Diagnostic accuracy of prostate cancer antigen 3 (PCA3) prior to first prostate biopsy: A systematic review and meta-analysis

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Abstract

Introduction: We aimed to determine the diagnostic accuracy of the prostate cancer antigen 3 (PCA3) test before performing the first biopsy compared with prostate biopsy for the diagnosis of prostate cancer.
Methods: A systematic search was performed in MEDLINE, EMBASE, CENTRAL, LILACS, reference lists, specialized journals in urology and cancer, and unpublished literature. The population was adults with suspected prostate cancer, and the intervention was the measurement of PCA3 in urine samples for the diagnosis of prostate cancer. The quality of studies was evaluated with the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. The operative characteristics were determined, and a meta-analysis was performed.
Results: Nine studies of diagnostic tests were included based on a cutoff value of 35. The following overall values were obtained: the sensitivity was 0.69 (95% confidence interval [CI] 0.61–0.75); specificity was 0.65 (95% CI 0.553–0.733); the diagnostic odds ratio (DOR) was 4.244 (95% CI 3.487–5.166); and the area under the curve was 0.734 (95% CI 0.674–0.805) with a heterogeneity of 0%.
Conclusions: Urinary PCA3 has an acceptable diagnostic accuracy, aids in the study of patients with suspected prostate cancer, and can be used as a guide for directing the performance of the first prostate biopsy and decreasing unnecessary biopsies.

Introduction

PCa is the second most common type of cancer in the world's male population. It is estimated that one in seven men will be diagnosed at the end of their life with PCa, and one in 38 men will die as a result of the disease in the long term [1].

Bray et al., based on Global Cancer Statistics 2018, reported 7.1% and 3.8% of incidence and mortality respectively (all cancers) and 13.5% and 6.7% of incidence and mortality respectively (Males). The incidence of PCa in High/Very High Human Development Index (HDI) is 37.5 Age-Standardized Rate (ASR) per 100.000 compared with a lower data in Medium/Low HDI which is 11.4 ASR per 100.000. Regarding the mortality, authors reported 8.0 and 6.3 ASR per 100.000 respectively [1].

Since the 1980s, the use of prostate specific antigen (PSA) has been implemented as an early detection test for prostate cancer [2]. However, PSA may be elevated in other benign pathologies, such as prostatitis and prostatic hyperplasia, leading to false positives that require an unnecessary prostate biopsy and that may be accompanied by clinical consequences related to the morbid complications associated with this procedure as well as over-treatment and increased costs to the health system [2].

Given this situation, new diagnostic methods have emerged, such as prostate cancer-specific antigen 3 (PCA3), which is a marker that detects overexpression of the PCA3 gene by molecular techniques. As the name implies, PCA3 is specific for prostate cancer, and it is expressed only in this disease and is not affected by benign conditions, as occurs with PSA, thereby decreasing the risk of false positives [3].

Although the majority of studies to date have shown the usefulness of PCA3 for the early diagnosis of prostate cancer and how it may contribute to the reduction of unnecessary biopsies to improve the survival and quality of life of patients by timely diagnosis as well as optimizing the resources of the health system, these studies were performed after the first biopsy [4]–[6]. Importantly, there are no systematic reviews on the use of PCA3 in patients without previous biopsy. The objective of the present study was to determine the diagnostic accuracy of the PCA3 test before performing the first biopsy compared to prostate biopsy for the diagnosis of prostate cancer.

Methods

The present systematic review was performed in compliance with the suggestions of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) writing recommendations. The protocol was previously published in PROSPERO: CRD42018099528

Inclusion and exclusion criteria

Studies were selected whose populations were adults with suspected prostate cancer due to digital rectal examination and/or an abnormal PSA and who did not have a previous biopsy. The index test for the diagnosis of prostate cancer was the quantitative measurement of PCA3 in urine samples after prostate massage. The reference standard was prostate biopsy. Studies of patients with a confirmed diagnosis of prostate cancer and studies of patients with one or more negative prostate biopsies were excluded.

The outcome was the diagnosis of prostate cancer with measures of sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−), diagnostic odds ratio (DOR), and area under the curve.

