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*Supplement of*

# Diagnostic cutoff values of synovial fluid biomarkers for acute postoperative prosthetic joint infection: a systematic review and meta-analysis

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Table S1: Search strategy for MedLine and Embase

| Search strategy for MedLine/PubMed—29/12/2021 |
| --- |
| ((("Arthroplasty, Replacement, Knee"[Mesh]) OR (prosthetic joint*[tiab]) OR (periprosthetic joint*[tiab]) OR (joint arthoplast*[tiab]) OR (joint arthroplast*[tiab]) OR (joint replace*[tiab]) OR (TKA*[tiab]) OR (arthroplast* [ti]) OR (arthoplast*[ti]) OR (periprosthetic[ti]) OR (knee*[ti])) AND (("Prosthesis-Related Infections"[Mesh]) OR (acute infection*[ti]) OR (PJI* [tiab]))) AND ((sensitivity[tiab]) OR (specificity[tiab]) OR (synovial count* [tiab]) OR (leucocyt* [tiab]) OR (PMN [tiab]) OR (neutrohpil [tiab]) OR (synovial [tiab])) |

| Search strategy for Embase—29/12/2021 |
| --- |
| ('replacement arthroplasty'/exp OR ((prosthetic NEAR/2 joint*):ab,ti) OR ((periprosthetic NEAR/2 joint*):ab,ti) OR ((arth*oplast* NEAR/2 joint*):ab,ti) OR tka*:ab,ti OR tja*:ab,ti OR arth*oplast*:ti OR periprosthetic:ti OR joint:ti OR joints:ti) AND ('prosthesis infection'/exp OR ((acute* NEAR/2 infection*):ti) OR pji*:ti) AND (specificity:ab,ti OR sensitivity:ab,ti OR ((synovial NEAR/2 count):ab,ti) OR ((synovial NEAR/2 fluid):ab,ti) OR synovial:ab,ti OR leucocyte*:ab,ti OR pmn*:ab,ti OR neutrophil*:ab,ti) |

Table S2: Characteristics of the excluded SR after full text reading

| | Author and publication year | Title | Reason for exclusion |
| --- | --- | --- | --- |
| 1 | Pagliaccetti J. et al. 2021 | Variability and Interpretation of Synovial Cell Count and Differential: A Perspective in Hip and Knee Arthroplasty | Wrong study design |
| 2 | Fernández-Sampedro, M et al. 2017 | Accuracy of different diagnostic tests for early, delayed and late prosthetic joint infection | Wrong Outcome |
| 3 | Zhang, Chao-Fan et al. 2020 | Debridement, Antibiotics, and Implant Retention for Acute Periprosthetic Joint Infection | Wrong Outcome |
| 4 | Yu, Bao-Zhan et al. 2020 | Neutrophil to lymphocyte ratio as a predictor for diagnosis of early Periprosthetic joint infection | Wrong Outcome |
| 5 | Li, Hao et al. 2021 | The concordance between preoperative aspiration and intraoperative synovial fluid culture results: intraoperative synovial fluid re-cultures are necessary whether the preoperative aspiration culture is positive or not | Wrong Outcome |
| 6 | Xu C. et al. 2019 | Reevaluating Current Cutoffs for Acute Periprosthetic Joint Infection: Current Thresholds Are Insensitive | Only reporting sensitivity |
| 7 | Mason, J Bohannon et al. 2003 | The value of white blood cell counts before revision total knee arthroplasty | Wrong population |

