World Health Organization

GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC SEXUALLY TRANSMITTED INFECTIONS

# **WEB ANNEX D.** SYSTEMATIC REVIEW FOR SYNDROMIC MANAGEMENT OF LOWER ABDOMINAL PAIN

JUNE 2021

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# **WEB ANNEX D.** SYSTEMATIC REVIEW FOR SYNDROMIC MANAGEMENT OF LOWER ABDOMINAL PAIN

JUNE 2021

Guidelines for the management of symptomatic sexually transmitted infections: Web Annex D. Systematic review for syndromic management of lower abdominal pain

ISBN 978-92-4-003481-5 (electronic version)



**Suggested citation.** Guidelines for the management of symptomatic sexually transmitted infections: Web Annex D. Systematic review for syndromic management of lower abdominal pain. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

**Cataloguing-in-Publication (CIP) data.** CIP data are available at http://apps.who.int/iris.

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This publication forms part of the WHO guideline entitled *Guidelines for the management of symptomatic sexually transmitted infections*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development*, 2nd edition (2014).

Design and layout by 400 Communications.

# CONTENTS

# 1. INTRODUCTION

Sexually transmitted infections (STIs), including human immunodeficiency virus (HIV), continue to present significant health, social, and economic problems in the developing world, leading to considerable morbidity, mortality, and stigma. In under-resourced settings, the lack of adequate laboratory infrastructure and/or high prohibitive costs of diagnostics means that in many settings, STI management relies on syndromic management rather than aetiological diagnosis and management. In these settings, the detection of asymptomatic STIs is largely non-existent. Therefore, synthesizing the latest evidence for the performance of syndromic STI case management would help the World Health Organization (WHO) in their guideline recommendations for syndromic STI management, last updated in 2003.[1]

To evaluate if there is still a role for syndromic STI management or whether STI diagnostics are critical for STI case management, we systematically reviewed the evidence for the performance of syndromic management of STIs. Specifically, we conducted reviews on the diagnostic accuracy and aetiologies of syndromic case management of genital ulcer, anorectal infection and lower abdominal pain. Our specific objectives were to review the flowcharts used for:

- people presenting with genital ulcer disease to detect herpes simplex virus (HSV) or syphilis or lymphogranuloma venereum (LGV) or chancroid, or if no flowcharts found, a minor review of test accuracy of different tests, or risk association/prevalence.
- people presenting with the anorectal syndrome to detect anal STIs or if no flowcharts found, a major review of test accuracy of different tests, or risk association/prevalence.
- people presenting with lower abdominal pain to detect pelvic inflammatory disease (PID) or vaginal or cervical infections, or if no flowcharts found, a major review of test accuracy of different tests, or risk association/prevalence.

# 2. METHODS

## Study inclusion

- Clinical guidelines/algorithms
  - Flow charts for genital ulcer (for syphilis, HSV, LGV, chancroid), anorectal syndromes (for Ct/Ng/Mg/LGV/HSV/Tp/Donovanosis), lower abdominal pain (for PID, vaginal/cervical infections), and vaginal discharge
- Randomized controlled trials
- Observational studies
- Report on at least one of:
  - Comparing syndromic case management against laboratory-confirmed STIs
  - Risk factor analysis of signs/symptoms associated with STI diagnoses and other risk factors associated with STI syndromes

## Study exclusion

- Contains no original data i.e. systematic reviews/Letter/editorials/Commentaries/Book chapters
  - But can use these to identify other relevant primary studies
- Qualitative research about outcomes
- Duplicated results from another study
- Laboratory studies about testing STI diagnostic performance
- Studies restricting study population, e.g. men with urethritis, women with cervicitis

## Search method

Three separate searches were conducted: one for each of the syndromes under investigation. We included papers that focused on other aspects of syndromic management (i.e. acceptability, feasibility, equity, resources) in addition to the accuracy or sensitivity of the syndromic management approach. The search for each syndrome has been constructed as below.

- Concept 1: syndromic management
- Concept 2: syndrome under investigation
- Concept 3: diagnostic accuracy and sensitivity papers
- Results group 1: concept 1 AND concept 2 AND concept 3
- Results group 2: (concept 1 AND concept 2) NOT Results group 1

A draft search strategy was compiled in the OvidSP Medline database by an experienced information specialist. The search strategy included strings of terms, synonyms and controlled vocabulary terms (where available). As the syndromic management approach was not introduced until 1996, the search was limited to papers published in 1995 or after. No other limits were added. This search strategy was refined with the project team until the results retrieved reflected the scope of the project. The agreed OvidSP Medline search was adapted for each database to incorporate database-specific syntax and controlled vocabularies. Full details of the search strings used for each database can be found in the appendix. A

The following databases were searched on 12 and 13 September 2019.

- Ovid SP Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, 1946 to September 11, 2019
- OvidSP Embase, 1974 to 11 September 2019
- OvidSP Global Health, 1910 to week 35, 2019
- OvidSP Northern Light Life Sciences Conference Abstracts, 2010 to Week 34, 2019
- Ebsco CINAHL Plus, complete database
- Ebsco Africa-Wide Information, complete database
- Clarivate Analytics Web of Science Core Collection, consisting of the following databases:
  - Science Citation Index Expanded (SCI-EXPANDED), 1970 - present
  - Social Sciences Citation Index (SSCI), 1970 - present
  - Arts & Humanities Citation Index (A&HCI), 1975 - present
  - Conference Proceedings Citation Index - Science (CPCI-S), 1990 - present
  - Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH), 1990 - present
  - Emerging Sources Citation Index (ESCI), 2015 – present
- BIREME/PAHO/WHO Virtual Health Library LILACS, complete database

All citations identified by our searches were imported into EndNote X9 software. Duplicates were identified and removed using the method described on the LAS blog.[1]

## Data extraction

We followed the guidelines in the Cochrane Handbook 5.1.[2] Three groups of two independent reviewers screened the title and abstracts of unduplicated papers. Discrepancies in screening were resolved by a third reviewer (JO). Each team extracted relevant data from deduplicated full publications. Risk of bias assessment was conducted using the Joanna Briggs Institute Checklist for diagnostic studies.[3]

## Statistical analysis

Diagnostic accuracy cannot be summarized by one measure as sensitivity and specificity are correlated. Therefore, we must choose hierarchical (multilevel) models that use a binomial data structure, i.e. we use a hierarchical logistic regression model in STATA 13.1. After pooling the studies, we report the sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratio. The inverse of the negative likelihood ratio (1/LR-) can be used to compare with the positive likelihood ratio to indicate whether the positive or negative test result has a greater impact on the odds of disease. Likelihood ratios assess the probability or likelihood that the test result obtained would be expected in a person with the condition, compared to the probability or likelihood that the same result would be seen in a person without the condition.