Search strategy

A systematic search of studies of diagnostic tests was performed in the following databases from their inception to the present: MEDLINE; EMBASE; Cochrane Controlled Trials Register Center (CENTRAL); and Latin American and Caribbean Literature in Health Sciences (LILACS). Additional studies were also sought in the reference lists of selected articles, abstracts, theses, and conferences of the American Urology Association (AUA) and the European Association of Urology (EAU) as well as in specialized journals in Urology and Cancer and in unpublished literature in databases, such as Open Gray, Google Scholar, and www.clinicaltrials.gov. There were no restrictions on language. The search strategy is described in Appendix 1.

Study selection and data collection

Researchers performed the initial selection blindly and independently based on the title and abstract. The chosen studies were then reviewed based on the full text, applying the inclusion and exclusion criteria, which was also performed independently by two researchers, reaching the final selection.

The data collection was performed using a standardized format, which included the study design, participants, variables, interventions, comparisons and final results. Researchers confirmed the data entry and verified the data at least twice for accuracy.

Risk of bias

The evaluation of each included study was performed with the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [7], which considers the risk of bias and applicability ratings. Each of the researchers rated these items. Disparities in the evaluation were resolved by joint review.

Synthesis of results

A 2×2 table was developed to determine the operative characteristics of sensitivity, specificity, LR+, LR−, and DOR with their respective 95% confidence interval (95% CI). A meta-analysis was performed, estimating the summary measures of the included studies (sensitivity and specificity) by means of a bivariate random-effects model. For the meta-analysis, five of the nine studies were selected because they used a PCA3 cut-off value of 35, decreasing the risk of heterogeneity.

The model proposed by Rutter and Gatsonis was used for the estimation of summary receiver operating characteristic (SROC) curves for exploratory purposes. It is assumed that the validity and the positivity threshold are random effects, so their variances are estimated by the model [8].

Review Manager 5.3 software (RevMan 5.3) was used to summarize the QUADAS-2 rating. R software was used for the estimates of sensitivity and specificity as well as the generation of forest plots and SROC graphs [9] using the meta-analysis of diagnostic accuracy (mada) package and the descriptive statistics for meta-analysis of diagnostic accuracy (madad) function.

The heterogeneity was also assessed with the visual inspection of the forest plots and the SROC, and the heterogeneity was more objectively assessed with the I^2 test, considering the interpretation that values of 25%, 50%, and 75% correspond to low, medium, and high levels of heterogeneity, respectively [10].

Sensitivity analysis

Additionally, a sensitivity analysis was performed based on the exclusion of each of the included studies and those of smaller sample size.

Analysis by subgroup

A subgroup analysis was intended to be performed, but the data were not sufficient for its realization.

Publication bias

Implementation of publication bias was not possible given the small number of studies included in the meta-analysis.

Results

In the initial search, a total of 742 studies were found, which were reviewed by title and abstract. After the initial filter by full text, nine studies met the inclusion criteria [Salami 2013 [11]; De Luca 2014 [12]; Leyten 2013 [13]; Ruffion 2013 [14]; Ferro 2013 [15]; Salagierski 2013 [16]; Hansen 2013 [17]; Dimitriadis 2013 [18]; Van Gils 2007 [17]] (Figure 1).

The studies were published between 2007 and 2014 with an average of 336 participants per study and an age range between 44 and 87 years. With regard to the methodology, the design of all the studies was a prospective cohort in which patients directed to have a prostate biopsy because of either an abnormal digital rectal examination or elevated PSA. Patients also had a urine sample taken after prostate massage to evaluate the PCA3 levels and to compare them with the results of the biopsy taken later, which was the reference standard in all the studies (Table 1).

Risk of bias assessment

All the included studies were evaluated with a low risk of bias with respect to the selection of patients, index test, and reference standard. However, with regard to the case of flow and timing, most of the studies had an unclear risk because they did not specify the follow-up time of the patients. One study had a high risk of bias in regard to this aspect because it did not mention the reason for the loss of three patients during the follow-up, and one study had a low risk (Figure 2).

Results of the individual studies

The diagnostic yield for each study showed sensitivity between 0.60 and 0.93, and it showed specificity between 0.37 and 0.76. The positive likelihood ratio in all the studies was greater than 1, with values ranging between 1.68 and 2.48, and the values ranged between 0.29 and 0.53 for the negative likelihood ratio (Table 2).