| | | | |
|---|---|---|---|
| 8 | den Bekerom, Michel P J et al. 2006 | The value of pre-operative aspiration in the diagnosis of an infected prosthetic knee: a retrospective study and review of literature | Wrong population |
| 9 | Baré et al. 2006 | Preoperative evaluations in revision total knee arthroplasty | Wrong population |
| 10 | Ghanem E. et al. 2008 | Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty | Wrong population |
| 11 | Schinsky, Mark F et al. 2008 | Perioperative testing for joint infection in patients undergoing revision total hip arthroplasty | Wrong population |
| 12 | Lee, Su Chan et al. 2010 | Analysis of synovial fluid in culture-negative samples of suspicious periprosthetic infections | Wrong population |
| 13 | Society of Unicondylar Research and Continuing Education. 2012 | Diagnosis of periprosthetic joint infection after unicompartmental knee arthroplasty | Wrong population |
| 14 | Zmistowski, Benjamin et al. 2012 | Periprosthetic joint infection diagnosis: a complete understanding of white blood cell count and differential | Wrong population |
| 15 | Dinneen, A et al. 2013 | Synovial fluid white cell and differential count in the diagnosis or exclusion of prosthetic joint infection | Wrong population |
| 16 | Christensen, Christian P. et al. 2013 | The natural progression of synovial fluid white blood-cell counts and the percentage of polymorphonuclear cells after primary total knee arthroplasty: a multicenter study | Wrong population |
| 17 | Lenski, Markus et al. 2014 | Synovial IL-6 as inflammatory marker in periprosthetic joint infections | Wrong population |
| 18 | Claassen, Leif et al. 2014 | Preoperative diagnostic for periprosthetic joint infection prior to total knee revision arthroplasty | Wrong population |
| 19 | Lenski Markus et al. 2015 | Diagnostic potential of inflammatory markers in septic arthritis and periprosthetic joint infections: a clinical study with 719 patients | Wrong population |
| 20 | Shafafy, R et al. 2015 | Use of leucocyte esterase reagent strips in the diagnosis or exclusion of prosthetic joint infection | Wrong population |
| 21 | Sousa, R et al. 2017 | Improving the accuracy of synovial fluid analysis in the diagnosis of prosthetic joint infection with simple and inexpensive biomarkers | Wrong population |
| 22 | Gallo, Jiri et al. 2017 | Excellent AUC for joint fluid cytology in the detection/exclusion of hip and knee prosthetic joint infection | Wrong population |
| 23 | Shahi, Alisina et al. 2017 | Diagnosing Periprosthetic Joint Infection: And the Winner Is? | Wrong population |
| 24 | De Vecchi, Elena et al. 2018 | Alpha defensin, leukocyte esterase, C-reactive protein, and leukocyte count in synovial fluid for pre-operative diagnosis of periprosthetic infection | Wrong population |
| 25 | Parvizi, Javad et al. 2018 | The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria | Wrong population and outcome |
| 26 | Strahm, Carol et al 2018 | Accuracy of Synovial Leukocyte and Polymorphonuclear Cell Count in Patients with Shoulder Prosthetic Joint Infection | Wrong population |
| 27 | Klim, S M et al. 2018 | Fibrinogen - A Practical and Cost Efficient Biomarker for Detecting Periprosthetic Joint Infection | Wrong population |