The positive likelihood ratio $LR+ = \frac{sensitivity}{(1-specificity)} = \frac{TP}{(TP+FN)} \div \frac{FP}{(FP+TN)}$ expresses how many times more likely people with the condition are to receive a positive test result compared to those who do not have the condition, while the negative likelihood ratio $LR- = \frac{(1-sensitivity)}{(specificity)} = \frac{FN}{(TP+FN)} \div \frac{TN}{(FP+TN)}$ expresses how likely it is that people with the condition will receive a negative test result compared to those who do not have the condition.

| Likelihood ratio | Approximate* change in probability[12] | Effect on posttest Probability of disease[13] |
|---|---|---|
| Values between 0 and 1 *decrease* the probability of disease (-LR) | | |
| 0.1 | -45% | Large decrease |
| 0.2 | -30% | Moderate decrease |
| 0.5 | -15% | Slight decrease |
| 1 | -0% | None |
| Values greater 1 *increase* the probability of disease (+LR) | | |
| 1 | +0% | None |
| 2 | +15% | Slight increase |
| 5 | +30% | Moderate increase |
| 10 | +45% | Large increase |

[12] *McGee, Steven (1 August 2002). "Simplifying likelihood ratios". Journal of General Internal Medicine. 17 (8): 647–650. doi:10.1046/j.1525-1497.2002.10750.x. ISSN 0884-8734. PMC 1495095. PMID 12213147.*

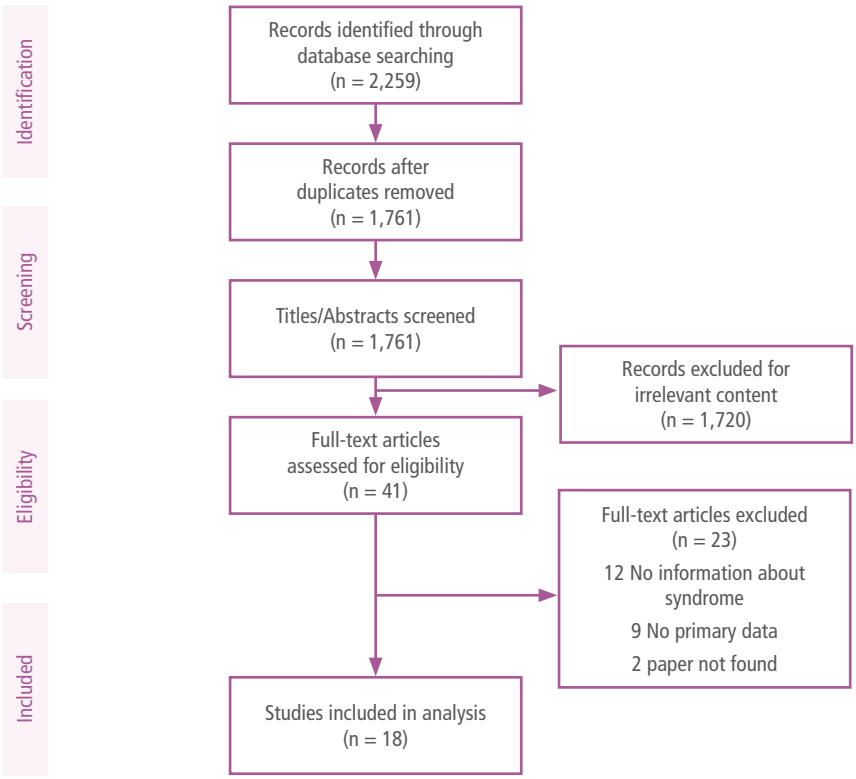
[13] *Henderson, Mark C.; Tierney, Lawrence M.; Smetana, Gerald W. (2012). The Patient History (2nd ed.). McGraw-Hill. p. 30. ISBN 978-0-07-162494-7.*

To graphically display the trade-off between sensitivity and specificity, we present the summary receiver operating characteristic (SROC) curve from the hierarchical summary receiver operating characteristic (HROC) model[4] and prediction region (i.e. for the forecast of the true sensitivity and specificity in a future study). We also plot the summary operating point and its confidence region. Forest plots for showing within-study estimates and confidence intervals for sensitivity and specificity separately.

In the meta-analyses below, we have only included papers where we could calculate the numbers of true positive, false positives, true negatives and false negatives. For the other papers without this data, we have summarized their results qualitatively (i.e. without pooling).

