* (%) | Nonpancreatic, *n* (%) | Needle gauge (G) | How many passes? |
|---|---|---|---|---|---|---|---|---|---|---|
| Attam, 2015 | USA | Multicenter | RCT | 117 | 117 | 66/51 | 63 (54) | 54 (46) | 22 | Dry - 46 Wet - 46 |
| Berzosa, 2014 | USA | Single center | Prospective (abstract) | 15 | 15 | Not reported | 14 (93) | 1 (7) | 22 | Dry - 12 Wet - 12 |
| Mok, 2018 | USA | Single center | RCT | 40 | 40 | 16/24 | 0 | 40 (100) | 19 | Dry - 3 Wet - 3 |
| Sugimoto, 2020 | Japan | Single center | Prospective | 23 | 11 | 27/7 | 34 (100) | 0 | 19/22 | Dry - 5 Wet - 4 |
| Wang, 2020 | China | Multicenter | RCT | 269 | 269 | 161/108 | 161 (59.9) | 108 (40.1) | 22 | Dry - 2 Wet - 2 |
| Hasan, 2014 | USA | Single center | Retrospective | 30 | 30 | 39/21 | 60 (100) | 0 | 25 | Dry - 1 Wet - 1 |

RCT: Randomized controlled trial

(CI: 53.65%–62.90%) in the wet-suction cohort and 54.60% (CI: 49.90%– 59.24%) in the dry-suction cohort (comparison *P* value = 0.256)

5. OR of histological diagnosis: The pooled odds of histological diagnosis was 3.68 (CI: 0.82–16.42) comparing the two study cohorts and this was not statistically different (*P* = 0.1)

6. Pooled rate of histological diagnosis: The pooled rate for histological diagnosis was 84.06% (CI: 79.38%–88.05%) in the wet-suction cohort and 68.87% (CI: 63.31%–74.05%) in the dry-suction cohort (comparison *P* value <0.001).

### *Validation of meta-analysis results*
### Heterogeneity and publication bias assessment

We assessed dispersion of the calculated rates using $I^2$ percentage values. $I^2$ tells us what proportion of the dispersion is true *versus* chance. We found no significant heterogeneity in reported sample adequacy analysis, moderate heterogeneity was observed in blood contamination analysis, and significant heterogeneity was observed in histological analysis. Publication bias analysis was visually assessed using funnel plots [Supplementary Table 4].

## DISCUSSION

We found that the wet-suction technique resulted in greater specimen adequacy when compared to the dry suction method. However, we found that blood contamination, and more importantly, histological accuracy, was comparable using either technique.

We found that the wet-suction cohort had a statistically significant improvement in the specimen adequacy when compared to the dry-suction cohort, with an OR of 3.18 (CI: 1.82–5.54, *P* = 0.001). Berzosa *et al.* had suggested that a column of water enhances tissue aspiration due to fluid dynamics and has been shown to allow greater volumes of tissue to be aspirated within the same simulation time when compared to a column of air.[5,27]

Our study also demonstrated that there were comparable rates of blood contamination in the wet-suction cohort when compared to dry-suction cohort (pooled OR: 1.18, CI: 1.75–1.86, *P* = 0.1). A concern when using EUS-FNA is that the use of suction can often lead to higher rates of blood contamination and can negatively impact the overall quality of a specimen.[2] It was previously thought

that the wet-suction technique would overcome this barrier.[4,5] However, this meta-analysis did not reveal a statistically significant difference in blood contamination using either method.

We found that both the methods had comparable histological accuracy. Our analysis also failed to show a statistically significant difference in histological accuracy. This could be due to differences in needle gauge as a uniform needle gauge was not used throughout all studies. Furthermore, both the techniques had very low rates of complications which is consistent with previous studies.[20,21]

The strengths of our review are as follows: systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, inclusion of good-quality studies with detailed extraction of data, rigorous evaluation of study quality, and statistics to establish and/or refute the validity of the results of our meta-analysis.

There were also several limitations to this study, most of which are inherent to any meta-analysis. We were unable to calculate the histological accuracy, tissue adequacy, and blood contamination between the pancreatic, hepatic, and other lesions as these data were not consistently provided in all the studies. In addition, the needle gauge was not consistent throughout studies.

Our study is the most comprehensive review comparing the wet-suction and dry-suction techniques for the sampling of solid lesions performed to date. Ultimately, EUS-FNA performed using the wet-suction technique offered higher specimen quality but comparable rates of histological accuracy and blood contamination when compared to EUS-FNA dry suction.