| | | | |
|---|---|---|---|
| 28 | Zahar, Akos et al. 2018 | How Reliable Is the Cell Count Analysis in the Diagnosis of Prosthetic Joint Infection? | Wrong population |
| 29 | Ding, Benjamin Tk et al. 2019 | Accuracy of the α-defensin lateral flow assay for diagnosing periprosthetic joint infection in Asians | Wrong population |
| 30 | Tahta, Mesut et al. 2019 | Does inflammatory joint diseases affect the accuracy of infection biomarkers in patients with periprosthetic joint infections? A prospective comparative reliability study | Wrong population |
| 31 | Shahi, Alisina et al. 2019 | The Leukocyte Esterase Test for Periprosthetic Joint Infection Is Not Affected by Prior Antibiotic Administration | Wrong population |
| 32 | Lazarides, Alexander L et al. 2019 | Traditional Laboratory Markers Hold Low Diagnostic Utility for Immunosuppressed Patients With Periprosthetic Joint Infections | Wrong population |
| 33 | Yermak, Katsiaryna et al. 2019 | Performance of synovial fluid D-lactate for the diagnosis of periprosthetic joint infection: A prospective observational study | Wrong population |
| 34 | Qin, Leilei et al. 2020 | Evaluation of synovial fluid neutrophil CD64 index as a screening biomarker of prosthetic joint infection | Wrong population |
| 35 | Chu, Lei et al. 2020 | The combinations of multiple factors to improve the diagnostic sensitivity and specificity after artificial joint infection | Wrong population |
| 36 | Bäcker, Henrik C et al. 2020 | Increased Synovial Inflammatory Markers in Aseptic Total Hip Arthroplasty Dislocation | Wrong population and outcome |
| 37 | Deirmengian, Carl A et al. 2020 | False-Positive Automated Synovial Fluid White Blood Cell Counting Is a Concern for Both Hip and Knee Arthroplasty Aspirates | Wrong population |
| 38 | Zhao, Guanglei et al 2020 | Predictive values of the postoperative neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio for the diagnosis of early periprosthetic joint infections: a preliminary study | Wrong population |
| 39 | Mihalič, René et al. 2020 | Synovial fluid interleukin-6 is not superior to cell count and differential in the detection of periprosthetic joint infection | Wrong population |
| 40 | Sharma, Katyayini et al. 2020 | Comparative analysis of 23 synovial fluid biomarkers for hip and knee periprosthetic joint infection detection. | Wrong population |
| 41 | Tirumala, Venkatsaiakhil et al. 2021 | Diagnostic Utility of Platelet Count/Lymphocyte Count Ratio and Platelet Count/Mean Platelet Volume Ratio in Periprosthetic Joint Infection Following Total Knee Arthroplasty. | Wrong population |
| 42 | Fink, Bernd et al. 2021 | The Graphical Representation of Cell Count Representation: A New Procedure for the Diagnosis of Periprosthetic Joint Infections. | Wrong population |
| 43 | Ivy, Morgan I et al. 2021 | Synovial fluid α defensin has comparable accuracy to synovial fluid white blood cell count and polymorphonuclear percentage for periprosthetic joint infection diagnosis | Wrong population |
| 44 | Salar, Omer et al. 2021 | Diagnosis of knee prosthetic joint infection; aspiration and biopsy | Wrong population |

Table S3: Additional information about QUADAS-2 application

**Paper 1: Bedair et al. 2011**

Domain 1 Patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 1.1 Was a consecutive or random sample of patients enrolled? | No | Retrospective |
| 1.2 Was a case-control design avoided? | Unclear | |
| 1.3 Did the study avoid inappropriate exclusions? | yes | |
| RISK OF BIAS: Could the selection of patients have introduced bias? (High, Low or Unclear) | HIGH | |
| APPLICABILITY: Are there concerns that the included patients do not match the review question? (High, Low or Unclear) | LOW | |

Domain 2 Index test: Describe the index test and how it was conducted and interpreted

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 2.1 Were the index test results interpreted without knowledge of the results of the reference standard? | Yes | |
| 2.2 If a threshold was used, was it pre-specified?? | Yes | |
| RISK OF BIAS: Could the conduct or interpretation of the index test have introduced bias? (High, Low or Unclear) | LOW | |
| APPLICABILITY: Are there concerns that the index test, its conduct, or interpretation differ from the review question?? (High, Low or Unclear) | LOW | |

Domain 3 Reference Standard: Describe the reference standard and how it was conducted and interpreted:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 3.1 Is the reference standard likely to correctly classify the target condition? | No | Cultures may be negative |
| 3.2 Were the reference standard results interpreted without knowledge of the results of the index test? | Yes | |
| RISK OF BIAS: | HIGH | |

| | | |
|---|---|---|
| Could the reference standard, its conduct, or its interpretation have introduced bias? (High, Low or Unclear) | | |
| APPLICABILITY:<br>Are there concerns that the target condition as defined by the reference standard does not match the review question? (High, Low or Unclear) | LOW | |

Domain 4 Flow and Timing: Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 4.1 Was there an appropriate interval between index test(s) and reference standard? | Unclear | Not mention when day did the aspiration and the cultures |
| 4.2 Did all patients receive a reference standard?? | yes | |
| 4.3 Did all patients receive the same reference standard?? | yes | |
| 4.4 Were all patients included in the analysis? | Yes | |
| RISK OF BIAS:<br>Could the patient flow have introduced bias? (High, Low or Unclear) | LOW | |

**Paper 2: Yi et al. 2014**

Domain 1 Patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 1.1 Was a consecutive or random sample of patients enrolled? | No | Retrospective |
| 1.2 Was a case-control design avoided? | Unclear | |
| 1.3 Did the study avoid inappropriate exclusions? | No | They only include patients undergoing surgery |
| RISK OF BIAS: Could the selection of patients have introduced bias? (High, Low or Unclear) | HIGH | |
| APPLICABILITY: Are there concerns that the included patients do not match the review question? (High, Low or Unclear) | UNCLEAR | |