# 3. RESULTS

## 3.1 PRISMA flow chart for lower abdominal pain syndromes



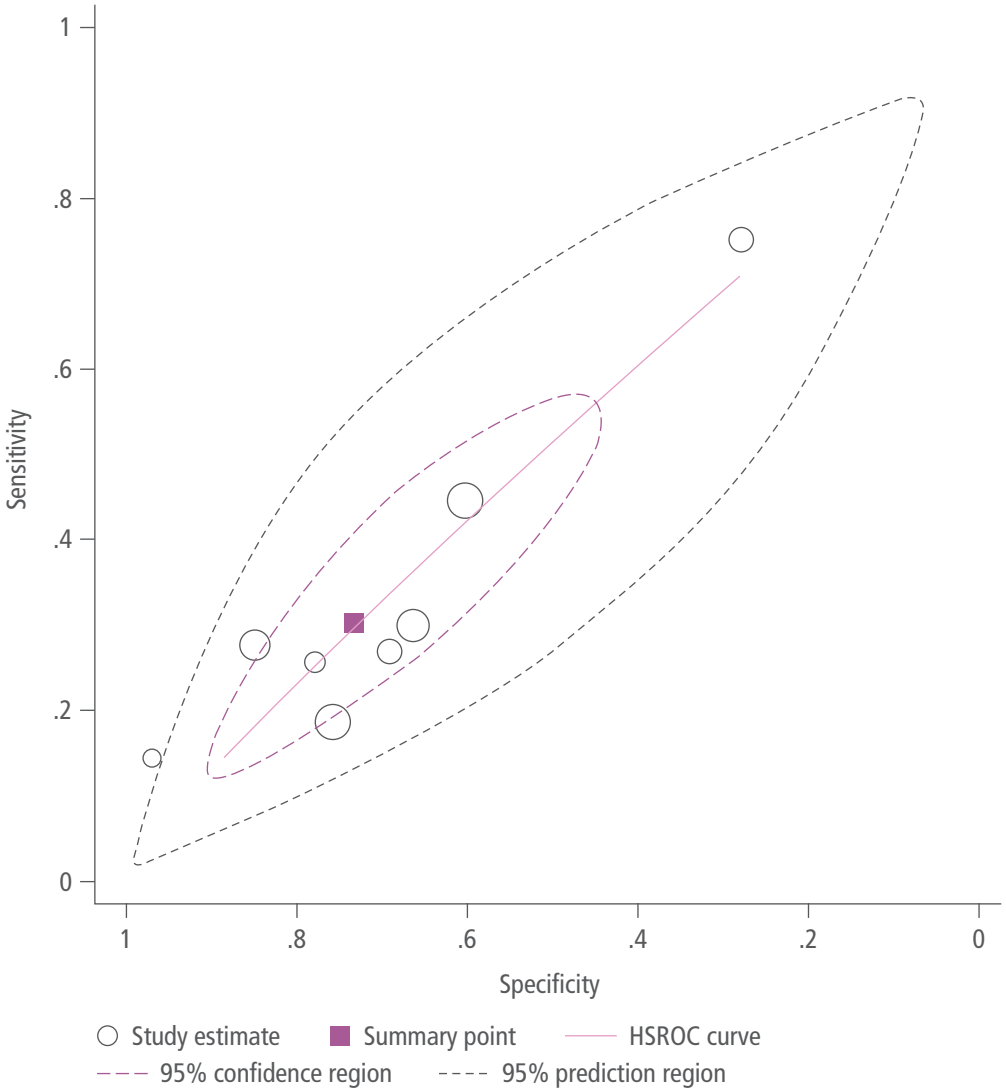
## 3.2 Lower abdominal pain syndrome

- Country income level
  - 12/18 (67%) High income
  - 4/18 (22%) Upper Middle
  - 1/18 (6%) Lower Middle
  - 1/18 (6%) Low
- Study population recruited from (may not add up to 100% because of multiple recruitment sites)
  - 13/18 (72%) Hospital
  - 3/18 (17%) Sexual health clinics
  - 2/18 (11%) General practice
  - 2/18 (11%) Pharmacy
  - 1/18 (6%) Antenatal clinic
  - 1/18 (6%) Family planning clinic
- Year of study
  - 10/18 (56%) 2009 and before
  - 5/18 (28%) 2010-2014
  - 3/18 (17%) 2015 and after

For detection of any STIs (chlamydia, gonorrhoea, trichomonas), five studies provided eight estimates for pooling. The pooled sensitivity for detecting chlamydia/gonorrhoea/trichomonas using a syndromic management approach (lower abdominal pain) is 30.0% (95% CI: 17.7-46.0), and pooled specificity is 73.3% (95% CI: 56.3-85.4). The diagnostic odds ratio is 1.17 (95% CI: 0.85-1.62). The positive likelihood ratio is 1.12 (95% CI: 0.88-1.42), and negative likelihood ratio is 0.96 (95% CI: 0.87-1.05). The inverse of the negative likelihood ratio is 1.05 (95% CI: 0.96-1.14).

For a cohort of 1000 individuals:

| Prevalence | Sensitivity | Specificity | PPV | NPV | Number of cases | Missed cases | False Positive (Overtreated) |
|---|---|---|---|---|---|---|---|
| 0.05 | 0.3 | 0.733 | 0.056 | 0.952 | 50 | 35 | 254 |
| 0.1 | 0.3 | 0.733 | 0.111 | 0.904 | 100 | 70 | 240 |
| 0.15 | 0.3 | 0.733 | 0.165 | 0.856 | 150 | 105 | 227 |
| 0.2 | 0.3 | 0.733 | 0.219 | 0.807 | 200 | 140 | 214 |
| 0.25 | 0.3 | 0.733 | 0.272 | 0.759 | 250 | 175 | 200 |
| 0.3 | 0.3 | 0.733 | 0.325 | 0.710 | 300 | 210 | 187 |
| 0.35 | 0.3 | 0.733 | 0.377 | 0.660 | 350 | 245 | 174 |
| 0.4 | 0.3 | 0.733 | 0.428 | 0.611 | 400 | 280 | 160 |
| 0.45 | 0.3 | 0.733 | 0.479 | 0.561 | 450 | 315 | 147 |
| 0.5 | 0.3 | 0.733 | 0.529 | 0.512 | 500 | 350 | 134 |
| 0.55 | 0.3 | 0.733 | 0.579 | 0.461 | 550 | 385 | 120 |
| 0.6 | 0.3 | 0.733 | 0.628 | 0.411 | 600 | 420 | 107 |
| 0.65 | 0.3 | 0.733 | 0.676 | 0.361 | 650 | 455 | 93 |
| 0.7 | 0.3 | 0.733 | 0.724 | 0.310 | 700 | 490 | 80 |
| 0.75 | 0.3 | 0.733 | 0.771 | 0.259 | 750 | 525 | 67 |
| 0.8 | 0.3 | 0.733 | 0.818 | 0.207 | 800 | 560 | 53 |
| 0.85 | 0.3 | 0.733 | 0.864 | 0.156 | 850 | 595 | 40 |
| 0.9 | 0.3 | 0.733 | 0.910 | 0.104 | 900 | 630 | 27 |
| 0.95 | 0.3 | 0.733 | 0.955 | 0.052 | 950 | 665 | 13 |
| 1 | 0.3 | 0.733 | 1.000 | 0.000 | 1000 | 700 | 0 |


1
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Sensitivity
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Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region