### *Conflicts of interest*
Douglas G. Adler is an Editor of Endoscopic Ultrasound. The article was subject to the journal's standard procedures, with peer review handled independently of this Editor and his research groups. There are no other conflicts of interest.

## *Supplementary Materials*

Supplementary information is linked to the online version of the paper on the *Endoscopic Ultrasound* website.

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## Supplementary Table 1. PRISMA checklist

| Section/topic | Number | Checklist item | Reported on page number |
|---|---|---|---|
| **Title** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both | 1 |
| **Abstract** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: Background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number | 3 |
| **Introduction** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS) | 4 |
| **Methods** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (*e.g.*, web address), and, if available, provide registration information including registration number | Not registered |
| Eligibility criteria | 6 | Specify study characteristics (*e.g.*, PICOS, length of follow-up) and report characteristics (*e.g.*, years considered, language, publication status) used as criteria for eligibility, giving rationale | 4, 5 |
| Information sources | 7 | Describe all information sources (*e.g.*, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched | 4, 5 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated | 4, 5 |
| Study selection | 9 | State the process for selecting studies (*i.e.*, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis) | 5 |
| Data collection process | 10 | Describe method of data extraction from reports (*e.g.*, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators | 6 |
| Data items | 11 | List and define all variables for which data were sought (*e.g.*, PICOS, funding sources) and any assumptions and simplifications made | 5, 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis | 6 |
| Summary measures | 13 | State the principal summary measures (*e.g.*, risk ratio, difference in means) | 6 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (*e.g.*, I2) for each meta-analysis | 6 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (*e.g.*, publication bias, selective reporting within studies) | 5, 6 |
| Additional analyses | 16 | Describe methods of additional analyses (*e.g.*, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified | 5,6 |
| **Results** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram | 7 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (*e.g.*, study size, PICOS, follow-up period) and provide the citations | 7 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12) | 810 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) Simple summary data for each intervention group (b) Effect estimates and confidence intervals, ideally with a forest plot | 810 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency | 810 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15) | 810 |
| Additional analysis | 23 | Give results of additional analyses, if done (*e.g.*, sensitivity or subgroup analyses, meta-regression [see Item 16]) | 9, 10 |
| **Discussion** | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (*e.g.*, healthcare providers, users, and policy makers) | 10, 11 |
| Summary of evidence | | | |

*Contd...*

## Supplementary Table 1. Contd...

| Section/topic | Number | Checklist item | Reported on page number |
|---|---|---|---|
| Limitations | 25 | Discuss limitations at study and outcome level (*e.g.*, risk of bias), and at review-level (*e.g.*, incomplete retrieval of identified research, reporting bias) | 11, 12 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research | 12 |
| Funding | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (*e.g.*, supply of data); role of funders for the systematic review | 1 |

Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6:e1000097.

## Supplementary Table 2. Search strategy

| Number | Searches | Results |
|---|---|---|
| **Medline [Ovid] August 21, 2020** <br> **Ovid MEDLINE (R) and Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily <1946 to August 20, 2020>** | |
| 1 | (Endoscopic Ultrasound-Guided Fine Needle Aspiration/or (Biopsy, Needle/and Ultrasonography/)) and (dry* or wet*).tw, kf | 12 |
| 2 | ((((endoscop* or ultrasound* or ultrason*) adj3 ((fine-needle adj (aspir* or suct* or biops*)) or FNA*)) or EUS-FNA or USFNA* or US-FNA*) and (dry* or wet*)).tw, kf | 23 |
| 3 | 1 or 2 | 28 |
| 4 | (Animals/or Models, animal/or Disease models, animal/) not Humans/ | 4694094 |
| 5 | ((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient*)).ti, kf, jw | 2385881 |
| 6 | 4 or 5 | 5110187 |
| 7 | 3 not 6 | 28 |
| **Embase [Ovid] August 21, 2020** <br> **Embase <1974 to 2020 August 20>** | |
| 1 | (endoscopic ultrasound guided fine needle aspiration/or (needle biopsy/and echography/)) and (dry* or wet*).tw, kw | 21 |
| 2 | ((((endoscop* or ultrasound* or ultrason*) adj3 ((fine-needle adj (aspir* or suct* or biops*)) or FNA*)) or EUS-FNA or USFNA* or US-FNA*) and (dry* or wet*)).tw, kw | 73 |
| 3 | 1 or 2 | 81 |
| 4 | limit 3 to (conference abstract or conference paper or "conference review") | 56 |
| 5 | (animal or animals or bitch or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterina *).ti, kw, dq, jx. not (human* or patient*).mp | 1938912 |
| 6 | 4 not 5 | 55 |
| 7 | 3 not 4 | 25 |
| 8 | (exp animal/or exp juvenile animal/or adult animal/or animal cell/or animal tissue/ or nonhuman/or animal experiment/or animal model/) not human/ | 6665876 |
| 9 | 7 not (5 or 8) | 25 |
| 10 | 6 or 9 | 80 |
| 11 | limit 10 to (conference abstract or conference paper or "conference review") | 55 |
| 12 | 10 not 11 | 25 |