Domain 2 Index test: Describe the index test and how it was conducted and interpreted

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 2.1 Were the index test results interpreted without knowledge of the results of the reference standard? | Yes | |
| 2.2 If a threshold was used, was it pre-specified?? | - | Non used |
| RISK OF BIAS: Could the conduct or interpretation of the index test have introduced bias? (High, Low or Unclear) | LOW | |
| APPLICABILITY: Are there concerns that the index test, its conduct, or interpretation differ from the review question?? (High, Low or Unclear) | LOW | |

Domain 3 Reference Standard: Describe the reference standard and how it was conducted and interpreted:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 3.1 Is the reference standard likely to correctly classify the target condition? | No | Cultures may be negative |
| 3.2 Were the reference standard results interpreted without knowledge of the results of the index test? | Unclear | retrospective |
| RISK OF BIAS: Could the reference standard, its conduct, or its interpretation | HIGH | |

| | | |
|---|---|---|
| have introduced bias? (High, Low or Unclear) | | |
| APPLICABILITY:<br>Are there concerns that the target condition as defined by the reference standard does not match the review question? (High, Low or Unclear) | LOW | |

Domain 4 Flow and Timing: Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 4.1 Was there an appropriate interval between index test(s) and reference standard? | Unclear | |
| 4.2 Did all patients receive a reference standard?? | Yes | |
| 4.3 Did all patients receive the same reference standard?? | Yes | |
| 4.4 Were all patients included in the analysis? | Yes | |
| RISK OF BIAS:<br>Could the patient flow have introduced bias? (High, Low or Unclear) | LOW | |

**Paper 3: Kim et al. 2017**

Domain 1 Patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 1.1 Was a consecutive or random sample of patients enrolled? | No | retrospective |
| 1.2 Was a case-control design avoided? | Unclear | |
| 1.3 Did the study avoid inappropriate exclusions? | Yes | They exclude patients but are justified |
| RISK OF BIAS: Could the selection of patients have introduced bias? (High, Low or Unclear) | HIGH | |
| APPLICABILITY: Are there concerns that the included patients do not match the review question? (High, Low or Unclear) | LOW | |

Domain 2 Index test: Describe the index test and how it was conducted and interpreted

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 2.1 Were the index test results interpreted without knowledge of the results of the reference standard? | Yes | |
| 2.2 If a threshold was used, was it pre-specified?? | Yes | |
| RISK OF BIAS: Could the conduct or interpretation of the index test have introduced bias? (High, Low or Unclear) | LOW | |
| APPLICABILITY: Are there concerns that the index test, its conduct, or interpretation differ from the review question?? (High, Low or Unclear) | LOW | |

Domain 3 Reference Standard: Describe the reference standard and how it was conducted and interpreted:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 3.1 Is the reference standard likely to correctly classify the target condition? | No | Negative cultures |
| 3.2 Were the reference standard results interpreted without knowledge of the results of the index test? | Yes | |
| RISK OF BIAS: Could the reference standard, its conduct, or its interpretation | HIGH | |

| | | |
|---|---|---|
| have introduced bias? (High, Low or Unclear) | | |
| APPLICABILITY:<br>Are there concerns that the target condition as defined by the reference standard does not match the review question? (High, Low or Unclear) | LOW | |

Domain 4 Flow and Timing: Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 4.1 Was there an appropriate interval between index test(s) and reference standard? | Unclear | |
| 4.2 Did all patients receive a reference standard?? | Yes | |
| 4.3 Did all patients receive the same reference standard?? | Yes | |
| 4.4 Were all patients included in the analysis? | No | Exclusions are justified |
| RISK OF BIAS:<br>Could the patient flow have introduced bias? (High, Low or Unclear) | Unclear | |