The meta-analysis was developed with five studies [De Luca 2014 [12]; Leyten 2013 [13]; Ruffion 2013 [14]; Salagierski 2013 [16]; Hanssen 2013, [17]] in which the PCA3 had a cut-off value of 35. A bivariate random-effects model and estimation of SROC curves indicated that the overall sensitivity was 0.69 (95% CI 0.61–0.75) $I^2 = 0\%$ and that the overall specificity was 0.65 (95% CI 0.553–0.733) $I^2 = 0\%$. For the DOR, the overall result was 4.244 (95% CI 3.487–5.166) $I^2 = 0\%$, and the area under the curve was 0.734 (95% CI 0.674–0.805) $I^2 = 0\%$. Thus, these results demonstrated a good discriminatory capacity of the index test (Figures 3 and 4).

Discussion

Summary of the principal findings

With a cut-off value of 35, PCA3 presented an overall sensitivity of 0.69 (95% CI 0.61–0.75) and an overall specificity of 0.65 (95% CI 0.553–0.733). Additionally, the overall DOR was 4.244 (95% CI 3.487–5.166), and the area under the curve was 0.734 (95% CI 0.674–0.805).

Comparison with literature

Currently, PSA is the marker that guides whether or not to have a prostate biopsy in patients with suspected prostate cancer, but the low specificity of this test has led to the search for new markers, such as PCA3. PCA3 reveals better results, suggesting a greater usefulness for PCA3 in directing patients to prostate biopsy. Due to the better specificity, only those patients who really need this procedure would be referred, thereby reducing biopsies in patients without cancer. Moreover, PSA is affected by benign conditions, such as prostatitis and prostatic hyperplasia, which is not the case of PCA3.

When comparing this meta-analysis with other studies, the overall results were in the range of 50–70% for sensitivity and specificity. Yong Luo et al. [19] reported a PCA3 cut-off value of 35, a sensitivity of 75%, and a specificity of 57%. Another meta-analysis developed by Wu Jin Xue [20] found an overall sensitivity of 62% and a specificity of 75%, similar to the values found in the present meta-analysis with an overall sensitivity and specificity that did not exceed 70%. Regarding the DOR and the values of the area under the curve, Yong Luo [19] reported values of 4.11 and 0.69, respectively, and Wu Jin Xue [20] reported values of 5.49 and 0.75, respectively, which are in the range of the present results, indicating a good discriminatory capacity of PCA3.

Strengths and limitations

The strengths of this study were the quality with respect to the selection of patients, the index test, and the reference standard because there was a low risk of bias related to these aspects in all the studies. Moreover, the homogeneity of the studies was 100%, including comparison with the studies available in the literature, which report some degree of heterogeneity. The lack of heterogeneity in the present meta-analysis is a positive aspect that favors the conclusions regarding the diagnostic accuracy of PCA3.
The limitation of the study was the quality of the included studies with respect to the flow and timing with risk of unclear bias because they did not describe the reason for the loss of some patients, which may be related to the published information.

Implications for practice

The results obtained in this meta-analysis are not sufficient to recommend the replacement of prostate biopsy by PCA3 as a reference standard for the diagnosis of prostate cancer because more studies are required in patients without previous biopsy. However, these results may be useful as a guide for directing patients who require this confirmatory test because PCA3 has few false positives and a better specificity with respect to PSA, especially in the gray area range. Adding PCA3 to flow charts for the diagnosis of prostate cancer would optimize the study of these patients, thus avoiding unnecessary prostate biopsies.

Another important aspect of the applicability is that the present study is a starting point for more studies in patients with suspected prostate cancer before the first biopsy for which the available literature is insufficient.

Conclusions

Urinary PCA3 with a cut-off value of 35 has an acceptable diagnostic yield, aids in the study of patients with suspected prostate cancer and can be used as a guide for directing the performance of the first prostate biopsy and decreasing unnecessary biopsies.

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Figures and Tables

Fig. 1. Flowchart for included studies. PCA3: prostate cancer antigen 3.