## Detection of any STIs for lower abdominal pain syndrome

| Study | Year of study | Country | Country income level | Sample size | Where recruited | Sub-population | How is a positive case defined | Pathogen, Diagnostic | True positive | False negative | False positive | True negative |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wilkinson[5] | 1998 | South Africa | Upper middle | 268 | Antenatal clinic | 100% pregnant women | Symptoms only | Ct/Ng<br>Ct = direct immuno-fluorescence<br>Ng = culture | 13 | 38 | 48 | 170 |
| Wilkinson[5] | 1998 | South Africa | Upper middle | 190 | Family planning clinic | 100% women | Symptoms only | Ct/Ng<br>Ct = direct immuno-fluorescence<br>Ng = culture | 3 | 18 | 5 | 163 |
| Alary[6] | 1988-91 | Demographic Republic of the Congo | Low | 771 | Unclear | 100% FSW | Symptoms only | Ct/Ng<br>Ct = EIA<br>Ng = culture | 100 | 125 | 217 | 329 |
| Meda[7] | 1994 | Burkina Faso | Low | 397 | Antenatal care | 100% pregnant women | Symptoms only | Ct/Ng<br>Ct = EIA<br>Ng = culture | 8 | 22 | 113 | 254 |
| Piper[8] | Unclear | USA | High | 518 | Public health clinic | 100% ethnic minority women | Symptoms only | Ct/Ng/TV<br>Ct/Ng = NAAT (GenProbe)<br>TV = culture | 106 | 279 | 20 | 113 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 765 | Antenatal clinic | 100% pregnant women | Symptoms only | Ct/Ng/TV<br>NAAT | 60 | 267 | 106 | 332 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 614 | Well woman clinic | 100% women | Symptoms only | Ct/Ng/TV<br>NAAT | 46 | 108 | 154 | 306 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 385 | Sexual health clinic | 100% women | Symptoms only | Ct/Ng/TV<br>NAAT | 109 | 36 | 173 | 67 |

For detection of gonorrhoea, four studies provided six estimates for pooling. Three estimates related to the accuracy of PID diagnosis to detect STIs, and three estimates related to the accuracy of lower abdominal pain to detect STIs. Meta-analysis was not possible here as there were too few estimates.

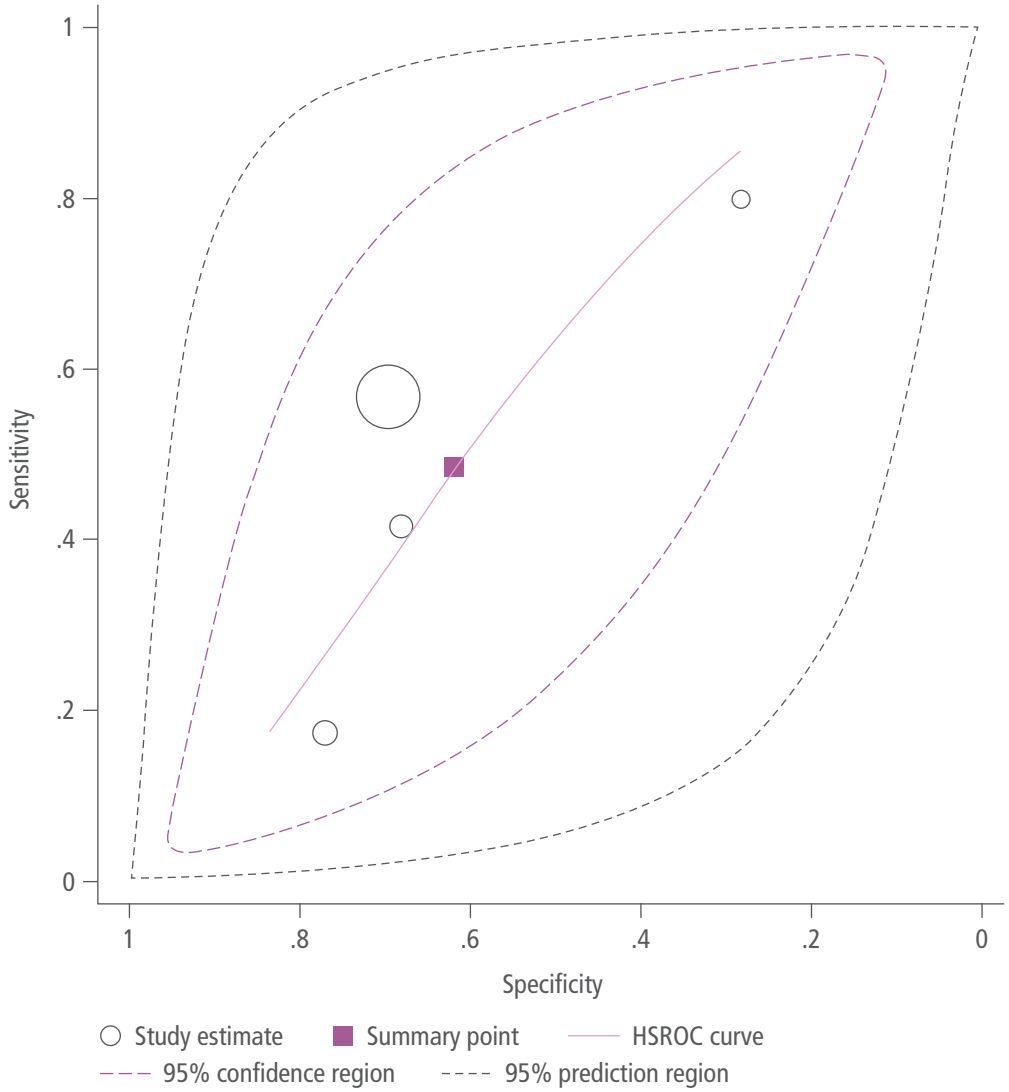
## Detection of gonorrhoea for lower abdominal pain syndrome

| Study | Year of study | Country | Country income level | Sample size | Where recruited | Sub-population | How is a positive case defined | Diagnostic | True positive | False negative | False positive | True negative |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wiesenfeld[10] | 1998-2000 | USA | High | 427 | Hospital, Sexual health clinic, ambulatory care sites | Excluded acute PID | Subclinical PID (endometrial biopsy) | Culture | 15 | 26 | 57 | 329 |
| Woods[11] | 2013 | USA | High | 150 | General practice, Emergency department | 100% diagnosed with PID | PID diagnosis according to ICD criteria (symptoms + examination) | Unclear | 19 | 6 | 98 | 27 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 765 | Antenatal clinic | 100% pregnant women | Symptoms only | PCR | 15 | 94 | 151 | 505 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 614 | Well woman clinic | 100% women | Symptoms only | PCR | 15 | 34 | 185 | 380 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 385 | Sexual health clinic | 100% women | Symptoms only | PCR | 46 | 17 | 236 | 86 |
| Cohen[12] | Unclear | Kenya | Low middle | 115 | Sexual health clinic | 100% had pelvic pain (14 days or less) | Endometritis (endometrial biopsy) | PCR | 9 | 4 | 49 | 53 |