**Paper 4: Xu et al. 2019**

Domain 1 Patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 1.1 Was a consecutive or random sample of patients enrolled? | No | Not mentioned but retrospective |
| 1.2 Was a case-control design avoided? | yes | |
| 1.3 Did the study avoid inappropriate exclusions? | No | |
| RISK OF BIAS: Could the selection of patients have introduced bias? (High, Low or Unclear) | HIGH | |
| APPLICABILITY: Are there concerns that the included patients do not match the review question? (High, Low or Unclear) | UNCLEAR | |

Domain 2 Index test: Describe the index test and how it was conducted and interpreted

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 2.1 Were the index test results interpreted without knowledge of the results of the reference standard? | Yes | |
| 2.2 If a threshold was used, was it pre-specified?? | Unclear | |
| RISK OF BIAS: Could the conduct or interpretation of the index test have introduced bias? (High, Low or Unclear) | UNCLEAR | |
| APPLICABILITY: Are there concerns that the index test, its conduct, or interpretation differ from the review question? (High, Low or Unclear) | LOW | |

Domain 3 Reference Standard: Describe the reference standard and how it was conducted and interpreted:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 3.1 Is the reference standard likely to correctly classify the target condition? | No | |
| 3.2 Were the reference standard results interpreted without knowledge of the results of the index test? | Yes | |
| RISK OF BIAS: Could the reference standard, its conduct, or its interpretation | UNCLEAR | |

| | | |
|---|---|---|
| have introduced bias? (High, Low or Unclear) | | |
| APPLICABILITY:<br>Are there concerns that the target condition as defined by the reference standard does not match the review question? (High, Low or Unclear) | LOW | |

Domain 4 Flow and Timing: Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 4.1 Was there an appropriate interval between index test(s) and reference standard? | Unclear | Not mentioned |
| 4.2 Did all patients receive a reference standard?? | Unclear | |
| 4.3 Did all patients receive the same reference standard?? | Unclear | |
| 4.4 Were all patients included in the analysis? | No | |
| RISK OF BIAS:<br>Could the patient flow have introduced bias? (High, Low or Unclear) | HIGH | |

**Paper 5: Sukhonthamarn et al. 2020**

Domain 1 Patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 1.1 Was a consecutive or random sample of patients enrolled? | No | Retrospective |
| 1.2 Was a case-control design avoided? | Unclear | |
| 1.3 Did the study avoid inappropriate exclusions? | Yes | |
| RISK OF BIAS: Could the selection of patients have introduced bias? (High, Low or Unclear) | HIGH | |
| APPLICABILITY: Are there concerns that the included patients do not match the review question? (High, Low or Unclear) | LOW | |

Domain 2 Index test: Describe the index test and how it was conducted and interpreted

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 2.1 Were the index test results interpreted without knowledge of the results of the reference standard? | Yes | |
| 2.2 If a threshold was used, was it pre-specified?? | Unclear | Not mentioned |
| RISK OF BIAS: Could the conduct or interpretation of the index test have introduced bias? (High, Low or Unclear) | LOW | |
| APPLICABILITY: Are there concerns that the index test, its conduct, or interpretation differ from the review question?? (High, Low or Unclear) | LOW | |

Domain 3 Reference Standard: Describe the reference standard and how it was conducted and interpreted:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 3.1 Is the reference standard likely to correctly classify the target condition? | No | Cultures may be negative |
| 3.2 Were the reference standard results interpreted without knowledge of the results of the index test? | Yes | |
| RISK OF BIAS: Could the reference standard, its conduct, or its interpretation | HIGH | |

| | | |
|---|---|---|
| have introduced bias? (High, Low or Unclear) | | |
| APPLICABILITY:<br>Are there concerns that the target condition as defined by the reference standard does not match the review question? (High, Low or Unclear) | LOW | |

Domain 4 Flow and Timing: Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 4.1 Was there an appropriate interval between index test(s) and reference standard? | Unclear | Not mentioned |
| 4.2 Did all patients receive a reference standard?? | Yes | |
| 4.3 Did all patients receive the same reference standard?? | Yes | |
| 4.4 Were all patients included in the analysis? | Yes | |
| RISK OF BIAS:<br>Could the patient flow have introduced bias? (High, Low or Unclear) | LOW | |