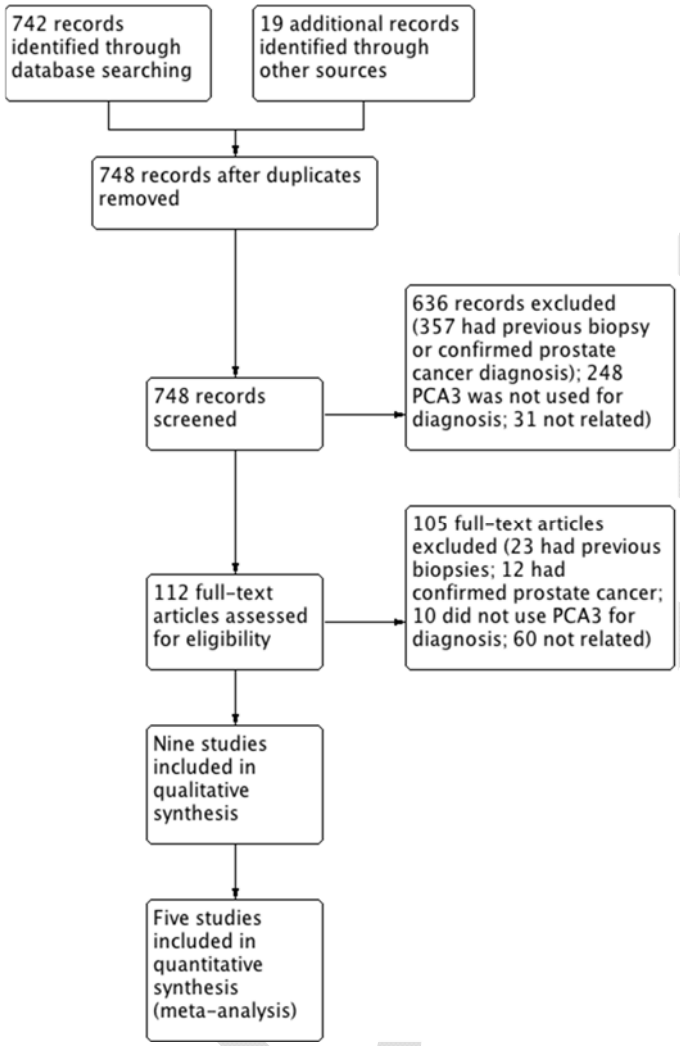
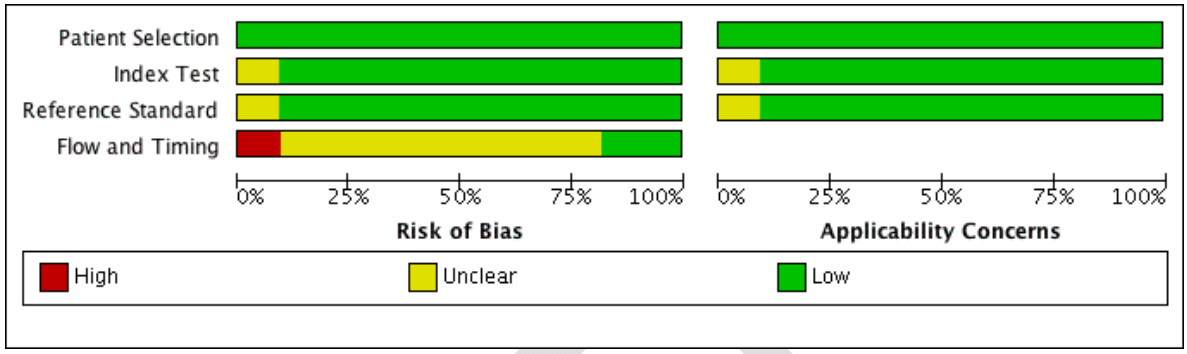


Fig. 2. Risk of bias assessment ***(A)*** across studies; and ***(B)*** within studies.