## Supplementary Table 3. Bias assessment

| Cohort studies | | | | | |
|---|---|---|---|---|---|
| Quality assessment criteria | Acceptable (*) | Berzosa *et al.* | Sugimoto *et al.* | Hasan *et al.* |
| Selection | | | | | |
|   Representativeness | Population based | | | | |
|   Cohort size | Drawn from the same community as exposed cohort | * | * | * |
|   Clinical outcomes | Secured records, clinical outcomes | * | * | * |
|   Demonstration that outcome of interest was not present at start of study? | Not present | | | | |
| Comparability | | | | | |
|   Factors comparable between groups? | Yes | * | * | * |
| Outcome | | | | | |
|   Assessment of outcome? | Independent blind assessment, record linkage | * | * | * |
|   Follow-up time | Mentioned or not mentioned | * | * | * |
|   Adequacy of follow-up of cohorts? | Complete follow-up, or subjects lost to follow-up unlikely to introduce bias | * | * | * |
| Overall quality score | | 6 | 6 | 6 |

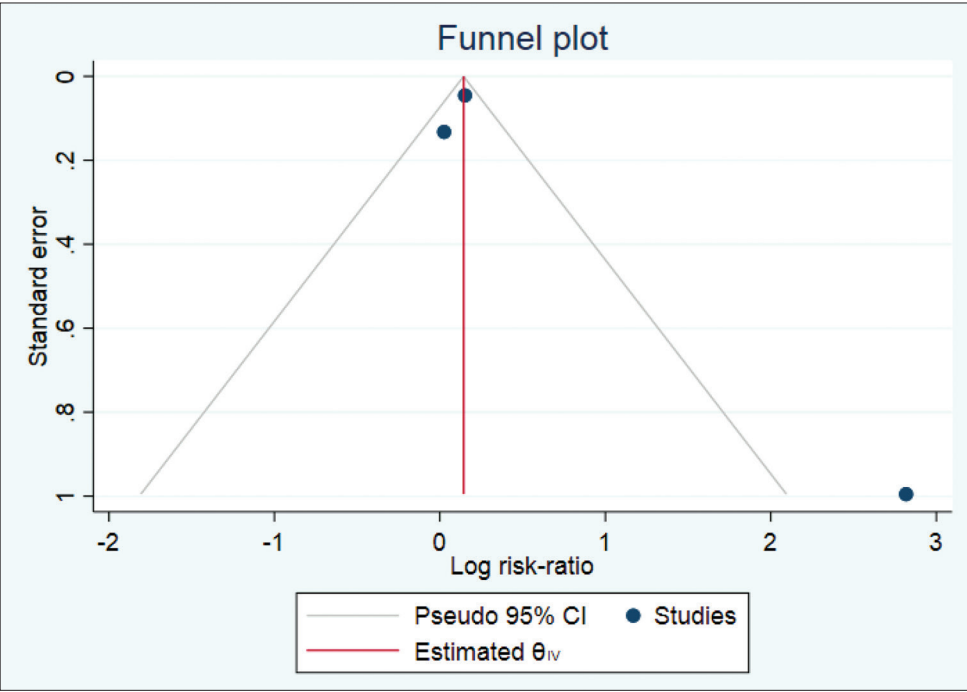| Randomized control trials | | | |
|---|---|---|---|
| Study quality | Attam *et al.* | Mok *et al.* | Wang *et al.* |
| Randomization present | * | * | * |
| Appropriate randomization utilized | * | * | * |
| Blinding present | * | * | * |
| Appropriate blinding method utilized | * | * | * |
| Appropriate long-term follow-up | * | * | * |
| Max score | 5 | 5 | 5 |