**Paper 6: Uvodich et al. 2021**

Domain 1 Patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 1.1 Was a consecutive or random sample of patients enrolled? | No | Retrospective |
| 1.2 Was a case-control design avoided? | Unclear | |
| 1.3 Did the study avoid inappropriate exclusions? | Yes | |
| RISK OF BIAS: Could the selection of patients have introduced bias? (High, Low or Unclear) | HIGH | |
| APPLICABILITY: Are there concerns that the included patients do not match the review question? (High, Low or Unclear) | LOW | |

Domain 2 Index test: Describe the index test and how it was conducted and interpreted

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 2.1 Were the index test results interpreted without knowledge of the results of the reference standard? | Yes | |
| 2.2 If a threshold was used, was it pre-specified?? | Unclear | Not specified |
| RISK OF BIAS: Could the conduct or interpretation of the index test have introduced bias? ? (High, Low or Unclear) | LOW | |
| APPLICABILITY: Are there concerns that the index test, its conduct, or interpretation differ from the review question?? (High, Low or Unclear) | LOW | |

Domain 3 Reference Standard: Describe the reference standard and how it was conducted and interpreted:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 3.1 Is the reference standard likely to correctly classify the target condition? | No | Major criteria, Cultures may be negative |
| 3.2 Were the reference standard results interpreted without knowledge of the results of the index test? | Yes | |
| RISK OF BIAS: Could the reference standard, its conduct, or its interpretation | HIGH | |

| | | |
|---|---|---|
| have introduced bias? (High, Low or Unclear) | | |
| APPLICABILITY:<br>Are there concerns that the target condition as defined by the reference standard does not match the review question? (High, Low or Unclear) | LOW | |

Domain 4 Flow and Timing: Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 4.1 Was there an appropriate interval between index test(s) and reference standard? | Unclear | Not mentioned |
| 4.2 Did all patients receive a reference standard?? | Yes | |
| 4.3 Did all patients receive the same reference standard?? | Yes | |
| 4.4 Were all patients included in the analysis? | Yes | |
| RISK OF BIAS:<br>Could the patient flow have introduced bias? (High, Low or Unclear) | LOW | |

**Paper 7: Dugdale et al.2021**

Domain 1 Patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 1.1 Was a consecutive or random sample of patients enrolled? | No | Retrospective |
| 1.2 Was a case-control design avoided? | Unclear | |
| 1.3 Did the study avoid inappropriate exclusions? | Yes | |
| RISK OF BIAS: Could the selection of patients have introduced bias? (High, Low or Unclear) | HIGH | |
| APPLICABILITY: Are there concerns that the included patients do not match the review question? (High, Low or Unclear) | LOW | |

Domain 2 Index test: Describe the index test and how it was conducted and interpreted

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 2.1 Were the index test results interpreted without knowledge of the results of the reference standard? | Yes | |
| 2.2 If a threshold was used, was it pre-specified?? | Unclear | Not specified |
| RISK OF BIAS: Could the conduct or interpretation of the index test have introduced bias? ? (High, Low or Unclear) | LOW | |
| APPLICABILITY: Are there concerns that the index test, its conduct, or interpretation differ from the review question?? (High, Low or Unclear) | LOW | |

Domain 3 Reference Standard: Describe the reference standard and how it was conducted and interpreted:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 3.1 Is the reference standard likely to correctly classify the target condition? | No | Major criteria, Cultures may be negative |
| 3.2 Were the reference standard results interpreted without knowledge of the results of the index test? | Yes | |
| RISK OF BIAS: Could the reference standard, its conduct, or its interpretation | HIGH | |

| | | |
|---|---|---|
| have introduced bias? (High, Low or Unclear) | | |
| APPLICABILITY:<br>Are there concerns that the target condition as defined by the reference standard does not match the review question? (High, Low or Unclear) | LOW | |

Domain 4 Flow and Timing: Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:

| Questions | Answer (Yes, No or Unclear) | Motive |
|---|---|---|
| 4.1 Was there an appropriate interval between index test(s) and reference standard? | Unclear | Not mentioned |
| 4.2 Did all patients receive a reference standard?? | Yes | |
| 4.3 Did all patients receive the same reference standard?? | Yes | |
| 4.4 Were all patients included in the analysis? | Yes | |
| RISK OF BIAS:<br>Could the patient flow have introduced bias? (High, Low or Unclear) | LOW | |