For the detection of chlamydia, five studies provided seven estimates. Four estimates for the accuracy of lower abdominal pain to detect chlamydia were available to pool. The pooled sensitivity for detecting chlamydia using a syndromic management approach (lower abdominal pain) is 48.0% (95% CI: 24.0-73.0), and pooled specificity is 61.7% (95% CI: 41.9-78.3). The diagnostic odds ratio is 1.49 (95% CI: 0.86-2.59). The positive likelihood ratio is 1.25 (95% CI: 0.95-1.66), and negative likelihood ratio is 0.84 (95% CI: 0.63-1.13). The inverse negative likelihood ratio is 1.19 (95% CI: 0.89-1.59).

For a cohort of 1000 individuals:

| Prevalence | Sensitivity | Specificity | PPV | NPV | Number of cases | Missed cases | False Positive (Overtreated) |
|---|---|---|---|---|---|---|---|
| 0.05 | 0.48 | 0.617 | 0.062 | 0.958 | 50 | 26 | 364 |
| 0.1 | 0.48 | 0.617 | 0.122 | 0.914 | 100 | 52 | 345 |
| 0.15 | 0.48 | 0.617 | 0.181 | 0.871 | 150 | 78 | 326 |
| 0.2 | 0.48 | 0.617 | 0.239 | 0.826 | 200 | 104 | 306 |
| 0.25 | 0.48 | 0.617 | 0.295 | 0.781 | 250 | 130 | 287 |
| 0.3 | 0.48 | 0.617 | 0.349 | 0.735 | 300 | 156 | 268 |
| 0.35 | 0.48 | 0.617 | 0.403 | 0.688 | 350 | 182 | 249 |
| 0.4 | 0.48 | 0.617 | 0.455 | 0.640 | 400 | 208 | 230 |
| 0.45 | 0.48 | 0.617 | 0.506 | 0.592 | 450 | 234 | 211 |
| 0.5 | 0.48 | 0.617 | 0.556 | 0.543 | 500 | 260 | 192 |
| 0.55 | 0.48 | 0.617 | 0.605 | 0.493 | 550 | 286 | 172 |
| 0.6 | 0.48 | 0.617 | 0.653 | 0.442 | 600 | 312 | 153 |
| 0.65 | 0.48 | 0.617 | 0.699 | 0.390 | 650 | 338 | 134 |
| 0.7 | 0.48 | 0.617 | 0.745 | 0.337 | 700 | 364 | 115 |
| 0.75 | 0.48 | 0.617 | 0.790 | 0.283 | 750 | 390 | 96 |
| 0.8 | 0.48 | 0.617 | 0.834 | 0.229 | 800 | 416 | 77 |
| 0.85 | 0.48 | 0.617 | 0.877 | 0.173 | 850 | 442 | 57 |
| 0.9 | 0.48 | 0.617 | 0.919 | 0.116 | 900 | 468 | 38 |
| 0.95 | 0.48 | 0.617 | 0.960 | 0.059 | 950 | 494 | 19 |
| 1 | 0.48 | 0.617 | 1.000 | 0.000 | 1000 | 520 | 0 |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Sensitivity
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Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region

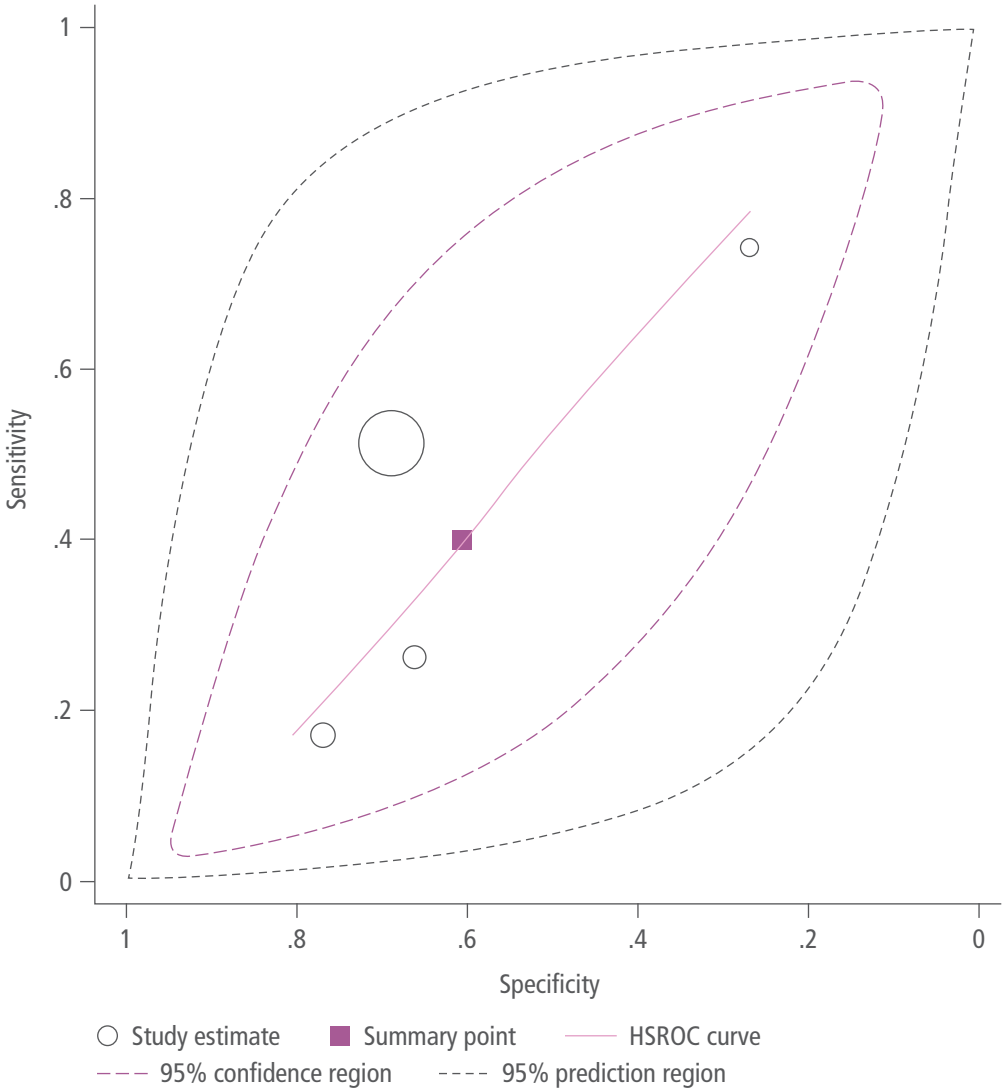
## Detection of chlamydia for lower abdominal pain syndrome