A



B

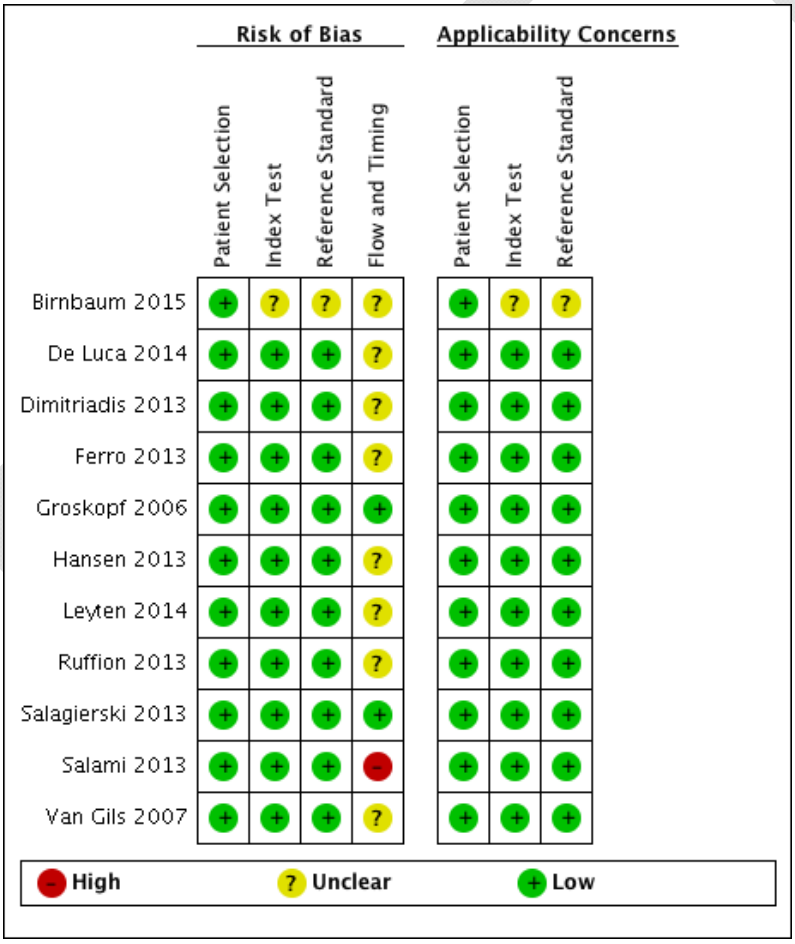


Fig. 3. Summary receiver operating characteristic curve (bivariate model) for prostate cancer antigen 3 data.

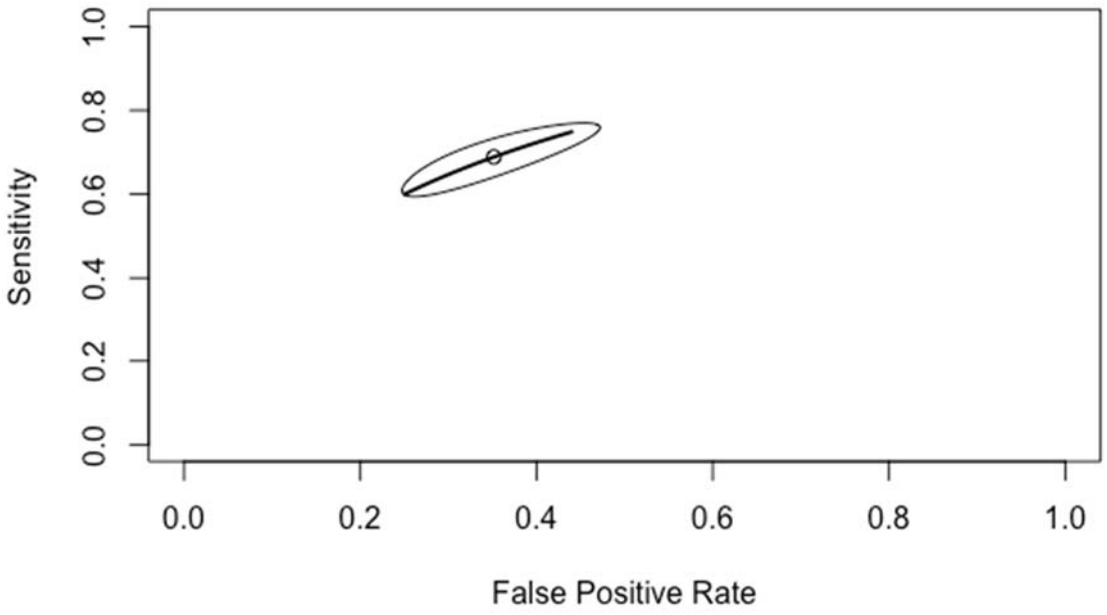


Fig. 4. Forest plot of diagnostic odds ratio.