**Supplementary Table 4. Funnel plots**
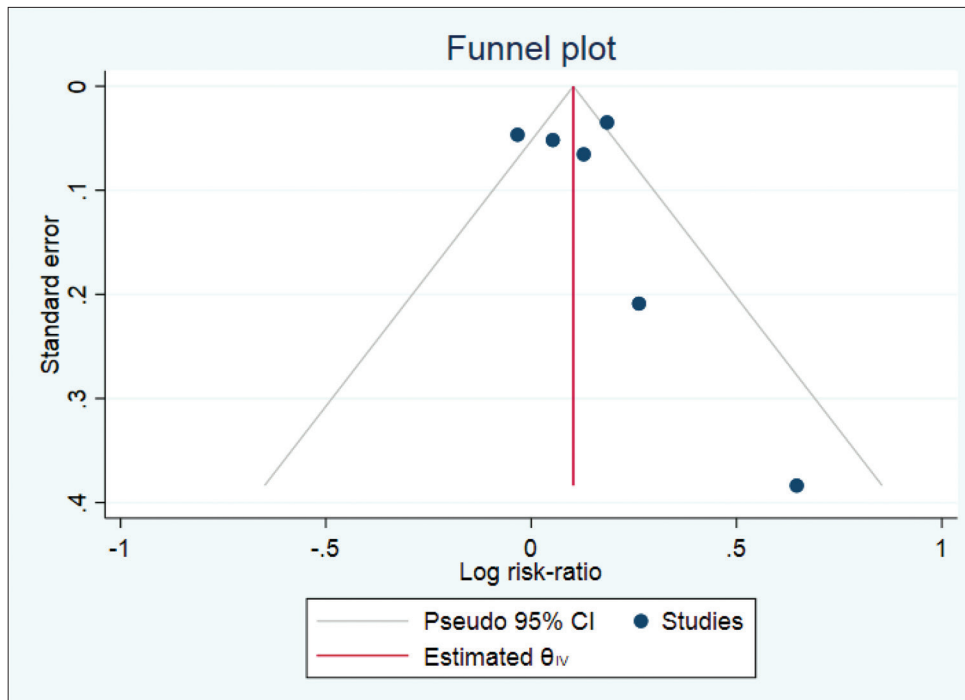


**A.** Funnel plot of sample adequacy
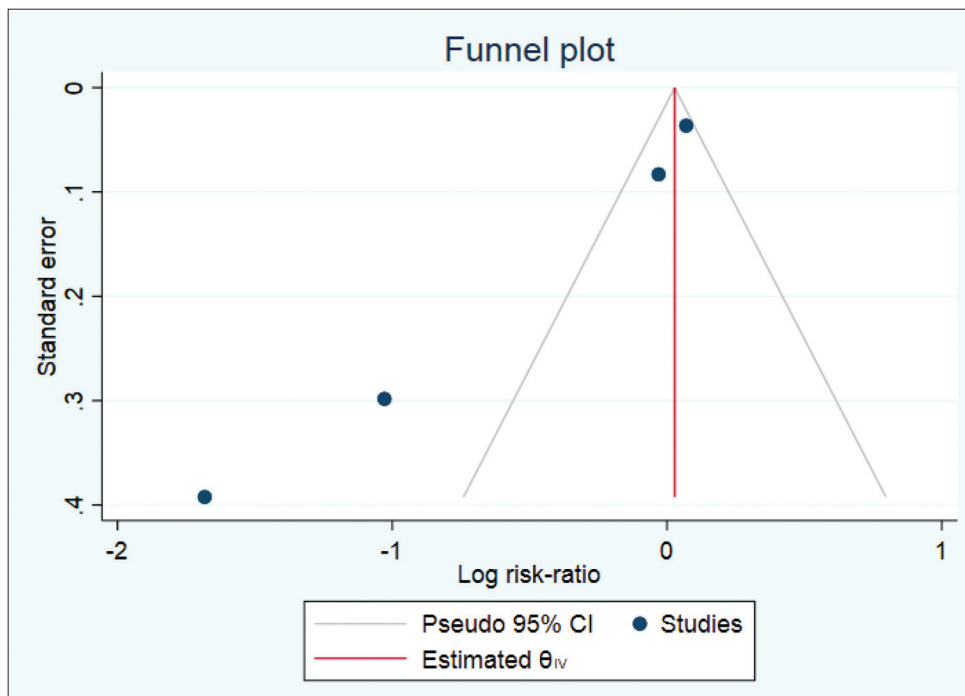


**B.** Funnel plot of blood contamination

**C.** Funnel plot of histological accuracy