| Study | Year of study | Country | Country income level | Sample size | Where recruited | Sub-population | How is a positive case defined | Diagnostic | True positive | False negative | False positive | True negative |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wiesenfeld[10] | 1998-2000 | USA | High | 403 | Hospital, Sexual health clinic, ambulatory care sites | Excluded acute PID | Subclinical PID (endometrial biopsy) | PCR | 27 | 44 | 46 | 286 |
| Woods[11] | 2013 | USA | High | 150 | General practice, Emergency department | 100% diagnosed with PID | PID diagnosis according to ICD criteria (Symptoms + Examination) | Unclear | 31 | 14 | 86 | 19 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 765 | Antenatal clinic | 100% pregnant women | Symptoms only | PCR | 30 | 145 | 136 | 454 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 614 | Well woman clinic | 100% women | Symptoms only | PCR | 19 | 27 | 181 | 387 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 385 | Sexual health clinic | 100% women | Symptoms only | PCR | 62 | 16 | 220 | 87 |
| Cohen[12] | Unclear | Kenya | Low middle | 115 | Sexual health clinic | 100% had pelvic pain (14 days or less) | PID (endometrial biopsy) | | 4 | 2 | 54 | 55 |
| Grio[13] | 1997-2001 | Italy | High | 5026 | Hospital | | Symptomatic for PID | LCR using Abbot LCx system | 49 | 38 | 1505 | 3434 |

For the detection of trichomonas, three studies provided five estimates. Four estimates for the accuracy of lower abdominal pain to detect trichomonas were available to pool. The pooled sensitivity for detecting trichomonas using a syndromic management approach (lower abdominal pain) is 39.7% (95% CI: 19.6-63.9), and pooled specificity is 60.6% (95% CI: 41.0-77.4). The diagnostic odds ratio is 1.01 (95% CI: 0.62-1.66). The positive likelihood ratio is 1.01 (95% CI: 0.75-1.36), and negative likelihood ratio is 0.99 (95% CI: 0.82-1.21). The inverse negative likelihood ratio is 1.01 (0.83-1.22).

For a cohort of 1000 individuals:

| Prevalence | Sensitivity | Specificity | PPV | NPV | Number of cases | Missed cases | False Positive (Overtreated) |
|---|---|---|---|---|---|---|---|
| 0.05 | 0.397 | 0.606 | 0.050 | 0.950 | 50 | 30 | 374 |
| 0.1 | 0.397 | 0.606 | 0.101 | 0.900 | 100 | 60 | 355 |
| 0.15 | 0.397 | 0.606 | 0.151 | 0.851 | 150 | 90 | 335 |
| 0.2 | 0.397 | 0.606 | 0.201 | 0.801 | 200 | 121 | 315 |
| 0.25 | 0.397 | 0.606 | 0.251 | 0.751 | 250 | 151 | 296 |
| 0.3 | 0.397 | 0.606 | 0.302 | 0.701 | 300 | 181 | 276 |
| 0.35 | 0.397 | 0.606 | 0.352 | 0.651 | 350 | 211 | 256 |
| 0.4 | 0.397 | 0.606 | 0.402 | 0.601 | 400 | 241 | 236 |
| 0.45 | 0.397 | 0.606 | 0.452 | 0.551 | 450 | 271 | 217 |
| 0.5 | 0.397 | 0.606 | 0.502 | 0.501 | 500 | 302 | 197 |
| 0.55 | 0.397 | 0.606 | 0.552 | 0.451 | 550 | 332 | 177 |
| 0.6 | 0.397 | 0.606 | 0.602 | 0.401 | 600 | 362 | 158 |
| 0.65 | 0.397 | 0.606 | 0.652 | 0.351 | 650 | 392 | 138 |
| 0.7 | 0.397 | 0.606 | 0.702 | 0.301 | 700 | 422 | 118 |
| 0.75 | 0.397 | 0.606 | 0.751 | 0.251 | 750 | 452 | 99 |
| 0.8 | 0.397 | 0.606 | 0.801 | 0.201 | 800 | 482 | 79 |
| 0.85 | 0.397 | 0.606 | 0.851 | 0.151 | 850 | 513 | 59 |
| 0.9 | 0.397 | 0.606 | 0.901 | 0.100 | 900 | 543 | 39 |
| 0.95 | 0.397 | 0.606 | 0.950 | 0.050 | 950 | 573 | 20 |
| 1 | 0.397 | 0.606 | 1.000 | 0.000 | 1000 | 603 | 0 |


1
.8
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Sensitivity
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.8
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.4
.2
0
Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region

## Detection of trichomoniasis for lower abdominal pain syndrome

| Study | Year of study | Country | Country income level | Sample size | Where recruited | Sub-population | How is a positive case defined | Diagnostic | True positive | False negative | False positive | True negative |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wiesenfeld[10] | 1998-2000 | USA | High | 428 | Hospital, Sexual health clinic, ambulatory care sites | Excluded acute PID<br>Women 15-30 years old | Subclinical PID (endometrial biopsy) | Culture | 14 | 35 | 60 | 319 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 765 | Antenatal clinic | 100% pregnant women | Symptoms only | | 29 | 142 | 137 | 457 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 614 | Well woman clinic | 100% women | Symptoms only | | 24 | 68 | 176 | 346 |
| Vallely[9] | 2011-15 | Papua New Guinea | Low middle | 385 | Sexual health clinic | 100% women | Symptoms only | | 40 | 14 | 242 | 89 |
| Grio[13] | 1997-2001 | Italy | High | 5516 | Hospital | 100% women | Symptomatic for PID | LCR using Abbot LCx system | 23 | 22 | 1697 | 3774 |