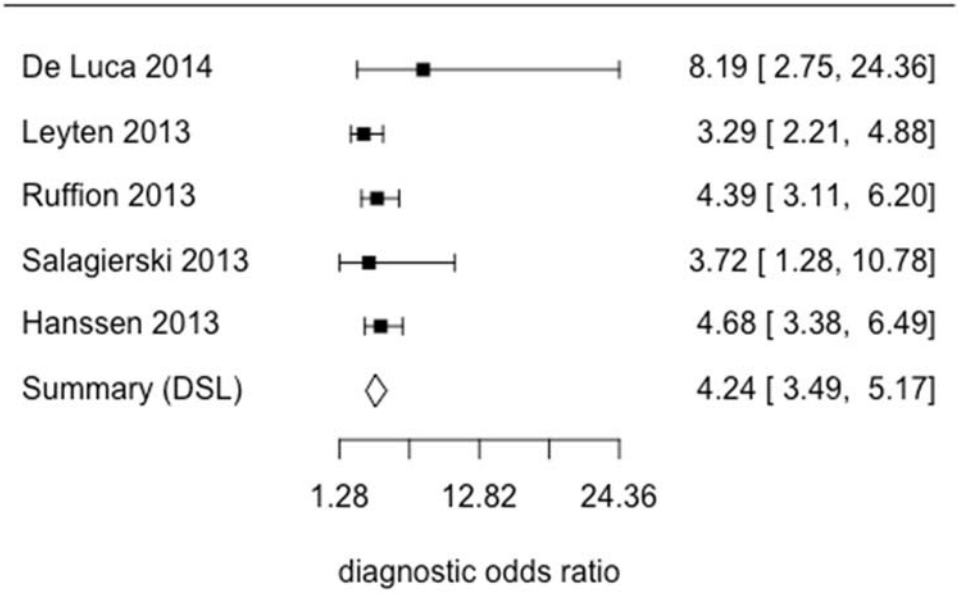


Table 1. Characteristics of the included studies

Author, year	Country	Number of participants	Age	Design	Biomarker	Reference standard	Cutoff value
Salami S et al, 2013	U.S.	45	56–71	Prospective cohort	PCA3 and TMPRSS2:ERG	Prostate biopsy	35
De Luca S et al, 2014	Italy	274	48–87	Prospective cohort	PCA3, PHI, and PSA	Prostate biopsy	35
Leyten G et al 2013	Netherlands	443	44–86	Prospective cohort	PCA3 and TMPRSS2:ERG	Prostate biopsy	35
Ruffion A et al, 2013	France	594	58–67	Prospective cohort	PCA3 and PSA	Prostate biopsy	21 and 35
Ferro M et al, 2013	Italy	300	50–73	Prospective cohort	PCA3, PHI, and PSA	Prostate biopsy	22
Salagierski M et al, 2013	Netherlands	80	50–81	Prospective cohort	PCA3 and PSA	Prostate biopsy	10 and 35
Hansen J et al, 2013	Germany and U.S	692	58–69	Prospective cohort	PCA3 and PSA	Prostate biopsy	17, 21, 24, and 35
Dimitriadis E et al, 2013	Greece	66	45–83	Prospective cohort	PCA3 and TMPRSS2:ERG	Prostate biopsy	30
Van Gils M et al, 2007	Netherlands	534	57–71	Prospective cohort	PCA3 and PSA	Prostate biopsy	58

PCA3: prostate cancer antigen 3; PHI: Prostate Health Index; PSA: prostate-specific antigen; TMPRSS2:ERG: transmembrane protease serine 2:v-ets erythroblastosis virus E26 oncogene homolog.

Table 2. Results of the individual studies

Study	True positives	False positives	False negatives	True negatives	Sensitivity (95% CI)	Specificity (95% CI)
De Luca, 2014	86	6	21	12	0.80 [0.72, 0.87]	0.67 [0.41, 0.87]
Dimitriadis, 2013	11	17	3	35	0.79 [0.49, 0.95]	0.67 [0.53, 0.80]
Ferro, 2013	97	116	11	76	0.90 [0.83, 0.95]	0.40 [0.33, 0.47]
Hansen, 2013	190	90	128	284	0.60 [0.54, 0.65]	0.76 [0.71, 0.80]
Leyten, 2014	134	98	62	149	0.68 [0.61, 0.75]	0.60 [0.54, 0.66]
Ruffion, 2013	175	90	101	228	0.63 [0.57, 0.69]	0.72 [0.66, 0.77]
Salagierski, 2013	18	24	6	32	0.75 [0.53, 0.90]	0.57 [0.43, 0.70]
Salami, 2013	14	19	1	11	0.93 [0.68, 1.00]	0.37 [0.20, 0.56]
Van Gils, 2007	113	122	61	238	0.65 [0.57, 0.72]	0.66 [0.61, 0.71]

CI: confidence interval.