Studies with relevant information for the evaluation of lower abdominal pain syndrome:


- Kurt S, Uyar I, Demirtas O, Celikel E, Beyan E, Tasyurt A. Acute pelvic pain: Evaluation of 503 cases. Archives of Iranian Medicine. 2013;16(7):397-400.
- Eggert J, Sundquist K, van Vuuren C, Fianu-Jonasson A. The clinical diagnosis of pelvic inflammatory disease - Reuse of electronic medical record data from 189 patients visiting a Swedish university hospital emergency department. BMC Women's Health. 2006;6.
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## 3.3 Risk of bias assessment using QUADAS-2

| Study | Patient selection | Index Test | Reference standard | | Flow and Timing |
|---|---|---|---|---|---|
| Wilkinson[5] | Low | Low | Low | High[1] | Low |
| Alary[6] | Low | Low | High | | Low |
| Meda[7] | Low | Low | Low | High[1] | Low |
| Piper[8] | Low | Low | Low | | Low |
| Vallely[9] | Low | Low | Low | | Low |
| Wiesenfeld[10] | High[2] | Low | Low | | Low |
| Woods[11] | Low | Low | Unclear | | Low |
| Cohen[12] | Low | Low | Low | | Low |
| Grio[13] | Low | Low | High | | Low |
| [1] High risk for CT/NG/TV, Low risk for TP | | | | | |
| [2] Excluded women with acute PID | | | | | |

**Extra information for further consideration**

Predicting PID in patients with acute pelvic pain with scoring systems[32]

- Sensitive prediction model to rule out PID
  - Scattered pain radiation and/or diffuse pain, insidious pain, peritoneal irritation, and abnormal vaginal discharge.
- Specific model to predict PID with high specificity
  - Abnormal vaginal discharge, bilateral pelvic pain, constipation, IUD.
- But 2/3rds unable to be classified by these rules
- Risk of sampling bias
  - Setting is women who are consulted in a gynaecology emergency department
  - 56% pregnant women
- Risk of overfitting
  - No cross-validation study with an independent sample
  - But split sample into 2 parts (2/3rds to create the model, 1/3 to validate)
  - Used jackknife estimators

**TABLE 2.** Diagnostic Performance of Selected Items of the SAQ-GE in the Univariate Analysis With $P < 0.20$ for Diagnosing PID

| | n/N* | Se | Sp | LR+ | LR− | P |
|---|---|---|---|---|---|---|
| Imprecise location of pain | 156/320 (48.7%) | 62.7 | 53.9 | 1.36 | 0.69 | 0.03 |
| Diffuse pain | 126/318 (39.6%) | 56.9 | 63.7 | 1.57 | 0.68 | 0.01 |
| Bilateral pelvic pain | 90/329 (27.4%) | 43.1 | 75.5 | 1.76 | 0.75 | <0.01 |
| Left-side pain | 75/329 (22.8%) | 13.7 | 75.5 | 0.56 | 1.14 | 0.09 |
| Lateralized pain | 151/320 (47.2%) | 56.9 | 54.6 | 1.25 | 0.79 | 0.13 |
| Pain in the uterus | 157/319 (49.2%) | 60.8 | 53.2 | 1.30 | 0.74 | 0.07 |
| Pain radiating to thighs | 47/319 (14.7%) | 23.5 | 87.0 | 1.81 | 0.88 | 0.05 |
| Pain radiating to ribs | 64/320 (20.0%) | 29.4 | 81.8 | 1.61 | 0.86 | 0.07 |
| Pain radiating to stomach | 60/318 (18.9%) | 29.4 | 83.1 | 1.75 | 0.85 | 0.04 |
| Intense pain | 193/323 (59.7%) | 76.5 | 43.4 | 1.35 | 0.54 | <0.01 |
| Progressive pain | 144/315 (45.1%) | 61.2 | 57.1 | 1.43 | 0.68 | 0.02 |
| Duration of pain >24 h | 144/318 (45.3%) | 58.8 | 57.3 | 1.38 | 0.72 | 0.03 |
| Ongoing pain | 176/329 (53.6%) | 64.7 | 48.9 | 1.27 | 0.72 | 0.07 |
| Pain crises >30 min | 120/329 (36.4%) | 27.5 | 61.9 | 0.72 | 1.17 | 0.15 |
| Increasing pain | 140/316 (44.3%) | 56.9 | 58.1 | 1.36 | 0.74 | 0.05 |
| Pain provoked by coughing | 130/315 (41.3%) | 66.0 | 63.4 | 1.80 | 0.54 | <0.01 |
| Pain provoked by palpation | 203/312 (65.1%) | 84.3 | 38.7 | 1.38 | 0.41 | <0.01 |
| Awakened by pain | 188/312 (60.0%) | 72.5 | 42.1 | 1.25 | 0.65 | 0.05 |
| Abnormal vaginal discharge | 85/317 (26.8%) | 41.2 | 75.9 | 1.71 | 0.78 | 0.01 |
| Fatigue | 209/322 (64.9%) | 76.5 | 37.3 | 1.22 | 0.63 | 0.06 |
| Constipation | 90/323 (27.9%) | 43.1 | 75 | 1.73 | 0.76 | 0.01 |
| No vaginal bleeding | 239/316 (75.6%) | 88.2 | 26.8 | 1.21 | 0.44 | 0.02 |
| Scattered pain radiating and/or diffuse pain | 244/329 (74.2%) | 94.1 | 29.5 | 1.33 | 0.19 | <0.00 |
| Insidious pain† | 248/329 (75.4%) | 98.0 | 28.8 | 1.38 | 0.07 | <0.00 |
| Peritoneal irritation‡ | 269/329 (81.8%) | 92.2 | 20.1 | 1.15 | 0.39 | 0.04 |

Se indicates sensitivity; Sp, specificity; LR+, positive likelihood ratio; LR−, negative likelihood ratio.
*n, patients with the criterion; N, total patients with or without the criterion.
†Progressive pain, and/or pain present since more than 24 hours, and/or increasing pain.
‡Pain provoked by coughing and/or pain provoked by abdominal palpation.

**TABLE 5.** Diagnostic Values of the 2 Prediction Rules in the Derivation and Validation Cohort

| | n/N* | Probability of PID (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | LR+ | LR− |
|---|---|---|---|---|---|---|
| Clinical prediction model for the low-risk group (sensitive model score ≤31 points) | | | | | | |
| Derivation cohort | 1/94 (1.1%) | 1.1% (0.03–5.8) | 98%† (89.6–100) | 33.5%† (27.9–39.3) | 1.47† | 0.06† |
| Validation cohort | 1/42 (2.4%) | 2.4% | 95.5%† | 27.7%† | 1.32† | 0.16† |
| Clinical prediction model for the high-risk group (specific model score ≥20 points) | | | | | | |
| Derivation cohort | 11/20 (55%) | 55% (31.5–76.9) | 21,6% (11.3–35.3) | 96,8% (93.9–98.5) | 6.70 | 0.80 |
| Validation cohort | 4/6 (66.7%) | 66.7% | 18.2% | 98.7% | 13.50 | 0.80 |

*n, patients with the criterion and having PID; N, total patients classified as having the criterion.
†Calculated with absence of PID as the correct outcome.
LR+ indicates positive likelihood ratio; LR−, negative likelihood ratio.

| Diagnosis | Adolescent | Reproductive | Menopause | Total | Percent |
|---|---|---|---|---|---|
| **Gynecologic** | | | | | |
| Ovarian neoplasm | 0 (%0) | 1 (%0,27) | 6 (%8,33) | 7 | 1,49 |
| Ovarian csyts | 18 (%50) | 133 (%36,84) | 25 (%34,72) | 176 | 37,53 |
| Uterine fibroid | 0 (%0) | 27 (%7,47) | 24 (%33.33) | 51 | 10,87 |
| Rupture of ovarian cysts | 7 (%19,44) | 41 (%11,35) | 0 (%0.00) | 48 | 10,23 |
| Endometriosis | 1 (%2,77) | 29 (%8,03) | 1 (%1.38) | 31 | 6,61 |
| Mullerian abnormality | 2 (%5,55) | 1 (%0,27) | 0 (%0.00) | 3 | 0,63 |
| Primary dysmenorrhea | 2 (%5,55) | 2 (%0,55) | 0 (%0.00) | 4 | 0,86 |
| Pelvic infection | 3 (%8,33) | 97 (%26,86) | 15 (%20,83) | 115 | 24,53 |
| Ectopic pregnancy | 1 (%2,77) | 21 (%5,81) | 1 (%1,38) | 23 | 4,91 |
| Ovarian torsion | 2 (%5,55) | 5 (%1,38) | 0 (%0) | 7 | 1,49 |
| OHSS** | 0 (%0) | 4 (%1,10) | 0 (%0) | 4 | 0,85 |
| **Nongynecologic** | | | | | |
| Acute appendicitis | 8 | 6 | 1 | 15 | 44,11 |
| Nephrolithiasis | 0 | 3 | 1 | 4 | 11,76 |
| İnguinal hernia | 0 | 1 | 2 | 3 | 8,83 |
| Colitis | 0 | 0 | 2 | 2 | 5,89 |
| Undetectable | 5 | 3 | 2 | 10 | 29,41 |

*APP: Acute Petvic Pain; **OHSS: Ovarian Hyper Stimulation Syndrome

**Aetiology of acute pelvic pain**

503 women from Turkey (2013)[15]

58 women with PID (endometrial biopsy) in Kenya[12]

- 4 had Ct
- 9 had Ng
- 9 had Mg
- 11 had TV

11 women with tubo-ovarian abscess (confirmed on laparotomy) in Kenya[33]

- 0 had Ct/Ng

45 women with laparoscopically confirmed PID in Kenya[34]

- 1 had CT
- 7 had NG

125 women with laparoscopically confirmed PID in Kenya[35]

- 23 had Ct and/or Ng
- 23 had TV

44 women clinically diagnosed with PID in Malaysia[36]

- 3 had CT
- 1 had NG

100 women clinically diagnosed with PID in Nepal[37]

- 6 had CT
- 0 had NG

40 women with laparoscopically confirmed PID in Sweden[38]

- 8 had CT
- 1 had MG
- 0 had NG

554 women with PID in India (2018) [39]

- 8 had NG
- 65 had TV
- 1 had HSV

52 women with PID (laparoscopically confirmed) in Lithuania (2008) [40]

- 24 had CT
- 14 had NG

104 women with PID (lap confirmed) in UK (before 1995) [41]

- 40 had CT
- 15 had NG
- 8 had dual infection

200 women with PID in China (2002) [42]

- 16% had CT
- 4% had TV
- 2.5% had NG

343 with (clinically diagnosed) PID in USA (2007-10)[43]

- 15 had NG
- 34 had CT
- 9 had CT and NG

Those with clinical diagnosis of PID and laparoscopy performed to check if PID was present or not:

- 52 out of 73 patients with suspected PID clinically[40]
- 82% had acute salpingitis out of 155 with clinically suspected PID[44]
- 104 (72%) out of 147 women with clinically suspected PID[41]
- 532 (65%) of 814 cases with clinically suspected PID[45]

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# 5. APPENDIX A - SEARCH RESULTS

## 5.1 Lower abdominal pain syndromes

The search retrieved a total of 2259 results. 498 (22%) were identified as duplicates. The number of results pre-and post-deduplication is listed in the table below.

| Database name | Diagnostic accuracy: Total number of results | Diagnostic accuracy: Number of results once duplicates removed | Other papers: Total number of results | Other papers: Number of results once duplicates removed |
|---|---|---|---|---|
| Ovid SP Medline and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily | 297 | 295 | 150 | 149 |
| OvidSP Embase | 895 | 740 | 442 | 370 |
| OvidSP Global Health | 97 | 44 | 37 | 12 |
| OvidSP Northern Light Life Sciences Conference Abstracts | 3 | 2 | 4 | 3 |
| Ebsco CINAHL Plus | 126 | 46 | 95 | 59 |
| Ebsco Africa-Wide Information | 12 | 0 | 0 | 0 |
| Clarivate Analytics Web of Science Core Collection | 77 | 29 | 21 | 9 |
| BIREME/PAHO/WHO Virtual Health Library LILACS | 1 | 1 | 2 | 2 |
| Total | 1508 | 1157 | 751 | 604 |

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